

Cross sectional survey of effectiveness of lipid lowering drugs in reducing serum cholesterol concentration in patients in 17 general practices

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Abstract

Objective To compare the effectiveness of lipid lowering drugs in lowering serum cholesterol concentrations.

Design Cross sectional study.

Setting 17 practices within 17 primary care groups in Trent region, United Kingdom.

Participants Patients aged 35 years or over taking lipid lowering drugs and with at least two serum cholesterol concentrations recorded on computer.

Main outcome measures Proportion of patients achieving serum cholesterol concentration of ≤ 5 mmol/l and mean percentage reduction in serum cholesterol concentration.

Results 1353 of 2469 (54.8%) patients receiving lipid lowering treatment had a last recorded serum cholesterol concentration of ≤ 5 mmol/l. Significantly more patients taking statins achieved the target value for serum cholesterol (5 mmol/l) than those taking fibrates (1307 (57%) *v* 46 (26%); $P < 0.0001$). Atorvastatin and simvastatin were the most effective drugs in achieving the target. Lipid lowering drugs differed significantly for pretreatment serum cholesterol concentration, most recent cholesterol concentration, and the associated percentage reduction. Atorvastatin and simvastatin achieved the greatest percentage reduction in serum cholesterol concentrations (30.1%, 95% confidence interval 28.8% to 31.4% and 28.0%, 26.7% to 29.3%, respectively). Although the mean serum cholesterol concentrations in this unselected population tended to be higher than those in clinical trials, the percentage reduction was consistent with the trials.

Conclusion The ability of individual statins to lower serum cholesterol concentration varied, with atorvastatin and simvastatin being the most effective. The percentage reductions agreed with those of randomised controlled trials indicating likely benefits in unselected patients in primary care. As the initial serum cholesterol concentrations were higher than those in randomised controlled trials, target serum cholesterol values of ≤ 5 mmol/l may be unrealistic even for patients on the most efficacious drugs. Also, the higher initial concentrations could mean that the absolute reduction in cardiovascular risk in primary care patients is greater than thought.

Introduction

Statins in patients with coronary heart disease help reduce further cardiovascular events and improve survival.¹⁻⁴ We know relatively little about the comparative effectiveness of different lipid lowering drugs because studies that make direct comparisons of the drugs are uncommon. We have only been able to find one study comparing the effectiveness of statins.⁵ This randomised controlled trial compared five statins, at different doses, over an eight week period in 534 patients. It was published by the manufacturer whose statin, atorvastatin, was most effective. Therefore we compared the effectiveness of individual lipid lowering drugs in lowering serum cholesterol concentration outside the setting of a clinical trial.

Methods

We conducted a cross sectional study using one year follow up data collected during 2001 from 17 practices in Trent that had taken part in a study of the workload implications of the national service framework for coronary heart disease.⁶ The study population consisted of people aged 35 years or over receiving current lipid lowering treatment (defined as a prescription within the past three months) who also had at least two serum cholesterol values (at least 28 days apart) recorded on their general practice's computer. We excluded patients whose last prescription for lipid lowering drugs was over three months ago as they may have stopped treatment.

We used MIQUEST to extract the following data from the general practice computer systems: pseudo-anonymous unique identifying code; age; sex; dates and values of all recorded serum cholesterol concentrations; date, dose, and type of lipid lowering drugs; smoking status; body mass index; blood pressure; and comorbidity (stroke, diabetes, ischaemic heart disease).

At the time of the study five statins were in general use (fluvastatin, cerivastatin, atorvastatin, simvastatin, and pravastatin); cerivastatin has since been withdrawn from the market. We grouped fibrates and other drugs together since the numbers were too few to make comparisons between individual preparations meaningful. We defined pretreatment serum cholesterol concentra-

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tion as the earliest recorded serum cholesterol value, closest to the start of lipid lowering treatment.

Outcome measures

Our main outcome measure was the proportion of patients taking each lipid lowering drug who achieved a serum cholesterol concentration of ≤ 5 mmol/l. This outcome was chosen in accordance with the type of binary outcome often stated in guidelines and used by general practitioners to monitor response to treatments. Our secondary outcome was the percentage reduction in serum cholesterol concentrations with each lipid lowering drug. We included this measure as it tends to be consistent with the method for reporting results of the randomised controlled trials.

Analysis

We used SPSS (version 11.0) and STATA (version 7.0). We undertook a random effects unconditional logistic regression in STATA to determine unadjusted and adjusted odds ratios for the outcome of having a serum cholesterol concentration of ≤ 5 mmol/l. We used simvastatin as the reference drug. Our main explanatory variable of interest was the type of drug (individual statins and fibrates as a group). We adjusted for the potential confounders of age, sex, obesity (body mass index < 25 , 25-30, > 30 , not recorded), smoking status (current, former smoker, non-smoker, not recorded), comorbidity (hypertension or not, ischaemic heart disease or not, diabetes or not, stroke or not), and pretreatment serum cholesterol concentrations (< 6.0 mmol/l, 6.0-6.9 mmol/l, 7.0-7.9 mmol/l, 8.0-8.9 mmol/l, ≥ 9 mmol/l, not recorded). We included registered general practice as a random effect.

We calculated the mean reduction in serum cholesterol values with 95% confidence intervals by one way analysis of variance, restricting the analysis to those patients with a pretreatment serum cholesterol value. We also undertook a random effects linear regression in STATA to determine the difference between the lipid lowering drugs (particularly atorvastatin) for the percentage reduction in serum cholesterol concentration achieved compared with simvastatin. We adjusted for age, sex, smoking status, comorbidity, obesity, and pretreatment serum cholesterol concentration. We included registered general practice as a random effect.

Results

Of the 2469 patients in our target population, 1612 (65.3%) had a diagnosis of ischaemic heart disease or had a current prescription for nitrates. Only 129 (8%)

patients did not have at least one of the comorbidities of ischaemic heart disease, stroke, hypertension, or diabetes. The flow of patients through the study and their characteristics are described on [bmj.com](#).

Effectiveness of statins

Table 1 shows the number of patients in each group with a last recorded serum cholesterol concentration of ≤ 5 mmol/l. Of the 2289 patients taking statins, 1307 (57.1%) reached the target range compared with 46 (25.6% of 180) of those taking fibrates and other drugs ($\chi^2 = 67.0$, $df=1$, $P < 0.0001$). Of the 951 patients taking atorvastatin, 567 (59.6%) reached the target range. A similar proportion of patients taking simvastatin (59.2%; 530 of 896) achieved target values. However, only 23 (35.4%) of the 65 patients taking fluvastatin achieved target values.

Patients taking atorvastatin were no more likely than patients taking simvastatin to have serum cholesterol concentrations within the target range (adjusted odds ratio 1.15, 95% confidence interval 0.93 to 1.42; table 1). Patients taking fluvastatin, pravastatin, or fibrates were significantly less likely to have a serum cholesterol concentration within the target range than patients taking simvastatin.

Table 2 shows the mean serum cholesterol concentrations before treatment and also the most recent values for each individual drug for the 1390 patients who had a pretreatment serum cholesterol concentration recorded. One way analysis of variance showed a significant difference between the drugs for pretreatment serum cholesterol concentrations ($F=7.07$, $df=5$; $P < 0.0001$), most recent serum cholesterol concentrations ($F=11.59$, $df=5$; $P < 0.0001$), and percentage reduction ($F=9.68$, $df=5$; $P < 0.0001$). Atorvastatin and simvastatin achieved the greatest reduction in serum cholesterol concentration, with a mean percentage reduction of 30.11% (28.84% to 31.38%) and 28.02% (26.71% to 29.34%), respectively. Simvastatin and atorvastatin achieved the lowest final serum cholesterol concentrations. The mean final concentration for patients taking simvastatin was 5.05 (4.95 to 5.16) mmol/l and for patients taking atorvastatin it was 4.99 (4.90 to 5.09) mmol/l.

Discussion

The statins vary significantly in their ability to lower serum cholesterol concentrations, with atorvastatin and simvastatin achieving the best results. We found that statins can achieve similar percentage reductions in serum cholesterol concentrations in a primary care

Table 1 Unadjusted and adjusted odds ratios associated with having a serum cholesterol concentration of ≤ 5 mmol/l for individual lipid lowering drugs compared with simvastatin

Drug	Total	Last recorded serum cholesterol concentration ≤ 5 mmol/l	Unadjusted odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
Simvastatin	896	530 (59.2)	1.00		1.00	
Pravastatin	136	62 (45.6)	0.58 (0.40 to 0.83)	0.003	0.60 (0.40 to 0.91)	0.015
Cerivastatin	241	125 (51.9)	0.74 (0.56 to 0.99)	0.04	0.85 (0.60 to 1.21)	0.38
Fluvastatin	65	23 (35.4)	0.38 (0.22 to 0.64)	< 0.0001	0.45 (0.25 to 0.81)	0.008
Atorvastatin	951	567 (59.6)	1.02 (0.85 to 1.23)	0.84	1.15 (0.93 to 1.42)	0.21
Fibrates and others	180	46 (25.6)	0.24 (0.17 to 0.34)	< 0.0001	0.24 (0.16 to 0.36)	< 0.0001

*Odds ratios adjusted for sex, age, obesity, smoking status, pretreatment serum cholesterol value, comorbidity (ischaemic heart disease, diabetes, hypertension, stroke), and registered general practice (as random effect).

Table 2 Pretreatment and most recent serum cholesterol concentration (mmol/l), and percentage reduction by individual lipid lowering drugs. Values are means (95% confidence intervals) unless stated otherwise

Drug	No of patients	Pretreatment serum cholesterol concentration	Last recorded serum cholesterol concentration	% reduction
Fluvastatin	45	7.41 (7.14 to 7.69)	5.64 (5.34 to 5.94)	23.66 (20.33 to 26.99)
Pravastatin	78	7.14 (6.89 to 7.39)	5.31 (5.09 to 5.53)	24.85 (22.03 to 27.67)
Cerivastatin	124	6.99 (6.73 to 7.24)	5.44 (5.22 to 5.66)	21.17 (18.69 to 23.65)
Simvastatin	480	7.12 (7.00 to 7.25)	5.05 (4.95 to 5.16)	28.02 (26.71 to 29.34)
Atorvastatin	554	7.26 (7.15 to 7.36)	4.99 (4.90 to 5.09)	30.11 (28.84 to 31.38)
Fibrates and others	109	7.94 (7.52 to 8.35)	5.71 (5.46 to 5.96)	25.14 (21.84 to 28.44)
Total	1390	7.24 (7.16 to 7.31)	5.15 (5.09 to 5.21)	27.70 (26.91 to 28.49)

Pretreatment serum cholesterol values, ranges, and associated percentage reduction in three randomised controlled trials: the 4S study of simvastatin included participants with serum cholesterol concentration of 5.5 to 8.0 mmol/l (mean 6.7 mmol/l) and achieved a 25% reduction; the LIPID study of pravastatin included participants with serum cholesterol concentrations of 4.0 to 7.0 mmol/l (mean 5.6 mmol/l) and achieved a 20% reduction; the CARE study of pravastatin included participants with serum cholesterol concentrations of <6.2 mmol/l (mean 5.4 mmol/l) and achieved an 18% reduction.

setting as in randomised double blind placebo controlled clinical trials.

Initial serum cholesterol concentrations in our study population were higher than those for patients in the clinical trials, which may partly explain the high proportion of patients who fail to achieve the target values set in guidelines, because a greater absolute reduction is needed to achieve the target value of ≤ 5 mmol/l.⁷ This is important not only for determining whether patients are receiving adequate treatment or require a change, but also for doctors whose performance may be monitored by using such targets in funding formulas. We also found that statins were being used in patients with established cardiovascular disease or in those who were likely to be at high risk because of comorbidity such as stroke, diabetes, or hypertension. This is compatible with the approach required in the national service framework for coronary heart disease.⁸ Our data, however, show that there is still room for improvement in the overall management of hyperlipidaemia in primary care and, given the expected benefits, there is a strong case for further directing resources to this end.

Cross sectional analysis of drug effectiveness in patients using routine clinical data has limitations as a research methodology. The patients are not randomised and biases may arise in the selection of a treatment for particular patient characteristics. For example, one statin might be preferred when cholesterol concentrations are highest or when a patient is non-responsive to another statin. We used multivariate analysis to adjust for differences in several baseline characteristics, including pretreatment serum cholesterol concentrations, to minimise any bias. The data may be incomplete or inaccurate and there may be recording biases—only increased cholesterol concentration being recorded, for example. As almost 80% of patients were in practices where test results are posted automatically into patients' records from the laboratory, we do not expect this to have substantially biased our results. Just over half of our population had pretreatment serum cholesterol concentrations recorded on computer, but we found no difference between each drug for the proportion of patients with such values recorded.

Although practices may be atypical in their behaviour, we have no reason to believe that any of the 17 practices in our study were unusual in their interest in or clinical behaviour towards hyperlipidaemia; we have evidence that the patients from such practices are representative of the population of Trent, and Trent is

similar to the rest of the United Kingdom.⁹ Certainly these patients represented a "real life" casemix: 92% had at least one of the four major comorbidities (ischaemic heart disease, stroke, hypertension, or diabetes), and 55% were aged over 65. Despite these limitations, descriptive studies, interpreted with suitable caution, can offer some useful insight to complement the data from studies using randomisation.

Three quarters of the patients in our study were taking atorvastatin or simvastatin, and these were the statins associated with the greatest percentage reduction in serum cholesterol concentrations and the highest proportions of patients achieving target levels.⁵ Pravastatin, fluvastatin, and fibrates were less effective in lowering serum cholesterol concentration. Our ranking of the effectiveness of the lipid lowering drugs

What is already known on this topic

Statins in patients with coronary heart disease help reduce further cardiovascular events and improve survival

This seems to be a class effect of statins, although there may be important differences in effectiveness between them

Less than half of patients in the community who take lipid lowering drugs achieve target serum cholesterol values

What this study adds

Statins vary in their ability to lower serum cholesterol concentration, with atorvastatin and simvastatin achieving the best results

The percentage reductions agreed with those found in randomised controlled trials

Since initial serum cholesterol concentrations were higher than in trials, absolute risk reductions in primary care patients may be greater than thought

Target values of ≤ 5 mmol/l may be unrealistic even for patients taking the most efficacious drugs, because the initial mean cholesterol values of primary care patients are higher than those of patients in trials

was similar to that found in the single previous randomised controlled trial comparing five statins.⁵

We are aware that there have been no direct comparisons of the clinical outcomes in patients taking different statins and, realistically, such studies are unlikely. Initial serum cholesterol concentrations were higher in our study than in the randomised controlled trials, therefore the absolute risk reductions in primary care patients (and hence the overall population benefits) may be greater than thought. Achieving target cholesterol values of $\leq 5\text{mmol/l}$ may, however, be unrealistic.

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Primary care in the United States

Primary care gatekeeping and referrals: effective filter or failed experiment?

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The use of primary care physicians as gatekeepers to specialists and other medical resources—considered to be a managed care innovation in the United States—has proliferated during the past few decades. Its introduction has been accompanied by a government sponsored programme of research into referrals from primary care (box 1). Findings from these studies may offer insights into how the UK's NHS could shape the gatekeeping function of general practitioners. This article discusses the concept of gatekeeping, contrasts the processes of referral to specialists in the United States and the United Kingdom, examines the mechanisms by which gatekeeping influences resource allocation, and discusses the effects of linking gatekeeping with financial incentives and utilisation review.

Gatekeeping in the United States and the United Kingdom

Within modern societies, gatekeepers are positioned between organisations and individuals who wish to use resources within those organisations. Gatekeepers use discretion when determining who will be granted access to these resources. Physician gatekeepers collaborate with patients to identify their healthcare needs and choose services that effectively meet those needs. Public acceptance of gatekeeping is strengthened when there are too few resources to satisfy everyone's demands. In the United Kingdom, where long queues to see specialists are common because specialists are in short supply, the general practitioner

Summary points

Gatekeeping systems have emerged in countries with scarce medical resources

Gatekeepers ensure equity by judiciously matching healthcare services, including specialty referrals, to healthcare needs

Gatekeeping alters patients' behaviour, increasing levels of first contact care with primary care physicians, thereby reducing patients' self referrals

Patients in US health plans with gatekeeping arrangements are twice as likely to be referred to specialist care as their UK counterparts

There is little evidence that gatekeeping has had much effect on patients' referral rates in the United States, a healthcare environment rich in specialists

gatekeeper has enjoyed widespread support. In the United States, the public perceives the supply of specialised healthcare resources as limitless and accessible to all—hence its dissatisfaction with primary care gatekeepers.²