

tools in clinical medicine, and doctors in training need to become proficient in their use.

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- Greenwald R. And a diagnostic test was performed. *N Engl J Med* 2005;359:2089-90.
- Chaudhry MA, Hajarnavis J. Paget-von Schrötter syndrome: primary subclavian-axillary vein thrombosis in sport activities. *Clin J Sport Med* 2003;13:269-71.
- Scott C. Diagnosing childhood conditions: have you considered...? *Medical Protection Society Casebook* 2005;13:22-5.

- Hoffer EP. Clinical problem solving: identifying Addison's disease. *N Engl J Med* 1996;334:1403-5.
- Kejjo DJ, Squires RH. Clinical problem-solving: just in time. *N Engl J Med* 1996;334:46-8.
- Wikipedia. Free encyclopedia. [http://en.wikipedia.org/wiki/Main\\_Page](http://en.wikipedia.org/wiki/Main_Page) (accessed 27 Jun 2006).
- Pauker SG, Gorro GA, Kassirer JP, Schwartz WB. Towards the simulation of clinical cognition taking a present illness by computer. *Am J Med* 1976;60:981-96.
- Giustini D. How Google is changing medicine. *BMJ* 2005;331:1487-8.
- Vise D, Malseed M. *The Google story*. New York: Delacorte Press, 2005.
- Steinbrook R. Searching for the right search—reaching the medical literature. *N Engl J Med* 2006;354:4-7.
- Oxford advanced learner's dictionary of current English*. 7th ed. New York: Oxford University Press, 2005.
- Powell J, Clarke A. The www of the world wide web: who, what, and why? *J Med Internet Res* 2002;4(1):e4.

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## Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from randomised trial of 20 536 people

Heart Protection Study Collaborative Group

### Abstract

**Objectives** To evaluate the cost effectiveness of 40 mg simvastatin daily continued for life in people of different ages with differing risks of vascular disease.

**Design** A model developed from a randomised trial was used to estimate lifetime risks of vascular events and costs of treatment and hospital admissions in the United Kingdom.

**Setting** 69 hospitals in the UK.

**Participants** 20 536 men and women (aged 40-80) with coronary disease, other occlusive arterial disease, or diabetes.

**Interventions** 40 mg simvastatin daily versus placebo for an average of 5 years.

**Main outcome measures** Cost effectiveness of 40 mg simvastatin daily expressed as additional cost per life year gained. Major vascular event defined as non-fatal myocardial infarction or death from coronary disease, any stroke, or revascularisation procedure. Results were extrapolated to younger and older age groups at lower risk of vascular disease than were studied directly, as well as to lifetime treatment.

**Results** At the April 2005 UK price of £4.87 (€7; \$9) per 28 day pack of generic 40 mg simvastatin, lifetime treatment was cost saving in most age groups and vascular disease risk groups studied directly. Gains in life expectancy and cost savings decreased with increasing age and with decreasing risk of vascular disease. People aged 40-49 with 5 year risks of major vascular events of 42% and 12% at start of treatment gained 2.49 and 1.67 life years, respectively. Treatment with statins remained cost saving or cost less than £2500 per life year gained in people as young as 35 years or as old as 85 with 5 year risks of a major vascular event as low as 5% at the start of treatment.

**Conclusions** Treatment with statins is cost effective in a wider population than is routinely treated at present.

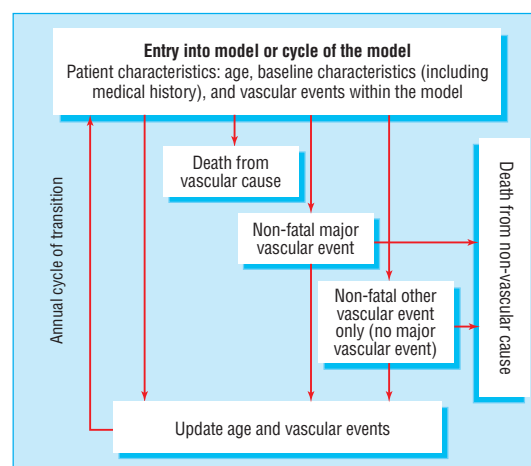


Fig 1 Schematic of the state transition model

### Introduction

Large randomised trials have shown that lowering blood concentrations of low density lipoprotein cholesterol with statins greatly reduces rates of heart attacks, strokes, and revascularisation procedures in a wide range of people at high risk, largely irrespective of their cholesterol concentrations and other characteristics at presentation.<sup>1</sup> The heart protection study has shown that, especially when cheaper generic versions are used, 40 mg simvastatin daily is cost effective for a wider range of people with vascular disease or diabetes than previously thought.<sup>2</sup>



A table, a technical appendix, and details of collaborators, participating hospitals, and committees are on [bmj.com](http://bmj.com)



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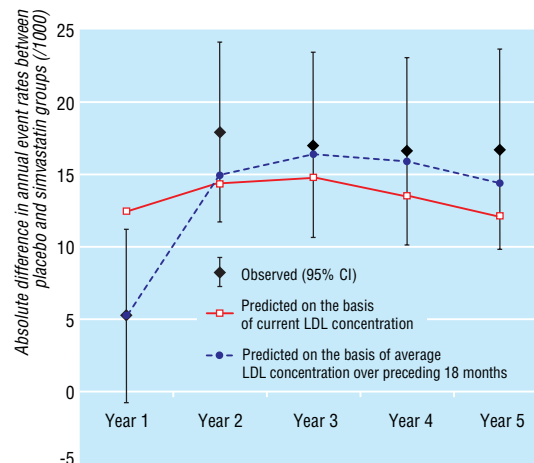
The present report extends this previous work in two ways. Firstly, a model was developed and validated that allowed extrapolation beyond the five year treatment period in the heart protection study and estimation of lifetime cost per life year gained and per quality adjusted life year gained; this facilitates comparison with other potential uses of healthcare resources. Secondly, these estimates were projected beyond the levels of risk of vascular disease and age represented in the study to provide guidance on the cost effectiveness of statins in a wider spectrum of people.

### Methods

We used data from the 20 536 participants in the heart protection study to develop a Markov disease state transition model. Participants were men and women who presented at 40-80 years with total cholesterol concentrations of at least 3.5 mmol/l (135 mg/dl) and a medical history of coronary disease, cerebrovascular disease, other occlusive arterial disease, diabetes mellitus, or (if a man aged  $\geq 65$ ) treated hypertension.<sup>3</sup> Figure 1 is a schematic representation of the model, which is based around the prediction of four key events. See [bmj.com](http://bmj.com) for details of model.

We used the model to predict the annual occurrence of death due to vascular or non-vascular causes, of non-fatal major vascular event, or of other vascular event, and the annual costs of hospital admissions for such events in people taking or not taking 40 mg simvastatin daily. Annual costs of hospital admissions (2001 UK prices) were estimated from data on hospital admissions in the heart protection study<sup>2</sup> on the basis of age, sex, disease history, other baseline characteristics, and vascular events or death within the study. Treatment affected the risk of an event occurring, but we found no evidence that it affected costs of hospital admissions once the event had occurred. Annual rates of vascular events predicted by the model were internally validated against the rates seen during the five year follow-up in the heart protection study. The model was then used to project events and costs beyond the five year scheduled treatment period and to estimate lifetime cost effectiveness of 40 mg simvastatin daily versus no statin treatment in people of different ages and with different underlying risks of vascular events. In the main analysis, we used the UK tariff price of £4.87 (€7; \$9) at which pharmacies were reimbursed for 28 days' treatment in April 2005. Future life years and costs were discounted at an annual rate of 3.5%.

Participants were divided into five similar sized groups of estimated five year risk of a major vascular event, with average risks in the groups ranging from 12% to 42% (which correspond to risks of 4% to 12% for non-fatal myocardial infarction or coronary death). These risk groups were subdivided by age at entry to the study to allow for the opposing effects of age on disease risk and life expectancy. Parameter uncertainty in the estimates of life years gained, cost savings in hospital stay, and cost per life year gained was assessed by non-parametric bootstrapping. We also examined several other scenarios. Firstly, predicted life expectancy was adjusted for age specific and sex specific health related quality of life derived from a representative sample of the UK population; secondly, it was related



**Fig 2** Observed (95% confidence interval) and predicted difference in annual rates of major vascular events or deaths from vascular causes between groups allocated to placebo and simvastatin in the heart protection study. LDL=low density lipoprotein

to only five years' use of generic simvastatin; and thirdly, it was related to lifetime use of proprietary simvastatin (2005 UK price of £29.69 for 28 days). Finally, the model was extrapolated to older and younger age groups and to people at lower risk of vascular disease than those included in the heart protection study. For additional details of the methods and model validation see [bmj.com](http://bmj.com).

### Results

#### Internal validation of the Markov state transition model

Annual rates of death from vascular disease, of major vascular events, and of all vascular events estimated from the state transition model (fig 1) were similar to those seen during the heart protection study, as were the differences in rates (see [bmj.com](http://bmj.com)). Figure 2 shows the similarity between predicted and observed differences in the annual rates of first and subsequent non-fatal major vascular events or deaths from vascular disease during the five year treatment period (especially when the average low density lipoprotein cholesterol difference during the preceding 18 months was used in the model).

#### Cost effectiveness of simvastatin for the study population

We used the model to estimate the life expectancy and costs associated with lifetime treatment with 40 mg simvastatin daily. On the basis of full compliance, relative reductions in the risk of death from vascular disease by 25%, of a non-fatal major vascular event or vascular death by 32%, and of any vascular event by 24% were derived from the risk equations. The undiscounted estimated gains in life expectancy for the participants ranged between 0.64 years for people aged over 70 with a 12% five year risk of a major vascular event and 2.49 years for those aged 40-49 with a 42% five year risk. Generic 40 mg simvastatin daily was cost saving for most of the risk and age categories in the heart protection study; that is, the reduced costs of hospital admissions as a result of fewer vascular events

**Table 1** Cost (£) per life year gained (unless stated otherwise) for various scenarios of full compliance with 40 mg simvastatin daily for the population of the heart protection study

Treatment	Five year risk of major vascular event at start of treatment				
	12%	18%	22%	28%	42%
<b>Lifetime use of generic simvastatin*</b>					
Age at start (years):					
40-49	-580	-1140	-1280	-1310	-1270
50-59	-500	-830	-890	-990	-930
60-69	-200	-480	-530	-580	-530
≥70	110	-100	-220	-250	-190
<b>5 year use of generic simvastatin</b>					
Age at start (years):					
40-49	-1230	-1890	-2030	-2050	-1930
50-59	-1010	-1330	-1380	-1470	-1350
60-69	-600	-840	-870	-900	-800
≥70	-240	-410	-500	-520	-410
<b>Lifetime use of proprietary simvastatin</b>					
Age at start (years):					
40-49	9260	6010	4710	3620	2610
50-59	8720	6170	4900	3870	2860
60-69	8470	6430	5230	4190	3040
≥70	8910	6910	5740	4610	3340

\*Values are adjusted for age specific and sex specific health related quality of life. Negative values indicate cost savings. £1=€1.5=\$1.9.

All discounted at 3.5% per annum; 28 day pack of generic simvastatin at £4.87 and proprietary simvastatin at £29.69.

outweighed the increased costs of statin treatment in all but one category (£80 per life year gained for people aged ≥70 at the start with a 12% five year risk). The upper limits of the 95% confidence intervals for all risk and age groups were below £1000 per life year gained (see bmj.com).

Quality of life adjusted estimates for lifetime use of generic 40 mg simvastatin daily were similar to the unadjusted estimates. Estimated costs per life year gained with only five years' use of generic 40 mg simvastatin daily were also similar to those for lifetime treatment, with both costs and benefits reduced proportionally (table 1). Cost effectiveness estimates were favourable even with proprietary 40 mg simvastatin at £29.69 per 28 day pack.

### Cost effectiveness of simvastatin beyond the study population

Extrapolations indicate that lifetime use of generic 40 mg simvastatin daily is cost effective for people below and above the age range included in the heart protection study with five year risk of a major vascular event as low as 5%. The estimated costs per life year gained ranged from about £450 to £2500 for people with a 5% five year risk of a major vascular event aged between 35 and 85 at the start of treatment. Adjusting for quality of life did not affect these conclusions; the cost per quality adjusted life year gained was either cost saving or less than £4000 across the extended age groups and risk categories for vascular events considered (table 2).

**Table 2** Cost effectiveness of full compliance with lifetime use of generic 40 mg simvastatin daily projected beyond the population of the heart protection study

Cost (£) per life year gained	Five year risk of major vascular event at start of treatment			
	5%	10%	20%	40%
Age at start (years):				
35	450*	-360*	-1070*	-1610*
45	330*	-360	-940	-1240
55	400*	-210	-680	-830
65	660*	50	-380	-450
75	1180*	450	-40	-110
85	2460*	1280*	490*	310*
<b>Cost (£) per quality adjusted† life year gained</b>				
Age at start (years):				
35	580*	-460*	-1370*	-2060*
45	430*	-480	-1210	-1600
55	550*	-280	-900	-1070
65	930*	70	-510	-590
75	1740*	650	-50	-140
85	3740*	1870*	690*	420*

\*Categories of patient not generally represented in the heart protection study.

†Adjusted for age specific and sex specific health related quality of life.

Negative figures indicate cost savings. £1=€1.5=\$1.9.

Discounted at 3.5% per annum; generic simvastatin at £4.87 per 28 day pack.

### What is already known on this topic

Statins reduce major vascular events, largely independent of a person's cholesterol concentrations at presentation

Overall risk of vascular disease events (not single risk factors) determines the absolute benefits of statin therapy

### What this study adds

Statins are cost effective well beyond the treatment thresholds proposed in current UK clinical guidelines

## Discussion

The present analyses indicate that, at current generic prices, the initiation of lifetime treatment with simvastatin is cost saving or very cost effective for people aged 35-85 with risks of major vascular events as low as 1% per annum (that is, about half the risk threshold proposed by the National Institute for Health and Clinical Excellence; NICE).<sup>4</sup> The estimated costs per life year gained in all these people were lower than those generally considered by NICE to be a cost effective use of health service resources.

The heart protection study did not collect data on the quality of life of participants. But, after adjusting for age specific and sex specific health related quality of life derived from the UK population, the estimated costs per quality adjusted life year from lifelong treatment with generic simvastatin remained highly favourable across the extended age and risk groups considered. Sensitivity analyses also indicated that lifetime and five year treatment with generic simvastatin would be similarly cost effective for the populations studied. Lifelong use in these groups even seemed to be cost effective at the much higher UK proprietary price. Although hospital outpatient costs or primary care costs were not measured, including such costs would be unlikely to alter the main conclusions given their comparatively low level.<sup>5</sup> Muscle symptoms were systematically sought in the heart protection study; compared with placebo, allocation to 40 mg simvastatin daily was not associated with significantly more reports of muscle symptoms or more cases of myopathy or rhabdomyolysis.<sup>3</sup>

The lifetime extrapolation was based on a model developed by using individual participant data from the five year treatment period of the heart protection study. The vascular event rates predicted by the model were comparable to the rates seen during the within-study period. Similar reductions in relative risk with statin therapy were modelled over time, including beyond the study treatment period, because currently available evidence shows that the relative effects are similar in different age groups and during each successive year of treatment, without evidence that the benefits are lost when treatment stops.<sup>1 6</sup>

## Conclusion

At current UK prices for generic simvastatin, 40 mg simvastatin daily is likely to be cost saving, or would

cost less than £2500 per life year gained, for people with an annual risk of major vascular events of 1% or more, independently of their age at the start of treatment. Hence, statin therapy should be considered routinely for people across a wider age range and at lower risk of vascular disease than is currently the case.

Most importantly we acknowledge the participants in the heart protection study, as well as the doctors, nurses, and other staff in hospitals and general practices throughout the UK who assisted with its conduct (see [bmj.com](http://bmj.com) for details).

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Ethical approval: Local ethics committee approval for each of the 69 participating hospitals.

- 1 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78.
- 2 Heart Protection Study Collaborative Group. Cost-effectiveness of simvastatin in people at different levels of vascular disease risk: economic analysis of a randomised trial in 20 536 individuals. *Lancet* 2005;365:1779-85.
- 3 Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
- 4 National Institute for Health and Clinical Excellence. *Statins for the prevention of cardiovascular events*. Technology appraisal 94. London: NICE, 2006. [www.nice.org.uk/page.aspx?o=TA094guidance](http://www.nice.org.uk/page.aspx?o=TA094guidance) (accessed 11 Oct 2006).
- 5 UK Prospective Diabetes Study Group. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. *BMJ* 1998;317:720-6.
- 6 Strandberg TE, Pyorala K, Cook TJ, Wilhelmsen L, Faergeman O, Thorgerisson G, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian simvastatin survival study (4S). *Lancet* 2004;364:771-7.

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### Endpiece

#### Dead or alive?

The living are ruled by the dead.  
One cannot practice a science well unless one knows its history.

Auguste Comte. In: Sournia J-C. *The Illustrated History of Medicine*

Submitted by Amar Bhat, senior house officer,  
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