Covid19 indirect impacts on cardiovascular health: rapid analytics using linked electronic health records

Protocol Synopsis

CVD Health Working Group

11 November 2022

Aim and study objectives

The aim of the study is to explore the hypothesis that higher than expected deaths after the Covid19 pandemic are at least partly caused by gaps in the diagnosis and management of major cardiovascular risk factors (hypertension and atrial fibrillation). The study will be a descriptive epidemiology study using the linked healthcare records of the adult population of England contained within the BHF-HDRUK CVD-COVID Trusted Research Environment

	Objectives
1	To describe the trends in incident diagnoses of hypertension and atrial fibrillation between November 2019 and March 2022 among the adult population of England, overall and in subgroups of interest
2	To estimate the incidence rates of acute myocardial infarction and acute stroke between November 2019 and March 2022 among the adult population of England, overall and in subgroups of interest
	Not included in initial analysis but may be carried out after Obj 1 & 2 have been completed:
3	To describe the trends between November 2019 and March 2022 in the frequency of repeat blood pressure measures recorded in the primary care electronic record in the 12 months after a new diagnosis of hypertension
4	To describe the patterns of secondary prevention treatment and monitoring in patients with established cardiovascular disease (Coronary artery disease, MI, stroke, heart failure, peripheral vascular disease) before, during and after the Covid19 pandemic

Study populations

Inclusion and Exclusion Criteria

Patients will be included in the analysis cohort if they meet **ALL** of the following inclusion criteria:

- Alive and aged ≥ 18 years on 1st November 2019[1]
- Registered with a GP practice[2] in England on 1st November 2019
- No history of a diagnosis of hypertension or atrial fibrillation at any time prior to 1st November 2019
- Have data linkage between the primary care electronic health record data and Hospital Episode Statistics in the BHF HDRUK CVD-COVID Trusted Research Environment

Patients will be excluded from the analysis cohort if they meet **ANY** of the following exclusion criteria:

- Missing information about sex or age or date of birth

1. Patients who died prior to November 2019 are not included in the CVD-COVID TRE. The inclusion criteria and index date have been chosen to avoid the risk of selection bias this might cause
2. Using definitions for ascertaining GP registration developed for previous study in the CVD-COVID TRE

Subgroups

The analyses will be carried out in the overall cohort and the following subgroups of the overall cohort:

1) Geography (*e.g. ICB and small area such as LSOA/MSOA feasibility permitting*)
2) Age at index (*Categories: 18-40, 41-50, 51-60, 61-70, 71-80, ≥ 81 years*)
3) Sex (*Categories: Male, Female*)
4) Ethnicity (*Using existing ethnicity categories defined in the CVD-COVID TRE*)[1]
5) Index of Multiple Deprivation (*Deciles*)
6) Cardiovascular comorbidity at baseline (*Categories: Prior stroke or MI, No prior stroke or MI*)

1. More granular ethnicity categories may be explored in addition (e.g. 16 category ethnicities already defined in the TRE)

Study design

- The study will be a retrospective cohort study using the BHF HDRUK CVD-COVID Trusted Research Environment ("CVD-COVID TRE").
- This will be a closed cohort design, where all patients in the cohort are followed up from the same index date (1st November 2019)

Parameter	Definition
Index date	Date of cohort entry and the start of follow up For Objectives 1 and 2, the index date is the 1st November 2019 For Objective 3, the index date is the date of incident hypertension diagnosis
Follow-up and censoring	Patients will be followed up until the first of death, 31st March 2022 or observed exit from the data source
Study time period	End: 31st March 2022
Lookback	All available information prior to 1st November 2019 will be considered in identifying participants' characteristics at index date.

Case definitions and variables

*Wherever possible, all case definitions will **use phenotypes already defined within the CVD-COVID TRE** and used in the current studies being carried out with this data source*

Main exposures and outcomes	Variables included in descriptive statistics and potential model covariates

• Incident diagnosis of hypertension
• Incident diagnosis of atrial fibrillation
• Hospital admission with a primary diagnosis of acute myocardial infarction
• Hospital admission with a primary diagnosis of stroke (ischemic stroke or primary intracerebral haemorrhage)
	• Age at index
	• Sex
	• Index of Multiple deprivation
	• Ethnicity
	• Comorbidity:
	  ○ Type 2 diabetes mellitus
	  ○ Hyperlipidemia
	  ○ Chronic heart failure
	  ○ Peripheral vascular disease
	  ○ Chronic kidney disease
	  ○ Myocardial infraction
	  ○ Stroke
	  ○ Comorbidity burden score (using definitions already developed for the CVD-COVID TRE)

Objective 1 Analysis Methods

All analyses will be carried out in the overall cohort and in the pre-specified subgroups:

1) Descriptive statistics:
   a) Characteristics of the cohort at index
   b) Characteristics of the patients at incident diagnosis of hypertension
   c) Characteristics of the patients at incident diagnosis of atrial fibrillation
2) Monthly[1] crude and age/sex standardized[2] incidence rates (plotted as a time series) for:
   a) Hypertension
   b) Atrial fibrillation
3) If there appears to be a meaningful change in incidence rates based on visual inspection of the data, this may be formally analyzed in an interrupted time series analysis

<u>Sensitivity analyses:</u>

4) Repeat (1b and 2a) using QOF codelists for hypertension, to align with the analysis of QOF hypertension data also being carried
5) Repeat (2a and 2b) using an index date of 1 Jan 2019 to allow seasonal patterns of diagnosis to be observed

1. Larger time intervals (e.g. 3 months) may be required depending on the size of subgroups
2. Standardized to the European Standard Population. Mid year ONS population estimates will be used for estimating incidence rates.
3. Note that this cohort will be at risk of selection bias for the Jan-Nov 2019 period due to the exclusion of patients who died prior to Nov 2019, but the intention is that this sensitivity analysis will allow for some understanding of how seasonal patterns in diagnosis may affect the main analysis

Objective 2 Analysis Methods

All analyses will be carried out in the overall cohort and in the pre-specified subgroups:

1) Descriptive statistics:
   a) Characteristics of the patients at first acute MI event after index
   b) Characteristics of the patients at first acute stroke event after index
   c) Characteristics of patients with and without an incident diagnosis of hypertension at first CV event (MI and stroke, separately) after index
   d) Characteristics of patients with and without an incident diagnosis of atrial fibrillation at first acute stroke event after index

2) Monthly crude and age/sex standardized incidence rates for acute MI and stroke after index (Larger time intervals if required for smaller subgroups), plotted as a time series

3) Monthly descriptive characteristics of patients with acute stroke or MI:
   1) Median age (and/or % in age categories of interest)
   2) % female
   3) Prevalence of comorbidities of interest

4) Crude and age/sex standardized incidence rates of acute MI and stroke after incident diagnosis of hypertension and atrial fibrillation

Study planning for Objectives 3 and 4

- Whilst Objectives 1 and 2 are being carried out, the working group will discuss and scope out Objectives 3 and 4
- The aim will be to develop a protocol synopsis for these objectives, which could be carried out either as a follow on to the rapid analytics work (e.g. in Q1 2023) or be developed further into a full research programme
- The clinical members of the working group have highlighted that Objective 4 as a likely driver of excess mortality, and this will be prioritized over Objective 3

Timelines

	Week commencing											
	7 Nov	14 Nov	21 Nov	28 Nov	5 Dec	12 Dec	19 Dec	26 Dec	2 Jan	9 Jan	16 Jan	23 Jan
Protocol synopsis												
CVD-COVID TRE study approvals (Protocol amendment & review)												
Setting up and onboarding new TRE analysts												
Data management and analysis plan												
Data analysis												
Working group review of results						Interim					Final	
Reporting: Objective 1 & 2												
Objective 3 & 4 planning												

Although some work may continue over the holiday period, we are assuming that progress will slow over this three week period

Members of the working group

LCP INSIGHT CLARITY ADVICE

Jonathan Pearson-Stuttard
Cathie Sudlow
Tom Porter
Ben Bray
Kate Cheema
Jenni Quint
Julia Critchley
Vahe Naifilyan
Reecha Sofat
Ami Banerjee
Alison Barnett
Alasdair Wood
Angela Wood
Will Whitely