Statins for primary prevention of stroke and heart disease (demonstrating QALYs for two example CVD risk groups)

Matrix Insight, in collaboration with Imperial College London, Kings College London and Bazian Ltd, were commissioned by Health England to undertake a research study to develop and apply a method for prioritising investments in preventative interventions for England. Seventeen preventative health interventions were included in the study. Each intervention was evaluated in terms of the following criteria: reach; inequality score; cost-effectiveness; and affordability. This report presents the results of the analysis for one of the interventions: statins for primary prevention of stroke and heart disease. The full report of the study is available from the ***H.E.L.P.*** website.

Summary

Description of the intervention
Statin therapy compared with no treatment for the prevention of stroke and coronary heart disease (CHD) in adults who have experienced, or who are at risk of, a coronary event. The results reported refer to statin therapy for lowering CHD annual risk from 1.5% to 1.0% and from 2.5% to 2.0% (Ward et al, 2007).

Criteria	Measure	Value	Certainty
1. Reach			
Percentage of population affected by the condition and that could potentially benefit from the intervention.	Individuals aged 45 to 84 years old with CHD risk of 1% to 2.5% per annum as a percentage of the population aged 15 and above in England (Ward et al, 2007)	6.25%	★★
2. Inequality score			
Ratio of the percentage of disadvantaged population to the percentage of the general population that could potentially benefit from the intervention.	Ratio of the prevalence of any CVD, IHD, or stroke in lowest quintile equivalised household income to the prevalence of any CVD, IHD, or stroke in the population (The Health and Social Care Information Centre, 2008).	1.076	★★
3. Cost-effectiveness			
Cost of the intervention per QALY gained (in £2007/08)	CHD risk of 1% to 1.5% per annum CHD risk of 2% to 2.5% per annum See cost-effectiveness	£21,844 £22,433	★★ ★★
Net cost of the intervention per QALY gained (in £2007/08)	CHD risk of 1% to 1.5% per annum CHD risk of 2% to 2.5% per annum See cost-effectiveness	£11,116 £7,339	★★ ★★
Timing of benefits	QALY gain and cost savings are estimated to occur in the long-run (5 years or more after the intervention).		
4. Affordability			
Total cost of implementing the intervention at the national level	Multiple of eligible individuals and weighted average unit cost of the intervention	Over £1 billion	★★

Key to certainty grading scales

★ Low quality evidence

★★ Medium quality evidence

★★★ High quality evidence

Box 1. Cost per QALY gained

A quality adjusted life year (QALY) is a simple way of combining quality of life with length of life.
One QALY is equivalent to one year in full health. The cost per QALY gained is therefore the cost of achieving one extra year of full health. Its calculation is based on the following formula:

$$cost\ per\ QALY\ gained = \frac{incremental\ cost\ of\ intervention}{QALYs\ gained}$$

The net cost per QALY gained is the cost per QALY considering the incremental cost of the intervention as well as the cost saved through health treatment avoided. Its calculation is based on the following formula:

$$net\ cost\ per\ QALY\ gained = \frac{incremental\ cost\ of\ intervention - cost\ savings}{QALYs\ gained}$$

Cost effectiveness

Cost. Statin therapy costs on average (£2007/08):

- £5,262 more than no treatment for males and females at CHD risk of 1.0% to 1.5% per annum
- £4,752 more than no treatment for males and females at CHD risk of 2.0% to 2.5% per annum

Effect. The effects of statins on the relative risks of stroke and CHD outcomes are reported in the effectiveness evidence section. These effects were obtained from a review undertaken to identify evidence on the effectiveness and cost-effectiveness of statins for primary prevention of stroke and heart disease.

Benefits. The benefits of the intervention derive from reduced probabilities of experiencing stroke and CHD. Compared to no treatment, statin therapy is associated with the following benefits:

For males and females at CHD risk of 1.0% to 1.5% per annum:

- An additional 0.24 QALYs on average
- Cost savings of £2,584 per person (£2007/08)

For males and females at CHD risk of 2.0% to 2.5% per annum.

- An additional 0.21 QALYs on average
- Cost savings of £3,198 per person (£2007/08)

Please refer to decision model for details on how the costs, QALY gain and health care cost saving estimates were calculated.

Decision model

The cost of statin therapy was estimated based on the following parameters drawn from the literature.

- The annual cost of treatment (Table 1).
- The duration of treatment (Table 1).

Table 1. Intervention costs and effects (monetary values in £2007/08)

Description	Value	Calculation and source
Annual cost of intervention	£482 (first year) £383 (subsequent years)	These include a weighted average cost of statins plus monitoring costs - that is, the costs associated with liver function tests, cholesterol tests and creatinine kinase tests (Ward et al, 2007).
Duration of treatment	17.7 years (1.0% to 1.5% CHD risk per annum) 15.4 years (2.0% to 2.5% CHD risk per annum)	These were calculated based on the weighted average age of individuals with the corresponding CHD risks per annum (Ward et al, 2007) and their mortality age (Matrix 2006 based on national statistics).

The cost-effectiveness estimates as well as the benefits of the intervention in terms of QALYs gained were drawn from an economic model built by Ward et al (2007). The model is based on the following parameters:

- **The cost of statin therapy**. The cost of each statin was weighted by the dose and number of people included in the trials. Expert opinion was also used to provide information on monitoring costs (that is, the costs associated with liver function tests, cholesterol tests and creatinine kinase tests).
- **The effect of the intervention on the chances of adults' experiences of stroke and CHD**. Data from UK epidemiological studies were used to estimate event rates. The model was run separately for specified risk levels, age groups and gender. The effect of statins on the reduction of events was based on relative risks of stroke and CHD outcomes estimated by a Bayesian meta-analysis of randomised controlled studies.
- **The benefits associated of statin therapy in terms of quality of life**. Health-related utility estimates included in the economic model were derived from published and unpublished studies. Health-related utilities were assumed to vary by age based on data from a large UK population-based survey using the EQ-5D questionnaire. Disutility associated with statin treatment was not included in the model.
- **The benefits associated of statin therapy in terms of health care cost savings**. The costs associated with treating stroke and CHD events were taken from published UK sources, supplemented by expert opinion where data from published sources were unavailable.

Given that the health care cost savings associated with statin therapy were not reported separately in Ward et al (2007), these were calculated by applying the net cost per QALY gained formula described in Box 1.

Unless stated otherwise, the analysis was undertaken in accordance with H.M. Treasury's Green Book (HM Treasury, 2003). Specifically:

- Any costs and effects incurred more than one year after the intervention were discounted at 3.5%.
- Where necessary monetary values were converted in 2007/8 prices using Gross Domestic Product (GDP) deflators (HM Treasury, 2008).

Effectiveness evidence

A literature review was undertaken by Bazian to identify evidence on the effectiveness and cost-effectiveness of statins for primary prevention of stroke and heart disease. Further details are available on the evidence methods page of the ***H.E.L.P.*** website.

The review of the evidence on the effectiveness of statins for primary prevention of stroke and heart disease identified one systematic review and two randomised controlled studies. Table 2 provides the following details of the studies identified:

- Population
- Intervention
- Results

The review of the evidence on the cost-effectiveness of statins for primary prevention of stroke and heart disease identified one cost-effectiveness study, one cost-utility study and two economic models. Table 3 provides the following details of the studies identified:

- Population, intervention and model
- Perspective, discounting, inflation, cost year
- Utility/benefit
- Unit costs
- Efficiency

Table 4, Table 5 and Table 6 provide a quality assessment of the studies. Further details are available on the quality appraisal methods page.

The following criteria were applied to select effectiveness evidence for undertaking the economic analysis:

- Location. Studies from the UK were preferred over studies from other locations.
- Population. Studies applied to the general population were preferred over studies applied to restricted population groups (e.g. pregnant women; individuals from specific communities/nationalities).
- Counterfactual. Studies for which the counterfactual intervention was ‘usual care’ or ‘do nothing’ in a UK setting were preferred over studies for which the counterfactual was different from ‘usual care’ or ‘do nothing’.
- Method. Studies using more rigorous design methods (e.g. randomised controlled trials or quasi experimental designs with regression models controlling for confounders) were preferred over studies using less rigorous design methods (e.g. before-after studies or simple correlation analysis).

Table 2. Effectiveness of statins for primary prevention of stroke and heart disease

Study reference	Population	Intervention	Results
Ward et al, 2007; international populations ▪ systematic review	Adults with or at risk of CVD: 28 RCTs were identified.	*Intervention* ▪ Statin therapy Control ▪ Placebo	RR of fatal event (primary and secondary prevention of CHD or CVD event): ▪ All-cause mortality 0.84 (0.78 to 0.90) ▪ Cardiovascular mortality 0.79 (0.74 to 0.85) ▪ CHD mortality 0.77 (0.72 to 0.83) ▪ Fatal MI 0.55 (0.44 to 0.67) ▪ Stroke mortality 0.92 (0.74 to 1.14 (ns)) RR of non-fatal events (primary and secondary prevention of CHD or CVD event): ▪ Non-fatal stroke 0.75 (0.63 to 0.90) ▪ TIA 0.79 (0.68 to 0.91) ▪ Non-fatal MI 0.70 (0.63 to 0.77) ▪ Unstable angina 0.82 (0.74 to 0.90) ▪ Hospitalisations for unstable angina 0.88 (0.84 to 0.94) ▪ Risk of requiring CABG or PTCA 0.75 (0.70 to 0.81) RR of fatal event (secondary prevention of CVD events): ▪ All-cause mortality 0.80 (0.71 to 0.89) ▪ CVD mortality 0.75 (0.68 to 0.83) ▪ CHD mortality 0.72 (0.64 to 0.80) ▪ Fatal MI 0.57 (0.45 to 0.72) ▪ Stroke mortality 1.07 (0.67 to 1.71 (ns)) RR of non-fatal event (secondary prevention of CVD events): ▪ Non-fatal MI 0.69 (0.59 to 0.79) ▪ Unstable angina 0.82 (0.72 to 0.94) ▪ Hospitalisation for unstable angina 0.90 (0.84 to 0.97) ▪ Non-fatal stroke 0.75 (0.59 to 0.95) ▪ New or worsening intermittent claudication 0.58 (0.42 to 0.80)

Study reference	Population	Intervention	Results
			▪ CABG or PTCA 0.77 (0.69 to 0.85) ▪ TIA 0.66 (0.37 to 1.17 (ns)) RR of fatal event (primary prevention of CVD): ▪ All-cause mortality 0.73 (0.53 to 1.01) ▪ CVD mortality 0.67 (0.40 to 1.10) ▪ CHD mortality 0.86 (0.49 to 1.52) ▪ Fatal MI 0.60 (0.12 to 3.04) ▪ Stroke mortality 0.20 (0.02 to 1.69) RR of non-fatal event (primary prevention of CVD): ▪ Non-fatal MI 0.60 (0.37 to 0.97) ▪ Unstable angina 0.77 (0.29 to 2.06) ▪ Non-fatal stroke 0.66 (0.38 to 1.15) ▪ CABG and PTCA 0.72 (0.49 to 1.21)
Shepherd et al, 1995 [WOSCOPS study]; ▪ randomised controlled trial	6,595 men aged 45 to 64 years, mean plasma cholesterol 272+/-23mg/decilitre. Medical records, electrocardiographic recordings and the national death registry were used to determine the clinical end points; average follow-up was 4.9 years.	*Intervention* ▪ Pravastatin therapy *Control* ▪ Pravastatin therapy vs. placebo	Risk reduction with pravastatin: ▪ Non-fatal MI or death from CHD: 31% (95% CI 17 to 43) ▪ Nonfatal MI: 31% (15 to 45) ▪ Death from CHD: 28% (-10 to 52) ▪ Coronary angiography: 31% (10 to 47) ▪ PTCA or CABG: 37% (11 to 56) ▪ Fatal or nonfatal stroke: 11% (-33 to 40) ▪ Death from all cardiovascular causes: 32% (3 to 53) ▪ Death from any cause: 22% (0 to 40) ▪ Death from non-cardiovascular cause: 11% (-28 to 38)
Scandinavian Simvastatin Survival Study Group (4S trial) ▪ randomised controlled trial	4,444 patients with angina pectoris or previous MI. Serum cholesterol 5.5 to 8.0 mmol/L and receiving a lipid lowering diet. Median follow-up was 5.4 years.	*Intervention* ▪ Simvastatin therapy *Control* ▪ Pravastatin therapy vs. placebo	▪ RR of death with treatment: 0.70 (95% CI 0.58 to 0.85) ▪ RR of coronary deaths with treatment: 0.58 (95% CI 0.46 to 0.73) ▪ RR of coronary events: 0.66 (95% CI 0.59 to 0.75)

Table 3. Cost-effectiveness of statins for primary prevention of stroke and heart disease

Study reference	Population, intervention and model	Perspective, discounting, inflation, cost year	Utility/benefit	Unit costs	Efficiency
Ebrahim, 1999; international populations ▪ life table model using effectiveness from a meta-analysis ▪ costs were converted to GBP2004 by Ward et al (2007)	▪ Statin (simvastatin or pravastatin) in primary and secondary prevention vs. placebo ▪ Primary and secondary prevention populations	▪ Health sector perspective ▪ Adjusted for inflation ▪ Discounted at 6% ▪ Cost year: GBP2004	NS	NS	▪ Central estimate cost/LYG at 2004 prices £5,291 (6% CHD risk) to £14,610 (0.5% CHD risk)
Pickin, 1999; international populations ▪ cost-effectiveness analysis using effectiveness results from WOSCOPS and 4S studies above	Statin (simvastatin and pravastatin combined) in men primary prevention [based on WOSCOPS RCT vs. placebo].	▪ Health sector perspective ▪ Adjusted for inflation ▪ Discounted at 6% ▪ Cost year: GBP2004	Costs avoided: ▪ CABG £5725 ▪ PTCA £2436 ▪ Admission for MI £2306 ▪ Admission for stroke £8823	Annual Statin cost: pravastatin £555 and simvastatin £811	Central estimate at 2004 prices with pravastatin in primary prevention £8154 (4.5% CHD Risk) to £20,053 (1.5% CHD risk)
NICE, 2007	Identifying people at high risk of developing CVD for statin and other therapies - four strategies tested: prior CVD, random identification, identification by age, identification those over 50 years then those over 40years (only prior CVD reported here).	▪ Health sector perspective ▪ Unclear whether adjusted for inflation ▪ Discounted at 4% ▪ Cost year: GBP2006/2007	NS	Unit costs healthcare: ▪ Practice nurse time costs £32 per hour of patient contact ▪ GP time £118 per hour of patient contact ▪ Biochemistry/lipid profile costs are taken £3.56 ▪ Base model assumed	▪ QALY gained from screening 10% of population using prior CVD compared to no screening 34.01 ▪ QALY gained from screening 30% of population using prior CVD compared

Study reference	Population, intervention and model	Perspective, discounting, inflation, cost year	Utility/benefit	Unit costs	Efficiency
	Markov model, estimated that 652 individuals will be diagnosed as clinically eligible for treatment if all 4,262 patients were assessed.			the cost of simvastatin 40mg (£18.12) Total costs: ▪ Cost of screening 10% of population using prior CVD compared to no screening £71,719 ▪ Cost of screening 30% of population using prior CVD compared to 20% £383,083 Lifetime costs (savings) by age in risk band 15-20% ▪ 34-44 yrs = -£616 ▪ 45-44 yrs = -£616 ▪ 55-64 yrs = -£404 ▪ 65-74 yrs = -£246 ▪ over 75 yrs = -£78	to 20% 51.66 ▪ £2109 per QALY screening 10% of population using prior CVD compared to no screening ▪ £37,644 per QALY screening 30% using prior CVD data compared to screening 20%
Ward et al, 2007; modelled on UK population ▪ cost-utility analysis	Atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin for the prevention of cardivascular events (all statins combined as a group in the ScHARR model) vs. treatment (lifestyle advice assumed).	▪ Health sector perspective ▪ Adjusted for inflation ▪ Discounted at 6% and 1.5% ▪ Cost year: GBP2004	Utilities: ▪ Stable angina 0.808 (with diabetes 0.724) ▪ Unstable angina 0.770 (with diabetes 0.690) ▪ 1st year MI 0.760	▪ £57 for 15 minutes GP contact plus other medication cost (excluding statin) ▪ £440 stable angina costs first year ▪ £4448 MI care in first year	▪ Men 3% CHD risk £20,000 ▪ Men 0.5% CHD risk £28,000 ▪ Women 3% CHD risk £21,000 ▪ Women 0.5% CHD risk £57,000

Study reference	Population, intervention and model	Perspective, discounting, inflation, cost year	Utility/benefit	Unit costs	Efficiency
	Markov with eight first event health states and transition probabilities: UK population without known CHD modelled (1,000 people modelled). Different baseline CHD risks modelled: average weighted by risk of CHD outcomes presented here.		(with diabetes 0.681) ▪ Post-MI 0.760 (with diabetes 0.681) ▪ TIA 1.000 (with diabetes 1.000) ▪ 1st stroke year 0.629 (with diabetes 0.526) ▪ Post 1st stroke 0.629 (with diabetes 0.526)	▪ £1166 fatal MI ▪ £1064 TIA care first year ▪ £264 TIA subsequent years ▪ £8046 stroke care first year ▪ £2163 stroke subsequent years ▪ £7041 fatal stroke ▪ Statins (combined) average £316.80 per annum ▪ Annual cost of statins weighted by prescribing is £273 (not used) ▪ Monitoring costs are £124 for the first year [(7*£10.63)+(4*£12)+ £1.59] and £33.42 [(2*£10.63)+£12+(0.1* £1.59)] for subsequent years ▪ Adverse event rates small and not modelled	

Table 4. Quality assessment for meta-analysis

Study reference	QA for meta-analysis			Score	Grading (++ 3; + 2; -1)
	Search and inclusion criteria?	Quant data each study?	Assessment of quality data?		
Ward et al, 2007; international populations	Yes	Yes	Yes	3	++

Table 5. Quality assessment for effectiveness studies

Study reference	QA for trials/RCTs					Score	Grading (++ 4-5; + 3; -0-2)
	Follow-up	Intention to treat?	Attrition	Groups similar or controlled?	Randomised?		
Shepherd et al, 1995 (WOSCOPS)	Yes	Yes	Yes	Yes	Yes	5	++
4S (Scandinavian Simvastatin Survival Study Group)52	Yes	Yes	Yes	Yes	Yes	5	++

Table 6. Quality assessment for economic studies

Study reference	QA for economic studies						Score	Grading (++ 4-6; + 3; -0-2)
	All costs of intervention included?	Market values used for costs?	Perspective reported?	Sensitivity analysis?	Reports base year adopted?	Effectiveness data from RCT or MA?		
Ebrahim, 1999	Yes	Yes	Yes	Yes	Yes	Yes	6	++
Pickin, 1999	Yes	Yes	Yes	Yes	Yes	Yes	6	++
NICE, 2007	Yes	Yes	Yes	Yes	Yes	Yes	6	++
Ward et al, 2007	Yes	Yes	Yes	Yes	Yes	Yes	6	++

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