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Longitudinal evaluation of treatment patterns, risk factors and outcomes in patients with cardiovascular disease treated with lipid-lowering therapy in the UK

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ABSTRACT

Objectives To compare treatment patterns, risk factors and cardiovascular disease (CVD) event rates in the UK from 2008 to 2017.

Design Retrospective cohort study using the Clinical Practice Research Datalink.

Setting UK primary care.

Participants We selected 10 annual cohorts of patients with documented CVD receiving lipid-lowering therapy and the subsets with myocardial infarction (MI). Each cohort included patients ≥18 years old, with ≥1 year of medical history and ≥2 lipid-lowering therapy prescriptions in the prior year.

Primary and secondary outcome measures For each annual cohort, we identified cardiovascular risk factors and lipid-lowering therapy and estimated the 1-year composite rate of fatal and non-fatal MI, ischaemic stroke (IS) or revascularisation.

Results The documented CVD cohort mean age was 71.6 years in 2008 (N=173 424) and 72.5 (N=94 418) in 2017; in the MI subset, mean age was 70.1 years in 2008 (N=38 999) and 70.4 in 2017 (N=25 900). Both populations had larger proportions of men. In the documented CVD cohort, the proportion receiving high-intensity lipid-lowering therapy from 2008 to 2017 doubled from 16% to 32%; in the MI subset, the increase was 20% to 48%. In the documented CVD cohort, the proportion of patients with low-density lipoprotein cholesterol (LDL-C) <1.8 mmol/L increased from 28% to 38%; in the MI subset, the proportion with LDL-C <1.8 mmol/L increased from 32% to 42%. The composite event rate per 100 person-years declined over time, from 2.5 to 2.0 in the documented CVD cohort, and from 3.7 to 2.8 in the MI subset. After excluding revascularisation from the composite outcome, the decline in the event rate in both populations was substantially attenuated.

Conclusions Despite an increase in high-intensity therapy use and a decline in revascularisation, more than half of patients did not receive high-intensity lipid-lowering therapy by 2017 and incidence rates of MI and IS remained virtually unchanged.

Strengths and limitations of this study

- The population included a broad range of patients from routine general practice.
- Cardiovascular event rates were measured over a relatively short period of time (1 year).
- The cohorts only included prevalent patients receiving lipid-lowering therapy.

INTRODUCTION

Cardiovascular disease (CVD) involves a group of disorders of the heart and blood vessels including coronary heart disease, cerebrovascular disease and peripheral vascular disease. In 2019, there were over 133 000 deaths from CVD, and over 6.4 million people living with CVD in the UK.[1] Hypercholesterolaemia is one of the most common causal modifiable risk factors for CVD, and lowering low-density lipoprotein cholesterol (LDL-C) is very important for prevention of cardiovascular events.[2] This is especially important for patients with a history of CVD, who are at very high risk for subsequent cardiovascular events. These patients, as well as those with other cardiovascular risk factors, are commonly prescribed lipid-lowering therapy to reduce the risk of further cardiovascular morbidity and mortality with statins being the standard of care.

The guidelines for dyslipidaemia management in patients at high risk of atherosclerotic CVD (ASCVD) have been updated, with the goal of improving patient outcomes. Guidelines have been released by the European Joint Task Force in 2007, 2012 and 2016, European Society of Cardiology (ESC) in 2011, 2016, 2019

and 2021, Joint British Societies in 2014, and National Institute for Health and Care Excellence (NICE) in 2014.[3–10]

Over time, the LDL-C treatment goals recommended in the guidelines have become progressively lower. In 2007, the ESC recommended that LDL-C levels should be <2.5 mmol/L in patients with documented CVD; however, by 2011, the guidance changed to recommend LDL-C levels<1.8 mmol/L or <50% than the pretreatment level. In 2019, ESC recommended LDL-C levels <1.4 mmol/L≥50% LDL-C reduction from pretreatment levels. Despite many patients receiving lipid-lowering therapy, there are still many who do not achieve recommended LCL-C levels and remain at very high risk for cardiovascular events.[3 5 11]

We previously conducted analyses that evaluated the prevalence of cardiovascular risk factors (including LDL-C levels), the prevalence of documented CVD, and the utilisation of different lipid-lowering therapies in a single cohort of patients treated with lipid lowering therapy in 2013.[12] However, this did not provide a perspective on the changes in LDL-C management made over time or their effect on LDL-C levels and rates of cardiovascular outcomes. Therefore, the purpose of this study is to describe temporal changes in LDL-C treatment patterns, LDL-C levels and cardiovascular event rates over a 10-year period from 2008 to 2017 in the UK. This information is important for understanding the unmet medical need of two overlapping groups of patients: those at a very high risk of cardiovascular events due to documented CVD, and the subset of these patients with a history of myocardial infarction (MI).

METHODS

This is a retrospective cohort study conducted across two sets of 10 annual cohorts using data from the Clinical Practice Research Datalink (CPRD) for the period from 2008 to 2017.

Patient and public involvement

No patient involved.

Data source

The CPRD contains the anonymous, longitudinal medical records of patients registered with contributing primary care practices across the UK including practices in England, Scotland, Wales and Northern Ireland. It includes over 35 million individuals, of whom 11 million are currently registered patients, of whom 25% have at least 20 years of follow-up.[13] CPRD contains information about patient registration with primary care practices over time, as well as records of all medical care events recorded by general practice staff. This information includes demographics, medical diagnoses, referrals to specialists, primary care prescriptions, immunisation records, diagnostic testing, as well as other clinically useful information (eg, smoking status and alcohol consumption).

Setting and study population

We created 10 annual cohorts, one for each year from 2008 to 2017. The study populations for each of the 10 annual cohorts consisted of adult (age ≥18) patients using lipid-lowering therapy who had documented CVD as defined below. Patients must have been alive and observable in the CPRD data as of the 1 January index date of each year.

For each annual cohort, we included all patients who received ≥2 prescriptions for lipid-lowering therapy within the prior year. For each annual cohort, we included all patients with at least one of the following conditions as of the index date: MI, unstable angina, chronic ischaemic heart disease, revascularisation (percutaneous coronary intervention or coronary artery bypass graft), stable angina, ischaemic stroke (IS), transient ischaemic attack, peripheral arterial disease or abdominal aortic aneurysm. The MI subset was created by including only those patients with a medical history of MI. Patients may have been in multiple annual cohorts (see online supplemental figure 1).

Exposures and outcomes

The baseline period was defined as the period prior to and including 1 January of each calendar year. The use and identification of lipid-lowering therapy was based on the previous 12-month period, while other comorbid conditions were based on all recorded medical history in CPRD.

All medical conditions, including those used to identify documented CVD, were based on READ codes in the primary care record. The code lists used to identify conditions were based, as much as possible, on definitions provided by the Quality Outcomes Framework business rules as well as previous research.[12 14–16] The analyses of laboratory values were based on the subset of patients with ≥1 available value in the year prior to the index date. For patients with more than one value, the mean of all values during the year was used.

Lipid-lowering therapy was identified based on general practice prescription data in CPRD, and was based on most-used drug and dose combination within each year for each person (for a tie, the most recent was used). The intensity of lipid-lowering therapy was based on the treatment regimen identified. Patients receiving statin therapy were classified based on the expected percent LDL-C reduction of their regimen as 'low intensity' (<30% reduction), 'moderate intensity' (30%–47% reduction) or 'high intensity' (≥48% reduction) using NICE-estimated expected LDL-C reductions for each drug and dose.[3 15] Accordingly, atorvastatin 40 mg and 80 mg and rosuvastatin 20 mg and 40 mg were classified as high intensity statins while atorvastatin 20 mg and rosuvastatin 10 mg were classified as moderate intensity. Patients receiving any statin plus ezetimibe were classified as receiving 'high intensity' therapy. Patients receiving any other lipid lowering therapy with a statin were classified solely based on the intensity of their statin regimen as described above. Patients who received lipid-lowering therapy other

than statins, or who received ezetimibe alone, were classified as receiving 'low intensity' therapy (there were no PCSK9 inhibitor users in our documented CVD cohort).

Vascular beds were defined as the following three groups, consistent with the definitions in the REACH study: coronary (MI, unstable angina, chronic ischaemic heart disease, revascularisations or stable angina), cerebrovascular (IS, or transient ischaemic attack), and peripheral (peripheral arterial disease or abdominal aortic aneurysm).[17] Patients with more than one vascular bed affected were defined as having polyvascular disease.

The outcome measures were a composite event of MI, IS, or revascularisation as well as a composite event without revascularisation. Outcomes were identified within the 1-year period after the index date for each of the 10 annual cohorts.

Analyses

All analyses were descriptive and based on means, proportions and rates. Cardiovascular event rates were defined as the number of patients with an event, divided by the person-time of follow-up. For the documented CVD cohort and the MI subset, we estimated the 1-year composite rate of MI, IS or revascularisation during the 1-year period following the index date. We also estimated the composite rate without revascularisation as a sensitivity analysis. Patient follow-up was censored at the earliest of the following: 1 year, end of data or the composite endpoint. The prevalence of risk factors and event rates were estimated separately for each annual documented CVD cohort from 2008 to 2017, as well as the MI subset.

RESULTS

Online supplemental table 1 contains study attrition as part of creating each cohort. Across both the documented CVD cohort and the MI subset, the available sample sizes in CPRD were relatively consistent from 2008 through 2013 and declined from 2014 to 2017. The documented CVD cohort mean age was 71.6 (SD 10.7) years in 2008 (N=173 424) and 72.5 (SD 11.1) in 2017 (N=94 418). In the MI subset, mean age was 70.1 (SD 11.7) years in 2008 (N=38 999) and 70.4 (SD 11.7) in 2017 (N=25 900). Both populations had larger proportions of men, with the documented CVD cohort having 60% men in 2008 and 63% in 2017, while in the MI subset the respective proportions of men were 69% and 71%. The proportion of patients with type 2 diabetes in both populations was 18% in 2008 and 22% in 2017 (table 1). See online supplemental tables 2,3 for demographic and clinical details on all 10 cohorts.

The proportion of patients receiving high-intensity lipid-lowering therapy from 2008 to 2017 doubled in the documented CVD cohort from 16% to 32% (figure 1). In the MI subset, the increase was larger, more than doubling from 20% to 48% from 2008 to 2017 (figure 1). In the documented CVD cohort, the proportion of patients with LDL-C <1.8 mmol/L increased from 28% to 38%, and the proportion with LDL-C <1.4 mmol/L increased from 10% to 16% (figure 2). In the MI subset, the proportion with LDL-C <1.8 mmol/L increased from 32% to 42%, and the proportion with LDL-C <1.4 mmol/L increased from 12% to 19% (figure 2).

The mean LDL-C level declined very slightly over time in both populations, from 2.2 to 2.1 mmol/L in the

Table 1 Baseline demographic and clinical characteristics of the 2008 and 2017 documented CVD cohort and MI subset

	Documented CVD cohort		MI subset	
Variable	2008 (n=173 424)	2017 (n=94 418)	2008 (n=38 999)	2017 (n=25 900)
Age (years)	71.6 (10.7)	72.5 (11.1)	70.1 (11.7)	70.4 (11.7)
Male (%)	59.9	63.1	68.7	70.9
Body mass index (kg/m^2)	28.1 (5.0)	28.8 (5.4)	28.0 (4.9)	28.9 (5.4)
Smoking	15.1%	13.9%	16.5%	15.2%
Type 2 diabetes	18.4%	22.4%	17.7%	21.9%
Chronic kidney disease stage 3–5	22.4%	22.8%	23.3%	22.1%
Hypertension	95.3%	94.0%	98.2%	98.1%
MI	22.5%	27.4%	100%	100%
IS	5.5%	7.9%	1.7%	2.2%
Peripheral artery disease	14.6%	15.4%	8.0%	7.2%
Total cholesterol (mmol/L)	4.2 (0.9)	4.1 (1.0)	4.1 (0.9)	4.0 (1.0)
LDL cholesterol (mmol/L)	2.2 (0.8)	2.1 (0.8)	2.1 (0.7)	2.0 (0.8)
HDL cholesterol (mmol/L)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.2 (0.4)

Mean (SD) is shown for age, body mass index and cholesterol levels. Total cholesterol levels were available for 72%–83% of patients, HDL cholesterol levels were available for 65%–69% of patients, and LDL cholesterol levels were available for 52%–55% of patients in each population in 2008 and 2017. Revascularisation includes percutaneous coronary intervention and coronary artery bypass grafting.
CVD, cardiovascular disease; HDL, high-density lipoprotein; IS, ischaemic stroke ; LDL, low-density lipoprotein; MI, myocardial infarction.

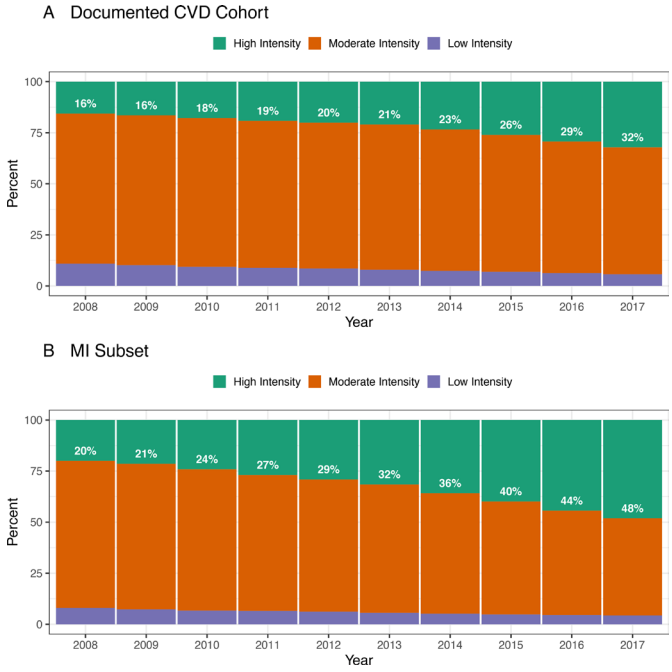

Figure 1 Intensity of lipid-lowering therapy by year and population. CVD, cardiovascular disease; MI, myocardial infarction.

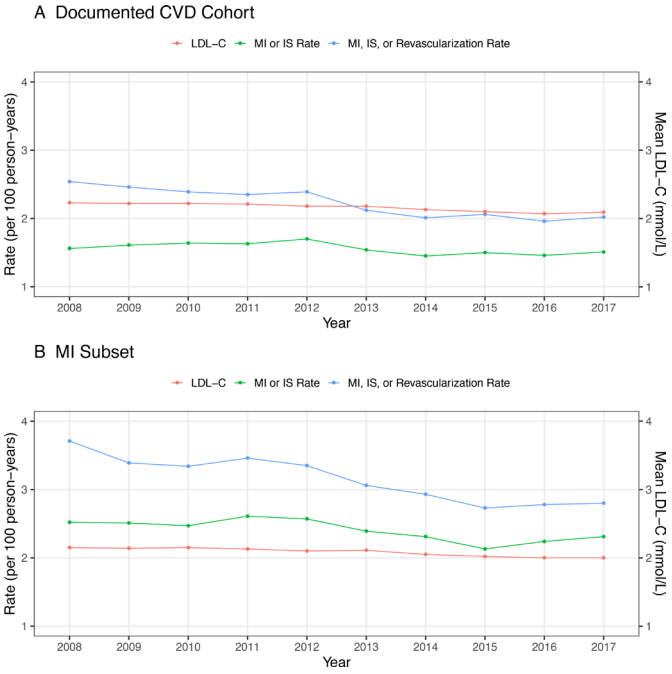

Figure 3 1-year cardiovascular event rate and mean LDL-C level by year and population. CVD, cardiovascular disease; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

documented CVD cohort and from 2.2 to 2.0 in the MI subset. The cardiovascular event rate also declined over time in both populations (figure 3), from 2.5 to 2.0 events per 100 person-years in the documented CVD cohort, and from 3.7 to 2.8 events per 100 person-years in the MI subset. The exclusion of revascularisation from the composite outcome attenuated the decline in the event rate in both populations, which then ranged from 1.6 to 1.5 events per 100 person-years in the documented CVD cohort, and from 2.5 to 2.3 events per 100 person-years in the MI subset.

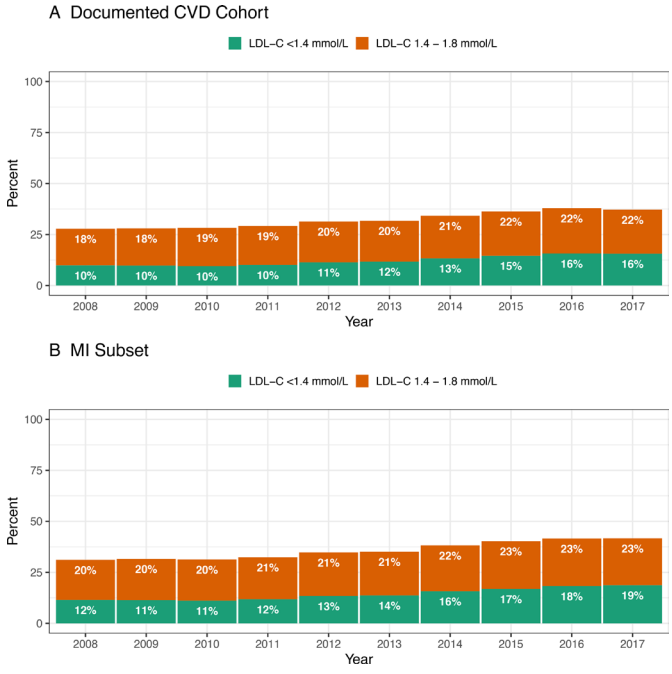

Figure 2 LDL-C <1.8 and 1.4 mmol/L by year and population. CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

DISCUSSION

We observed that the use of high-intensity lipid-lowering therapy increased by two-fold in the overall very high-risk population over the 10-year period, and by 2.4-fold in the MI subset, echoing the increasingly more aggressive goals of the various guidelines introduced during the study period. Furthermore, the 1-year CV event rate that included revascularisation declined over the time period. These are promising findings that indicate that more intensive lipid-lowering therapy goals can be implemented in clinical practice and can improve cardiovascular outcomes. However, despite the increasing use of high-intensity lipid-lowering therapy over the 10-year period, the proportion of very high-risk patients receiving high-intensity therapy was still less than 50% as of 1 January 2017. Furthermore, mean LDL-C and 1-year rates of MI and IS declined only slightly. As a result, it appears that there is room for improvement, particularly with regard to reducing rates of MI and IS. The relatively recent availability of PCSK9 inhibitors may have the potential to improve outcomes, but there was no PCSK9 inhibitor use in our cohort.

These findings are similar to those of other recent studies. In the UK, Curtis *et al* found that the proportion of practices prescribing high-intensity increased from 20% in 2011/2012 to 55% in 2019.[18] This study evaluated prescribing data for all general practice patients, and not

the very high-risk patients in our study, and only evaluated statin therapy. In a large US health system, Sidebottom *et al* studied cohorts of patients age 40–75 in 2013 and 2017, including cohorts of patients with ASCVD.[19] They showed that in patients with ASCVD receiving statin therapy, high-intensity statin use was 39% in 2013 and 50% in 2017. The utilisation rates in Curtis *et al* are higher than our high-intensity therapy rates in the documented CVD population because, similar to Sidebottom *et al*, we classified atorvastatin 20 mg and rosuvastatin 10 mg as moderate intensity based on its estimated 43% reduction in LDL-C. If we were to allocate the 14% using atorvastatin and the 2% using rosuvastatin in 2017 to the high intensity group, our utilisation rates would be similar to Curtis, *et al*. We mention these studies, not to identify differences between the UK and the USA, but to demonstrate that there is room for improvement in both countries. Unfortunately, since neither of these studies estimated cardiovascular event rates, we cannot discuss trends in event rates over time.

Yao *et al*, followed incident cohorts of patients with a first ASCVD event from 2007 to 2016 and used a similar definition for high intensity statins as we did.[20] As with the other studies, the authors showed an increase high-intensity statin use (as a percent of all patients receiving statins) ranging from 25% in 2007 to 49% in 2016. These figures are higher than our high-intensity lipid-lowering therapy estimates in documented CVD cohort. Utilisation of high-intensity statins in the subset of patients with MI, angina or revascularisation was even higher, increasing from 32% to 66% from 2007 to 2016. The authors also estimated the 1-year cumulative risk of a composite endpoint of MI, IS and revascularisation that declined over time from 12% to 10%. Interestingly, although the magnitudes of the absolute risks over time in the populations were different because Yao *et al* used incident ASCVD patients and we used prevalent patients, the risk of the composite endpoint declined modestly (by approximately 20%) over a decade.

For a broader comparison, both geographically and temporally, EUROASPIRE has conducted multiple international surveys of practice patterns and outcomes related to CVD prevention since 1994. The first three surveys, which predated our cohorts and spanned from 1994 to 2007, showed an increase in lipid-lowering therapy utilisation in patients with CVD from 32% to 89%.[21] In the fourth survey (2012–2013), 90% of patients with CVD were treated with lipid lowering therapy on discharge from the hospital, but only 33% were prescribed a high-intensity statin, comparable to the 29%–32% of patients in our MI subgroup for the same years.[22] At the time of the fifth EUROASPIRE survey (2016–2018), approximately half of patients discharged for a coronary event were on a high-intensity lipid-lowering therapy at least 6 months after discharge, which is comparable to the 48% in our MI subgroup in 2017. Importantly, between hospital discharge and the follow-up visit, lipid-lowering intensity was reduced or interrupted in 21% patients. The reason for the change was reported as intolerance to lipid-lowering therapy by 16% and reported as being on advice of their treating physician by 37%.[23] This suggests physician discretion is a potentially modifiable contributor to the results shown in our study.

There are limitations to our analyses. Cardiovascular event rates were measured over a relatively short period of time (1 year). Laboratory values were only available for approximately 55% of the documented CVD cohort. This is generally a practice-level variable related to the availability of a linkage for the practice, and unlikely to indicate substantial selection bias. Furthermore, cardiovascular event rates in patients with no LDL-C values were comparable to those with LDL-C data, and the distribution of low, medium, and high intensity statin use was virtually identical in those with and without LDL-C data (data not shown). We included prevalent patients who received ≥2 prescriptions in the previous calendar year, to avoid biasing the results towards highly compliant patients. Since we know that both intensity and adherence are important to reducing risk, our results reflect some degree of non-adherence, although we did not measure adherence in this study.[15 16] Along these lines, we evaluated prevalent patients who may be reluctant to change their therapy or dose for a variety of reasons including the potential for adverse effects. Note that, because of variations in the number of practices reporting complete data, the raw patient counts were lower for the most recent years.

As a result, these findings should not be interpreted to mean that therapy is not effective; the effectiveness of these therapies has been demonstrated in numerous randomised controlled trials.[24 25] Rather, these findings suggest that it can be challenging to implement aggressive LDL-C reduction in clinical practice with statins alone or with a combination of a statin and ezetimibe. After all, 58% of the MI subset had an LDL-C ≥1.8 mmol/L on lipid-lowering therapy. Instead, these results suggest that a substantial unmet medical need still remains and more efforts are necessary to intensify lipid-lowering therapy to decrease LDL-C in this very high-risk patient population. These results also indicate that PCSK9 inhibitors may be required in patients with the high LDL-C levels to achieve treatment goals recommended by 2019 EAS/ESC guidelines for management of dyslipidaemias. It also underscores the need for other interventions that can reduce the risk of cardiovascular events in these patients, including assistance with appropriate lifestyle modification, better diabetes care, and better adherence to cardiovascular medications.

In conclusion, despite substantial improvement, more than half of patients did not receive high-intensity lipid-lowering therapy by 2017. LDL-C levels remained higher than the treatment goals recommended by the guidelines current at the time. At the same time, while the incidence of revascularisation declined, incidence rates of MI or IS remained virtually unchanged, indicating that a more intensive lipid-lowering treatment is necessary in this very-high risk population. Emphasis should be placed on

understanding why high-intensity lipid-lowering therapy is not utilised more commonly, and clinicians should continue their efforts to further reduce LDL-C in these patients.

Contributors MD, ES, GV, DC, MI, MG, DL and JP contributed to the conception and study design. MD was responsible for data acquisition and was the guarantor for the study which includes full responsibility for the finished work and/or the conduct of the study, the data, and the decision to publish. MG conducted the data analyses. MD, ES and GV were responsible for drafting the initial draft. MD, ES, GV, DC, MI, MG, DL and JP were involved in revising the initial draft and approving the final version. MD, ES, GV, DC, MI, MG, DL and JP agreed to be accountable for the integrity of the research.

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Competing interests Amgen is a manufacturer of lipid-lowering therapies. ES and GV are full-time employees of Amgen (Europe) GmbH and hold stock of Amgen. DC and MI are full-time employees of Amgen and hold stock of Amgen. MD, MG and DL were employed by Outcomes Insights, who was funded by Amgen to conduct this research. JP received honoraria for providing consultant services to Amgen (Europe) GmbH.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by CPRD's Independent Scientific Advisory Committee (ISAC; protocol number 20_041R). The CPRD Division within the Medicines and Healthcare Products Regulatory Agency (MHRA) has received Institutional Review Board approval for all observational research using de-identified CPRD data; therefore, no additional approvals were required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. To ensure patient privacy, the data for this study cannot be shared.

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