Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Use of pravastatin in addition to the usual lipid-lowering dietary advice in the prevention of cardiovascular disease.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Scottish men aged 45-64 years with hypercholesterolaemia (LDL cholesterol level higher than 4.5 mmol/l (174 mg/dl)), with no history of myocardial infarction.

Setting
Primary care. The economic study was carried out in the UK (Scotland).

Dates to which data relate
Effectiveness and resource use data were derived from the subjects recruited in the West of Scotland Coronary Prevention Study (WOSCOPS) between 1 February 1989 and 30 September 1991 and who were followed up until final visits made between February and May 1995. The price year was 1996.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Costing was prospectively performed on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were used to determine the sample size. The study was designed to recruit about 6,000 subjects based on several assumptions regarding the mean annual IHD mortality rate in the base population (4.6/1000) and in the study population (50% higher than the base population), the distribution of fatal and non-fatal events (twice as much) based on a combined rate of 20.7/1000, and the efficacy of the intervention in reducing CHD morbidity and mortality by 30%. A power of 99% was achieved for the combined end-point based on a two-sided alpha of 5%. The study sample consisted of 6,595 subjects (out of about 160,000 individuals invited and 81,161 who attended the first visit) randomly assigned to either the intervention group (n=3302) or a placebo group (n=3293) The intervention group had a
mean (SD) age of 55.3 (5.5) years and received pravastatin (40mg/day). The placebo group had a mean (SD) age of 55.1 (5.5) years.

**Study design**
The study was a double-blind, randomized, placebo controlled trial, carried out in three health board districts. The mean duration of the follow-up was 4.9 years. The cumulative rates of loss to follow up at the end of 5 year follow-up were 30.8% in the placebo group and 29.6% in the pravastatin group (NS). Permuted blocked randomisation was used to stratify patients in terms of centre and time of recruitment. Subjects were evaluated every three months by trial nurses and every year by the trial physicians.

**Analysis of effectiveness**
The principle used in the analysis of effectiveness was intention to treat. The primary endpoints over the five years of the study were the combined endpoint of CHD death plus non-fatal myocardial infarction, CHD death, and non-fatal myocardial infarction. The number of deaths from non-cardiovascular causes was also reported. Transition rates from health to cardiovascular disease were calculated for each of the following definitions:

Definition 1: death from CHD,

Definition 2: deaths from CHD or from cardiovascular causes, including fatal stroke;

Definition 3: death from CHD or from cardiovascular causes or definite MI (myocardial infarction);

Definition 4: death from CHD or from cardiovascular causes, definite MI, or silent (unrecognised) MI;

Definition 5: death from CHD or from cardiovascular causes, definite MI, silent MI, PTCA (percutaneous transluminal coronary angioplasty), or CABG (coronary artery bypass grafting);

Definition 6: death from CHD or from cardiovascular causes, definite MI, silent MI, PTCA, CABG, or angiography;

Definition 7: death from CHD or from cardiovascular causes, definite MI, silent MI, PTCA, CABG, angiography, or hospital admission for angina;

Definition 8: death from CHD or from cardiovascular causes, definite MI, silent MI, PTCA, CABG, angiography, hospital admission for angina, or non-fatal stroke;

Definition 9: death from CHD or from cardiovascular causes, definite MI, silent MI, PTCA, CABG, angiography, hospital admission for angina, non-fatal stroke, or TIA (transient ischaemic attack).

An exponential regression model was used to estimate the adjusted hazard rates in various subgroups according to various risk profiles for cardiovascular disease. The study groups were found to be well balanced in terms of baseline characteristics.

**Effectiveness results**
The use of the intervention drug was associated with a reduction of 31% (95% CI: 17% - 43%, p<0.001) in the combined endpoint of death from CHD or non-fatal MI (248 cases in the placebo group versus 174 in the intervention group). Relative risk reduction for nonfatal MI alone was 31% (15% - 45%, p<0.001; 204 cases in the placebo group versus 143 in the intervention) and for death from CHD alone was 28% (-10% - 52%, p=0.13; 52 cases and 38 cases). The number of deaths from non-cardiovascular causes was 62 in the placebo group versus 56 in the intervention group (p=0.54) with a risk reduction of 11% (-28% - 38%).

The transition rates for the cohort of patients receiving pravastatin in terms of hazards/1000 person years were as follows:
definition 1, 2.6;
definition 2, 3.1;
definition 3, 9.9;
definition 4, 14.5;
definition 5, 16.4;
definition 6, 17.8;
definition 7, 22.7;
definition 8, 24.7;
and definition 9, 26.4.

For the placebo group the values were as follows:
definition 1, 3.9;
definition 2, 4.6;
definition 3, 15.1;
definition 4, 20.2;
definition 5, 23;
definition 6, 24.3;
definition 7, 29.6;
definition 8, 31.5,
and definition 9, 33.9.

Clinical conclusions
Treatment with pravastatin significantly reduced the incidence of myocardial infarction and death from cardiovascular causes without adversely affecting the risk of death from non-cardiovascular causes in men with moderate hypercholesterolaemia and no history of myocardial infarction.

Modelling
The transition rates (hazards) over the five years of the trial and the proportion of transitions due to each type of event, plus the cost of transition, were estimated in the framework of an economic model.

Measure of benefits used in the economic analysis
The measures of benefits were life years gained and number needed to treat (NNT) to prevent transition. These were based on the difference between the age and sex specific cumulative curve for Scotland (data from a report published in 1994) and the event specific curves (from a study addressing the Scottish record linkage system on comparable cardiovascular events in Scotland between 1981 and 1994), with the simplifying assumption of risk factors for cardiovascular disease having no other effects on life expectancy.
Direct costs
Costs were discounted. Quantities were not reported separately from the costs. Cost components were reported separately. Cost analysis covered the costs of first hospital admission for each type of cardiovascular disease-related event such as non-fatal MI, silent MI, fatal MI, etc., the cost of pravastatin (40 mg), and monitoring (liver function test, lipid profile, and a visit to the general practitioner every six months). The perspective adopted in the cost analysis was that of the National Health Service (NHS). The main source of resource use data was the WOSCOPS study. The sources of cost data were extra-contractual tariffs from over 200 Trusts. 1996 price data were used. The cost analysis did not cover the costs of subsequent hospital admissions, preadmission management (such as ambulance), and patients' costs. The costs associated with adverse events of the intervention were not considered since the clinical trial (the WOSCOPS study) showed no evidence of substantial cases of adverse events of the study drug.

Indirect Costs
Not considered.

Currency
UK pounds sterling (£).

Sensitivity analysis
One-way sensitivity analyses were conducted on discount rate, the initial risk of cardiovascular disease, the price of the drug, the costs of monitoring, the costs of subsequent care, the efficacy of prevention, and the age of subjects. Multi-way sensitivity analysis was also performed using a Monte Carlo simulation.

Estimated benefits used in the economic analysis
The use of pravastatin (40 mg) was associated with an undiscounted gain of 2,460 years of life based on an estimation of 318 out of 10,000 men starting taking the drug not making the transition from health to cardiovascular disease (31.4 subjects would need to be treated to prevent one transition from health to sickness). Restricting the analysis to the 40% of subjects in the high-risk category decreased the number needed to treat to 22.5. The discount rate used for life years gained was 6%.

Cost results
Costs were discounted at 6%. The net discounted cost of the intervention over 5 years for a population of 10,000 men was 19,973,401.

Synthesis of costs and benefits
Cost per life year gained was calculated as the measure of cost-effectiveness, resulting in a value of 8,121 (when the benefit was undiscounted) and 20,375 (when the benefit was discounted). The corresponding values for the 40% of men in the high-risk category were 5,601 and 13,995. The sensitivity analyses established the relative robustness of the results, the price of the drug being the most sensitive parameter.

Authors' conclusions
In subjects without evidence of prior myocardial infarction but who have hypercholesterolaemia, the use of pravastatin yields substantial health benefits at a cost that is not prohibitive overall and can be quite efficient in selected high risk subgroups.

CRD COMMENTARY - Selection of comparators
The reason for the choice of the comparator is clear. You, as a user of this database, should determine the relevance of the assessed technology to your own setting.
Validity of estimate of measure of benefit
The internal validity of the estimate of benefit measure is likely to be high given that the data on effectiveness measures were derived from a study with randomized design plus intention to treat analysis. Lack of relevant data prevented the authors from conducting utility analysis (based on quality-adjusted life years gained), which might have better reflected the potential benefits of the intervention.

Validity of estimate of costs
Quantities were not reported separately from the costs. Adequate details of methods of cost estimation were given. The authors noted, however, that their cost estimates only included initial events while subsequent events such as stroke (7% of cases) can be costly. Productivity losses for these patients could be highly relevant but were not included in the cost analysis.

Other issues
The authors’ conclusions appear to be justified given the extensive sensitivity analyses performed and the use of a randomized design in the effectiveness analysis. The issue of generalisability to other settings or countries was addressed by performing an extra multi-way sensitivity analysis using the data from a Scandinavian study and by making appropriate narrative comparisons with other studies. It was reported that one recent paper estimating much higher cost failed to consider the adverse implications of cardiovascular disease that do not result in death within the trial, thus severely underestimating the life years gained from prevention. It was further reported that all other studies addressing primary prevention were based on projections of the effect of cholesterol lowering rather than on actual data from a clinical trial.

Note: The issue of generalisability was further addressed in a 1999 paper (see Other Publications section below) which aimed to generalise the WOSCOPS results to the perspective of any national health service or other organisation responsible for societal health care costs.

Implications of the study
Practitioners must now consider using pravastatin to prevent cardiovascular disease in men with hypercholesterolaemia.

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