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Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study

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Aims To assess the impact on healthcare resource utilization, costs, and quality of life over 15 years from 5 years of statin use in men without a history of myocardial infarction in the West of Scotland Coronary Prevention Study (WOSCOPS).

Methods Six thousand five hundred and ninety-five participants aged 45–54 years were randomized to 5 years treatment with pravastatin (40 mg) or placebo. Linkage to routinely collected health records extended follow-up for secondary healthcare resource utilization to 15 years. The following new results are reported: cause-specific first and recurrent cardiovascular hospital admissions including myocardial infarction, heart failure, stroke, coronary revascularization and angiography; non-cardiovascular hospitalization; days in hospital; quality-adjusted life years (QALYs); costs of pravastatin treatment, treatment safety monitoring, and hospital admissions.

Results Five years treatment of 1000 patients with pravastatin (40 mg/day) saved the NHS £710 000 ($P < 0.001$), including the cost of pravastatin and lipid and safety monitoring, and gained 136 QALYs ($P = 0.017$) over the 15-year period. Benefits per 1000 subjects, attributable to prevention of cardiovascular events, included 163 fewer admissions and a saving of 1836 days in hospital, with fewer admissions for myocardial infarction, stroke, heart failure and coronary revascularization. There was no excess in non-cardiovascular admissions or costs (or in admissions associated with diabetes or its complications) and no evidence of heterogeneity of effect over sub-groups defined by baseline cardiovascular risk.

Conclusion Five years' primary prevention treatment of middle-aged men with a statin significantly reduces healthcare resource utilization, is cost saving, and increases QALYs. Treatment of even younger, lower risk individuals is likely to be cost-effective.

Keywords Pravastatin • Cardiovascular outcomes • Record linkage • Cost effectiveness • Primary prevention

Introduction

The West of Scotland Coronary Prevention Study (WOSCOPS) was a randomized placebo-controlled primary prevention trial of pravastatin in middle-aged men.[1–3] Five years of treatment with pravastatin reduced the primary outcome of death from coronary heart disease (CHD) or nonfatal myocardial infarction (7.9% on placebo to 5.5% on pravastatin, $P < 0.001$). Definite or suspected CHD deaths were also reduced (1.9–1.3%, $P = 0.04$) with no increased risk of death from non-cardiovascular causes nor an increase in incident cancers.[3] Post-trial extended follow-up for a further 10 years demonstrated a continued reduction in coronary events with no emerging

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safety issues. Overall, over 15 years, there was a reduction in all-cause mortality [hazard ratio, HR = 0.88, 95% CI (0.79–0.99), $P = 0.03$] and in coronary heart disease death or hospitalization [HR = 0.75, 95% CI (0.68–0.83), $P < 0.001$].[4]

A previous cost-effectiveness analysis modelled post-trial benefits only on the basis of deaths prevented due to the reduction of coronary events within the formal 5-year trial.[5]

Recently, the cost effectiveness of statin treatment in a primary prevention context has been questioned,[6] as was the use of statins in healthy men.[7] In this extended analysis of the WOSCOPS long-term follow-up, we directly address these issues and incorporate new data on cardiovascular cause-specific reasons for admission to hospital (first and recurrent), non-cardiovascular admissions (including diabetes-related admissions), duration of admission, use of angiography and coronary revascularization, leading to an assessment of the costs and effectiveness of statin treatment in the primary prevention of cardiovascular disease.

Methods

Original trial

The design of WOSCOPS and its follow-up have been described elsewhere.[1–4] It was a randomized trial comparing pravastatin (40 mg once daily) with placebo in men, aged 45–64 years, with hypercholesterolaemia who had no evidence of previous myocardial infarction. The trial was approved by the ethics committees of the University of Glasgow and participating health boards in Scotland. Between 1989 and 1991, 6595 men gave written informed consent and were randomized. The average follow-up was 4.9 years with final study visits in May 1995.

Post-trial follow-up

The post-trial use of lipid-lowering therapy was similar (38.7 and 35.2% in the pravastatin and placebo arms, respectively) in the two groups during the first 5 years of extended follow-up.[4] All follow-up in this report, both within-trial and post-trial, is from electronic linkage to hospital discharge records, the cancer registry and General Register Office death records using established methods, and includes both first and recurrent events.[8,9]

Outcome determination

Outcomes were identified using the International Classification of Diseases codes and Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures codes until December 2004. Follow-up and record linkage was approved by the ethics committee of the Royal Infirmary, Glasgow and the Privacy Advisory Committee of the National Health Service for Scotland.

Previous analyses[4] focussed on time-to-first event for deaths, incident cancers, and composite cardiovascular outcomes. Here, we have analysed in detail healthcare resource utilization (cause-specific hospital admissions, length of stay and need for coronary investigations, procedures and operations), with the consequent impact on the quality of life, additional healthcare costs resulting from a change in disease status after a hospital admission (referred to herein as 'incremental costs of events') and cost effectiveness. We focussed on cardiovascular admissions involving myocardial infarction, stroke, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), coronary angiography, any coronary cause (including CABG, PCI, or coronary angiography), and heart failure. Myocardial infarction and stroke events were considered outcomes whether or not they were the reason for admission. Other coronary or heart failure codes had to be the primary discharge diagnosis to be counted. Each admission could be represented more than once across the various outcomes. For the length of stay and cost of the acute admissions, each continuous period of in-patient stay was categorized under the most significant included event, defined hierarchically as a stroke if the period of stay involved a stroke, otherwise as a myocardial infarction, otherwise as heart failure, and otherwise as a coronary event if it involved another coronary reason. The composite of these hospitalizations is described as cardiovascular. Other hospitalizations are classed as non-cardiovascular. Because of recent concerns about increased incidence of diabetes in statin-treated individuals, we specifically identified hospitalizations where diabetes or its complications was given as the reason for admission or as a complicating factor. Because of the reduction in cardiovascular hospital admissions associated with statin use, we analysed diabetes-related admissions overall and within hospital admissions with non-cardiovascular causes.

Statistical methods

Cumulative incidence functions, accounting for the competing risk of death from other causes, were used to describe the incidence of events. Cause-specific Cox proportional hazards models were fitted including the treatment group and baseline risk factors as described previously[4] [age, body mass index, systolic and diastolic blood pressures, high- and low-density lipoprotein cholesterol levels, log-transformed triglyceride level, nitrate use, history of angina, history of diabetes, history of hypertension (all yes or no), smoking status (current, former, never), and a social deprivation score].[10] Effects of randomized treatment assignment (pravastatin versus placebo) were expressed as HRs with 95% confidence intervals and corresponding P values. Although it was plausible that the proportional-hazards assumption would not be valid over the full period of follow-up, we concluded that the estimated HRs would still reflect an average effect over the period.

For the hierarchical groupings of continuous periods of hospital stay, total days of admission and lengths of stay for those admitted to hospital were compared between treatment groups using re-randomization t-tests. Re-randomization t-tests were used as a precaution because of the highly non-Normal distribution of these data, particularly the large numbers of zero values.

Economic evaluation

We evaluated the costs and benefits of the initial 5 years treatment with pravastatin over the full available follow-up period of ~15 years in a cost-utility analysis, as this allows a comparison with other uses of health care resources. We used the perspective of the NHS for costs and savings, and health benefits [measured in quality-adjusted life years (QALYs) over the follow-up period of 15 years] for patients; this is consistent with health technology assessments carried out by NICE.

NHS Scotland staff, blinded to randomized treatment, assigned Health Resource Grouping codes to each acute hospital episode, to enable costing with NHS Scotland Tariff costs.[11] We used current (2012) costs of £9.07[12] for a 3-month prescription for 40 mg pravastatin and calculated drug costs from the months of pravastatin used in the trial. In the post-trial period, the 3% excess of statin treatment in the pravastatin group was extrapolated throughout the follow-up. We assumed two liver function and cholesterol tests at the initial consultation, repeated annually whilst on statin treatment (£1.34/test, plus £31 for the initial doctor consultation and £10/annum for nurse consultations).

Table 1 shows the incremental costs of events for care after discharge from hospital and was based on a previous Health Technology Assessment (HTA) report[13] and updated to 2011 costs using the Hospital and Community Health Services Index.[14] The incremental costs of events reflect outpatient follow-up, primary and community services and reduce after the

first year. For multiple events, only the highest applicable additional healthcare costs was used.

Quality of life was assumed to decline with age according to equation: 1.060−0.004 × age (in years). Quality of life was decremented after each admission using the factors given in *Table 1* and was set to zero at death. The disutilities shown in *Table 1* were taken from the previous HTA report.[13] quality-adjusted life years were calculated over the 15-year horizon of the study.

Cumulative mean costs and QALYs per 1000 patients randomized were calculated for each treatment group and compared using bootstrapping with 5000 replicates to calculate *P* values and 95% confidence intervals. Analyses were repeated after discounting costs and quality-of-life decrements at a rate of 3.5% per annum, reflecting the rate recommended by the UK government.

We created three approximately equal sub-groups on the basis of their estimated cardiovascular risk using the ASSIGN Risk score.[15] Participants with a history of angina or stroke or a positive rose questionnaire for angina were assigned to the highest-risk group.

Results

Time-to-first event analyses

Time-to-event analyses are presented in *Table 2* and *Figure 1*. Reflecting within-trial results for fatal and non-fatal cardiovascular outcomes, myocardial infarction risk was reduced by 31% ($P < 0.001$), CHD admission risk by 26% ($P < 0.001$), and stroke risk by 19% ($P = 0.038$). There were 31, 27, and 31% reductions in the need for PCI, CABG, and use of angiography ($P = 0.009$, 0.003, and <0.001, respectively). There was a 43% reduction in the risk of admission for heart failure ($P = 0.002$) and a 28% reduction in overall cardiovascular admissions ($P < 0.001$). There was no evidence of a difference in the risk of non-cardiovascular admissions [HR 0.99, 95% CI (0.94, 1.05), $P = 0.75$)]. Overall hospital admissions associated with diabetes occurred in 142 participants randomized to placebo and 128 randomized to pravastatin [HR 0.78, 95% CI (0.60, 1.00), $P = 0.05$]. When restricted to hospital admissions classed as non-cardiovascular, these occurred in 105 and 102 participants in the placebo and pravastatin groups, respectively, $P = 0.29$. *Figure 1*A–D shows the cumulative incidence functions for PCI or CABG, all CHD, heart failure, and stroke admissions. For PCI or CABG and CHD admissions, there is evidence of benefit during the initial trial period with a strong suggestion of ongoing benefit. For stroke, and particularly for heart failure, most of the benefit appears to accumulate in the post-trial period.

Days in hospital, mean length of stay

During 15 years of follow-up, patients allocated originally to the placebo arm spent 20 447 days in hospital for cardiovascular

Table 1 Incremental costs of events and quality of life decrements applied following each type of cardiovascular event

Event Type	Additional healthcare costs		
	First year after discharge	Second and subsequent years after discharge	Quality-of-life decrement as percentage of baseline
1: Stroke	£9248	£2486	−37.1%
2: MI	£506	£197	−24%
3: HF	£506	£197	−23%
4: Other CHD	£197	£197	−19%

Table 2 Numbers of subjects with at least one event and total numbers of events occurring over a period of approximately 15 years for hospital admissions involving the various types of event (events are not necessarily mutually exclusive), split by randomized treatment group

Event type	Placebo ($n = 3293$)		Pravastatin ($n = 3302$)		HR	*P* value
	Subjects	Events	Subjects	Events	HR (95% CI)	
MI	369	426	265	311	0.69 (0.59, 0.81)	<0.0001
PCI	119	137	84	90	0.69 (0.52, 0.91)	0.0089
CABG	209	213	157	159	0.73 (0.59, 0.90)	0.0031
Angiography	356	417	255	304	0.69 (0.59, 0.81)	<0.0001
CHD	755	1707	586	1264	0.74 (0.66, 0.82)	<0.0001
HF	80	130	48	69	0.57 (0.39, 0.81)	0.0018
Stroke	216	341	184	305	0.81 (0.67, 0.99)	0.038
Any CV	935	2131	727	1598	0.72 (0.66, 0.80)	<0.0001
Non CV	2476	11362	2496	11680	0.99 (0.94, 1.05)	0.75

Hazard ratios (HR) (pravastatin vs. placebo), 95% confidence intervals and *P* values are derived from Cox proportional hazards models for time-to-first event analyses.
MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CHD, coronary heart disease; HF, heart failure; CV, cardiovascular.

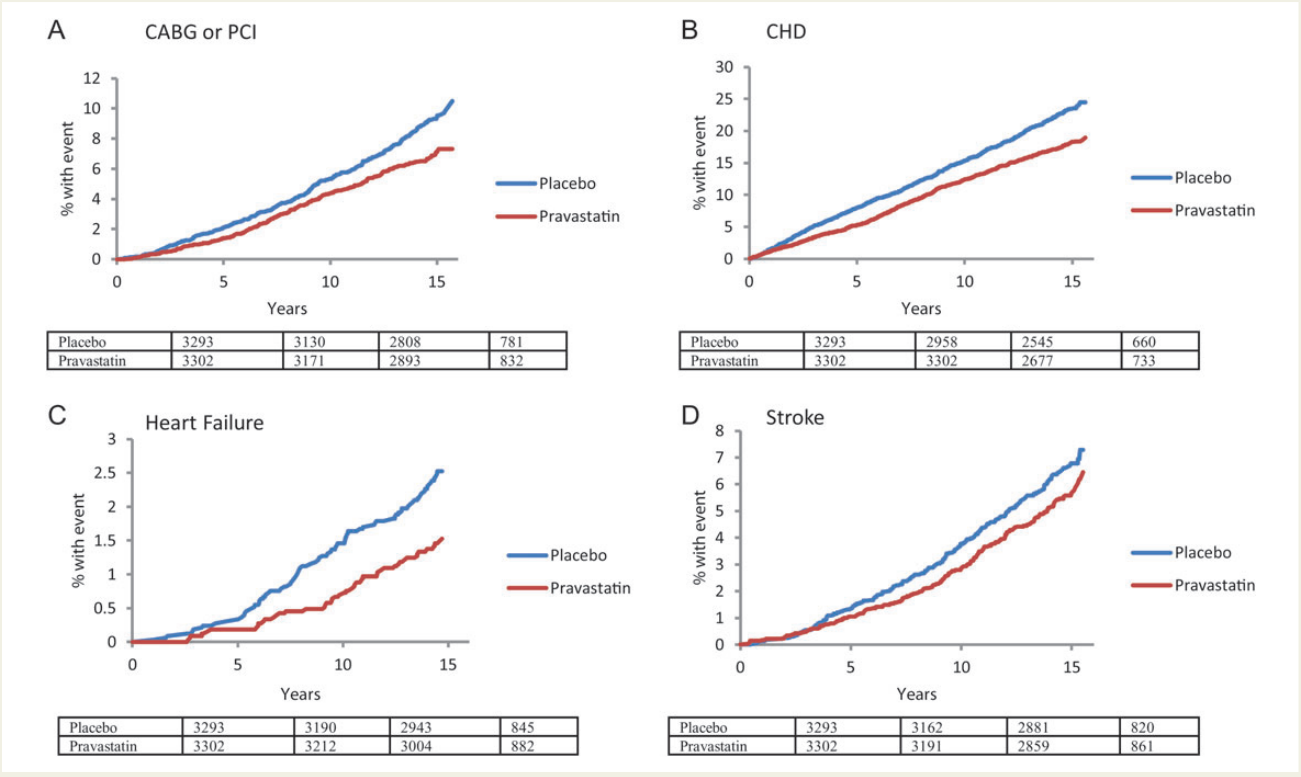

Figure 1 Cumulative incidence curves for cause specific admission to hospital [(*A*) for CABG or PCI, (*B*) for CHD, (*C*) for Heart Failure and (*D*) for Stroke], split by a randomized treatment group.

Table 3 The table contains the number of subjects, number of events, total length of continuous periods of hospital stay (LOS) and mean length of continuous periods of hospital stay

Event type	Placebo ($n = 3293$)				Pravastatin ($n = 3302$)				P_T	P_M
	Subjects	Events	Total LOS (days)	Mean LOS (days)	Subjects	Events	Total LOS (days)	Mean LOS (days)		
Any CV	935	2131	20447	10.68	727	1598	14440	10.34	0.0026	0.80
Stroke	216	341	9296	26.94	184	305	6754	25.02	0.27	0.78
MI	362	416	3523	8.47	260	301	2484	8.29	<0.0001	0.73
HF	76	122	1713	14.71	47	67	828	10.26	0.074	0.17
Other CHD	536	1252	5915	4.75	433	925	4374	4.71	0.0022	0.91
Non CV	2476	11362	48248	4.17	2496	11680	49298	4.19	0.70	0.90

All cardiovascular event type categories are mutually exclusive with periods of stay classified hierarchically as stroke if the period involved a stroke, otherwise as myocardial infarction (MI) if it involved myocardial infarction, otherwise as heart failure (HF) if it involved HF and otherwise as other coronary heart disease (CHD) if it involved another coronary heart disease event. The table also contains *P* values comparing the total length of continuous inpatient stay (P_T) and mean length of continuous periods of inpatient stay (P_M, comparing subjects in each group with at least one hospital admission)) between the randomized treatment groups.

conditions compared to 14 440 for those allocated to pravastatin ($P = 0.003$) (*Table 3*). There were trends to reductions for all cardiovascular admission subtypes with statistically significant reductions for myocardial infarction and other coronary admissions. Average lengths of stay did not differ between treatment groups, nor did the total length of stay for non-cardiovascular causes.

Acute admission, incremental costs of events, and drug and monitoring costs

In *Table 4*, we present the costs of acute admissions, treatment and monitoring, and the incremental costs of events with and without discounting at 3.5% per annum.

Net costs and quality-adjusted life years

Net costs and QALYs are reported in *Table 5*. There was no impact on non-cardiovascular admission costs. We estimated that treatment of 1000 patients for an initial 5 years with pravastatin (40 mg/day) would save the NHS £710 000 ($P < 0.001$) and generate a gain of 136 QALYs ($P = 0.017$), over 15 years of follow-up.

In the three subgroups defined according to ASSIGN baseline risk, actual 10-year placebo-group risks were estimated for the two outcomes defined by (i) coronary death or non-fatal myocardial infarction (MI) and (ii) coronary or stroke death, MI or stroke hospitalization, or PCI or CABG. The 10-year risks for the (low-, medium-, high-) risk groups were (7.5, 10.1, 17.8%) and (10.3, 17.1, 28.0%) for these two outcomes, respectively. Our analyses by subgroups of baseline risk did not reveal any evidence of heterogeneity in the cost savings or QALYs gained (*Table 6*).

Figure 2 shows the development of the cardiovascular cost savings and QALY gains over time suggesting ongoing accumulation of benefits at 15 years. In *Figure 3*, we show results of 5000 bootstrap simulations presented in the cost-effectiveness plane defined by the mean cost difference and the mean QALY difference.

Sensitivity analyses

Sensitivity analyses (Appendix) suggests that our conclusions are robust to reasonable changes in key parameters. A 25% reduction in admission costs changed the cardiovascular savings per 1000 patients over 15 years from £710 100 in the base case to £555 000. A reduction in the assumed health loss from a cardiovascular event by 25% changed the QALY gain per 1000 patients over 15 years from 136 to 120. The only scenario without net cost savings was where we multiplied the prescribing and monitoring costs by 5. Here, the added cost per 1000 patients was £112 000, and the added cost per QALY gained (£112 000/136) was £824.

Discussion

Cardiovascular effects

We have significantly extended the results reported previously that show that 5 years of treatment with a statin, in middle-aged hypercholesterolaemic men without a history of myocardial infarction, leads to long-term benefit by reducing coronary and all-cause death and

Table 4 Distribution of participants by numbers of cardiovascular (CV) hospital admissions occurring in long-term follow-up

	Number of CV hospital admissions								
	0	1	2	3	4	5	6	7	>7
Placebo	2358	453	227	95	70	36	21	11	22
Pravastatin	2575	344	184	83	51	34	11	6	14

$P < 0.001$, chi-square test.

Table 5 Total assumed average cost (in £) of hospital care based on HRGs

	Undiscounted costs		Discounted costs	
	Placebo ($N = 3293$)	Pravastatin ($N = 3302$)	Placebo ($N = 3293$)	Pravastatin ($N = 3302$)
Acute costs				
Any cardiovascular	10 409 011	7 888 709	7 807 932	5 918 407
Stroke	2 275 133	1 868 289	1 642 418	1 335 683
MI	2 098 593	1 540 131	1 647 004	1 196 578
HF	646 103	413 505	457 378	297 868
Other CHD	5 389 182	4 066 784	4 061 133	3 088 278
Cardiovascular admission additional healthcare costs	4 626 854	3 357 666	3 296 839	2 397 851
Treatment and monitoring costs	–	724 074	–	706 647
Acute costs				
Non-cardiovascular	25 275 491	25 329 616	18 998 233	19 036 472

All cardiovascular event type categories are mutually exclusive with periods of stay classified hierarchically as stroke if the period involved a stroke, otherwise as myocardial infarction (MI) if it involved myocardial infarction, otherwise as heart failure (HF) if it involved HF and otherwise as other coronary heart disease (CHD) if it involved another coronary heart disease event. Also shown are estimated post admission incremental costs of events for cardiovascular admissions, and pravastatin treatment and associated lipid and safety monitoring costs within the pravastatin group. Costs are shown without and with discounting at an annual rate of 3.5%.

Table 6 Cumulative mean costs (per 1000 people treated) and quality-adjusted life years after 15 years, in those originally randomized to receive pravastatin or placebo, with mean, 95% confidence interval, and *P* value for the difference between randomized groups (pravastatin − placebo)

	Placebo	Pravastatin	Difference (Prava − Plac)	Interaction *P* value
Cardiovascular disease costs (£million/1000 people)				
All	3.55	2.84	−0.71 (−1.09 to −0.32), $P < 0.001$	
Low risk	2.11	1.27	−0.84 (−1.27 to −0.42), $P < 0.001$	0.85
Intermediate risk	3.47	2.89	−0.58 (−1.27 to 0.08), $P = 0.086$	
High risk	5.04	4.36	−0.68 (−1.49 to 0.11), $P = 0.088$	
QALYs (per 1000 people)				
All	11 057	11 193	136 (25 to 247), $P = 0.017$	
Low risk	11 905	12 016	111 (−12 to 238), $P = 0.079$	0.95
Intermediate risk	11 075	11 207	131 (−51 to 309), $P = 0.17$	
High risk	10 220	10 371	151 (−72 to 376), $P = 0.18$	
Non-Cardiovascular disease costs (£million/1000 people))				
All	6.00	6.03	0.03 (−0.44 to 0.52), $P = 0.87$	
Low risk	4.42	4.33	−0.09 (−0.81 to 0.66), $P = 0.83$	0.65
Intermediate risk	5.84	6.20	0.36 (−0.44 to 1.18), $P = 0.37$	
High risk	7.68	7.55	−0.13 (−1.00 to 0.75), $P = 0.78$	

Costs shown are for all cardiovascular admissions and incremental costs of events, plus treatment and monitoring costs, and for non-cardiovascular disease admission costs. Costs and quality-adjusted life years shown for all randomized subjects, and separately by thirds of cardiovascular risk. Interaction *P* values test whether between-treatment differences are equal across cardiovascular risk groups. All costs and quality-adjusted life year decrements are discounted annually at 3.5%. Costs are given in units of £1 million.

coronary events. The current analysis of health care resource utilization indicated that these benefits were accompanied by a reduction in the risk of a first hospital admission for a cardiovascular event (myocardial infarction, stroke, heart failure, and hospitalizations involving PCI, CABG, or angiography or any other coronary cause). Recurrent cardiovascular events of all such types were reduced with substantially fewer days spent in hospital. To put this in perspective, we estimate that treatment of 1000 WOSCOPS-eligible patients for 5 years would prevent 163 cardiovascular inpatient stays (involving 1836 days in hospital), including 35 myocardial infarctions, 11 strokes, 17 heart failure admissions, and 100 involving other aspects of coronary heart disease (including 14 PCIs, 17 CABGs, and 35 coronary angiograms), over a period of 15 years. The resulting acute cardiovascular hospitalization savings (per 1000 treated with pravastatin) to the NHS are estimated to be £771 881 with additional healthcare costs savings of £388 199, all at a cost of £219 283 for pravastatin treatment (at 2012 prices) and monitoring costs (undiscounted figures), giving the net undiscounted savings of £941 397.

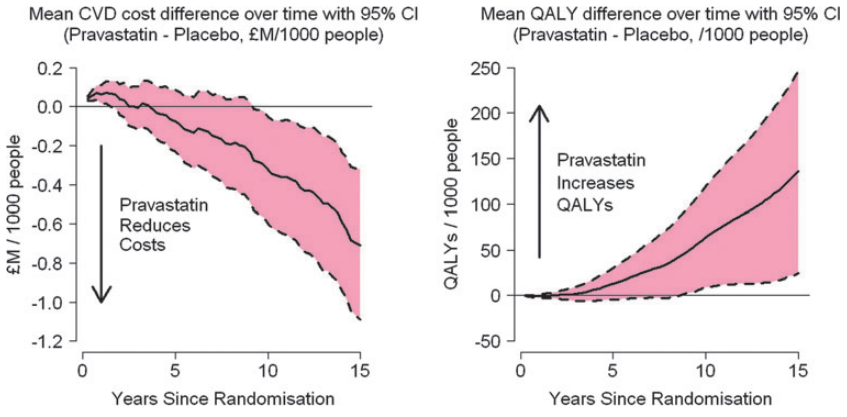

Figure 2 Figures showing the cumulative cardiovascular cost differences (*A*) and mean quality-adjusted life year differences (*B*) for pravastatin group - placebo group over time, with 95% confidence intervals. Estimates are shown as solid lines and 95% confidence bounds as dotted lines.

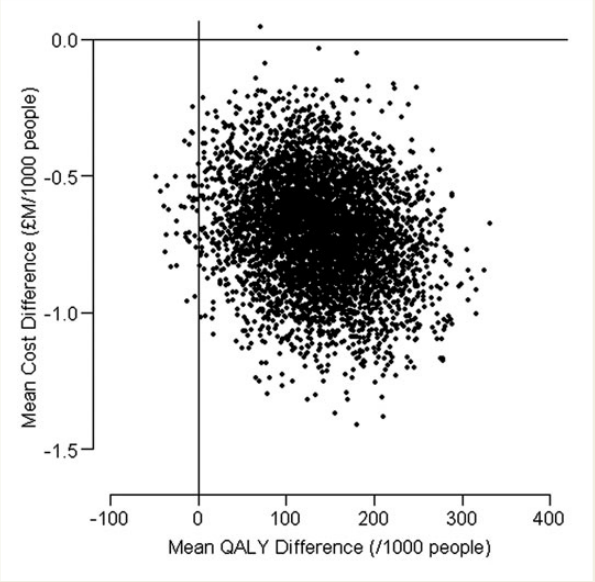

Figure 3 Plot of bootstrap results on the cost-effectiveness plane.

Non-cardiovascular effects

We found no evidence of any increase in hospitalization for non-cardiovascular causes, or in the associated costs. In particular, we found no evidence of any excess in-hospital admissions related to diabetes or its complications.

Interpretation

Reducing days spent in a hospital for cardiovascular causes and preventing the need for coronary revascularization procedures and surgery have significant benefits for the health service and patients. After discounting, there was a net saving to the NHS over 15 years with an associated gain of QALYs. Analysis of subgroups according to the baseline risk did not identify heterogeneity of these effects across subgroups. The suggestion of longer-term benefits in preventing strokes and heart failure admissions is interesting, possibly as a consequence of preventing earlier coronary events and slowing disease progression and hints at the potential for even greater cost savings and better quality of life in the pravastatin-allocated group with longer follow-up.

Results in a broader context

Interest in the cost-effectiveness of statin treatment, particularly in the primary prevention context, shows no signs of waning. Our analysis adds to existing knowledge in two ways.

First, previous analyses have focussed on model-based extrapolations from trial results, and none had access to actual long-term follow-up data. In WOSCOPS, we had the opportunity to link electronically to comprehensive national databases of hospital discharges and deaths, providing information on estimated costs and benefits over a meaningful period of time, and we were able to derive evidence of cost savings and patient benefits without extrapolating results into very old ages where the complexities of multi-morbidity make typical unvalidated modelling assumptions open to question. Second, our analyses suggest that statins are even more cost-effective in primary prevention than had previously been suspected. While most economic evaluations have concluded that the cost per QALY is within acceptable limits, previous evaluations have not suggested that statin prescribing in this patient group could be cost saving. This, in combination with our risk-based sub-group analyses, raises the prospect that statin treatment could be cost saving at lower levels of risk than was previously suspected.

For example, a previous WOSCOPS economic evaluation,[5] based on a model that extrapolated lifetime benefits only via the prevention of within-trial coronary events, estimated an added cost per life-year gain of £20 375 (1996 prices), which is a much less favourable estimate than that indicated in our current analysis. More recently, an economic evaluation in a low-risk population,[16] was based on a review of trial and Canadian registry data. In a 'low-potency statin' versus 'no statin' comparison, the authors predicted an added cost per QALY of Can$30 000 (about £20 000) using a lifetime perspective; low risk was defined as a 10-year risk of $\leq$20% for cardiovascular death or non-fatal MI. For this type of endpoint, the WOSCOPS 10-year placebo risk is 12.8% overall and 7.7, 10.8, and 20.0% in our low-, medium- and high-risk subgroups defined by baseline ASSIGN risk. Their QALY estimates were similar to ours. The difference between our results and those of the Canadian registry study is in the hospital admissions and consequent savings from reducing these over time: the actual rates in our data are much more favourable to statin treatment.

Our results are based on the treatment with pravastatin 40 mg, a drug that is well tolerated but is recognized as being less potent than widely used agents such as atorvastatin and rosuvastatin. It is likely that more potent statins, particularly at higher doses, would confer greater benefits in reducing the cardiovascular risk. However, there are safety issues associated with using more potent statins at the highest doses, and higher doses of statins have been linked recently with an increased risk of new-onset diabetes.[17] In the context of treating younger, lower risk individuals with a statin for a lifetime, the drive to improve a patient's cardiovascular risk profile would have to be balanced against issues of tolerability and safety. In WOSCOPS we have reported previously a lower rate of new-onset diabetes in the participants randomized to pravastatin over the 5 years of randomized treatment.[18] The meta-analysis of incident diabetes risk in statin trials,[17] although suggesting a modest overall increase in the risk of diabetes with statin treatment, also suggested an interaction with participant age, with oldest participants having the greatest increase in the risk of diabetes on statin treatment. WOSCOPS participants had the lowest mean age in the meta-analysis. In combination with the fact that we found no suggestion of an increase in diabetes-associated hospital admissions over 15 years of follow-up, we believe that this evidence provides reassurance about the long-term safety of treating middle-aged subjects for 5 years with pravastatin at a dose of 40 mg.

Limitations of our analysis

While there are undoubted strengths in our approach, there are also limitations. Our follow-up spans a period during which the management of cardiovascular events (e.g. the increase in use of coronary revascularization) and even event definitions (myocardial infarction)

changed. We have avoided the issue of trends in hospital length of stay by using a cost per event reflecting current practice in many countries. Record linkage is subject to error, and there is a possibility that some events have been missed and some wrongly assigned and that coding variation may have mis-assigned reasons for admission. However, we believe that these issues are minor and if anything would add noise and serve only to reduce any treatment effects detected. In any case, these factors will apply equally to both treatment arms. WOSCOPS patients have not all been followed up to death and hence we cannot, without extrapolation, project to lifetime benefits. Nevertheless, it is all the more remarkable that we were able to demonstrate cost savings over a finite time period. In fact, this could be seen as an advantage as we avoid the need for extrapolating benefits to the complex situation at the end of life in the very old. While the events, hospital admissions, and deaths are observed, we had to estimate costs and quality-of-life impacts retrospectively. For acute costs, we selected national tariff rates and for utilities and incremental costs of events from a previously published independent health technology assessment report. We also subjected these assumptions to sensitivity analysis and have shown that if the figures are changed by 25% in a direction that reduces the cost-effectiveness of statin prescribing then our conclusions would be unchanged. Although an increase in the costs of pravastatin treatment and monitoring by a factor of 5 removed the cost savings in our analysis, this scenario is particularly unlikely given the fact that monitoring of patients is much less common in practice than we have assumed in the model and likely to become even less so because of recent FDA advice not to carry out long-term routine liver function monitoring. Our sub-group analysis by baseline risk is possibly underpowered. Nevertheless, if anything, there was a trend to greater cardiovascular cost savings in the lowest risk subjects.

Finally, our findings are limited to randomized allocation to placebo or pravastatin over 5 years. It seems inevitable that longer treatment with a statin, for instance lifetime treatment, which would be normal clinical practice, would yield greater cardiovascular health gains. However, we cannot say with certainty that this would be more cost-effective. In addition, although in this population of middle-aged men treated with pravastatin 40 mg/day, we found no evidence of increased risk of diabetes within the trial or of risk of hospital admission associated with diabetes or its complications in the 15 years of follow-up, we cannot extrapolate these safety findings to patients treated for much longer periods.

Conclusions

Five years of treatment with pravastatin 40 mg of middle-aged men with hypercholesterolaemia and no history of myocardial infarction significantly reduced cardiovascular hospital admissions, incremental costs of events and net costs taking into account the cost of the drug and associated monitoring. Quality adjusted life years lived were significantly increased. There was no evidence of any increase in non-cardiovascular admissions or associated costs. These effects, seen across a range of underlying cardiovascular risks, suggest that treatment of even lower-risk individuals would still be economically efficient and deliver significant public health benefits. Our results add to and support a recent call for expanded use of statins.[19] However, there remains uncertainty in relation to the potential for increased risk of diabetes with treatment of more than 5 years duration.

Authors' contributions

I.F. obtained funding. A.McC., A.W., I.F., S.M.C., and C.J.P. contributed to the study design. L.M. and J.P. contributed to the data collection. A.McC., M.R., and I.F. were responsible for all statistical analyses. A.W. and A.McC. were responsible for economic analyses. All authors contributed to the data interpretation, critical review, and editing of the manuscript.

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References

1. West of Scotland Coronary Prevention Study Group. A coronary primary prevention study of Scottish men aged 45–64 years: trial design. *J Clin Epidemiol* 1992;**45**:849–860.
2. The WOSCOPS Study Group. Screening experience and baseline characteristics in the West of Scotland Coronary Prevention Study. *Am J Cardiol* 1995;**76**:485–491.
3. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;**333**:1301–1307.
4. Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane P, Cobbe SM. Long-term follow-up of the West of Scotland Coronary Prevention Study. *N Engl J Med* 2007;**357**:1477–1486.
5. Caro J, Klittich W, McGuire A, Ford I, Norrie J, Pettitt D, McMurray J, Shepherd J. The West of Scotland coronary prevention study: economic benefit analysis of primary prevention with pravastatin. *BMJ* 1997;**315**:1577–1582.
6. Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas JP, Ebrahim S. Statins for the primary prevention of cardiovascular disease. *The Cochrane Library* DOI: 10.1002/14651858.CD004816.pub4.
7. Redberg RF, Katz MH. Healthy men should not take statins. *JAMA* 2012;**307**:1491–1492.
8. Kendrick S, Clarke J. The Scottish Record Linkage System. *Health Bull* 1993;**51**:72–79.
9. The West of Scotland Coronary Prevention Study Group. Computerised record linkage: comparison with traditional patient follow-up methods in clinical trials and illustrated in a prospective epidemiological study. *J Clin Epidemiol* 1995;**48**:1441–1452.
10. McLoone P, Boddy FA. Deprivation and mortality in Scotland, 1981 and 1991. *BMJ* 1994;**309**:1465–1470.
11. Scottish National Tariffs. http://isd.scot.nhs.uk/isd/6458.html.
12. Joint Formulary Committee. *British National Formulary*. 61 ed. London: BMJ Group and Pharmaceutical Press; 2011.
13. Ward S, Lloyd-Jones M, Pandor A, Holmes M, Ara R, Ryan A, Yeo W, Payne N. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 2007;**11**.

14. Curtice L. *Unit Costs of Health and Social Care 2010*. Personal Social Services Research Unit, University of Kent at Canterbury (http://www.pssru.ac.uk/publication-details.php?id=131).
15. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart* 2007;**93**:172–176. doi: 10.1136/hrt.2006.108167.
16. Conly J, Clement F, Tonelli M, Hemmelgarn SMB, Klarenbach S, Lloyd A, McAlister FA, Husereau D, Wiebe N, Au F, Manns B. for the Alberta Kidney Disease Network: cost-effectiveness of the use of low- and high-potency statins in people at low cardiovascular risk. *CMAJ* 2011;**183**:E1185.
17. Preiss D, Seshasai SRK, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, Sabatine MS, Braunwald E, Kastelein JJP, de Lemos JA, Blazing MA, Pederson TR, Tikkanen MJ, Sattar N, Ray KK. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy a meta-analysis. *JAMA* 2011;**305**:2556–2564.
18. Freeman DJ, Norrie J, Sattar N, Neely RDG, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 2001;**103**:357–362.
19. Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *The Lancet, Early Online Publication* 2012; doi:10.1016/S0140-6736(12)60367-5.

Appendix

Sensitivity analyses. Estimated difference (pravastatin—placebo, with 95% CI) between those originally randomized to receive pravastatin or placebo for the cumulative mean costs (per 1000 people treated) and QALYs after 15 years, under alternative scenarios. Costs include all cardiovascular hospitalizations and associated additional healthcare costs, plus pravastatin treatment and monitoring costs. Alternative scenarios are: hospitalization costs ±25%; additional healthcare costs ±25%; 50% reduction; and two- and five-fold increase in treatment/monitoring costs; QALY decrements ±25%. All costs and QALY decrements are discounted at 3.5%. Costs are given in units of £1 million.

	Costs (£) (per 1000 people)	QALYs
Base case	−0.71 (−1.09 to −0.32)	136 (25–247)
Changes to hospitalization costs		
+25%	−0.86 (−1.30 to −0.41)	
−25%	−0.56 (−0.88 to −0.22)	
Changes to incremental costs of events		
+25%	−0.78 (−1.20 to −0.36)	
−25%	−0.64 (−0.98 to −0.28)	
Changes to treatment and monitoring costs		
/2	−0.81 (−1.19 to −0.42)	
×2	−0.50 (−0.89 to −0.16)	
×5	0.11 (−0.27 to 0.50)	
Changes to QALY decrements		
+25%		153 (40–265)
−25%		120 (10–230)