

Impact of lipid-lowering therapy on the prevalence of dyslipidaemia in patients at high-risk of cardiovascular events in UK primary care – a retrospective database study

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Disclosures

K. Jameson, V. Amber, K. D'Oca and B. Ambegaonkar are all employees of Merck & Co Inc. or its subsidiaries, and hold shares in the company. D. Mills is an independent consultant, and received a restricted grant to carry out all analyses reported in this study. A. Giles has no conflicts of interest.

SUMMARY

Aims: To estimate the prevalence of dyslipidaemias in high-risk patients new to lipid-modifying therapy (LMT), and establish the extent to which these lipid abnormalities are addressed by treatment in UK clinical practice. **Methods:** The PRIM-ULA study was a retrospective analysis, conducted using the UK General Practice Research Database. Two periods were studied as follows: a pretreatment period, defined as the 12 months before initiation of LMT (the index date), and a follow-up period of at least 12 months. Patients included in the study (n = 25,011) had dyslipidaemia with at least one abnormal lipid measurement [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) or triglycerides (TG)] in the pretreatment period. All patients were at high risk of cardiovascular events, which was defined as having a history of cardiovascular disease, a 10-year Framingham risk score higher than 20%, diabetes or hypertension, as defined by the Joint British Societies 2 guidelines. **Results:** At the index date, 98% of patients were initiated on statin monotherapy. After 12 months of treatment, 15.2% (sub-group range: 11.0–22.9%) of all high-risk patients had no lipid abnormalities. The proportions of patients with high TC or LDL-C levels decreased from 98.8% to 68.9%, and from 99.2% to 68.7%, respectively, over 12 months. The prevalence of high TG levels decreased from 45.0% to 26.9%, whereas that of low HDL-C levels increased, from 16.6% to 18.0%. Risk factors for cardiovascular events were not consistently associated with the likelihood of attaining optimal lipid levels. **Conclusions:** Despite widespread use of statins, many individuals at high risk of cardiovascular events have persistently abnormal lipid levels, with over two-thirds of patients not achieving target levels of LDL-C or TC. Management of dyslipidaemia is therefore suboptimal in this important high-risk group in UK standard practice.

What's known

- High levels of cholesterol (particularly low-density lipoprotein cholesterol) and other lipids (e.g. triglycerides) are risk factors for cardiovascular disease.
- Management of total and low-density lipoprotein cholesterol leads to a reduction in the incidence of cardiovascular events.
- Rates of achieving target lipid levels defined by UK national guidelines are suboptimal, possibly reflecting poor adherence of physicians to guidelines and under-treatment of the disease.
- Evidence for the prevention of cardiovascular events comes largely from statin trials, although some data are available from non-statin trials.

What's new

- This analysis, based on a large-scale clinical database, is the first review of dyslipidaemia after the implementation of the National Health Service Quality and Outcomes Framework in the UK.
- The study focused on high-risk patients, where guidelines make clear recommendations for lipid management to reduce the incidence of cardiovascular disease.
- Despite financial incentives and widespread statin use, over two-thirds of patients in this analysis did not reach cholesterol targets.

Introduction

Despite significant improvements in prevention and treatment of cardiovascular disease (CVD) during the past two decades, CVD remains the leading cause of death in the UK. In 2010, CVD accounted for almost 180,000 deaths (one-third of all deaths) in the UK; of these, just over 46,000 occurred in people under 75 years of age (1). Approximately half (80,568) of all CVD deaths were caused by coronary heart disease (CHD), which is the principal cause of premature CVD death in people under the age of 75 years and accounts for 17% and 8% of all deaths

in men and women in the UK, respectively (1). CHD mortality rates in the UK are the fourth highest in Europe (2).

In the UK, as in other countries, dyslipidaemia is a major risk factor for CVD (3). Treatment of dyslipidaemia, particularly high levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), is therefore a central strategy in the prevention of CVD. Dyslipidaemia is included in the UK National Health Service Quality and Outcomes Framework (QOF), which provides financial incentives for primary care physicians (PCPs) to meet specified targets for the management of chronic

disease; in CVD, these targets focus on controlling TC (4).

UK clinical guidelines for the management of CVD set minimum 'audit standards' for TC and LDL-C of less than 5 and 3 mmol/l, respectively, with more stringent targets (< 4 mmol/l for TC and < 2 mmol/l for LDL-C) being recommended in patients at high risk of cardiovascular events (5–7). Similarly, the UK National Institute for Health and Clinical Excellence (NICE) currently recommend that consideration is given to reduction in cholesterol to achieve levels of TC < 4.0 mmol/l or LDL-C < 2.0 mmol/l in patients with CVD, with an audit TC level of below 5 mmol/l (8). In patients with type 2 diabetes and new/existing CVD (or an increased albumin excretion rate), NICE also recommend cholesterol targets of TC < 4.0 mmol/l or LDL-C < 2.0 mmol/l (9). This focus reflects the epidemiological evidence that a high LDL-C level is a strong risk factor for CVD (10), and the consistent finding in clinical trials that lowering raised LDL-C levels significantly reduces the incidence of CVD (11). However, there is evidence that residual cardiovascular risk remains even after effective reduction in TC and LDL-C levels by statins (12). This residual risk may be partly attributable to high triglyceride (TG) and reduced high-density lipoprotein cholesterol (HDL-C) levels, both of which are now recognised as independent risk factors for CHD (13–16).

Limited information is available about the extent to which high TG or low HDL-C levels are being addressed in routine clinical practice. A study based on the UK General Practice Research Database (GPRD) reported that, following a year of statin treatment, 65% of patients achieved target TC levels (< 5 mmol/l) and 73% achieved target LDL-C levels (< 3.0 mmol/l), while only 32% and 42% of patients achieved desirable HDL-C and TG levels (HDL-C: ≥ 1.0 mmol/l in men, ≥ 1.2 mmol/l in women; TG: < 1.7 mmol/l) (17). This would suggest that, although TC and LDL-C appear to be well managed, control of TG and HDL-C levels is poor, despite the fact that abnormal levels of these lipids have been identified as important cardiovascular risk factors. However, this study was conducted before the introduction of the QOF, and hence the findings are unlikely to be applicable to current practice. Further data are therefore required to assess the extent to which HDL-C and TG levels are being managed in routine practice in the UK.

The Prevalence, Treatment Patterns and Resource Use in Patients with Mixed Dyslipidaemia Using Lipid-Modifying Agents (PRIMULA) study was conducted to estimate the prevalence of forms of dyslipidaemia in high-risk patients new to lipid-modifying

therapy (LMT) for 12 months in UK primary care, to establish the extent to which these lipid abnormalities are addressed by treatment in UK clinical practice. Secondary objectives were to assess treatment patterns and to investigate morbidity-related use of healthcare resources in patients with dyslipidaemia.

Methods

PRIMULA was a retrospective database study with cross-sectional assessments of patients in the 12 months preceding and following initiation of first-line LMT. The study consisted of two periods: a pretreatment period, defined as the 12 months before initiation of LMT (the index date), and a followup period of at least 12 months after the index date. Following initiation of LMT, patients received continual treatment until 6 weeks or less before the end of the follow-up period; treatment gaps of up to 6 weeks were permitted during this period, except for the first 6 weeks after the index date.

Data were obtained from the UK GPRD (18), which includes information from 8.5 million patients (approximately 13% of the UK population) registered with more than 400 primary care practices across the UK. The patients are representative of the general population in terms of age and gender. Data were assessed between April 2006 and December 2008 (i.e. after the introduction of the QOF in April 2004). All data were obtained from medical records and anonymized before analysis. The study protocol was reviewed and approved by the UK Independent Scientific Advisory Committee, governing the use of the GPRD.

Patients

Patients included in the GPRD were eligible for inclusion in the PRIMULA study if they were aged 35 years or older and had a diagnosis of dyslipidaemia, lipid levels (TG, HDL-C, LDL-C, TC) characteristic of dyslipidaemia, or both, at the index date. Patients were included if they had not received LMT in the 12 months prior to the index date, and had at least one abnormal value [as defined in the Joint British Societies (JBS) 2 guidelines (7)] in any of four lipid assays (TC, LDL-C, HDL-C, TG) within the year preceding the index date. If multiple measurements were made during the pretreatment period, the measurement taken closest to the index date was recorded. In addition, documentation of cardiovascular risk factors or conditions during the pretreatment period was required for inclusion in the study. Patients were included in the analysis only if all baseline data (see below) were available; they were excluded if they had received statins or other

LMTs during the pretreatment period. Anonymized data for all patients meeting the inclusion criteria were included in the study.

Data recorded

Baseline demographic and clinical data were obtained at the most recent time point before the index date in the following categories: age; gender; body mass index (BMI); smoking status; baseline levels of TG, HDL-C, LDL-C and TC; fasting levels of blood glucose and glycated haemoglobin (HbA_{1c}); systolic and diastolic blood pressure; and cardiovascular risk factors (hypertension, diabetes) or disorders (CHD, cerebrovascular disease, peripheral arterial disease). Twelve months after the index date, the same information was collected, as well as data on LMTs received, diagnosis of hypertension, diabetes, CVD or peripheral arterial disease, and major cardiovascular events such as myocardial infarction, stroke, angina, transient ischaemic attack and congestive heart failure. In addition, data on healthcare resource utilisation, such as consultations with physicians or other healthcare professionals, visits to the emergency department and hospitalizations related to CVD, were extracted from the GPRD at the end of the follow-up period.

Definitions

LDL-C levels were calculated using the Friedewald formula (19); the calculations were considered invalid if TG concentrations were higher than 4.5 mmol/l. Mixed dyslipidaemia was defined as the presence of at least two abnormal lipid values. As defined in the JBS 2 guidelines (7), TC and LDL-C target levels were lower than 4 and 2 mmol/l, respectively; desirable levels for TG were considered to be lower than 1.7 mmol/l, and for HDL-C, higher than 1.0 mmol/l in men and 1.2 mmol/l in women.

The 10-year risk of CHD was calculated using the Framingham risk score (FRS) algorithm (20). This calculates the relative probability of a specific outcome (e.g. CHD, fatal CHD or stroke) over a given period of time, based on weightings for a number of modifiable and non-modifiable risk factors [age, gender, systolic and diastolic blood pressure, TC and HDL-C levels, smoking status, diabetes and electrocardiographic evidence of left ventricular hypertrophy (LVH)].

The JBS 2 guidelines were used to categorise patients as facing a high-risk of future cardiovascular event (7). The study divided patients into four subgroups, according to whether they had: diabetes, a history of CVD, an FRS higher than 20% or hypertension. A history of CVD was defined as the presence of a Read code, recorded before the index date,

for LVH, congestive heart failure, stroke, transient ischaemic attack, CHD (myocardial infarction and angina), ischaemic heart disease or peripheral vascular disease. Diabetes was defined as a Read code for type 1 or type 2 diabetes, or diabetes not otherwise specified, recorded before the index date; patients with gestational diabetes were excluded. Hypertension was defined as a systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg within the 12 months preceding the index date, or lower degrees of hypertension (≥ 130 or ≥ 80 mmHg, respectively) associated with target organ damage (hypertensive grade 3/4 retinopathy; raised creatinine, microalbuminuria, macroalbuminuria or proteinuria; or LVH) (7).

The subgroups with CVD, FRS higher than 20% and diabetes were not mutually exclusive (i.e. a patient could be categorised in multiple groups). However, the hypertension subgroup was defined as being mutually exclusive and was thus intended to include patients deemed to be at high risk of CHD according to measures of hypertension alone, despite not qualifying for any of the other subgroups.

Statistical analyses

The data analysis was essentially descriptive. No formal sample size estimation was performed because the study was not based on a hypothesised effect size. The prevalence of various dyslipidaemia profiles at baseline and at follow-up was calculated for the entire study population and for each of the high-risk subgroups. Differences in patient characteristics between groups with mutually exclusive lipid abnormalities (e.g. high LDL-C only; low HDL-C only; high LDL-C plus low HDL-C and/or high TG; high TG only) were analyzed by *t*-tests.

Multivariate models were used to analyze treatment patterns according to the type of dyslipidaemia at index date and at follow-up, and relationships between patient characteristics and attainment of desirable lipid levels. Covariates in these models included diabetes, hypertension, CVD history, FRS higher than 20%, baseline lipid levels, age, gender, year of LMT initiation, smoking status, BMI and treatment. Similar models were used to investigate associations between attainment of desirable lipid levels and utilisation of healthcare resources.

Results

The UK GPRD included information on 404,119 patients who had had at least one prescription for LMT recorded on or after the start date of 1 April 2006, of whom 109,503 had not received LMT within the 12 months preceding the study index date. Of

the latter patients, 92,764 had had at least one lipid measurement recorded within the 12 months preceding the index date, and 69,334 had a record for each of the four lipid assays of interest (TC, LDL-C, HDL-C and TG) in this period, with at least one abnormal measurement as defined in the JBS 2 guidelines (7). Of these, 25,011 met all remaining inclusion criteria and were therefore included in the final analysis. The high-risk study population consisted of patients with a history of CVD ($n = 3392$), an FRS higher than 20% ($n = 14,279$), diabetes ($n = 5554$) or hypertension ($n = 4993$).

Baseline demographical characteristics of the overall study population are summarised in Table 1. The mean age of the patients at the index date was approximately 65 years, and men and women were represented almost equally. Approximately 31% of patients ($n = 7273$) were considered obese, defined as a BMI of 30 kg/m² or higher. In patients with diabetes (22%), the mean HbA_{1c} level was 7.48%, and the mean blood glucose concentration was 8.29 mmol/l. Approximately 50% of patients with diabetes ($n = 2789$) were receiving medication for their condition.

Statins were by far the most commonly initiated LMT. Overall, 98% of patients were prescribed statin monotherapy as their initial LMT. A further 1.1% of patients were receiving ezetimibe alone and 0.5% were receiving fibrates alone; only 0.01% were receiving niacin.

The proportions of patients with various non-mutually exclusive lipid abnormalities at baseline and after 1 year of LMT are summarised in Table 2 and

Figure 1. At baseline, all patients had at least one abnormal lipid value, as specified in the inclusion criteria. After 1 year of treatment, 15.2% of patients had no lipid abnormalities; the proportion of patients with no such abnormalities in specific groups ranged from 11.0% in patients with hypertension to 22.9% in patients with diabetes. In the overall study population, high TC and LDL-C levels were present at baseline in 98.8% and 99.2% of patients, respectively; after 1 year of LMT, the proportion of patients with these high levels had decreased to 68.9% and 68.7%, respectively. In contrast, LMT appeared to have a lesser effect on TG and HDL-C levels. At baseline, 45.0% of patients in the overall population had high TG levels and 16.6% had low HDL-C levels. After 1 year, the proportion of patients with high TG levels had decreased to 26.9%, while the proportion of patients with low HDL-C levels had increased to 18.0% (Table 2).

As shown in Figure 1, the proportion of patients with high TC or LDL-C levels was similar in all high-risk groups at baseline. After 1 year of LMT, the greatest reductions in these lipids were achieved in patients with diabetes, whereas those with hypertension showed the smallest decreases. The prevalence of high TG or low HDL-C levels, or a combination of these, was highest in patients with diabetes, both at baseline and after 1 year.

In the diabetes subgroup, the proportion of patients with mixed dyslipidaemia consisting of high TG with low HDL-C levels decreased from 17.3% at baseline to 12.6% after 1 year of LMT. The proportion of patients with diabetes who had either high TG or low HDL-C levels decreased from 57.4% at baseline to 44.9% after 1 year.

Multivariate analyses were performed to identify factors associated with attainment of LDL-C targets or desirable levels of TG and HDL-C (Figure 2); data for TC targets are not presented here, but were similar to those for LDL-C. In the analysis, a 'successful outcome' was defined as achievement of the lipid target/desirable level; an odds ratio (ORs) of less than 1.0 identifies a variable which is associated with a lower likelihood of achieving the successful outcome. Age was a significant predictor of attaining LDL-C targets or desirable TG levels, but not desirable HDL-C levels, and male gender was a significant predictor of attaining desirable levels of HDL-C and TG, but not of reaching LDL-C targets. Patients with a history of CVD were significantly less likely to attain desirable levels of HDL-C than those without such a history (OR 0.77, $p < 0.001$), whereas patients with an FRS higher than 20% were less likely to achieve desirable TG levels (OR 0.77, $p < 0.001$) than those with an FRS of 20% or lower. Patients with

Table 1 Baseline demographics

Variable	Total population (n = 25,011)
Mean age (years)	64.6
Male, n (%)	12,612 (50.4)
Obese: BMI \geq 30 kg/m ² , n (%)	7273 (31.3)
Mean systolic BP (mmHg)	142.5
Mean diastolic BP (mmHg)	82.0
Current smokers, n (%)	3891 (15.6)
High-risk subgroups*, n (%)	
History of CVD	3392 (13.6)
FRS > 20%	14,279 (57.1)
Diabetes	5554 (22.2)
Hypertension	4993 (20.0)

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; FRS, Framingham risk score.

*The high-risk subgroups reported here are not mutually exclusive, with the exception of the hypertension group.

Table 2 Prevalence of lipid abnormalities in the high-risk subgroups before and after LMT*

Lipid profile	Patients (n, %)																			
	Total study population (n = 25,011)																			
	BL		FU		CVD history (n = 3392)		FRS > 20% (n = 14,279)		Diabetes (n = 5554)		Hypertension (n = 4993)									
	n	%	n	%	n	%	n	%	n	%	n	%								
No lipid abnormality	0	(0)	3811	(15.2)	0	(0)	755	(22.3)	0	(0)	2327	(16.3)	0	(0)	1270	(22.9)	0	(0)	548	(11.0)
↑LDL-C	24,813	(99.2)	17,190	(68.7)	3326	(98.1)	1972	(58.1)	14,178	(99.3)	9646	(67.6)	5441	(98.0)	2955	(53.2)	4977	(99.7)	3762	(75.4)
↓HDL-C	4154	(16.6)	4503	(18.0)	560	(16.5)	647	(19.1)	2709	(19.0)	2855	(20.0)	1382	(24.9)	1501	(27.0)	515	(10.3)	618	(12.4)
↑TC	24,703	(98.8)	17,231	(68.9)	3276	(96.6)	1971	(58.1)	14,105	(98.8)	9343	(65.4)	5382	(96.9)	2919	(52.6)	4974	(99.6)	3972	(79.6)
↑TG	11,257	(45.0)	6918	(26.9)	1223	(36.1)	724	(21.3)	6879	(48.2)	4005	(28.1)	2770	(49.9)	1695	(30.5)	2013	(40.3)	1246	(25.0)
↑LDL-C and TG	11,120	(44.5)	4842	(19.4)	1184	(34.9)	475	(14.0)	6810	(47.7)	2875	(20.1)	2690	(48.4)	1025	(18.5)	2000	(40.1)	964	(19.3)
↑LDL-C and ↓HDL-C	4038	(16.1)	2835	(11.3)	521	(15.4)	325	(9.6)	2642	(18.5)	1784	(12.5)	1314	(23.7)	757	(13.6)	509	(10.2)	456	(9.1)
↑TG and ↓HDL-C	2908	(11.6)	2073	(8.3)	305	(9.0)	245	(7.2)	1924	(13.5)	1300	(9.1)	963	(17.3)	700	(12.6)	361	(7.2)	288	(5.8)
↑LDL-C and either ↑TG or ↓HDL-C	12,319	(49.3)	6271	(25.1)	1415	(41.7)	649	(19.1)	7571	(53.0)	3761	(26.3)	3082	(55.5)	1381	(24.9)	2152	(43.1)	1205	(24.1)
↑TG or ↓HDL-C	12,503	(50.0)	9148	(36.6)	1478	(43.6)	1126	(33.2)	7664	(53.7)	5560	(38.9)	3189	(57.4)	2496	(44.9)	2167	(43.4)	1576	(31.6)

BL, baseline; CVD, cardiovascular disease; FRS, Framingham risk score; FU, follow-up; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

*The high-risk subgroups reported here are not mutually exclusive, with the exception of the hypertension group.

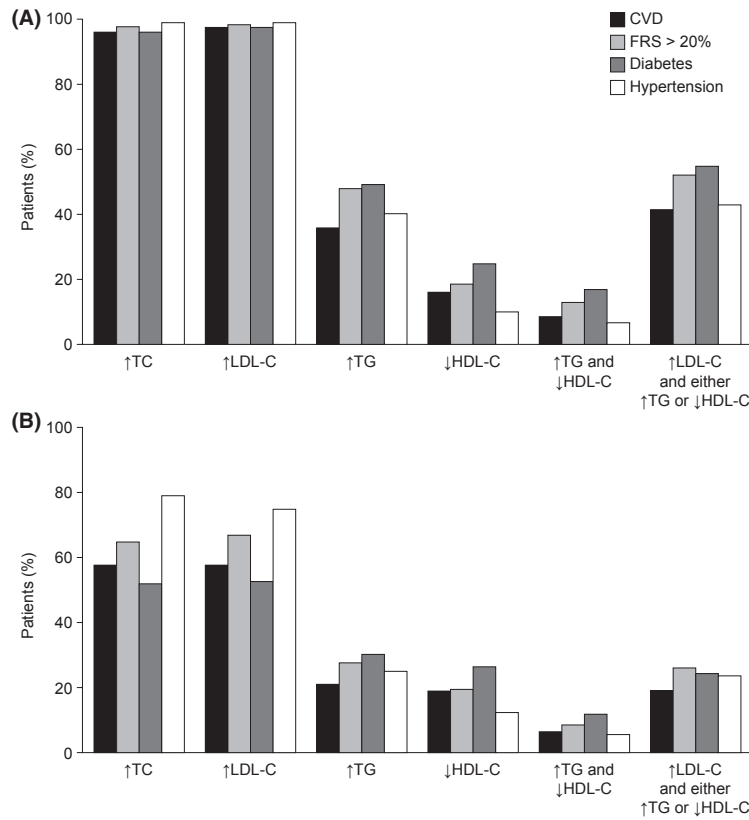


Figure 1 Prevalence of lipid abnormalities (A) at baseline and (B) after 12 months LMT*. *The lipid groups reported here are not mutually exclusive

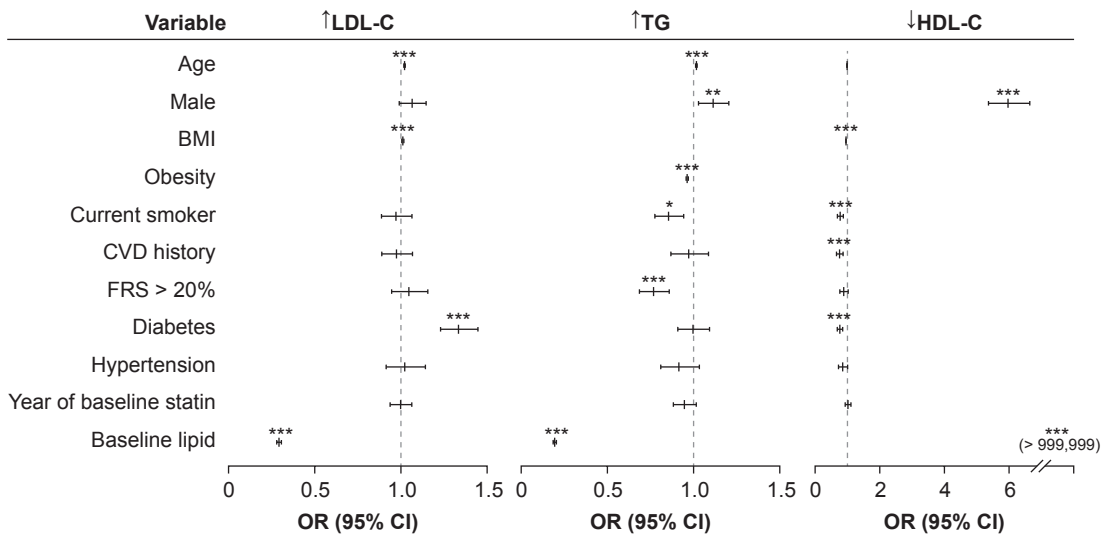


Figure 2 Clinical predictors for attainment of TC and LDL-C targets, and HDL-C and TG desirable levels at follow-up. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. CHD, coronary heart disease; CVD, cardiovascular disease; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

diabetes were significantly more likely than those without diabetes to reach LDL-C targets (OR 1.34, $p < 0.001$), but were less likely to achieve desirable levels of HDL-C (OR 0.78, $p < 0.001$).

Healthcare resource utilisation data for the total study population revealed that patients made a mean of 8.5 visits to their PCP, and 9.9 healthcare visits overall during the follow-up period (Figure 3).

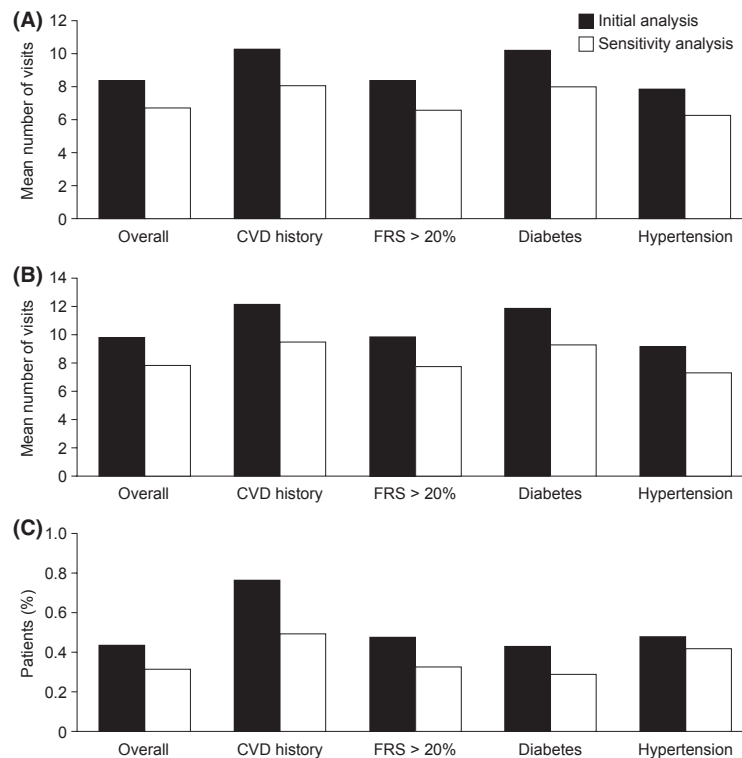


Figure 3 Healthcare utilisation during 1 year of LMT among the total study population and high-risk subgroups (A) primary care physician visits; (B) total healthcare visits (C) proportion of patients hospitalised.

Patients with a history of CVD or diabetes made more primary care or healthcare visits on average than the overall study population; furthermore, the proportion of patients with a history of CVD who were hospitalised during the follow-up period was higher than that in the general study population (0.77% vs. 0.44% in the initial analysis). In the primary analysis, patients were able to consult a healthcare professional more than once a day, which could lead to high-count outliers. A sensitivity analysis was therefore conducted in which consultations with healthcare providers were limited to one visit per provider per day. Results of this analysis were consistently lower than those for the primary analysis, but followed a similar pattern (Figure 3).

Discussion

Our analysis identified that, of all patients in this study who were at high risk of a future cardiovascular event, only 15.2% were without any lipid abnormality after 12 months of treatment. It is noteworthy that more than two-thirds of patients had high LDL-C or TC levels at follow-up, despite the fact that all patients received LMT for 1 year (statin monotherapy in 98% of patients). These figures are higher than those recorded by an earlier study which found that

only 35% and 27% of patients did not reach the target levels for TC or LDL-C, respectively (17). Although this earlier study assessed lipid target attainment using cut-off levels similar to those of QOF (which incentivises management of TC to < 5.0 mmol/l rather than the more clinically relevant JBS 2 targets of < 4.0 mmol/l for TC and < 2.0 mmol/l for LDL-C used in current UK guidelines), it is clear that further optimization of dyslipidaemia management is required, and the disconnect between QOF and clinical targets leads to clinicians focusing on the former. The apparent under-treatment of LDL-C or TC may partly reflect under-dosage: in the registry-based Guidelines-Oriented Approach to Lipid Lowering study, only 10% of high-risk patients who did not achieve their LDL-C targets were receiving high-dose statins (21). Furthermore, physician adherence to guidelines may be limited by their complexity (22) and the variable evidence base supporting certain recommendations (23). A report based on data obtained before the introduction of the QOF indicated that inadequate monitoring of lipid levels during LMT may also contribute to suboptimal management of dyslipidaemia (24).

The results of this study also indicate that HDL-C and TG levels are also poorly managed in primary

care in the UK (although it should be noted that, to date, no pharmacologic intervention for raising HDL-C has been shown to confer clinical benefit). This finding applies both to the overall study population and the specific subgroups such as patients with a history of CVD and those with hypertension or diabetes. This is consistent with the results of other observational studies [including analyses from other PRIMULA studies in Europe and Asia (25–27), the DYSlipidemia International Study (DYSIS) in Europe and Canada (22,28) and the EUROASPIRE III study in eight European countries (29)], which have all shown that lipid abnormalities persist in a significant proportion of patients despite effective lowering of LDL-C and TC levels with statins. In DYSIS, for example, 48% of statin-treated patients did not achieve target LDL-C levels (28). The present findings are also consistent with a previous study in the UK, which suggested that, while LDL-C and TC levels appeared to be managed appropriately in primary care, more than half of statin-treated patients were not reaching optimal levels of HDL-C or TG (17).

Consistent with the results from DYSIS (22), the present study found that patients with diabetes were significantly more likely to achieve their LDL-C goals than those without diabetes, possibly reflecting a greater focus on the management of dyslipidaemia in this patient population. However, patients with diabetes were less likely to have desirable levels of HDL-C following 12 months of treatment. Similar findings have been reported in Sweden, where 69% of patients with diabetes receiving LMT had low levels of HDL-C, high TG levels, or both (27), and in Thailand, where 43% of high-risk patients had low HDL-C levels despite receiving LMT (26). It is interesting to note that only 50% of patients with diabetes were receiving treatment for their condition in the present study, which is lower than might be expected in UK primary care. Given the high-risk of patients with diabetes developing CVD, this may be a contributing factor to the overall under-treatment of CVD reported in this study.

Growing evidence suggests that low levels of HDL-C are associated with increased cardiovascular risk, even in statin-treated patients (30). In the present study, approximately 17% of patients had low levels of HDL-C at baseline, and a similar proportion had a combination of high LDL-C and low HDL-C levels. Furthermore, when lipid abnormalities are considered as mutually exclusive groups (as opposed to the non-mutually exclusive groupings presented in Table 2), up to 50% of patients had mixed dyslipidaemia, which often included low HDL-C levels (data not shown). Such cases of mixed dyslipidaemia

appeared to be less amenable to statin therapy than high levels of LDL-C or TC alone. The potential significance of this is highlighted by the finding in a previous study based on the GPRD that decreased levels of HDL-C and/or high TG levels are associated with an increased risk of cardiovascular events in statin-treated patients with persistently high LDL-C levels (16). However, in the recent Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) and Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) studies, the addition of extended-release niacin to statin-based therapy did not cause a further reduction in incidence of cardiovascular events compared with statin monotherapy (31,32). In HPS2-THRIVE (where extended-release niacin was used with the anti-flushing agent laropiprant in fixed-dose combination), rates of myocardial infarction and stroke were quantitatively reduced in European patients, although these benefits were outweighed by the increased risk of adverse events experienced with niacin.

In the present study, risk factors such as a history of CVD, diabetes or hypertension were not consistently associated with the likelihood of attaining optimal lipid levels. Analysis of PRIMULA data from hospital-treated patients in Hong Kong (25) showed that the strongest factors affecting the likelihood of attaining desirable levels of at least two lipids included diabetes [OR 0.43, 95% confidence interval (CI) 0.23–0.78], obesity (OR 0.91, 95% CI 0.86–0.97) and an FRS higher than 20% (OR 0.33, 95% CI 0.15–0.71) (25) (note that the direction of the ORs as predictive variables in the Hong Kong study are in reverse to those presented here).

A key strength of the present study is the use of data from the GPRD, a data source with comprehensive coverage of the UK population and which operates in a healthcare system where PCPs act as 'gatekeepers' to secondary and specialist care; as a result, all relevant clinical data are included in PCP records. The study results can therefore be considered a reliable assessment of the impact of LMT under real-world conditions. Furthermore, the electronic linkage provided by the GPRD means that laboratory data, such as lipid test results, are captured effectively and comprehensively. Further strengths include the focus on clearly defined groups of high-risk patients, and the duration of follow-up, which allowed appropriate dose titration and the addition of further medication as required. Also, patients were only included if they had not received LMT during the 12 months preceding the index date;

as a result, the study clearly demonstrated the impact of treatment on lipid levels.

A potential limitation of this study is the lack of specific targets for HDL-C and TG. This necessitated the use of a less stringent measure, desirable levels, according to the JBS-2 guidelines (7), to assess the extent to which these lipids are being treated. This may not be directly relevant to current practice because more recent guidance is now available from NICE, both for routine clinical practice and for high-risk patients such as those with existing CVD (8), type 2 diabetes (9) or familial hypercholesterolaemia (33). However, these guidelines were not available throughout the period covered by this study; therefore, use of the JBS 2 guidelines is the most appropriate reflection of clinical practice during that time. The levels recommended by NICE are similar to the JBS 2 targets for LDL-C and TC in high-risk patients. The study may also have benefited from the inclusion of patients who should have been initiated on LMT, based on their preindex lipid profile and cardiovascular risk, but were not. Such a cohort would have provided a comparator against which to judge the impact of LMT initiation in UK standard practice. However, this was not an aim in the original study and was not specified in the protocol. As such, these data were not collected, although they could be the focus of future research. Another potential limitation is that the data are relatively old, having been collected between April 2006 and December 2008. Nevertheless, this study still represents the most up-to-date assessment of lipid management in primary care in the UK and, as described above, the findings are consistent with other current data, including the results of the EUROASPIRE III and DYSIS studies (22,29). Finally, the study was not

powered on a specific hypothesis and the sample size was not based on a power calculation. This may result in generation of both false positives and false negatives, where statistically significant predictors may not confer biological importance and predictors which are not statistically significant may not indicate a lack of biological predictive ability.

In conclusion, this study has shown that management of dyslipidaemia is suboptimal in the UK. Despite widespread use of statins, many individuals at high risk of cardiovascular events have persistently abnormal lipid levels, with over two-thirds of patients not achieving target levels of LDL-C or TC. Abnormal levels of HDL-C and TG are also common in high-risk patients. This indicates that intensive LMT with particular focus on the reduction in LDL-C and TC is required. Further evidence from ongoing clinical trials may shed some light on whether patients may also benefit from treatment to modify HDL-C and TG levels.

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Author contributions

The study protocol was developed by B. Ambegaonkar, K. Jameson and V. Amber. Analyses were conducted by D. Mills and interpreted by all authors. All authors participated in the development and writing of the manuscript, and approved the final article for publication.

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