**Assessing the Impact of Cardiovascular Disease through Medicines**

* **ANALYSIS PLAN**
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**Background:**

Cardiovascular disease (CVD) remains the most common cause of mortality and morbidity in the UK despite advances in both prevention and acute treatments. The numbers of acute CVD events admitted to acute care settings during the first phase of the COVID-19 pandemic fell, which followed trends in other diseases as well as GP attendances. The indirect effects of COVID on CVD are yet to be fully experienced or measured. Some of these estimates may not be available for many years and it therefore may be difficult to judge in the short term what these impacts might be for individuals as well as the health economy.

What is even more intangible are the reduction in treatment of CVD risk factors which, when adequately controlled, reduce the number of CVD events. For example, high blood pressure accounts for half of all myocardial infarctions (MI) and strokes; having atrial fibrillation (AF) makes it five times more likely that an individual will have a stroke; and in those with diabetes (when adequately diagnosed), CVD is the leading cause of morbidity and premature mortality.

Detection and treatment of risk factors has until now been through the Quality and Outcomes Framework (QOF), CVD health checks, and opportunistic screening most commonly in primary care. A Health Foundation analysis (using Clinical Practice Research Datalink, CPRD https://www.health.org.uk/news-and-comment/charts-and-infographics/use-of-primary-care-during-the-covid-19-pandemic) demonstrated that primary care visits fell an average of 30% from March-June 2020 with many of the existing visits being replaced by e- or telephone-consults. Primary care prescription pathways were also significantly affected, with repeat prescriptions spiking a week before the March lockdown and a reduction of new prescriptions following this.

Medicines are the method by which most conditions are treated and or prevented. This is particularly true of chronic, long term conditions like CVD where control of risk factors can have a significant impact. If CVD risk factors are not being adequately detected and/ or treated this will logically lead to more CVD events in the future. Therefore, the reduction in new prescriptions for CVD risk factors could be used to model the impact on CVD to come.

In this proposal we seek to begin to estimate the changes in prescribing of drugs used for CVD and its major risk factors (high blood pressure, hyperlipidemia, atrial fibrillation, type II diabetes) at several time points prior to and during the COVID-19 pandemic to begin to estimate the longer-term effects this may have on CVD in the future.

**Research Question:**

**Can medicines that are used to treat and/ or prevent CVD be used as a proxy to estimate the future CVD events?**

**Rationale:** We will use GPES extracts linked to dispensing data to estimate the change in prescribing in drugs used for the treatment and/ or prevention of CVD during the course of the COVID-19 pandemic. Knowledge of the patterns in the prescription of CVD drugs will inform understanding of the indirect impact of the COVID-19 pandemic on the control of CVD and its risk factors in the population, and can be used to model the likely impact on future CVD events in the UK population.

**Objective 1:** To describe patterns in monthly prescription and dispensing of CVD medicines before and during the COVID-19 pandemic; how these may vary from each other and according to other co-variates of interest such as sex, age, geographical region, ethnicity.

**Study Population:** The population resident in Wales, Scotland, England and Northern Ireland, aged 18 years or older registered with primary care practices who have opted into data linkage. Analyses will be restricted to individuals with the following criteria: (i) those registered with a primary care practice on or after 1 January 2018, (ii) had “GPES research quality acceptable” data at the time of study entry, (iii) aged 18 years or older on or after 1 January 2018, (iv) with recorded female or male gender, (v) with a valid pseudo-identifier id available. Analysis end date will be the latest available monthly download at time of analysis.

**Exposures:** Medications will be extracted from the primary\_care\_meds and GDPPR (GPES Data for Pandemic Planning and Research) datasets. We will include medications commonly prescribed for CVD, diabetes, and their risk factors, following the BNF framework assigning medicines to their primary indication. BNF codes will mapped to relevant codes for extraction depending on the format of the dataset (e.g. SNOWMED in GDPPR). Date closest to prescription by GP/ dispensing to patient will be recovered (rather than system collection or processing date). We will initially focus on frequency of dispensing and prescribing (monthly counts); but subsequently consider the relevance of changes to medication quantity/ dosing/ scheduling.

Medicines will be selected from British National Formulary (BNF0 Chapters 2 (Cardiovascular System) and 6 (Endocrine System) and categorised into 11 CVD sub-groups: Antihypertensives, Antiplatelets secondary prevention (primary for DM), DOAC, Warfarin, Heparins, Lipid lowering, T2DM, Insulin, Heart failure, AF, Angina

**Outcomes:** This is primarily a descriptive rather than analytical analysis, although we will investigate how prescribing and dispensing patterns may vary according to other socio-demographic covariates

**Covariates:**

* Age (categorised ≥18-29 and thereafter in 10 year age bands to 90+ years)
* Gender
* Geographical region (categorised as East Midlands, East of England, London, North East, North West, South East, South West, West Midlands, Yorkshire and The Humber, plus Scotland and Wales)
* Ethnicity (categorised as White, Asian, Black, Mixed and Other)

**Analyses:** Monthly counts and their percentage change will be calculated for each of the 11 CVD medicines sub-groups for both prevalent and incident medications and stratified by covariate sub-groups (secondary). R heatmap() / ggplot2 will be used to provide visualisations of the data (columns=months; rows=years).

Incident medicines will be identified as the first recorded per person occurrence of a dispensed medicine within each CVD sub-group during the study period, allowing an initial clearance window for the first year of data availability to allow monthly incidence counts to stabilise. Individuals may be counted as receiving incident medication for more than one of the CVD medicines sub-groups. Differences in the number of incident medications by CVD sub-group in the post-pandemic period will be calculated by subtracting the monthly count from the equivalent monthly count in 2019.

**Sensitivity analyses:** To account for the potential impact of higher mortality due to the COVID-19 pandemic itself, in sensitivity analyses we will exclude medications dispensed to individuals who died from COVID-19 and, separately, from any cause across the study period.

**Objective 2:** To model disruption in trends in weekly prescription and dispensing of CVD medicines due to the COVID-19 pandemic at the population level using interrupted time-series analysis.

**Study Population:** The population resident in Wales, Scotland, England and Northern Ireland, aged 18 years or older registered with primary care practices who have opted into data linkage. Analyses will be restricted to individuals with the following criteria: (i) those registered with a primary care practice on or after 1 January 2018, (ii) had “GPES research quality acceptable” data at the time of study entry, (iii) aged 18 years or older on or after 1 January 2018, (iv) with recorded female or male gender, (v) with a valid pseudo-identifier id available. Analysis end date will be the latest available monthly download at time of analysis.

**Outcome:** Weekly counts for prescribed medications will be calculated for each CVD risk factor (following the same data preparation pipelines as Objective 1).

**Analyses:** Interrupted time-series analysis (ITS) will be used to model the population level changes in medication prescription trends following the onset of the COVID-19 pandemic (Lopez Bernal, J et al., 2017). Weekly counts data will be modelled from June 2018 to May 2021. Preliminary inspection of data using scatterplots will be undertaken to help identify the underlying trend and outliers. A priori segments for anticipated regular effects associated with Christmas and New Year each year. Segments corresponding to the four-week periods prior to national lockdowns will be introduced (23rd March 2020, 5th November 2020) and one week prior to the final lockdown (6th January 2021; shortened due to overlap with the Christmas & New Year period 2020-21). To account for possible non-stationarity and autocorrelation in the data, ARIMA models will be fitted to each CVD medicines sub-group following Schaffer et al. (2021)23 Evidence of autocorrelation will be assessed through examination of the residuals, autocorrelation plots and with Durbin’s and Breusch Godfrey tests. Analysis will be undertaken using the auto.arima function from the forecast package in R

**Covariates:** A strength of ITS is that it is typically less affected by common confounding variables (e.g. age, sex etc.) as these change slowly over time. These will be taken into account during the modelling of the underlying long term trend, alongside relevant time-varying confounders (e.g. seasonality).

**Objective 3:** **To estimate the impact of missed treatment on future CVD events**

The potential impact of missed cardiovascular risk factor treatment on CVD events will be estimated using the most recent cost-effectiveness analysis model developed for the National Institute of Health and Care Excellence (NICE) (NICE guideline NG136) for hypertension as an example, adapting the base case to reflect characteristics of the hypertensive population not receiving incident medication due to the pandemic. Characteristics of the 2019 population receiving incident antihypertensive medication (mean age and proportion male/female, with T2DM and smokers) will be entered into the QRISK2 calculator to calculate the weighted 10-year QRISK2 scores for the NICE treatment effect model base case, additionally specifying SBP at 150mmHg (the threshold for stage 2 antihypertensive treatment using home blood pressure monitoring). Inputting these 10-year QRISK2 scores into the NICE model, we will calculate the number of CVD events expected with and without hypertensive treatment (including stratification by stable and unstable angina, MI, transient ischaemic attack, stroke and heart failure). This will be scaled to the number of people with missed incident hypertension treatment observed in our analyses across the whole populations of England, Scotland and Wales.