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Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis

M R Law, N J Wald, A R Rudnicka



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Abstract

Objectives To determine by how much statins reduce serum concentrations of low density lipoprotein (LDL) cholesterol and incidence of ischaemic heart disease (IHD) events and stroke, according to drug, dose, and duration of treatment.

Design Three meta-analyses: 164 short term randomised placebo controlled trials of six statins and LDL cholesterol reduction; 58 randomised trials of cholesterol lowering by any means and IHD events; and nine cohort studies and the same 58 trials on stroke.

Main outcome measures Reductions in LDL cholesterol according to statin and dose; reduction in IHD events and stroke for a specified reduction in LDL cholesterol.

Results Reductions in LDL cholesterol (in the 164 trials) were 2.8 mmol/l (60%) with rosuvastatin 80 mg/day, 2.6 mmol/l (55%) with atorvastatin 80 mg/day, 1.8 mmol/l (40%) with atorvastatin 10 mg/day, lovastatin 40 mg/day, simvastatin 40 mg/day, or rosuvastatin 5 mg/day, all from pretreatment concentrations of 4.8 mmol/l. Pravastatin and fluvastatin achieved smaller reductions. In the 58 trials for an LDL cholesterol reduction of 1.0 mmol/l the risk of IHD events was reduced by 11% in the first year of treatment, 24% in the second year, 33% in years three to five, and by 36% thereafter ($P < 0.001$ for trend). IHD events were reduced by 20%, 31%, and 51% in trials grouped by LDL cholesterol reduction (means 0.5 mmol/l, 1.0 mmol/l, and 1.6 mmol/l) after

results from first two years of treatment were excluded ($P < 0.001$ for trend). After several years a reduction of 1.8 mmol/l would reduce IHD events by an estimated 61%. Results from the same 58 trials, corroborated by results from the nine cohort studies, show that lowering LDL cholesterol decreases all stroke by 10% for a 1 mmol/l reduction and 17% for a 1.8 mmol/l reduction. Estimates allow for the fact that trials tended to recruit people with vascular disease, among whom the effect of LDL cholesterol reduction on stroke is greater because of their higher risk of thromboembolic stroke (rather than haemorrhagic stroke) compared with people in the general population.

Conclusions Statins can lower LDL cholesterol concentration by an average of 1.8 mmol/l which reduces the risk of IHD events by about 60% and stroke by 17%.

Introduction

Statins are highly effective in lowering serum cholesterol concentrations and preventing ischaemic heart disease (IHD).¹⁻³ Three issues remain. We do not know by how much different statins at different doses reduce low density lipoprotein (LDL) cholesterol concentrations. Secondly, the full effect of statins in preventing IHD events has been underestimated because IHD events in the first two years (before the full effect is attained⁴) were not censored, many trials used less effective statins, and trials were affected by non-adherence to the allocated regimen. Thirdly, there

Department of Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Barts and the London, Queen Mary's School of Medicine and Dentistry, University of London, London EC1M 6BQ
M R Law
professor
N J Wald
professor
A R Rudnicka
lecturer

Correspondence to: M R Law
m.r.law@qmul.ac.uk

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A full list of references and two extra tables can be found on bmj.com

Table 1 Absolute reductions* (mmol/l) (with 95% confidence intervals) and percentage reductions† in serum LDL cholesterol concentration according to statin and daily dose (summary estimates from 164 randomised placebo controlled trials)

Statin	Daily dose (mg)				
	5	10	20	40	80
Atorvastatin	1.51 (1.28 to 1.74), 31%	1.79 (1.62 to 1.97), 37%	2.07 (1.90 to 2.25), 43%	2.36 (2.12 to 2.59), 49%	2.64 (2.31 to 2.96), 55%
Fluvastatin	0.46 (0.18 to 0.75), 10%	0.74 (0.55 to 0.93), 15%	1.02 (0.90 to 1.13), 21%	1.30 (1.19 to 1.41), 27%	1.58 (1.40 to 1.76), 33%
Lovastatin	—	1.02 (0.71 to 1.34), 21%	1.40 (1.21 to 1.59), 29%	1.77 (1.60 to 1.94), 37%	2.15 (1.86 to 2.43), 45%
Pravastatin	0.73 (0.54 to 0.92), 15%	0.95 (0.83 to 1.07), 20%	1.17 (1.10 to 1.23), 24%	1.38 (1.31 to 1.46), 29%	1.60 (1.46 to 1.74), 33%
Rosuvastatin	1.84 (1.74 to 1.94), 38%	2.08 (1.98 to 2.18), 43%	2.32 (2.20 to 2.44), 48%	2.56 (2.42 to 2.70), 53%	2.80 (2.63 to 2.97), 58%
Simvastatin	1.08 (0.93 to 1.22), 23%	1.31 (1.22 to 1.40), 27%	1.54 (1.46 to 1.63), 32%	1.78 (1.66 to 1.90), 37%	2.01 (1.83 to 2.19), 42%

*Absolute reductions are standardised to usual serum LDL cholesterol concentration of 4.8 mmol/l before treatment (mean concentration in trials).

†Percentage reductions are independent of pretreatment LDL cholesterol concentration; 95% confidence intervals on percentage reductions can be derived by dividing those on absolute reductions by 4.8.

is a paradox in that meta-analyses of randomised trials showed that statins reduced the incidence of strokes by about 30%,^{5–8} but cohort studies showed no association between serum cholesterol concentrations and stroke.⁹

Methods

We carried out three analyses. The first was a meta-analysis of 164 short term (typically a few weeks) randomised placebo controlled trials of six statins (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin (recently marketed)), used in fixed dose.^{w1-w164} The meta-analysis examined the efficacy of reducing total and LDL cholesterol by dose and pretreatment serum cholesterol concentrations. The second meta-analysis was of 58 randomised trials (including eight of the above 164 trials) of reducing serum cholesterol concentration by any means and IHD events to estimate the reduction in risk by LDL cholesterol reduction and by duration of treatment. This updates our 1994 analyses.^{4 10 11} In the third analysis we examined data from nine cohort studies and the 58 randomised trials to determine the effect of a decrease in LDL cholesterol concentration on thromboembolic, haemorrhagic, fatal, and non-fatal stroke.

164 short term trials of statins and LDL cholesterol reduction

We searched Medline, Cochrane Collaboration, and Web of Science databases (see www.smd.qmul.ac.uk/wolfson/bpchol and bmj.com for full list of references^{w1-w164}). We included all double blind placebo controlled trials, irrespective of participants' age or disease. Participants in most trials were healthy with above average lipid concentrations. We excluded trials that had no placebo group, lasted less than two weeks, used variable doses (titrating), or used cholesterol lowering drugs in combination, and trials in which the order of treatment and placebo periods in crossover trials was not randomised or patients had chronic renal failure or organ transplantation. Drug efficacy was defined as the reduction in LDL cholesterol concentration for a given dose, expressed as the change in the treated group or period minus that in the placebo group or period.

58 randomised trials of serum cholesterol reduction (by any means) and IHD events

We expanded the literature search to include methods of reducing serum cholesterol concentrations other than statins; 58 trials met our inclusion criteria. We excluded trials in which risk factors other than lipids were changed, LDL cholesterol reduction was <0.2

mmol/l, fewer than five IHD events were recorded, or there was no untreated control group. We defined IHD events as IHD death or non-fatal myocardial infarction, ignoring subsequent events in an individual and excluding "silent" infarcts. In each trial we determined the numbers of IHD events separately for years one, two, three to five, and six years or more after trial entry.

We combined the odds ratios (treated/placebo) of disease events, stratified according to duration of scheduled treatment, to yield summary estimates. Each trial result was standardised to an LDL cholesterol reduction of 1.0 mmol/l.

Nine cohort studies and 58 randomised trials of serum cholesterol and stroke

We identified nine cohort studies of serum cholesterol concentration and stroke that distinguished between thromboembolic and haemorrhagic strokes by using computed tomography or autopsy findings. We used Medline (1980 to October 2002). We determined the difference in incidence for a difference in LDL cholesterol of 1.0 mmol/l. Data on stroke from the 58 randomised trials were combined. For more details of all our statistical analyses, see the unabridged paper on bmj.com.

Results

164 short term trials of statins and LDL cholesterol reduction

Details of the 164 trials are given on bmj.com. There were about 24 000 treated and 14 000 placebo participants.

See bmj.com for dose-response relations for the doses tested (2.5–30 mg/day). The straight lines fit the data well. Table 1 shows the estimated reductions in LDL cholesterol, according to statin and dose, calculated from the straight lines (see fig 1 on bmj.com) and standardised to the average pretreatment LDL cholesterol concentration in these trials (4.8 mmol/l; about the average in people having an IHD event). Rosuvastatin 5 mg/day, atorvastatin 10 mg/day, lovastatin and simvastatin 40 mg/day reduced LDL cholesterol concentration by about 35% (1.8 mmol/l), but fluvastatin and pravastatin produced smaller reductions even at the highest doses tested (80 mg/day). Rosuvastatin 10 mg/day, atorvastatin 20 mg/day, lovastatin and simvastatin 80 mg/day reduced LDL cholesterol concentration by about 45% (2.1 mmol/l) and rosuvastatin 80 mg/day by about 60% (2.8 mmol/l).

Statins significantly lowered LDL cholesterol from all pretreatment concentrations. The absolute reductions (in mmol/l) were greater in people with higher

Table 2 Reduction in risk (95% confidence intervals) of ischaemic heart disease events* for 1.0 mmol/l decrease in serum LDL cholesterol concentration, according to number of years in trial (58 trials)

Year in trial	% Reduction in risk
1st	11 (4 to 18)
2nd	24 (17 to 30)
3rd-5th	33 (28 to 37)
6th and subsequent	36 (26 to 45)

*IHD death and non-fatal myocardial infarction.

pretreatment LDL cholesterol concentrations; the percentage reductions were independent of pretreatment concentrations. The reductions in total and LDL cholesterol concentrations were highly correlated across trials ($r=0.83$). Statins increased HDL cholesterol by 0.07 mmol/l (0.06 mmol/l to 0.08 mmol/l) on average, with no detectable dose effect.

58 trials of serum cholesterol reduction by any means and IHD events

These 58 trials included 76 359 participants allocated treatment and 71 962 controls, with 5440 and 7102 IHD events respectively: 52% of participants had known vascular disease on entry. See tables A and B on bmj.com for details.

Table 2 shows the reduction in IHD events by duration of treatment; each trial result is standardised to a reduction in LDL cholesterol of 1.0 mmol/l (about the average reduction in the trials). In the first year the reduction was 11%, in the second 24%, and in the first and second years combined 18%. The reduction in the third, fourth, and fifth years combined was 33%, and for the sixth and subsequent years was 36%. Risk reduction was similar for fatal and non-fatal IHD events, for different methods of reducing serum cholesterol (fibrates, resins, niacin, statins, or dietary change), and in participants with and without known IHD on entry.

The trials tend to cluster into three groups, with mean reductions of LDL cholesterol of 0.5 mmol/l ($n=21$), 1.0 mmol/l ($n=24$), and 1.6 mmol/l ($n=5$). With reductions in LDL cholesterol of around 0.5, 1.0, and 1.6 mmol/l the reduction in IHD events after two or more years' treatment were 20%, 31%, and 51%, respectively; the greater the reduction in LDL cholesterol the greater the reduction in IHD events.

Serum cholesterol and stroke

Nine cohort studies

Analysis of data from nine cohort studies^{w201-w209} showed a 15% (6% to 21%) decrease in thromboembolic stroke ($P<0.001$) and a 19% (10% to 29%) increase in haemorrhagic stroke ($P<0.001$) for a 1.0 mmol/l decrease in LDL concentration. These opposing effects explain the absence of an association between serum cholesterol and stroke in a meta-analysis of cohort studies.⁹ The studies generally recorded only fatal stroke and deaths from the two types of stroke cancel because at age 60 (about the average in the studies), about half of fatal strokes are thromboembolic and half haemorrhagic.^{12 w210-w214} As 76% of non-fatal strokes are thromboembolic and 24% haemorrhagic and 71% of all strokes are thromboembolic and 29% haemorrhagic, the expected decrease in non-fatal stroke (per 1 mmol/l reduction in LDL cholesterol) is 7% (a 15% decrease in 76% plus a 19% increase in 24%).¹² Similarly the expected decrease for all stroke is 6%.

58 randomised trials of cholesterol reduction (by any means) and stroke

Fifty six of the 58 trials reported on deaths from stroke (though in 21 trials none occurred) and 40 reported on non-fatal strokes (in 10 none occurred) (see tables A and B on bmj.com for details).

Table 3 shows the main results on stroke from randomised trials and the above expected results from the nine cohort studies, standardised to an LDL cholesterol reduction of 1.0 mmol/l. Stroke risk in all the trials was reduced by 20% on average ($P<0.001$) but this varied. In people without known vascular disease the reduction was the same ($-6%$) as that expected from the cohort studies, but in people with known vascular disease it was higher ($-22%$ v $-6%$; $P<0.001$). This difference probably arises because thromboembolic stroke is more common in people with known vascular disease so more of their strokes will be thromboembolic. Reduction in LDL cholesterol concentration prevents thromboembolic but not haemorrhagic strokes, accounting for the greater than expected effect of treatment in this group. This also explains the greater than expected reduction in non-fatal stroke in shown table 3 ($-23%$ v $-7%$; $P<0.001$) as most non-fatal strokes are thromboembolic.

Table 3 Change in risk of stroke (relative odds reduction) for 1.0 mmol/l reduction in LDL cholesterol in randomised trials and estimates from analysis of cohort studies (fig 2) according to whether trial participants had known vascular disease on entry and whether stroke was thromboembolic or haemorrhagic and fatal or non-fatal

Category	Randomised trials			Estimated % change in risk in cohort studies† (95% CI)
	No of trials	No of events	Estimated % change in risk (95% CI)	
All stroke	41	3319	-20* (-14 to -26)	—
All stroke in people with known vascular disease	32†	2311	-22* (-28 to -16)	—
All stroke in people without known vascular disease	7†	752	-6 (-22 to 14)	-6‡ (-12 to 1)
Thromboembolic stroke	8	1204	-28* (-35 to -20)	-15* (-21 to -6)
Haemorrhagic stroke	8	149	-3 (-35 to 47)	19* (10 to 29)
Fatal stroke	56	678	-2 (-17 to 16)	0‡§ (-6 to 6)
Non-fatal stroke	40	2519	-23* (-29 to -16)	-7‡ (-13 to -1)

* $P<0.001$.

†Trials in which there were similar numbers of strokes in patients with and without vascular disease on entry are omitted, except one in which separate numbers were available.^{w168}

‡From data in figure 2 (taking account where necessary of proportions of non-fatal and all strokes that are thromboembolic and haemorrhagic).

§Meta-analysis of 45 cohort studies¹¹ (in which nearly all strokes recorded were fatal) gave similar result (2, -1 to 6).

The 20% reduction in stroke for a 1.0 mmol/l reduction in LDL cholesterol concentration is specific to these trial populations in which 80% of all strokes were in people with known vascular disease. In the general population, stroke registry data indicate that about 25% of first strokes are in people with known vascular disease.^{w217-w219} Therefore a reduction of 1.0 mmol/l in LDL cholesterol would reduce stroke in the general population by 10% (25% of the 22% reduction in people with known vascular disease and 75% of the 6% reduction in people without known vascular disease, from table 3).

Adverse effects

Forty eight of the 164 trials of statins and LDL cholesterol reported the number of participants with one or more symptoms possibly caused by the drug (1063/14197 allocated to statins and 923/10568 allocated to placebo). Meta-analysis of these data showed no excess risk in people allocated to statins. On average 1% fewer treated patients than placebo patients reported symptoms.

The only known serious adverse effects of statins are rhabdomyolysis and liver failure from hepatitis. The absolute risks are low. In the trials of statins and disease events, with about 35 000 people and 158 000 person years of observation in both treated and placebo groups (see table A on bmj.com), rhabdomyolysis was diagnosed in eight treated and five placebo patients, none with serious illness or death. From 1987 to May 2001 the Food and Drug Administration recorded 42 deaths from rhabdomyolysis attributable to statins in the United States,¹³ a rate of about one per million person years of use. There were no cases of liver failure in the trials. From 1987 to May 2000 the Food and Drug Administration recorded 30 cases of liver failure attributable to statins,¹⁴ again about one per million person years of use.

Concern over hazards from serum cholesterol reduction was resolved by earlier studies.⁷⁻¹¹ Data from the 58 randomised trials of cholesterol reduction and disease events confirm this. The odds ratios (treated/placebo) for a 1.0 mmol/l decrease in serum cholesterol were 0.87 (0.73 to 1.03; 675 deaths) for circulatory diseases other than IHD and stroke, 1.06 (0.96 to 1.16; 2293 deaths) for cancer, 0.94 (0.72 to 1.23; 324 deaths) for injuries and suicide, and 0.88 (0.78 to 1.01; 1363 deaths) for diseases other than circulatory diseases and cancer.

Discussion

Randomised trials show directly that a reduction in LDL cholesterol of 1.6 mmol/l halves the risk of IHD events after two years and that this reduction can be achieved with low doses of some statins (for example, simvastatin 20 mg/day, table 1). Certain statins achieve larger reductions (for example, 2.6 mmol/l with atorvastatin 80 mg/day and 2.8 mmol/l with rosuvastatin 80 mg/day), which would lead to greater reductions in IHD events. The corresponding risk reduction from such large reductions in LDL cholesterol cannot be observed directly from the trials but can be determined from cohort studies as it can be shown that the results from the trials and cohort studies are close if data from the first two years of treatment are excluded.

What is already known on this topic

Statins lower LDL cholesterol, but the size of the reduction according to statin and dose is uncertain

Statins prevent heart disease, but meta-analyses of randomised trials have underestimated their effect

The effect of statins on risk of stroke is uncertain

What this study adds

Simvastatin 40 mg/day, lovastatin 40 mg/day, and atorvastatin 10 mg/day lower LDL cholesterol by about 37% from all pretreatment concentrations

These interventions reduce the risk of ischaemic heart disease events at age 60 by an estimated 61% in the long term, with little reduction in the first year but a 51% reduction by the third year

The interventions reduce the overall risk of stroke by 17%, preventing thromboembolic but not haemorrhagic stroke

Data from published cohort studies predict that at age 60 years a 2.2 mmol/l reduction in serum LDL cholesterol concentration (attainable by using atorvastatin 40 mg/day, lovastatin 80 mg/day, or rosuvastatin 20 mg/day) would reduce the risk of IHD by nearly 70%.⁹ However, adverse effects are also dose related,¹³ and rosuvastatin is relatively untested. As moderate doses of statins substantially reduce the risk of IHD events it may be prudent to select commonly used doses of the older drugs for general use. This would also be cheaper, as simvastatin comes off patent in 2003 and lovastatin is already off patent. At doses of 40 mg/day these drugs lower LDL cholesterol by 1.8 mmol/l, which can reduce IHD events at age 60 years by 61% (51% to 71%).⁹ This is about double the currently recognised preventive effect of 30%.¹⁻³

Reasons for underestimation of effect on IHD

Why are the current estimates of effect so low? Firstly, five of the seven largest statin trials used pravastatin, which is relatively less effective (table 1). Secondly, risk falls relatively little within the first two years, and inclusion of these early events underestimates the preventive effect. Thirdly, a particular problem for the statin trials was the extent to which the intention to treat analysis underestimated the true preventive pharmacological effect because of non-adherence to the protocol (treated patients not taking their tablets and placebo patients taking statins).

Effects of LDL cholesterol reduction on stroke

The 10% estimated overall reduction in stroke (relative risk 0.90) for a 1.0 mmol/l reduction in LDL cholesterol is equivalent to a 17% (9% to 25%) reduction in stroke for a 1.8 mmol/l reduction LDL cholesterol, readily achievable with a statin (as $0.90^{1.8/1}$ = relative risk of 0.83). The interpretation of the cohort study result showing a higher incidence of haemorrhagic stroke for a lower LDL cholesterol concentration is uncertain. Too few haemorrhagic strokes were identified in the randomised trials to resolve the uncertainty. An increased risk cannot be excluded, but this

should not preclude the use of statins in the prevention of cardiovascular disease. The evidence is clear: statins substantially reduce IHD events (by 61%), and prevent stroke by 17% overall, through the prevention of non-fatal strokes with little effect on the risk of fatal stroke. Any possible excess of haemorrhagic stroke is greatly outweighed by the protective effect against IHD events and thromboembolic stroke.

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Contributors: See bmj.com

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Competing interests: NW and ML have filed a patent application on the formula of a combined pill to simultaneously reduce four cardiovascular risk factors.

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Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials

M R Law, N J Wald, J K Morris, R E Jordan

Abstract

Objective To determine the average reduction in blood pressure, prevalence of adverse effects, and reduction in risk of stroke and ischaemic heart disease events produced by the five main categories of blood pressure lowering drugs according to dose, singly and in combination.

Design Meta-analysis of 354 randomised double blind placebo controlled trials of thiazides, β blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and calcium channel blockers in fixed dose.

Subjects 40 000 treated patients and 16 000 patients given placebo.

Main outcome measures Placebo adjusted reductions in systolic and diastolic blood pressure and prevalence of adverse effects, according to dose expressed as a multiple of the standard (recommended) doses of the drugs.

Results All five categories of drug produced similar reductions in blood pressure. The average reduction was 9.1 mm Hg systolic and 5.5 mm Hg diastolic at standard dose and 7.1 mm Hg systolic and 4.4 mm Hg diastolic (20% lower) at half standard dose. The drugs reduced blood pressure from all pretreatment levels, more so from higher levels; for a 10 mm Hg higher blood pressure the reduction was 1.0 mm Hg systolic and 1.1 mm Hg diastolic greater. The blood

pressure lowering effects of different categories of drugs were additive. Symptoms attributable to thiazides, β blockers, and calcium channel blockers were strongly dose related; symptoms caused by ACE inhibitors (mainly cough) were not dose related.

Angiotensin II receptor antagonists caused no excess of symptoms. The prevalence of symptoms with two drugs in combination was less than additive. Adverse metabolic effects (such as changes in cholesterol or potassium) were negligible at half standard dose.

Conclusions Combination low dose drug treatment increases efficacy and reduces adverse effects. From the average blood pressure in people who have strokes (150/90 mm Hg) three drugs at half standard dose are estimated to lower blood pressure by 20 mm Hg systolic and 11 mm Hg diastolic and thereby reduce the risk of stroke by 63% and ischaemic heart disease events by 46% at age 60-69.

Introduction

Lowering systolic blood pressure by 10 mm Hg or diastolic blood pressure by 5 mm Hg reduces the risk of stroke by about 35% and that of ischaemic heart disease (IHD) events by about 25% at age 65.¹⁻³ This applies across all levels of blood pressure in Western populations, not only in "hypertension."¹⁻⁷ Blood pressure lowering drugs should be more widely used,^{6,7} but which drugs are most appropriate, whether combina-



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Department of Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Barts and the London, Queen Mary's School of Medicine and Dentistry, University of London, London EC1M 6BQ

M R Law
professor

N J Wald
professor

J K Morris
senior lecturer

R E Jordan
research assistant

Correspondence to:
M R Law
m.r.law@qmul.ac.uk

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