Articles

Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial

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Summary

Background Although statins reduce coronary and cerebrovascular morbidity and mortality in middle-aged individuals, their efficacy and safety in elderly people is not fully established. Our aim was to test the benefits of pravastatin treatment in an elderly cohort of men and women with, or at high risk of developing, cardiovascular disease and stroke.

Methods We did a randomised controlled trial in which we assigned 5804 men (n=2804) and women (n=3000) aged 70–82 years with a history of, or risk factors for, vascular disease to pravastatin (40 mg per day; n=2891) or placebo (n=2913). Baseline cholesterol concentrations ranged from 4·0 mmol/L to 9·0 mmol/L. Follow-up was 3·2 years on average and our primary endpoint was a composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke. Analysis was by intention-to-treat.

Findings Pravastatin lowered LDL cholesterol concentrations by 34% and reduced the incidence of the primary endpoint to 408 events compared with 473 on placebo (hazard ratio 0·85, 95% CI 0·74–0·97, p=0·014). Coronary heart disease death and non-fatal myocardial infarction risk was also reduced (0·81, 0·69–0·94, p=0·006). Stroke risk was unaffected (1·03, 0·81–1·31, p=0·8), but the hazard ratio for transient ischaemic attack was 0·75 (0·55–1·00, p=0·051). New cancer diagnoses were more frequent on pravastatin than on placebo (1·25, 1·04–1·51, p=0·020). However, incorporation of this finding in a meta-analysis of all pravastatin and all statin trials showed no overall increase in risk. Mortality from coronary disease fell by 24% (p=0·043) in the pravastatin group. Pravastatin had no significant effect on cognitive function or disability.

Interpretation Pravastatin given for 3 years reduced the risk of coronary disease in elderly individuals. PROSPER therefore extends to elderly individuals the treatment strategy currently used in middle aged people.

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Introduction

Findings of clinical trials[1–6] of 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) have shown significant benefits in both primary and secondary prevention of coronary and cerebrovascular disease events. Most of this evidence comes from studies done on middle-aged men. The rationale for such treatment in people older than age 70 years, most of whom die of vascular disease, is less clear because the association between plasma cholesterol and risk of coronary artery disease diminishes with increasing age.[7–9] The frequency of stroke, an important manifestation of vascular disease in elderly individuals, is associated with hypertension and seems independent of plasma cholesterol.[10] However, investigators of previous statin trials[11] have reported benefits on stroke, and results of observational studies have raised the possibility that statins could reduce the rate of cognitive decline in elderly people.[12] However, in the oldest old people, low plasma cholesterol is associated with increased mortality.[8,9] In view of these conflicting observations, we concluded that the balance of the efficacy and safety of cholesterol lowering in older people had yet to be established, and we launched the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Our aim was to ascertain if treatment with pravastatin reduces the risk of cardiac events, stroke, cognitive decline, and disability in those with existing (secondary prevention) and in those at high risk of developing (primary prevention) vascular disease.[13–15] We chose a treatment period of a minimum of 3 years as a reasonable time frame to test the efficacy of the medication in what for many individuals is the last decade of their life.

Methods

The protocol of PROSPER has been published elsewhere.[13]

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Participants

Between Dec 15, 1997, and May 7, 1999, we screened and enrolled individuals from Scotland, Ireland, and the Netherlands. Briefly, men and women aged 70–82 years were recruited if they had either pre-existing vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension, or diabetes. Their plasma total cholesterol was required to be 4·0–9·0 mmol/L and their triglyceride concentrations less than 6·0 mmol/L. After screening, eligible individuals entered a 4-week single-blind placebo lead-in period. Those who used less than 75% or more than 120% of the placebo medication were excluded. To assess changing cognitive function, the mini mental state examination and a series of psychometric tests (picture-word learning test, Stroop colour word test, letter digit coding test) were administered at each of two baseline visits, and disability questionnaires (20 point Barthel and instrumental activities of daily living) were completed.[13–15] We excluded individuals with poor cognitive function (mini mental state examination score <24). The institutional ethics review boards of all centres approved the protocol, and all participants gave written informed consent. The protocol was consistent with the Declaration of Helsinki.

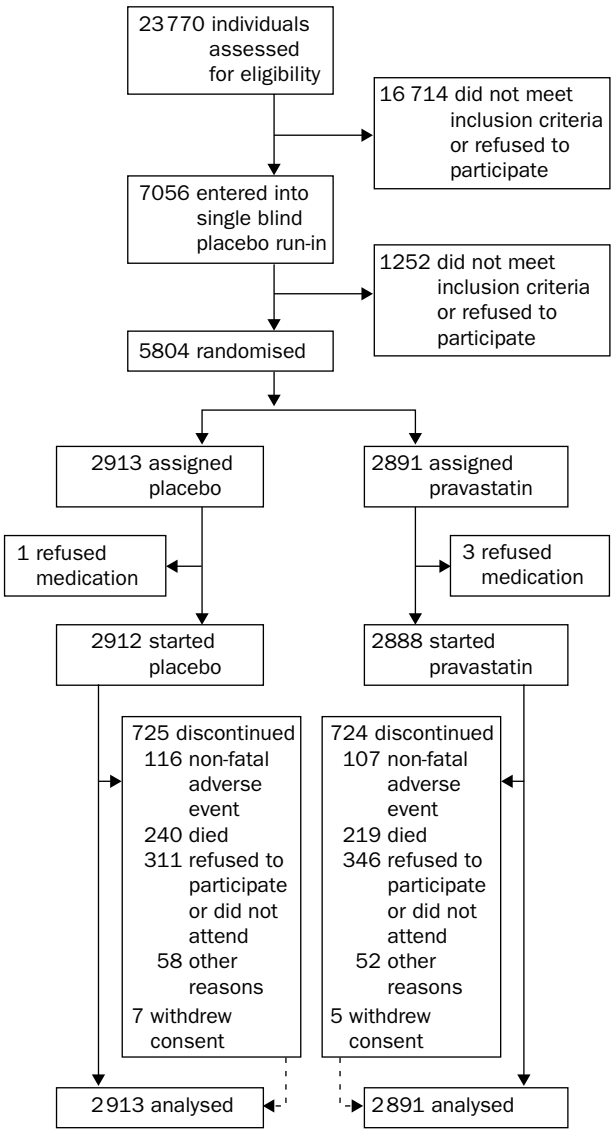

Figure 1: **Trial profile**

Protocol

The randomisation sequence was generated with a computerised pseudorandom number generator and consisted of balanced blocks of size four. Randomisation was done by telephone call or through fax exchange with the study data centre. Emergency unblinding was available via an interactive voice response telephone system. Only two requests for emergency unblinding were implemented. All study personnel, including the endpoint adjudication committee, remained unaware of the allocated study medication status of the patients throughout the study.

We reviewed participants every 3 months. Lipoprotein profiles were measured at the Centre for Disease Control certified central lipoprotein laboratory in Glasgow. A 12-lead electrocardiogram was recorded annually and transmitted electronically to the electrocardiogram core laboratory at Glasgow Royal Infirmary, where all computer interpretations were reviewed and automated Minnesota coding done.[16] The cognitive function tests and disability assessments were repeated annually. All data were processed and analysed at the study data centre in The Robertson Centre for Biostatistics, Glasgow.

Our primary outcome was the combined endpoint of definite or suspect death from coronary heart disease, non-fatal myocardial infarction, and fatal or non-fatal stroke, assessed in the entire cohort. Secondary outcomes included examination of the coronary and cerebrovascular components separately. Additionally, we assessed the primary outcome separately for men and women and for those with and without pre-existing disease. Tertiary endpoints included an assessment of transient ischaemic attack, disability, and cognitive function. We also planned to examine the magnitude of benefit in relation to degrees of

	Placebo (n=2913)	Pravastatin (n=2891)
Continuous variates (mean, SD)		
Age (years)	75·3 (3·4)	75·4 (3·3)
Systolic blood pressure (mm Hg)	154·6 (21·8)	154·7 (21·9)
Diastolic blood pressure (mm Hg)	83·9 (11·7)	83·6 (11·2)
Height (m)	1·7 (0·1)	1·7 (0·1)
Weight (kg)	73·4 (13·5)	73·4 (13·3)
Body-mass index (kg/m^2)	26·8 (4·3)	26·8 (4·1)
Alcohol (units per week)*	5·1 (8·9)	5·3 (9·7)
Number of concomitant drugs†	3·6 (2·3)	3·6 (2·3)
Total cholesterol (mmol/L)	5·7 (0·9)	5·7 (0·9)
LDL cholesterol (mmol/L)	3·8 (0·8)	3·8 (0·8)
HDL cholesterol (mmol/L)	1·3 (0·3)	1·3 (0·4)
Triglycerides (mmol/L)	1·5 (0·7)	1·5 (0·7)
Mini mental state examination score	28·0 (1·6)	28·0 (1·5)
Barthel index score	19·8 (0·7)	19·8 (0·8)
Instrumental assessment of activities of daily living score	13·6 (1·0)	13·6 (1·0)
Categorical variates (n, %)		
Men	1408 (48·3)	1396 (48·3)
Current smoker	805 (27·6)	753 (26·0)
History of diabetes	320 (11·0)	303 (10·5)
History of hypertension	1793 (61·6)	1799 (62·2)
History of angina	753 (25·8)	806 (27·9)
History of claudication	192 (6·6)	198 (6·8)
History of myocardial infarction	399 (13·7)	377 (13·0)
History of stroke or transient ischaemic attack	321 (11·0)	328 (11·3)
History of percutaneous transluminal coronary angioplasty and coronary artery bypass graft	108 (3·7)	129 (4·5)
History of peripheral arterial disease surgery	56 (1·9)	67 (2·3)
History of vascular disease‡	1259 (43·2)	1306 (45·2)

*1 unit=60 mL distilled spirits, 170 mL wine, or 300 mL beer. †Maximum number=14 placebo, 16 pravastatin. ‡ Any of stable angina, intermittent claudication, stroke, transient ischaemic attack, myocardial infarction, peripheral arterial disease surgery, or amputation for vascular disease more than 6 months before study entry.

Table 1: **Baseline characteristics**

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baseline risk factors (including smoking status, history of hypertension, sex, diabetes, and LDL and HDL cholesterol concentrations[13]).

Statistical analysis

Our target sample size was 5500 individuals (3000 women and 2500 men) distributed evenly between those with existing vascular disease and those who qualified because of high risk. The study had 92% power to detect a 20% reduction in the primary outcome, assuming a 16% placebo event rate; 95% power to detect a 25% risk reduction in death from coronary heart diseases or a non-fatal myocardial infarction, assuming a 12% placebo event rate; and 95% power to detect a 28% reduction in stroke, assuming an 8% placebo event rate.[13] The study was not considered to be adequately powered to detect an effect on all-cause mortality.

An independent data and safety monitoring committee reviewed safety and efficacy data. Consideration of stopping because of overwhelming evidence of benefit was based on a p value of less than 0·001 (two sided log rank test), indicating benefit for all-cause mortality. No adjustment has been made to the reported analyses because of this conservative rule.

Statistical analyses followed a predefined plan. Baseline summary statistics are reported as mean (SD) for continuous variables and as number (%) for categorical variables. Time to event outcomes were analysed with Cox proportional hazards models, containing treatment as a factor and with adjustment for covariates as indicated in the results tables. Results are reported as number of participants and events (with crude percentages) for each treatment group, and hazard ratios (95% CI) and p values from the Cox model analyses. Prespecified subgroup analyses were done in a similar manner, with the addition of an analysis to investigate a treatment by risk factor interaction. In the instance of lipoprotein tertiles, this analysis was done as a two degrees of freedom test for heterogeneity. Time to event curves were constructed with the Kaplan-Meier method. All analyses were by intention-to-treat. An analysis of the effect of pravastatin on lipids was done both on compliant patients (as evidenced by study medication having been issued on their regular study visit and at the previous study visit) and on the entire cohort. In the instance of the entire cohort, individuals with missing data for lipoprotein cholesterol concentrations had their baseline values imputed. Results were analysed as percentage change over baseline. Cognitive decline, and dependency and disability between the two treatments were assessed by comparison of the difference between the last on-treatment and the second of two baseline measurements, using linear models that adjusted the treatment effect for the covariates in the table of baseline characteristics, for country, and for version of test (if applicable). The first baseline measurement was used as a practice measurement to reduce possible learning effects. Further discussion of the issues with respect to the cognitive analyses are detailed elsewhere.[15] We did a meta-analysis of the risk of first-incident cancer associated with statin treatment in all major randomised double-blind placebo-controlled clinical trials of statins that were of at least 3 years' duration. The odds ratios (95% CI) were calculated for individual trials, for all pravastatin trials, for all trials that involved other statins, and for all statin trials, and tests of heterogeneity were done.[17]

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Figure 1 shows the trial profile, and table 1 the baseline characteristics of participants. 23 770 men and women were screened, and 5804 randomly assigned to pravastatin or placebo (2520 from Scotland, 2184 from Ireland, and 1100 from the Netherlands). The groups were balanced with respect to all relevant characteristics (table 1).

	Placebo (n, %) (n=2913)	Pravastatin (n, %) (n=2891)	Hazard ratio (95% CI)	p*
Primary endpoint				
Coronary heart disease death or non-fatal myocardial infarction or fatal or non-fatal stroke	473 (16·2)	408 (14·1)	0·85 (0·74–0·97)	0·014
Secondary endpoints				
Coronary heart disease death or non-fatal myocardial infarction	356 (12·2)	292 (10·1)	0·81 (0·69–0·94)	0·006
Fatal or non-fatal stroke	131 (4·5)	135 (4·7)	1·03 (0·81–1·31)	0·81
Other outcomes				
Non-fatal myocardial infarction	254 (8·7)	222 (7·7)	0·86 (0·72–1·03)	0·10
Coronary heart disease death or non-fatal myocardial infarction (excluding silent and unrecognised events)	246 (8·4)	193 (6·7)	0·77 (0·64–0·93)	0·007
Non-fatal stroke	119 (4·1)	116 (4·0)	0·98 (0·76–1·26)	0·85
Transient ischaemic attack	102 (3·5)	77 (2·7)	0·75 (0·55–1·00)	0·051
Percutaneous transluminal coronary angioplasty and coronary artery bypass graft	48 (1·6)	39 (1·3)	0·82 (0·54–1·26)	0·36
Peripheral arterial surgery/angioplasty	45 (1·5)	35 (1·2)	0·78 (0·50–1·21)	0·27
All cardiovascular events†	523 (18·0)	454 (15·7)	0·85 (0·75–0·97)	0·012
Fatal or non-fatal stroke or transient ischaemic attack	212 (7·3)	204 (7·1)	0·96 (0·79–1·16)	0·64
Heart failure hospitalisation	122 (4·2)	112 (3·9)	0·91 (0·71–1·18)	0·49
Deaths				
Coronary heart disease	122 (4·2)	94 (3·3)	0·76 (0·58–0·99)	0·043
Stroke	14 (0·5)	22 (0·8)	1·57 (0·80–3·08)	0·19
Vascular	157 (5·4)	135 (4·7)	0·85 (0·67–1·07)	0·16
Non-vascular	149 (5·1)	163 (5·6)	1·11 (0·89–1·38)	0·38
Cancer	91 (3·1)	115 (4·0)	1·28 (0·97–1·68)	0·082
Trauma or suicide	7 (0·2)	2 (0·1)	N/A	N/A
All causes	306 (10·5)	298 (10·3)	0·97 (0·83–1·14)	0·74

N/A=not analysed. *Significance of treatment effect in a Cox proportional hazard model adjusted for covariates presented in table 1. No formal analysis was done for events with a low incidence. †All cardiovascular events are primary endpoint or coronary artery bypass graft or percutaneous transluminal coronary angioplasty or peripheral arterial surgery or angioplasty.

Table 2: **Endpoints of PROSPER**

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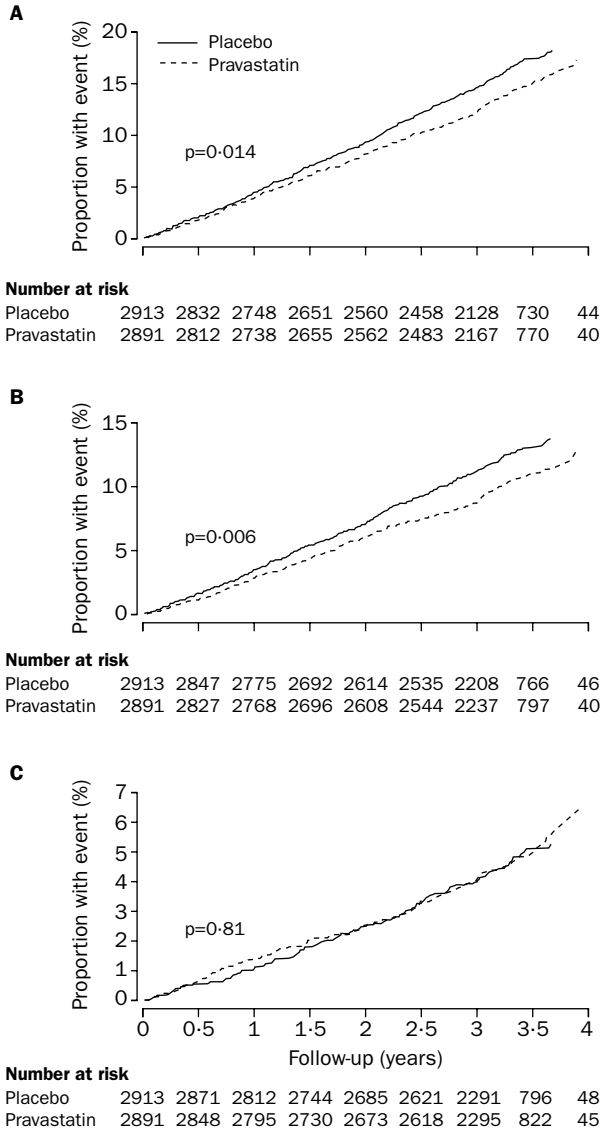

Mean follow-up was 3·2 years (range 2·8–4·0) for participants who did not die or withdraw consent. The proportion of potential visits to trial centres actually attended, and at which study medication was issued, was 86% in both the placebo and pravastatin groups. For participants given study medication, the average adherence, calculated as the number of pills received less the number returned at the next visit, divided by the days between these two visits, was 94% in both the placebo and pravastatin groups. 277 (10%) and 131 (5%) individuals, respectively, initiated non-study statin therapy.

At 3 months' follow-up, mean LDL cholesterol in the pravastatin group was 2·5 mmol/L, 34% lower than the value in the placebo group, HDL cholesterol was 5% higher, and plasma triglyceride concentrations 13% lower in compliant individuals (LDL 32% lower, HDL 5% higher, and triglyceride 12% lower for the entire cohort). The LDL cholesterol reduction was sustained in those who continued to take pravastatin, and at the second annual visit postrandomisation, the pravastatin-induced decrease in LDL cholesterol was 33% in compliant individuals and 27% in the entire cohort.

Table 2 and figure 2 show the main outcomes. Pravastatin reduced the risk of a primary endpoint by 15%. When the primary endpoint was separated into its coronary and cerebrovascular components, we noted a 19% reduction in coronary events, but no discernible effect on cerebrovascular events (table 2). Transient ischaemic attacks were reduced by 25% as a result of treatment, though this effect was not significant. The frequencies of revascularisation procedures (both coronary and peripheral), undertaken infrequently in this population, were lower in the intervention group, but these reductions were not significant. The rates of hospital admissions for heart failure did not differ significantly between the groups. Risk of coronary heart disease death was reduced by 24% in those allocated pravastatin. There was no observed difference in all-cause mortality (table 2).

Figure 2: **Kaplan-Meier analysis of time to primary and secondary endpoints**

A=coronary heart disease death, non-fatal myocardial infarction, or fatal or non-fatal stroke. B=coronary heart disease death or non-fatal myocardial infarction. C=fatal or non-fatal stroke.

	Placebo		Pravastatin		Hazard ratio (95% CI)	p*
	Total number	Number with event (%)	Total number	Number with event (%)		
Previous vascular disease†						
No	1654	200 (12·1)	1585	181 (11·4)	0·94 (0·77–1·15)	0·19
Yes	1259	273 (21·7)	1306	227 (17·4)	0·78 (0·66–0·93)	
Sex						
Female	1505	194 (12·9)	1495	186 (12·4)	0·96 (0·79–1·18)	0·13
Male	1408	279 (19·8)	1396	222 (15·9)	0·77 (0·65–0·92)	
LDL cholesterol (mmol/L)						
<3·41	978	158 (16·2)	972	137 (14·1)	0·88 (0·80–1·10)	0·69
3·41–4·11	1000	173 (17·3)	956	153 (16·0)	0·88 (0·70–1·10)	
>4·11	935	142 (15·2)	963	118 (12·3)	0·77 (0·60–0·98)	
HDL cholesterol (mmol/L)						
<1·11	1035	200 (19·3)	1016	132 (13·0)	0·64 (0·52–0·80)	0·0069
1·11–1·37	925	162 (17·5)	926	155 (16·7)	0·93 (0·75–1·16)	
>1·37	953	111 (11·6)	949	121 (12·8)	1·09 (0·84–1·41)	
Current smoker						
No	2108	348 (16·5)	2138	293 (13·7)	0·81 (0·69–0·95)	0·30
Yes	805	125 (15·5)	753	115 (15·3)	0·96 (0·74–1·24)	
History of hypertension						
No	1120	190 (17·0)	1092	162 (14·8)	0·85 (0·69–1·05)	0·91
Yes	1793	283 (15·8)	1799	246 (13·7)	0·84 (0·71–1·00)	
History of diabetes						
No	2593	414 (16·0)	2588	338 (13·1)	0·79 (0·69–0·91)	0·015
Yes	320	59 (18·4)	303	70 (23·1)	1·27 (0·90–1·80)	

*p for interaction values for heterogeneity of treatment across subgroups. †Any of stable angina or intermittent claudication, or stroke, transient ischaemic attack, myocardial infarction, arterial surgery, or amputation for vascular disease more than 6 months before study entry.

Table 3: **Incidence of primary end point, according to subgroup**

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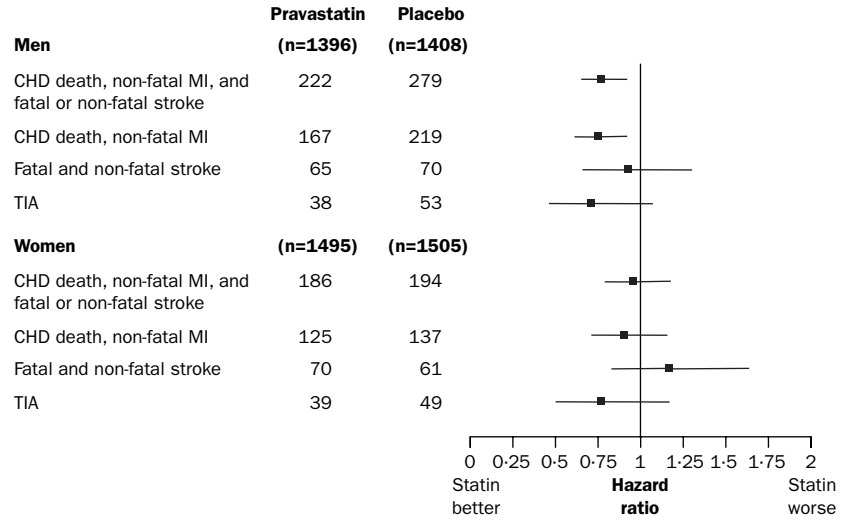

Figure 3: **Major cardiovascular outcomes, according to sex**
CHD=coronary heart disease. MI=myocardial infarction. TIA=transient ischaemic attack. The primary endpoint of the study is reproduced for comparative purposes.

Table 3 shows the occurrence of the primary endpoint in various predefined subgroups. Risk reduction seemed more pronounced in men than in women and in secondary than in primary prevention. However, testing for interaction revealed no significant differences between these subgroups. Variation in baseline LDL concentrations did not relate to risk of a coronary event or treatment efficacy. Benefit was predominantly in the lowest tertile of HDL-cholesterol and, here, the interaction was significant (p=0·0069). In smokers and in individuals with a history of hypertension, there was no evidence of selective benefit. The number of individuals with diabetes was too small to permit accurate interpretation of the treatment effect.

In view of the difference in treatment effect between the two components of the primary endpoint, we undertook a post-hoc analysis of the separate responses in cardiovascular and cerebrovascular endpoints in men versus women (figure 3) and in primary versus secondary prevention (figure 4). Coronary risk reduction (coronary heart disease death or myocardial infarction) seemed more pronounced in men (figure 3) and in those with previous vascular disease (figure 4). However, testing for interaction revealed no significant differences between these subgroups (p=0·25 and p=0·24, respectively). There was no clear effect of treatment in these subgroups with respect to cerebrovascular disease.

Cognitive function declined at the same rate in both treatment groups. There were no significant differences between the two randomised treatment groups in the difference between the last on-treatment and the second baseline value for the number of correct letter digit codes (pravastatin–placebo –0·01, 95% CI –0·24 to 0·23, p=0·95), or in the number of words remembered in the picture word learning test (0·02, –0·12 to 0·16, p=0·80), or for the time needed to complete the Stroop test (0·8 s, –0·4 to 2·0, p=0·19). Similarly, there were no significant differences between the two groups in the difference between the last on-treatment and the second baseline value for the mini mental state examination score (0·06, –0·04 to 0·16, p=0·26), in activity levels over time as measured by the Barthel index (0·06, –0·03 to 0·15, p=0·18), or in the instrumental activities of daily living questionnaire (0·03, –0·08 to 0·14, p=0·59).

Serious adverse events were reported with similar frequency in both groups. One or more events were reported by 1604 (55%) individuals allocated to placebo and by 1608 (56%) allocated to pravastatin. There were no reported cases of rhabdomyolysis. There were 36 instances of reported myalgia in the pravastatin group and 32 in those given placebo. At the 3-month visit (the only formal safety laboratory assessment), there were no participants in either group with creatine kinase concentrations higher than ten times the upper limit of normal, and increased plasma concentrations of alanine and aspartate transaminases (greater than three times the upper limit of normal) were recorded in one patient in each group.

Table 4 shows the first newly diagnosed cancers that appeared in each treatment group (excluding non-melanotic skin cancers), according to site and by year. Gastrointestinal cancers were more common in the pravastatin treated group (65 cases *vs* 45 in the placebo cohort). Overall, there was an imbalance in new cancer diagnosis, which was 25% more frequent in the pravastatin group. To put this finding in context we did a meta-analysis of cancer rates in previous randomised placebo controlled studies, lasting more than 3 years and that used pravastatin[2,3,5] or other statins (figure 5).[1,4,6,18] Treatment with either pravastatin (hazard ratio 1·06, 95% CI 0·96–1·17, p=0·20) or all statins taken together (1·02,

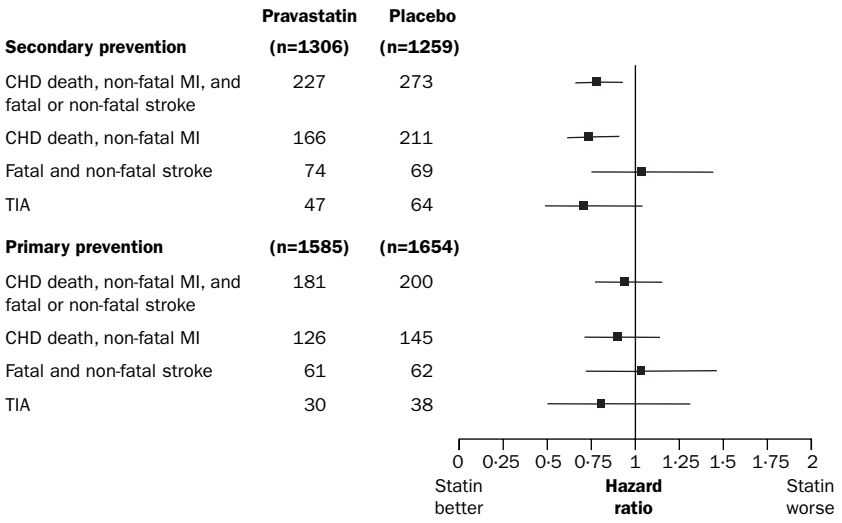

Figure 4: **Major cardiovascular outcomes, according to primary or secondary prevention status of participants**
CHD=coronary heart disease. MI=myocardial infarction. TIA=transient ischaemic attack. The primary endpoint of the study is reproduced for comparative purposes.

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Site	Treatment	Year				Hazard ratio (95% CI)	p
		1 (placebo n=2869, pravastatin n=2839)	2 (placebo n=2729, pravastatin n=2704)	3 (placebo n=2622, pravastatin n=2584)	4 (placebo n=804, pravastatin n=814)		
Breast	Placebo	4	4	2	1		
	Pravastatin	7	5	4	2	1·65 (0·78–3·49)	0·19
Gastrointestinal	Placebo	16	12	13	4		
	Pravastatin	15	18	21	11	1·46 (1·00–2·13)	0·053
Renal or genitourinary	Placebo	18	17	14	10		
	Pravastatin	13	19	19	7	1·00 (0·69–1·43)	0·99
Respiratory	Placebo	9	19	11	3		
	Pravastatin	10	15	13	8	1·12 (0·74–1·70)	0·60
Other	Placebo	11	18	10	3		
	Pravastatin	20	22	12	4	1·41 (0·95–2·09)	0·092
Total	Placebo	58	70	50	21		
	Pravastatin	65	79	69	32	1·25 (1·04–1·51)	0·020

Numbers=first new cancers, by site. Number of individuals at risk shown in table header are those at the midpoint of each year of study. Hazard ratio for effect of treatment adjusted for the covariates in table 1.

Table 4: **First new cancer diagnoses by site and year**

0·96–1·09, p=0·32) was not associated with an excess of cancer. There was no evidence of heterogeneity of increased risk among the pravastatin studies or overall.

Discussion

Treatment of elderly individuals for 3 years with pravastatin produced a 15% relative reduction (2·1% absolute reduction) in the risk of the primary endpoint in PROSPER. Over this period, individuals on pravastatin had less coronary events than those on placebo, but rates of stroke remained the same. However, an apparent reduction in transient ischaemic attacks suggests that the treatment did have an effect on the cerebrovascular circulation. Caution should be taken in interpretation of these results, since although the observed coronary event rate (12·2%) was near to that expected (12·0%), the stroke rate at 4·5% was about half of that predicted. The actual power to detect an assumed stroke benefit of a relative reduction of 20% was 41%. Pravastatin was well tolerated in this patient population, who were taking a high number of concomitant medications, and there was no indication of adverse effects on liver function or muscle enzymes.

Results of previous long-term trials[1–6] have proven the benefits of cholesterol lowering treatment with statins. In these trials, about 50 000 individuals were randomly assigned to drug or placebo, and all had follow-up of around 5 years. Long-term trials of pravastatin account for about 20 000 of these individuals.[19] Findings of the studies consistently showed benefit with a lack of associated concerns about safety. Results of PROSPER need to be interpreted in view of these earlier trials. Our study differs from previous studies in several ways; by design, we included men and women with a higher mean age than had been previously examined, combined both primary and secondary vascular disease prevention, and had a shorter follow-up.

We observed a dissociation between the cardiovascular and cerebrovascular components of treatment benefit, so that the overall reduction in risk seen in the composite primary endpoint was less than predicted. This finding was not due to an inability to lower LDL cholesterol, since the 34% fall was greater than that seen in previous long-term trials of 40 mg per day pravastatin. The lack of effect on stroke might be the consequence of a lack of statistical power, or might follow from the short duration of the trial. Recent publications[20,21] suggest that stroke benefit from statins does not begin to appear until after 3 years, whereas coronary risk reduction is an early event.[1,2,4]

Vascular factors contribute to cognitive impairment and dementia in old age.[22,23] This fact not only holds for large cortical infarcts and non-cortical microinfarcts, but also for white-matter lesions, thought to be of vascular origin.[24] We tested the notion that treatment with statins might slow this decline. The outcomes do not provide evidence for such benefit over the 3 years of the study. This finding may not be surprising, however, since there was no effect on clinical stroke. Lipophilic statins that efficiently cross the blood-brain barrier might work better than water soluble pravastatin. 5-year treatment with a high dose of the lipophilic simvastatin, however, did not prevent cognitive impairment.[6] Taken together, these experiments cast doubt on the suggestions from cross-sectional observations that statins might reduce risk of dementia by up to 70%.[11,12]

We noted that baseline HDL cholesterol (by contrast with LDL cholesterol) was strongly inversely related to risk of the primary endpoint, and that those in the lowest

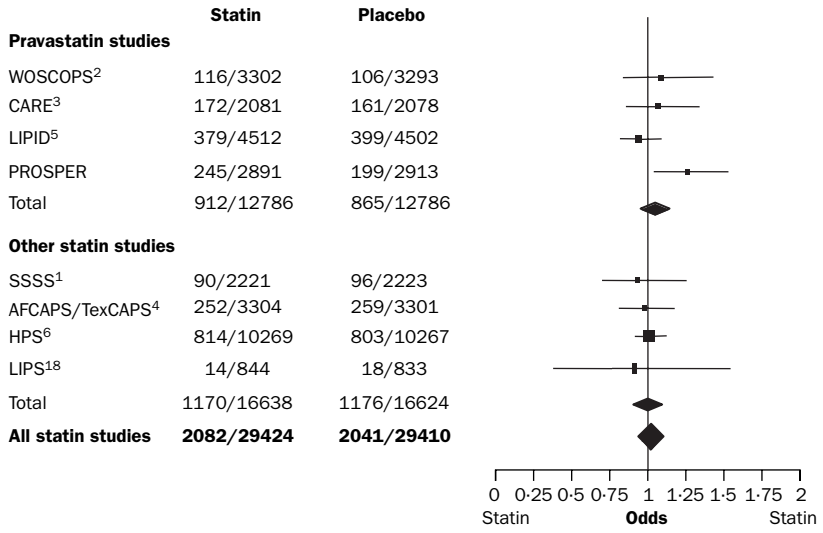

Figure 5: **Meta-analysis of cancer incidence in major statin trials**

Data are number of individuals with cancer/number of individuals in treatment group for each treatment group with odds ratio (95% CI) for risk of cancer in statin treated group relative to placebo.

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HDL tertile had the greatest benefit. The variation in treatment effect by HDL cholesterol tertile remained significant after adjustment for all other interactions involving HDL, sex, and history of vascular disease. This observation could help to target therapy in this age range. There were too few patients with diabetes to permit reliable assessment of the benefit seen previously.[25,26]

The potential for increased risk of cancer with the lowering of cholesterol was widely debated in the pre-statin era. Controversy arose from the finding of an inverse association between plasma cholesterol and cancer rates, especially in older persons,[8] and from the results of early trials.[27,28] More recent experience with statins in long-term trials[29] allayed concerns that there was a cause and effect relation, and formal meta-analyses indicate no effect of these drugs on cancer incidence.[29] The finding in PROSPER of more diagnosed cancers in those allocated to pravastatin should be interpreted in the context of this body of evidence. A meta-analysis of pravastatin trials, including PROSPER, revealed no significant effect of the drug on cancer rates. Inclusion of other statin trials in this analysis lends support to this contention. Furthermore, the Heart Protection Study,[6] to which large numbers of women and elderly individuals were recruited, showed no effect of the drugs on cancer. That said, the PROSPER population differed in age from the other trials used in the meta-analyses, and cancer risk in all statin trials that recruit elderly individuals should be assessed. In view of the available evidence, the most likely explanation is that the imbalance in cancer rates in PROSPER was a chance finding, which could in part have been driven by the recruitment of individuals with occult disease.

Translation of the results of PROSPER into daily clinical practice is not straightforward. The study provides clear evidence that, as in middle-aged people, statin therapy in elderly individuals reduces the risk of coronary disease, even in as short a period as 3 years. Although the apparent reduction in transient ischaemic attacks seen with pravastatin was encouraging, a clear result on stroke is likely to require a longer period of treatment, if indeed statins are beneficial in this age range. Duration of therapy could also affect benefit in terms of cognitive decline, disability, and dependency. Subgroup analyses support the view that the percentage cardiovascular risk reduction is similar across all subgroups, with the exception of HDL, where the subgroup with the lowest HDL seem to get the greatest benefit. Hence, PROSPER suggests that the strategy for vascular risk management in middle aged people should also be applied to elderly individuals.

The PROSPER study group

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Contributors

All authors contributed to the study design and interpretation and to the drafting of this manuscript. Local conduct of the study was undertaken by each respective national group under the Chairmanship of J Shepherd (Glasgow, Scotland), M B Murphy (Cork, Ireland), and G J Blauw (Leiden, Netherlands). I Ford and P Macfarlane respectively managed the database and electrocardiographic laboratory in the Robertson Centre and the Department of Medical Cardiology of the University of Glasgow. Invaluable advice on cognition testing came from P Houx of the University of Maastricht.

Conflict of interest statement

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