Meade, T; Zuhrie, R; Cook, C; Cooper, J (2002) Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. BMJ (Clinical research ed), 325 (7373). p. 1139. ISSN 0959-8138
DOI: https://doi.org/10.1136/bmj.325.7373.1139

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Bezafibrate in men with lower extremity arterial disease: randomised controlled trial

Tom Meade, Riaz Zuhrie, Claire Cook, Jackie Cooper on behalf of MRC General Practice Research Framework

Abstract

**Objective** To assess the effect of bezafibrate on the risk of coronary heart disease and stroke in men with lower extremity arterial disease.

**Design** Double blind placebo controlled randomised trial.

**Setting** 85 general practices and nine hospital vascular clinics.

**Participants** 1568 men, mean age 68.2 years (range 35 to 92) at recruitment.

**Interventions** Bezafibrate 400 mg daily (783 men) or placebo (785 men).

**Main outcome measures** Combination of coronary heart disease and of stroke. All coronary events, fatal and non-fatal coronary events separately, and strokes alone (secondary end points).

**Results** Bezafibrate did not reduce the incidence of coronary heart disease and stroke. There were 150 and 160 events in the active and placebo groups respectively (relative risk 0.96, 95% confidence interval 0.76 to 1.21). There were 90 and 111 major coronary events in the active and placebo groups respectively (0.81, 0.60 to 1.08), of which 64 and 65 were fatal (0.95, 0.66 to 1.37) and 26 and 46 non-fatal (0.60, 0.36 to 0.99). Beneficial effects on non-fatal events were greatest in men aged < 65 years at entry, in whom benefit was also seen for all coronary events (0.38, 0.20 to 0.72). There were no significant effects in older men. There were 60 strokes in those on active treatment and 49 in those on placebo (1.34, 0.80 to 2.01). There were 204 and 195 deaths from all causes in the two groups respectively (1.03, 0.83 to 1.26). Bezafibrate reduced the severity of intermittent claudication for up to three years.

**Conclusions** Bezafibrate has no effect on the incidence of coronary heart disease and of stroke combined but may reduce the incidence of non-fatal coronary events, particularly in those aged < 65 years at entry, in whom all coronary events may also be reduced.

**Introduction**

Evidence from epidemiological research has shown strong associations between high plasma fibrinogen concentrations and the onset and progression of arterial disease at all three main sites—that is, heart, brain, and lower extremities. High concentrations are also associated with venous thrombosis and may impair the outcome of percutaneous coronary angioplasty. Fibrinogen affects several pathways involved in thrombogenesis. This evidence suggests that high fibrinogen concentrations are an important cause. On the other hand, the effects of lowering concentrations need to be established through randomised trials so that not only can the role of fibrinogen be clarified but also any clinical implications defined.

Apart from ancond, which has to be given by infusion, there are no drugs available that selectively lower fibrinogen concentrations. However, several fibrates lower concentrations as well as modifying lipid profiles, for which they were originally introduced. (If any clinical benefits of bezafibrate could be apportioned between its effects on fibrinogen and on lipids we would be able to clarify the part played by fibrinogen in altering the risk of coronary heart disease.)

To establish any benefits, the lower extremity arterial disease event reduction (LEADER) trial of bezafibrate was carried out in men with lower extremity arterial disease. This condition was selected partly because raised triglyceride concentrations may contribute to it and the greatest effect of bezafibrate is to lower triglycerides, but also because of the high incidence of coronary heart disease events and strokes in such patients.

**Methods**

The trial was carried out in men on the lists of 85 practices throughout the United Kingdom in the Medical Research Council's general practice research framework and in nine hospital vascular clinics. Entry from another vascular clinic was discontinued because of unreliable and poor quality data, which were discarded. Recruitment to the trial started in 1992 and was mainly completed in 1997 with a few further entrants in 1998. Follow up ended in September 2001. Identification of men with possible lower extremity arterial disease (confirmed with the Edinburgh claudication questionnaire), eligibility criteria, and the recruitment process including blood tests at entry have been described in full detail elsewhere (http://cvm.controlled-trials.com/content/2/4/195). Active treatment was bezafibrate 400 mg daily (as Bezalip Mono, Roche) for men with creatinine plasma concentrations <135
Table 1 Reasons for exclusion or refusal in 937 of 2505 men screened

<table>
<thead>
<tr>
<th>Reason</th>
<th>No of men</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAD not confirmed</td>
<td>277</td>
</tr>
<tr>
<td>Patient unwilling</td>
<td>248</td>
</tr>
<tr>
<td>Lipid modifying agent</td>
<td>87</td>
</tr>
<tr>
<td>Blood test results*</td>
<td>64</td>
</tr>
<tr>
<td>Renal or hepatic disease</td>
<td>45</td>
</tr>
<tr>
<td>Other significant disease</td>
<td>36</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>17</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>16</td>
</tr>
<tr>
<td>Died before trial entry</td>
<td>15</td>
</tr>
<tr>
<td>Other, unknown</td>
<td>132</td>
</tr>
<tr>
<td>Total</td>
<td>937</td>
</tr>
</tbody>
</table>

*LEAD—lower extremity arterial disease.

Analysis of results on clinical end points was on an intention to treat basis, with all first end point events up till September 2001 being assigned to originally allocated treatment groups, whether or not men had withdrawn from treatment at any stage. (Deaths from all causes include those occurring after first end point events, so ratios are based on more person years than shown.)

Table 2 Characteristics of 1568 men entering trial. Figures are numbers (percentage) unless stated otherwise

<table>
<thead>
<tr>
<th></th>
<th>Active (n=783)</th>
<th>Placebo (n=785)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>68.4 (8.9)</td>
<td>68.0 (8.8)</td>
</tr>
<tr>
<td>Smoking:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>306 (39.1)</td>
<td>287 (36.6)</td>
</tr>
<tr>
<td>Former</td>
<td>447 (57.1)</td>
<td>460 (58.6)</td>
</tr>
<tr>
<td>Never</td>
<td>30 (3.8)</td>
<td>38 (4.8)</td>
</tr>
<tr>
<td>History*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>151 (20.5)</td>
<td>160 (21.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>95 (12.9)</td>
<td>88 (11.9)</td>
</tr>
<tr>
<td>Stable angina</td>
<td>176 (22.5)</td>
<td>200 (25.5)</td>
</tr>
<tr>
<td>None</td>
<td>444 (60.4)</td>
<td>420 (56.8)</td>
</tr>
<tr>
<td>Mean (SD) blood pressure (mm Hg):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>148.4 (22.6)</td>
<td>148.0 (21.9)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77.2 (11.9)</td>
<td>77.6 (11.4)</td>
</tr>
<tr>
<td>Diabetes†</td>
<td>137 (17.5)</td>
<td>131 (16.7)</td>
</tr>
<tr>
<td>Antiplatelet medication‡</td>
<td>484 (65.9)</td>
<td>482 (65.2)</td>
</tr>
<tr>
<td>Median (IQR) fibrinogen concentration (g/l)</td>
<td>3.37 (2.96-3.76)</td>
<td>3.35 (2.99-3.74)</td>
</tr>
<tr>
<td>Median (IQR) cholesterol concentration (mmol/l):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5.6 (5.0-6.3)</td>
<td>5.6 (5.0-6.2)</td>
</tr>
<tr>
<td>Low density lipoprotein</td>
<td>3.37 (2.78-3.97)</td>
<td>3.40 (2.85-3.96)</td>
</tr>
<tr>
<td>High density lipoprotein</td>
<td>1.11 (0.95-1.40)</td>
<td>1.13 (0.99-1.37)</td>
</tr>
<tr>
<td>Median (IQR) triglyceride concentration (mmol/l)</td>
<td>2.11 (1.53-3.01)</td>
<td>2.15 (1.56-2.89)</td>
</tr>
</tbody>
</table>

IQR=interquartile range.
*Some men had more than one condition, and for some data were missing
†Treatment: 95% on aspirin, 5% on dipyridamole. For some men data were missing.
‡Treatment: 95% on aspirin, 5% on dipyridamole. For some men data were missing.
(37%) at screening, at the baseline medical examination, or at trial entry for the reasons shown in table 1. The 1568 patients randomised represent 86% of the 1816 eligible participants, and their characteristics are given in table 2, which shows that the two randomised groups were similar. At entry concentrations of fibrinogen and lipids were not grossly abnormal. The median follow up period was 4.6 years (range 3.1 to 7.8 years). The cumulative proportions withdrawn according to time from entry are shown in fig 2. Many withdrawals took place after several years' participation on randomly assigned treatment so that 70% of person years were spent on allocated treatment. Results from alkaline phosphatase tests indicated a high level of compliance in participants who continued with treatment.8 The total proportions who withdrew were similar in the two groups. However, significantly more men in the placebo group withdrew because they started a drug treatment incompatible with bezafibrate, nearly always a statin, and significantly more men in the active treatment group were withdrawn because of raised creatinine concentrations (table 3).

The effects of active treatment on concentrations of lipids, fibrinogen, creatinine, and alkaline phosphatase have been considered fully elsewhere.9 Final overall results were a reduction in total cholesterol of 7.6% (95% confidence interval 6.7% to 8.6%) and in low density lipoprotein cholesterol of 8.1% (6.5% to 9.8%) and a rise in high density lipoprotein cholesterol of 8.0% (6.4% to 9.6%). Triglyceride concentration was reduced by 23.3% (20.6% to 26.0%) and fibrinogen by 13% (11.7% to 14.4%) (all \(P<0.0001\)).

The main results are summarised in table 4 and fig 3. There was no effect of treatment on the combined incidence of coronary heart disease and stroke, with 150 and 160 events in those in the active and placebo groups, respectively (relative risk 0.96, 95% confidence interval 0.76 to 1.21, \(P=0.72\)). When we considered fatal and non-fatal coronary heart disease together, there were 90 events on active and 111 events on placebo treatment, a reduction of 19% (0.81, 0.60 to 1.08, \(P=0.15\)). This result is the net effect of 64 and 65 fatal events in the two groups (\(P=0.79\)) and 26 and 46 non-fatal events, a reduction of 40% (0.60, 0.36 to 0.99, \(P=0.05\)).

There were 60 strokes in those on active treatment compared with 49 in the placebo group, an excess of 34% in those on active treatment (0.80 to 2.01, \(P=0.49\)). There were 13 fatal strokes in the active treatment group and nine in the placebo group (\(P=0.19\)).

Table 5 shows that in men aged <65 years at entry bezafibrate reduced the incidence of non-fatal coronary events. Also, all events, fatal and non-fatal combined, were 62% lower than in the placebo group (0.38, 0.20 to 0.72).

The Edinburgh claudication questionnaire assesses severity of claudication to some extent by recording whether pain occurs only when the patient is walking up hill or hurrying or if it also occurs both then and on walking at an ordinary pace on the level. There was some improvement in the placebo group, but bezafibrate resulted in a significantly greater improvement from baseline at one, two, and three years though not thereafter (table 6). (Degree of severity was not recorded at baseline for 192 (12%) men, with equal numbers in the two treatment groups.)

**Discussion**

We found that bezafibrate had no significant effect on our primary end point of coronary heart disease and stroke combined. For various possible reasons (“healthy volunteer” effect, variability of data for determining the required sample size, increasing statin use in the placebo group) the incidence of primary end points was less than that estimated. In particular, there were far fewer non-fatal events than we expected. This is unlikely to have been due to incomplete ascertainment as the methods for identifying and reporting end
points were identical to those in other trials in the framework, in which the proportions of fatal and non-fatal episodes have been as expected. Apart from chance, one possibility is a particularly high case fatal-event rate among 207 on active and 211 on placebo treatment, though neither of these differences was significant. However, there was a significant reduction of about 40% in the secondary end point of non-fatal coronary artery disease events among those allocated to active treatment. Besides our trial, two other trials of fibrates have shown greater treatment effects on non-fatal than fatal events. When we looked at deaths from all causes we found no adverse effect on cancer. Bezafibrate may have reduced the incidence of all coronary heart disease events, particularly non-fatal events, in men under 65 years at entry, the absolute benefit being appreciable. We did not prespecify any possibility of an interaction between age and active treatment so any response to treatment by age should be considered in data from other trials. Our trial contributes to the cholesterol treatment trialists collaboration, which will include other trials that used fibrates, so this point can eventually be examined in analyses based on considerably larger numbers of events. Bezafibrate may improve the severity of claudication for a year or two.

**Other trials**

The bezafibrate infarction prevention trial in Israel recruited 3090 men and women aged 45 to 74 years with an established history of coronary heart disease. The trial's underlying hypothesis was that bezafibrate would reduce rates of recurrence by raising concentrations of high density lipoprotein cholesterol and lowering triglyceride. Overall, the 9.4% reduction in the incidence of the combined primary end point of fatal or non-fatal myocardial infarction or sudden death was not significant. In those whose triglyceride concentrations at entry were >2.26 mmol/l (200 mg/dl), the nearly 40% reduction was significant (P=0.02) whereas there was no difference among those with lower concentrations. Our results, however, provide no support for the possibility raised by the Israeli trial of significant benefit among those with high triglyceride concentrations (data not shown).

The bezafibrate coronary atherosclerosis intervention trial (using bezafibrate 200 mg three times daily) was carried out in 92 people aged <45 years who had survived a myocardial infarction. The main purpose of the trial was to see whether treatment could retard or prevent the progression of atherosclerotic lesions assessed by coronary angiography at baseline and then at two, three, and five years, which was achieved. In addition, three of the 47 patients receiving active treatment had coronary events compared with 11 of the 45 in the placebo group, a reduction of nearly 75% (P=0.019).

In the diabetes atherosclerosis intervention study that used micronised fenofibrate, angiographic progression of coronary artery disease was reduced by active treatment and there were 38 and 50 clinical end points among 207 on active and 211 on placebo treatment respectively, though the difference was not significant.

Two trials that used gemfibrozil, which has different properties compared with bezafibrate and fenofibrate,
Bianca De Stavola advised on statistical analyses. End point reports were assembled by Katherine Garrow, Christine Knottenbelt, and George Miller and independently assessed by John Dickinson. The data monitoring and ethics committee comprised S Pocock (chair), G Fowkes, and D Julian.

Competing interests: Trial tablets were supplied free of charge by Boehringr-Mannheim.

Funding: Medical Research Council and British Heart Foundation.

showed that it significantly reduced the incidence of clinical end points.19 20 Bezafibrate and homocysteine Bezafibrate increases homocysteine concentrations,19 and high concentrations are an important risk factor for vascular disease. A further trial could usefully see whether the concurrent use of folie acid and bezafibrate would allow its beneficial effects on fibrino-
gen and lipid profiles to reduce the risk of heart attacks and strokes to a worthwhile extent.

We thank the nurses and doctors in the following areas whose practices were in the general practice research framework: Abing-
don, Alexandria, Ashstead, Balbycastle, Balsall Common, Barrow-in-Furness, Bath, Bedford, Belford, Bovey Tracey, Brack-
nell, Brechin, Brewdstock, Bude, Bungay, Camberley, Carnforth, Comber, Crawley, Credilton, Culdaffton, Darling-
ton, Darwen, Deal, East Grinstead, Exmouth, Fleet, Fovant, Glas-
gow, Gosforth, Guildford, Guisborough, Hayfield, Herne Bay, Hildenborough, Horwich, Itchen, Keadby, Kidderminster, Leeds, Lichfield, Lisburn, Liskeard, Brondesbury (London), Mansfield, Martock, Naibake, Neumarket, Newton, Northampton, Norwich, Ormskirk, Perth, Poole, Portadown, Queensferry, Rotherham, Rugby, Sheffield, Shipston-on-Stour, Southport, Tilehurst, Walsall, Wellingborough, Whitehaven, Wigston, Wimborne, Woodley. We also thank the staff at hospital vascular clinics at Northwick Park, Harrow; St Bartholomew’s and London Chest, St Thomas’s, Charing Cross, and Whipps Cross in London; Royal United Hospital, Bath; Royal Infirmary, Glasgow; Princess Royal Hospital, Telford; Royal Victoria Hospital, Belfast; and nursing colleagues in the MRC Epidemiology and Medical Care Unit, Wendy Browne, Anne Walgrove, and Louise Letley, who managed the training and day-to-day contacts with the practices and Ken Whyte and Wendy Quy, trial managers and data processing, and other unit staff involved.

Contributors: The trial was designed and implemented by TM (who is also guarantor), RZ, and CC and JC analysed the results.

What is already known on this topic

The beneficial effects of bezafibrate on blood lipids and fibrinogen concentrations should reduce the incidence of heart attacks and strokes

So far, however, there is only limited evidence on clinical outcomes from randomised controlled trials

What this study adds

Treatment with bezafibrate was not associated with a reduction in the combined incidence of heart attacks and strokes, though there were substantially fewer non-fatal heart attacks in those taking bezafibrate

Bezafibrate was associated with a reduction in the incidence of all heart attacks, especially non-fatal, in men aged <65 years

Bezafibrate seems to reduce the severity of intermittent claudication for two or three years