

## CARDIOVASCULAR MEDICINE

# Low prevalence of lipid lowering drug use in older men with established coronary heart disease

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**Objective:** To determine the prevalence and correlates of lipid lowering drug use among older British men with established coronary heart disease (CHD).

**Design:** Cross sectional survey within a cohort study (British regional heart study) carried out at 20 years of follow up in 1998–2000.

**Setting:** General practices in 24 British towns.

**Participants:** 3689 men aged 60–75 years (response rate 76%).

**Main outcome measures:** Diagnoses of myocardial infarction and angina based on detailed review of general practice records. Lipid lowering drug use and blood cholesterol concentrations ascertained at 20 year follow up examination.

**Results:** Among 286 men with definite myocardial infarction, 102 (36%) were taking a lipid lowering drug (93 (33%) a statin); among 360 men with definite angina without myocardial infarction, 84 (23%) were taking a lipid lowering drug (78 (21%) a statin). Most men with documented CHD who were not receiving a lipid lowering drug had a total cholesterol concentration of 5.0 mmol/l or more (87% of those with myocardial infarction, 82% with angina). Fewer than half of men with CHD receiving a statin had a total cholesterol concentration below 5.0 mmol/l (45% of those with myocardial infarction and 47% of those with angina). Only one third of the men taking a statin were receiving trial validated dosages. Among men with CHD, a history of revascularisation, more recent diagnosis, and younger age at diagnosis were associated with a higher probability of receiving lipid lowering drug treatment.

**Conclusion:** Among patients with established CHD, the prevalence of lipid lowering drug use remains low and statin regimens suboptimal. Major improvements in secondary prevention are essential if the benefits of statins are to be realised.

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Decreasing total and low density lipoprotein cholesterol by treatment with hydroxymethyl glutaryl coenzyme A (HMG-coA) reductase inhibitors (statins) reduces the risk of coronary heart disease (CHD) both in patients with pre-existing CHD<sup>1–3</sup> and in those without.<sup>4–5</sup> The absolute benefits and cost effectiveness of statin treatment are strongly related to the level of coronary risk and are therefore particularly pronounced among patients with established CHD.<sup>6,7</sup> Evidence for the benefits of other lipid lowering drugs, particularly fibrates, in the secondary prevention of CHD is also increasing, though significant reductions in total mortality in this context have not yet been obtained,<sup>8</sup> as they have for statins.<sup>1–3</sup>

There is widespread agreement that patients with established CHD, at least up to 75 years of age (the upper age of patients recruited into the statin trials), should be offered lipid lowering treatment, particularly with statins, though recommended treatment thresholds vary. The Standing Medical Advisory Committee has recommended that patients with a history of myocardial infarction should receive a statin if their total cholesterol concentration is 4.8 mmol/l or more and that patients with angina should receive statins if their total cholesterol concentration is 5.5 mmol/l or more.<sup>9</sup> More recently, the joint British recommendations on prevention of CHD in clinical practice advised that all patients with established CHD should receive statin treatment if their total cholesterol is 5.0 mmol/l or more or their low density lipoprotein cholesterol is 3.0 mmol/l or more, at a dose sufficient to reduce lipid concentrations to below these thresholds.<sup>10</sup> The new National Service Framework for CHD recommends that all patients with a history of myocardial infarction or angina should receive statins to reduce total cholesterol to below 5.0 mmol/l

or by 30%, whichever is the greater.<sup>11</sup> All three reports also recommend that subjects without established CHD but who have an annual risk of 3% or more of developing major CHD should be considered for statin treatment.<sup>9–11</sup> The joint British recommendations advise that the risk threshold should be reduced to 1.5% per annum once all patients in the 3% risk category have been treated.<sup>10</sup>

Despite the clear efficacy of statin treatment, previous reports have suggested that lipid lowering drugs are not being widely used in Britain.<sup>12–15</sup> A recent report from the Health Survey for England suggested that these drugs were being underused in both primary and secondary prevention.<sup>14</sup> However, the Health Survey for England report was based only on doctors' diagnoses recalled by patients, could not identify types of lipid lowering drugs or dosages, and did not examine characteristics of patients receiving and not receiving lipid lowering treatment. We have used a population based study of cardiovascular disease carried out between 1998 and 2000 to examine the use of lipid lowering drugs among men aged 60–75 years, particularly those with a CHD diagnosis confirmed by a doctor, and to examine factors related to the use of lipid lowering drugs in this context.

## METHODS

The British Regional Heart Study is a national prospective study of cardiovascular disease in one general practice in each of 24 British towns, representing all major British regions. Participants were enrolled in 1978–80, aged 40–59 years, and have been followed up for all cause mortality using the National Health Service (NHS) central registers and for cardiovascular morbidity through regular biennial reviews of

**Table 1** Prevalence and correlates of lipid lowering drug use in men with documented myocardial infarction (MI) or angina

	Definite MI (n=286)			Definite angina, no MI (n=360)		
	N	n	%	N	n	%
Overall prevalence						
Any lipid lowering drug	286	102	36	360	84	23
Statins	286	93	33	360	78	21
Previous revascularisation						
Yes	62	30	48	73	40	55
No	224	72	32	287	44	15
p value		0.018			< 0.001	
Year of last diagnosis						
Pre-1994	180	50	28	147	28	19
1994–1997	74	37	50	133	36	27
Post-1997	32	15	47	80	20	25
p value		< 0.001			0.26	
Age at last diagnosis (years)						
< 60	129	49	38	102	25	25
60–69	131	46	35	215	51	24
≥ 70	26	7	27	43	8	19
p value		0.55			0.73	
Social class*						
Non-manual	124	49	40	157	44	28
Manual	146	49	34	189	39	21
p value		0.31			0.15	
Geographic residence						
South	87	34	39	89	22	25
Scotland	37	17	46	46	11	24
North, Midlands, and Wales	162	51	31	225	51	23
p Value		0.18			0.92	
Cigarette smoking status†						
Current	34	11	32	46	8	17
Former	181	63	35	196	45	23
Never	60	25	42	103	28	27
p value		0.56			0.41	

N, total in category; n, number within the category taking lipid lowering drugs.

\*Social class not available for 16 subjects in the MI group and 20 in the angina group; †Smoking status not available for 11 subjects in the MI group and 15 in the angina group.

general practice records. Fewer than 1% of participants have been lost to follow up.<sup>16, 17</sup>

Between February 1998 and February 2000, all surviving men were invited to attend for a 20 year follow up at 60–79 years of age. Men who were still living in the same town as in 1978–1980 were invited to return to their original practice for reassessment; men who had moved from the original study town were given a choice of returning to their original town, of being measured in another (more convenient) town, or of travelling to a London assessment centre. Men were asked to attend for screening after a minimum six hour fast and with all their medications. At screening, men completed a study questionnaire, which was checked by research nurses. All current medications were recorded and verified either against the medication container or (if the container was not available) against a prescription record; any participant in whom the completeness of the medication record was uncertain was excluded from this analysis. Diabetes diagnosed by a doctor and current smoking habit, including number of cigarettes smoked per day, were recorded. Two seated blood pressure measurements were made with the Dinamap 1846 oscillometric blood pressure recorder (Critikon, Tampa, Florida, USA); overreading of systolic pressure by the instrument<sup>18</sup> was corrected. A 12 lead ECG was recorded and analysed in accordance with Minnesota criteria (Professor P Macfarlane, Glasgow University) and a blood sample was taken for measurement of total cholesterol, using a Hitachi 747 (Hitachi, Tokyo, Japan) automated autoanalyser (Professor A F Winder, Department of Chemical Pathology, Royal Free Hospital).

In July 2000, the general practice records of all participants were reviewed in detail to identify all diagnoses and procedures related to CHD such as myocardial infarction,

angina, coronary angiography, coronary artery bypass graft surgery, and percutaneous transluminal coronary angioplasty, including dates, that had occurred up to the time of examination. Before a practice diagnosis of myocardial infarction was accepted as definite, additional clinical information on standard World Health Organization criteria (requiring two of the following: (a) a history of severe chest pain, (b) changes in cardiac enzymes, and (c) characteristic electrocardiographic changes) was obtained from the general practitioner.<sup>17</sup> Among patients without CHD diagnosed, absolute CHD risk was calculated by the standard Framingham equation, using age, diabetic status, systolic pressure, smoking status, total and high density lipoprotein cholesterol, and left ventricular hypertrophy.<sup>19</sup>

## RESULTS

In all, 3689 men aged 60–75 years participated in the 20 year follow up examination and provided a full medication history (76% of those invited). Almost all (3495, 95%) had a study total cholesterol measurement. A total of 294 men (8.0%) were taking lipid lowering medication; of these 259 (88%) were taking statins, 31 (11%) fibrates, and 4 (1%) ion exchange resins. Of these 294 men, 208 (71%) had cardiovascular disease documented in their general practice records and a further 48 (16%) recalled a cardiovascular diagnosis.

### Lipid lowering drug use in men with documented CHD

In all, 286 patients (7.8%) had definite myocardial infarction diagnosed, of which 33 (12%) were recurrent. Three hundred and sixty patients (9.8%) had angina diagnosed, of which 117 (33%) were recurrent. Men who had both of these conditions diagnosed were included in the myocardial infarction group. Table 1 shows the prevalences of lipid lowering drug use

**Table 2** Odds of receiving a lipid lowering drug in men with documented MI or angina

Covariates	Full model					
	MI group (n=262)			Angina group (n=326)		
	OR	95% CI	p value	OR	95% CI	p value
Previous revascularisation	1.65	0.86 to 3.19	0.13	6.74	3.68 to 12.34	<0.001
Age at last diagnosis						
<60	1.00	–	–	1.00	–	–
60–69	0.47	0.24 to 0.90	0.024	0.63	0.31 to 1.28	0.199
≥70	0.18	0.05 to 0.62	0.006	0.30	0.10 to 0.95	0.041
Year of last diagnosis						
Pre-1994	1.00	–	–	1.00	–	–
1994–1997	4.56	2.26 to 9.20	<0.001	2.00	0.98 to 4.08	0.057
Post-1997	6.68	2.29 to 19.47	<0.001	2.12	0.92 to 4.89	0.078
Manual social class	0.69	0.39 to 1.22	0.205	0.75	0.42 to 1.32	0.319
Geographic residence						
North England and Midlands	1.00	–	–	1.00	–	–
South	1.45	0.79 to 2.65	0.226	0.86	0.44 to 1.69	0.658
Scotland	2.16	0.95 to 4.95	0.068	0.71	0.30 to 1.68	0.441
Cigarette smoking status						
Never	1.00	–	–	1.00	–	–
Former	0.81	0.42 to 1.57	0.528	0.85	0.46 to 1.57	0.612
Current	0.67	0.25 to 1.79	0.427	0.78	0.31 to 1.94	0.478

Odds ratios (OR) are adjusted for all factors shown in the table. CI, confidence interval.

among these groups. Approximately one third of patients with a history of myocardial infarction and one fifth of those with angina were receiving lipid lowering drugs; most of these were statins. The overall prevalence of lipid lowering drug use among patients with documented CHD was 186 of 646 (29%). Among men with myocardial infarction not being treated, 87% had a total cholesterol concentration of 5 mmol/l or more and 91% had one above 4.8 mmol/l. Among men with angina who were not receiving treatment, 82% had a total cholesterol concentration of 5 mmol/l or more and 60% had one above 5.5 mmol/l.

#### Control of blood total cholesterol among men with documented CHD receiving lipid lowering treatment

Among 186 men with CHD diagnosed who were on any lipid lowering treatment, 44% had a total cholesterol concentration below 5 mmol/l; this proportion was similar both among men with myocardial infarction and angina. When this analysis was restricted to 171 men with CHD diagnosed who were receiving statin treatment, 46% had a total cholesterol concentration below 5 mmol/l (45% of those with myocardial infarction, 47% of those with angina). Of patients with documented CHD and a presumed baseline total cholesterol of 5 mmol/l or above (that is, those with a current total cholesterol  $\geq$  5.0 mmol/l and/or receiving lipid lowering drug treatment), 75 of 630 (12%) had a total cholesterol concentration below 5 mmol/l. Of 171 men with CHD receiving a statin, 104 (61%) were taking simvastatin and 19 (11%) pravastatin (the drugs used in the secondary prevention trials<sup>1-3</sup>); 26 (15%) were taking atorvastatin. Of the patients taking simvastatin, only 41% were taking a daily dose similar to that used in the 4S (Scandinavian simvastatin survival study) (20–40 mg daily); most (59%) were taking a smaller dose (10 mg daily). All the patients receiving pravastatin were taking either 10 or 20 mg daily; none was taking the 40 mg daily dose used in the CARE (cholesterol and recurrent events) and LIPID (long-term intervention with pravastatin in ischaemic disease) trials.<sup>2,3</sup> Most (85%) of the patients receiving atorvastatin were taking a daily dose of 10 mg. These dosage patterns did not vary greatly when men whose myocardial infarction or angina had been diagnosed in the last year were excluded, or when men with total cholesterol concentrations below 5 mmol/l were excluded.

#### Factors related to use of lipid lowering drug treatment in men with CHD

Table 1 presents factors related to the use of lipid lowering drug treatment in men with myocardial infarction or angina. A history of coronary revascularisation was related to increased lipid lowering drug use in both groups of men. Year of last diagnosis was strongly related to drug use in men with myocardial infarction, with prevalence of treatment being much higher among recently diagnosed cases; results of the year of first diagnosis (data not presented) were similar. Prevalence of lipid lowering drug use appeared to be slightly (though not significantly) higher in patients who were younger at last diagnosis, in patients who were of non-manual social class, and among men studied in Scotland and southern England compared with those in the Midlands and the north of England. Men who were cigarette smokers were slightly though not significantly less likely than non-smokers to receive lipid lowering drugs. Table 2 shows odds ratios after adjustment for these interrelated factors. For patients with either myocardial infarction or angina, a history of previous coronary revascularisation, younger age at last diagnosis, and more recent date of last diagnosis were strongly related to increased lipid lowering drug use. The weak and non-significant relation between social class, region, cigarette smoking, and lipid lowering drug use were little altered by adjustment for these other factors.

#### Lipid lowering drug use among men at high risk of CHD

Among 2868 men with no CHD diagnosis in whom a Framingham risk score could be calculated, 578 (20%) had a Framingham risk score consistent with an absolute CHD risk of 3.0% per year or more. However, of these men only 19 (3%) were receiving lipid lowering drug treatment of any kind.

#### DISCUSSION

These results suggest that most older men with established CHD are not receiving lipid lowering drug treatment, and that even those who receive treatment are in many cases receiving inadequate drug doses. The CHD ascertainment methods in this investigation were used specifically to avoid falsely low prevalence estimates of lipid lowering drug use. Cases in which there was any doubt about the completeness of the medication record were excluded. The CHD diagnoses on

which analyses were based were all known to the general practitioners and did not depend on patient recall, which is less specific than a diagnosis based on general practice records.<sup>20</sup> Although the long term involvement of participating practices in the British regional heart study could have affected lipid lowering drug use in this study population, participation might have been expected to increase (rather than decrease) preventive activities, including prescription of lipid lowering drugs. However, the study has maintained a low profile in the participating practices and avoided making any specific recommendations about treatment practices to the general practitioners involved in the study.

The prevalence of lipid lowering drug use in patients with established CHD (29%) is very similar to the estimates provided by Primates and Poulter in men aged 65–75 years in the Health Survey for England (25%) and from general practice statistics in men aged 65–74 years (29%).<sup>14, 15</sup> The overall proportion of patients with increased blood cholesterol concentrations controlled by lipid lowering drugs is also very similar to the estimate of 16% in the Health Survey for England.<sup>14</sup> The present results show clearly that a large proportion of patients are taking inadequate doses of statins, in most cases well below the dosages shown to be effective in the randomised controlled trials of secondary prevention.<sup>1, 3</sup> Although these findings are only for men, recent studies suggest that the extent of secondary prevention in women is even less complete.<sup>14, 15, 21</sup> The lower rates of lipid lowering drug use in older patients in the present study (a group at particularly high CHD risk and who, up to 75 years of age, are known to benefit from statins) are also consistent with earlier reports.<sup>14, 15</sup> Our findings that the prevalence of lipid lowering drug use is lower among patients with angina than those with myocardial infarction, among those who have not undergone revascularisation, and among those whose condition was diagnosed less recently, are consistent with our earlier report on the use of aspirin in the secondary prevention of cardiovascular disease<sup>22</sup> and with European experience.<sup>23</sup> Our results are also consistent with the possibility of an adverse social gradient in lipid lowering drug use, though they also suggest that there is a particularly high prevalence of lipid lowering drug use in Scotland; this may result from the high local profile of the West of Scotland coronary prevention study (WOSCOPS).<sup>4</sup>

Several factors may be responsible for the low use of lipid lowering drugs observed in this study. There is always a lag period before research findings influence clinical practice. Controversy, initially about the benefits of cholesterol reduction<sup>24</sup> and latterly about the extent to which statins should be used in primary CHD prevention,<sup>25–27</sup> may have delayed widespread use of statin drugs in secondary prevention. The costs of statin treatment have been an additional concern. However, with the strong evidence that statin use is cost effective, particularly in secondary prevention of CHD,<sup>6, 7</sup> it is important that priority is given to meeting these prescribing costs.

Although this study cannot establish the relative contribution of primary and secondary care in the underprovision of lipid lowering treatment, the results emphasise that action in primary care is particularly important if comprehensive and effective secondary prevention of CHD is to be achieved. Several categories of patients at risk of not receiving lipid lowering treatment in this study (older patients, those with relatively longstanding CHD, particularly angina, and those not receiving invasive treatment) are likely to receive most or all of their clinical care in the primary care setting and will only be identified by systematic retrospective identification and management. The low current levels of lipid lowering drug use suggest that a strongly proactive approach to implementation of secondary prevention, both prospectively and retrospectively, will be essential.<sup>28</sup> This will need to build on the framework of CHD registers now being established under National Service Framework directives.<sup>11</sup> Such an approach

will need to be based on clear guidance, giving appropriate priority to secondary prevention in relation to primary prevention, and providing clear recommendations on treatment regimens to ensure that patients receive optimal benefit.<sup>29</sup> However, since the cost effectiveness of statin treatment for secondary prevention of CHD is greater than that of many procedures currently performed under the NHS,<sup>6, 7</sup> such action would be amply justified.

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## IMAGES IN CARDIOLOGY

### Intercoronary communication between the circumflex and right coronary arteries: distinct from coronary collaterals

A 49 year old man presented with atypical chest pain for five months. He had no risk factors for atherosclerosis. Exercise electrocardiography was stopped prematurely because of leg cramp. Coronary angiography was performed and revealed normal left ventricular function. Left and right coronary angiography did not show any evidence of luminal narrowing or occlusion of either coronary artery (below left). However, with the selective injection of the right coronary artery (RCA) in a left anterior oblique view, the RCA and distal and mid portion of left circumflex artery (CX) were simultaneously visualised. An intercoronary connection was also seen near the crux (below centre). The RCA and CX were then catheterised at the same time. There was no pressure damping during selective placement of the catheter tip in either coronary ostium. In the left anterior oblique view with cranial angulation, simultaneous injection of contrast material into both coronary ostia revealed interarterial continuity between the RCA and CX (below right: arrowheads show both antegrade and retrograde filling of CX lumen).

Intercoronary artery continuity or "coronary cascade" is a rare variant of the coronary circulation. Two types have been described: communication between the CX and the RCA in the posterior atrioventricular groove (as in this patient), and communication between left anterior descending and posterior descending artery in the distal interventricular groove. Compared with collaterals, intercoronary

arterial connections are larger in diameter ( $\geq 1$  mm), extramural, and straight. Furthermore, the structure of an intercoronary arterial connection is typical of an epicardial coronary artery, with a well defined muscular layer. Intercoronary arterial connections are thought to be congenital in origin. It is suggested that faulty embryological development allows the existing intercoronary channel to remain prominent and maintain a large calibre.

In our case selective injection of the left coronary artery did not demonstrate retrograde filling of the distal RCA. One may propose that both the force of injection and the velocity of flow in the left coronary artery would account for this discrepancy.

True prevalence of this entity is unknown but we identified only one patient among the 7086 angiograms performed at our laboratory during the last 10 years. The functional significance of this large anastomotic connection between normal coronary arteries is unclear but one may speculate that they have a potential role in protecting the myocardium should significant atherosclerosis develop in either of the parent arteries.

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