

## 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

L Wei, S Ebrahim, C Bartlett, P G Davey, F M Sullivan, T M MacDonald

### 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

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.

We reviewed the literature relating to the effects of statin treatment on cardiovascular outcomes, but found no studies that directly compared the socio-demographic 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.<sup>1</sup> We recently reported a meta-analysis that included 27 secondary prevention trials of statins published up to December 2001.<sup>2</sup> 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 risk 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.<sup>3</sup> The database 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 data have been validated and anonymised.

### 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 those people in the study population who were discharged from Tayside hospitals during the study window with an incident

Medicines Monitoring Unit, Health Informatics Centre, Division of Medicine and Therapeutics, Ninewells Hospital and Medical School, Dundee DD1 9SY

Li Wei  
*research fellow*  
Peter G Davey  
*professor*

Thomas M MacDonald  
*professor*

MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol, Bristol B8S 2PR

Shah Ebrahim  
*professor*

Christopher Bartlett  
*research associate*

Tayside Centre for General Practice, Division of Community Health Sciences, University of Dundee, Dundee DD2 4BF

Frank M Sullivan  
*professor*

Correspondence to: T M MacDonald  
t.m.macdonald@dundee.ac.uk

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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.

**Statistical analysis**

We summarised data as means with standard deviations for continuous variables and as numbers (percentages) of subjects for categorical variables. We used  $\chi^2$  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.

**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)). See *bmj.com* for 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 were available during the study period; about 80% used 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). The table 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,  $\beta$  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  $\geq 65$ ) 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 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

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

Predictor	All cause mortality			Non-fatal myocardial infarction or death from cardiovascular disease		
	Overall	Women	Older people	Overall	Women	Older people
Sex (male <i>v</i> 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	—	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)	
$\geq 75$	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)
$\beta$ 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).

numbers needed to treat were 35, 20, and 35, respectively).

## Discussion

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

### Observational studies versus randomised trials

In drug treatment research, randomised controlled trials are the gold standard for judging efficacy although observational studies can have advantages as they often have large sample sizes, can be more representative of the general population and can assess effectiveness in routine clinical practice. However, there may be “confounding by indication” when making comparisons between patients prescribed and not prescribed specific treatments. 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, 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 (see tables on [bmj.com](http://bmj.com)).

### 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, and less than perfect adherence to treatment by patients and to guidelines by prescribers.<sup>4</sup> 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.

### Concurrent drug use

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.

## 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 patients 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

Prescribing of statins has clearly become more common in Tayside in recent years. From 2000, more than 60% of patients after a myocardial infarction were prescribed statins. This is a similar proportion to that seen in other studies.<sup>5</sup> Two other large trials were outside the timeframe of our study, but were relatively inclusive in respect of women and older patients and the results were broadly in accord with ours.<sup>6-7</sup>

### Limitations of the study

Firstly, we assumed that if a prescription was filled then patients would comply with treatment, but we had no way of knowing this. The higher risk of cardiovascular events in men than women may be partly explained by compliance differences between the sexes.<sup>8</sup> 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.<sup>9</sup>

### 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.

### 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, Spedel, 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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### *A memorable patient*

#### **In the bad old days**

I embarked on medical training in 1961 as a mature student with two years of general dental practice and three years of hospital oral surgery and maxillofacial trauma behind me. My second six month preregistration post was as a surgical house officer at a busy London hospital. My responsibilities spread over four firms, each headed by a teaching hospital consultant, and included 60 beds on-take alternate weeks with an additional 60 to cover plus casualty at night time. The experience of "hands on" general surgery, urology, and gynaecology was fantastic, but so was the fatigue.

One evening I was called to casualty to find an obese, partially collapsed lady bleeding copiously from the vagina who had missed a couple of periods. Her pulse was weak, her blood pressure barely recordable, and her major veins impalpable. As I started to catheterise the patient to provide fluid, I sent for the resident surgical officer (who was 10 minutes away at a dinner), O+ blood, and the theatre team. I was told that the team was already working at a nearby hospital. By the time the surgical officer arrived, resplendent in his dinner jacket, fluid was running in nearly as fast as the patient was losing blood.

He made a rapid decision to operate. "No theatre team or anaesthetist available," I told him.

After a few seconds he said, "Hoppy, you give the anaesthetic." I had had considerable experience of dental anaesthesia and had given gaseous anaesthetics to patients in casualty for minor surgery, so with the confidence of youth and ignorance I agreed.

The porter had not yet returned with the blood, so the two of us pushed the patient's trolley to the lift, with me keeping fingers on her carotid pulse. It became impalpable, and I said, "It's too late, she's gone."

The top half of the patient raised up and said, "No I've not gone yet." After that embarrassment, we got her to theatre and somehow, using wooden poles, lifted her on to the theatre table.

The surgeon took off his dinner jacket and brought in the theatre packs of instruments. Not having the confidence to use thiopentone (thiopental) or knowledge of the patient's weight, I opened up the gas, oxygen, and trichloroethylene of the Boyle's machine, applied the facemask, and pushed the patient's

mandible forward in the approved manner. By the time the surgeon was ready, her eyelash reflexes had gone, and she seemed relaxed. He opened the abdomen, sucked out pints of blood, and somehow identified and clipped off the ectopic pregnancy. We felt elated: job done, crisis over.

A few seconds later, however, and the patient was attempting to get off the table. Clearly her relaxation had owed more to hypovolaemia than anaesthesia. The surgeon held on to her from inside the abdomen, and I held down her shoulders while I opened up the trichloroethylene. This pantomime gradually subsided, and the surgeon was able to finish his work and close up the wound. By this time, the porter had arrived with the blood, which we pumped in.

The next morning we found our patient sitting up eating a hearty breakfast without any memory of the previous evening's surgery. So ended my anaesthetic career. It is worth adding that the patient's wounds healed without infection.

The memory of these events, which some readers may find difficult to believe, has never left us. Today such a patient would not be admitted to a hospital so ill prepared to deal with a life threatening emergency. Nowadays, I expect there would have been a major investigation as a result of a critical incident report and even possible disciplinary action. (The management refused to reimburse my colleague for the dry cleaning of his blood stained trousers.) On the other hand, a life was saved by the courage and initiative of the resident surgical officer, whose surgical training had included considerable operative practice.

Russell Hopkins *retired maxillofacial surgeon, University Hospital of Wales*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. Please submit the article on <http://submit.bmj.com> Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.