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ORIGINAL RESEARCH

Prevalence and Patient Outcomes of Adult Primary Hypercholesterolemia and Dyslipidemia in the UK: Longitudinal Retrospective Study Using a Primary Care Dataset from 2009 to 2019

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Background: Guidelines for the management of dyslipidemias recommend intensive low-density lipoprotein (LDL-C) control through lifestyle advice and lipid-lowering drugs to reduce the risk of cardiovascular disease (CVD).

Objective: This retrospective study aimed to characterize the adult primary care population with primary hypercholesterolemia (PH)/mixed dyslipidemia (MD).

Methods: Data on adults with PH/MD between 1 January 2009 and 31 December 2019 in the UK were extracted from linked primary Clinical Practice Research Datalink (CPRD) and secondary care (Hospital Episode Statistics) datasets and analyzed.

Results: A total of 279,221 patients met the inclusion criteria. Mean follow-up was 8.6 years. Crude prevalence of PH/MD increased from 13.5% in 2009 to 23.5% by 2019. The incidence decreased from 176 to 49 per 100,000 population. Mean age of the cohort was 58 years, baseline LDL-C was 4.32 mmol/L, 19.6% had atherosclerotic CVD, 30.1% diabetes, and 8.5% heterozygous familial hypercholesterolemia. Estimated LDL-C reductions of 40% and 50% were achieved in 2.6% and 2.3% of patients, respectively. Most received moderate-intensity statins as monotherapy (62.4%); high-intensity statins were used less frequently (24.3% as initial treatment). Less than 10% of patients received ezetimibe plus statins of different intensities.

Conclusion: The prevalence of dyslipidemia doubled between 2009 and 2019, likely due to more systematic identification of PH/MD. A large proportion of patients with PH/MD are of high and very high CV risk, remain suboptimally treated in terms of lipid lowering, and may experience CV events with associated non-negligible clinical and economic sequelae. Despite intensive LDL-C-lowering recommendations, these do not translate in clinical practice to the wider population.

Keywords: lipid management, atherosclerosis, cardiovascular disease, NICE guidelines

Plain Language Summary

When a person has high levels of cholesterol, also known as lipids, they can build up in blood vessels and increase the risk of atherosclerotic cardiovascular disease. This can result in some cases in cardiac events such as heart attack and stroke. Low-density lipoprotein cholesterol, is directly associated with atherosclerotic cardiovascular disease. Guidelines therefore recommend reducing levels of low-density lipoprotein cholesterol through changes to lifestyle and the intensive use of drugs that reduce lipid levels.

We extracted data on adults with two forms of lipid abnormalities – primary hypercholesterolemia and mixed dyslipidemia – from primary care and hospital records. We analysed the data to identify the characteristics of adults with these conditions and how their lipid levels were managed.

The number of people diagnosed with primary hypercholesterolemia and mixed dyslipidemia doubled between 2009 and 2019, although this may be because doctors looked for these conditions due to increased awareness, education, evidence, and

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recommendations. A large proportion of the people in the analysis were at high or very high risk of cardiovascular disease. Although they should have been treated intensively to reduce low density lipoprotein cholesterol levels, many did not receive the recommended combinations of lipid-lowering drugs and so did not achieve recommended reductions in cholesterol levels.

Introduction

Cardiovascular disease (CVD) is a leading cause of mortality, morbidity, and reduced quality of life in Europe, including the UK, and is associated with significant clinical and economic burden.[1–3] It is the cause of about 4 million deaths every year in Europe, accounting for 45% of all deaths, and including more than 160,000 deaths each year in the UK, accounting for 27% of all deaths and equivalent to one death every three minutes.[1–3] With more patients surviving their first cardiovascular (CV) event,[2] CVD is also a major cause of disability, reduced quality of life, and poor clinical outcomes.[3,4] About 85 million people in Europe, including approximately 7.6 million people in the UK, are living with CVD;[1,3] in the UK, this represents twice as many people living with cancer and Alzheimer's disease combined.[1] Cardiovascular disease also has major economic and humanistic burden: it is estimated to cost about €210 billion a year in the EU (including direct healthcare costs, productivity losses, and informal care of people with CVD) and about £19 billion annually in the UK (including informal costs and costs associated with premature death and disability).[1,3]

Increased low-density lipoprotein cholesterol (LDL-C) is recognized as a direct cause of atherosclerotic CVD (ASCVD)[5] and its major clinical sequelae.[6] Although many people with hypercholesterolemia and mixed dyslipidemia are asymptomatic, the accumulation of atherogenic lipoproteins increases the total atherosclerotic burden, which, upon a sudden rupture, can lead to a thrombus and subsequent unstable angina, myocardial infarction, or death.[7] Evidence from meta-analyses of Mendelian randomization studies have shown that LDL-C has a dose-dependent, log-linear causative association with atherosclerotic CVD and that the causal effect of LDL on ASCVD is largely independent of the mechanism by which LDL is lowered.[5] Furthermore, integrated data analyses suggest that each 1 mmol/L reduction in LDL-C reduces the relative risk of ASCVD events by ~10% during the first year of treatment and ~20% after 3 years of treatment.[2,8]

The British Heart Foundation estimated that about half of adults in the UK are living with cholesterol levels higher than the national recommendations for total cholesterol (TC) of <5 mmol/L.[1] National guidance for the UK advocates primary prevention in patients with CV risk factors, recommending that people at high risk of CVD (>10% chance of a heart attack or stroke) are first offered lifestyle advice to lower cholesterol and, if that is not effective, are then offered lipid-lowering treatments, starting with statins.[9,10] The aim according to NICE is a reduction of non-high-density lipoprotein cholesterol (non-HDL-C) >40% from baseline using high-intensity statins – defined as statins resulting in LDL-C reductions >40% (Supplementary Table A in Supplementary Appendix A).[10,11] The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) also strongly recommend intensive control of LDL-C, aiming for a ≥50% reduction from baseline and a goal of LDL-C <1.4 mmol/L among patients at high to very high risk of CVD.[2]

In the UK, lipid management is predominantly undertaken in primary care.[12] Despite treatment with current oral lipid-lowering therapies, many patients fail to achieve guideline-recommended cholesterol reductions.[2] For some patients, statins are not tolerated or are contraindicated, so other treatment options are needed.[10] Current add-on and alternative options include the cholesterol absorption inhibitor ezetimibe, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors alirocumab and evolocumab, and bempedoic acid – a novel, first-in-class, oral, small-molecule adenosine triphosphate-citrate lyase (ACL) inhibitor.[2,5,10,13–16]

We undertook a study to characterize the adult primary care population in England who have primary hypercholesterolemia and mixed dyslipidemia and their current management using real-world data from the past decade.

Methods

Study Design

Our retrospective cohort used Clinical Practice Research Datalink (CPRD) and hospital episode statistics (HES) data in adult patients diagnosed with primary hypercholesterolemia or mixed dyslipidemia over the 11-year period from 1 January 2009 to 31 December 2019 (Figure 1). The study protocol titled "Prevalence, Treatment Pathway and

Patient Outcomes of Primary Hypercholesterolaemia and Dyslipidaemia in England: The 4Ps Study" has been approved for the use of CPRD data by the ISAC (protocol number 19_238R2, approval date: 27 January 2020).

Objectives

We aimed to characterize the adult primary care population (that is, patients registered with general practitioners [GPs]) in England with primary hypercholesterolemia or mixed dyslipidemia using real-world data. Specific characteristics of interest included the incidence and prevalence of dyslipidemia; patient demographics and characteristics, including comorbidities; lipid-lowering treatments prescribed, including in patients for whom statins are contraindicated or not tolerated; cardiovascular (CV) outcomes of those patients; achievement of LDL-C control (reduction in LDL-C ≥40% and ≥50% from baseline); and healthcare resource use for adult patients with primary hypercholesterolemia or mixed dyslipidemia.

Dataset

We used linked primary and secondary care datasets. The primary care dataset was the Clinical Practice Research Datalink (CPRD), which contains more than 11 million live patient clinical records from primary care general practices across the UK. The secondary care dataset was the hospital episode statistics (HES), which comprises the administrative healthcare records managed by NHS Digital in England and includes every single interaction of all patients in secondary care in England. Combining these two datasets to create a CPRD–HES-linked dataset provides a powerful tool to understand epidemiology across the UK and the impact of disease on the whole healthcare system.

Ethics

In line with regulations on healthcare data privacy in the UK, all data collection included aggregated data and did not include patient identifiable information.

Study Cohorts and Inclusion Criteria

From the intersection of the two CPRD–HES datasets, a cohort of adult patients with primary hypercholesterolemia or mixed dyslipidemia was defined from a list generated from the CPRD using the following inclusion criteria (see Figure 1):

- Age ≥18 years or birth year ≤1997 with 12 or more months follow up)

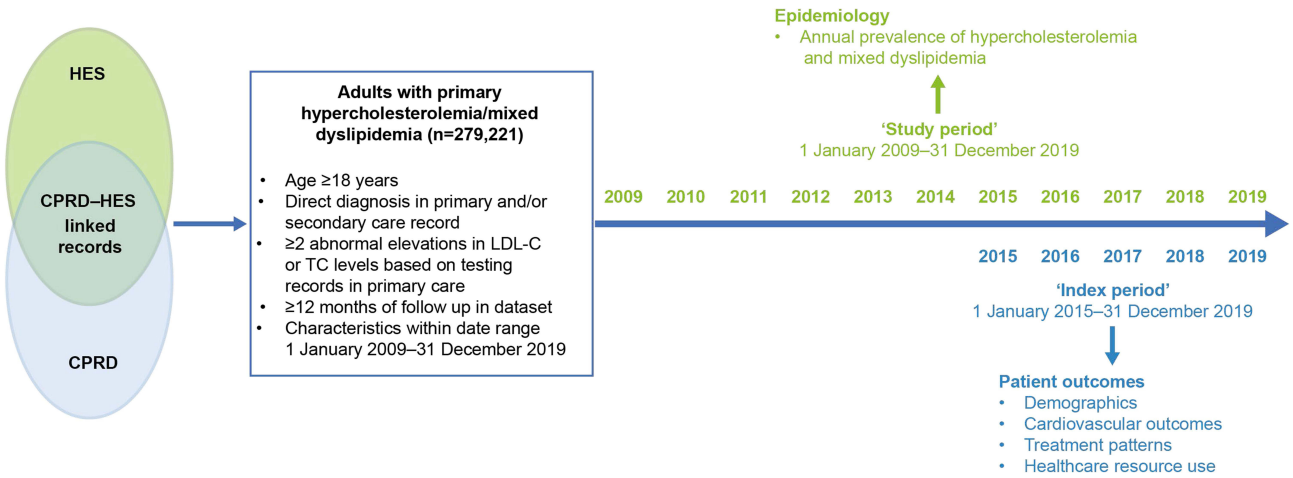

Figure 1 Overview of study cohort selection, study and index periods, and outcomes.
Abbreviations: CPRD, Clinical Practice Research Datalink; HES, hospital episode statistics; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

- Primary care record with primary hypercholesterolemia or mixed dyslipidemia based on read codes and codes from the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) or patients with a code that indicated high pre-treatment LDL-C or TC (based on clinical coding) (Supplementary Table B in Supplementary Appendix B)
- Minimum of 12 months of follow-up in the dataset (this did not apply to prevalence and incidence metrics)
- Patients must have had these characteristics within the date range 1 January 2009–31 December 2019.

The index date for all patients was the diagnosis of primary hypercholesterolemia or mixed dyslipidemia. To ensure this was the first diagnosis date, we applied a 6-month lookback period for no diagnosis of primary hypercholesterolemia or mixed dyslipidemia. The observation period for each patient extended from the index date until their latest record in the dataset. Only patients with minimum follow-up of one year were included in the analysis. We also performed an analysis on a subcohort of patients from the overall study cohort, in whom statins were contraindicated or not tolerated, defined by using the following inclusion criteria: i) code for statin intolerance, ii) code for conditions where statins are contra-indicated based on contraindications in the summary of product characteristics for simvastatin,[17] or iii) code for adverse events related to statin intake after statin prescription.

We did not have any exclusion criteria.

Outcomes

Demographics and Clinical Characteristics

The following demographics and clinical characteristics were extracted for patients in the "index period" of 1 January 2015–31 December 2019: index date; age; systolic and diastolic blood pressure (BP), LDL-C and TC levels, and comorbidities at index date; and date of the end of the study period.

We calculated the total number of patients as the number of patients with an index date within the study period. We calculated means, medians and standard deviations for age on inclusion, duration of follow-up (time from index date to end of study period), BP, LDL-C levels, and TC levels. We calculated the age distribution by decade, the percentage of men, and the total time in the cohort (total time from index date to end of study period, reported as patient-days). We calculated the prevalence of comorbidities as the number of patients with a comorbidity based on the number of codes and number of patients in the cohort.

Epidemiology

We calculated the annual incidence and prevalence for the whole 11-year period between 2009 and 2019 based on the denominators of all patients who were currently registered at primary care practices contributing to the dataset. Per-year calculations were based on patient-years in the cohort – that is, only the time patients were followed up during the study period. Annual prevalence was calculated for the period 1 January 2009–31 December 2019 (the "study period").

Clinical Outcomes

We extracted the following CV events as individual outcomes – myocardial infarction, unstable angina, stable angina, ischemic stroke, and transient ischemic attack – and used these to create a composite outcome including all five of these CV events. We also calculated the percentage of patients who achieved LDL-C reductions <40% or <50% from baseline, in line with NICE and ESC/EAS recommendations, respectively.[2,10]

Treatment Patterns from 2015–2019

We sought to explore the sequencing of treatments in order to understand treatment practices, especially regarding use of combination therapies. Treatment patterns were analyzed for the period 1 January 2015–31 December 2019 (the "index period"). We determined the total number of patients diagnosed, comorbidities, and clinical outcomes based on a list of MedCODES and ICD-10 codes (Supplementary Table B in Supplementary Appendix B). Procedures were determined using codes according to version 4 of the Office of Population Censuses and Surveys (OPCS) Classification of Interventions and Procedures (Supplementary Table C in Supplementary Appendix B). Medications were identified

based on product codes (Supplementary Table D in Supplementary Appendix B). Statin dose was defined by intensity according to NICE (see Supplementary Table A in Supplementary Appendix A).

Healthcare Resource Use Outcomes

We extracted data on use of the following healthcare resources and calculated the total, mean per patient, and mean per year use of these resources in our study cohort:

- Products prescribed in primary care (defined as any medication or treatment prescribed, as signified by a *British National Formulary* [BNF] entry[18] or product read code in the CPRD part of a patient record) (data not shown)
- Inpatient admissions (defined as an admission in HES; total admissions [elective, defined as a planned admission] and non-elective [defined as an unplanned admission, usually an emergency admission])
- Inpatient length of stay (defined as the number of days spent in an admission in HES, excluding zero-day length-of-stay admissions)
- Outpatient appointments (defined as an outpatient appointment in HES)
- Emergency department (ED) attendances (defined as the number of ED attendances in HES)
- GP appointments overall and with diagnosis codes for primary hypercholesterolemia or mixed dyslipidemia
- Referrals from primary care to secondary care (all referrals and referrals to endocrinology, cardiology, and gastroenterology).

For the mean per patient per year estimations of healthcare resource use, the cohort of patients who had at least one (≥1-year) follow-up in the database was used.

We used inpatient healthcare resource group (HRG) tariffs (defined as HRG tariff tagged in each admission, Supplementary Appendix C) and ED HRG tariffs to calculate healthcare resource use.

Results

Study Cohort

A total of 279,221 patients met the inclusion criteria and comprised the analysis cohort (see Figure 1).

Epidemiology

Based on CPRD General practitioner OnLine Database (GOLD) in patients registered to a GP, we identified an increasing trend of crude prevalence of primary hypercholesterolemia and mixed dyslipidemia – from 13.5% in 2009 to almost double at 23.5% by 2019 (Figure 2). The calculated incidence of primary hypercholesterolemia and mixed dyslipidemia showed a downward trend from 2009 to 2019, with estimated incidences of 176 per 100,000 population for 2009 and 49 per 100,000 population for 2019.

Patient Demographics and Clinical Characteristics

Table 1 summarizes the patient demographics and clinical characteristics of the cohort with primary hypercholesterolemia or mixed dyslipidemia. Mean follow-up (time from index date to end of study period) was 8.6 years. The mean age was 58 years, and 47% were men (Table 1). Mean TC and LDL-C levels at index in the cohort were 6.31 mmol/L and 4.32 mmol/L, respectively. Mean systolic and diastolic BPs were 138.53 and 81.91 mmHg, respectively.

A large proportion of patients had atherosclerotic CVD (19.6%), diabetes (30.1%) or both (8.0%), or other CV risk factors that would categorize them as at high or very high CV risk according to the most recent 2019 ESC/EAS guidelines (Table 1).[2] More than 10% of patients overall had moderate to severe chronic kidney disease (moderate CKD: estimated glomerular filtration rate [eGFR] 30–59 mL/min; severe CKD: eGFR <30 mL/min) and 8.5% had a diagnosis of heterozygous familial hypercholesterolemia.

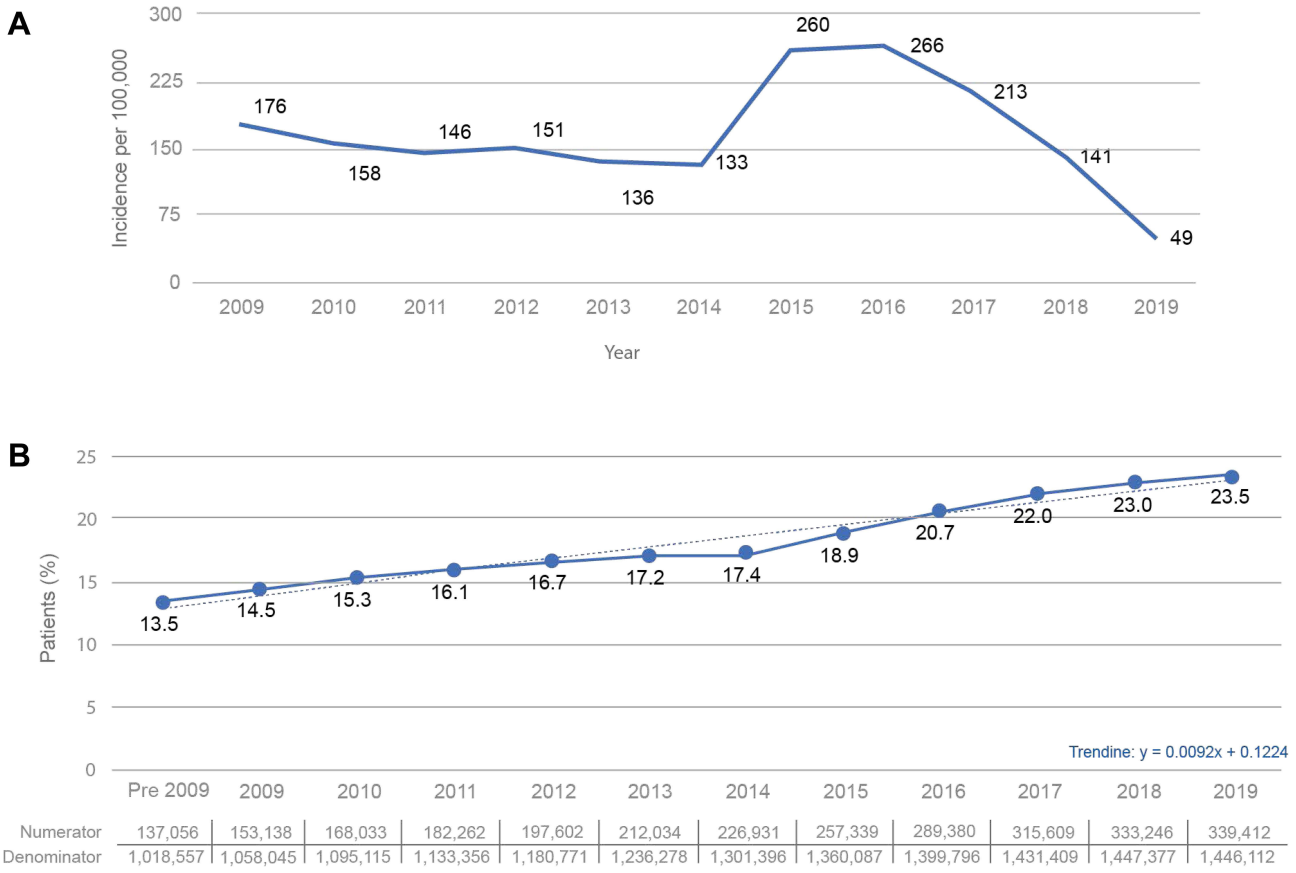

Figure 2 (**A**) Estimated annual incidence per 100,000 population: standardized per 1,000,000 of patients registered to a GP in dataset and (**B**) Crude prevalence of primary hypercholesterolemia and mixed dyslipidemia: total number of patients in the cohort (cases) that did not die on their index date divided by the total number of patients actively registered to a GP practice participating in CPRD GOLD within the stated period minus the number of recorded dead patients.
Abbreviations: CPRD, Clinical Practice Research Datalink; GP, general practitioner.

Use of Lipid-Lowering Therapies

Within the study period, a total of 35 million prescriptions were written for 276,343 patients in the cohort with more than one year of follow up, corresponding to a mean of 14 prescriptions per patient per year (Table 2). When examining the prescriptions for lipid-lowering therapies in the cohort of interest (statins, ezetimibe, and PCSK9 inhibitors), the vast majority were for statins of any intensity and type (n=13,073,658), corresponding to a mean of 6.55 prescriptions per patient per year, while 582,452 of prescriptions were for ezetimibe (2.90 prescriptions per patient per year) (Table 2). Less than 0.01% of prescriptions in the CPRD/HES among the cohort were for PCSK9 inhibitors alone or in combination with another lipid-lowering therapy.

Some patients may have received different drugs, drug combinations, and intensities of statins as treatments changed during their follow up in the study period. Among the cohort (n=205,040), moderate-intensity statins were more often used (69.3%) as monotherapy than high- (49.8%) or low-intensity statins (16.4%) (Table 3). Combination therapy comprising ezetimibe with a statin was used in only small proportions of patients; ezetimibe plus a moderate-intensity statin was the most frequently used combination (6.8%). Ezetimibe monotherapy was prescribed in 5.7% of patients who had a coding of statin intolerance or a contraindication to statin. The low number of patients prescribed ezetimibe as monotherapy or in combination is consistent with previous studies within CPRD in the past.[19,20]

When examining the treatment sequencing in the cohort of patients who received any of the above treatments, 62.4% were prescribed monotherapy of moderate-intensity statins as their first treatment (for a mean of 1920 days), about a quarter (24.3%) a high-intensity statin (mean time 1250 days), 11.1% a low-intensity statins (mean time 1420

Table 1 Patient Demographics and Characteristics of the Study Cohort

Demographic/Characteristic	Overall Population n=279,221
Men, n (%)	130,335 (46.7)
Mean age (SD), years	58.00 (11.73)
Age group, n (%)	
10–19 years (≥18 years by inclusion)	291 (0.1)
20–39 years	15,584 (5.6)
40–69 years	215,752 (77.3)
70–100+ years	47,594 (17.0)
Mean follow-up (years)	8.64
Total time in cohort (days)[a]	880,884,517
Total cholesterol levels (mmol/L), mean (SD)	6.31 (1.31)
LDL-C (mmol/L), mean at index date (SD)	4.32 (1.26)
Systolic blood pressure (mmHg), mean (SD)	138.53 (51.30)
Diastolic blood pressure (mmHg), mean (SD)	81.91 (11.43)
Comorbidities, n (%)	
Diabetes	83,957 (30.1)
Diabetes >10 years	36,299 (13.0)
Diabetes with target organ damage	19,139 (6.9)
Atherosclerotic CVD	54,666 (19.6)
Atherosclerotic CVD and diabetes	22,416 (8.0)
Moderate CKD (eGFR 30–59 mL/min)	31,893 (11.4)
Severe CKD (eGFR <30 mL/min)	3765 (1.4)
Heterozygous familial hypercholesterolemia	23,671 (8.5)

Notes: [a]The sum of the number of days between the date on which the patients were included in the study and the patients' last observation dates.
Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

Table 2 Primary Care Prescriptions in the Primary Care Cohort of Patients with ≥1 Year Follow-Up During 2015–2019 (n=279,220)

Prescriptions	Total Prescriptions, n	Number of Patients	Mean (SD) Prescriptions per Patient per Year
Overall[a]	35,131,665	276,343	14.26 (9.50)
Lipid lowering therapies			
Statin	13,073,658	204,101	6.55 (4.76)
Ezetimibe	582,452	18,264	2.90 (3.59)
PCSK9 inhibitor	144	21	0.97 (1.31)

Note: [a]Includes all prescriptions for any medicines, not just those for lipid-lowering therapies.
Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9; SD, standard deviation.

Table 3 Use of Lipid-Lowering Therapies in the Cohort (n=205,040) Within the Study Period (2015–2019)

Lipid Lowering Treatment	Number of Patients, n (%)
Statins alone	
High-intensity statin[a]	102,073 (49.8)
Moderate- intensity statin[a]	142,137 (69.3)
Low-intensity statin[a]	33,539 (16.4)
Statin in combination	
Ezetimibe + high- intensity statin[a]	12,021 (5.9)
Ezetimibe + moderate-intensity statin[a]	14,031 (6.8)
Ezetimibe + low-intensity statin[a]	7235 (3.5)
PCSK9 inhibitor ± statin	21 (<0.01)
Ezetimibe[b]	11,735 (5.7)

Notes: Numbers do not add up to 100%, as patients may have received different treatments within their follow-up period; only patients with at least one-year follow-up were included in the analysis. [a]Low intensity if reduction in LDL-C is 20–30%, medium intensity if reduction is 31–40%, and high intensity if reduction >40%.[10] [b]Corresponds to patients within the cohort who received ezetimibe as monotherapy.
Abbreviation: PCSK9, proprotein convertase subtilisin/kexin type 9.

days), and 1.3% started with ezetimibe (mean time 984 days). The mean time on treatment was overall 1780 days (about 4.9 years) in the cohort, and the mean time to switch to a subsequent treatment was 1217 days (about 3.5 years).

As ezetimibe is often a lipid-lowering treatment used as an add-on option in patients not controlled on statins (which may include no, low-, moderate-, or high-intensity statin), we sought to examine treatment patterns in those patients receiving ezetimibe during their follow-up (as monotherapy or combination) by retrospective analysis of their immediate prior treatment. As shown in the Sankey diagram (Figure 3), the most common pattern was addition of ezetimibe with a moderate-intensity statin rather than a high-intensity statin or low-intensity statin. A smaller proportion of patients received statin as add-on therapy to ezetimibe (potentially as part of a rechallenge with statin treatment).

Patients with Intolerance or Contraindication to Statins

More than half of patients (52.7%, n=147,201) in the overall cohort had a code for statin intolerance, history of a code for conditions where statins would be contraindicated, or a code for adverse events related to statin intake after statin prescription. Their mean age was 56 (SD) 13.86) years, 22% had ASCVD, 34% diabetes and 14% moderate or severe CKD. The mean LDL-C was 2.98 (SD 1.28) mmol/L and mean total cholesterol was 5.11 (SD 1.33) mmol/L. Among those with a prescription (n=147,111), 74.6% (n=109,817) were on a statin and 7.7% (n=11,297) on ezetimibe, while a small number had a PCSK9 inhibitor prescription (n=17). Their treatment pattern was similar to that of the overall cohort (data not shown).

Cardiovascular Events

Excluding patients who had already experienced a CV event by their index date, 23.6% of patients in our cohort experienced a CV event during the study period (Table 4). The most common CV events were myocardial infarction (14.8%), stable angina (7.9%), and ischemic stroke (7.6%) (Table 4). Mean follow-up of these patients was 103.68 months (about 8.6 years).

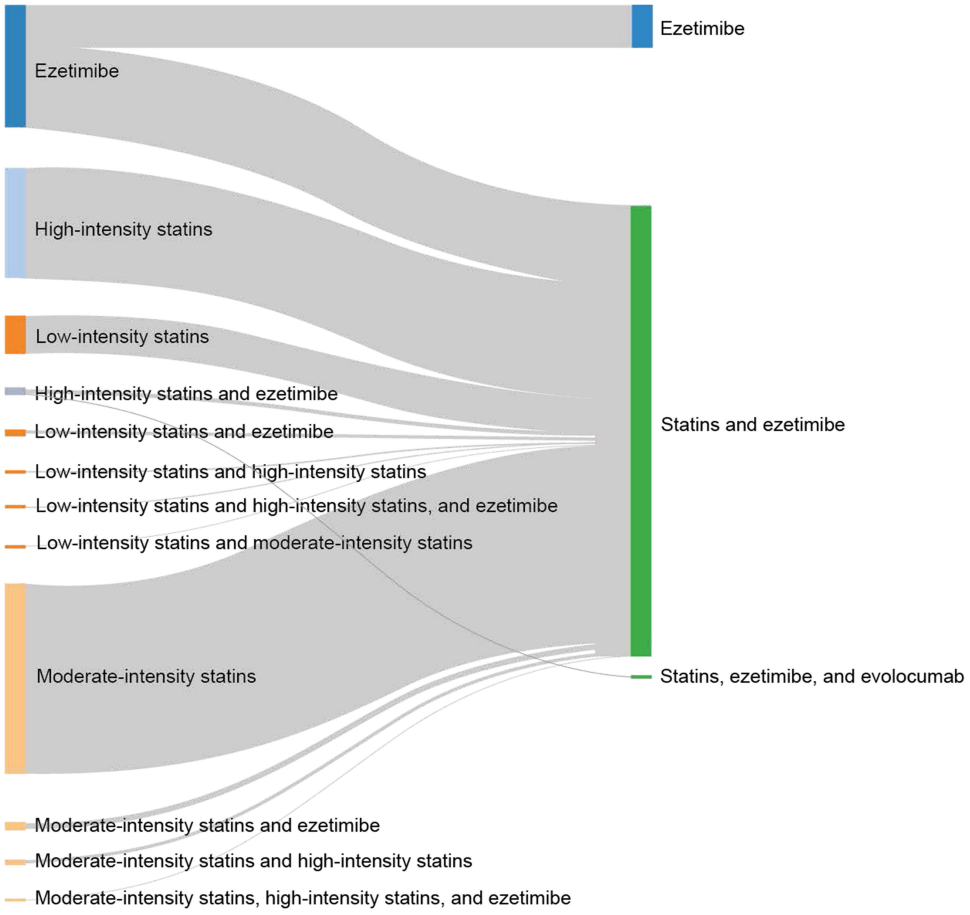

Figure 3 Sankey diagram depicting the sequencing of lipid-lowering treatments. Low intensity, moderate intensity, and high intensity based on drug codes (see also Supplementary table A in Supplementary Appendix A).

Achievement of LDL-C Reduction

The proportions of patients with estimated reductions in LDL-C of 40% and 50% between the last measurement recorded prior to their inclusion and the end of their follow-up period were 2.6% and 2.3%, respectively (Table 5).

Table 4 Occurrence of Cardiovascular Events

Clinical Outcome	Patients with Event Between Index Date and Observation Period (n)	Patients Without Event Diagnosis pre Index Date (n)	Unadjusted Incidence (%)[a]
Myocardial infarction	39,492	267,370	14.8
Unstable angina	5418	277,522	2.0
Stable angina	21,473	270,424	7.9
Ischemic stroke	20,806	274,268	7.6
Transient ischemic attack	8062	276,940	2.9
Composite cardiovascular events[b]	60,635	256,849	23.6

Notes: [a]This crude incidence does not include patients who have already experienced a cardiovascular event at index. Mean follow-up was 103.68 months. [b]Composite of myocardial infarction, unstable angina, stable angina, ischemic stroke, transient ischemic attack.

Table 5 Achievement of LDL-C Goals of 40% and 50% Reduction

Clinical Outcome	Patients with Achieved Outcome (n)	Patients with LDL-C Measurements Within Study Period (n)	Proportion (%)
≥40% LDL-C reduction from index[a]	7105	272,116	2.6
≥50% LDL-C reduction from index[a]	6300	272,921	2.3

Notes: [a]Number of patients with given % LDL-C reduction between the last measurement recorded prior to their inclusion and the end of their follow-up period divided by the number of patients with no recorded reduction of LDL-C by up to and including 40% or 50% prior to the patient's index date from their baseline LDL-C reading – that is, the last recorded LDL-C level before their index date.
Abbreviation: LDL-C, low-density lipoprotein cholesterol.

Table 6 Primary Care and GP Visits/Appointments and Referrals to Specialty Care in the Cohort of Patients with ≥1 Year Follow Up (n=279,220)

Resource	Total Appointments (n)	Number of Patients (n)	Mean (SD) Appointments per Patient per Year
All appointments in primary care	75,390,901	279,220	31.29 (17.22)
GP appointments related to PH/MD	227,206	142,237	0.21 (0.22)
Referrals to specialty care	1,519,730	226,102	0.79 (0.74)
Referrals to cardiology	36,769	26,281	0.17 (0.17)
Referral to endocrinology	4929	4255	0.19 (0.20)

Abbreviations: GP, general practitioner; MD, mixed dyslipidemia; PH, primary hypercholesterolemia; SD, standard deviation.

Healthcare Resource Use

Primary Care

For our cohort of interest, a total of 75 million primary care appointments were recorded for the study period 2015–2019, with a total of 227,206 of these related to primary hypercholesterolemia or mixed dyslipidemia (mean 0.21 per patient per year) (Table 6). A mean of 0.8 referrals to specialties per patient per year was recorded; referrals for selected specialties are shown in Table 6.

Table 7 Secondary Healthcare Resource Use: Inpatient (Elective and Non-Elective) Admissions in the Cohort (Inpatient) with ≥1 Year Follow Up (n=66,258) Within the Observation Period 2015–2019

Type of Admission	Number of Admissions	Mean (SD) Admissions per Patient	Mean (SD) Admissions per Patient/Year	Mean Length of Stay/Admission (Days)	Mean (SD) Cost/Admission (£)
All inpatient	352,625	5.30 (18.53)	0.62 (1.96)	2.19 (8.80)	1278 (1975)
Elective (planned)	252,006	3.79 (17.95)	0.44 (1.89)	0.75 (4.21)	1046 (1769)
Non-elective	95,764	1.44 (2.80)	0.17 (0.36)	5.47 (13.86)	1954 (2333)

Abbreviation: SD, standard deviation.

Table 8 Secondary Healthcare Resource Use: Outpatient Visits and Emergency Department Attendances (Total Population: n=89,944) for the Observational Period (Follow-Up) 2015–2019

Type of Attendance	Number of Visits	Mean (SD) Visits per Patient	Mean (SD) Visits per Patient/ Year	Mean Cost (SD) per Visit (£)
All outpatient	2,250,177	25.02 (35.93)	3.05 (4.21)	NA
Cardiology	41,686	5.17 (7.75)	0.59 (0.87)	91.57 (91.57)
General medicine	25,740	5.17 (15.45)	0.52 (1.71)	111.45 (111.45)
Anticoagulant service	17,476	24.37 (36.55)	2.62 (4.35)	NA
Diagnostic imaging	13,727	2.56 (2.67)	0.41 (0.57)	NA
Diabetic medicine	12,906	9.76 (15.68)	1.19 (1.95)	88.85 (88.85)
Endocrinology	6293	5.03 (6.21)	0.64 (0.91)	122.51 (122.51)
Vascular surgery	6253	3.81 (5.40)	0.42 (0.63)	115.36 (115.36)
Cardiac surgery	864	2.67 (2.31)	0.33 (0.49)	143.40 (143.40)
Emergency department	463	1.54 (1.28)	0.17 (0.16)	NA

Notes: Given the heterogeneity of the patient population in terms of medical history and comorbidities, only select specialty visits of interest are shown that may be potentially associated with primary hypercholesterolemia, mixed dyslipidemia, related clinical sequelae, other comorbidities, and CV risk factors.
Abbreviations: NA, not applicable; SD, standard deviation.

Secondary Care

A total of 352,625 secondary care inpatient admissions were recorded for patients with at least one year follow-up during the study period, of which 71% (n=252,006) were elective, 27% (n=95,764) were non-elective, and the nature of the remainder was not documented within the dataset (Table 7). For patients among the cohort with any secondary care admissions (n=66,258), the mean number of admissions per patient per year was 0.62, mean length of stay was 2.2 days per admission (including elective and non-elective) and, based on inpatient tariff costs, mean cost was £1278 per admission (Table 7). Overall, we estimated a total cost of £450 million for hospitalization (elective and non-elective procedures) for this cohort of patients with primary hypercholesterolemia or mixed dyslipidemia.

The total number of all outpatient appointments over the study period was 2,250,177 visits (Table 8); 28% of these were first appointments and 71% were follow-up visits (data not shown). The mean number of appointments during follow-up was 25.0 per patient for the study period, equivalent to 3.1 outpatient appointments per patient per year (Table 8). Given the heterogeneity of the patient population in terms of medical history and comorbidities, a wide range of referrals were recorded; Table 8 therefore includes secondary healthcare resource use for outpatient visits and ED attendances that may be potentially associated with primary hypercholesterolemia, mixed dyslipidemia, related clinical sequelae, other comorbidities, and CV risk factors, as well as less frequent outpatient appointments with a higher mean cost per visit.

Discussion

This study aimed to characterize the adult primary care population in England who have primary hypercholesterolemia or mixed dyslipidemia using the most recently available CPRD-HES data. We aimed to describe epidemiologic trends by examining data from 2009 through 2019 and to understand patient characteristics in primary hypercholesterolemia or mixed dyslipidemia, as well as treatment patterns and resource utilization within the five most recent years of our dataset (2015–2019).

Our cohort comprised, by definition, patients with high LDL-C levels at index or a diagnosis of primary hypercholesterolemia or mixed dyslipidemia. We identified a steadily increasing trend in the crude prevalence of dyslipidemia

from 13.5% prior to 2009 to almost double at 23.5% by 2019. The annual incidence was highest between 2014 and 2018, with a peak in 2016. Increasing awareness and education led by European guidelines,[2,21,22] studies demonstrating the causality of LDL-C to CVD and thus the importance of LDL-C lowering in preventing CV events,[5,23,24] and the publication of NICE Clinical Guideline 181 in July 2014 and its update in 2016[10,25] may have contributed to this increase by encouraging a more systematic strategy of assessing and identifying people with primary hypercholesterolemia or mixed dyslipidemia in England.

A large proportion of our cohort had ASCVD or other risk factors that classified them as at high or very high CV risk, such as hypertension (mean systolic and diastolic BPs were 138.53 and 81.91 mmHg, respectively), diabetes, or kidney disease,[2] which is consistent with previous studies in England and Europe.[20,26,27] Nearly 80% of patients with dyslipidemias in our study were aged 40–69 years. Patients in these three productive decades from middle to later adulthood thus are at high risk of CVD related to dyslipidemia.

In accordance with current guidelines and recommendations,[2,10,28] and as seen in previous studies with real-world evidence,[20,29] our study confirms that England's use of lipid-lowering therapy is anchored on statins.[2,10] Despite guidelines, it is notable that 26.6% of patients did not receive any prescription for a lipid-lowering drug during the study period, although the cohort characteristics showed that a large proportion of these are at high and very high CV risk. Most patients in our cohort received moderate-intensity statins as monotherapy (62.4%), while high-intensity statins were used less frequently (24.3% as initial treatment). Combination therapies with ezetimibe were underused, with less than 10% of patients receiving ezetimibe plus statins of different intensities, despite statins and ezetimibe being generic and affordable. However, our results suggest that, when intensifying lipid-lowering therapies, some prescribers combine ezetimibe with lower intensity of statins, rather than maximizing statin intensity alone. Further research on this would shed light on physician and patient perspectives behind treatment choices. Within this UK database, we have also noted that ezetimibe prescription has not increased notably in the past decade (data on file). Low ezetimibe usage in the UK is consistent with recent pan-European studies, such as DaVinci and EUROASPIRE, that demonstrate the low rates of ezetimibe utilization in clinical practice even after the publication of IMPROVE-IT CV outcomes in 2015.[23,30] We also noted, as in previous studies,[20,29] the very low utilization of PCSK9 inhibitors (0.01%); there are known reimbursement restrictions to the use of PSCK9 inhibitors in terms of patient eligibility and treatment setting. We also recognize that the percentage use reported here may be an underestimate of true patient numbers due to the lack of data in primary care records, as these drugs are available only via specialty care/secondary care channels in England.

In our cohort, baseline mean LDL-C level was 4.32 (SD 1.26) mmol/L. Although limitations in the continuity and completeness of clinical records may hinder our estimates, only 2.6% and 2.3% of patients achieved NICE- and ESC/EAS-recommended LDL-C reductions[2,10] despite follow-up of 9–10 years. This finding, together with the underutilization of combination therapies, shows that there is more room for optimization and intensification of lipid lowering in order to better control LDL-C. Our cohort also had a high incidence of CV events (23.6% for the composite CV endpoint). Another CPRD analysis found that, despite the wider and increased use of high-intensity statins after 2011, a greater proportion of patients within guideline-recommended LDL levels, and lower one-year CV event rates, <40% of very high-risk patients and <20% of high-risk patients still achieve an LDL of <1.4 mmol/L and <1.8 mmol/L, respectively, as recommended by the 2019 ESC/EAS guideline.[2,29] Our results confirm these and other reports that many patients fail to achieve guideline-recommended reductions in LDL-C despite treatment with existing oral lipid-lowering therapies[2,10] and continue to experience CVD and CV events.[1,20,29] In patients in whom LDL-C remains uncontrolled despite treatment and who therefore remain at increased CV risk, further reductions of LDL-C are required, and our findings confirm the need to shift from the concept of maximizing statin intensity towards maximizing the lipid-lowering therapy (including add-on therapy) to achieve control of LDL-C.[31] Recent studies using real-world cohorts in European countries showed that even after maximizing statins and ezetimibe, there is a 40–50% proportion of very high risk patients who remain above LDL-C recommended goals and would be in need of further lipid lowering treatment.[32–34] The low utilization of intensive regimens within England and small proportion of patients attaining target LDL-C levels is likely to result in excess risk of mortality and morbidity.

Our analysis highlighted that more than half of the patients in our cohort were coded as intolerant to statins or having a potential contraindication to statins in their history, with three-quarters of these having a prescription for statins during

the study period – either as monotherapy or in combination with other therapies and of different statin intensities and types (data not shown). The high proportion of patients coded as intolerant or contraindicated may be due to the broad nature of the code list used to identify potential contraindications (such as liver abnormalities, hepatitis or prescription of antibiotics such as erythromycin, ciclosporin or clarithromycin) but does not necessarily mean proven statin intolerance or association to statins. However, it highlights the lack of standardized definition of statin intolerance in the UK and the need for personalized treatment according to each patient's history and co-medications.[30] For those patients, whose mean LDL-C was 2.93 mmol/L and thus above guideline-recommended goals, there is an unmet need for further intensification of lipid-lowering therapies to better control LDL-C levels by utilizing non-statin treatments; this is becoming more apparent from the emerging scientific guidance on lipid lowering.[31]

In terms of healthcare resource usage, our cohort represents a high and very high CV risk group and thus a high burden to the healthcare system was noted. We identified about 0.2 primary care visits per patient/year, about 0.8 referrals to specialty per patient/year, and 3.1 outpatient visits per patient/year, most commonly to cardiology, anticoagulant service, diagnostic imaging, diabetes, and endocrinology specialties. Some other less frequent visits – endocrinology, vascular surgery, or cardiac surgery – were notable, as they were associated with a higher mean cost per visit. Taking into account hospital admissions, most of which were elective, we estimated about £450 million in total for hospitalizations of this cohort, although we were not able to analyze whether these visits were related to the clinical sequelae of ASCVD, such as stroke, myocardial infarction, revascularization, or other conditions. Our analysis demonstrates that patients with primary hypercholesterolemia or mixed dyslipidemia are mainly of high and very high CV risk and remain suboptimally treated and that their management is often associated with large healthcare resource utilization.

Strengths

This study uses recent real-world data from two datasets that include all patients in primary care in the UK and all patients using secondary care services in England. Combining these two datasets to create a CPRD–HES linked dataset provides a powerful tool to understand epidemiology across the UK and the impact of disease on the whole healthcare system. The management of dyslipidemia is very well reported in primary care data, which can therefore be used to sequence the treatment pathway.

Limitations

The data quality for our cohort is limited by the coding policies and practices of individual trusts, NHS Digital, data supplier intermediaries, other governing institutions, and coding from physicians and hospitals, although reimbursement in the NHS in England is dependent on coding, so there is a strong incentive to code all comorbidities to maximize financial reimbursement. However, as coding may not be complete, this study may underestimate the prevalence of primary hypercholesterolemia and mixed dyslipidemia (including patients not captured in primary or secondary care) and clinical outcomes.

Our analysis focused on cohorts defined by the diagnosis of primary hypercholesterolemia, mixed dyslipidemia, or elevated lipid levels rather than CV risk or baseline characteristics. Consequently, the definitions used are restrictive and may not capture the entire cohort of patients with AS CVD or other conditions, who may be receiving lipid-lowering therapy but not have been coded for primary hypercholesterolemia, mixed dyslipidemia, or elevated LDL-C levels.

Data collection included aggregated data. Small aggregate counts between 1 and 7 and sums and calculations with small numbers were suppressed and so not included in this analysis. There were observed differences in healthcare utilization and costs between the different treatment groups due to the heterogeneity of the patient population examined, so the statistical significance of these estimates needs to be examined further. As only limited numbers of patients overall received PCSK9 inhibitors, this may limit interpretation of results and the strength of any conclusions.

The analysis did not include geographical breakdown, year-on-year analysis, age groups, comorbidities, or inferential statistics (p-values, confidence intervals, sensitivities, specificities, and positive and negative predictive values).

Conclusion

This study showed a doubling in the prevalence of primary hypercholesterolemia and mixed dyslipidemia between 2009 and 2019, likely due to increasing awareness, education, evidence and recommendations encouraging a more systematic strategy of assessing and identifying people with primary hypercholesterolemia or mixed dyslipidemia. Despite LDL-C lowering remaining a primary goal for management of patients with high CVD risk and guidance recommending intensive cholesterol lowering, England's experience shows that recommendations on LDL-C reductions still do not translate successfully to the wider population. Our findings indicate an opportunity to change our healthcare strategy and ensure patients' risk profile is considered so that they receive optimized therapy in order to reduce LDL-C and help prevent CVD.

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