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
The use of pravastatin (20 mg/day) for the primary prevention of coronary heart disease (CHD). A dose of 10 mg/day pravastatin was also considered for a different sub-group of patients.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of Japanese men and women aged 60 years with hypercholesterolaemia and no history of CHD. The initial TC level was 240 mg/dL. Patients were assumed to have already tried therapeutic lifestyle modifications for several months. In particular, the analysis targeted men aged 45 to 70 years and women aged 55 to 70 years. In terms of the initial TC level and the dosage of pravastatin, two scenarios were assumed. In one, the patients had an initial TC level of 240 mg/dL and received 20 mg/day pravastatin, while in the other patients had an initial TC level of 220 mg/dL and received 10 mg/day pravastatin. Eight sub-groups of patients were considered:

- persons who met the criteria for hypercholesterolaemia and age;
- smoking;
- hypertension;
- hyperglycaemia;
- smoking and hypertension;
- smoking and hyperglycaemia;
- hypertension and hyperglycaemia; and
- smoking, hypertension and hyperglycaemia.

Setting
The setting was primary care. The economic study was carried out in Japan.

Dates to which data relate
The effectiveness data were derived from studies published between 1987 and 2002. No dates for resource use were
explicitly reported. The price year was 2002.

**Source of effectiveness data**
The effectiveness evidence was derived from a synthesis of completed studies.

**Modelling**
A Markov model was constructed to assess the clinical and economic impact of pravastatin therapy in the hypothetical cohort of Japanese patients with hypercholesterolaemia. Annual cycles were considered, and the time horizon was lifetime. The following health states were considered:

- healthy;
- acute myocardial infarction (MI) treated by percutaneous transluminal coronary angioplasty or coronary artery bypass grafting (invasive treatment);
- acute MI treated conservatively (conservative treatment);
- chronic stage of MI;
- recurrent MI; and
- death.

Adverse events associated with pravastatin therapy were not considered because they were mild. Angina pectoris was also excluded because of the lack of data. A simplified version of the model was reported.

**Outcomes assessed in the review**
The outcomes estimated from the literature were:

- the incidence of MI;
- the proportion of patients with MI under invasive treatment;
- the case-fatality rate of MI;
- the recurrence rate of MI;
- the relative risk (RR) of MI associated with cardiac risk factors;
- pravastatin effect; and
- the utility values.

**Study designs and other criteria for inclusion in the review**
A review of the literature was undertaken to identify primary estimates. The inclusion and exclusion criteria for clinical studies were not reported. Most of the studies were based on an observational design. Epidemiological and clinical data came from Japanese sources. The utility values were obtained from studies that used the time trade-off approach.

**Sources searched to identify primary studies**
MEDLINE (from 1965 to March 2004), articles in Japanese, and government publications were searched. The authors stated that studies of familial hyperlipidaemia and secondary dyslipidaemia were excluded.
Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Nine studies provided data.

Methods of combining primary studies
A narrative approach appears to have been used to derive clinical data.

Investigation of differences between primary studies
Not stated.

Results of the review
The rate of incidence of MI (per 10,000 person-years) was 3.5 in men aged 40 - 49 years, 14 in men aged 50 - 59, 42 in men aged 60 - 69, and 68 in men aged 70 - 79. The corresponding values in women were 0.9 (age 40 - 49), 3.1 (age 50 - 59), 13 (age 60 - 69) and 35 (age 70 - 79), respectively.

The proportion of patients with MI under invasive treatment was 22% (range: 0 - 50).

The case-fatality rate of MI in the first year was 23% (range: 9 - 36).

The recurrence rate of MI during 2 to 5 years was 6.3% (range: 3.15 - 12.6).

The RR of MI was 1.0 with TC 200 mg/dL, 1.5 (range: 1 - 4) with TC 220 mg/dL, and 2.0 (range: 1.25 - 4) with TC 240 mg/dL.

Pravastatin 20 mg/day reduced the TC level from 240 to 200 mg/dL (a 17% reduction), while pravastatin 10 mg/day reduced the TC level from 220 to 200 mg/dL (a 10% reduction).

The utility values were 0.73 (range: 0.63 - 0.83) for acute stage of MI, 0.91 (range: 0.86 - 0.96) for chronic stage of MI, and 0.73 (range: 0.63 - 0.83) for recurrent MI.

The RR of MI associated with cardiac risks was also reported.

Measure of benefits used in the economic analysis
The summary benefit measure used was the expected number of quality-adjusted life-years (QALYs). This was estimated by combining data on survival and quality of life derived from the literature. Given the long time horizon of the analysis, an annual discount rate of 3% was applied.

Direct costs
The cost analysis appears to have been undertaken from the perspective of the social insurance system. Thus, only the direct medical costs associated with the treatment of hyperlipidaemia (pravastatin, physician visits, and monitoring lipid profiles), hospitalisations due to acute MI (invasive or conservative treatment), and treatment of the chronic phase of MI (pravastatin, evaluation of cardiac function, and other drugs needed for heart conditions) were considered. The unit costs were not reported separately from the quantities of resources used since most costs were presented as macro-
categories. The costs were estimated from medical charges based on social insurance medical fee payments. The source of the resource use data was not reported clearly for all items. The length of hospitalisation was derived from Japanese Diagnosis Related Group data. Discounting was relevant because the lifetime costs were considered, and an annual rate of 3% was applied. The price year was 2002, and costs taken from different sources were inflated to the year 2002 using the medical component of the Consumer Price Index.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
Japanese yen (Y).

**Sensitivity analysis**
Univariate sensitivity analyses were performed to assess the robustness of the base-case cost-utility ratios to variations in several inputs. For example, the incidence of MI, the proportion of patients with MI under invasive treatment, the case-fatality rate of MI, the recurrence rate of MI, and the RR of MI associated with cardiac risk factors. Also varied were the medical costs, utility and discount rate. The ranges of values were derived from the literature or were set by the authors. A second-order Monte Carlo simulation was also conducted to vary the transitional probabilities, costs and utilities simultaneously. The types of probabilistic distributions assigned to each variable in the model were reported (beta for probabilistic parameters and log-normal for unit costs and RR parameters).

**Estimated benefits used in the economic analysis**
In persons aged 60 years treated with pravastatin 20 mg/day (initial TC 240 mg/dL), the QALYs associated with no intervention were 10.363 among men and 11.734 among women. The QALYs associated with pravastatin were 10.413 (men) and 11.769 (women), respectively.

**Cost results**
In persons aged 60 years treated with pravastatin 20 mg/day (initial TC 240 mg/dL), the costs associated with no intervention were Y400,000 among men and Y215,000 among women. The costs associated with pravastatin were Y2,620,000 (men) and Y2,886,000 (women), respectively.

**Synthesis of costs and benefits**
Incremental cost-utility ratios were calculated to combine the costs and benefits of pravastatin over no intervention.

In persons aged 60 years treated with pravastatin 20 mg/day (initial TC 240 mg/dL), the incremental cost per QALY gained was Y44,000,000 for men and Y76,000,000 for women.

In the eight different groups of patients considered, the incremental cost per QALY gained ranged from Y2,400,000 to Y120,000,000, depending on cardiac risk. For example, for men with an initial TC level of 240 mg/dL, the incremental cost per QALY gained was less than Y10 million only in two cardiac risk groups: hypertension and hyperglycaemia; and cigarette smoking, hypertension and hyperglycaemia.

The cost per QALY was more favourable in middle-aged patients at high cardiac risk. It was more favourable in men than in women at low cardiac risk, and more favourable in women than in men at high cardiac risk.
Within the same risk group, the cost per QALY was generally lower in men at 60 years of age, and progressively lower with age in women.

The sensitivity analysis showed that none of the variations in model inputs led to substantial variations in the cost-utility ratios (never lower than 10,000,000 per QALY). The most influential parameters were the RR of MI and the cost for patients with hyperlipidaemia.

The probabilistic sensitivity analysis showed that in 90.7% of trials, pravastatin therapy was more costly at 5,000,000 per QALY gained.

**Authors’ conclusions**
The cost-effectiveness of pravastatin therapy for the primary prevention of hypercholesterolaemia varied considerably among patients with different cardiac risk factors. In general, the cost per quality-adjusted life-year (QALY) of preventive pravastatin therapy did not compare favourably with that of currently accepted therapeutic or diagnostic interventions implemented in Japan.

**CRD COMMENTARY - Selection of comparators**
The comparator (no intervention) appears to have been selected to reflect usual care in Japan. The use of other statins was not considered. You should decide whether this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from a review of the literature. Information on the methods and conduct of the review was limited. Most of the studies included in the review were based on an observational design, and it would appear that no clinical trials provided any data. This might limit the robustness of the primary estimates. However, extensive sensitivity analyses were performed to address the issue of uncertainty in some clinical data. A strength of the study lay in its use of sub-group analyses, the results of which were clearly reported.

**Validity of estimate of measure of benefit**
QALYs were the most appropriate benefit measure because they capture the impact of the intervention on quality of care and survival, which are the most relevant dimensions of care. Utility was derived from the literature, and the instrument used to assess the utility weights was reported. The use of QALYs permits comparisons with the benefits of other health care interventions. Discounting was applied, as economic evaluation guidelines recommend.

**Validity of estimate of costs**
The cost analysis was performed from the perspective of the social insurance system, although the authors stated that a societal perspective was adopted. It was noted that the inclusion of indirect costs was a matter of debate in the literature, thus they were not included. A breakdown of the cost items was not provided since the costs were mainly presented as macro-categories. Thus, information on the unit costs and quantities of resources used was not provided, which may limit the possibility of replicating the results of the analysis in other settings. The source of the data was reported and was consistent with the real perspective of the analysis. The price year was given, which will facilitate reflation exercises in other settings. The costs were treated deterministically in the base-case, but probabilistic distributions were given to each economic input in the stochastic sensitivity analysis.

**Other issues**
The authors stated that their cost-effectiveness estimates were, in general, higher than those reported in other studies. The main reason for such differences was likely to have been the use of different epidemiological data. The issue of the generalisability of the study results to other settings was not explicitly addressed, but the extensive sensitivity analyses enhance the external validity of the study. The authors noted that a potential limitation of the model was the fact that angina pectoris was not modelled as a possible health state. However, this decision was based on the lack of reliable
data assessing the impact of pravastatin on angina pectoris. Other benefits derived from the reduction of cholesterol levels, such as prevention of stroke, were not modelled.

**Implications of the study**
The study results suggested that pravastatin is not cost-effective in persons at low cardiac risk in Japan.

**Source of funding**
None stated.

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**Other publications of related interest**


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