

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

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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.¹⁻³ Fibrinogen affects several pathways involved in thrombogenesis.⁴ 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 aniclod, 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. The lower extremity arterial disease event reduction trial of bezafibrate was carried out in men with lower extremity arterial disease to establish any benefits.

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. Recruitment started in 1992 and was completed in 1998. Follow up ended in September 2001. Identification of men with possible lower extremity arterial disease, eligibility criteria, and the recruitment process including blood tests at entry and during the trial have been described elsewhere⁵ (<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 µmol/l. The placebo group received tablets identical in appearance. Men with creatinine concentrations of 135-149 µmol/l at entry took 400 mg on alternate days.

Details about follow up and ascertainment of end points are available elsewhere.⁵ All deaths were notified

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Table 1 Characteristics of 1568 men entering trial. Figures are numbers (percentage) unless stated otherwise

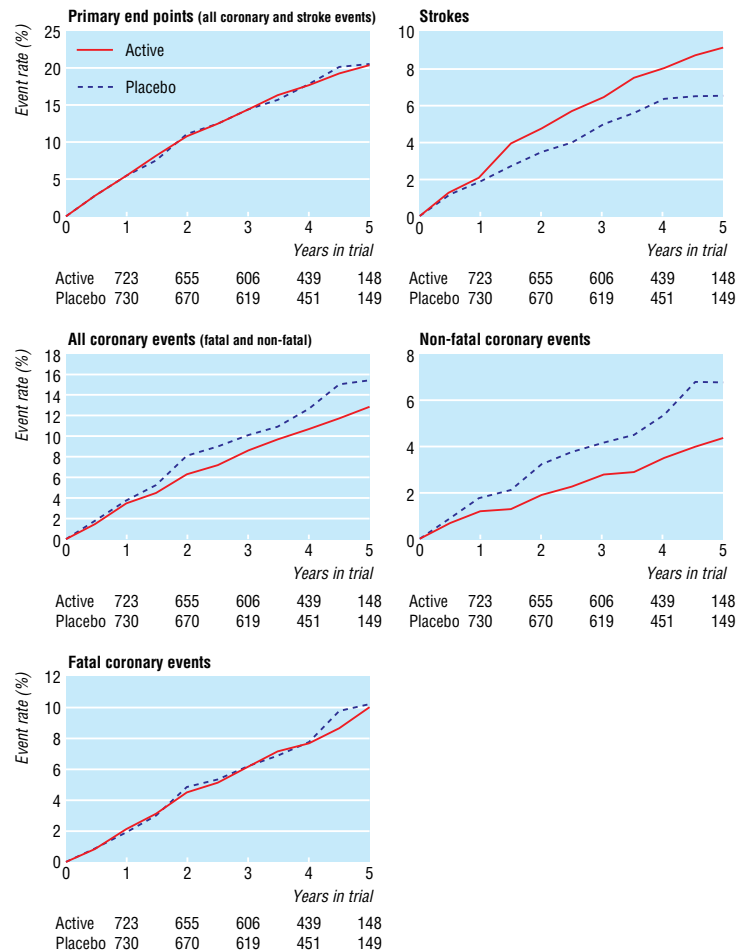
	Active (n=783)	Placebo (n=785)
Mean (SD) age (years)	68.4 (8.9)	68.0 (8.8)
Smoking:		
Current	306 (39.1)	287 (36.6)
Former	447 (57.1)	460 (58.6)
Never	30 (3.8)	38 (4.8)
History*:		
Myocardial infarction	151 (20.5)	160 (21.7)
Stroke	95 (12.9)	88 (11.9)
Stable angina	176 (22.5)	200 (25.5)
None	444 (60.4)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

IQR=interquartile range.

*Some men had more than one condition, and for some data were missing

†Treatment: 24% on insulin, 57% on oral therapy; 22% diet only.

‡Treatment: 95% on aspirin, 5% on dipyridamole. For some men data were missing.



Proportion of men who experienced end points during trial: totals at baseline were 783 in active treatment group and 785 in placebo group

from the NHS central register. Details on non-fatal events were unavailable for only 21 (1.3%) men.

Analysis

The primary end point was the combination of all coronary heart disease events (non-fatal and fatal) and all strokes. We classified all coronary events and fatal and non-fatal events of coronary heart disease and of stroke separately as secondary end points. We

calculated that we could detect a reduction of 30% in the primary end point due to bezafibrate in 1500 men at 5% level of significance with 80% power.⁵ Analysis of results on clinical end points was on an intention to treat basis. We used entry characteristics in Cox regressions to estimate relative risks.

Results

Recruitment

Of about 3200 men invited to attend the first or screening visit, 2505 did so. The 1568 patients finally randomised represent 86% of the 1816 eligible participants, and their characteristics are given in table 1, 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). About 70% of person years were spent on allocated treatment (see the full version of this paper on bmj.com). The proportions who withdrew were similar in the two groups. However, significantly more men in the placebo group withdrew because they started a drug treatment that was incompatible with bezafibrate, nearly always a statin, and significantly more men in the active treatment group were withdrawn because of raised creatinine concentrations.

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 (table 2 and figure). Of the secondary end points, only non-fatal coronary heart disease events occurred significantly less often in the active treatment group than in the placebo group (table 2).

In men aged <65 years at entry bezafibrate substantially reduced the incidence of coronary heart disease, principally of non-fatal events (0.13, 95% confidence interval 0.03 to 0.56). Also, all coronary 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 by recording whether pain occurs only when the patient is walking up hill or hurrying or if it also occurs both then and when the patient is walking at an ordinary pace on the level. Bezafibrate resulted in a significant improvement from baseline at one, two, and three years though not thereafter (see bmj.com).

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, increased statin use in the placebo group) the incidence of primary end points was less than 60% of 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,⁶⁻⁸ in which the proportions of fatal and non-fatal episodes have been as expected. Apart from chance, one possibility is a particularly high case fatality from heart attacks in

Table 2 Number of events and rates/1000 person years* according to randomly allocated treatment and relative risks (95% confidence interval)

	Active (n=783; 3029 person years)		Placebo (n=785; 3076 person years)		RR (95% CI)†	P value
	Events	Rate	Events	Rate		
All primary end points	150	49.5	160	52.0	0.96 (0.76 to 1.21)	0.72
Coronary heart disease:						
Fatal	64	21.1	65	21.1	0.95 (0.66 to 1.37)	0.79
Non-fatal	26	8.6	46	15.0	0.60 (0.36 to 0.99)	0.05
All	90	29.7	111	36.1	0.81 (0.60 to 1.08)	0.15
Stroke:						
Fatal	13	4.3	9	2.9	1.24 (0.46 to 3.37)	0.67
Non-fatal	47	15.5	40	13.0	1.34 (0.86 to 2.10)	0.19
All	60	19.8	49	15.9	1.34 (0.80 to 2.01)	0.49
Deaths, all causes‡	204	63.9	195	59.6	1.03 (0.83 to 1.26)	0.81

*Calculated as time to first event or time in trial for event-free men.

†Adjusted for entry characteristics.

‡Mainly cancer (47 active treatment, 47 placebo), heart failure, and respiratory disease (see text).

these men with lower extremity arterial disease. Another is that two thirds of the men were taking platelet anti-aggregating agents, nearly all as aspirin, which may reduce non-fatal more than fatal events.⁶⁻⁹

There were more strokes and deaths from all causes in those on active treatment than 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 events among those allocated to active treatment. Besides our trial, two other trials of fibrates¹⁰⁻¹² have shown greater treatment effects on non-fatal than on fatal events, though the Israeli bezafibrate infarction prevention trial did not show a significant reduction (9%) in all coronary events.¹¹ Two trials that used gemfibrozil, which has different properties compared with bezafibrate and fenofibrate, showed that it significantly reduced the incidence of clinical end points.¹³⁻¹⁴

Bezafibrate increases homocysteine concentrations,¹⁵ and high concentrations are an important risk factor for vascular disease. A further trial could usefully see whether the concurrent use of folic acid and bezafibrate would allow its beneficial effects on fibrinogen and lipid profiles to reduce the risk of heart attacks and strokes to a worthwhile extent.

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Contributors: See bmj.com

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

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What is already known on this topic

The beneficial effects of bezafibrate blood on 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

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The child whisperer

Over the past four years, since retirement from active practice, I have conducted an experiment that has only anecdotal evidence. None the less, our son, also a doctor, has carried out a similar test with the same results. Neither of us can explain these results nor can we find it mentioned in any reference book, but perhaps we have not looked in the right places.

And what is this startling finding? Over 90% of children from the age of 8 weeks up to 2 years will invariably smile if you whisper to them with a pleantry, rather than speaking in a normal voice, whatever their mood. It takes longer if they are unhappy at the start. Both of us have been able to show this phenomenon to amused mothers who had not believed us. My own tests have been conducted at supermarkets while I have been selling flags for a charity.

I first noticed the effect some 11 years ago, when our first grandchild, then aged 10 weeks, smiled in the middle of a tantrum when I whispered to him. A visual effect—my funny face or spectacles—does not seem to be involved, since our son has

neither of these and I achieve the same effect when I take off my spectacles.

Clearly this work is not leading to the Nobel prize, but if it is true it might have implications for the treatment of children, which could, among other things, produce a welcome, though small, degree of contentment in a discontented world.

I would be interested to know if any readers have had any experience of such a phenomenon and, even better, an explanation.

J A M Wright

We welcome articles up to 600 words on topics such as *A memorable patient*, *A paper that changed my practice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to.