BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2012.04282.x

Commentary

The clofibrate saga: a retrospective commentary

Michael Oliver

University of Edinburgh, UK

Introduction

After many years of study clofibrate, the first of the fibrates, seemed in the 1960s, to be an effective means of lowering raised plasma cholesterol. It provided an opportunity for examining the key question of whether reduction of plasma cholesterol might lead to reduction in the incidence of coronary heart disease (CHD). While small secondary prevention trials looked promising, a large primary prevention trial (the WHO trial) carried out over 5.3 years on 15 745 men aged 30–59 years provided contradictory results with reduction in nonfatal myocardial infarction, less hypertension, no change in coronary mortality but an increase in non-cardiovascular mortality. Clofibrate also increased gall stone formation and the need for cholecystectomies. Clofibrate was not an appropriate drug to recommend for population control of CHD. It did, however, usher in other fibrates and foreshadowed successful statin trials.

Background

The start of the story of clofibrate goes back to the early 1950s. Gofman, a physicist in the Berkeley Campus of the University of California, published a paper suggesting that patients with coronary heart disease (CHD) have high plasma concentrations of cholesterol [1]. These studies were based on ultracentrifugal analysis showing a distinctive lipoprotein pattern. Barr from New York confirmed this using a cold precipitation method [2]. George Boyd in Edinburgh developed a simple micromethod of analysis using paper electrophoresis [3] and in 1953 we published the first paper in Europe reporting that patients with CHD have higher concentrations of cholesterol, particularly the younger ones, when compared with an age-matched control group [4].

Meanwhile, Cottet reported that farm workers exposed to an insecticide which was sprayed from the air over fields in the region of Clermont-Ferrand in France became ill and were found to have remarkably low plasma cholesterol [5].

Funding: None.

This insecticide (phenyl ethyl acetic acid) had been developed by the agricultural division of Imperial Chemical Industries (ICI). A chemist in ICI, Jeff Thorp, recognized the potential of this substance and synthesized an analogue, chlorophenoxyisobutyrate (later called Atromid-S or clofibrate). Because of our published interest in cholesterol metabolism and plasma lipoproteins [4, 6], Thorp telephoned me one day in 1957 asking whether Boyd and I might be willing to study the cholesterol-lowering effects of this analogue. For 3 years, we explored its effects, mostly in rats, finding it to be particularly effective in adrenalectomized rats.

In those days, there were no requirements to present a clinical programme to any scientific or ethics committee, since there were no such committees! Therefore, slowly, I began to use it in healthy men starting with a dose of 250 mg daily. After a further 2 years, we identified that a daily dose of 1.5 g or more reduced plasma cholesterol concentrations consistently and significantly but wrongly labelled it as an orally active androsterone [7]. Our subsequent research showed that its action was not related to androsterone activity, though we did not understand the mechanisms through which it lowered plasma cholesterol and more impressively plasma triglycerides. Thorp was delighted [8, 9] and we were excited with its potential [10].

Clinical trials

WHO primary prevention trial

Encouraged by the effect of clofibrate on plasma cholesterol, I began in 1964 to plan a large trial in healthy men using clofibrate to decrease plasma total cholesterol and the incidence of CHD. This was the first primary prevention trial to use a cholesterol-lowering drug. We estimated that clofibrate would reduce raised plasma cholesterol by about 15% and that such a reduction might be associated with a 30% reduction in CHD. This turned out to be a serious miscalculation.

The first need was to identify a large population of healthy men with raised plasma cholesterol. We did this by measuring plasma cholesterol concentrations in men

attending blood donor clinics and in volunteers from the general public inviting them to participate in a trial to reduce heart disease. All were asked to sign a form of consent to participate for 5 years in a trial to prevent CHD and my recollection is that very few declined. With the advice of Jerry Morris (MRC Social Medicine Unit, London) and Austen Heady (statistician at the Royal Free Hospital School of Medicine), we aimed at recruiting 15 000 or more men. We were not able to achieve such numbers in Edinburgh alone and, after consultation with Zdenek Fejfar at WHO, we invited Jiri Fodor in Prague and George Lamm in Budapest to join the organization of the trial. These were communist countries at that time and it was the law to have 100% autopsies. Follow-up was easier there than in Edinburgh. In all, we recruited 15 745 men of whom 10 627 had raised plasma cholesterol concentrations. These were randomized into a clofibrate-treated group and a control group given 1 g olive oil. The remainder with low concentrations were given olive oil tablets and acted as a second control group. This was to provide a contrasting group of the prevalence of CHD in each centre. Were I to design such a trial now, I would not have included this additional control group of 5118 men since it increased the work by one-third. Investigators and participants were unaware of the groups to which the men belonged.

The organization and conduct of a trial this size was not easy and we had no previous experience to call upon. We had to establish 'Heart Disease Prevention Clinics' in each centre and recruit a dedicated staff of doctors and nurses. In Edinburgh, the Clinic was partly mobile so that we could interview and follow-up men in the Borders, Lothians and Fife. The men were all seen 3 months after the start of the trial and 6 monthly thereafter.

A mean reduction of 9% in serum cholesterol was achieved in the clofibrate-treated group. This was less than the 15% expected and seriously undermined the prediction of CHD reduction.

The incidence of nonfatal myocardial infarction was 25% lower in the clofibrate group compared with the high cholesterol control group ($P < 0.05$) but the incidence of fatal heart attacks and of angina was not different. The reduction in nonfatal events was greatest in those with the highest initial concentrations and in those with greatest reduction in cholesterol. Excluding vascular diseases, there was an excess of deaths (77 *vs.* 47) due principally to biliary and intestinal causes in the clofibrate-treated group and an excess of gall stones and cholecystectomies ($P < 0.001$) (see Table 1). Fuller tabulation and figures showing all results are available [11].

There was a crisis 1 year before the completion of the trial when, during a flight to Prague, Heady (the unblinded statistician) revealed to Morris that there was a significant excess of non-cardiovascular deaths. Morris decided to convene a meeting of the principal investigators in order to consider whether to stop the trial prematurely. A vote was taken and, in view of the complexity of stopping such a large trial and the fact that there was only 1 more year to go, it was agreed that it should continue. Had there been a regulatory committee, outside the trial, it is possible that the trial would have been terminated prematurely. This would have aborted the 6 year follow-up and pre-empted the finding that there was no excess cardiovascular mortality after clofibrate was discontinued.

This trial confirmed the basic hypothesis that reduction of elevated plasma cholesterol concentrations can reduce the incidence of CHD.

But we concluded that the increase in gall stones and intestinal deaths indicated that clofibrate should not be recommended as a lipid-lowering drug for community-wide prevention of CHD. A 7.9 year follow-up, which was 97% complete, showed that the 47% excess of non-cardiovascular deaths during the trial period disappeared after treatment with clofibrate was discontinued. The substantial excess remains unexplained [12].

Table 1

Summary of main results of WHO Clofibrate Trial [11]

Morbidity/Mortality	Clofibrate with high cholesterol		Controls with high cholesterol	
Numbers	5331		5296	
Numbers and rates per 1000 per annum	*n*	Rate	*n*	Rate
Nonfatal MI	167*	5.9*	208*	7.4*
Fatal MI	36	1.3	34	1.2
Hypertension	192*	6.8*	242*	8.6*
Nonfatal stroke	18	0.6	13	0.5
New diabetes	129	4.6	102	3.6
Cholecystectomies	59**	2.1**	24**	0.9**
Malignant neoplasms	40	3.6	24	2.8
Other medical causes	16*	~	5*	~
All causes other than CHD	108*	~	79*	~

*$P < 0.05$, **$P < 0.001$.

Secondary prevention trials

Two small double-blind clinical studies using clofibrate were published in 1971. This was halfway through the conduct of the WHO primary prevention trial. Both had positive results. In the Newcastle trial, there was a significant reduction in sudden deaths and total CHD mortality and in the rate of first nonfatal infarct [13]. In the Scottish trial, clofibrate had a beneficial but not statistically significant effect in reducing morbidity and mortality from CHD, particularly in patients with pre-existing angina [14]. In both trials, these results were independent of the initial serum cholesterol and of the extent to which cholesterol and triglycerides were lowered. There were no adverse effects during the 5 years duration of these trials.

Diabetic retinopathy

We were also able to show that, over a 3 year period, clofibrate caused regression of exudative lipid-rich lesions

as demonstrated by retinal photography [15]. We related this to the substantial triglyceride-lowering effect of clofibrate.

Consequences and developments

The results of the WHO trial were a great disappointment. When the higher mortality rate from non-cardiovascular causes is considered together with the higher number of gallstone operations in the clofibrate group, the 'cost' in terms of pathology associated with clofibrate exceeded the benefits for primary prevention of CHD. These results from the first and largest primary prevention trial set back research into the hypothesis that reducing elevated plasma cholesterol and low density lipoprotein (LDL) might reduce the incidence of CHD without adverse effects for more than 10 years (1978 to 1994).

Was this due to clofibrate or to lowering of plasma cholesterol and LDL? This seems a strange question now but not in the mid 1980s. Indeed, so much so that I wrote an article questioning the need for and safety of lowering raised plasma cholesterol [16]. Yet the results of the Helsinki Heart Study published 3 years later using gemfibrozil, a structurally different fibric acid derivative, in 4081 subjects were encouraging [17]. It was a double-blind 5 year trial and showed an increase in high density lipoproteins (HDL) and a decrease in LDL. There was a 34% reduction in the incidence of CHD compared with an age matched control group. There were slightly more deaths overall in the gemfibrozil group.

While it is likely that all fibrates act by the same pharmacological mechanism, we do not yet know this for certain. But all have the same outcome when the trial databases are of equivalent size. Only when huge data sets are collected, as in the WHO clofibrate trial, is the true detriment discovered. No individual fibrate database disproves the likelihood that they increase mortality.

All was not lost. In the mid 1980s, there were two far reaching developments in the field of lipidology. Brown & Goldstein's identification of the LDL receptor [18] for which they were rewarded with a Nobel Prize and the finding by a Japanese microbiologist (Endo) that inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), which is a rate-limiting enzyme in the cholesterol biosynthetic pathway, led to reduction of plasma LDL [19]. Endo was recently awarded the Lasker–DeBakey Prize. Merck began clinical trials of lovastatin in the 1980s. But it was not until 1994 when the Scandinavian Simvastatin Survival Study (4S) secondary prevention trial showed that, after 5.4 years reduction of plasma cholesterol by simvastatin in 4444 patients, there was a significant reduction of myocardial infarction [20] that faith in the hypothesis was restored. There was no increase in the 4S trial in non-cardiovascular morbidity or mortality. The West of Scotland primary prevention trial using pravastatin over 5 years in 6595 men without CHD confirmed this [21] and the REGRESS trial using pravastatin showed less progression of coronary atherosclerosis [22].

While clofibrate was a profound disappointment, it introduced the fibrates and more recently has led to extensive research into their mechanism of action, into activation of PPAR-alpha (peroxisome proliferator-activated receptors) and the regulation of HDL metabolism [23].

Conclusion

After 30 years of basic and clinical research and a great deal of work, it became apparent in about 1978 that clofibrate was not an appropriate drug to use to reduce raised plasma cholesterol and LDL and morbidity and mortality from CHD. The positive effects were small and the adverse effects unacceptably large. Yet, it was the only lipid-lowering drug available in the early 1960s.

Competing Interests

There are no competing interests to declare.

REFERENCES

1 Gofman JW, Jones HB, Lindgren FT, Lyon TP, Elliott HA, Strisower B. Blood lipids and human atherosclerosis. Circulation 1950; 5: 161–78.

2 Barr DP, Russ EM, Eder HA. Protein-lipid relationships in human plasma. II in atherosclerosis and related conditions. Am J Med 1951; 11: 480–93.

3 Boyd GS. The estimation of serum lipoproteins: a micromethod based on zone electrophoresis and cholesterol estimations. Biochem J 1954; 58: 680–5.

4 Oliver MF, Boyd GS. The plasma lipids in coronary artery disease. Br Heart J 1953; 15: 387–41.

5 Cottet J, Mathivat A, Redel J. Therapeutic study of a synthetic hypocholesterolaemic agent: phenyl ethyl acetic acid. Presse Med 1954; 62: 939–41.

6 Oliver MF, Boyd GS. Serum lipoprotein patterns in coronary sclerosis and associated conditions. Br Heart J 1955; 17: 299–304.

7 Oliver MF. Reduction of serum lipid and uric acid levels by an orally active androsterone. Lancet 1962; i: 1321–3.

8 Thorp JM. Experimental evaluation of an orally active combination of androsterone with ethyl chlorophenoxyisobutyrate. Lancet 1962; i: 1323–6.

9 Thorp JM, Waring WS. Modification of metabolism and distribution of lipids by ethyl chlorophenoxyisobutyrate. Nature 1962; 194: 948–9.

10 Oliver MF. Further observations on the effects of Atromid and ethyl chlorophenoxyisobutyrate on serum lipid levels. J Atheroscler Res 1963; 3: 427–44.

11 Report of the Committee of Principal Investigators. A cooperative trial in the primary prevention of ischaemic heart disease using clofibrate. Br Heart J 1978; 40: 1069–118.

12 Report of the Committee of Principal Investigators. WHO cooperative trial on primary prevention of ischaemic heart disease with clofibrate to lower serum cholesterol: final mortality follow-up. Lancet 1984; ii: 600–60.

13 Dewar HA, Oliver MF. Secondary prevention trials using clofibrate: a joint commentary on the Newcastle and Scottish trials. Br Med J 1971; 4: 784–6.

14 Oliver MF. Ischaemic heart disease: a secondary prevention trial using clofbrate. Br Med J 1971; 4: 775–84.

15 Duncan LJP, Cullen JF, Ireland JT, Nolan J, Clarke BF, Oliver MF. A three year trial of Atromid therapy in exudative diabetic retinopathy. Diabetes 1968; 17: 458–64.

16 Oliver MF. Might treatment of hypercholesterolaemia increase non-cardiac mortality? Lancet 1991; 338: 1529–31.

17 Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Maenpaa H, Malkonen M, Manttari M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjoblom T, Nikkila EA. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, change in risk factors, and incidence of coronary heart disease. N Engl J Med 1987; 317: 1237–45.

18 Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science 1986; 232: 34–47.

19 Endo A, Kuroda M, Tanzawa K. Competitive inhibition of 3-hydroxy-3- methylglutaryl coenzyme A reductase by ML-236A and ML-236B fungal metabolites, having hypocholesterolaemic activity. FEBS Lett 1976; 72: 323–4.

20 Scandinavian Simvastatin Survival Study (4S). Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease. Lancet 1994; 344: 1383–9.

21 Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolaemia. West of Scotland Study Group. N Engl J Med 1995; 333: 1301–7.

22 Jukema JW, Bruschke AVG, van Boven AJ, Reiber JHC, Bal ET, Zwindermann AH, Jansen H, Boerma GJM, van Rappard FM, Lie KI. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels (REGRESS). Circulation 1995; 91: 2528–40.

23 Fruchart JC, Duriez P. Mode of action of fibrates in the regulation of triglyceride and HDL-cholesterol metabolism. Drugs Today 2006; 42: 39–64.

RECEIVED
6 March 2012

ACCEPTED
20 March 2012

ACCEPTED ARTICLE PUBLISHED ONLINE
5 April 2012

CORRESPONDENCE
Professor Michael Oliver, 12 Narrow Street, London E14 8DH, UK.
Tel.: +207 790 4203
E-mail: michaeloliver@mac.com