Cost effectiveness of lowering cholesterol

Cost consequence analysis may be more useful to decision makers

EDITOR,—If economic analyses are to provide guidance on population health strategies they should consider all relevant costs and consequences associated with medical interventions. We have identified five methodological deficiencies in the economic analysis of P D P Pharoah and W Hollingworth.¹

Firstly, their study examines the impact of treatment only on death; it ignores the value of averting non-fatal consequences such as unstable angina, myocardial infarction, revascularisation procedures, and stroke. These consequences decrease both the length and quality of patients' lives.^{2,3} By failing to account for these supplementary outcomes, the analysis underestimates the reduction in risk attributed to treatment and the associated incremental life years gained.

Secondly, the net intervention cost may not adequately reflect the true number of myocardial infarctions averted. Seven myocardial infarctions would be averted for every four lives saved over six years in the population of the Scandinavian simvastatin survival study⁴, and 20 non-fatal myocardial infarctions would be averted for every seven lives saved over five years in the west of Scotland coronary prevention study.⁵ These results yield higher proportion ratios than the 0.28 non-fatal myocardial infarctions prevented for each life year saved used by Pharoah and Hollingworth.

Thirdly, the analysis does not capture the costs of unstable angina or stroke.

Fourthly, the authors focus only on the cost of the initial clinical events or revascularisation procedures, without accounting for the long term follow up costs of treating the event and subsequent clinical complications.

Finally, considerable patient withdrawal rates were observed in the Scandinavian and Scottish studies—10% and 30% respectively—which would decrease the overall cost of the intervention as some patients were not being dispensed the study drug.

Thus, the current analysis fails to account for the survival and quality of life benefits incurred by averting non-fatal clinical events; it underestimates the costs of treating these events and overestimates the cost of providing the preventive interventions. The net result of these methodological deficiencies is to overestimate significantly the incremental cost effectiveness ratios. Pharoah and Hollingworth attempt to perform an assessment of statin treatment without access to the clinical event datasets associated with the specific studies, making it difficult to conduct an analysis that is accurate and reflective of the true economic value of either prevention strategy. Since the intention of the west of Scotland coronary prevention study was to evaluate the avoidance of all coronary events, as opposed to death alone, a cost consequence analysis may be more informative to decision makers. We are currently engaged in conducting such an exhaustive analysis of this study population.

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Advice to authors

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When deciding which letters to publish we favour originality, assertions supported by data or by citation, and a clear prose style. Wit, passion, and personal experience also have their place.

Letters should have fewer than 400 words (please give a word count) and no more than five references (including one to the *BMJ* article to which they relate); references should be in the Vancouver style. We welcome pictures.

Letters should be typed and signed by each author, and each author's current appointment and address should be stated. We encourage you to declare any conflict of interest.

Please enclose a stamped addressed envelope if you would like to know whether your letter has been accepted or rejected.

Letters will be edited and may be shortened.

- 1 Pharoah PDP, Hollingworth W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population. *BMJ* 1996;312:1443-8. (8 June.)
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- 5 Shepherd JS, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al for the west of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.

Study greatly underestimates the cost effectiveness of statin treatment

EDITOR,—The analysis of P D P Pharoah and W Hollingworth of the cost effectiveness of lowering cholesterol concentration is flawed.¹

With respect to secondary prevention, the authors do not take account of the significant reductions in the incidence of strokes and transient ischaemic attacks, chronic heart failure, and unstable angina requiring admission with simvastatin in the Scandinavian simvastatin survival study.² Although strokes and transient ischaemic attacks and chronic heart failure are

comparatively infrequent events, they are expensive. In the placebo group, for example, stroke accounted for 1280 days in hospital compared with 4473 for acute myocardial infarction. Admission for angina is both common and expensive. In the Scandinavian study the number of hospital admissions for angina (401 in the placebo group) was second only to that for acute myocardial infarction (630 in the placebo group). The number of days spent in bed by patients with unstable angina was 1585.

With regard to primary prevention, few physicians would advocate anything but "high risk" primary prevention—for example, treating men with two or more risk factors—in which the clinical benefits of treatment are substantial.^{3,4} Consequently, the authors' analysis is irrelevant for ordinary clinical practice.

Lastly, Pharoah and Hollingworth seem to assume 100% compliance with treatment and the costs associated with that. Many patients do not comply, especially those receiving primary prevention. For example, in the west of Scotland coronary prevention study 31% of patients had withdrawn from the active treatment group by the end of five years of follow up, many voluntarily.⁵ If prescriptions are not collected, there is no treatment cost. Consequently, Pharoah and Hollingworth's analysis will have substantially reduced the cost effectiveness of treatment, especially as the incremental cost effectiveness ratio is likely to be most sensitive to the cost of treatment (effectively reduced by up to one third if non-compliance is accounted for).

- 1 Pharoah PDP, Hollingworth W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population. *BMJ* 1996;312:1443-8. (8 June.)

- 2 Pedersen TR, Kjekshus J, Berg K, Olsson AG, Wilhelmsen L, Wedel H, et al for the Scandinavian Simvastatin Survival Study Group. Cholesterol lowering and the use of health care resources: results of the Scandinavian Simvastatin Survival Study. *Circulation* 1996;93:1796-802.
- 3 Davey Smith G, Song F, Sheldon T. Cholesterol lowering and mortality: the importance of considering initial level of risk. *BMJ* 1993;306:1367-73.
- 4 Haq IU, Jackson PR, Yeo WW, Ramsay LE. Sheffield risk and treatment table for cholesterol lowering for primary prevention of coronary heart disease. *Lancet* 1995;346:1467-71.
- 5 Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.

Study did not take account of confounders

EDITOR,—We welcome the approach taken by P D P Pharoah and W Hollingworth in using life tables to evaluate the cost effectiveness of reducing cholesterol concentration.¹ This approach has been widely used elsewhere² and is a valuable technique for evaluating health service interventions aimed at modifying the risk profiles of a population. Unfortunately, however, their analysis may be flawed as such analyses depend on obtaining an accurate assessment of the overall manner in which population death rates are influenced by the intervention being evaluated. Such relations are extremely complex as they

must take account of behavioural factors that may confound the impact of the health intervention. In this case three such factors must be taken into account.

Firstly, a lifestyle that leads to high cardiovascular risk (poor diet, smoking, etc) will also increase the risk of premature death generally. This undermines the assumption of Pharoah and Hollingworth that people with cardiovascular disease have the same all cause mortality as the general population. This is unlikely because treatment with cholesterol lowering drugs alone will not modify the underlying behaviour that places people at high risk of dying prematurely.

Secondly, the use of magic bullets may instil a feeling of invulnerability, which significantly reduces the motivation for modifying lifestyle. Statins may even encourage deleterious health behaviour in people at high risk,³ which counterbalances the benefits arising from treatment to lower lipid concentrations by increasing mortality from other causes—for example, lung cancer. This indirect behavioural effect may outweigh the benefits arising from an initial reduction in cardiac mortality related to the use of such drugs.

Thirdly, compliance is a large problem for any treatment in which a symptom free patient is required to take drugs for no apparent immediate benefit. The analysis of Pharoah and Hollingworth assumes degrees of compliance equal to those seen in the Scandinavian simvastatin survival study⁴ and the west of Scotland coronary prevention study,⁵ but compliance in reality is significantly lower. Thus the long term efficacy of lipid lowering drugs is likely to be significantly below the values in the trials because of reduced patient compliance.

Despite such reservations, some of which are difficult if not impossible to overcome with currently available data, we agree with the general conclusion of Pharoah and Hollingworth that lipid lowering drugs should be targeted at groups with the highest baseline cardiovascular risk. We question, however, the exact level and nature of overall health benefits that are likely to arise as a consequence of the use of such treatment.

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- 1 Pharoah PDP, Hollingworth W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population. *BMJ* 1996;312:1443-8. (8 June.)
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Full treatment of the costs and benefits is needed

EDITOR,—P D P Pharoah and W Hollingworth have produced an interesting article that is of little benefit to the debate on the health economics of lowering lipid concentrations.¹ The life table approach suffers from the same deficiency as we² have pointed out for the Sheffield risk factor table.³ Megnien *et al* have shown that the risk

table does not differ significantly from the currently accepted guidelines once correct assumptions are made.⁴

The major deficiency in the life table approach is simple—death is cheap for the health service. The principal saving for lipid lowering agents is in procedures not needed and hospital beds not required. A full cost analysis has already been published for the Scandinavian simvastatin survival study for the United States and shows reductions in cardiovascular procedures of 31% and hospital stays of 34%.⁵ This leads to a net cost of the drug of 28 cents (19p) a day. The data for primary prevention in men in the west of Scotland coronary prevention study would imply a cost of treble that for secondary prevention on the basis of the number of events.⁶ The cost analysis for secondary prevention for the United Kingdom seems to imply a cost per life year saved of £3000-6000, depending on the assumptions made, not £361 000 for secondary prevention.⁷ This is based on reducing 86 cardiovascular deaths to 23, 679 hospital days to 231, and 19 angioplasties to six—that is, £237 000 reduced to £73 800 per 100 patients treated.⁷

It is difficult to find other treatments that have been as thoroughly evaluated as lowering lipid concentrations in terms of cost-return analysis. For secondary prevention the data are as good as those for severe hypertension (diastolic pressure >110 mm Hg), and for primary prevention they are similar to those for treating moderate hypertension. Unless cost analyses are conducted in full and include the cost of procedures, visits to outpatient departments and general practitioners, and stays in hospital any data that arise are highly misleading and not useful in health economic terms.

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- 1 Pharoah PDP, Hollingworth W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population. *BMJ* 1996;312:1443-8. (8 June.)
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- 8 lowering: results from the Scandinavian simvastatin Survival study (4S). *Eur Heart J* 1996; 17:1001-7.

Statin treatment should be started early

EDITOR,—As doctors who have managed patients with hypercholesterolaemia despite widespread scepticism, particularly in the *BMJ*,¹ we should be feeling pleased that one of our main treatments has been proved safe and effective. However, the results of the recent statin trials²⁻³ were perhaps too good and we are now told by P D P Pharoah and W Hollingworth that the NHS cannot afford such treatment.⁴ Given that reduction in coronary events is a class effect, then one simple way to double cost effectiveness is to

prescribe fluvastatin rather than simvastatin or pravastatin because at therapeutically equivalent doses it costs about half as much.⁵ The fundamental problem with focusing on short term cost effectiveness as the criterion for rationing these drugs is, however, that it ignores the underlying pathophysiology of atherosclerosis, which is a chronic disorder starting in early adulthood and progressing over decades. By middle age much of the damage is already done. Despite the favourable results of the statin trials it should not be overlooked that two thirds of the coronary events were not prevented. If the argument that only those at highest initial risk should be treated is taken to its logical conclusion then we should start statin treatment only on the day before an infarction.

We are worried that papers such as those by Pharoah and Hollingworth will be used by purchasing authorities to deny treatment to young patients with hypercholesterolaemia in whom coronary disease might be preventable altogether. This can never be shown to be cost effective if "lives saved in the future are worth less than those saved today." Such a statement should make us all shudder.

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- 1 Davey Smith G, Pekkanen J. Should there be a moratorium on the use of cholesterol lowering drugs? *BMJ* 1992; 304:431-3.
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Costs in general practice

EDITOR,—P D P Pharoah and W Hollingworth have calculated the potential costs and benefits of the increased use of statins to prevent deaths from coronary heart disease in a health authority.¹ A similar and simpler calculation can be done for the patients of a British general practice.

The results of the west of Scotland coronary prevention study of pravastatin treatment in men with raised cholesterol concentration showed a headline reduction of 32% in cardiovascular mortality and 22% in all cause mortality after five years.² The Scandinavian simvastatin survival study of simvastatin treatment in the secondary prevention of coronary heart disease addressed a related issue but in a group with a much higher risk of premature death.³

What are the costs and benefits of these interventions likely to be in practice?

In the case of primary prevention, a general practitioner's list of 2000 patients will contain about 75 men aged 45-65 with a cholesterol concentration in the study range (average 7 mmol/l).⁴ To treat each man with pravastatin 40 mg daily will cost £808 a year, a total of £60 600. In Oxfordshire this one intervention would therefore require an increase of around 50% in the current total drugs budget for general practice. This assumes that no women and no one outside the study age range of 45-65 years will be