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Management of lipid-lowering therapy in patients with cardiovascular events in the UK: a retrospective cohort study

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ABSTRACT

Objectives To describe low-density lipoprotein (LDL) cholesterol management and lipid-lowering treatment patterns in patients with a cardiovascular (CV) event.

Design Retrospective cohort study using Clinical Practice Research Datalink records linked with Hospital Episode Statistics data.

Setting Routine clinical practice in the UK from 2006 to 2012.

Participants Individuals ≥18 years were selected at their first CV-related hospitalisation (first event cohort) if they had received ≥2 lipid-lowering therapy prescriptions within 180 days beforehand. Patients were stratified into four mutually exclusive subgroups based on the presence or absence of vascular disease and of diabetes. Those with a second CV hospitalisation within 36 months were included in a separate cohort (second event cohort).

Primary and secondary outcome measures LDL levels in the year prior to the CV event and 12 months later as well as measures of adherence to lipid-lowering therapy during the 12 months after the CV hospitalisation.

Results There were 24 093 patients in the first event cohort, of whom 5274 were included in the second event cohort. Most received moderate intensity statins at baseline and 12 months. Among the four first event cohort subgroups at baseline, the proportions with an LDL of <1.8 mmol/L was similar between the two diabetic cohorts (36% to 38%) and were higher than those in the two non-diabetic cohorts (17% to 22%) and in the second event cohort (31%). An incremental 5% to 9% had an LDL below 1.8 mmol/L at 12 months, suggesting intensification of therapy. The proportion of adherent patients (medication possession ratio of≥0.8) was highest for statins, ranging from 68% to 72%. For ezetimibe, the range was 65% to 70%, and for fibrates, it was 48% to 62%.

Conclusions Despite the existence of effective therapies for lowering cholesterol, patients do not reach achievable LDL targets.

Strengths and limitations

- Data were derived from routine clinical practice from general practitioner data in the UK.
- Results are specific to patients receiving lipid-lowering therapy prior to experiencing a cardiovascular event.
- Low-density lipoprotein cholesterol values were missing for a large portion of patients, limiting the generalisability to those with values recorded in the general practitioner data.

INTRODUCTION

Patients with established cardiovascular (CV) disease are at the highest risk of CV events, making secondary prevention an important public health concern.[1] Because of this high risk, such patients stand to benefit the most from interventions to reduce the number and severity of CV risk factors; this includes reducing low-density lipoprotein (LDL) cholesterol levels. Based on recent data from the Cholesterol Treatment Trialists Collaboration, more versus less intensive lipid reduction was associated with a 26% reduction in major vascular events per 1.0 mmol/L reduction in LDL cholesterol.[2] Therefore, current recommendations encourage lowering LDL levels aggressively, to below 2 mmol/L, if possible, to reduce the risk of subsequent events.[1 3]

However, despite the existence of effective therapies for lowering cholesterol, patients often do not adhere to the existing therapies in an optimal fashion. One recent study using the data from general practitioners (GPs) in the UK showed that 43% of patients with atherosclerotic CV disease had discontinued their medication 1 year after initiation and that 31.5% had a mean LDL level above 2.5 mmol/L over 2 years of follow-up.[4] Another study showed that 43% of patients who were prescribed statin after hospitalisation for acute coronary syndrome were still receiving it 4 years later.[5] A large European survey recently showed that many patients with coronary heart disease were not achieving lifestyle, risk factor and therapeutic targets; in particular, 80% of patients on lipid-lowering therapy had LDL cholesterol levels above 1.8 mmol/L.[6] Hence, there is ample room for improvements both

in adherence to lipid-lowering medications and in the efficacy of these interventions.

Recent introductions of lipid-lowering interventions present the potential to reduce LDL cholesterol to levels that were previously difficult to achieve.[7 8] More importantly, they are dosed at less frequent schedules that may improve long-term compliance and adherence. Therefore, it is possible that these new interventions can have improved outcomes, particularly in high-risk or poorly compliant patients. For individuals who have experienced a CV event, the benefits are potentially substantial, but information on LDL levels, compliance and persistence with current therapies is not well studied in this population.

This is a study of treatment patterns and LDL levels in individuals receiving lipid-lowering therapy who experienced a CV event. This study had three primary aims: to characterise LDL levels achieved before and after a CV event, to characterise lipid-modifying therapy that is used before and after a CV event and to characterise compliance and persistence with lipid-lowering therapy in patients after CV event.

METHODS

Study overview

This was a retrospective cohort study to describe LDL levels and treatment patterns in patients who had their first CV event and who were receiving lipid-lowering therapy prior to the event. Primary care data from the Clinical Practice Research Datalink (CPRD) and inpatient hospitalisation data from the Hospital Episode Statistics (HES) were used for this study. Detailed information about the cohort was published previously.[9]

Data sources

The CPRD contains GP electronic health record data including diagnoses, test results and prescriptions and is a widely used database globally.[10 11] These patients are broadly representative of the UK general population in terms of age, sex and ethnicity. HES data were used to identify CV events requiring inpatient hospitalisation. The National Research Ethics Service Committee has approved research using de-identified CPRD data that do not involved direct patient involvement. Therefore, this study was exempt from further review.

Patient populations

The study population included adult patients (≥18 years) who were alive and observable in both the CPRD and HES data as of 1 January 2005 and were hospitalised for their first CV event between January 2006 and 31 March 2012 (end of HES observation period). Patients were selected at the time they had their first qualifying CV event in the HES data (first event cohort). Only patients who had a CV event in the HES data were included in the study, and at least 1 year of data prior to the first CV event was required. To ensure that patients had hypercholesterolaemia prior to their first CV event, patients had to have received at least two prescriptions for any lipid-lowering therapy in the 180 days prior to the CV event date.

Multiple CV hospitalisations within 30 days of the first were considered to be a single clinical event. Patients in the first event cohort were divided into four subgroups based on the presence or absence of vascular disease or diabetes prior to the CV event. Because patients were prescribed lipid-lowering therapy, those with neither vascular disease nor diabetes were considered to be at high risk due to other factors (other high risk). Vascular disease was defined as a history in the GP's record of abdominal aortic aneurysm, stable angina or other cardiac ischaemia, peripheral vascular (arterial) disease, transient ischaemic attack or carotid stenosis. We also identified a subset of first event cohort patients who had a second CV event more than 30 days after but within 3 years of the first (second event cohort, see figure 1).

Definitions of CV events and lipid-lowering therapy

CV events were defined as hospitalisations with a primary International Classification of Diseases, 10th Revision (ICD-10) diagnosis code for myocardial infarction, ischaemic stroke, heart failure, transient ischaemic attack or unstable angina. Also included were other hospitalisations for revascularisation that included coronary artery bypass graft, percutaneous transluminal coronary angioplasty or percutaneous coronary intervention based on Office of Population, Censuses and Surveys codes (see online supplementary 1). Patients with a history of an acute myocardial infarction or ischaemic stroke in their medical history (CPRD) were also excluded to minimise inclusion of individuals with previous CV hospitalisations that were not recorded in the HES data for any reason. Conditions in CPRD were identified using READ codes based on code lists from the Quality Outcomes Framework (QOF).[12]

Prescription records for lipid-lowering therapy were used to identify patients receiving treatment to reduce serum lipid levels. Lipid-lowering therapy included statins, ezetimibe, fibrates, nicotinic acid and bile acid sequestrants.

Study time horizon and follow-up

The date of the event that qualified the patient to be in a cohort was defined as the 'index' date. To rule out previous events more accurately, patients were required to have at least 12 months of data before this date; they were also required to have at least 30 days of follow-up afterwards. For analyses of the second event cohort, the date of the second CV event was the index date (see figure 1).

The assessment of demographics and comorbidity information was based on information present at the time of the index CV event. The follow-up period started with the date of the index CV event and continued for up to 18 months, or until the end of data availability (31 March 2012), date of death or date of last known up-to-standard

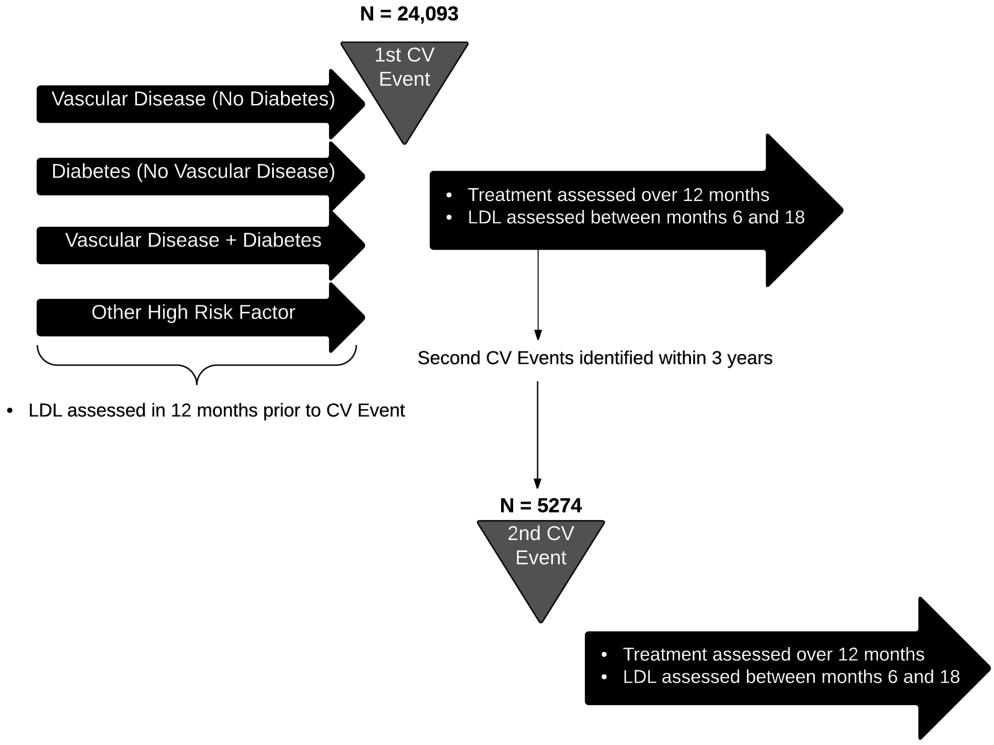

Figure 1 Study overview. Patients were stratified into four subgroups as indicated, based on their medical history prior to the first CV event. CV, cardiovascular; LDL, low-density lipoprotein.

CPRD record for the patient in the practice, whichever came first.

Endpoints

For analyses of LDL levels and treatment patterns, the time at risk was the 12-month period following the index CV event date. The baseline LDL was the value closest to the index CV event from within the 12-month interval before the event. The follow-up LDL was estimated by using the measure after the index date that was closest to month 12 and was limited to values between month 6 and month 18. The percentage achieving targets was based on recommendations for reducing LDL below <1.8 mmol/L for the prevention of recurrent events.[1 13] A series of other LDL levels was also evaluated at baseline and at 12 months. To maximise the sample size, LDL results were estimated for patients with baseline values and for patients with month 12 values separately. A sensitivity analysis restricting to patients with values at both time points was also conducted.

For evaluating treatment patterns during the 12 months after the index CV event, patients were required to have a lipid-lowering therapy prescription that covered the index date; therefore, the sample sizes for these analyses were slightly smaller than the entire cohort. Prescription data from CPRD was used to estimate all quantities, using the 'days supplied' field and the calendar dates of each prescription. Bile acid sequestrants and niacin generally did not have valid entries for 'days supplied' and could not be analysed. Statins were classified as high, moderate and low intensity (see online supplementary material 1).[14]

Treatment duration was calculated from the index date to the most recent prescription date plus days' supply up to a maximum of 365 days. Prescriptions separated by time gaps of more than 60 days were considered to reflect discontinuation and were not included as part of the treatment course. Switching was defined as a different prescription for a medication other than the index drug where the index drug was stopped. Augmentation occurred when a new drug was started and the index drug was continued. Changes in statin intensity were defined by comparing a patient's initial and final statin prescriptions. Compliance was defined using the medication possession ratio (MPR), calculated as the number of days of drug supplied during the follow-up interval and divided by 365.[15] Patients were considered 'adherent' if their MPR was 0.80 or greater. Persistence was measured as a dichotomous variable and defined as no gaps of more than 60 days.

Analyses were primarily descriptive. Means and SD were estimated for continuous variables, and the number and proportion were estimated for categorical variables.

RESULTS

We identified unique patients with CV hospitalisations in the study time window (105 526), selected those with linked, up-to-standard GP data (69 248), selected those who received at least two lipid-lowering therapy prescriptions within 180 days (28 051) and selected those without a prior history of myocardial infarction or ischaemic stroke (24 093). Of the 24 093 patients in the first event

cohort, 5274 experienced a subsequent event and were also evaluated as the second event cohort.

In the first event cohort, the four subgroups included 9434 with a prior history of vascular disease but without diabetes before their initial CV event (prior history of vascular disease), 3784 with a prior history of diabetes but not vascular disease (prior history of diabetes), 3559 with a prior history of both vascular disease and diabetes (prior history of vascular disease + diabetes) and 7316 with another high-risk factor that leads to the prescription of lipid-lowering therapy prior to their first CV event (other high risk). Results below are generally reported for the four first event subgroups and for the entire second event cohort.

The mean ages across the four first event subgroups and the second event cohort were very similar, ranging from 72 to 73 years. Mean body mass index was higher in the two diabetes subgroups (30–31 kg/m^2) than it was in the other two subgroups (28 kg/m^2) and in the second event cohort (29 kg/m^2). Across the four first event subgroups, mean LDL cholesterol ranged from 2.1 to 2.6 mmol/L, and mean systolic blood pressure ranged from 136 to 137 mm Hg. In the second event cohort, the corresponding values were 2.2 mmol/L and 133 mm Hg. Thirty-six per cent of patients in the second event cohort had diabetes. Additional baseline characteristics are provided in table 1.

Among the four first event subgroups at baseline, the proportion with an LDL of <1.8 mmol/L was similar between the two diabetic cohorts (36% to 38%), and these proportions were higher than in the two non-diabetic cohorts (17% to 22%). In the second event cohort 31% had an LDL <1.8 mmol/L. In all cohorts, the percentage with an LDL <1.8 mmol/L was higher at 12 months than it was at baseline. The percentage was between 42% and 43% in the two diabetic cohorts and between 25% and 29% for the two non-diabetic cohorts; it was 35% in the second event cohort (see figure 2). At 12 months after the CV event across all patients, between 22% and 36% had an LDL of >2.5 mmol/L, and 3% to 8% had an LDL of >3.5 mmol/L (see figure 2). As a proxy for intensified therapy, an incremental 5% to 9% across the cohorts had an LDL below 1.8 mmol/L between by 12 months.

To assess the impact of missing data, we re-estimated the LDL results using only patients with LDL values at both time points, and the results were virtually identical. Among the four first event subgroups at baseline, the proportion with an LDL of <1.8 mmol/L was similar between the two diabetic cohorts (34% to 37%), and these proportions were higher than in the two non-diabetic cohorts (15% to 20%). In the second event cohort 31% had an LDL of <1.8 mmol/L. In all cohorts, the percentage with an LDL of <1.8 mmol/L was higher at 12 months than it was at baseline. The percentage was 42% in the two diabetic cohorts and was between 23% and 29% for the two non-diabetic cohorts; it was 35% in the second event cohort. At 12 months after the CV event across all patients, between 22% and 36% had an LDL of >2.5 mmol/L, and 3% to 8% had an LDL of >3.5 mmol/L. As a proxy for intensified therapy, an incremental 5% to 9% across the cohorts had an LDL below 1.8 mmol/L between by 12 months.

Prior to their first CV event, most patients were receiving statins, the majority of whom (76% of all patients) were receiving moderate intensity statins (figure 3). High-intensity statins were used by 11% of all patients, and ezetimibe with or without statins was used by 4% of all patients. As of the date of the CV event, between 79% and 82% of the first event cohorts had an active prescription; in the second event cohort, the percentage was 75%. Patients without an active prescription were not included in detailed analyses of treatment patterns. Throughout the study, most patients receiving lipid-lowering therapy were receiving statins.

Of patients receiving statins on the date of their CV event (index date), between 12% and 16% patients in the four first event subgroups increased their statin intensity; in the second event cohort, the proportion increasing intensity was 7% (table 2). Between 1% and 2% of patients decreased their statin intensity across the four first event subgroups; in the Second Event cohort 2% decreased their statin intensity (table 2). The majority of patients in the four first event cohorts receiving ezetimibe augmented their therapy (55% to 63%) and a substantial portion of patients receiving fibrates augmented therapy (35% to 57%). In the second event cohort, 61% of ezetimibe patients and 51% of fibrate patients augmented their therapy. Across the first event and second event cohorts, statin users rarely switched therapies (2%), compared with ezetimibe (8% to 14%) and fibrates (11% to 20%).

In terms of compliance and persistence (table 3) across the first event and second event cohorts, the mean MPR was higher for statins and ezetimibe (72% to 79%) than it was for fibrates (58% to 73%). The mean treatment duration was above 200 days for statins and ezetimibe across all cohorts but ranged from 161 to 207 days for fibrates. The proportion of adherent patients was highest for statins, ranging from 68% to 72%. For ezetimibe, the range was 65% to 70%, and for fibrates it was 48% to 62%.

DISCUSSION

These results suggest at least two important findings. First, patients are not at their lowest achievable LDL levels prior to their initial CV hospitalisation event. Prior to the hospitalisation, between 26% and 29% of diabetic patients had LDL levels above 2.5 mmol/L, while 43% to 49% of those with vascular disease or other risk factors had LDL levels above this threshold. A year later, these proportions declined in all groups. Presumably, the postevent levels were achievable prior to the event, but some combination of patient adherence and physician prescribing limited the degree of LDL lowering achieved in these patients. Furthermore, both subgroups of first event patients with diabetes

Table 1 Baseline characteristics

		First event (n=24 093)				
		Prior history of vascular disease	Prior history of diabetes	Prior history of vascular disease + diabetes	Other high risk	Second event
Variable	**Level**	**n=9434**	**n=3784**	**n=3559**	**n=7316**	**n=5274**
Continuous variables (mean (SD))						
	Age at index	73.02 (10.95)	71.87 (11.58)	72.30 (10.19)	72.85 (11.47)	72.81 (10.80)
	BMI (kg/m^2)	27.54 (4.90)	30.51 (6.36)	30.05 (5.60)	27.93 (5.47)	28.65 (5.58)
	Systolic blood pressure (mm Hg)	135.62 (18.41)	137.01 (18.75)	136.03 (18.59)	136.90 (18.94)	133.02 (19.31)
	LDL cholesterol (mmol/L)	2.50 (0.97)	2.16 (0.88)	2.07 (0.81)	2.63 (1.01)	2.23 (0.89)
	Total cholesterol (mmol/L)	4.47 (1.08)	4.17 (1.07)	4.05 (0.98)	4.66 (1.13)	4.19 (1.06)
	Triglycerides (mmol/L)	1.53 (1.00)	1.84 (1.51)	1.81 (1.19)	1.57 (1.11)	1.63 (1.04)
Categorical variables (N (%))						
Index event	CABG	1253 (13.3)	121 (3.2)	438 (12.3)	325 (4.4)	442 (8.4)
	HF	1005 (10.7)	870 (23.0)	588 (16.5)	1133 (15.5)	1104 (20.9)
	IS	1016 (10.8)	698 (18.4)	373 (10.5)	1402 (19.2)	532 (10.1)
	MI	1358 (14.4)	873 (23.1)	665 (18.7)	1572 (21.5)	769 (14.6)
	PTCA	1650 (17.5)	245 (6.5)	483 (13.6)	567 (7.8)	814 (15.4)
	TIA	579 (6.1)	304 (8.0)	180 (5.1)	594 (8.1)	266 (5.0)
	UA	2573 (27.3)	673 (17.8)	832 (23.4)	1723 (23.6)	1347 (25.5)
Vascular disease	AAA	117 (1.2)	0 (0.0)	26 (0.7)	0 (0.0)	25 (0.5)
	Angina	5359 (56.8)	0 (0.0)	1880 (52.8)	0 (0.0)	1861 (35.3)
	PVD	1153 (12.2)	0 (0.0)	819 (23.0)	0 (0.0)	524 (9.9)
	TIA	1511 (16.0)	0 (0.0)	494 (13.9)	0 (0.0)	442 (8.4)
	Cardiac ischaemia	7535 (79.9)	0 (0.0)	2726 (76.6)	0 (0.0)	2508 (47.6)
	Carotid stenosis	164 (1.7)	0 (0.0)	59 (1.7)	0 (0.0)	54 (1.0)
Important risk factors	Hypertension	3913 (68.5)	1645 (43.5)	1794 (50.4)	2939 (40.2)	2364 (44.8)
	Diabetes	0 (0.0)	3784 (100.0)	3559 (100.0)	0 (0.0)	1905 (36.1)
	COPD	813 (8.6)	267(7.1)	313 (8.8)	565 (7.7)	524 (9.9)
	CKD	2096 (22.2)	1179 (31.2)	1162 (32.6)	1601 (21.9)	1815 (34.4)
CV risk factors	AF	1260 (13.4)	423 (11.2)	494 (13.9)	908 (12.4)	715 (13.6)
	Type 2 diabetes	0 (0.0)	3611 (95.4)	3362 (94.5)	0 (0.0)	1714 (32.5)

Continued

Table 1 Continued

Variable	Level	First event (n=24 093)				
		Prior history of vascular disease	Prior history of diabetes	Prior history of vascular disease + diabetes	Other high risk	Second event
		n=9434	n=3784	n=3559	n=7316	n=5274
Medications	Antihypertensives	8468 (89.8)	3277 (86.6)	3371 (94.7)	5857 (80.1)	4979 (94.4)
	Antithrombotics	8322 (88.2)	2548 (67.3)	3172 (89.1)	4776 (65.3)	4901 (92.9)
	Antidiabetics	0 (0.0)	3151 (83.3)	2922 (82.1)	0 (0.0)	1599 (30.3)
Year of index event	2006	1846 (19.6)	491 (13.0)	617 (17.3)	994 (13.6)	425 (8.1)
	2007	1737 (18.4)	557 (14.7)	597 (16.8)	1084 (14.8)	782 (14.8)
	2008	1538 (16.3)	625 (16.5)	586 (16.5)	1109 (15.2)	877 (16.6)
	2009	1513 (16.0)	641 (16.9)	615 (17.3)	1254 (17.1)	986 (18.7)
	2010	1323 (14.0)	662 (17.5)	519 (14.6)	1297 (17.7)	980 (18.6)
	2011	1173 (12.4)	658 (17.4)	503 (14.1)	1296 (17.7)	987 (18.7)
	2012	304 (3.2)	150 (4.0)	122 (3.4)	282 (3.9)	237 (4.5)
Age group	<60	1175 (12.5)	606 (16.0)	424 (11.9)	965 (13.2)	652 (12.4)
	60–69	2195 (23.3)	859 (22.7)	857 (24.1)	1664 (22.7)	1167 (22.1)
	70–79	3152 (33.4)	1241 (32.8)	1380 (38.8)	2408 (32.9)	1932 (36.6)
	≥80	2912 (30.9)	1078 (28.5)	898 (25.2)	2279 (31.2)	1523 (28.9)
Gender	Male	5896 (62.5)	2065 (54.6)	2232 (62.7)	4028 (55.1)	3177 (60.2)
Smoking status	Current	1037 (11.0)	497 (13.1)	396 (11.1)	937 (12.8)	488 (9.3)
	Former	3820 (40.5)	1378 (36.4)	1601 (45.0)	2221 (30.4)	2248 (42.6)
	Never	2380 (25.2)	1266 (33.5)	1072 (30.1)	1765 (24.1)	1375 (26.1)
	Missing	2197 (23.3)	643 (17.0)	490 (13.8)	2393 (32.7)	1163 (22.1)

AAA, abdominal aortic aneurysm; AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney; COPD, chronic obstructive pulmonary disease; HF, heart failure; IS, ischemic stroke; LDL, low-density lipoprotein; MI, myocardial infarction; PVD, peripheral vascular disease; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischaemic attack; UA, unstable angina.

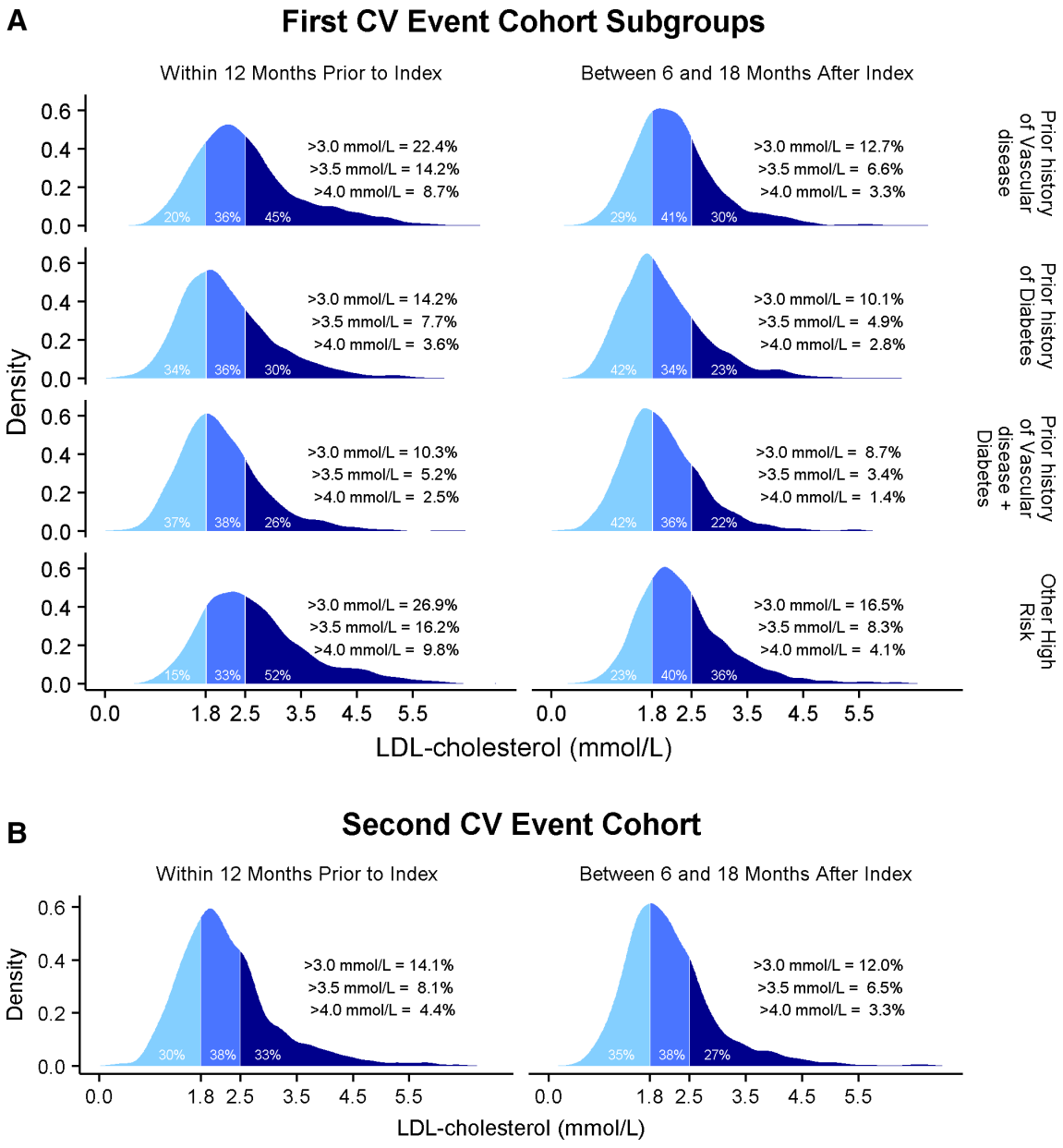

Figure 2 Management of LDL cholesterol. Note: distributions of LDL cholesterol at baseline represent the value closest to the index date. Distributions at 12 months represent the value closest to month 12. Across the cohorts, between 49% and 62% of the first event cohort and 53% of the second event cohort had an analysable LDL value. The proportion was between 40% and 46% at 12 months in the first event subgroups and 40% in the second event cohort. CV, cardiovascular; LDL, low-density lipoprotein.

had lower LDL levels than the other subgroups at both baseline and follow-up. This suggests that the patients without diabetes might be able to achieve even lower LDL levels, matching those of the patients with diabetes. In fact, the same is true of the second event cohort that also did not achieve the degree of LDL reduction that the patients with diabetes achieved.

Second, a large proportion of patients did not consistently take their medications even after a CV hospitalisation event. Patients already receiving statins prior to the event had modest increases in statin intensity or other augmentation of therapy; those receiving fibrates or ezetimibe were much more likely to augment or switch therapy. Importantly, during the year following the CV event, only about half of patients were persistent with therapy (ie, they continued receiving prescriptions with no more than a 60-day gap in therapy). This was true for the four first event subgroups and for the second event cohort. This raises the question about what is truly achievable in clinical practice over the long term without improvements in therapy or patient management.

The main strength of these analyses is that they are derived from patients in actual clinical practice in the UK. Furthermore, the analyses are tightly focused on patients who experienced a CV event, a population that is at particularly high risk of subsequent events. This is

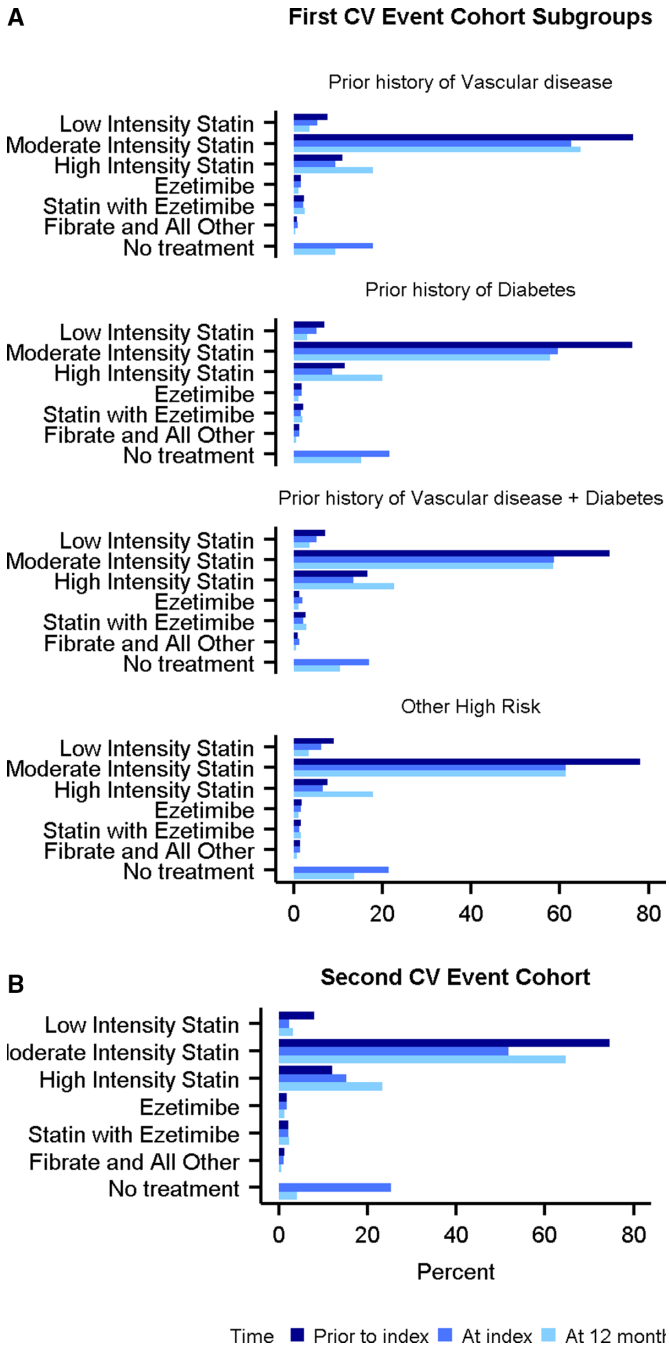

Figure 3 Category of lipid-lowering therapy over time. Note: lipid-lowering therapy category prior to index refers to the prescription qualifying the patient for the study. Not all patients had an active prescription on their index CV event date, as indicated by the no treatment group. Proportions at 12 months reflect the closest prescription prior to or at month 12 regardless of discontinuation. Patients who died were included in the no treatment group. CV, cardiovascular.

evidenced by the fact that 22% of patients had a second event during our follow-up period. Other strengths of this study include the stratification by known vascular disease and diabetes status prior to the CV event and the inclusion of the subset of patients experiencing a second CV event.

There are also limitations to these data and analyses. LDL measurements were missing on a substantial number of patients (>40%). This level of missing data is consistent with another study using CPRD data showing that 42% of patients initiating a statin had no LDL cholesterol values during the previous year.[16] According to the authors, this may be partly related to practice-related factors including the availability of electronic transfer of information between the laboratory and the practice as well as to the incentives to the practice for recording such data. Because of the missing data, we conducted a sensitivity analysis comparing the results in patients with both before and after LDL measures to the group means based on all patients with before or after LDL measures and the results were highly consistent.

Prescription data is based on primary care prescription records and may not reflect the actual doses taken. While we have evidence showing that lipid-lowering therapy was more aggressive after the CV event, we do not know whether adherence and compliance improved. Our study design did not permit us to estimate comparable measures of compliance and persistence before the CV event. However, we do know that approximately 20% of patients did not have an active prescription on the date of their CV event despite receiving at least two prescriptions within the previous 180 days. Finally, current practice may be different from this study based on data from 2006 to 2012.

These findings do not appear to be unique to the UK. For example, in a cohort of high-risk patients in the USA, 58% of patients initiating a statin failed to achieve at least a 30% reduction in LDL.[17] Even among the patients with the best adherence (>80% of doses taken), 42% did not achieve at least a 30% reduction. In Spain, at least 30% of patients at high CV risk discontinued their therapy within 12 months, with decreases in statin potency of at least 43%, depending on cohort.[18] In contrast, in Denmark, discontinuation within 1 year of statin initiation appears to be lower at 18% in 2010. Interestingly, the rate increased from 6% in 1995 with an OR for discontinuation of 1.04 per year, and the odds of discontinuation for the non-Danish population within Denmark were 67% higher.[19] Hence, while adherence may be high in Denmark, it may be limited to the Danish native population.

There are several implications of these analyses. First, the fact that patients achieved lower LDL levels after a CV event, compared with before, suggests that more could have been done to lower LDL levels prior to the event. Second, the lower LDL levels in the two diabetic subgroups (compared with those without diabetes) suggest that the other patient groups could have achieved similar LDL levels. This is particularly true for the subgroup of patients with identified vascular disease. A combination of factors may explain this observation, including better patient education and awareness, more frequent lipid testing and reinforcement of target lipid goals (especially due to contact with multiple teams of specialists and generalists)

Table 2 Changes in lipid-modifying therapy

Dose change	First event				
	Prior history of vascular disease N (%)	Prior history of diabetes N (%)	Prior history of vascular disease + diabetes N (%)	Other high risk N (%)	Second event N (%)
	n=7716	n=2959	n=2940	n=5725	n=3928
Statin	n=7380	n=2807	n=2773	n=5470	n=3725
Switched therapy	169 (2.29)	51 (1.82)	58 (2.09)	103 (1.88)	61 (1.64)
Augmented therapy	268 (3.63)	86 (3.06)	108 (3.89)	163 (2.98)	157 (4.21)
Intensity decrease	129 (1.75)	34 (1.21)	56 (2.02)	82 (1.5)	75 (2.01)
Intensity increase	887 (12.02)	399 (14.21)	339 (12.23)	874 (15.98)	264 (7.09)
Ezetimibe	n=258	n=101	n=120	n=161	n=148
Switched therapy	30 (11.63)	8 (7.92)	16 (13.33)	23 (14.29)	16 (10.81)
Augmented therapy	163 (63.18)	59 (58.42)	74 (61.67)	88 (54.66)	91 (61.49)
Fibrate	n=78	n=51	n=47	n=94	n=55
Switched therapy	9 (11.54)	10 (19.61)	5 (10.64)	17 (18.09)	6 (10.91)
Augmented therapy	35 (44.87)	20 (39.22)	27 (57.45)	33 (35.11)	28 (50.91)

Changes measured from first to last prescription in the 12-month follow-up period, ignoring gaps in therapy. Individuals receiving statins with ezetimibe were classified as statin users.

and glycaemia control per se with its beneficial impact on lipid metabolism in general.[20] Most patients with diabetes will be on the diabetes QOF registry, providing financial incentives for primary care physicians to monitor them more closely.[21] Third, recommendations to lower LDL levels as much as possible may be difficult to achieve without more aggressive treatment and better compliance and persistence. It is instructive to look at Denmark to see that better persistence is theoretically achievable but that even in the best situations almost one in five patients discontinue therapy within a year.

Table 3 Compliance and persistence with lipid-modifying therapy

Outcome measure by therapy	First event				
	Prior history of vascular disease	Prior history of diabetes	Prior history of vascular disease + diabetes	Other high risk	Second event
Statin (N)	7380	2807	2773	5470	3725
Compliance (mean (SD))	0.79 (0.33)	0.76 (0.35)	0.79 (0.33)	0.76 (0.35)	0.79 (0.32)
Adherence (N (%))	5261 (71.3)	1905 (67.9)	1990 (71.8)	3748 (68.5)	2671 (71.7)
Treatment duration (mean (SD))	237.57 (142.08)	202.28 (149.14)	228.87 (144.83)	210.56 (148.38)	215.76 (144.89)
Persistence (N (%))	3747 (50.8)	1413 (50.3)	1415 (51.0)	2807 (51.3)	1947 (52.3)
Ezetimibe (N)	258	101	120	161	148
Compliance (mean (SD))	0.77 (0.35)	0.77 (0.34)	0.74 (0.36)	0.72 (0.37)	0.79 (0.32)
Adherence (N (%))	179 (69.4)	70 (69.3)	78 (65.0)	104 (64.6)	104 (70.3)
Treatment duration (mean (SD))	235.83 (143.81)	206.86 (147.95)	207.23 (146.65)	208.23 (154.10)	239.56 (134.94)
Persistence (N (%))	120 (46.5)	39 (38.6)	56 (46.7)	67 (41.6)	74 (50.0)
Fibrate (N)	78	51	47	94	55
Compliance (mean (SD))	0.69 (0.39)	0.65 (0.40)	0.72 (0.32)	0.58 (0.42)	0.73 (0.35)
Adherence (N (%))	46 (59.0)	29 (56.9)	26 (55.3)	45 (47.9)	34 (61.8)
Treatment duration (mean (SD))	201.09 (148.83)	170.76 (144.28)	216.87 (138.19)	160.75 (149.41)	206.75 (147.16)
Persistence (N (%))	36 (46.2)	17 (33.3)	17 (36.2)	32 (34.0)	25 (45.5)

See methods for definitions of outcome measures. Individuals receiving statins with ezetimibe were classified as statin users.

Despite the existence of effective therapies for lowering cholesterol, patients in the UK do not adhere to them in an optimal fashion and do not reach achievable LDL targets. These results highlight the importance of aggressively managing LDL cholesterol levels in patients that have already been identified with elevated risk to ensure that targets are met. They also highlight what is possible to achieve through improvements in therapy and management.

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