TITLE

The impact of the COVID-19 pandemic on cardiovascular disease prevention and management

AUTHOR LIST

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ABSTRACT

How the COVID-19 pandemic has affected prevention and management of cardiovascular disease (CVD) is not fully understood. Here, we use medication data as a proxy for CVD management using routinely collected, de-identified individual-level data comprising 1.32 billion records of community-dispensed CVD medications from England, Scotland and Wales between April 2018 and July 2021. We describe monthly counts of prevalent and incident medications dispensed, as well as percentage changes compared to the previous year, for a number of CVD-related indications, focusing on hypertension, hypercholesterolaemia and diabetes. We observed a decline in the dispensing of anti-hypertensive medications between March 2020 and July 2021, with 491,306 fewer individuals initiating treatment than expected. This decline was predicted to result in 13,662 additional CVD events, including 2,281 cases of myocardial infarction (MI) and 3,474 cases of stroke, should individuals remain untreated over their lifecourse. Incident use of lipid-lowering medications decreased by 16,744 patients per month during the first half of 2021 as compared to 2019. By contrast, incident use of medications to treat type-2 diabetes (T2DM), other than insulin, increased by approximately 623 patients per month for the same time period. In light of these results, methods to identify and treat individuals who have missed treatment for CVD risk factors and remain undiagnosed are urgently required to avoid large numbers of excess future CVD events, an indirect impact of the COVID-19 pandemic.

236 words

INTRODUCTION

Cardiovascular disease (CVD) remains the commonest cause of mortality and morbidity worldwide; it is therefore vital to understand the impact of the COVID-19 pandemic on CVD and its risk factors. In the UK, strategies for CVD prevention include screening for health conditions and risk factors that can be modified through medication, including Type-2 diabetes (T2DM), hypertension, hypercholesterolaemia, and atrial fibrillation (AF). When adequately controlled, such measures reduce the level of CVD in the population.

The COVID-19 pandemic has disrupted health care in multiple ways, putting additional pressure on both primary and secondary care services[1-4]. How these have impacted on screening and treatment of common risk factors, including CVD risk factors, and the downstream impact of missed detection of risk factors in terms of CVD outcomes including myocardial infarction (MI) and stroke remains under-studied at a national level[5].

Examining the change in prescribed and dispensed medications used to treat CVD risk factors over the course of the COVID-19 pandemic can be used to assess the impact on future CVD events of not treating these risk factors. This approach is complementary to studying reduction in the level of disease diagnoses and risk factor control. The latter is harder to track, given reductions in testing during the pandemic, and so medication changes may provide a closer representation of the real-world control (or lack thereof) of CVD risk factors within the population, following the patient pathway from diagnosis, through prescription, to dispensing of medication, to the treatment of the condition.

In this study, we investigate the impact of the COVID-19 pandemic on non-COVID harm in eleven sub-populations, specifically the management of CVD defined by medications. By highlighting monthly trends in first (incident) medication use, we can understand changes in the rate of identification of actionable CVD risk factors and reduced control within individuals due to the pandemic. Using the UK's comprehensive national medical records, which can track health over the life course, we show, for the first time across >60M people in England, Scotland and Wales, how a data-informed medicines-based treatment approach can provide precise and comprehensive quantification of the reduction in the treatment of CVD risk factors due to the pandemic.

RESULTS

Data

We studied de-identified individual-level population-scale data from England, Scotland and Wales accessed through the respective national Trusted Research Environments (TREs), i.e. NHS Digital's TRE for England (referred to throughout as 'the English TRE'), the Scottish National Safe Haven and the SAIL Databank. Motivated by the public health importance of understanding the relationship between COVID-19 and CVD, the Health Data Research UK (HDR UK) British Heart Foundation (BHF) Data Science Centre (DSC) established the CVD-COVID-UK consortium and related research programme[6,7]. Through this initiative, linked, nationally-collated electronic health record (EHR) data for the population of England, Scotland and Wales have been made available to support research into the impacts of CVD on COVID-19 and vice versa. Details of the collaboration and the data included within each of the national TREs are described in full elsewhere (https://www.hdruk.ac.uk/projects/cvd-covid-uk-project/)[8].

Figure 1 describes the selection of data from the source to the analytical datasets, specifying the inclusion criteria applied such as valid pseudo-identifier ID required for incident and stratification analyses.

Trends in the dispensing of CVD medications:

We present results for the four CVD medication sub-groups of antihypertensives, lipid-lowering medications, T2DM and insulin since these represent the major CVD risk factor / disease groups in the population. Additional tables and figures for the remaining seven CVD medication sub-groups are available in the **Extended Data** (AF, angina, DOACs, warfarins, heparins, antiplatelets and heart failure).

Overall, we observed a downward trend in CVD medications dispensed over the course of 2020 and into 2021 suggesting a decline in the active management of CVD in the population (**Figure 2**). There was an increase in total items of medications dispensed for the combined CVD medications sub-groups of hypertension, dysliplidemia and diabetes (including insulin) in the immediate pre-pandemic period (+11.8% March 2020 versus March 2019) (**Figure 2; Supplemental Table 1**). This compared to annual monthly percentage change ranging between -1.4 and 4.9% in the year before pandemic onset. Year-on-year dispensing did not fall below 2019 levels until May 2020 when initial lockdown restrictions were beginning to be relaxed. Dispensed items again fell below 2019 levels in August 2020 (-9.3%), October 2020 (-1.2%) ahead of the second national lockdown and November 2020 (-0.3%). In comparison, year-on-year dispensing was 4.7% higher in December 2020 ahead of the third national lockdown. The number of medications was below the previous year throughout early 2021 until April. Mean quantity per dispense remained stable over time within most CVD medications sub-groups, except for a brief increase in March 2020, followed by a smaller decline in April 2020 (**Extended Data Figure 1**).

Trends by CVD medications sub-groups, proxied by prevalent medications:
The general pattern of sharp growth in year-on-year medications dispensed in the pre-pandemic period followed by dispensing below 2019 levels in May 2020 is seen across the CVD medication sub-groups (**Figure 2**). The most marked spike was observed for insulin at +24% in March 2020, followed by dispensing levels below 2019 in May and August 2020. Marked changes were also observed for dispensing of anticoagulant medications with an acceleration in the decline in warfarin during 2020-21 after an initial spike in March 2020 (**Extended Data Figure 2)**. In contrast DOAC dispensing maintained year-on-year growth, but the rate of growth declined (**Extended Data Figure 2**).

Dispensing trends by socio-demographic characteristics are presented in **Extended Data Figures 3 & 4 and Supplemental Table 2**). A valid pseudo-identifier ID is required for linkage with individual demographic characteristics; the proportion of data linked increased over time within the English dispensed data (**Extended Data Figure 5**) and this should be considered when interpreting socio-demographic trends. Data were missing on region for 6.5% of dispensed CVD medications and on ethnicity for 1.6%. The highest year-on-year uplifts ahead of the first national lockdown were observed in the age bands 18-29 and 30-39. Similar patterns were observed in males and females. Yorkshire saw the most pronounced year-on-year uplift in dispensed medications associated with the first national lockdown and further subsequent peaks in June-July and September reflecting additional local restrictions during those times. London also saw more marked uplifts for subsequent peaks compared to other regions, including in December, coinciding with the earlier local introduction of Tier 4 restrictions[26]. Similar trends were observed in Scotland and Wales with marked change in year-on-year dispensing associated with the first national lockdown. Black individuals had a delayed uplift in dispensing with year-on-year growth peaking in April 2020 rather than March.

Interrupted time-series analyses
We observed a sharp increase in the prescription of CVD medications in England prior to the first national lockdown, similar to increases characteristically observed prior to Christmas (**Extended Data Figure 6**). However, unlike Christmas there was no clear subsequent drop in medications prescribed in the week(s) immediately following. The period between the first and second national lockdowns was characterised by declining CVD prescriptions, and, unlike before the first lockdown, there was no clear uplift in CVD prescriptions observed in the four-week period preceding the second national lockdown

(**Extended Data Figure 7**). There was some evidence that the third national lockdown was preceded by a week of uplift, although the overlap with Christmas and New Year fluctuations complicates interpretation. A similar pattern was observed across all CVD medications sub-groups.

Trends for incident CVD medications:
We observed a marked decrease in incident dispensing for antihypertensives, lipid-lowering medications and T2DM medications in the immediate post-pandemic period (**Figure 3; Extended Data Figure 8; Supplemental Table 3**). The easing of lockdown restrictions in May 2020 was followed by a slow recovery in incident medications, but this recovery plateaued with the second and third national lockdowns (5th November 2020 and 6th January 2021 respectively). Incident medications continued to recover through the first half of 2021, with a spike in March 2021 coinciding with the end of the "stay at home" message; however, levels remained markedly lower than in the pre-pandemic period. On average 27,070 fewer patients per month were being commenced on antihypertensives and 16,744 fewer patients on lipid-lowering medications per month compared with the same months in 2019 (**Table 1**). The equivalent change for T2DM was 623 more incident patients per month.
Results from the incidence plus lapsing analyses are presented in **Extended Data Figure 9**. Defining incidence in this way generates higher counts in both the pre- and post- pandemic periods; however a large fall in the dispense of incident medications following the first national lockdown is again evident.

Impact of missed treatment on future CVD events:
During the period April 2020 to end July 2021, 491,306 fewer individuals initiated antihypertensive treatment across England, Scotland and Wales than would have been expected had 2019 incident treatment levels sustained. Using the NICE hypertension treatment model[23] we estimated that 13,662 additional CVD events would result from the non-initiation of hypertension treatment associated with the COVID-19 pandemic, were these individuals to remain untreated for the duration of their lifetime (**Table 2**). This would equate to an additional 2,281 myocardial infarctions and 3,474 strokes resulting from the under-treatment of hypertension alone during the period March 2020 to July 2021. If, however, individuals could be identified for treatment within five years this would reduce the total number of CVD events associated with the pandemic to 2,716 CVD events; suggesting that at least 1,554 myocardial infarctions and 3,014 strokes can be avoided. We did not estimate CVD outcomes for other risk factors (e.g. lipid lowering, T2DM medications), or the additive risk of having one or more of the CVD risk factors. In addition, we considered first treatment with any antihypertensive (rather than specific medications), including individuals commencing on more than one agent as well as those commenced on monotherapy. As such, we have generated conservative estimates of CVD events associated with non-treatment of CVD risk factors due to the pandemic.

Sensitivity analyses:
Excluding medications dispensed to individuals who died from COVID-19[25] and from any cause we observed trends consistent with those presented in our main findings (**Extended Data Figure 10**), suggesting that the declines observed do not result from the excess mortality of these individuals.

DISUCSSION:

The UK has comprehensive national medical records which can track health over the life course. We present the largest study to date using English, Scottish and Welsh data together to describe patterns in dispensed medications. Developing a novel method of categorising medications for an indication, we have used the unique capability of linked health records across three UK nations with a population coverge of >60 million people to describe how the use of medications to manage CVD has changed during the course of the COVID-19 pandemic and the potential impact on future CVD health as a measure of the indirect impact of COVID-19. Whilst this work is limited to Great Britain, it is likely that this is reflective of similar health economies, and paints a sobering picture of CVD health in the coming years if it is not addressed. This work complements and meaningfully extends other evidence on the indirect health impacts of the pandemic.[2,18]

Our main findings demonstrate the number of individuals who are likely to have missed having a major cardiovascular risk factor treated during the course of the COVID-19 pandemic, using existing models to assess the impact of this on future CVD events. Our results also demonstrate that, whilst there has been some recovery in dispensing of medications from the initial declines following the first lockdown, crucial first detection of CVD risk factors as indicated by medications has not returned to pre-pandemic levels. The numbers presented here focus on hypertension; a fuller analysis of the impact would need to include all CVD categories. Moreover, further analyses using these data could incorporate other measures such as blood pressure, lipids and glucose, although with reduced primary care visits during the pandemic, many fewer measurements will be available[2-4]. Therefore this medications method presents an important objective adjunct to existing research methods.

In contrast to the other categories of CV medications (blood pressure and lipid lowering medications), use of incident medications to treat T2DM increased by 623 patients per month in the first half of 2021 despite the likely reduced detection, potentially reflecting an increase in new onset T2DM in the population as a result of the events of 2020-21and/or an awareness of the additional risk of COVID-19 amongst the population and GPs for those with T2DM. Lower levels of diagnosis of T2DM during 2020 following the first lockdown in April have been reported[5]; the subsequent higher level of incident T2DM observed in these analyses in 2021, despite the known reduction in primary care screening, could suggest an increase in the prevalence of T2DM in the UK population, or that there is now a 'catch up' in diabetes diagnosis, which may indicate individuals are being diagnosed later with more advanced disease. In the UK ZOE COVID study, 34% of participants gained a mean of 3.7kg[27] and other adverse lifestyle factors have also been reported to have worsened (snacking, alcohol consumption, reduced physical activity), which will further contribute to the risk of hypertension, dyslipidaemia and T2DM[28]. Evidence from other countries also suggests that CVD risk factors may have increased during the course of the pandemic, including blood pressure[29]. The uptake of DOACs was increasing pre-pandemic and the pandemic may have accelerated this uptake and the switch away from warfarin as described elsewhere[30,31]. However, declining year-on-year growth in DOAC dispensing during the pandemic may indicate reduced diagnoses of AF and thrombo-embolic disease. In addition, the reduced level of warfarin may reflect missed diagnoses requiring anti-coagulation with warfarin such as valvular heart disease.

Alternative potential explanations for the trends in CVD medications observed include changing population dynamics of the UK and/or concurrent changes in the quantity of medications dispensed. However, the Office for National Statistics (ONS) data on mid-year population for 2020 which includes the period of disruption associated with the first national lockdown suggested that population growth remained at ~0.4%, a level consistent with the previous year[32]. Migration patterns also remained relatively constant, excluding this as a possible explanation. Deaths were ~67k higher than the five year average likely reflecting the impact of the COVID-19 pandemic; however in sensitivity analyses where we exclude medications dispensed to individuals who died from COVID-19[25] and from all-causes, we observed trends consistent with those presented in our main findings. For these reasons, changes in the demographic structure of the UK population are unable to explain the change in trends of CVD medications observed during the study period. Another potential explanation would

be changes in the quantity of medications dispensed per item concurrent and in the opposite direction to changes in the volume of items. However, our analyses suggest that quantity of medications per dispense remained relatively constant over the analysis period and that the small fluctuations observed would tend to inflate the count trends observed; this would suggest that our medications-based estimates of the impact of the COVID-19 pandemic are conservative.

A major driver of the identification and improvement of CVD risk factors is the mechnism for screening of CVD and its risk factors in primary care. Across GB, CVD risk factors are detected in primary care using mechanisms such as the Quality of Outcomes Framework (QOF) in England[33], the Quality Assurance and Improvement Framework (QAIF) in Wales[34] and the Transitional Quality Arrangements (TQA) Framework in Scotland[35]. During the pandemic, primary care visits fell markedly, with many that did occur being replaced by electronic or telephone consultations[2,3,5,36]. This mirrors a decrease in acute CVD events presenting to secondary care[37]. While there has been a re-opening of services during the pandemic, standard mechanisms for screening risk factors have not been wholly re-introduced[38]. Declines in consultation rates varied by age, ethnicity and region[3]; with some sub-groups known to have a higher risk of CVD and risk factors associated with CVD[39], including men, less affluent patients and immigrants, less likely to access remote consultations[40]..

Whilst it is likely that as services return to normal, cardiovascular risk in missed individuals may well be detected, it remains unclear what mechanisms are in place to re-introduce methods of screening or what consequences a delay in diagnosis might have. There are also broader public policy considerations from this study, including more general implications about health service provision during pandemics and planning for how routine health care could be sustained despite demands on the overall system in the event of future pandemics. Our analyses suggest potential mechanisms using medications data to identify and then target those at highest CVD risk. However, there will also be a need for alternative mechanisms of risk factor management, incorporating support services in primary care, e.g. primary care pharmacists and local pharmacies, which may be able to address large numbers of less complex cases. Of course, differing health systems will have their unique structures and challenges but the patterns in dispense of CVD medications we describe are likely to be similar in many high income (and potentially other) countries.

There are many further opportunities for uses of medications data that are beyond the scope of the analyses presented here. It is now possible to link de-identified dispensing data with primary and secondary care data at individual level in the UK, facilitating detailed analysis of characteristics associated with life-course use and accumulation of medications (polypharmacy), adverse drug reactions and adherence. Understanding how medications are being used can act as an objective barometer for the 'health' or disruption to a clinical pathway and, as these analyses demonstrate, may also help target recovery.

There are, however, a number of limitations worthy of discussion. First, whilst we have used a medicines lens and applied a new categorisation of CVD medications according to prescribed medication use, difficulty in assigning diseases for overlapping indications for some medications may result in underestimates of certain CVDs. For example, heart failure is likely to be underestimated as medications management options overlap with hypertension and type-2 diabetes (e.g. ACE-I, beta blockers and SGLT-2 inhibitors). Our analysis could be extended in future work by linking to disease diagnosis codes to refine estimates for conditions such as heart failure. However, the analyses presented here do give an indication of the overall missed CVD risk factors to alert policymakers to the indirect impacts of COVID-19. Second, the medication data analysed here represent "real world data" that were not collected for research purposes; it is possible that artefacts may exist within the data due to differences in collection, processing or transfer and these may vary over time and by source. For example, we observed a decline in the proportion of medications dispensed with invalid ("null") IDs over time in the English data, corresponding with an ongoing switch from paper-based to electronic processing[41]; this is relevant because valid IDs are required for linkage with other data to derive individual characteristics such as age, gender, ethnicity and co-morbidities.

Third, the estimates derived on the impact of a reduction in medications on CVD events rely on many assumptions that may change over time and in direct response to the pandemic. The final impact of the pandemic on CVD events in the UK is highly dynamic and will be influenced by many factors not captured by the model we used. These include future changes in population structure, underlying levels of CVD risk factors and their treatment (including non-pharmacological approaches), the additional impact of COVID-19 infection on future CVD risk, the rate at which "missed" individuals are identified for treatment and any changes in the medications-based management of CVD risk factors and associated guidelines. For these reasons, we did not attempt to make a comprehensive estimate of the impact of all missed CVD medications treatment on all future CVD events but rather to illustrate, using hypertension as an example, the potential impact using an established, externally validated model. Our aim is to highlight the public health importance of urgently identifying individuals for treatment and the clear potential for harm should this not occur. Fourth, a full cost-effectiveness model to fully expand on the impact of medications estimates that are reported in these analyses for future CVD events was out of scope here, but would need take into account a revised base case with additional risk that COVID-19 itself may have on CVD risk (at least in the short term) and triangulate this with other CVD risk factors as well as timescales and economic impacts. However, the analysis does provide an indication of the scale of the potential issue which, if not addressed, could lead to substantial undertreatment in causal CV risk factors, thereby meaningfully worsening the impact of the pandemic.

We have shown that medications used as a proxy for disease can complement investigation using electronic health records and disease diagnostic codes. Such analyses can be incorporated into methods to identify and treat individuals who have missed treatment, and these are urgently required to avoid additional future CVD events. Whilst excess event predictions are by nature dynamic and reflect many - including some as yet unknown - factors, we highlight the level of harm that could accrue should systems not improve to promptly tackle and treat missed CVD risk factors. This medications approach can provide policy makers with an additional lens to monitor healthcare pathways, providing a rapid response tool in the event of a future pandemic or other similar disruption.

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The study makes use of anonymised data held in the Scottish National Safe Haven. The authors would like to acknowledge the support of the eDRIS Team (Public Health Scotland) for their involvement in obtaining approvals, provisioning and linking data and the use of the secure analytical platform within the National Safe Haven.

This study makes use of anonymised data held in the Secure Anonymised Information Linkage (SAIL) Databank. This work uses data provided by patients and collected by the NHS as part of their care and support. We would also like to acknowledge all data providers who make anonymised data available for research. We wish to acknowledge the collaborative partnership that enabled acquisition and access to the de-identified data, which led to this output. The collaboration was led by the Swansea University HDR UK team under the direction of the Welsh Government Technical Advisory Cell (TAC) and includes the following groups and organisations: the SAIL Databank, Administrative Data Research (ADR) Wales, Digital Health and Care Wales (DHCW), Public Health Wales, NHS Shared Services Partnership (NWSSP) and the Welsh Ambulance Service Trust (WAST). All research conducted has been completed under the permission and approval of the SAIL independent Information Governance Review Panel (IGRP) project number 0911.

Public and Patient Involvement
The project was approved by the BHF DSC Approvals & Oversight Board which included patient and public partners, who were also consulted as results were produced and provided input into the final manuscript.

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and specialist teams within the Welsh Government to develop new evidence which supports Prosperity for All by using the SAIL Databank at Swansea University, to link and analyse anonymised data. ADR Wales is part of the Economic and Social Research Council (part of UK Research and Innovation) funded ADR UK (grant ES/S007393/1). This work was supported by the Wales COVID-19 Evidence Centre, funded by Health and Care Research Wales. All three national TREs receive support from the Data and Connectivity National Core Study, led by HDR UK in partnership with the Office of National Statistics and funded by United Kingdom Research and Innovation (grant MC_PC_20029)

AUTHOR CONTRIBUTIONS STATEMENT

†*Authors RC, MK & FT jointly supervised this work*

CS is the Director of the BHF Data Science Centre and coordinated approvals for and access to data within NHS Digital's TRE for England, the SAIL Databank and the Scottish National Safe Haven for CVD-COVID-UK/COVID-IMPACT.

CD, RT, RC, MK, SM, AH, MAH, PL, NS, RS contributed to the design of the study and oversight.

TM, SH, RL, RG, JL, GD, DH, RP contributed to data collection.

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All authors critically reviewed and provided input to manuscript drafts and approved the final version for submission to the journal.

COMPETING INTERESTS STATEMENT

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All other authors declare no competing interests

TABLE 1: Differences in incident medication counts dispensed by month for England, Scotland and Wales, comparing data for 2020 and 2021 to data for 2019, for 4 subgroups of CVD medications.

		Antihypertensives	Lipid lowering	Type 2 diabetes	Insulin
March	2020	-18,707	-3,624	-1,798	-418
April	2020	-41,445	-28,121	-10,144	-1,144
May	2020	-56,649	-40,766	-14,196	-2,042
June	2020	-41,154	-30,340	-8,567	-970
July	2020	-30,189	-24,693	-5,789	-543
August	2020	-33,926	-24,589	-6,390	-1,333
September	2020	-24,394	-15,535	-2,014	-201
October	2020	-27,630	-16,835	-2,057	-320
November	2020	-23,946	-15,945	-1,042	-22
December	2020	-14,277	-9,780	999	458
January	2021	-43,196	-27,039	-4,661	-1,199
Feburary	2021	-31,258	-24,969	-1,843	-3
March	2021	-25,668	-18,001	1,642	187
April	2021	-21,777	-13,898	2,382	242
May	2021	-25,022	-12,957	1,169	-32
June	2021	-15,499	-3,598	5,047	908
July	2021	-16,569	-5,328	3,643	379
Total March 2020 to July 2021		-491,306	-316,018	-43,619	-6,053
Mean January 2021 to June 2021		-27,070	-16,744	623	17

TABLE 2: Estimated number of CVD events resulting from missed initiation of anti-hypertensive medication since March 2020 for England, Scotland and Wales.

	QRISK2%	Treatment effect	Estimated N CVD events in "missed" treatment initiation population						
			Stable Angina	Unstable Angina	MI	Transient Ischaemic Attack	Stroke	Heart Failure	Total CVD events
A) Lifetime									
Male	11.3	NT	21,617	7,134	15,997	6,269	22,266	16,645	89,929
		Tx	19,456	6,485	14,484	5,837	21,185	16,213	83,660
		Additional cases pandemic (NT-Tx)	2,162	649	1,513	432	1,081	432	6,269
Female	4.9	NT	15,132	3,852	6,603	6,878	25,862	12,656	70,984
		Tx	13,092	3,295	5,835	6,015	23,469	11,884	63,591
		Additional cases pandemic (NT-Tx)	2,040	556	768	863	2,393	772	7,393
Total			4,202	1,205	2,281	1,296	3,474	1,205	13,662
B) 5 years									
Male	11.3	NT	3,459	1,297	3,459	649	1,513	865	11,241
		Tx	3,026	1,081	2,810	649	1,297	649	9,512
		Additional cases pandemic (NT-Tx)	432	216	649	0	216	216	1,729
Female	4.9	NT	2,000	720	492	985	1,410	385	5,993
		Tx	1,683	606	414	815	1,166	322	5,007
		Additional cases pandemic (NT-Tx)	317	114	78	170	244	63	986
Total			750	330	727	170	460	279	2,716

Estimated numbers are shown assuming non-treatment ongoing over the individual's lifetime (a) or for a duration of five years (b). Estimates were derived as detailed in the Methods.

NT = Not treated; Tx = Treated; NT-Tx = Difference between Not Treated and Treated; QRISK2% = cardiovascular disease risk calculator (https://www.qrisk.org/2017/index.php)

FIGURE LEGENDS/ CAPTIONS

FIGURE 1: Flowchart showing selection of analytical datasets

FIGURE 2: Trends in dispensed CVD medications for England, Scotland and Wales. (a,b) Medication counts by month (**a**) and the year-on-year percentage change in medications (**b**) over the indicated time frames for the 4 different subgroups of CVD medications. Vertical dotted lines indicate the timing of the first, second and third national lockdowns on 26th March 2020, 5th November 2020 and 6th January 2021, respectively.

FIGURE 3: Trends in the count of incident medications dispensed for England, Scotland and Wales. Counts by month for incident medications dispensed for the 4 different subgroups of CVD medication are shown. Vertical dotted lines indicate the timing of the first, second and third national lockdowns on 26th March 2020, 5th November 2020 and 6th January 2021, respectively.

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METHODS

Categorisation of CVD risk factor medications:

Medications were selected from British National Formulary (BNF0 Chapters 2 (Cardiovascular System) and 6 (Endocrine System)[20]. These were manually curated (initially by RS; reviewed by AS) selecting therapies used and/or licenced to treat CVD into 11 sub-groups: Antihypertensives, Antiplatelets secondary prevention (primary for DM), DOAC, Warfarin, Heparins, Lipid lowering, T2DM, Insulin, Heart failure, AF, Angina (**Supplemental Table 4)**.

Medications were categorised according to their primary indication to prevent double counting. Hence most blood pressure lowering agents were classified as antihypertensives apart from some classes of beta blockers, loop diuretics (and some thiazides e.g. metolazone), and sacubitril/valsartan, which are used specifically for heart failure. Like antihypertensives, other medications may have more than one indication, e.g. SGLT-2 inhbitors are now additionally licenced for heart failure as well as T2DM, and anticoagulants used to treat AF (most commonly VKAs and DOACs) can also be used to treat deep vein thrombosis and pulmonary embolism. This may result in undercounting for medications used for some CVDs in these analyses and in particular heart failure as a condition may be under-represented. Additional analyses could be carried out linking to disease codes although this was out of scope for the analyses presesented here.

Insulin preparations and other glucose lowering therapies for T2DM were categorised separately, even though some individuals with T2DM will also take insulin and therefore insulin will partially proxy T2DM as well as T1DM. Anticoagulants were categorised by class: vitamin K antagonists (VKA), direct oral anticoagulants (DOAC) and heparins. This allowed analysis of behaviours within each anticoagulant category, for example, differential use of VKAs and DOACs during the pandemic. Antiplatelets were classified as a separate group since they can be used for primary and secondary prevention for MI, stroke and peripheral vascular disease (PVD). An additional and separate category of medications that are mainly used as anti-anginals was created. Excluded medications were all intravenous preparations, those used to treat pulmonary hypertension, anti-arrhythmics where the indication is unlikely to be AF, sclerosants and rare medications.

Medication Data

England

Medication data are available from a number of sources within the English TRE. First, the NHS Business Service Authority (NHSBSA) dispensing data are updated on a monthly basis and include prescriptions for all medications dispensed in the community in England[9]. Second, prescribing data are available within the General Practice Extraction Service (GPES) extract Data for Pandemic Planning and Research (GDPPR), including data from 98% of all English general practices. These medications include those *a priori* selected by the CVD-COVID-UK programme predominently for their relevance to CVD and its risk factors (e.g. antihypertensive, cholesterol lowering, diabetes, antiplatelet/ anticoagulant)[8]. The English TRE also provides data for some secondary care Electronic Prescribing and Medicines Administration (EPMA), but these are not included in the current analyses as most medications to prevent and treat CVD are accounted for by primary care prescribing. Dates in NHSBSA reflect the month in which the script was submitted for payment rather than the date a medication was dispensed to the patient; whereas the date variable in the prescribing (GDPPR) data reflects the actual day on which a medication is prescribed by the GP. The first available month of NHSBSA data is April 2018; we therefore applied an April 2018 start date to the majority of analyses. The analysis end date was the latest available monthly download at time of analysis for NHSBSA and the most recent prescriptions available in the prescribing data at the time of analysis (31st July 2021).

Scotland

The medications data available within the Scottish National Safe Haven[10,11] come from the Prescribing Information System (PIS), which provides a repository for all community prescribing related information, including payments, but excluding prescriptions dispensed in hospitals.[12,13]. PIS comprises three different records/sources of data: 1) ePrescibed – details submitted through the prescribing system

(usually a GP practice), 2) eDispensed – details submitted through the dispensing system (community pharmacy), 3) DCVP – details used for payment to the pharmacy. The dispensed data in this study contains those prescriptions which have been processed completely through the system from prescription to payment. PIS uses a drug categorisation system based on the British National Formulary (BNF; a dictionary of descriptions and codes which represent medications and devices used across the NHS) with the majority of the data coming through community pharmacies via the Data Capture Validation Pricing (DCVP) system. Both paper and electronic prescriptions are provided as part of Scotland's eHealth strategy. The data is updated monthly in the Safe Haven. The dates in the individual records include the date the prescription was issued, the date it was dispensed, and the date payment was made. Dispensed dates used here are not necessarily real dates but could be default dates, for example the last day of a month.

Wales

Primary care prescribing and dispensing data for the population of Wales are available from two main data sources within the Secure Anonymised Information Linkage (SAIL) Databank[14,15]. Firstly, prescribing data from approximately 80% of all Wales general practices are available within the Welsh Longitudinal General Practice (WLGP) data, which is updated on a monthly basis[16]. These data include the exact date of prescription for each drug item and are coded using Read codes. Secondly, dispensing data from all community pharmacies in Wales is available within the Welsh Dispensing Data Set (WDDS)[17], which is updated on a monthly basis. Within SAIL upon each monthly release of WDDS, a research ready data asset (RRDA) is created and maintained[18] based on COVID-19 population e-cohort RRDA[14], which enhances the dispensing data for research purposes with mapping to additional coding classifications and meta-data. Although primary care prescribing data is available for the population of Wales, it is not comprehensively mapped between Read and BNF. Therefore, in these analyses we have focused only on Welsh dispensing data.The available range of the Welsh Dispensing DataSet (WDDS) at the time of this study was from 1st January 2016 to 25th August 2021. The raw data arrives in two separate extracts, one including all dispensed items per practice (each person within a general practice setting is identified by a unique ID in the data extract) and the other including an anonymised linkage field (ALF) that enables linkage of dispensing records to other available patient information[17]. Within WDDS, all medications are coded in DM+D. We established a pipeline that is applied to each monthly release of WDDS data that links both ALF and Dispensing record tables and maps drug items from DM+D codes to BNF. NHSBSA was used to map all dispensed items from DM+D codes to BNF coding system[19]. In order to match the existing data range available in England and Scotland, a snapshot of Wales data starting from March-2018 up to July-2021 was used for these analyses.

Medication Data Processing

A detailed description of the medications data processing undertaken in each national TRE is given at https://github.com/BHFDSC/CCU014_01. For all analyses (except the interrupted time-series analysis – see below), dispensing data were used as these are more likely to be indicative of individuals taking medications and were available in all three nations. Within the English TRE, the NHSBSA dispensing dataset was screened to identify all possible dispensed medications. Both dispensing and prescribing data were mapped to the British National Formulary (BNF)[20] (via Dictionary of Medicines and devices (DM+D) or SNOMED concepts), and the medication substance identified using the 8th BNF character to facilitate categorisation according to CVD medication sub-group.

Analyses in the Scottish National Safe Haven & SAIL Databank used the same inclusion criteria, code lists and categorisation for CVD medications, using BNF codes selected and extracted from the English TRE, with adjustments as required to accommodate specific features of the datasets in each. Summary output files from each nation were extracted and combined with results from other nations.

Study Population

Inclusion criteria:

These analyses focused on medications data with linkage to individual data for demographic characteristics (**Figure 1**). We included medications dispensed to individuals aged between 18 and 112 years, with gender self-reported as male or female, at pharmacies in the relevant nation. We excluded individuals with a date of death recorded before 1st April 2018 or a null date of birth. Medications dispensed between 1st April 2018 and 31st July 2021 were included for all three nations. For stratified and incident analyses, medication records were required to have a valid pseudo-identifier ID (a non-identifying unique master key that replaces the NHS number across all datasets) to enable individual-level matching to socio-demographic and regional characteristics.

Age was calculated at the date of dispensing for each medication by subtracting the month and year of birth from the dispense date (Monday of the week of birth in Wales).

Sub-groups:

We analysed results within subgroups according to key demographic characteristics of interest, including: age (categorised ≥18-29 and thereafter in 10 year age bands to 90+ years), gender, and 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 data were extracted from a combination of electronic health record data sources in England and Wales, and harmonised into the following five groupings: White, Asian, Black, Mixed and Other. Ethnicity is not available as part of the PIS data on the Scottish National Safe Haven, and more generally ethnicity has historically not been reliably recorded in Scottish health care records; ethnicity data from Scotland are therefore not included in these analyses.

Individuals with missing values for a given stratification variable are reported as a separate group for those sub-analyses.

Statistical Analyses

Trends in dispensed medications:

We counted items dispensed for the medications of interest from 1st April 2018 to end July 2021. We also calculated monthly percentage change compared to the previous year in dispensed medications from April 2019 to July 2021. Analyses were conducted for the combined group of CVD medications and separately for the major CVD medication sub-groups: antihypertensives, lipid-lowering medications, T2DM and insulin.

Stratification by sub-groups (CVD and socio-demographic)

Monthly counts and their percentage change were calculated for each of the 11 CVD medications sub-groups for both prevalent and incident medications. We also investigated variation in dispensing of prevalent medications by age, gender, region and ethnicity.

Interrupted time-series analyses

Interrupted time-series (ITS) using segmented regression, following Bernal et al.(2017)[21], was used to evaluate the impact of the COVID-19 pandemic and associated restrictions on prescription of CVD medications in England. The purpose of the interrupted ITS was to identify the key periods of change in the prescription of CVD medications in England during the course of the COVID-19 pandemic and to quantify the pre-lockdown increases observed. Weekly counts data were modelled from June 2018 to May 2021 comprising 153 data points, including data both prior to the first national lockdown and into 2021 after the third national lockdown. Preliminary inspection of data using scatterplots was undertaken to help identify the underlying trend and outliers. We defined a priori segments for anticipated regular effects associated with the two-week period including Christmas and New Year each year and the two-week period prior to each of these events. Outside these periods, prescription of

CVD medications is relatively consistent month to month and, unlike CVD events, not expected to be higher in Winter. We introduced segments corresponding to the four-week periods prior to national lockdowns (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 were fitted to each CVD medications sub-group following Schaffer et al. (2021)[22] Evidence of autocorrelation was assessed through examination of the residuals, autocorrelation plots and with Durbin's and Breusch Godfrey tests. This analysis was undertaken using the auto.arima function from the forecast package in R.

Incident CVD medications

To calculate person-level incident medication, we identified the first recorded per person occurrence of a dispensed medication within each CVD sub-group during the study period March 2019 to May 2021. We allowed an initial clearance window for the first year of data availability to allow monthly incidence counts to stabilise. This was to correct for the high levels of artefact "incidence" in the first few months of the study period resulting from records first becoming available for analysis. Incident medications results are therefore presented from 1st March 2019 to 31st July 2021. Individuals may be counted as receiving incident medication for more than one of the CVD medications sub-groups. Differences in the number of incident medications by CVD sub-group in the post-pandemic period were calculated by subtracting the monthly count from the equivalent montly count in 2019.

Impact of missed treatment on future CVD events

Whilst a full economic analysis was out of scope for this analysis, taking hypertension as an example, we estimated the potential impact of missed cardiovascular risk factor treatment on CVD events using the most recent cost-effectiveness analysis model developed for the National Institute of Health and Care Excellence (NICE)[23], adapting the base case to reflect characteristics of the hypertensive population not receiving incident medication. We chose hypertension because it is the most common CVD risk factor for which medications are prescribed. Estimates of number of future CVD events in individuals who missed initiation of antihypertensive treatment are derived using a Markov cohort model (further details on the model including its structure and parameter inputs provided in NICE Guideline NG136). Each year the cohort may remain in the CVD free state or transition to a CVD state or death. The risk of having a non-fatal CVD event is determined by the QRISK2 score with the distribution across types of CVD events taken from Ward 2005. Hypertensive treatment is assumed to act directly on CVD risk with treatment effects taken from Brunström 2018. The model was run deterministically. Estimates of additional CVD events due to pandemic reflect: A) the number of additional CVD events that would be experienced by the cohort over the life-course were non-treatment to persist, and B) the number of CVD events if antihypertensive treatment were to be initiated after five years.

We identified characteristics of the 2019 population receiving incident antihypertensive medication within the English TRE (mean age and proportion male/female, with T2DM and smokers. This population was found to be 56% female with the mean age of females equal to 52 years, 4.8% of whom had a record of T2DM and 29.8% smoking; for males the mean age was 55 years, 6.4% with a record of T2DM and 28.0% smoking. Using this information in the QRISK2 calculator[24] we calculated 10-year QRISK2 scores for the NICE treatment effect model base case equal to 11.3% (male) and 4.9% (female), weighted for prevalence of T2DM and smoking and 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 calculated 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). The difference in N of events per 1000 expected for treatment (Tx) and non-treatment (NT) based on these characteristics was scaled to the 491,306 individuals estimated to have missed treatment in England April 2020 - July 2021

Sensitivity analyses

To account for the potential impact of higher mortality due to the COVID-19 pandemic itself, in sensitivity analyses we excluded medications dispensed to individuals who died from COVID-19[25] and, separately, from any cause across the study period.

In sensitivity analyses we also explored calculating person-level incident medication by identifying any new dispense or any dispense more than 365 days after a previous one in the same CVD sub-group (incidence plus lapsing).

Ethical approval
The North East-Newcastle and North Tyneside 2 research ethics committee provided ethical approval for the CVD-COVID-UK research programme (REC No 20/NE/0161) to access, within secure trusted research environments, unconsented, whole-population, de-identified data from electronic health records collected as part of patients' routine healthcare.

DATA AVAILABILITY

Data used in this study are available in NHS Digital's Trusted Research Environment (TRE) for England, but as restrictions apply they are not publicly available (https://digital.nhs.uk/coronavirus/coronavirus-data-services-updates/trusted-research-environment-service-for-england). The CVD-COVID-UK/COVID-IMPACT programme led by the BHF Data Science Centre (https://www.hdruk.ac.uk/helping-with-health-data/bhf-data-science-centre/) in partnership with HDR UK received approval to access data in NHS Digital's TRE for England from the Independent Group Advising on the Release of Data (IGARD) (https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/independent-group-advising-on-the-release-of-data) via an application made in the Data Access Request Service (DARS) Online system (ref. DARS-NIC-381078-Y9C5K) (https://digital.nhs.uk/services/data-access-request-service-dars/dars-products-and-services). The CVD-COVID-UK/COVID-IMPACT Approvals & Oversight Board (https://www.hdruk.ac.uk/projects/cvd-covid-uk-project/)) subsequently granted approval to this project to access the data within the TRE for England, the Scottish National Safe Haven and the Secure Anonymised Information Linkage (SAIL) Databank. The de-identified data used in this study were made available to accredited researchers only. Those wishing to gain access to the data should contact bhfdsc@hdruk.ac.uk in the first instance.

Data used in this study are available in the Scottish National Safe Haven (Project Number: 2021-0102), but as restrictions apply they are not publicly available. Access to data may be granted on application to the Public Benefit and Privacy Panel for Health and Social Care (PBPP (https://www.informationgovernance.scot.nhs.uk/pbpphsc/). Applications are co-ordinated by eDRIS (electronic Data Research and Innovation Service (https://www.isdscotland.org/Products-and-services/Edris/). The anonymised data used in this study was made available to accredited researchers only through the Public Health Scotland (PHS) eDRIS User Agreement (https://www.isdscotland.org/Products-and-services/Edris/_docs/eDRIS-User-Agreement-v16.pdf).

Data used in this study are available in the SAIL Databank at Swansea University, Swansea, UK, but as restrictions apply they are not publicly available. All proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). Before any data can be accessed, approval must be given by the IGRP. The IGRP gives careful consideration to each project to ensure proper and appropriate use of SAIL data. When access has been granted, it is gained through a privacy protecting data safe haven and remote access system referred to as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL at https://www.saildatabank.com/application-process

Data processing details for this work are available under an open source license at https://github.com/BHFDSC/CCU014_01.

CODE AVAILABILITY

All data preparation and analyses were conducted using Databricks (SQL, Python), R or Stata within the English TRE. All data preparation and analyses within the Scottish National Safe Haven were conducted on the secure analytical platform using R. All data processing in the SAIL Databank was performed using R. All code is available on GitHub https://github.com/BHFDSC/CCU014_01.

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