Medicines & Healthcare products Regulatory Agency

CPRD

1

General information

Protocol reference Id

22_001872

Study title

Trends and inequalities in statin use for the primary and secondary prevention of cardiovascular disease

Research Area

Drug Utilisation

Health Services Delivery

Does this protocol describe an observational study using purely CPRD data?

No

Does this protocol involve requesting any additional information from GPs, or contact with patients?

No

2 Research team

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Status	Confirmed

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Will this person be analysing the data?	No
Status	Confirmed

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Access to data

Sponsor

London School of Hygiene & Tropical Medicine (LSHTM)

Funding source for the study

Is the funding source for the study the same as Chief Investigator's affiliation?

No

Funding source for the study

British Heart Foundation

Institution conducting the research

Is the institution conducting the research the same as Chief Investigator's affiliation?

Yes

Institution conducting the research

London School of Hygiene & Tropical Medicine (LSHTM)

Method to access the data

Indicate the method that will be used to access the data

Institutional multi-study licence

Is the institution the same as Chief Investigator's affiliation?

Yes

Institution name

London School of Hygiene & Tropical Medicine (LSHTM)

Extraction by CPRD

Will the dataset be extracted by CPRD

No

Multiple data delivery

This study requires multiple data extractions over its lifespan

No

Data processors

Data processor is	Same as the chief investigator's affiliation
Processing	Yes
Accessing	Yes
Storing	Yes
Processing area	UK

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Information on data

Primary care data

CPRD Aurum

Do you require data linkages

Yes

Patient level data

HES Admitted Patient Care

NCRAS data

Covid 19 linkages

Area level data

Do you require area level data?

Yes

Practice level (UK)

Patient level (England only)

Patient Level Townsend Index

Withheld concepts

Are withheld concepts required?
No

Linkage to a dataset not listed

Are you requesting a linkage to a dataset not listed?
No

Patient data privacy

Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?
No

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Protocol information

Lay Summary

Cardiovascular disease, which includes strokes and heart attacks, is a leading cause of death in the UK and globally. Statins have been proven to be effective in reducing cardiovascular events and guidelines recommend the use of statins in those at risk of developing or with known cardiovascular disease. Despite this, previous studies suggest statins are under-prescribed and underused which leads to preventable heart attacks, strokes, and death. Previous studies have shown that certain patient groups such as ethnic minorities and older age groups are less likely to receive treatment. However, trends in statin prescribing and ongoing use in recent years are unclear. Additionally given the potential impact of the COVID-19 pandemic, it is also important to examine how statin use changed during the pandemic.

Our study will use anonymous GP and hospital records to determine the proportion of patients starting and continuing or stopping statins over time between 2009 and 2021. We will explore characteristics associated with statin use. We will also investigate the impact of the COVID-19 pandemic on statin use. This study will provide insight on whether statin guidelines are being followed and which patient groups are missing out on statins or stopping treatment. Our findings will inform strategies to improve statin uptake.

Technical Summary

Statins are effective in the primary and secondary prevention of cardiovascular disease. Guidelines for the primary prevention of cardiovascular disease recommend prescribing statins in those with a 10-year cardiovascular risk score of 10% or higher from 2014 onwards or a 20% risk between 2005 and 2013. Secondary prevention of statins is recommended for all patients who have already had a cardiovascular event. However, previous studies suggest that these medicines are under-prescribed, which results in preventable cardiovascular outcomes and mortality. Previous studies also suggest there are inequalities in statin prescribing with certain patient groups such as ethnic minorities and older age groups less likely to receive treatment. Adherence to statins has been known to be poor thus limiting the potential for cardiovascular disease prevention. In more recent years, statin adherence and uptake may have been impacted by the COVID-19 pandemic which led to a dramatic reduction in access to health care services.

We will use data from the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES) to carry out a cohort study, examining trends and factors associated with statin prevalence, cardiovascular risk scoring and initiation of statins between 2009 and 2021. We will also examine trends and factors associated with statin persistence and cessation and we will estimate the number of cardiovascular events that can be prevented with optimal statin use. We will explore statin prevalence, initiation and persistence in the pre-pandemic and pandemic period. Our study will provide insight on the extent to which cardiovascular prevention guidelines for statins are being implemented, better understanding of any disparities in statin prescribing and inform strategies to improve statin uptake and future planning for pandemics.

Outcomes to be measured

1) Monthly proportion current statin users,
2) Monthly proportion of patients with a recorded cardiovascular risk score,
3) Monthly proportion of first ever statin prescription,
4) Time from initiation to discontinuation of statins.
5) Time from statin cessation to first subsequent statin prescription
6) Number of cardiovascular events prevented with optimal statin use

Objectives, specific aims & rationale

Objective: The overall objective is to investigate trends and inequalities in statin use for the primary and secondary prevention of cardiovascular disease between 2009 and 2021 using CPRD data linked to HES.

Specific aims:

1. To describe the prevalence of statin prescriptions over time, stratified by primary and secondary prevention, patient characteristics, and statin type and dose.
2. Among those eligible for cardiovascular risk scoring, to understand trends in, and factors associated with, recording of a cardiovascular risk score in primary care.
3. To examine statin initiation for primary and secondary prevention over time, and to describe factors associated with statin initiation.
4. To investigate persistence (remaining on therapy) among statin initiators, and to describe patterns of statin adherence, and restarting after stopping a statin.

5. To estimate the numbers of fatal and non-fatal CVD events that could be prevented with more complete uptake of long-term statins among all those eligible for therapy.

Rationale

Statins are widely prescribed for the primary and secondary prevention of cardiovascular disease, however, inequalities in statin prescribing mean certain patient groups miss out on statins and are thus at an increased risk of cardiovascular outcomes. Our study will improve understanding of the extent to which cardiovascular risk guidelines are being implemented. We will establish where along the pathway of identifying eligible patients, initiating statins, and persisting on statin therapy certain patient groups missing out on therapy. Our findings may inform strategies to improve statin uptake, adherence and reduce inequalities in prescribing.

Study background

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, accounting for 32% of all global deaths in 2019 and a quarter of all deaths in the UK.[1, 2] Statins have been shown to be effective pharmacological therapies in reducing cardiovascular disease events and are widely prescribed, with atorvastatin the most commonly dispensed medication in England between 2020 and 2021.[3-7]

Statins are prescribed for the primary and secondary prevention of CVD. In April 2009, National Health Service (NHS) health checks were introduced in England which included cardiovascular risk assessment every 5 years to reduce the risk of CVD. NHS health checks have been associated with greater cardiovascular risk factor detection and higher statin prescribing.[8] From 2014 onwards, National Institute for Health and Care Excellence (NICE) guidelines recommended that individuals with a 10% or higher risk of developing CVD over 10 years were prescribed statins, a change from a 20% or higher 10 year cardiovascular disease risk before 2014.[9] A study of UK primary care records investigated trends in recording of the QRISK2 cardiovascular risk score and statin prescribing. The study found a steady increase in QRISK2 recording between 2012 and 2015, however, the majority of patients with a QRISK2 score were not prescribed statins with only 35% of high-risk patients initiated on statins.[10] Another study using CPRD data found that the proportion of statin initiations with an associated QRISK score increased from less than 5% before 2010-2011 to 66.3% by 2017-2018.[11] However, there is a lack of studies examining trends in cardiovascular risk scoring and statin initiation in more recent years. Trends in statin initiation have been described previously. Two cohort studies using UK primary care data from The Health Improvement Network database (THIN) found that statin initiation rapidly increased from 1995 to 2006 and slowly declined by 2013 and 2015.[10, 12] A similar trend was found in another UK study using CPRD data with a peak in statin initiation between 1998-2005 and a decline thereafter with a slight increase by 2017, after the 2014 statin guideline change.[11] Statin trends beyond this period however are unclear.

Despite the guidelines in the use of statins for cardiovascular disease prevention, previous UK

studies suggest that statins are under-prescribed in individuals at high risk of CVD or overused in those at low risk, with a similar trend also observed in the US.[10, 13-16] Studies have found disparities in statin prescribing with certain ethnic minority groups and older adults associated with lower rates of statin prescribing.[10, 17-22] For secondary prevention, evidence suggests statins are under-prescribed following a cardiovascular event, with disparities in prescribing in terms of age and sex.[23] However, in more recent years it is unclear whether inequalities in statin initiation or cardiovascular risk scoring remain and which patient groups eligible for statins are missing out on treatment. For secondary prevention, it is unclear whether statins are routinely offered after a CVD diagnosis and which eligible patients are not being offered statins.

Persistence to statin therapy is suboptimal and poor adherence is associated with worsening of clinical outcomes and higher healthcare costs.[24, 25] A UK study using CPRD data found that 40% of statin users discontinue treatment, though 70% of those who discontinue restart treatment.[26] Other studies including a Swedish study of stroke patients and a Canadian study of patients without cardiovascular disease also found that use of statin therapy decreases over time in secondary prevention and that patients with higher adherence have a reduced risk of cardiovascular events.[27, 28] Changes in guidelines regarding statin use may have had an impact on statin adherence. As the 2014 NICE guidelines expanded the proportion of patients eligible for statins, it is unclear how these changes in guidelines have affected the proportion of individuals in the 10-20% risk group who had now became eligible for statins and whether these individuals persisted on statins. Statin persistence, initiation and risk recorded may also have been impacted by the COVID-19 pandemic.

The COVID-19 pandemic has led to over 5 million deaths worldwide, with more than 15 million cases and 150,000 deaths in the UK as of January 2022.[29-31] In response to the rising cases of COVID-19, the UK government introduced physical distancing measures on 16th March 2020 and on March 23rd 2020, population wide restrictions were introduced.[32] In primary and secondary care, these restrictions included prioritisation of NHS services, reduced access to primary care and led to patients delaying or avoiding to seek medical help due to fear of contracting or transmitting COVID-19 infection or burdening the NHS. Consequently, these restrictions resulted in a substantial decline in hospital admissions and there was a 40% decline in attendance at the accident and emergency department for acute coronary syndrome by the end of March 2020.[33] A study using data from a Scottish general hospital showed that the COVID-19 pandemic has resulted in a reduction in the provision of cardiac services such as cardiac admissions, procedures, diagnoses and interventions.[34] In a large scale UK primary care study of around 10 million patients, primary care contacts (consultations, diagnoses from hospital discharge letters and secondary care referrals) for various physical conditions including myocardial infarction, stroke and other cardiovascular events, reduced following the introduction of population-wide restrictions.[34-36] This delay in consultations and diagnoses may likely lead to an increase in complications and severity of disease, mortality and missed opportunities for the pharmacological prevention of CVD. A small cohort study of general practices in a deprived city in England showed that the number of new prescriptions for cardiovascular disease declined between March and May 2020,[36] however, to our knowledge, no large-scale nationally representative studies have yet been published investigating the statin prescribing beyond this period or have explored persistence and cardiovascular risk scoring during the pandemic.

We will use data from the CPRD linked to HES to carry out a cohort study, examining trends and factors associated with statin prevalence, cardiovascular risk scoring and initiation of statins between 2009 and 2021. We will also examine trends and factors associated with statin persistence and cessation and we will estimate the number of cardiovascular events that can be prevented with optimal statin use. We will explore statin prevalence, initiation and persistence in the pre-pandemic and pandemic period. Our study will provide insight on the extent to which

cardiovascular prevention guidelines for statins are being implemented, better understanding of any disparities in statin prescribing and inform strategies to improve statin uptake and future planning for pandemics.

Study type

Descriptive
Hypothesis testing (factors associated with statin initiation)

Study design

Historical cohort design

Feasibility counts

We undertook feasibility counts for aims 1-3 using the June 2021 CPRD Aurum build. We used June 2015 as the reference month and year, the midpoint of our study period. Feasibility and sample size calculations are provided in appendix 1 and are discussed below. Codelists for cardiovascular disease are provided in appendix 2.

Aim 1: Monthly proportion of current statin users
From our feasibility counts, we found that by June 2015, 8,178,710 people aged 25 years and older did not have any history of CVD and 685,171 had existing CVD. We used prevalence proportion estimates based on a recent population-based study which found a 25% prevalence of statins in a UK population of adults aged 40-99 years old.[37] We also used more conservative estimates of 15% and 10%.

Aim 2: Monthly proportion of patients with a recorded cardiovascular risk score
For aim 2, there were 7,997,868 individuals aged 25-84 without any history of CVD by June 2015. Based on a previous UK primary care study using The Health Improvement Network (THIN) database by Finnikin et al, we estimated that 11% of patients eligible for CVD risk assessment would be expected to have a recorded risk score.[10]

Aim 3: Statin initiation for primary and secondary prevention
(i) Monthly proportion of statin initiations for primary prevention
We estimated that 6,882 patients would be eligible for statin initiation in a single month based on results from the study by Finnikin et al, which found that 32,405 patients had a 10% or higher 10-year CVD risk between 2014 and 2015 and were thus eligible for statin initiation.[10]
(ii) Monthly proportion of statin initiations for secondary prevention
For secondary prevention, we found that 13,175 individuals had a diagnosis for cardiovascular disease within 56 days of 31/06/2015 and were thus eligible for statin initiation. We estimated the proportions of individuals initiated on statins using from previous studies and a more conservative estimate of 50%.[38, 39]
(iii) Factors associated with statin initiation for primary prevention
We also provide feasibility counts for our analysis on factors associated with statin initiation using ethnicity as an example. There were 24,535,971 individuals aged 25 years and older in CPRD Aurum with linked HES data between 1st April 2009 and 22nd March 2020 with and without CVD. In the pandemic period, 23rd March 2020 to 30th June 2021, there were 9,771,573 people in our study population. Using the 2011 UK census and a previously reported statin initiation of 8.2% for primary prevention among individuals with a 10% or higher 10-year CVD risk, we estimated the minimum detectable odds ratios with an alpha of 0.05 at 80% power using the power twoproportions command in STATA 17.[40]

Sample size considerations

See Feasibility counts and supplementary appendix 1

Planned use of linked data and benefit to patients in England and Wales

Our study population will comprise of only individuals with linked HES Admitted Patient Care (APC) data. Linked HES APC data will be used to improve the identification of cardiovascular events (which are used to define whether a person is eligible for statins as secondary prevention), as hospital admission following a cardiovascular event is likely. We also plan to use linked patient level Townsend score data, as we will stratify our main analyses by deprivation. Our findings may enable us to identify patient groups that are not assessed for CVD risk and groups that are not being prescribed statins according to guidelines for both primary and secondary prevention. In addition, our findings will inform strategies to improve statin uptake, adherence and reduce inequalities in prescribing.

Definition of the study population

Our overall study population will include all individuals aged 25 years and older between 1st April 2009 and 31st December 2021 with linked HES data and at least 12 months research standard follow up in CPRD Aurum. Our study period begins in April 2009 as this corresponds to when NHS health checks, which assess CVD risk and can inform statin prescribing, were first introduced. Our overall study population will include people with and without documented eligibility for statins. Documented eligibility for primary prevention of statins will change over the course of our study period. In accordance with NICE guidelines, from 2014 onwards, those eligible for primary prevention of statins include adults aged 84 years or younger with a 10% or greater 10-year risk of developing CVD. Prior to 2014, individuals with a 20% or greater CVD risk were eligible for statin initiation. Adults aged 85 years and older will also be eligible for primary prevention without the need for cardiovascular risk assessment. For secondary prevention, individuals with a history of cardiovascular disease will be eligible for statin treatment throughout our study. To address the key aims of our study, we will include sub-cohorts specific to each aim.

Aim 1: Prevalence of statins over time
Our primary prevention cohort will include patients without a prior CVD, chronic kidney disease, type 1 diabetes or familial hypercholesterolaemia. The secondary prevention cohort will include individuals with an existing CVD (e.g. past or current history of myocardial infarction, angina, revascularisation procedures, stroke, transient ischaemic attack, or peripheral arterial disease) with diagnoses identified in CPRD or HES using SNOMED codes and ICD-10 codes. Secondary analyses exploring characteristics of statin users and non-users will include all patients in the overall study population mentioned above.

Aim 2: Trends in cardiovascular risk scoring over time

We will include patients aged 25-84 years with no previous statin prescription and no history of CVD, chronic kidney disease, type 1 diabetes or familial hypercholesterolaemia.

Aim 3: Statin initiation for primary and secondary prevention
We will identify patients aged 25 years and older eligible for statin initiation with no previous statin prescription and no cardiovascular event prior to statin initiation. For primary prevention, we will calculate risk scores for all patients and restrict to those with a 20% or higher 10-year risk of CVD after 2014 and a 10% or higher 10-year risk of CVD before 2014, consistent with NICE guidelines on CVD prevention. For the secondary prevention, we will include patients with a statin prescription within 56 days after an incident cardiovascular event.

Aim 4: Persistence, adherence and restarting on statins

We will include patients aged 25 years and older with a first ever statin prescription. Our study population will comprise of those initiating statins for primary and secondary prevention.

For analyses stratifying by the COVID-19 pandemic, the pre-pandemic period will be between 1st April 2009 to 22nd March 2020 and the pandemic period will be between 23rd March 2020 to 31st December 2021. This date was chosen as it is the date when population wide restrictions were introduced in England.[32]

Selection of comparison groups/controls

Our study will be describing trends and factors associated with statin use as such there will be no specific comparator group.

Exposures, outcomes and covariates

Exposures
There is no specific exposure of interest. We will describe trends in statin use over calendar time and explore a range of individual-level factors that may be associated with different aspects of statin use (see also covariates).

Outcomes

Aim 1: Proportion of patients who are current statin users each month. A patient will be defined as a current statin user if they have an ongoing statin prescription based on the number of days prescribed, allowing for a grace period of 28 days.

Aim 2: Proportion of patients with a recorded cardiovascular risk score within the last 5 years with stratification by type of CVD risk score

Aim 3: Proportion of first ever statin prescription for each calendar month. For primary prevention this will be the proportion of first ever statin prescription and for secondary prevention this will be the proportion of first statin prescription within 60 days of CVD event.

Aim 4: For persistence the outcome will be the time to discontinuation of statins. For restarting statins, the outcome will be the time from statin cessation to first subsequent statin prescription.

Covariates

The following covariates will either be used for stratifying our main analyses in aims 1-4 and/or as factors associated with initiation and persistence. These covariates will include:
• Age (25-39, 40-49, 50-59, 60-69, 70-79, 80+, using patient file in CPRD)
• Sex (male, female) - using patient file in CPRD
• Ethnicity (White, black, South Asian, mixed ethnicity and other using data from CPRD or HES)
• Townsend deprivation scores (quintiles ranging from least deprived to most deprived, using linked Townsend score data)
• BMI (underweight, <18.5, normal weight 18.5-25, overweight/obese >25, additional file in CPRD)
• Systolic blood pressure, mm Hg (additional file in CPRD)
• Diastolic blood pressure, mm Hg (additional file in CPRD)
• Total cholesterol – (normal <5 mmol, moderate-high 5-8 mmol and high >8 mmol - additional file in CPRD)
• High-density lipoprotein (HDL) cholesterol, mmol (using additional file in CPRD)
• Low-density lipoprotein (LDL) cholesterol, mmol (using additional file in CPRD)
• Smoking status - (Non-smoker, ex-smoker and current smoker using additional file in CPRD)
• Family history of coronary heart disease - SNOMED codes in CPRD clinical file and HES ICD-10 codes data
• Type 2 diabetes - SNOMED codes in CPRD clinical file and HES ICD-10 codes data
• Diagnosed hypertension - SNOMED codes in CPRD clinical file and HES ICD-10 codes data
• Atrial fibrillation - SNOMED codes in CPRD clinical file and HES ICD-10 codes data
• Rheumatoid arthritis - SNOMED codes in CPRD clinical file and HES ICD-10 codes data
• Chronic kidney disease - SNOMED codes in CPRD clinical file and HES ICD-10 codes data
• Polypharmacy – BNF chapters in CPRD prescriptions file
• Duration in GP registration – using data in patient and practice files in CPRD
• Consultation rate – using data in consultation file in CPRD
• Charlson index – using SNOMED codes in CPRD clinical file
• Cardiovascular risk score levels (0-10, 10-20, 20-30 and 30+, using QRISK2 scores obtained using patient, clinical and additional file)
• CVD phenotype which will include coronary heart disease; angina, myocardial infarction); cerebrovascular disease (ischaemic and haemorrhagic stroke, transient ischaemic attack, non-stroke cerebrovascular disease); peripheral arterial disease (abdominal aortic aneurysm, intermittent claudication); heart failure. Obtained using SNOMED codes in CPRD clinical file and HES ICD-10 codes data

Data/statistical analysis

Aim 1: Prevalence of statins over time

In patients aged 25 years and older between 2009 and 2021, we will describe the overall proportion of individuals with a current statin prescription each calendar month. In subgroup analyses, prevalence will be stratified by age, sex, ethnicity, deprivation (using Townsend deprivation scores) and CVD history. We will use descriptive analyses to compare the characteristics of statin users and non-users in terms of explanatory factors specifically; age, sex, ethnicity, deprivation, primary and secondary statin prevention, CVD phenotype, statin type and statin intensity. A statin user will be defined as a patient with at least one statin prescription in the last three months.

Aim 2: Trends in cardiovascular risk scoring over time

Using all available cardiovascular risk assessment tools (QRISK, QRISK2, Framingham, Joint British Society, ASSIGN, or unspecified), we will describe the monthly proportion of individuals with a recorded cardiovascular risk score in the last 5 years and stratify by age, sex, ethnicity, deprivation, type of cardiovascular risk score. We will describe the proportion of patients eligible for statins without a recorded cardiovascular risk score and examine the descriptive characteristics of these patients. To identify the patients eligible for statins, we will generate QRISK2 scores for all patients using risk factors identified in patients' CPRD medical records specified in the QRISK2 algorithm (such as age, sex, ethnicity, deprivation etc). These variables will then be used to calculate an individual's 10-year risk of cardiovascular disease. In final analyses, we will explore the presence and level of GP recorded cardiovascular risk scores, time in GP registration, consultation rate and Charlson index. Given that NHS health checks are carried out among those aged between 40-74 years, we will stratify our analyses for this aim by age group (25-39, 40-74 and 75-84).

Aim 3: Statin initiation for primary and secondary prevention

We will describe monthly statin initiation according to level of GP-calculated cardiovascular risk or cardiovascular phenotype and patient level characteristics. We will consider a 20% or higher 10-year cardiovascular risk before 2014 as the treatment threshold for statin CVD prevention and a 10% or higher risk as the statin treatment threshold from 2014 onwards in accordance with changes in NICE guidelines. We will then calculate a QRISK2 score for all patients based on the data available in the patients' clinical records and compare patients that have and have not been formally risk scored by their GP. We will describe the proportion of eligible patients who initiate statins. For primary prevention, statin initiation will be defined as having a first statin prescription within 28 days of a first recorded risk score above the guideline high-risk threshold. For secondary prevention, statin use will be defined as having a first statin prescription within 60 days of a cardiovascular event. We chose a 60-day grace period between cardiovascular event and subsequent statin prescription to account for patients who may be initiated statins in secondary care and may wait until they have used up their prescription before getting a statin prescription in primary care. We will examine which factors are associated with initiating a statin prescription using logistic regression. In this analysis we will stratify analyses for the pre-pandemic and pandemic period. In further secondary analyses, we will quantify the impact of the first lockdown on statin initiation using interrupted time series analysis with the interruption on the date of the first UK lockdown (23rd March 2020). Lastly, we will explore statin initiation among patients without documented eligibility and examine characteristics of those who initiate statins compared to those who do not initiate.

Aim 4: Persistence, adherence and restarting on statins

We will identify patients with a first ever statin prescription. Then:

a) We will Investigate the time from first statin prescription to first cessation of statins. We will first describe cumulative incidence of statin cessation using Kaplan Meier curves. We will then explore explanatory variables to understand predictors of cessation using flexible parametric survival

models. Cessation will be defined as reaching the end of a pre-specified grace period without a new prescription.
b) For restarting of statins, we will quantify the time from statin cessation to first subsequent statin prescription using Kaplan Meier curves.
c) We will use the refill compliance rate to explore medication adherence among patients continuing statin use. The refill compliance rate will be calculated using the total number of days of medication supplied divided by the number of days from the first and last prescription.[41]
d) We will also explore the reasons for stopping treatment by describing the frequency of muscle symptoms (such as muscle stiffness, pain, cramps, weakness or loss of strength) associated with statin cessation in the primary and secondary prevention cohorts.
Analyses will be run separately for primary and secondary prevention groups and we will stratify analyses by pre-pandemic period (before 23rd March 2020) and pandemic period (23rd March 2020 onwards).

Aim 5: Estimation of the numbers of CVD events that could be prevented

We will estimate the number of CVD events that can be prevented with optimal statin use using rate ratios from the most recent meta-analysis of randomised controlled trials to the age- and sex-specific event rates seen in the untreated eligible populations, scaled up to the UK population size using the 2011 Census.[3, 42] In a secondary analysis, we will also use the NHS Drug Tariff to estimate the drug cost of full coverage of those currently taking statins in our study and for

everyone eligible for statins. For this analysis, we will match each statin to its corresponding cost record in the drug tariff and calculate the total cost of statins using the cost per unit of statins and the quantity of statins prescribed in the CPRD prescriptions dataset.

Plan for addressing confounding

This study will describe trends in statin use, therefore, no causal inference will be sought and confounding will not be addressed. However, we will be looking at factors associated with statin initiation by carrying out stratified analyses, and fitting covariates into regression models, as outlined in the previous sections.

Plans for addressing missing data

We expect some missing data on the recording of certain variables such as cholesterol, smoking status and BMI. These data are unlikely to be missing at random as GPs are more likely to record information with clinical implications (e.g. current smoking, BMI in the obese range) thus multiple imputation may be biased. We will therefore conduct a complete case analysis which is valid providing missingness is independent of the outcome under study. We will discuss this approach and our assumptions in our outputs. For aims 2 and 3 in which we will calculate our own QRISK2 scores, our algorithm will use a population-average imputation approach to handle missing data, reflecting the QRISK2 algorithm in clinical practice.

Patient or user group involvement

We have not involved patient or user groups in developing this protocol. Our study will examine the extent to which cardiovascular prevention guidelines are implemented by clinicians which will provide insight on whether the clinical practice of prescribing statins is aligned with clinical guidelines and whether there are disparities in statin prescribing. Given that the focus of our study will be on clinical practice rather than patient behaviour, and resource limitations, we decided not to prioritise patient involvement at the protocol/design stage. However, we will consider patient or user group involvement in the dissemination stage of this research.

Plans for disseminating & communicating

We will disseminate our findings at relevant conferences, events, meetings and we will submit our results for publication in a peer reviewed journal.

Conflict of interest statement

We have no conflict of interest to declare.

Limitations of study design

There are a number of limitations to this study. First missing data, particularly for cardiovascular risk scores, is likely to be an issue. Although recording of cardiovascular risk scores such as QRISK2, has increased since its introduction, previous studies suggest cardiovascular risk scores are underused in primary care.[10, 43] To maximise inclusion of eligible patients into our study, we will use all relevant cardiovascular risk scores rather than just one specific risk score. Second, previous studies have found substantial variability in the prediction of individual CVD risk prediction using QRISK models.[44] These models have been found to have limited generalisability and accuracy in terms of estimating individual cardiovascular risks in heterogeneous settings.[45] However, QRISK models have been previously validated, are better calibrated for the UK population and provide more appropriate estimates for CVD risk prediction than Framingham and ASSIGN models.[46] Third, misclassification of statin use is possible. Although medicines prescribed by the GP are automatically recorded in CPRD, it is not clear whether patients collected their prescription and/or took the medication as prescribed thus there are challenges in measuring persistence to statin treatment. Fourth, low dose statins that have been approved for over-the-counter use since 2004 will not be captured in our study which can also lead to misclassification. However, low dose over the counter statins are generally not made available by pharmaceutical companies and have a low uptake.[47, 48] Fifth, data on statin initiation will only be available in primary care thus we will be unable to capture prescriptions initiated in secondary care. To account for this delay, we will identify prescriptions issued within 60 days of a cardiovascular event for analyses on secondary prevention of statins. Sixth, we will not have data on whether a patient was offered statin treatment and refused but rather on the recording of a cardiovascular risk score and whether a statin prescription was issued or not. Therefore, in this instance, it will be unclear whether the absence of a statin prescription in those with a high cardiovascular risk score was due to the prescriber failing to offer treatment or the patient refusing treatment. Seventh, it is likely that the reasons for statin cessation may not be well-recorded in primary care as some patients may not consult their GP on the reason for stopping treatment. In addition, the GP may record the reason a patient has stopped treatment as uncoded free text which is unavailable to researchers as it may contain identifiable information.

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Appendices

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