

# Cardiovascular Outcomes in Type 2 Diabetes

## A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study

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**OBJECTIVE** — To determine whether serum lipid intervention, in addition to conventional diabetes treatment, could alter cardiovascular outcomes in type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — There were 164 type 2 diabetic subjects (117 men, 47 women) without a history of clinical cardiovascular disease randomized to receive either bezafibrate or placebo daily on a double-blind basis in addition to routine diabetes treatment and followed prospectively for a minimum of 3 years. Serial biochemical and noninvasive vascular assessments, carotid and femoral artery B-mode ultrasound measurements, and those pertaining to coronary heart disease (CHD)—clinical history, the World Health Organization (WHO) cardiovascular questionnaire, and resting and exercise electrocardiogram (ECG)—were recorded.

**RESULTS** — Bezafibrate treatment was associated with significantly greater reductions over 3 years in median serum triglyceride (−32 vs. 4%,  $P = 0.001$ ), total cholesterol (−7 vs. −0.3%,  $P = 0.004$ ), and total-to-HDL cholesterol ratio (−12 vs. −0.0%,  $P = 0.001$ ), and an increase in HDL cholesterol (6 vs. −2%,  $P = 0.02$ ) as compared with placebo. There was a trend toward a greater reduction of fibrinogen (−18 vs. −6%,  $P = 0.08$ ) at 3 years. No significant differences between the two groups were found in the progress of ultrasonically measured arterial disease. In those treated with bezafibrate, there was a significant reduction ( $P = 0.01$ , log-rank test) in the combined incidence of Minnesota-coded probable ischemic change on the resting ECG and of documented myocardial infarction.

**CONCLUSIONS** — Improving dyslipidemia in type 2 diabetic subjects had no effect on the progress of ultrasonically measured arterial disease, although the lower rate of “definite CHD events” in the treated group suggests that this might result in a reduction in the incidence of coronary heart disease.

Cardiovascular disease, particularly coronary heart disease (CHD), is the most important cause of morbidity and mortality in type 2 diabetes in Western society. For men with type 2 diabetes, mortality from CHD is two to four times higher than in nondiabetic men, and the corresponding increase is even greater for women (1).

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**Abbreviations:** AUS, arterial ultrasound score; CHD, coronary heart disease; ECG, electrocardiogram; IMT, intima media thickness; MI, myocardial infarction; WHO, World Health Organization.

In the general population, increased incidence of CHD is associated with raised serum cholesterol, while there is an inverse relationship with HDL cholesterol. The evidence that elevated serum triglyceride levels is an independent risk factor for CHD in the general population (2,3) is even stronger in the diabetic population (4–6). A raised serum triglyceride level and low HDL cholesterol are characteristic abnormalities in type 2 diabetes. There is much evidence that these two related abnormalities, often referred to as dyslipidemia, are important in the etiology of the accelerated vascular disease in type 2 diabetes (4–6). Fibrinogen elevation has been shown to be an independent risk factor for cardiovascular disease in the general population (7) and also seems to be important in diabetes (8).

Primary prevention studies in middle-aged men with hyperlipidemia, without known CHD, have shown that the incidence of CHD can be reduced by modification of serum lipid concentrations (9–11), but there are as yet no comparable studies specifically in type 2 diabetic subjects. Conventional diabetes therapy has, as yet, not been shown to reduce the incidence of cardiovascular disease (1). Because subjects with type 2 diabetes are a group at high risk for cardiovascular disease, there is a clear need for a prospective study to ascertain whether its progress can be modified. It seems logical to prevent progression of cardiovascular disease by correcting the metabolic abnormalities that are thought to contribute to it, namely by lowering serum triglyceride and cholesterol, raising HDL cholesterol, and lowering fibrinogen. The fibrate drugs provide a means of correcting these abnormalities. Bezafibrate has been shown to decrease serum triglyceride and cholesterol and raise HDL cholesterol over 3 months in type 2 diabetic subjects and to have a small glucose-lowering effect (6,12). In addition, it has also been shown to lower fibrinogen (13).

We set up a prospective study specifically to test the hypothesis that reducing serum triglyceride and cholesterol and raising HDL cholesterol could modify cardiovascular outcomes in type 2 diabetes. Carotid intima media thickness (IMT) is considered to be an indicator of generalized atherosclerosis and to give information on the progression and regression of atherosclerotic lesions (14), we used B-mode ultrasound of carotid and femoral arteries to measure IMT and an arterial ultrasound score (AUS) (15). In addition, we used standard indexes of CHD, clinical history, the World Health Organization (WHO) cardiovascular questionnaire, resting electrocardiogram (ECG) (Minnesota coded), and ECG chest wall mapping (a modified exercise ECG) as secondary end points.

## RESEARCH DESIGN AND METHODS

### Subjects

Men and women with type 2 diabetes, attending routine diabetic clinics at St. Mary's, St. Charles, Ealing, Northwick Park, and Wembley Hospitals, were invited for screening for possible study inclusion. They were treated with diet and/or oral hypoglycemic agents. Aged 35–65 years, they were of any ethnic group, and without history of clinical cardiovascular disease. Those included had any of the following in at least one screening sample: serum cholesterol  $\geq 5.2$  mmol/l, serum triglyceride  $\geq 1.8$  mmol/l, HDL cholesterol  $\leq 1.1$  mmol/l, and total-to-HDL cholesterol ratio  $\geq 4.7$ .

### Exclusion criteria

Those with serum triglyceride  $> 8.0$  mmol/l or cholesterol  $> 8.0$  mmol/l with total-to-HDL cholesterol ratio  $\geq 7.2$  in at least one screening blood sample were excluded, as were subjects with renal impairment (serum creatinine  $\geq 150$   $\mu\text{mol/l}$ ), dipstick positive proteinuria on more than one occasion over the previous year, clinically detectable retinopathy or neuropathy, or abnormal liver function (transaminases greater than twice the upper limit of normal).

Further exclusion criteria were a positive ECG chest wall mapping test, severe hypertension, systolic blood pressure  $\geq 180$  mmHg and/or diastolic blood pressure  $\geq 110$  mmHg, or grade D and greater carotid stenosis ( $\geq 50\%$ ) on carotid ultrasound.

We also excluded those with serious acute or chronic disease, history of poor compliance or alcohol abuse, or previous

or current administration of anticoagulants or lipid-lowering drugs.

### Screening

At the first screening visit, the medical history was checked against the exclusion criteria, fasting blood samples were taken, and ultrasound measurements and resting and exercise ECG were performed. The study was approved by the Parkside Ethics Committee and ethics committees of the contributing hospitals.

### Timing of measurements, and safety and compliance

Subjects who were not excluded at the second visit were seen 3 weeks later for randomization and receipt of their first tablets. They were seen thereafter every 3 months for distribution of study tablets and recording of adverse events. Biochemical measurements, including liver function tests, and serum creatinine were carried out every 6 months. Cardiovascular assessments were made every year. Compliance was assessed by tablet count every three months and every six months by measurement of serum alkaline phosphatase, which is consistently lowered by fibrate therapy.

Subjects remained in the study for a minimum of 3 years unless the cholesterol reached 9.0 mmol/l or triglyceride reached 8.0 mmol/l at two successive 6-month visits. Subjects were also withdrawn from the study if they developed serious intercurrent disease in which bezafibrate therapy was contraindicated. Subjects were asked to remain in the study for a minimum of 3 years and a maximum of 5 years. The safety committee reviewed all adverse events annually. No drug-related events were identified.

### Intervention and blinding

A randomized list was prepared by the statistician in advance so that numbers assigned to each treatment would be approximately equal after every 10 subjects. Subjects satisfying entry criteria were given the next consecutive number in a double-blind fashion.

Subjects received either bezafibrate (400 mg Bezalip Retard) or placebo daily. In addition to the identical appearance of placebo and active study medication, the results of the determination of the lipid parameters, fibrinogen and alkaline phosphatase, were concealed from the clinical personnel in the study. All measurements were carried out by personnel who were blinded to the treatment group of the subjects.

Subjects continued to receive their usual diabetic care and treatment. Subjects also followed the standard dietary advice given to them in the individual clinics, and this advice was not changed during the study.

### Power of the study

The power of the study was based on the primary outcome measure: change in carotid IMT. The increase in IMT over 2 years in nondiabetic men had previously been found by others to be  $\sim 0.12$  mm (16). There were no longitudinal data on diabetic patients on which to base firm figures for the power of our study, but cross-sectional data showed diabetic patients had higher IMT values than nondiabetic individuals (17). We therefore assumed that there would be a greater increase in our untreated patients of 0.24 mm over 3 years in IMT and that treatment would reduce this increase to 0.12 mm; thus, the difference ( $\mu$ ) between the change in the two groups would be 0.12 mm over 3 years. We assumed from previous work (16) that the standard deviation ( $\sigma$ ) of change in IMT would be 0.2 mm in each group. Using the formula,

$$N = \frac{\sigma^2 4(Z_{\alpha} + Z_{\beta})}{\mu^2},$$

120 subjects (60 in each group) followed over 3 years would give 80% power to identify a difference of 0.12 mm between the two groups with a two-sided test at a significance level of 5% and no interim analysis. To allow for a 25% loss to follow-up over 3 years, we aimed to recruit 160 subjects.

### Ultrasonic measurement of vascular disease

**Technique.** All scans were performed on an Advanced Technology Laboratories Ultramark-4 (Bothel, WA) black-and-white duplex scanner with a high-resolution 7.5-MHz linear array scan head and a 7.5-MHz sector array scan head with a 5-MHz pulsed Doppler probe. Scan settings (power output 50%, dynamic range 47 dB gain, grayscale, filters, and ramp) were preset at machine start-up and are not altered during the examination. A commercially available tissue equivalent phantom (Resolution Test Object; Diagnostic Sonar, Livingston, U.K.; attenuation 0.86 dB  $\cdot$  cm $^{-1}$   $\cdot$  MHz $^{-1}$ , transmission velocity 1,540 m/s) was used regularly to ensure that the system sensitivity, beam width, and axial and lateral resolution remained constant.

**Scanning protocol.** All subjects were examined in the supine position with their head slightly extended. The common carotid and common femoral artery bifurcations were scanned longitudinally to visualize the intima media complex on the far (deeper) wall of the artery and any plaques related to the internal carotid artery. The position of the probe was adjusted so that the maximum thickness of the intima media complex and of any plaque was visualized. Images showing the maximum IMT and maximum plaque thickness were frozen on the screen and printed on thermal paper.

**Measurements.** Measurements of the thickness of the intima media complex of the common carotid and femoral arteries were made on prints of the frozen images with a digitizing board (CalComp California, Anaheim, CA). All images were magnified so the area of interest, which included both anterior and posterior walls of the artery, filled the screen. The intima media complex of the common carotid artery was defined as the distance on the far wall between the leading edge of the I band and the leading edge of the M band (18). A mean of three measurements was obtained at the site of maximum thickness in the region 1–2 cm proximal to the bifurcations. Measurements were made of the maximum thickness of the intima media (maximum IMT) in any part of the carotid bifurcation; such measurements included thickness of the plaque where present.

**Reproducibility of IMT measurements.** All scans were read by the same observer. In our hands the coefficient of variation for the intraobserver variability of the measurement of IMT was 5.7% (18).

**Arterial ultrasound score and plaque.** The carotid and femoral bifurcations were scanned at multiple levels to establish the presence and extent of plaque and to determine an AUS (0, normal; 2, intimal disruption; 4, intimal thickening >1 mm with granulation; 6, plaque <50% stenosis; 8, plaque causing ≥50% stenosis). Plaque was considered to be present if there was a localized irregular thickening that was at least 1.2-mm thick. Continuous thickening (i.e., not localized) was not reported as plaque. A total AUS was calculated for each patient by totaling the score in each of the four arteries (15).

### CHD assessment

Clinical evidence of myocardial infarction (MI) was confirmed by determining history

of hospital admission or admission to a coronary care unit, checking hospital records, rendering an ECG, and assessing enzyme changes.

Coronary heart disease symptoms and history were assessed annually by the WHO cardiovascular questionnaire (19) and by resting 12-lead ECG and ECG chest wall mapping at rest and during and after bicycle ergometry (20). Resting ECGs were Minnesota coded (19) independently by two experienced observers, and any disagreements were adjudicated by a third observer. Results were classified as probable ischemia: major and medium Q/QS waves or complete left bundle branch block (Minnesota codes 1.1, 1.2, or 7.1); and possible ischemia: ST segment abnormalities, abnormal T waves, minor Q/QS wave changes (Minnesota codes 1.3, 4.1, 4.2, 4.3, 4.4, 5.1, 5.2, or 5.3), or ischemia unlikely (all other codes) (21). Exercise was performed on an Elema Schonander bicycle ergometer at a constant speed of 60 rpm. The test was considered to be positive if an ST segment depression of >1 mm occurred. In the absence of ST depression, the test was described as inconclusive if <85% maximal heart rate for age was achieved and normal if this heart rate was achieved.

A CHD event identified as a change in resting ECG, exercise ECG, or WHO questionnaire was treated as occurring midway between the first test at which it was seen and the previous test. Absence of an event was documented at the last annual visit.

Documented MI was treated as occurring on the date when symptoms associated with the event were first investigated. This date was established at final review of subjects with events by a clinician blind to treatment. Absence of MI was recorded at the latest point of routine contact with the subject.

“Definite CHD event” was defined as occurring in subjects who sustained documented MI or probable ischemic change on Minnesota coding, which was treated as occurring at the earliest date, as defined above. Absence of “definite CHD event” was documented at the latest annual visit.

Possible CHD events were defined as the first appearance of a positive response in the WHO questionnaire, positive exercise ECG, or possible ischemic change on Minnesota coding in the absence of probable ischemic change.

### Biochemical measurements

Fasting blood samples were obtained after

an overnight fast. Serum triglyceride and cholesterol were assayed enzymatically. HDL cholesterol was assayed after precipitation of other lipoproteins with dextran sulfate and magnesium sulfate. LDL cholesterol was calculated from Friedewald's formula. We also measured non-HDL cholesterol (total HDL cholesterol) to show cholesterol in the apoprotein B containing lipoproteins VLDL and LDL. Serum apoprotein B and A1 and plasma fibrinogen were measured by rate immunonephelometry. Glucose control was assessed from fasting blood glucose and glycosylated Hb (HbA<sub>1</sub> normal <8%) by the Corning Glytrac electro-osmosis method.

### Statistical analysis

Recruitment for the study started in June 1990. Of 253 subjects screened, 36 were unwilling to participate or were outside the age range, 34 did not satisfy the lipid criteria for entry, and 19 had other exclusion criteria. There were 164 subjects recruited over the next 32 months, and the study was stopped 3 years after the end of recruitment. Of the subjects, 128 remained in the study for 3 years as planned. In addition, we report on 74 who completed 4 years and 20 who completed 5 years. There was no significant difference in the follow-up rate in the placebo and bezafibrate groups. Cumulative annual rates of withdrawal in the two groups for administrative reasons, adverse events, or noncompliance were 8.4, 15.7, 22.9, 31.3, and 36.1% and 11.1, 13.6, 21.0, 28.4, and 33.3%, respectively.

The two groups were well-matched for sex, age, ethnic group, smoking, use of oral hypoglycemic drugs, antihypertensive drugs, blood pressure, duration of diabetes, and BMI (Table 1).

Changes were calculated within subject and only for subjects present the entire time. The differences in lipid changes between treatment groups were assessed by Wilcoxon's rank-sum test, since some of the variables considered were not normally distributed. Ultrasound changes over 3 years were compared between treatment groups by Student's *t* test.

Rate of development of ischemic events over the first 3 years of the study was compared by log-rank test with censoring of withdrawn subjects at their latest annual visit. For the log-rank test for MI alone, subjects were censored at the last point of contact, which was either a routine quarterly visit or a telephone call from a subject withdrawing from the study.

**Table 1—Demographic variables at baseline in placebo- and bezafibrate-treated subjects**

|                                 | Placebo      | Bezafibrate  |
|---------------------------------|--------------|--------------|
| <i>n</i>                        | 83           | 81           |
| Men (%)                         | 67.5         | 75.3         |
| Afro-Caribbean (%)              | 8.4          | 6.2          |
| Asian (%)                       | 28.9         | 32.1         |
| Caucasian (%)                   | 54.2         | 58.0         |
| Other (%)                       | 8.4          | 3.7          |
| Oral hypoglycemic agents (%)    | 72.3         | 74.1         |
| Antihypertensive agents (%)     | 16.9         | 14.8         |
| Current smoking (%)             | 19.3         | 16.3         |
| Age (years)                     | 50.9 ± 8.1   | 50.8 ± 8.0   |
| BMI (kg/m <sup>2</sup> )        | 28.7 ± 4.6   | 28.7 ± 5.1   |
| Systolic blood pressure (mmHg)  | 128.9 ± 20.0 | 124.6 ± 15.6 |
| Diastolic blood pressure (mmHg) | 83.6 ± 11.0  | 80.9 ± 9.8   |
| Duration of diabetes (years)    | 5.8 ± 5.7    | 4.3 ± 4.3    |

Continuous data are means ± SD.

All tests were two-sided, and a *P* value of 0.05 was considered significant.

**RESULTS**

**Lipid and biochemical changes**

Baseline values for biochemical variables were similar in the two treatment groups (Table 2). Bezafibrate treatment was associated with significantly greater proportionate reductions from baseline of serum triglyceride and total cholesterol and an

increase of HDL cholesterol compared with placebo (Table 2). There were significantly greater reductions in total-to-HDL cholesterol ratio and in non-HDL cholesterol in the bezafibrate-treated group. There were no significant differences in the changes in apoproteins A1 or B. Similar results were found for the absolute changes. The results both for absolute and proportionate changes over 4 years were similar to those for 3 years (data not shown). There was a trend for fibrinogen to be reduced at 3

years. The increases in both fasting blood glucose and glycated Hb over the course of the study were less in the bezafibrate group than in the placebo group, but these differences were not significant. Serum alkaline phosphatase, which was used as an index of drug compliance, was significantly reduced in the bezafibrate-treated group.

**Cardiovascular outcomes**

There were no differences in baseline measurements of IMT or in changes over time between left and right sides. Therefore, we have reported the mean of the two sides.

Changes in IMT measurements over the period of study were small and did not differ between placebo and bezafibrate-treated groups. There was a small increase in AUS in both groups, but there was no difference between the groups (Table 3). No correlations were found between changes in any of the lipid parameters and changes in IMT or AUS. There were no differences in progression of any of these ultrasonic measurements between those subjects who sustained an MI or probable ischemic change on ECG compared with those who did not.

Within the first 3 years, 21 subjects had either an MI or a probable ischemic event on an ECG, of whom 2 (both on placebo) also had three “possible CHD events.” Another 32 subjects (12 on placebo and 20 on bezafibrate) had a further 36 pos-

**Table 2—Biochemical variables at baseline and 3 years.**

|                                | Baseline            |                     | Year 3              |                     | % change from baseline to year 3 |                      | <i>P</i> |
|--------------------------------|---------------------|---------------------|---------------------|---------------------|----------------------------------|----------------------|----------|
|                                | Placebo             | Bezafibrate         | Placebo             | Bezafibrate         | Placebo                          | Bezafibrate          |          |
| <i>n</i>                       | 64                  | 64                  | 64                  | 64                  | 64                               | 64                   | —        |
| Blood glucose (mmol/l)         | 10.30 (7.30, 13.90) | 10.30 (8.40, 12.90) | 11.60 (8.30, 14.0)  | 10.60 (8.80, 13.50) | 12.3 (−6.2, 35.1)                | 5.8 (−13.7, 31.3)    | 0.4      |
| HbA <sub>1c</sub> (%)          | 9.35 (7.80, 11.75)  | 9.60 (8.40, 11.20)  | 10.10 (8.75, 11.80) | 10.30 (9.20, 12.00) | 8.6 (−3.5, 20.4)                 | 4.3 (−8.4, 19.2)     | 0.4      |
| Fibrinogen (g/l)               | 2.94 (2.59, 3.30)   | 3.00 (2.31, 3.50)   | 2.65 (2.30, 3.10)   | 2.35 (2.10, 2.70)   | −6.4 (−23.8, 11, 5)              | −17.9 (−31.2, 0.0)   | 0.08     |
| Triglyceride (mmol/l)          | 2.09 (1.46, 3.10)   | 2.24 (1.73, 2.94)   | 2.00 (1.56, 2.685)  | 1.44 (1.08, 2.24)   | 4.1 (−19.0, 26.9)                | −32.5 (−48.4, 1.0)   | 0.001    |
| Total cholesterol (mmol/l)     | 5.60 (5.02, 6.24)   | 5.77 (5.09, 6.45)   | 5.80 (5.00, 6.40)   | 5.29 (4.64, 5.90)   | −0.3 (−8.8, 8.3)                 | −7.4 (−15.9, −0.2)   | 0.004    |
| HDL cholesterol (mmol/l)       | 0.94 (0.81, 1.08)   | 1.02 (0.87, 1.13)   | 0.92 (0.78, 1.10)   | 1.04 (0.89, 1.32)   | −2.0 (−9.7, 6.5)                 | 6.4 (−4.9, 17.2)     | 0.02     |
| LDL cholesterol (mmol/l)       | 3.98 (3.25, 4.46)   | 3.66 (3.25, 4.49)   | 3.94 (2.98, 4.46)   | 3.31 (2.89, 3.86)   | 0.6 (−12.9, 10.8)                | −9.6 (−17.6, 4.2)    | 0.06     |
| Non-HDL cholesterol (mmol/l)   | 4.68 (4.08, 5.37)   | 4.72 (4.13, 5.49)   | 4.83 (3.97, 5.30)   | 4.08 (3.50, 4.62)   | −0.8 (−11.4, 8.1)                | −12.3 (−19.7, −1.6)  | 0.002    |
| Total-to-HDL cholesterol ratio | 6.01 (5.43, 6.84)   | 5.66 (4.94, 6.52)   | 6.00 (5.10, 7.37)   | 5.03 (3.94, 5.82)   | −0.0 (−11.5, 8.0)                | −12.0 (−24.6, −2.5)  | 0.001    |
| Apo protein A1 (g/l)           | 1.28 (1.14, 1.44)   | 1.41 (1.21, 1.61)   | 1.22 (1.09, 1.35)   | 1.34 (1.16, 1.55)   | −6.6 (−16.0, 8.0)                | −6.2 (−14.9, 2.6)    | 0.8      |
| Apo protein B (g/l)            | 1.30 (1.07, 1.70)   | 1.31 (1.06, 1.58)   | 1.55 (1.32, 1.87)   | 1.39 (1.19, 1.54)   | 14.8 (−1.4, 32.1)                | 8.3 (−11.1, 29.5)    | 0.3      |
| Alkaline phosphatase (U/l)     | 86.5 (73, 100.5)    | 87.5 (71, 102)      | 90 (76, 106)        | 62 (49, 74)         | 1.3 (−10.4, 12.8)                | −26.3 (−37.4, −21.0) | 0.0001   |

Data are median (Q1, Q3). *P* values were determined by Wilcoxon’s rank-sum test.

Table 3—Ultrasound measurements

|   | <i>n</i> | Baseline    | 1 year      | 2 years     | 3 years     | Change from entry to year 3 | <i>t</i> test for change between bezafibrate and placebo |
|---|----------|-------------|-------------|-------------|-------------|-----------------------------|--|
| Intima media complex in common carotid (mm) |          |             |             |             |             |                             |  |
| Bezafibrate                                 | 63       | 0.77 ± 0.17 | 0.76 ± 0.14 | 0.74 ± 0.12 | 0.73 ± 0.14 | −0.04 ± 0.14                | <i>t</i> = 0.13 <i>P</i> = 0.9                           |
| Placebo                                     | 64       | 0.78 ± 0.17 | 0.77 ± 0.14 | 0.75 ± 0.15 | 0.74 ± 0.15 | −0.04 ± 0.19                |  |
| Maximum IMT in carotid bifurcation (mm)     |          |             |             |             |             |                             |  |
| Bezafibrate                                 | 63       | 1.20 ± 0.53 | 1.23 ± 0.56 | 1.15 ± 0.53 | 1.27 ± 0.62 | 0.06 ± 0.38                 | <i>t</i> = 0.67 <i>P</i> = 0.5                           |
| Placebo                                     | 64       | 1.08 ± 0.48 | 1.08 ± 0.49 | 1.07 ± 0.46 | 1.09 ± 0.44 | 0.02 ± 0.41                 |  |
| Intima media complex in common femoral (mm) |          |             |             |             |             |                             |  |
| Bezafibrate                                 | 44       | 0.73 ± 0.16 | 0.69 ± 0.15 | 0.64 ± 0.16 | 0.59 ± 0.14 | −0.14 ± 0.15                | <i>t</i> = 0.91 <i>P</i> = 0.4                           |
| Placebo                                     | 42       | 0.77 ± 0.19 | 0.72 ± 0.17 | 0.65 ± 0.17 | 0.59 ± 0.12 | −0.18 ± 0.21                |  |
| Maximum IMT in common femoral (mm)          |          |             |             |             |             |                             |  |
| Bezafibrate                                 | 58       | 1.16 ± 0.76 | 1.15 ± 0.65 | 1.18 ± 0.73 | 1.25 ± 0.81 | 0.09 ± 0.57                 | <i>t</i> = 0.26 <i>P</i> = 0.8                           |
| Placebo                                     | 60       | 1.19 ± 0.65 | 1.25 ± 0.71 | 1.20 ± 0.62 | 1.25 ± 0.71 | 0.06 ± 0.41                 |  |
| Arterial ultrasound score                   |          |             |             |             |             |                             |  |
| Bezafibrate                                 | 63       | 16.0 ± 6.4  | 17.1 ± 5.9  | 17.1 ± 5.9  | 17.1 ± 6.0  | 1.17 ± 3.71                 | <i>t</i> = 0.81 <i>P</i> = 0.4                           |
| Placebo                                     | 64       | 16.1 ± 5.2  | 16.2 ± 5.9  | 16.6 ± 6.1  | 17.0 ± 5.8  | 0.91 ± 3.62                 |  |

Data are means ± SD.

sible events. There was a significantly lower 3-year cumulative incidence rate of definite CHD event in the bezafibrate-treated group than in the placebo group (7 vs. 23%, *P* = 0.01 log-rank test, Table 4, Fig. 1). This incidence rate was not explained by any difference between the two groups in respect to baseline cardiovascular risk factors or ECG abnormalities. Although the incidence of possible CHD events in subjects on bezafibrate was higher, this difference was not statistically significant.

**CONCLUSIONS** — Our study was designed to show the effect of treating dys-

lipidemia, commonly seen in asymptomatic type 2 diabetic subjects attending diabetic clinics, as a single risk factor intervention on cardiovascular outcomes. Subjects chosen included those with mild dyslipidemia found in type 2 diabetic subjects, a group usually thought to be at high risk of cardiovascular disease. Indeed, the 23% cumulative incidence rate over 3 years of definite CHD events in the placebo group would appear to support this.

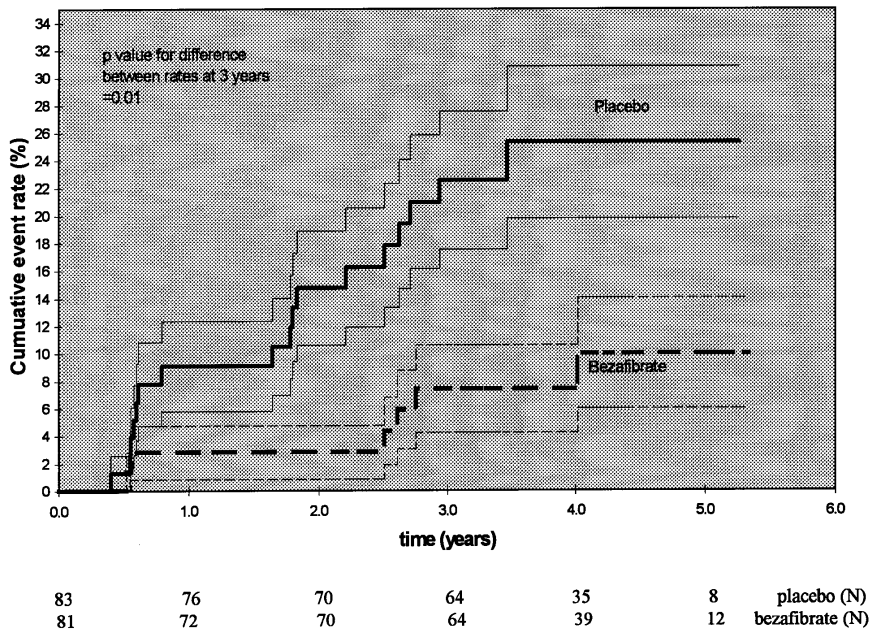
We have shown that effective reduction in serum triglyceride and cholesterol, a reduction in total-to-HDL cholesterol ratio, and an increase in HDL cholesterol could be

achieved in these subjects over 4 years. We found no significant effects of bezafibrate treatment on LDL cholesterol or on apoprotein B concentrations. In previous studies, the effects of fibrate treatment on LDL cholesterol have shown conflicting results, though any effects have been small. Bezafibrate was associated with a small reduction in LDL cholesterol over 3 months in type 2 diabetic subjects with fasting serum triglyceride of ~2.5 mmol/l (12). Gemfibrozil treatment in hypertriglyceridemic type 2 diabetic subjects was associated with a rise in LDL cholesterol and no change in apoprotein B (22), while a recent study comparing the

Table 4—Total incidence and 3-year CHD event rates according to treatment group

|                                      | Total incidence after 5 years |             | Total incidence after 3 years |             | Cumulative event rate at 3 years* |             | <i>P</i> |
|--------------------------------------|-------------------------------|-------------|-------------------------------|-------------|-----------------------------------|-------------|----------|
|                                      | Placebo                       | Bezafibrate | Placebo                       | Bezafibrate | Placebo                           | Bezafibrate |          |
| <i>n</i>                             | 83                            | 81          | 83                            | 81          | 83                                | 81          |          |
| Possible CHD events                  |                               |             |                               |             |                                   |             |          |
| Angina†                              | 4                             | 7           | 4                             | 6           | 5.6% (2.8)                        | 8.5% (3.3)  | 0.49     |
| Chest pain suggestive of infarction† | 3                             | 1           | 2                             | 1           | 3.0% (2.1)                        | 1.7% (1.6)  | 0.57     |
| Positive exercise ECG                | 1                             | 1           | 1                             | 1           | 6.2% (6.0)                        | 2.8% (2.7)  | 0.83     |
| Possible ischemia‡                   | 11                            | 16          | 9                             | 15          | 16.0% (4.9)                       | 27.0% (6.0) | 0.20     |
| Definite CHD events                  |                               |             |                               |             |                                   |             |          |
| Confirmed myocardial infarction      | 4                             | 2           | 3                             | 1           | 4.0% (2.2)                        | 1.5% (1.5)  | 0.33     |
| Probable ischemia§                   | 13                            | 4           | 13                            | 4           | 19.5% (4.9)                       | 6.5% (3.1)  | 0.03     |
| Subjects with definite CHD event¶    | 17                            | 6           | 16                            | 5           | 22.6% (5.0)                       | 7.4% (3.2)  | 0.01     |

\*Kaplan-Meier 5-year event rate (SE). *P* values for difference between rates are based on the log-rank test. †WHO cardiovascular questionnaire; ‡resting ECG Minnesota codes (1.3, 4.1, 4.2, 4.3, 4.4, 5.1, 5.2, or 5.3) only; §resting ECG Minnesota codes (1.1, 1.2, or 7.1); ||including 1 death; ¶subjects with definite CHD event may also have possible CHD events.



**Figure 1**—Rate of onset of definite CHD event in placebo- and bezafibrate-treated type 2 diabetic subjects. Lines show rates  $\pm$  1 SEM; P value by log-rank test for difference between placebo and bezafibrate-treated groups N is number of subjects in study each year.

effects of simvastatin and bezafibrate on the dyslipidemia of type 2 diabetes showed an increase in LDL cholesterol with bezafibrate (23). This was attributed to a change in size of LDL particles in which they become less dense and hence less atherogenic. Because the validity of Friedewald's formula for LDL cholesterol measurement in type 2 diabetes has been questioned (24) and because VLDL cholesterol appears to be a risk for cardiovascular disease in type 2 diabetes (5,6), non-HDL cholesterol, which includes both VLDL and LDL cholesterol, may be a more valid measurement in this group (22). Non-HDL cholesterol was significantly reduced by bezafibrate treatment.

We used ultrasonic measurements of arterial disease as surrogate end points for cardiovascular disease. It was surprising that no differences in progression were observed between the placebo and bezafibrate-treated groups.

Measurement of IMT is a relatively new technique but is becoming accepted as a means of establishing the effects of medical intervention in atherosclerotic disease (14). In a male population sample in Kuopio, Finland, carotid IMT was found to be a reproducible measurement, which correlated with age, smoking, LDL cholesterol, fibrinogen, and systolic blood pressure (25). In a prospective study, the maximal carotid IMT associated significantly with

the risk of acute MI (25). In addition, we have used the AUS (15), which is an expression of overall qualitative change in the arterial wall and of plaque formation. High AUS score has been shown to be predictive of cardiovascular events (15).

Several prospective studies have used carotid ultrasonic measures as an end point of arterial disease progression in nondiabetic populations with moderately elevated LDL cholesterol and have shown that cholesterol reduction was associated with either small reductions in progression or regression in IMT measurements together with reduction in CHD events (25–28). Although the number of subjects was larger in some studies (15,27) than in this study, making it easier to detect small differences in IMT change, this did not apply in others (26,28).

More recent work has suggested that carotid IMT measurements correlate only weakly with the extent and severity of angiographically measured coronary artery disease, especially in diabetic subjects (29). Furthermore, there appears to be poor correlation between conventional risk factors for cardiovascular disease, such as blood pressure, lipids, smoking, duration of diabetes, fibrinogen, and IMT measurements in type 2 diabetic subjects (29–32) who have significantly greater IMT than age- and sex-matched control subjects (17,30). Our baseline data revealed an inverse relationship

between fasting serum insulin and IMT and AUS, indicating that relative insulin deficiency may be important in the genesis of early ultrasonically measured arterial disease in type 2 diabetes (32). Early thickening of the arteries in people with diabetes may be due to changes other than those caused by atherosclerosis. The term diabetic macroangiopathy has been used to describe such changes, which include an increase in periodic acid Schiff-positive material in the tunica media (33). These ultrasonically measured changes in the arterial wall of type 2 diabetic subjects may have occurred much earlier (long before entry into the study) and possibly may not be amenable to changes in serum lipids. The projected increase in IMT did not occur. Therefore, although our scans were read by one ultrasonographer and the standard deviation of change was as predicted, we are unable to make post hoc power calculations.

Another possible explanation for the lack of difference in progression between the two groups could have been that the follow-up period was insufficient. Our original hypothesis was based on previous work (16), which suggested that measurable changes in IMT were detectable over a 2-year period. A longer follow-up period may have been required to demonstrate a difference between the two groups, as was suggested in an analysis of the Asymptomatic Carotid Artery Progression Study (ACAPS) (34). We suggest that in type 2 diabetic subjects, the use of this type of arterial ultrasound measurements may not be a useful method of monitoring the progress of cardiovascular disease or that longer follow-up periods are needed.

By contrast, bezafibrate treatment was associated with a lower incidence of definite CHD event defined as documented MI or major Minnesota-coded ECG changes over 4 years. The early separation between placebo and treatment group seen in the Kaplan-Meier plot was similar to that seen in two other lipid intervention studies: one using bezafibrate (35) and the other pravastatin (28). There was no significant difference in the incidence of possible CHD events, which may be softer end points. Lesser ECG abnormalities, ST segment, and T wave items may represent ischemic heart disease, but an unknown and probably variable proportion may also have other causes such as myocarditis, metabolic, and nutritional disorders (36,37).

Primary prevention studies have shown a reduction in the risk of CHD events with

lipid lowering in middle-aged nondiabetic men (9–11), but no such study has yet been carried out in diabetic subjects.

In a subset of 135 diabetic subjects in the Helsinki Heart Study, gemfibrozil therapy reduced serum cholesterol and triglyceride and increased HDL cholesterol and was associated with a 70% reduction in incidence of MI and death from coronary disease (38). The number of subjects was small and the results failed to reach significance. Furthermore, the majority of the subjects were treated for diabetes with diet only so that they were not entirely representative of subjects with type 2 diabetes.

In secondary prevention, a post hoc subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) (39) of middle-aged men and women with known CHD and serum cholesterol levels of 5.5–8.0 mmol/l and triglyceride levels of <2.5 mmol/l showed that reduction in serum cholesterol with simvastatin significantly reduced the risk for major coronary events in those who had diabetes—the reduction being even greater than that in nondiabetic subjects. However, this trial excluded those with triglyceride levels of >2.5 mmol/l, which limits applicability to many diabetic subjects.

There are several possible explanations for the observed reduction in definite CHD events in our treated patients. The reduction in the total-to-HDL cholesterol ratio may have helped to stabilize vulnerable lipid-laden plaques that may initiate coronary thrombosis (40,41). The reduction in serum cholesterol may have improved endothelial function known to be impaired in type 2 diabetic subjects (42). Triglyceride-rich lipoproteins are thought to have an important role in both atherogenesis and thrombogenesis through a variety of mechanisms. Lowering serum triglyceride has also been shown to be associated with a fall in the hemostatic variable factor VII, a risk factor for ischemic heart disease, and with an increase in fibrinolytic activity (43). The reduction in fibrinogen, another independent risk factor for CHD (7) in the bezafibrate group (albeit not significant), may also have contributed to the reduction in the incidence of definite CHD events.

We have been unable to show that modification of serum lipids had an effect on the primary end point of our study: ultrasonically measured arterial disease. However, the reduction seen in definite CHD events (albeit secondary end points) in this study suggests that correcting the dyslipidemia

commonly found in type 2 diabetes may result in a reduction in the incidence of CHD, which is the main cause of mortality in these subjects. Because of its small size and use of secondary end points, this study cannot be considered to be definitive. To show that lipid modifying therapy in type 2 diabetes will reduce the incidence of CHD, much larger longer-term prospective studies with sufficient numbers and power to detect differences in clinical event rate are needed.

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