International economic analysis of primary prevention of cardiovascular disease with pravastatin in WOSCOPS

J. Caro, W. Klittich, A. McGuire, I. Ford, D. Pettitt, J. Norrie and J. Shepherd for the WOSCOPS Economic Analysis Committee*

Aims The results of the West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated the clinical benefit of using pravastatin for the primary prevention of cardiovascular disease in hypercholesterolaemic men. To inform decision makers, who must also consider costs, this study assesses the economic efficiency of such an intervention in a broad range of countries.

Methods and Results A generalized model of cardiovascular disease prevention was used to estimate the cost-effectiveness of primary prevention with pravastatin compared to diet alone. This model follows a cohort of hypercholesterolaemic men over a given period quantifying the effect in terms of the avoidance of cardiovascular disease based on treatment-specific risks derived from WOSCOPS data and extensive record-linkage data on disease-specific survival. Country-specific costs are accounted for by expressing all such parameters in terms of the ratio of monthly treatment to that of managing a myocardial infarction. Over a broad range of inputs the cost-effectiveness ratios remain below $25 000 per life years gained, regardless of country. Subgroups with even better economic efficacy can be defined on the basis of higher baseline risk.

Conclusions In contrast to some previous reports, this analysis based on trial data demonstrates that pravastatin provides not only an effective means of primary cardiovascular disease prevention, but also an efficient one.

Key Words: Lipids, cost-effectiveness, cholesterol-lowering, coronary heart disease, prevention, general economic model.

See page 245 for the Editorial comment on this article

Introduction

The West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated, for the first time, that intervention in hypercholesterolaemic middle-aged men with no evidence of previous myocardial infarction can substantially lower the risk of cardiovascular disease with no increase in mortality from other causes. In today’s cost-conscious health care environment, however, such impressive clinical results are not sufficient — decision makers must also consider the economic implications of this intervention.

In a previous analysis, we estimated the economic efficiency of preventing cardiovascular disease with pravastatin instead of diet alone from the perspective of the National Health Service in the United Kingdom. For those results to provide guidance to those who set policy in other jurisdictions, they must account for differences among health care systems. Thus, this study was undertaken to generalize the results of WOSCOPS to the perspective of any national health service or other organization responsible for societal health care costs. To do so, a formula was derived using the United Kingdom model as the basis. In this paper, the derivation of the cost-effectiveness formula is presented, together with its validation by comparing the results it provides with those of the original United Kingdom model and a separate Canadian model. In addition, sample calculations are made for three new countries, Sweden, Belgium and South Africa. The general model thus created can be used to derive the specific economic consequences for any given health jurisdiction.

Methods

United Kingdom model

The United Kingdom cost-effectiveness analysis used a Markov model expressly created for economic analysis
of interventions of this type. Full details are provided elsewhere[3]. Briefly, primary prevention of cardiovascular disease using pravastatin treatment was compared to no primary intervention, each on top of normal dietary advice. This analytic framework computes the number of initial cardiovascular events (‘transitions’ from health to illness) in a population defined by a set of risk factors that include hypercholesterolaemia. The model runs in one month cycles for whatever time period is being considered. In each month, those who suffer a non-cardiovascular death are removed from the cohort before applying the relevant cardiovascular disease risk. This risk determines the number of individuals who will manifest cardiovascular disease (coronary or cardiovascular deaths, definite non-fatal myocardial infarction, unrecognized or silent myocardial infarction, angio-plasty, bypass grafting, angiography, hospitalized angina, non-fatal stroke, and transient ischaemic attack) for the first time during that month. These men are then also removed from the cohort for subsequent months. The process was carried out over a period of 60 months (corresponding to the approximate average follow-up time for a randomized subject in the trial) and the net consequence of not using pravastatin was estimated as the cumulative difference in the number of transitions.

### Generalized formula

The original model was generalized to allow country-specific assessments by deriving a formula that re-expresses the cost-effectiveness ratio, C/E in terms of the elements that might be country-specific and those that ought to be more general.

The cost-effectiveness ratio can be reformulated as:

\[
\frac{C}{E} = \frac{\text{treatment cost} - \text{offsetting cost}}{\text{effectiveness}} = \frac{m}{V} \left[ \frac{U}{PB} - R \right] xs
\]

Table 1 lists the variables used in this formula, their meanings, and baseline values.

### General parameters

To estimate \( P \), the proportion of transitions from health to cardiovascular disease prevented by pravastatin use, the WOSCOPS data were re-analysed. The type of event indicating the transition was considered by deriving the corresponding proportion that each represents of the
for five specific countries: United Kingdom, Canada, Sweden, Belgium and South Africa. The values were then compared to the results derived from country-specific models developed for the United Kingdom and Canada (personal communication, WOSCOPS Economic Analysis Committee, 10 November 1997). This was done to validate the generalized equation methodology. For the two validation countries, the annual cost of using 40 mg of pravastatin per day, \( m \), was based upon the tablet price and the cost of monitoring, and included a lipid profile and a visit to the general practitioner every 6 months. As there was no evidence in WOSCOPS of significant side-effects due to pravastatin, no costs for their management were included. Consistent with recent labelling changes, liver function tests were also not included.

For the United Kingdom, the cost of managing a myocardial infarction was derived by combining estimates of average cost taken from extra-contractual tariffs from a sample of over 200 Trusts and event-specific average lengths of stay calculated from WOSCOPS data (Table 2). For Canada, the cost was based on data obtained for the Ontario Case Cost Project[7], covering 13 hospitals. Neither costs of management subsequent to the initial hospitalization nor pre-admission costs were considered.

To aid comparisons across countries, all costs are presented in US dollars based on currency exchange rates published in the Wall Street Journal on 23 April 1997.

### Results

#### Validation

Validation of the generalized formula for the United Kingdom yields a cost-effectiveness ratio of $13 273 (£8297) per life years gained, which is the same as the published estimate based on the detailed model. The results for Canada are also quite accurate: $8876 per life years gained for the generalized formula compared to
$7669 per life years gained for the independent model. This concordance holds when assumptions, such as discounting, are varied.

**Sample countries**

To illustrate the method we used the formula to calculate the cost-effectiveness for Sweden, Belgium and South Africa. We obtained estimates for the costs of treatment and of managing a myocardial infarction (Table 2). Using the Swedish estimates an \( R \) ratio of 0·22 was derived and combined with the values in Table 1. We thus estimate a cost-effectiveness ratio of $8150 per life year gained for Sweden. For Belgium, the \( R \) ratio is 0·16. This yields a cost-effectiveness ratio of $14 773/life-year gained. In South Africa, the cost effectiveness ratio is $10 999/life year gained, based on an \( R \) ratio of 0·13.

**Sensitivity analysis**

The economic efficiency of preventing cardiovascular disease is according to baseline risk, \( B \). The costs of this treatment and the savings due to preventing events is shown in Fig. 1. Assuming that the factors that increase cardiovascular disease risk do not adversely affect \( V \), the cost-effectiveness ratios improve with higher cardiovascular disease risk. \( R \) has limited effect as can be seen by the width of the bands (0·01 to 0·4). Moreover, as treatment cost decreases, the impact of \( R \) lessens further. As expected, at any given risk, higher treatment costs imply less favourable cost-effectiveness ratios, but within the range examined in this analysis, the values remain below $25 000 per life years gained at a risk of cardiovascular disease as low as 9·5% over 5 years (undiscounted benefits). If the benefits are discounted, then a 5-year risk of at least 19·5% is required to stay below $25 000 per life years gained at the highest treatment and lowest event costs.

Apart from discounting, another factor that can have some impact on the results is the gain in life years ascribed to prevention of an event. This depends both on the expected survival without events and the post-event life expectancy. Both of these quantities are difficult to estimate precisely. Nevertheless, some idea can be obtained. For example, if Canadian instead of Scottish life tables are used, \( V \) increases by 0·81 to 4·74 (discounted), or by 2·46 to 10·13 (undiscounted); with corresponding cost-effectiveness ratios of $6768 per life years gained (undiscounted benefits) and $16 199 per life years gained (discounted). Thus, the change in values does not significantly alter the results. Indeed, when the \( V \) estimated by the Scottish data is increased by 25%, the range of resulting cost-effectiveness ratios is still only $6520 per life years gained to $10 850 per life years gained (undiscounted) or $14 350 per life years gained to $23 881 per life years gained (discounted). Decreasing \( V \) by 25%...
produces a range of $10,867 per life years gained to $18,084 per life years gained (undiscounted) or $23,917 per life years gained to $39,801 per life years gained (discounted).

Other factors and assumptions affect the results relatively little. Variation in the scaling factor, $s$, over the range observed in the selected countries has minimal impact. This together with the limited effect of $R$ indicates that the offsetting costs do not materially affect the economic efficiency. Although they were estimated very conservatively by considering only the first hospital admission, it seems that expansion to include additional elements within a reasonable range, would not alter the results in a decision relevant way.

**Discussion**

The generalized formula described in this paper provides a ready means for local adaptations of the WOSCOPS United Kingdom economic model. Based on the validation carried out, the results appear sufficiently accurate for health policy decision. Two major findings emerged from this study. First, the resulting cost-effectiveness ratios place this practice within bounds typically considered as 'moderate to strong evidence for adoption and appropriate utilization'[9]. Second, although the precise estimate does depend on the specifics of the country, it is notable that these variations do not have much of an impact on the treatment decision that this study supports.

One important issue in this analysis is the value placed on preventing one transition. As already noted, in order to quantify this transition in terms of life years gained, projections of its impact on cumulative survival were made beyond the end of the trial. This is fraught with difficulty due to the scarcity of information on the implications of cardiovascular disease for life expectancy[10]. Nevertheless, to properly inform decision makers these projections must be made and we have done so on the basis of extensive contemporary data. Not to do so, would imply the untenable assumption that cardiovascular disease that does not result in immediate death will not shorten life[11,12]. In any case, over a fairly broad range of $V$, the positive conclusions implied by the cost-effectiveness ratios remain consistent.

Other questions about the applicability of these results may arise. This analysis did not include the costs of detecting elevated cholesterol. It focused on patients whose condition has already come to the attention of the physician. Another concern may be that randomized trial results do not reflect clinical practice. The compliance observed in WOSCOPS, however, was obtained without extensive measures to ensure adherence to the prescribed regimen — an average clinical practice should be able to replicate them and organized programmes may even be able to exceed them. A third issue with applicability has to do with the nature of the WOSCOPS population. At its most strict interpretation, the results apply to middle-aged Scottish males. Most would extend these results to similar males in other locations. Extension to females or to broader definitions of the male population is more problematic, however, as the efficacy of pravastatin has not been documented for them. Nevertheless, so long as the hypercholesterolaemic baseline risk is within the range explained here, the economic efficiency should be similar.

The implications of this analysis using the generalized model are consistent over a broad range of factors that might be country-specific. This range covers health care systems similar to those prevailing in most industrialized nations. In countries where either the pravastatin intervention costs are much higher than those in the United Kingdom or the life expectancy is much worse, the conclusions might not hold. However, it would take an extremely unlikely treatment cost more than seven-fold higher to do so (exceed $100,000 per life years gained, discounted); or an equally implausible scenario of gaining only one year of life by preventing a transition. Needless to say, if very precise estimates of the cost-effectiveness ratio, or its components, are required for decision-making in a given country, then a detailed analysis specific to that country may be required. This would be the case if an aggregate analysis aimed at estimating the total cost of primary prevention, rather than just its economic efficiency, were to be carried out.

The impact of baseline risk on cost-effectiveness is somewhat unclear. While the number of events prevented increases as risk increases, the relation of $V$ to baseline risk remains uncertain. It is possible that the same factors that increase risk diminish $V$ when it is quantified in terms of life expectancy. In this situation, an increase in risk would also be associated with a reduced $V$, perhaps even cancelling each other out. In any case, such projections are unpredictable. A more in-depth analysis which considers this relation is necessary to provide guidance for policy that envisions restricting primary prevention according to risk.

In some countries, it may be felt that the implications of given risk factors for baseline risk would be different from those observed in Scotland. If this were the case, the risk equations derived in WOSCOPS may not be applicable but the relationship of economic efficiency to baseline risk would remain valid as long as the relative efficacy of pravastatin, $P$, were considered applicable. Thus, this model would still provide the cost-effectiveness ratio for any population identified by a given baseline risk.

Caution should be used when attempting to extrapolate the clinical benefits used within this analysis to other HMG-CoA reductase inhibitors, as no clinical trial has shown that these benefits would be similar for other statins. The analyses of the WOSCOPS data have produced risk equations that suggest that even when cholesterol lowering and other known determinants of disease are controlled for, pravastatin use still lowers the risk of clinical events further[13]. This additional effect
emphasizes the importance of basing analyses on direct measurement of outcomes as opposed to using proxies such as lipid values.

Health policy makers increasingly face the kind of decision posed by WOSCOPS—a proven highly effective means of primary prevention of cardiovascular disease, which is perceived to be a serious strain on constrained budgets. This analysis suggests that the cost-effectiveness of primary prevention with pravastatin should fit within bounds set by accepted therapies in most countries.

This work was supported by grants from Bristol–Myers Squibb.

References

Appendix

WOSCOPS Economic Analysis Committee
Jaime Caro, Ian Ford, Wendy Klittich, Alistair McGuire, John McMurray, John Norrie, Daniel Pettitt, James Shepherd

WOSCOPS Executive Committee