For Debate

Should there be a moratorium on the use of cholesterol lowering drugs?

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Recent reviews of the primary prevention of coronary heart disease through lowering cholesterol concentrations have varied considerably in their evaluation of the benefits of the intervention.[1-4] The degree of disagreement is surprising as they review essentially the same data, from clinical trials of cholesterol lowering by drugs or by diet. There is agreement about a reduced risk for coronary events, but there are differing interpretations of the increase in mortality from non-cardiovascular causes that has generally been seen. Particular concern was generated by a recent meta-analysis that showed a significantly increased risk of death from accidents and violence when the results of six randomised primary prevention trials were pooled.[3]

Despite the uncertainty an aggressive approach to cholesterol reduction features in most of the official guidelines for the primary prevention of coronary heart disease.[5-9] In Britain the introduction of the new general practitioner contract, with its focus on health promotion, is likely to result in an increase in cholesterol testing. High percentages of the British population would become candidates for drug treatment if the guidelines currently advanced by some authorities were put into practice. For middle aged men and women with other coronary risk factors the European Atherosclerosis Society recommends a cut off level, above which the use of lipid lowering drugs should be considered,[6] well below the mean population cholesterol concentration.[10-12] The entry criteria for the expanded clinical evaluation of lovastatin study (EXCEL)[13] would include a third of the British population.[10-12]

Does lowering cholesterol reduce mortality?

The cholesterol lowering enterprise threatens to turn a large percentage of the healthy population into patients, at a substantial potential cost to the NHS. Do the results of the clinical trials of primary prevention of coronary heart disease justify this? Tables I and II present the mortality results from these trials. The reduction in non-fatal coronary events in these trials has, in general, been greater than the reduction in fatal events,[2] although not all trials have published data on this. Morbidity from causes other than coronary disease has generally not been reported, however, so it has not been possible to evaluate the overall effect of lowering cholesterol concentration on morbidity. Our assessment is therefore based solely on the effect on mortality.

Table I gives the basic data from the trials analysed. Table II gives the odds ratios for death from any cause and for various specific causes, for diet and drug trials separately. Pooling of odds ratios and calculation of variances for determining confidence intervals and statistical tests used a modification of the Mantel-Haenszel procedure.[23]

We have made some important additions to the previous analysis by Muldoon *et al*.[3] Firstly, Muldoon *et al* included only randomised trials. But there has also been a large crossover trial, the Finnish mental hospital study. Serum cholesterol concentrations were reduced by about 15% with a diet low in saturated fats and cholesterol and high in polyunsaturated fats.[16 24] When results from this trial are added, death from injury, which caused concern in the earlier report,[3] is not greatly or significantly increased in the treatment groups of the dietary trials (odds ratio 1·20; p=0·4). In the treatment groups of the drug trials, on the other hand, there is a markedly increased odds ratio for death from injury of 1·75 (p=0·026). The difference between these two odds ratios is not significant, but the ratios are based on a relatively small number of deaths.

Secondly, we have treated deaths from causes other than coronary heart disease as a separate group. Mortality from these causes is substantially raised in the drug trials but not the diet trials; the difference between the two types of trial is large and significant. The pattern for causes of death other than coronary heart disease, cancer, and injury is essentially the same as that for all causes other than coronary heart disease.

Thirdly, the 6·5 year follow up results from the Helsinki heart study, required by the United States Food and Drug Administration,[21] have been added. These results show an increased risk of death from causes other than coronary heart disease of borderline statistical significance (p=0·056) in this trial alone. During the initial five years of the Helsinki heart study mortality from cancer was equal in the treatment and placebo groups[20]; by 6·5 years, however, there had been 39 incident cancers in the treatment group compared with only 29 in the placebo group.[21] Gemfibrozil, used in the Helsinki heart study, is closely related to clofibrate, used in the World Health Organisation trial.[17] In the WHO trial, total mortality increased by 44% in the clofibrate group during treatment. The increase in mortality levelled off within a few years after clofibrate use was stopped.[25]

Fourthly, data on all cause mortality from the first year of follow up of the EXCEL trial of lovastatin (a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor) have been added.[13 22] These results are not encouraging as 33 out of 6582 (0·50%) patients treated with drugs died compared with only three out of 1663 (0·18%) patients taking the placebo.

Total mortality was lower among subjects in the intervention groups in the diet trials (odds ratio 0·95)

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TABLE I—*Trials of primary prevention of coronary heart disease by reducing cholesterol concentrations*

	No of participants		No of deaths from coronary heart disease		No of deaths from causes other than coronary heart disease								All causes		
					All		Cancer		Injury		Other				
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Years of follow up
Diet trials:															
Veterans Administration diet study[14]	424	422	41	50	133	127	33	20	4*	0*	NA	NA	174	177	8
Minnesota coronary survey[15]	2197	2196	39	34	119	119	16	12	21	14	82	93	158	153	1
Finnish mental hospital[16]†	902	928	34	76	154	141	23	24	13	18	118	99	188	217	6
Drug trials:															
WHO study[17]	5331	5296	36	34	92	53	42	25	18	15	32	13	128	87	5
Colestipol-Upjohn study[18]	548	546	9	22	8	5	2	2	2	0	4	3	17	27	2
Lipid Research Clinics[19]	1906	1900	32	44	36	27	16	15	11	4	9	8	68	71	7
Helsinki heart study[20]	2051	2030	14	19	31	23	11	11	10	4	10	8	45	42	5
extended follow up[21]			16	28	43	27	NA	NA	NA	NA	NA	NA	59	55	6·5
EXCEL[22]	6582	1663	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	33	3	1

*Only available for six to eight year follow up on an incomplete section of the trial entrants.
†The Finnish Mental Hospital study was a crossover trial with entry and exit of participants. The number of participants given is a figure for number of person-equivalents completing the six year intervention and control periods.
NA = Not available.

TABLE II—*Meta-analysis of mortality during trials of primary prevention of coronary heart disease by lowering cholesterol concentrations.*

Cause of death	Odds ratio (95% confidence interval)		Difference*	
	Dietary intervention studies	Drug intervention studies	Z score	p Value
All	0·95 (0·82 to 1·09)	1·16 (0·98 to 1·38)	1·82	0·069
Coronary heart disease	0·71 (0·55 to 0·90)	0·72 (0·55 to 0·94)	0·11	0·9
All non-coronary heart disease	1·07 (0·92 to 1·25)	1·59 (1·26 to 2·00)	2·76	0·006
Cancer	1·31 (0·92 to 1·86)	1·33 (0·93 to 1·89)	0·07	0·9
Injury	1·20 (0·75 to 1·93)	1·75 (1·07 to 2·85)	1·07	0·29
Other non-coronary heart disease	1·06 (0·86 to 1·31)	1·69 (1·11 to 2·57)	1·93	0·054

*Difference between odds ratios for diet and drug intervention studies.

but higher in the intervention groups in the drug trials (odds ratio 1·16). The difference in odds ratios for total mortality in the drug and diet trials approached significance (p=0·069), as did the increase in total mortality in the treatment groups of the drug trials (p=0·087). Baseline cholesterol concentrations were generally higher in the drug trials than the diet trials, and since lowering cholesterol has greatest potential benefit for subjects with high concentrations,[4] it would be expected that the drug trials, rather than the diet trials, would be more likely to show benefit in terms of total mortality.

Muldoon *et al*[3] considered that dietary and drug lowering of cholesterol had the same effect on mortality on the basis of statistical tests of heterogeneity between the two types of study. These statistical tests lack power[26] and can therefore miss important differences. Furthermore, as we showed above, differences emerge when additional studies are included in the analysis.

The dietary intervention trials suffer from particular weaknesses in terms of design, size, and length of follow up. The apparent difference in outcome between them and the drug trials is not definitive. But support for the notion that dietary lowering of cholesterol may be safe, whereas lowering of cholesterol with drugs may not be, comes from other sources. Firstly, prospective epidemiological studies do not provide good evidence that low blood cholesterol concentrations in themselves increase the risk of violent death,[27,28] cancer,[29] or other non-cardiovascular causes of death.[30] Because falling cholesterol concentrations could have different biological effects than consistently low concentrations the findings of prospective studies should not be overinterpreted. Secondly, lowering of blood cholesterol was also achieved in some of the multiple risk factor intervention studies. In those in which blood cholesterol was reduced by diet, the interventions seem safe and perhaps beneficial.[31-33] But in the Finnish multifactorial primary prevention trial, in which clofibrate and probucol were used to treat high cholesterol concentrations, total mortality was significantly (p<0·05) increased in the intervention group over a 15 year follow up period.[34] Increased mortality from non-cardiovascular causes may therefore be restricted to drug induced lowering of cholesterol, contrary to the suggestion of other commentators.[3,35]

Use of cholesterol lowering drugs in Britain

Given the failure to show that cholesterol lowering drugs reduce mortality, their current widespread promotion and use may seem surprising. Figures 1 and 2 present prescription data for England, Wales, and Scotland. Data on clofibrate were available from 1975 and data regarding other drugs from 1980. Prescriptions of clofibrate began to fall from a high point in 1978, after the publication that year of the WHO trial, which showed adverse effects on mortality.[17] Prescriptions for other cholesterol lowering drugs have increased considerably since the mid-1980s, perhaps in

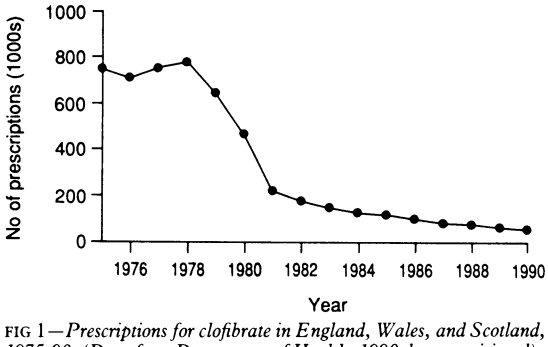

FIG 1—*Prescriptions for clofibrate in England, Wales, and Scotland, 1975-90. (Data from Department of Health; 1990 data provisional)*

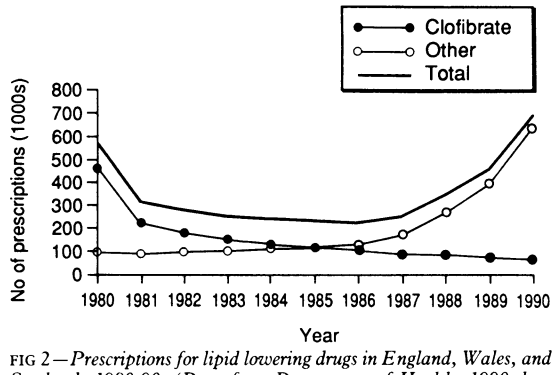

FIG 2—*Prescriptions for lipid lowering drugs in England, Wales, and Scotland, 1980-90. (Data from Department of Health; 1990 data provisional)*

response to the reports from the Lipid Research Clinics and Helsinki heart studies.[20 36] Nearly half of the total prescriptions in 1990 were for bezafibrate, the efficacy and safety of which have not been shown in any long term trials. This lack of information is of particular relevance as bezafibrate is related to clofibrate and gemfibrozil, whose effects on total mortality have not been favourable. Switching from clofibrate, a drug with an adverse effect on mortality, to bezafibrate, a related drug whose effect on mortality is unknown, is perhaps not the appropriate response to a clinical trial producing unwelcome results.

It is not possible to ascertain how many people take cholesterol lowering drugs from the prescription data, but the average number of tablets contained in a prescription would cover one month or longer, given the currently recommended dosages.[37] For 1990 this gives a minimum estimate of 58 000 patients, assuming 12 prescriptions per patient. This is likely to underestimate the number taking the drugs as some patients would have been started treatment during the year, and some would have died or stopped treatment and not received 12 prescriptions.

Should use of cholesterol lowering drugs be expanded?

The use of cholesterol lowering drugs in Britain. is well behind that in the United States, where similar prescription data to those presented here give a minimum estimate of 1 000 000 patients being treated in 1988.[38] The prevalence of use of cholesterol lowering drugs in 1988 was about eight times higher in the United States than in Britain. In the United States total prescriptions decreased from the late 1970s to early 1980s because of large reductions in the prescription of clofibrate. Between 1983 and 1988 total prescriptions increased fivefold.[38] The rapid increase was due to the introduction of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor lovastatin and the greatly increased prescription of gemfibrozil. By 1988, these were the most prescribed cholesterol lowering drugs.[38]

In the United Kingdom total prescriptions for cholesterol lowering drugs trebled from 1986 to 1990. Prescriptions of gemfibrozil and simvastatin (a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) look set to increase substantially. Increased mortality from non-cardiovascular causes more than counter-balanced the decrease in mortality from cardiovascular causes in the only long term trial of gemfibrozil.[21] 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors are being introduced without their long term efficacy and safety having been proved. The early results of the EXCEL study,[13] discussed above, are not auspicious in this regard.

Quantitative estimates of the improvements in life expectancy consequent on lowering cholesterol concentrations are not impressive,[39 40] even when generous assumptions are made. It is difficult to justify the general use of cholesterol lowering drugs when the data available from clinical trials fail to show reductions (and may show increases) in mortality. The cholesterol concentrations of the participants in the clinical trials that have reported long term follow up were considerably higher than the concentrations above which treatment is currently being recommended. Since benefit in terms of reduction in coronary heart disease is greater when baseline cholesterol concentration is higher,[4] the trials are likely to give a maximal estimate of benefit in terms of total mortality—that is, less benefit (or greater harm) will be seen during use outside of the trials in people with lower initial cholesterol concentrations.

High serum cholesterol concentrations can be lowered with moderate dietary modifications at the individual and population level. If it is decided that cholesterol lowering is an important public health goal then dietary change is more cost effective,[41 42] and probably safer, than widespread drug treatment. The overenthusiastic prescribing of antihypertensive drugs has led to stopping such treatment becoming an important clinical topic.[43] It would be best to avoid this situation with lipid lowering drugs. There are a series of ongoing trials of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors which are large enough to detect changes in total mortality, which contain women as well as men, which are exploring the effects of treating moderate as well as severe hypercholesterolaemia, and which are studying the results of cholesterol lowering in elderly patients.[44 45] With the current uncertainty surrounding the benefits and risks of cholesterol lowering drugs in primary prevention we suggest that their general use, other than in patients with severe familial hyperlipidaemias, should await the results of these trials.

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Medicine in Europe

This is the 10th in a series of articles looking at medical issues in Europe.

A common ethics for a common market?

Søren Holm

Inevitably the growing economic and political integration in Europe will lead to attempts to integrate the legal rules and the paralegal regulations, declarations, and statements that govern medical ethics. There have already been some moves in this direction.

The main institutions on the European scene are the Commission of the European Community, the European Parliament, the Council of Ministers of the European Community, and the Council of Europe. The last of these is a non-EC body of which all democratic states in the European region are members.

The Council of Europe has been the most active, through resolutions in its committee of ministers and its parliamentary assembly and through its standing committee of experts in bioethics. Medical ethical questions fall outside the scope of the Treaty of Rome unless they coincide with questions concerning consumer protection or other market related issues.[1] This explains the relatively limited involvement of the EC in the field. The Council of Ministers has, however, recently issued a series of statements on AIDS. This anticipates the probable inclusion of health and social issues in the coming treaty on European union.

All these official bodies issue statements, declarations, and directives with widely different legal status.* They are supplemented by powerful but less official bodies like the Standing Committee of Doctors of the EC and the Roman Catholic Congregation for the Doctrine of Faith. Researchers interested in medical ethics have also formed the European Society for Philosophy of Medicine and Health Care and the European Association of Centres of Medical Ethics.

When in doubt form a committee

A consistent feature of the debates about medical ethics in Europe has been that governments have felt a need to establish investigative committees, commissions, or councils to discuss and clarify the problems. Some of these bodies have been able to reach agreement on specific policy proposals whereas others have been divided. Most have been single issue ad hoc bodies, but some countries—for example, France and Denmark—have established permanent ethical councils.[2,3]

Apart from their stated objectives of fact finding and policy making such commissions fulfil a variety of other political purposes.[4] So it is likely that the same approach will be chosen at the European level, initially in the form of ad hoc committees and perhaps later as permanent organisations. But it is doubtful that such commissions can represent the full width of the cultural diversity in the EC. The Glover working party on reproductive technologies authorised by the commission managed to reach a consensus, but its seven members did not represent the full diversity of the EC.[5]

Abortion, IVF, and embryo research

Almost every European country has had its own commission on abortion, in vitro fertilisation, and embryo research, and these have been supplemented by the Congregation of the Doctrine of Faith,[6] the Glover working party,[5] and by the standing committee of experts in bioethics (CAHBI).[7] The guidelines proposed vary from the relatively liberal to the conservative. The resulting legislation is also divergent,[8] and it is difficult to see how a common European policy could be established. The commission took no action after the Glover report and it is unlikely that any action will be taken.

Genetic screening

European guidelines for the use of genetic information do not exist, although the EC has allocated resources for research on the ethical issues created by the use of genetic information in the general genome research programme.[9] During the planning phase of this programme the emphasis was changed from "prediction" to "medical importance" because of sustained criticism of the programme's ethical basis.[10] Research on germ line treatment and somatic cell treatment was deleted from the programme. The future guidelines will probably be rather restrictive.

*Only directives issued by the European Commission or the Council of Ministers have legal force in the member countries of the EC. The European parliament can issue resolutions, but these have no immediate legal force. Recommendations and resolutions of the Council of Europe have legal force only in so far as they influence the legislatures in the member countries.

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