Who receives lipid-lowering drugs: the effects of comorbidities and patient characteristics on treatment initiation

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Aims Little is known about the effects of comorbidities and patient characteristics on treatment initiation of lipid-lowering drugs (LLDs), which can be helpful in the evaluation of the risks and benefits of LLDs.

Methods Baseline characteristics among subjects who received their first ever-recorded LLD prescription in general practice between 1 January 1990 and 31 December 1997, and hyperlipidaemic patients without LLD therapy during the same period were obtained from the UK General Practice Research Database. Differences between patients who received and patients who did not receive LLDs, as well as patients who received different classes of LLDs were compared by fitting multivariate logistic regression models that adjusted for age, sex, body mass index, smoking status, and year of treatment initiation or hyperlipidaemia diagnosis.

Results We found that there were many differences in the baseline characteristics, such as number of general practitioner visits, diagnosis and severity of cardiovascular diseases, and concurrent medications, between the 25 331 patients who received and the 16 287 patients who did not receive LLDs. We also noted that patients with statin therapy had more prior hospitalization, more recent myocardial infarction/stroke, and more concurrent cardiovascular medications, than those patients who received other LLDs.

Conclusions Patients who received LLDs in primary care, especially patients with statin therapy, were more likely to be elderly and to have more concomitant severe cardiovascular comorbidities than those hyperlipidaemic patients who did not receive LLDs. Examining the medical records of individuals eligible for LLD therapy is an important first step in selectively targeting who will experience the greatest benefit to risk ratio for the treatment of hyperlipidaemia, and is an important step in avoiding confounding by indication when designing epidemiological studies comparing the risks and benefits of treatments for hyperlipidaemia.

Keywords: comorbidity, General Practice Research Database, hydroxymethylglutaryl-CoA reductase inhibitors, hyperlipidaemia, lipid-lowering drugs

Introduction

The effectiveness of lipid-lowering therapy in reducing the risk of cardiovascular morbidity and mortality has been firmly established in clinical trials [1–5], and lipid-lowering drugs (LLDs) are frequently used in everyday

practice. In recent years, the use of LLDs, especially 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), has rapidly increased [6, 7]. Moreover, the potential benefits of LLDs on diseases other than coronary heart disease (CHD) have gradually become a hot topic in epidemiologic research [8–12]. Despite the broad use of LLDs and the increased knowledge of their pharmacological effects, little is known about the effects of comorbidities or patient characteristics on treatment initiation among patients who are eligible for lipid-lowering therapy.

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The initial choice of treatment is a complex phenomenon in which the physician, the patient, and the presence of various comorbidities all play a role. For example, treatment initiation with hypoglycaemic or nonsteroidal anti-inflammatory medications has been found to be related to age or certain comorbidities [13, 14]. The difference between patients with or without LLDs has also been partly evaluated in a study of multiple drugs and mortality among elderly residents in the US [15]. In that study, LLD users were found to have lower adjusted rates of death within 1 year relative to nonusers, which suggested that LLDs might be preferentially prescribed to older patients with lower risk of mortality in the year after drug prescription. That study, however, did not evaluate the differences between patients receiving different classes of LLDs.

In addition to the possible differences between treated and untreated hyperlipidaemic patients, the initial choice of a specific LLD is likely to be affected by comorbidities and patient characteristics as well. As the lipid-altering mechanism, potency, and safety profile of various LLDs are different [16–19], the choice of a specific drug may depend on the type of hyperlipidaemia as well as on pre-existing comorbidities. Different LLDs have also been reported to be associated with the frequency of treatment discontinuation [18–22], and compliance has been generally found to be higher among users of statins than among users of other LLDs. Such an observation, together with other potential determinants of compliance, may affect the physicians' initial choice of LLDs. Although it is not possible to achieve a full understanding of the decision for treatment initiation, a study of the baseline characteristics can be helpful in the evaluation of the risks and benefits of LLDs. As little information is available about the potential effects of comorbidities and patient characteristics on treatment initiation of LLDs, we decided to study these factors in a general population-based research database.

Methods

Data source and study population

The General Practice Research Database (GPRD) has been previously described in detail elsewhere [23, 24]. Currently, the GPRD encompasses some 3 million residents in the UK enrolled with selected general practitioners (GPs) who use office computers to record anonymized information on demographics and patient characteristics (e.g. weight, height, smoking status), symptoms, medical diagnoses, referrals, hospitalizations, and drug prescriptions (including preparation, route of administration, dose, and number of tablets for each prescription). Previous studies have shown the accuracy

and completeness of the data recorded in the GPRD [23, 24].

Within the GPRD, we identified subjects from 368 active practices (i.e. practices that continually updated computerized records for research purposes), who initiated lipid-lowering therapy in primary care by receiving a prescription for a statin (atorvastatin, cerivastatin, fluvastatin, pravastatin, and simvastatin), a fibrate (bezafibrate, ciprofibrate, clofibrate, fenofibrate and gemfibrozil), or another lipid-lowering drug (colestipol, cholestyramine, acipimox, nicotinic acid, and probucol) between 1 January 1990 and 31 December 1997; and patients who had a computer-recorded diagnosis of hyperlipidaemia without any LLD treatment during the same period. Patients who had prior use of LLDs or diagnosis of hyperlipidaemia before 1 January 1990 were excluded. The index date for a given subject was the date on which they had a first ever-recorded prescription for any LLD in primary care, or the date on which an untreated hyperlipidaemic patient had the first diagnosis of hyperlipidaemia. Exposure was categorized according to the first ever-recorded LLD prescription among patients receiving LLD therapy. To be included in this study, subjects were required to have at least 1 year of information recorded in the computer database before the index date.

Data collection

We collected the following data on or before the index date (baseline characteristics) to evaluate the effects of potential determinants on prescribing LLDs: demographic and patient characteristics [age, sex, smoking status, body mass index (BMI), and calendar year of treatment initiation or diagnosis of hyperlipidaemia]; serum lipid concentrations; number of risk factors for CHD (other than serum cholesterol); concurrent use of other medications; abnormal liver or renal function within 3 months before the index date; record of stressful life events (e.g. bereavement, marital problem), hospitalization, and diagnosis of myocardial infarction (MI) or stroke in the prior 6 months; number of general practitioner (GP) visits and selected comorbidities (mainly cardiovascular diseases) within the previous 1 year; current benzodiazepine use; and any history of alcohol/drug misuse or certain psychiatric disorders. In addition, we evaluated the relation between the use of LLD and any hospitalization or death within 1 year after the index date.

To assess the impacts of comorbidities on treatment initiation in primary care, we not only employed a modified Charlson comorbidity index to calculate the overall chronic disease burden in the previous year [25, 26], but we also looked at various individual comorbidities,

including hypertension, congestive heart failure (CHF), CHD, peripheral vascular diseases, cerebrovascular diseases, diabetes, hypothyroidism, and nephrotic syndrome. Because severity of cardiovascular diseases and diabetes is likely to be important in affecting the initiation of treatment, we further categorized those diseases into 'severe', 'mild to moderate', or 'none' based on certain predefined criteria, such as the date of diagnosis, the likelihood of requiring hospitalization, and the presence of complication or long-term disability. For example, severe diabetes was identified if a subject had recent hospitalization or had any end-organ damage due to diabetes (e.g. nephropathy); while severe CHD was defined as follows: angina requiring recurrent hospitalization or treatment with $\geq$ three prescriptions for nitroglycerin within a year; MI with post-MI severe CHF or angina; recurrent MI; or MI within 6 months before the index date. In a separate analysis, such classification of disease severity has been found to be a good predictor of the probability of hospitalization within 1 year after the index date, after adjusting for age and sex, among a random sample of the study population [27].

Certain data, such as serum lipid concentrations, and severity of illness could not be obtained directly from an automated computer search. To derive the relevant information, we manually reviewed the computerized records of a random sample of 4000 patients (including 1500 statin users, 1000 fibrate users, 500 other LLD users, and 1000 untreated hyperlipidaemic patients). Analyses related to these variables were restricted to the 4000 individuals with available information only.

Statistical analysis

We assessed the differences in baseline characteristics between patients receiving LLDs and patients without LLD treatment using the Pearson chi-squared test and logistic regression modelling. We fitted a multivariate logistic regression model adjusting for age, sex, BMI, smoking status, and year of treatment initiation or hyperlipidaemia diagnosis to further assess the relative odds of initiating LLDs in primary care for other baseline characteristics. Because of the large sample size and the possibility of chance variation, we excluded variables that had a prevalence of less than 1% or variables that had an odds ratio (OR) ranging between 0.67 and 1.50 in the final analysis, unless they were disorders of the kidney or liver that could heavily influence LLD prescribing. The association between LLD prescribing and death or hospitalization within 1 year after the index date was evaluated by further adjustment for other significant variables in multivariate analyses. We also compared people who received different classes of LLDs (i.e. statins, fibrates, and other LLDs) by employing the same analytical strategies

as previously described. We then explored the association between baseline characteristics and LLD treatment among patients receiving individual LLDs within different classes of LLDs. In the evaluation of the severity of cardiovascular diseases and diabetes, we used ordinal scores to test the linearity of the trends.

All analyses were performed using SAS software (version 6.12; SAS Institute Inc, Cary, NC). Odds ratios of treatment initiation are presented with point estimates and relevant 95% confidence intervals (CIs). All *P* values are two-sided.

Ethical considerations

All data used in the analyses were anonymous. In addition, the research protocol was approved by the GPRD Scientific and Ethical Advisory Group (SEAG).

Results

We identified 42 201 patients who started receiving LLDs in primary care or who had a first-time diagnosis of hyperlipidaemia without LLD treatment during the study period. Among them, we excluded 583 patients because the indication for treatment was not related to either prevention of CHD or treatment of other atherosclerotic diseases (e.g. receipt of cholestyramine due to diarrhoea). The study base thus comprised 41 618 subjects, including 25 331 patients with LLDs (17 061 statin users, 6551 fibrate users, and 1719 other LLD users), and 16 287 patients with untreated hyperlipidaemia. A diagnosis of CHD with or without hyperlipidaemia was the most common reason for initiating LLD therapy (12 501 patients, 49.4%; with 7173 patients having concomitant hyperlipidaemia), followed by a diagnosis of hyperlipidaemia without CHD (9397 patients, 37.1%), and other atherosclerotic diseases (217 patients, 0.9%). A subject was considered to have CHD if the GP entered a code for MI and/or angina into the patient's computer record. Although CHD was the major reason for starting a LLD, only 12.2% of all patients diagnosed with CHD in the GPRD who also fulfilled the inclusion criteria of this study received LLD therapy. For 3216 patients (12.7%), there was no apparent recorded indication for starting LLD therapy.

There were many differences in measured baseline characteristics between patients who received and patients who did not receive LLDs (Table 1). Firstly, the initiation of LLDs increased rapidly during the study period, while the number of patients with a first-time diagnosis of hyperlipidaemia without LLD treatment only slightly decreased (OR of treatment initiation 4.47; 95% C.I. 4.19, 4.76). Secondly, patients who started receiving LLD therapy were more likely than those untreated

Table 1 Distribution of various characteristics between patients with and patients without lipid-lowering drug therapy, and the relevant odds ratio for treatment initiation.

	Number of patients with lipid-lowering drugs (%) (n = 25 331)	Number of patients without lipid-lowering drugs (%) (n = 16 287)	Crude OR for treatment initiation (95% CI)	Adjusted OR for treatment initiation* (95% CI)
<i>Age (years)</i>				
< 50	4 382 (17.3)	5 546 (34.1)	1.0	N/A*
50–59	7 436 (29.4)	4 787 (29.4)	1.97 (1.86, 2.08)	N/A
60–69	9 442 (37.3)	4 213 (25.9)	2.84 (2.69, 2.99)	N/A
≥ 70	4 071 (16.1)	1 741 (10.7)	2.96 (2.76, 3.17)	N/A
<i>Sex</i>				
Male	13 436 (53.0)	7 842 (48.2)	1.0	N/A
Female	11 895 (47.0)	8 445 (51.9)	0.82 (0.79, 0.86)	N/A
<i>Calendar year of treatment initiation or diagnosis of hyperlipidaemia</i>				
1990–1991	2 375 (9.4)	3 242 (19.9)	1.0	N/A
1992–1993	4 210 (16.6)	5 267 (32.3)	1.09 (1.02, 1.17)	N/A
1994–1995	6 513 (25.7)	4 038 (24.8)	2.20 (2.06, 2.35)	N/A
1996–1997	12 233 (48.3)	3 740 (23.0)	4.47 (4.19, 4.76)	N/A
<i>Body mass index (kg m⁻²)</i>				
< 25.0	6 644 (26.2)	4 138 (25.4)	1.0	N/A
25.0–29.9	9 079 (35.8)	5 411 (33.2)	1.05 (0.99, 1.10)	N/A
≥ 30.0	4 248 (16.8)	2 748 (16.9)	0.96 (0.91, 1.02)	N/A
Unknown	5 360 (21.2)	3 990 (24.5)	0.84 (0.79, 0.89)	N/A
<i>Smoking status</i>				
None	12 800 (50.5)	8 589 (52.7)	1.0	N/A
Current	4 854 (19.2)	3 452 (21.2)	0.94 (0.90, 0.99)	N/A
Past	4 480 (17.7)	1 981 (12.2)	1.52 (1.43, 1.61)	N/A
Unknown	3 197 (12.6)	2 265 (13.9)	0.95 (0.89, 1.01)	N/A
<i>Record of any hospitalization in the prior 6 months</i>				
No	20 744 (81.9)	15 410 (94.6)	1.0	1.0
Yes	4 587 (18.1)	877 (5.4)	3.89 (3.60, 4.19)	3.12 (2.88, 3.37)
<i>Number of general practitioner visit in the prior 1 year</i>				
0–2	2 611 (10.3)	3 465 (21.3)	1.0	1.0
3–4	3 367 (13.3)	3 290 (20.2)	1.34 (1.25, 1.45)	1.36 (1.27, 1.46)
5–6	3 725 (14.7)	2 615 (16.1)	1.83 (1.70, 1.98)	1.89 (1.76, 2.03)
7–9	4 914 (19.4)	2 798 (17.2)	2.22 (1.70, 2.39)	2.33 (2.18, 2.50)
10–12	3 618 (14.3)	1 682 (10.3)	2.73 (2.51, 2.96)	2.86 (2.64, 3.08)
≥ 13	7 096 (28.0)	2 437 (15.0)	3.53 (3.28, 3.81)	3.86 (3.61, 4.14)
<i>Myocardial infarction within 6 months</i>				
No	23 546 (93.0)	16 104 (98.9)	1.0	1.0
Yes	1 785 (7.1)	183 (1.1)	6.67 (5.72, 7.78)	4.74 (4.05, 5.55)
<i>Diabetes mellitus</i>				
No	22 004 (86.9)	15 280 (93.8)	1.0	1.0
Yes	3 327 (13.1)	1 007 (6.2)	2.29 (2.13, 2.47)	1.95 (1.81, 2.11)
<i>Congestive heart failure</i>				
No	23 545 (93.0)	15 916 (97.7)	1.0	1.0
Yes	1 786 (7.1)	371 (2.3)	3.25 (2.91, 3.65)	2.21 (1.97, 2.49)
<i>Stroke within 6 months</i>				
No	24 992 (98.7)	16 200 (99.5)	1.0	1.0
Yes	339 (1.3)	87 (0.5)	2.53 (1.99, 3.20)	1.77 (1.38, 2.27)
<i>Peripheral vascular disease</i>				
No	22 385 (88.4)	15 493 (95.1)	1.0	1.0
Yes	2 946 (11.6)	794 (4.9)	2.57 (2.37, 2.79)	1.98 (1.82, 2.16)
<i>Number of risk factors for coronary heart disease (CHD) or a history of CHD†</i>				
0–1	7 574 (29.9)	10 371 (63.7)	1.0	1.0
2–4	5 256 (20.8)	3 890 (23.9)	1.85 (1.76, 1.95)	1.53 (1.45, 1.62)
Prior CHD	12 501 (49.4)	2 026 (12.4)	8.45 (7.99, 8.93)	6.32 (5.94, 6.71)

Table 1 continued

	Number of patients with lipid-lowering drugs (%) (n = 25 331)	Number of patients without lipid-lowering drugs (%) (n = 16 287)	Crude OR for treatment initiation (95% CI)	Adjusted OR for treatment initiation* (95% CI)
<i>Charlson comorbidity index score</i>				
0	11 244 (44.4)	11 396 (70.0)	1.0	1.0
1	8 327 (32.9)	3 482 (21.4)	2.42 (2.31, 2.54)	2.00 (1.90, 2.11)
≥ 2	5 760 (22.7)	1 409 (8.7)	4.14 (3.89, 4.42)	2.94 (2.75, 3.15)
<i>Classes of cardiovascular medications</i>				
0	7 900 (31.2)	10 579 (65.0)	1.0	1.0
1	5 609 (22.1)	3 204 (19.7)	2.34 (2.23, 2.47)	2.12 (2.00, 2.24)
2	4 718 (18.6)	1 557 (9.6)	4.06 (3.81, 4.33)	3.27 (3.06, 3.51)
≥ 3	7 104 (28.0)	947 (5.8)	10.05 (9.33, 10.82)	7.25 (6.71, 7.84)
<i>Number of noncardiovascular medications</i>				
0	8 932 (35.3)	8 377 (51.4)	1.0	1.0
1	5 946 (23.5)	3 734 (22.9)	1.49 (1.42, 1.57)	1.39 (1.31, 1.46)
2–3	6 192 (24.4)	2 879 (17.7)	2.02 (1.91, 2.13)	1.75 (1.65, 1.85)
≥ 4	4 261 (16.8)	1 297 (8.0)	3.08 (2.88, 3.30)	2.54 (2.36, 2.73)

*OR denotes odds ratio and CI denotes confidence interval. N/A indicates that the OR estimates for the variables were not available. All other variables were adjusted for age, sex, year of treatment initiation or hyperlipidaemia diagnosis, body mass index, and smoking status. †The following risk factors other than serum cholesterol for coronary heart disease were included: (1) male ≥ 45 years or female ≥ 55 years or premature menopause without oestrogen replacement therapy; (2) current cigarette smoking; (3) hypertension; and (4) diabetes.

hyperlipidaemic patients to be older people and past smokers; they also had more prior hospitalizations, GP visits, diabetes, CHF, peripheral vascular disease, higher Charlson comorbidity index scores, concurrent cardiovascular [including β -adrenoceptor antagonists, angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers (CCB), nitrates, α -adrenoceptor blockers, digitalis and related agents, aspirin, and anticoagulants] and noncardiovascular medications, risk factors for CHD, and recent MI/stroke, even after adjusting for age, sex, BMI, smoking status and calendar year. A diagnosis of nephrotic syndrome (adjusted OR 6.58; 95% CI 3.33, 12.98) and recent renal disorders (adjusted OR 2.89; 95% CI 1.79, 4.67), both with a prevalence of less than 1%, occurred more frequently among patients who received LLDs as well. For the other variables, the results were either insignificant (depression, mild psychiatric diseases, and history of alcohol/drug abuse), or significant but had an OR ranging between 0.67 and 1.50, or had a prevalence of less than 1% (record of stressful life events, hypothyroidism, hypertension, cerebrovascular disease, severe psychiatric diseases, concurrent benzodiazepine use, and recent liver disorders).

Although treatment with a LLD was related to the probability of hospitalization or death within 1 year after the index date after adjusting for demographics, BMI, and smoking status, no association was found after further adjustment for other variables, such as CHD (adjusted OR for hospitalization 1.06; 95% CI 0.99, 1.13; adjusted OR for mortality 1.06; 95% CI 0.86, 1.30). There was

also no effect modification by age (< 65 *vs* ≥ 65 years). After excluding nonstatin, nonfibrate LLD users who appeared to have the highest 1-year mortality, LLD therapy was associated with a lower risk of mortality, but not hospitalization, within 1 year after the index date (adjusted OR for mortality 0.76; 95% CI 0.61, 0.95; adjusted OR for hospitalization 1.00; 95% CI 0.93, 1.08).

The severity of cardiovascular diseases and diabetes was also associated with treatment initiation of LLDs in primary care. In the sample of 4000 patients, after excluding 79 subjects who received LLDs for an indication other than CHD or hyperlipidaemia, the probability of receiving LLD therapy consistently increased with disease severity. Such a trend remained for CHD, CHF, diabetes, and peripheral vascular disease, after adjusting for demographic and patient characteristics (test for trend with $P = 0.0001$, Table 2). As expected, treatment initiation of LLDs was also associated with serum lipid concentrations. However, these data were frequently unavailable in the computerized records (e.g. only 42.4% of patients had a record of serum cholesterol), and were thus excluded from further analyses. The recording of serum lipid concentrations was not associated with demographics, patient characteristics, concurrent medications or comorbidities (data not shown).

Baseline characteristics appeared to vary between patients receiving different classes of LLDs as well. The use of statins increased dramatically during the study period, especially after the year of 1994; while the pre-

Table 2 Distribution of severity of cardiovascular disease and diabetes between patients with and patients without lipid-lowering drug therapy and the relevant odds ratio for treatment initiation among a sample of 3921 patients.

	Number of patients with lipid-lowering drugs (%) (n = 2921)	Number of patients without lipid-lowering drugs (%) (n = 1000)	Crude OR for treatment initiation (95% CI)	Adjusted OR for treatment initiation* (95% CI)
<i>Coronary heart disease</i>				
No	1674 (57.3)	864 (86.4)	1.0	1.0
Mild to moderate	782 (26.8)	91 (9.1)	4.44 (3.52, 5.59)	3.63 (2.84, 4.63)
Severe	465 (15.9)	45 (4.5)	5.33 (3.89, 7.32)	3.89 (2.80, 5.41)
<i>Congestive heart failure</i>				
No	2782 (95.2)	985 (98.5)	1.0	1.0
Mild to moderate	116 (4.0)	15 (1.5)	2.74 (1.59, 4.71)	1.70 (0.97, 2.96)
Severe	23 (0.8)	0 (0.0)	N/A†	N/A†
<i>Diabetes mellitus</i>				
No	2526 (86.5)	934 (93.4)	1.0	1.0
Mild to moderate	329 (11.3)	60 (6.0)	2.03 (1.52, 2.70)	1.87 (1.39, 2.53)
Severe	66 (2.3)	6 (0.6)	4.07 (1.76, 9.41)	4.01 (1.59, 10.13)
<i>Peripheral vascular disease</i>				
No	2673 (91.5)	966 (96.6)	1.0	1.0
Mild to moderate	217 (7.4)	33 (3.3)	2.38 (1.64, 3.45)	2.06 (1.40, 3.03)
Severe	31 (1.1)	1 (0.1)	11.20 (1.53, 82.18)	6.90 (0.93, 51.28)
<i>Serum cholesterol concentration</i>				
< 5.0 mmol l ⁻¹	4 (0.1)	8 (0.8)	0.11 (0.03, 0.38)	0.08 (0.02, 0.28)
5.0–6.4 mmol l ⁻¹	161 (5.5)	74 (7.4)	0.49 (0.35, 0.68)	0.31 (0.22, 0.45)
6.5–7.7 mmol l ⁻¹	474 (16.2)	212 (21.2)	0.50 (0.39, 0.64)	0.42 (0.32, 0.54)
≥ 7.8 mmol l ⁻¹	597 (20.4)	133 (13.3)	1.0	1.0
Unknown	1685 (57.7)	573 (57.3)	0.66 (0.53, 0.81)	0.55 (0.44, 0.69)

*OR denotes odds ratio and CI denotes confidence interval. All variables were adjusted for age, sex, year of treatment or diagnosis, body mass index, and smoking status. †N/A denotes nonavailable because the odds ratio is infinite.

scription of other LLDs gradually decreased (Figure 1). Furthermore, although only 4.7% of patients over the age of 75 years received statin therapy, these people were more likely to receive a statin than any other LLD. There were proportionally more patients with fibrate therapy who were diabetic and who received LLDs due to hypertriglyceridaemia. The distribution of prior hospitalization, hypertension, number of concurrent medications, risk factors for CHD, recent MI/stroke, and the probability of death or hospitalization in the year after starting LLD therapy were also different between the three groups of patients in the adjusted analysis (Table 3). In addition, treatment with statins was found to be associated with more severe CHD, and more frequent use of β -adrenoceptor blockers, ACEIs, CCBs, nitrates, aspirin, and anticoagulants (data not shown). A diagnosis of nephrotic syndrome (adjusted OR 2.95; 95% CI 1.47, 5.92 *vs* fibrates; and adjusted OR 1.16; 95% CI 0.50, 2.67 *vs* other LLDs) and recent renal disorders (adjusted OR 2.38; 95% CI 1.29, 4.37 *vs* fibrates; and adjusted OR 0.93; 95% CI 0.49, 1.93 *vs* other LLDs) were related to statin therapy, while the presence of recent liver disorders was inversely associated with statin use (adjusted OR

0.59; 95% CI 0.28, 1.27 *vs* fibrates; and adjusted OR 0.01; 95% CI < 0.01, 0.02 *vs* other LLDs). These variables all had a prevalence of less than 1%. For the following variables, the results were either insignificant, or significant but had a less prominent OR and/or a prevalence of less than 1%: record of stressful life events, hypothyroidism, peripheral vascular disease, GP visits, CHF, peripheral vascular disease, Charlson comorbidity index scores, psychiatric diseases, concurrent benzodiazepine use, and history of alcohol/drug abuse.

In the analysis of individual LLDs, we only compared the differences between patients treated with pravastatin (*n* = 2373) and patients with simvastatin treatment (*n* = 12 723). We did not look at other LLDs because, except for bezafibrate (*n* = 4893), the relevant information was limited due to the small number of users of these drugs. Patients who received pravastatin were largely similar to subjects with simvastatin therapy in their baseline characteristics, although simvastatin appeared to be more frequently prescribed after the year of 1994–95 (OR 2.34; 95% CI 1.95, 2.83 for the year of 1994–95; and OR 1.79; 95% CI 1.51, 2.11 for the year of 1996–97), and was associated with more prior

Figure 1 Treatment initiation of various lipid-lowering drugs between calendar year 1990–1997. Δ , Statins; $\circ$, fibrates; $\times$, other lipid-lowering drugs; $\bullet$, all drugs.

hospitalization (adjusted OR 1.52; 95% CI 1.34, 1.71), more recent MI (adjusted OR 1.97; 95% CI 1.62, 2.39), more pre-existing CHD (adjusted OR 1.50; 95% CI 1.36, 1.65), and less severe peripheral vascular disease (adjusted OR 0.18; 95% CI 0.05, 0.74 for severe disease). Patients treated with simvastatin did not differ from patients with pravastatin treatment in the 1-year probability of hospitalization or death.

Discussion

Our findings suggest that initiation of LLD therapy in primary care is associated with many baseline characteristics, including age, smoking status, calendar year of treatment initiation or diagnosis of hyperlipidaemia, prior hospitalization, number of GP visits, diabetes, CHF, recent MI/stroke, peripheral vascular disease, Charlson comorbidity index scores, concurrent cardiovascular and noncardiovascular medication, risk factors for CHD, and severity of various diseases. There also appears to be a relation between the initial choice of a specific class of LLDs and patients' demographics, prior hospitalization, diabetes, hypertension, recent MI/stroke, use of concurrent medications, risk factors for CHD, and the probability of death or hospitalization in the following year. Patients with pravastatin therapy were largely similar to patients treated with simvastatin, although they differed somewhat in the year of treatment initiation, prevalence of recent MI or prior CHD, and the severity of peripheral vascular disease.

Several studies have evaluated the change in, and factors related to, the use of LLDs during the 1990s [6, 7, 28–30]. All of them found a dramatic increase in the rate of statin use in the 1990s, especially after the year of 1994. Majeed *et al.* also examined the association between statin use and age, sex, and general practice in the UK, and found that statins were mostly prescribed

to people aged 55–74 years and the prescribing rates were higher in men than in women [7]. None of these studies has evaluated the relation between factors other than demographics and the prescribing of LLDs.

Our findings of the association between demographic characteristics and the prescribing of statins were consistent with the aforementioned studies. We further noted that the prescribing of nonstatin LLDs has decreased, and there remained many patients eligible for lipid-lowering therapy who did not receive LLDs. Although these data are interesting, the main purpose of this study was to explore other characteristics of patients at the time of starting LLD therapy where we did find many differences between those who did and those who did not receive LLDs.

We are not aware of any previous studies that have specifically examined the potential determinants of treatment initiation with LLDs. Majumdar *et al.*, in a study of 622 patients who were hospitalized for acute MI and who were eligible for LLD therapy, found that the use of LLDs on admission was associated with past smoking status, use of $\geq$ four concurrent medications, prior coronary revascularization, and aspirin use. They also noted an inverse association between LLD use and age greater than 74 years, female sex, and severe noncardiovascular comorbidity [31]. Although the study was somewhat related to our study and showed similar findings, it did not assess the effects of comorbidities or patient characteristics on initiation of LLD therapy or the differences between patients who received various classes of LLDs.

According to the recommended national guidelines on the use of LLDs in the UK [32–35], one might expect to see preferential prescribing of LLDs to patients with established CHD and/or other major atherosclerosis (secondary prevention), and individuals with multiple risk factors for CHD that put them at higher risk of developing CHD (primary prevention). Patients who had more severe CHD or other atherosclerotic diseases; or patients who remained at high risk of developing CHD after nonpharmacological intervention should also be more likely to receive LLD therapy. The relationship between treatment with LLDs and various baseline characteristics found in this study (Table 1) was consistent with such therapeutic recommendations. Our findings on the probability of death in the year after starting LLD therapy, however, were somewhat different from that observed in a US study using data from New Jersey's Medicaid and PAAD program, which found an inverse association between LLD therapy and 1-year mortality [15]. The discrepancy between the study findings may be due to differential prescribing of nonstatin, nonfibrate LLDs to patients with the highest risk of 1-year mortality after the index date as the results became similar after excluding nonstatin, nonfibrate LLD users.

Table 3 Distribution of various characteristics between patients receiving different classes of lipid-lowering drug therapy and the relevant odds ratio for treatment initiation.

	Number of patients with statins (%) (n = 17 061)	Number of patients with fibrates (%) (n = 6551)	Number of patients with other lipid-lowering drugs (%) (n = 1719)	Adjusted OR for treatment initiation* (95% CI)	
				Statins vs fibrates	Statins vs other lipid-lowering drugs
<i>Age (years)</i>					
< 50	2 545 (14.9)	1327 (20.3)	510 (29.7)	N/A*	N/A*
50–59	4 928 (19.5)	2063 (31.5)	445 (25.9)	N/A	N/A
60–69	6 492 (38.1)	2476 (37.8)	474 (27.6)	N/A	N/A
≥ 70	3 096 (18.2)	685 (10.5)	290 (16.9)	N/A	N/A
<i>Sex</i>					
Male	9 320 (54.6)	3391 (51.8)	725 (42.2)	N/A	N/A
Female	7 741 (45.4)	3160 (48.2)	994 (57.8)	N/A	N/A
<i>Calendar year of treatment initiation</i>					
1990–1991	856 (5.0)	1053 (16.1)	466 (27.1)	N/A	N/A
1992–1993	1 749 (10.3)	1854 (28.3)	607 (35.3)	N/A	N/A
1994–1995	3 922 (23.0)	2165 (33.1)	426 (24.8)	N/A	N/A
1996–1997	10 534 (61.7)	1479 (22.6)	220 (12.8)	N/A	N/A
<i>Body mass index (kg m⁻²)</i>					
< 25	4 598 (27.0)	1515 (23.1)	531 (30.9)	N/A	N/A
25–29.9	6 343 (37.2)	2302 (35.1)	434 (25.3)	N/A	N/A
≥ 30.0	2 859 (16.8)	1234 (18.8)	155 (9.0)	N/A	N/A
Unknown	3 261 (19.1)	1500 (22.9)	599 (34.9)	N/A	N/A
<i>Smoking status</i>					
None	8 746 (51.3)	3291 (50.2)	763 (44.4)	N/A	N/A
Current	3 325 (19.5)	1217 (18.6)	312 (44.4)	N/A	N/A
Past	3 197 (18.7)	1088 (16.6)	195 (11.3)	N/A	N/A
Unknown	1 793 (10.5)	955 (14.6)	449 (26.1)	N/A	N/A
<i>Record of any hospitalization in the prior 6 months</i>					
No	13 490 (79.1)	5827 (89.0)	1427 (83.0)	1.0	1.0
Yes	3 571 (20.9)	724 (11.1)	292 (17.0)	1.72 (1.57, 1.89)	0.85 (0.74, 0.99)
<i>Diabetes mellitus</i>					
No	15 040 (88.2)	5379 (82.1)	1585 (92.2)	1.0	1.0
Yes	2 021 (11.9)	1172 (17.9)	134 (7.8)	0.51 (0.46, 0.55)	1.06 (0.87, 1.29)
<i>Hypertension</i>					
No	9 894 (58.0)	3826 (58.4)	1267 (73.7)	1.0	1.0
Yes	7 167 (42.0)	2725 (41.6)	452 (26.3)	0.92 (0.87, 0.99)	1.68 (1.49, 1.90)
<i>Myocardial infarction within 6 months</i>					
No	15 528 (91.0)	6320 (96.5)	1698 (98.8)	1.0	1.0
Yes	1 533 (9.0)	231 (3.5)	21 (1.2)	2.05 (1.76, 2.38)	4.88 (3.13, 7.60)
<i>Stroke within 6 months</i>					
No	16 793 (98.4)	6488 (99.0)	1711 (99.5)	1.0	1.0
Yes	268 (1.6)	63 (1.0)	8 (0.5)	1.25 (0.93, 1.68)	2.52 (1.21, 5.26)
<i>Classes of cardiovascular medications</i>					
0	4 400 (25.8)	2512 (38.4)	988 (57.5)	1.0	1.0
1	3 636 (21.3)	1612 (24.6)	361 (21.0)	1.18 (1.08, 1.28)	1.92 (1.66, 2.21)
2	3 413 (20.0)	1111 (17.0)	194 (11.3)	1.43 (1.30, 1.57)	2.90 (2.43, 3.45)
≥ 3	5 612 (32.9)	1316 (20.1)	176 (10.2)	1.79 (1.64, 1.95)	4.41 (3.69, 5.28)
<i>Number of noncardiovascular medications</i>					
0	5 816 (34.1)	2537 (38.7)	579 (33.7)	1.0	1.0
1	4 067 (23.8)	1514 (23.1)	365 (21.2)	1.04 (0.96, 1.13)	0.93 (0.80, 1.09)
2–3	4 323 (25.3)	1472 (22.5)	397 (23.1)	1.07 (0.98, 1.16)	0.80 (0.69, 0.93)
≥ 4	2 855 (16.7)	1028 (15.7)	378 (22.0)	0.91 (0.83, 1.00)	0.47 (0.40, 0.55)
<i>Number of risk factors for coronary heart disease (CHD) or a history of CHD†</i>					
0–1	4 197 (24.6)	2354 (35.9)	1023 (59.5)	1.0	1.0
2–3	3 169 (18.6)	1761 (26.9)	326 (19.0)	0.80 (0.73, 0.88)	1.80 (1.54, 2.10)
Prior CHD	9 695 (56.8)	2436 (37.2)	370 (21.5)	1.74 (1.61, 1.88)	4.12 (3.58, 4.74)

Table 3 continued

	Number of patients with statins (%) (n = 17 061)	Number of patients with fibrates (%) (n = 6551)	Number of patients with other lipid-lowering drugs (%) (n = 1719)	Adjusted OR for treatment initiation* (95% CI) Statins vs fibrates	Statins vs other lipid-lowering drugs
Any hospitalization within 1 year after the index date					
No	13 973 (81.9)	5584 (85.2)	1371 (79.8)	1.0	1.0
Yes	3 088 (18.1)	967 (14.8)	348 (20.2)	0.98 (0.90, 1.07)	0.62 (0.54, 0.71)
Death within 1 year after the index date					
No	16 794 (98.4)	6464 (98.7)	1598 (93.0)	1.0	1.0
Yes	267 (1.6)	87 (1.3)	121 (7.0)	0.86 (0.67, 1.12)	0.16 (0.12, 0.21)

*OR denotes odds ratio, and CI denotes confidence interval. N/A indicates that the OR estimates for the variables were not available. All other variables were adjusted for age, sex, year of treatment initiation, body mass index, and smoking status. For the two variables hospitalization and death within 1 year after the index date, further adjustment for all statistically significant variables, including various comorbidities, concurrent medication use, and recent hospitalization, were also performed. †The following risk factors other than serum cholesterol for coronary heart disease were included: (1) male (≥ 45 years) or female (≥ 55 years) or premature menopause without oestrogen replacement therapy; (2) current cigarette smoking; (3) hypertension; and (4) diabetes.

Although studies assessing the benefits and risks of LLDs frequently assumed that patients receiving different LLDs were similar in their baseline characteristics because all LLDs can be used to treat dyslipidaemia [8–10], such an assumption may not be valid because the pharmacological mechanisms, safety profiles, and potency of these drugs differ [16, 17]. For example, the prescribing of statins is likely to be avoided in people with hepatitis, an important adverse effect of statins [16]; while fibrates may be less favoured in patients with renal disorders, as they are largely excreted by the kidney [16, 33]. Physicians may also tend to prescribe fibrates to patients with combined diabetes and hyperlipidaemia, as hypertriglyceridaemia is the most common dyslipidaemia in such patients [36]. The publication of the Scandinavian Simvastatin Survival Study in 1994 [37], and two other statin trials during 1995–96 [38, 39] could have affected the initial choice of LLDs as well. Our findings supported the above proposition, as evidenced by an exponential increase in the prescribing of statins after the year of 1994, a higher prevalence of recent MI/stroke, number of cardiovascular drugs, more risk factors, and renal dysfunction among patients with statin therapy, and an association between diabetes and the prescribing of fibrates.

In this study, patients who received simvastatin were similar to patients treated with pravastatin in their baseline characteristics, except for a history of CHD, recent MI, prior hospitalization, and the severity of peripheral vascular disease. As there are no clinically appreciable differences in the safety profiles of these two statins and the ORs for the 'significant' determinants were modest, the differences could have arisen by chance, or through unmeasured baseline characteristics.

The use of computerized records in the GPRD to assess factors potentially associated with the initiation of

LLD therapy has the advantage that both drug exposure and baseline characteristics are not likely to be misclassified, as most LLDs are initiated and prescribed on an outpatient basis and are usually filled continually, and the recording of diagnostic information for major comorbid illnesses in the GPRD has been found to be accurate and complete [23, 24]. Although the relationship between certain baseline characteristics found in this study (e.g. prior hospitalization) and treatment initiation may change when initiation of LLD therapy occurs during hospitalization, most findings should remain valid.

For this study, we did not have adequate information on serum lipids or blood pressure. Therefore, we were unable to calculate the risk of developing CHD for individual patients and to assess the appropriateness of prescribing of LLDs among these people. However, based on the available findings of this study, it appeared that the GPs did prescribe LLDs to high-risk patients with or without CHD, although the rate of LLD treatment in people reporting a history of CHD who either had or did not have hyperlipidaemia remained low during the study period. There are many possible explanations for the low rate of LLD therapy among patients with pre-existing CHD, but physician-prescribing behaviour in this group of patients is not the objective of this study, and thus we did not pursue this finding. Nevertheless, it would be of great clinical importance to investigate this further in future studies.

Incomplete recording of serum lipids also raised concern about the accuracy of hyperlipidaemia diagnoses. Although we did not validate the diagnosis, the diagnosis itself is not likely to be misclassified, because in the manual review process it was found that most hyperlipidaemic patients had repeated diagnoses of hyperlipidaemia and/or records of raised serum lipid

concentrations after the index date. In addition, most patients with documented serum lipids had raised cholesterol concentrations (Table 2), and there was no association between recording of serum lipids and important predictors of LLD therapy, which suggested that the failure to record serum lipids is probably a random process. Therefore, the likelihood of diagnostic misclassification should be minimal.

In conclusion, we found that the use of statins in primary care has rapidly increased since 1994 but the proportion of people who received a LLD to treat CHD or hyperlipidaemia remains low. The decision to begin LLD therapy is likely to be affected by patient characteristics and a number of medically related factors, especially the prevalence and severity of diabetes and various cardiovascular diseases. Similarly, there appears to be differential prescribing of different classes of LLDs to patients eligible for lipid-lowering therapy, and patients receiving statins generally had more cardiovascular comorbidities than patients treated with nonstatin LLDs. Examining the medical records of individuals eligible for LLD therapy is an important first step in selectively targeting who will experience the greatest benefit to risk ratio for the treatment of hyperlipidaemia. It is also an important step in avoiding confounding by indication when designing epidemiological studies comparing the risks and benefits of treatments for hyperlipidaemia.

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