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Primary care

Statin use in the secondary prevention of coronary heart disease in primary care: cohort study and comparison of inclusion and outcome with patients in randomised trials

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Abstract

Objective To compare the social and demographic profiles of patients who receive statin treatment after myocardial infarction and patients included in randomised trials. To estimate the effect of statin use in community based patients on subsequent all cause mortality and cardiovascular recurrence, contrasting effects with trial patients.

Design Observational cohort study using a record linkage database.

Setting Tayside, Scotland (population size and characteristics: about 400 000, mixed urban and rural).

Subjects 4892 patients were discharged from hospital after their first myocardial infarction between January 1993 and December 2001. 2463 (50.3%) were taking statins during an average follow-up of 3.7 years (3.1% in 1993 and 62.9% in 2001).

Main outcome measures All cause mortality and recurrence of cardiovascular events.

Results 319 deaths occurred in the statin treated group (age adjusted rate 4.1 per 100 person years, 95% confidence interval 3.2 to 4.9), and 1200 in the statin untreated group (12.7 per 100 person years, 11.1 to 14.3). More older people and women were represented in the population of patients treated with statins than among those recruited into clinical trials (mean age 67.8 *v* 59.8; women 39.6% *v* 16.9%, respectively). The effects of statins in routine clinical practice were consistent with, and similar to, those reported in clinical trials (adjusted hazard ratio for all cause mortality 0.69, 95% confidence interval 0.59 to 0.80; adjusted hazard ratio for cardiovascular recurrence 0.82, 0.71 to 0.95).

Conclusions The community effectiveness of statins in those groups that were not well represented in clinical trials was similar to the efficacy of statins in these trials.

Introduction

Statins are effective cholesterol lowering agents and are prescribed for prevention of cardiovascular events. Several large clinical trials (the Scandinavian simvastatin survival study (4S), the cholesterol and recurrent events (CARE) study, the long term intervention with pravastatin in ischaemic disease (LIPID) study, and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione (GISSI-P) study)[1–4] of secondary prevention of coronary heart disease have shown that statins reduce the risk of death by about 30%. However, it is common for clinical trials to apply selection criteria that may protect the internal validity of the trial at the expense of reducing the applicability of the trial's findings to the wider population of patients seen in routine clinical practice. Consequently, patients who are prescribed statins in the "real world" may differ systematically from those people who receive statins in clinical trials and may have different outcomes from those reported in trials.

We reviewed the literature relating to the effects of statin treatment on cardiovascular outcomes, but we found no studies that directly compared the sociodemographic profile and clinical outcomes between patients routinely treated in the community and in clinical trials. However, a recent paper has shown that the effect of statins prescribed in general practice had similar effects on serum cholesterol concentrations to that seen in trials.[5] We recently reported a meta-analysis that included 27 secondary prevention trials of statins published up to December 2001.[6] This analysis showed that the mean age of patients was 59.8, the proportion of female patients was 16.9%, and statins reduced mortality by 21% (relative risks 0.79, 95% confidence interval 0.73 to 0.85). We characterised those subjects who received statin treatment in the community after myocardial infarction; we estimated the effect of statin use on subsequent all cause mortality and cardiovascular recurrence; and we compared the sociodemographic profile and clinic outcome between these community based patients and clinical trial patients.

Methods

We carried out a cohort study in the population (about 400 000, mixed urban and rural) of Tayside in Scotland, using the record linkage database of the Tayside medicine monitor unit. The database has been described previously.[7] It contains several data sets, including all dispensed community prescriptions, hospital discharge data, mortality data, biochemistry data, sociodemographic descriptors, and other data that are linked by a unique patient identifier, the community health index number. The data have been validated by inspection of general practitioners' records[8 9] and made anonymous for the purposes of research.

Study population and patients

The study population was composed of all residents of Tayside who were registered with a general practitioner between 1993 and 2001 inclusive (the "study window"), or from 1 January 1993 until their date of death if they died before the end of the study window.

The study patients were composed of those people in the study population who were discharged from Tayside hospitals during the study window with an incident myocardial infarction.

We divided patients into two groups after their hospital episode: statin users and non-statin users.

Outcomes

The study outcomes were all cause mortality and cardiovascular events, defined as a new non-fatal myocardial infarction or cardiovascular mortality during the follow-up period. We defined all cause mortality from mortality data from the General Register Office and cardiovascular mortality as ICD-9 codes 390-459 and ICD-10 codes I00-I99.

Statistical analysis

We summarised data as means with standard deviations for continuous variables and as numbers (percentages) of subjects for categorical variables. We used χ^2 and t tests to determine significant differences. We also used Cochran-Armitage trend tests if there were more than two categorical variables. In the analyses of the outcomes we calculated adjusted hazard ratios with 95% confidence intervals in Cox regression models with a time dependent variable for statin use. The other covariates in the models were age, sex, Carstairs deprivation category,[10] and the different types of cardiovascular co-medication during the follow-up period: β blockers, angiotensin converting enzyme (ACE) inhibitors, other antihypertensive drugs, antiplatelet drugs, nitrates, warfarin, calcium channel blockers, hormone replacement therapy, oral contraceptives, steroids, non-steroidal anti-inflammatory drugs, disease modifying antirheumatic drugs, previous disease histories of angina, stroke, heart failure, peripheral vascular disease, diabetes mellitus, obstructive airway disease, cancer, renal failure, and rheumatoid arthritis. We used SAS, version 8.0 (SAS Institute, Cary, North Carolina, USA) for all statistical analyses.

Results

A total of 4892 patients were included in the study. Of these, 2463 (50.3%) were treated with statins during an average follow-up of 3.7 years. In the group treated with statins, 319 patients died (age adjusted rate 4.1 per 100 person years, 95% confidence interval 3.2 to 4.9), and in the group not treated with statins 1200 died (12.7 per 100 person years (11.1 to 14.3)). Table 1 shows the characteristics of statin users and non-users. Statin use was more common in younger patients. Men were more likely to be prescribed statins than women. Statin use rose significantly from 3.1% in 1993 to 62.9% in 2001 (trend test, $P<0.001$). Statin use in older patients also rose over the study period. However, statin use did not change significantly between the sexes or with social deprivation.

Five statins (atorvastatin, cerivastatin, fluvastatin, pravastatin, and simvastatin) were available during the study period, and simvastatin was the most commonly used statin in Tayside patients. About 80% of statin use was simvastatin, at a median daily dose of 10 mg.

Proportions of older and female patients in the community in Tayside were higher than in clinical trials (mean age 67.8 (62.9 for statin users and 72.7 for non-users) *v* 59.8; women 39.6% (37.1 for statin users and 42.1 for non-users) *v* 16.9%, respectively). Table 2 shows the details of the multivariate analysis. Statin reduced all cause mortality by 31% (95% confidence interval 20% to 41%) and recurrent myocardial infarction or cardiovascular death by 18% (5% to 29%). Antiplatelet drugs, β blockers, nitrates, calcium blockers, and angiotensin converting enzyme inhibitors were also each independently associated with diminished risk except antihypertensive drugs and warfarin. Compared with patients who had had a myocardial infarction who did not take any cardiovascular drugs, statin users who took up to two other cardiovascular drugs had lower risks of cardiovascular events (hazard ratio 0.70, 95% confidence interval 0.50 to 0.97 for statin plus one cardiovascular drug and 0.73, 0.58 to 0.91 for statin plus two cardiovascular drugs). The risk of cardiovascular events did not differ between those statin users who took more than two additional cardiovascular drugs and those post-myocardial infarction patients who received no drug treatments.

We also did subgroup analyses of older patients (aged ≥65) and women. In the group of women, 633 patients died (crude rate 9.1 per 100 person years, 8.5 to 9.8), and in the group of older patients, 1286 died (13.0 per 100 person years, 12.3 to 13.6). The adjusted hazard ratios of mortality in patients receiving statin treatment were 0.63 (0.49 to 0.80) for female and 0.72 (0.61 to 0.84) for older patients (table 2). The numbers needed to treat with statin for 3.7 years for all cause mortality were 21 for overall, 20 for women, and 20 for older people (for non-fatal myocardial infarction, the numbers needed to treat were 35, 20, and 35, respectively).

Table 1 Distribution of statin use in patients after myocardial infarction, Tayside, 1993-2001. Values are numbers (percentages) of patients unless otherwise indicated

	Group treated with statins (n=2463)	Group not treated with statins (n=2429)	P value (χ^2 test)
Age:*			
<45	145 (5.9)	35 (1.4)	<0.001†
45-54	420 (17.1)	160 (6.6)	
55-64	745 (30.3)	334 (13.8)	
65-74	786 (31.9)	708 (29.2)	
75+	367 (14.9)	1192 (49.1)	
Sex:			
Male	1550 (62.9)	1406 (57.9)	<0.001†
Female	913 (37.1)	1023 (42.1)	
Deprivation category:‡			
1 (least deprived)	184 (7.5)	144 (6.0)	=0.004†
2	373 (15.2)	401 (16.6)	
3	595 (24.3)	639 (26.4)	
4	470 (19.2)	473 (19.5)	
5	253 (10.3)	280 (11.6)	
6 (most deprived)	578 (23.5)	481 (19.9)	
Cardiovascular drug use during follow up:			
β blockers	1705 (69.2)	805 (33.1)	<0.001
Angiotensin converting enzyme inhibitors	1414 (57.4)	739 (30.4)	<0.001
Antihypertensive drugs	1151 (46.7)	1271 (52.3)	<0.001
Antiplatelets	2193 (89.0)	1591 (65.5)	<0.001
Nitrates	2024 (82.2)	1510 (62.7)	<0.001
Calcium blockers	1033 (41.9)	778 (32.0)	<0.001
Warfarin	253 (10.3)	232 (9.6)	=0.399
Comorbidity:			
Diabetes mellitus	327 (13.3)	420 (17.3)	<0.001
Obstructive airway disease	12 (0.5)	31 (1.3)	=0.003
Cancer	33 (1.3)	76 (3.13)	<0.001
Renal failure	5 (0.2)	6 (0.3)	=0.745
Rheumatoid arthritis	9 (0.4)	5 (0.2)	=0.296
Number of types of cardiovascular drugs used:			
Statin plus one drug	63 (2.6)	—	—
Statin plus two drugs	196 (8.0)	—	—
Statin plus three or more drugs	2195 (89.1)	—	—

*Trend test, P<0.001.
† Overall χ^2 test between the group treated with statins and the group not treated with statins.
‡For 4871 subjects.

Table 2 Adjusted hazard ratios with 95% confidence intervals for cardiovascular recurrence and all cause mortality after myocardial infarction in the community, 1993-2001

	All cause mortality			Non-fatal myocardial infarction or death from cardiovascular disease		
Predictor	**Overall**	**Women**	**Older people**	**Overall**	**Women**	**Older people**
Sex (male *v* female)	1.19 (1.07 to 1.33)	to	1.15 (1.03 to 1.29)	1.11 (1.00 to 1.24)	to	1.11 (0.99 to 1.25)
Age:						
<45	1.00	1.00	to	1.00	1.00	—
45-54	0.96 (0.48 to 1.94)	1.40 (0.18 to 11.24)		0.99 (0.60 to 1.61)	0.55 (0.19 to 1.53)	
55-64	1.58 (0.83 to 3.02)	2.91 (0.40 to 21.37)		1.26 (0.79 to 2.00)	0.79 (0.31 to 2.02)	
65-74	2.57 (1.36 to 4.84)	3.26 (0.45 to 23.59)		1.59 (1.01 to 2.51)	0.79 (0.32 to 1.99)	
≥75	3.57 (1.90 to 6.73)	4.50 (0.62 to 32.50)		1.90 (1.20 to 2.99)	0.95 (0.38 to 2.38)	
Deprivation category:						
1 (least deprived)	1.00	1.00	1.00	1.00	1.00	1.00
2	1.13 (0.89 to 1.43)	0.93 (0.66 to 1.32)	1.10 (0.86 to 1.40)	1.14 (0.90 to 1.43	0.88 (0.62 to 1.24)	1.04 (0.81 to 0.34)
3	1.18 (0.95 to 1.48)	0.92 (0.65 to 1.29)	1.19 (0.95 to 1.50)	1.12 (0.90 to 1.39	0.75 (0.53 to 1.06)	1.06 (0.84 to 1.35)
4	1.37 (1.09 to 1.72)	1.13 (0.81 to 1.59)	1.30 (1.03 to 1.66)	1.24 (0.99 to 1.56	0.92 (0.65 to 1.30)	1.13 (0.88 to 1.44)
5	1.39 (1.09 to 1.78)	1.03 (0.70 to 1.50)	1.29 (1.00 to 1.68)	1.34 (1.06 to 1.71)	0.92 (0.63 to 1.36)	1.15 (0.88 to 1.50)
6 (most deprived)	1.27 (1.01 to 1.60)	0.97 (0.68 to 1.37)	1.24 (0.97 to 1.58)	1.21 (0.97 to 1.52)	0.86 (0.60 to 1.21)	1.12 (0.88 to 1.44)
Statins	**0.69 (0.59 to 0.80)**	**0.63 (0.49 to 0.80)**	**0.72 (0.61 to 0.84)**	**0.82 (0.71 to 0.95)**	**0.69 (0.54 to 0.88)**	**0.84 (0.71 to 0.99)**
β blockers	0.38 (0.33 to 0.43)	0.46 (0.37 to 0.56)	0.39 (0.34 to 0.45)	0.40 (0.35 to 0.46)	0.48 (0.39 to 0.59)	0.46 (0.40 to 0.53)
Angiotensin converting enzyme inhibitors	0.54 (0.48 to 0.61)	0.55 (0.45 to 0.66)	0.56 (0.50 to 0.64)	0.57 (0.50 to 0.64)	0.64 (0.53 to 0.78)	0.61 (0.54 to 0.70)
Nitrates	0.68 (0.61 to 0.77)	0.68 (0.57 to 0.82)	0.66 (0.58 to 0.75)	0.78 (0.69 to 0.88)	0.78 (0.65 to 0.94)	0.75 (0.65 to 0.85)
Calcium blockers	0.76 (0.67 to 0.86)	0.74 (0.61 to 0.89)	0.73 (0.65 to 0.83)	0.79 (0.70 to 0.89)	0.75 (0.62 to 0.91)	0.76 (0.66 to 0.87)
Antihypertensive drugs	1.14 (1.01 to 1.29)	0.83 (0.70 to 0.99)	1.13 (1.00 to 1.28)	0.90 (0.80 to 1.02)	0.72 (0.60 to 0.86)	0.91 (0.80 to 1.03)
Antiplatelet drugs	0.44 (0.39 to 0.50)	0.49 (0.41 to 0.58)	0.41 (0.36 to 0.47)	0.42 (0.37 to 0.47)	0.44 (0.37 to 0.53)	0.39 (0.34 to 0.45)
Warfarin	0.97 (0.84 to 1.14)	0.94 (0.74 to 1.20)	0.89 (0.75-1.06)	0.93 (0.78 to 1.10)	0.84 (0.64 to 1.09)	0.86 (0.71 to 1.04)

Other covariates included in the multivariate analysis: non-steroidal anti-inflammatory drugs, disease modifying antirheumatic drugs, hormone replacement therapy, and oral contraceptives, steroids, previous cardiovascular disease, and comorbidity (diabetes, obstructive airway disease, cancer, renal failure, rheumatoid arthritis).

Discussion

The beneficial effects of statins can be extended to all patients with coronary heart disease, including older patients and women.

Observational studies versus randomised trials

In drug treatment research, observational studies can have advantages over randomised controlled trials as they often have large sample sizes and can be more representative of the general population.[11] Although randomised controlled trials are the gold standard for judging efficacy, well designed observational studies can examine the findings from randomised controlled trials and assess the effectiveness of drug treatment in routine clinical practice. However, it is important to be aware of "confounding by indication" in making comparisons between patients prescribed and not prescribed specific treatments.[12] This phenomenon arises because the risk of bad outcomes is intrinsically higher in patients selected for treatment and because most treatments reduce, but do not remove, risk. Thus, comparisons of treated patients with not treated patients may spuriously imply that drug treatments are actually harmful. Although our study sought to minimise this effect by studying only patients who had had a myocardial infarction, all of whom had a strong indication to receive a statin,[13] only half were treated, which implies that some form of selection was involved. The untreated patients were older, more likely to be women, and to have more comorbidity but fewer concurrent cardiovascular drugs (table 1).

Trial versus "real world" population differences

We compared the sociodemographic profile and clinical outcomes between community based patients and patients from randomised controlled trials. We found that older patients and women made up a bigger proportion of the population treated in routine practice than randomised controlled trials, which focused mainly on younger and male patients.

Efficacy versus effectiveness

Compared with the efficacy findings of clinical trials, the effectiveness of drugs in observational analysis of clinical practice is expected to be reduced. This arises because of inaccurate diagnosis, lack of drug dose titration, confounding by indication, less than perfect adherence to treatment by patients and to guidelines by prescribers.[14] Despite these potential influences, we found that the benefits of statins observed in our community patients were similar to those observed in randomised controlled trials (0.69, 95% confidence interval 0.59 to 0.80 *v* 0.79, 0.73 to 0.85). The numbers needed to treat for statin treatment in the community were also similar to those reported in clinical trials.[1–3]

Concurrent drug use

In our study, use of β blockers, antiplatelet drugs, and angiotensin converting enzyme inhibitors was independently associated with lower risk of mortality and cardiovascular outcomes, as others have found.[15 16] These findings support the notion that some of the different treatments available for secondary prevention do have independent effects and that their combined use may result in synergistic reductions in clinical outcomes.[17] Interestingly, patients taking warfarin did not experience any independent reduction in risk of recurrence or death, perhaps owing to confounding or small numbers. Our analysis of the combined effects of cardiovascular drugs shows that patients who took one or two additional drugs had lower risks of death and recurrent myocardial infarction, which indicates that additional treatments are synergistic. However, the risks of death and recurrent myocardial infarction among patients who received a statin and more than two other cardiovascular drugs were similar to the risks in patients after a myocardial infarction who did not receive any drugs. This probably reflects confounding by disease severity in those patients who took three or more drugs, resulting in any synergistic effects of drug treatments

being obscured by the intrinsically higher risk of patients treated with more than two additional drugs.

Prescribing of statins has clearly become more common in Tayside in recent years. From 2000, more than 60% of patients after a myocardial infarction in Tayside were prescribed statins. This is a similar proportion to that seen in the second European action on secondary prevention by intervention to reduce events (EUROASPIRE II) study[18] across nine European countries. Two large clinical trials (the heart protection study[19] and the prospective study of pravastatin in the elderly at risk (PROSPER) study[20]) were published in 2002, which were outside the timeframe of our study. These trials were relatively inclusive in respect of women and older patients. However, the results were broadly in accord with those observed in our study cohorts.

Limitations of the study

Our study has some limitations. Firstly, we assumed that if a prescription was filled then patients would comply with treatment, but we had no way of knowing whether patients actually took their treatment. We found that men had higher risk of cardiovascular events than women. This may be partly explained by compliance differences between the sexes.[21] Secondly, we were limited by the number of covariates on which we had data. Consequently we were not able to adjust for smoking, obesity, and exercise. However, we used the Carstairs socioeconomic deprivation score as a surrogate, which provides adjustment for at least some of these factors.[22]

Strength of the study

A strength of our study is the population based cohort design, with complete follow-up over the study period. This approach allows a real population to be studied that represents all socioeconomic groups in a universal healthcare coverage scheme.[23]

Conclusion

About half of patients were taking statins during the study period. Statin use increased from 3.1% for 1993 to 62.9% for 2001. Statin users tended to be younger than non-users and tended to be prescribed more cardiovascular co-medication. Although co-medication provided benefits, statins were independently effective, reducing the likelihood of both the combined cardiovascular outcome and all cause mortality. Older patients and women, who were not well represented in trials, had similar benefit to other people.

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Competing interests: TMM has received honorariums for lectures and advisory boards in the last year from Pfizer, Roche, Speedel, Medeus, Novartis, and Sankyo. PGD serves on advisory boards for Aventis and Pfizer.

Ethical approval: Tayside Research Ethics Committee and the Tayside Caldicott Guardians.

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What is already known on this topic

Trials of the secondary prevention of cardiovascular disease with statins have been biased against the inclusion of older and female patients

Meta-analyses of secondary prevention statin trials have shown consistent beneficial effects on cardiovascular outcome

What this study adds

In comparison with the patients recruited into clinical trials, older patients and female patients were represented more frequently in the population of patients treated with statins in Tayside (mean age 67.8 *v* 59.8; women 39.6% *v* 16.9%, respectively).The overall effects of statins in routine clinical practice were consistent with, and similar to, those reported in clinical trials

The effects of statins for all cause mortality in women and older patients who were not well represented in trials were similar to the effects seen in subjects included in trials

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