British Journal of General Practice

Association between oral anticoagulants and COVID-19 related outcomes: a population-based cohort study

Wong, Angel; Tomlinson, Laurie; Brown, Jeremy; Elson, William; Walker, Alex; Schultze, Anna; Morton, Caroline; Evans, David; Inglesby, Peter; MacKenna, Brian; Bhaskaran, Krishnan; Rentsch, Christopher; Powell, Emma; Williamson, Elizabeth; Croker, Richard; Bacon, Seb; Hulme, William; Bates, Chris; Curtis, Helen J; Mehrkar, Amir; Cockburn, Jonathan; McDonald, Helen; Mathur, Rohini; Wing, Kevin; Forbes, Harriet; Eggo, Rosalind; Evans, Stephen; Smeeth, Liam; Goldacre, Ben; Douglas, Ian

DOI: <https://doi.org/10.3399/BJGP.2021.0689>

To access the most recent version of this article, please click the DOI URL in the line above.

Received 08 December 2021

Revised 28 January 2022

Accepted 06 February 2022

© 2022 The Author(s). This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0/>). Published by British Journal of General Practice. For editorial process and policies, see: <https://bjgp.org/authors/bjgp-editorial-process-and-policies>

When citing this article please include the DOI provided above.

Author Accepted Manuscript

This is an 'author accepted manuscript': a manuscript that has been accepted for publication in British Journal of General Practice, but which has not yet undergone subediting, typesetting, or correction. Errors discovered and corrected during this process may materially alter the content of this manuscript, and the latest published version (the Version of Record) should be used in preference to any preceding versions

Association between oral anticoagulants and COVID-19 related outcomes: a population-based cohort study

The OpenSAFELY Collaborative: Angel YS Wong^{a†}, PhD, assistant professor; Laurie Tomlinson^a, PhD, associate professor; Jeremy P Brown^a, MSc, PhD student; William Elson^a, MBBS, general practitioner; Alex J Walker^b, PhD, epidemiologist; Anna Schultze^a, PhD, research fellow; Caroline E Morton^b, MBChB, epidemiologist; David Evans^b, MPhil, software developer; Peter Inglesby^b, MPhil, consultant engineer; Brian MacKenna^b, MPharm, honorary clinical researcher; Krishnan Bhaskaran^a, PhD, professor of statistical epidemiology; Christopher T Rentsch^a, PhD, assistant professor; Emma Powell^a, MSc, PhD student; Elizabeth Williamson^a, PhD, biostatistician; Richard Croker^b, MSc, honorary research fellow; Seb Bacon^b, BA, chief technical officer; William Hulme^b, PhD, statistician; Chris Bates^c, PhD, director of research and analytics; Helen J Curtis^b, DPhil, postdoctoral researcher; Amir Mehrkar^b, nMRCGP, honorary clinical researcher; Jonathan Cockburn^c, BSc, developer; Helen I McDonald^{a,d}, PhD, clinical research fellow; Rohini Mathur^a, PhD, assistant professor; Kevin Wing^a, PhD, assistant professor; Harriet Forbes^e, PhD, epidemiologist; Rosalind M Eggo^a, PhD, associate professor; Stephen JW Evans^a, PhD, professor; Liam Smeeth^{a,d}, PhD, professor of clinical epidemiology; Ben Goldacre^{b*†}, MRCPsych, director, The DataLab; Ian J Douglas^{a*†}, PhD, professor

^a Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine

^b The DataLab, Nuffield Department of Primary Care Health Sciences, University of Oxford

^c TPP, TPP House, Horsforth, Leeds

^d NIHR Health Protection Research Unit (HPRU) in Immunisation

^e Bristol Medical School, University of Bristol, Bristol

† Joint principal investigators

‡ Corresponding: Angel YS Wong
Department of Non-Communicable Disease Epidemiology
Faculty of Epidemiology and Population Health
London School of Hygiene and Tropical Medicine
Keppel Street
London WC1E 7HT
Phone: +44 020 7927 2622
Email: Angel.Wong@lshtm.ac.uk

Word count: 2785

Abstract (<=250 words)

Background: Early evidence showed that anticoagulant reduces the risk of thrombotic events amongst those infected. However, evidence of the role of routinely prescribed oral anticoagulants (OACs) in COVID-19 outcomes is limited.

Aim: To investigate the association between OACs and COVID-19 outcomes in those who had atrial fibrillation and a CHA₂DS₂-VASc score of 2.

Design and setting: On behalf of NHS England, we conducted a population-based cohort study.

Method: We used primary care data and pseudonymously-linked SARS-CoV-2 antigen testing data, hospital admissions, and death records from England. We used Cox regression to estimate HRs for COVID-19 outcomes comparing current OAC use versus non-use, accounting for age, sex, comorbidities, other medications, deprivation and general practice.

Results: Among 71,103 people with AF who had a CHA₂DS₂-VASc score of 2, we included 52,832 current OAC users and 18,271 non-users. We observed no difference in risk of being tested for SARS-CoV-2 associated with current use (adjusted HR (aHR), 0.99, 95%CI, 0.95–1.04) versus non-use. We observed a lower risk of testing positive for SARS-CoV-2 (aHR, 0.77, 95%CI, 0.63–0.95), and marginally lower risk of COVID-19 deaths (aHR, 0.74, 95%CI, 0.53–1.04) associated with current use versus non-use.

Conclusions: Among those at low baseline stroke risk, people receiving OACs had a lower risk of testing positive for SARS-CoV-2 and severe COVID-19 outcomes than non-users; this might be explained by a causal effect of OACs in preventing severe COVID-19 outcomes or unmeasured confounding including more cautious behaviours leading to reduced infection risk.

Keywords: oral anticoagulants, warfarin, direct oral anticoagulants, COVID-19

Introduction

Early studies reported that heparin lowers the risk of pulmonary embolism and mortality during hospitalisation among patients with COVID-19¹⁻⁴. However, the protective role of oral anticoagulants in severe COVID-19 outcomes is unclear. A randomised controlled trial reported that therapeutic anticoagulation with rivaroxaban in hospitalised patients with COVID-19 did not improve all-cause mortality but an increased risk of major bleeding compared with prophylactic anticoagulation with enoxaparin or unfractionated heparin during hospitalisation⁵. Notably, as this study excluded people with an indication for therapeutic anticoagulation, it remains uncertain whether there is a role of routinely prescribed OACs for atrial fibrillation (AF) on COVID-19 outcomes. In particular, anticoagulants are underutilised among people with AF in the UK.⁶ Understanding the effects of routinely prescribed OACs on COVID-19 can be of significant clinical importance that further informs OAC prescribing guidance in the context of COVID-19 pandemic, given that AF may have a prognostic role in COVID-19 disease⁷.

Some observational studies investigated the role of OACs in COVID-19 outcomes but the findings were conflicting⁸⁻¹⁹. Importantly, most were of small sample size or in hospital settings only, leading to a lack of power and/or selection bias. Further, people taking OACs are likely to have more comorbidities than those not, and so comparing COVID-19 outcomes for OAC use with non-use could be subject to confounding in these studies.

In order to address these limitations, we conducted a population-based cohort study to investigate the association between routinely prescribed OACs and COVID-19 outcomes versus non-use, restricting the study population to people with AF who had a CHA₂DS₂-VASc score of 2 in England. The CHA₂DS₂-VASc score is a validated measure to predict the risk of stroke among people with atrial fibrillation. The use of CHA₂DS₂-VASc score is to determine the need for prescribed anticoagulants in people with non-valvular atrial fibrillation as a prophylactic therapy against stroke. According to the guidelines for the management of

patients with AF^{20–22}, people with a CHA₂DS₂-VASc score of ≥ 2 should be offered an anticoagulant. For those with a score of 2, there is possibly a degree of variation in OAC prescribing, offering a useful group in whom OAC users are likely to be more comparable with non-users to minimise confounding. Further, a UK study showed that patients with a CHA₂DS₂-VASc score of 2 were more likely to remain untreated with anticoagulants than patients with a score ≥ 3 .⁶ A better understanding of the impact of OACs on COVID outcomes may alter the balance of benefits and risks of prescribing OACs for those around such a threshold.

Methods

Study design

We conducted a population-based cohort study between 1/3/2020 and 28/9/2020.

Data Source

Primary care records managed by the software provider TPP were linked to SARS-CoV-2 antigen testing data from the Second Generation Surveillance System, COVID-19 related hospital admissions from the secondary uses service, and Office for National Statistics death data through OpenSAFELY, a data analytics platform created by our team on behalf of NHS England²³. The dataset analysed within OpenSAFELY is based on 24 million people currently registered with primary care practices using TPP SystmOne software, representing 40% of the English population. It includes pseudonymised data such as coded diagnoses, prescribed medications and physiological parameters. Details on information governance can be found in Supplementary Method S2.

Study populations

We identified people with a diagnosis of AF on/before study start date (1/3/2020). To reduce confounding, we limited the cohort to those with a CHA₂DS₂-VASc score of 2 as the indication for OAC therapy would typically be borderline among people with this score. We calculated their CHA₂DS₂-VASc score based on their records of demographics and diagnoses which contribute to the score before cohort entry.

People with missing data for gender, Index of Multiple Deprivation, <1 year of primary care records, or aged <18 or >110 and prescribed injectable anticoagulants 4 months before study start date were excluded.

Exposure

Current OAC users were those ever had an OAC prescription (i.e. warfarin/ dabigatran/ rivaroxaban/ apixaban/ edoxaban) in the 4 months before study start, and non-users are those with no record of OAC prescription in the same period.

Outcomes and follow-up

The outcomes were 1) testing positive for SARS-CoV-2, 2) COVID-19 related hospital admission, and 3) COVID-19 related death (defined as the presence of ICD-10 codes U071 (confirmed COVID-19) and U072 (suspected COVID-19) on the death certificate). Testing outcomes were obtained from the UK's Pillar 1 (NHS and Public Health England laboratories) and Pillar 2 (commercial partners) testing strategies and results from polymerase chain reaction (PCR) swab tests used to identify symptomatic individuals²⁴. As pre-specified analyses, we also included time to the first SARS-CoV-2 test as a negative control outcome. We anticipated that, within our population of people with AF, there were unlikely to be marked differences in the likelihood of being tested for SARS-CoV-2 infection in relation to drug treatment with OACs.

Follow up began on the 1/3/2020 and ended at the latest of the outcome of interest in each analysis, deregistration from the TPP practice, death or study end date (28/9/2020) (Figure 1).

Covariates

Clinical covariates were identified using the Read clinical classification system and included body mass index (BMI) to classify obesity, and smoking status. We classified obesity using BMI in kg/m²: no record of obesity or BMI < 30.0; obese I (BMI: 30.0–34.9 kg/m²); obese II (BMI: 35.0–39.9 kg/m²); and obese III (≥40 kg/m²). Smoking status was grouped into current, former, and never smokers. Those with missing smoking status were categorised as never smokers. The following covariates were pre-specified using a Directed Acyclic Graph (DAG) (Supplementary Figure 1), including age, sex, obesity, smoking status, hypertension, heart failure, myocardial infarction, peripheral arterial disease, stroke/transient ischemic attack, venous thromboembolism, diabetes, flu vaccination, current antiplatelet use, current oestrogen/oestrogen-like therapy use, Index of Multiple Deprivation. We further added dementia to the regression during the peer-review process as it could be an important confounder. We identified these covariates that are both associated with the exposure and severe COVID-19 outcomes²³. Some covariates that are associated with the exposure and venous thromboembolism, possibly leading to severe COVID-19 outcomes were also included^{25,26}. All codelists for identifying exposures, covariates and outcomes are openly shared at <https://codelists.opensafely.org/>.

Statistical Methods

We present adjusted cumulative incidence/mortality curves using the Royston-Parmar model. We estimated hazard ratios (HRs) with 95% confidence intervals (CIs) using Cox regression with time since cohort entry as the underlying timescale. We accounted for competing risk by modelling the cause-specific hazard (i.e. censoring non-COVID-19 other deaths for COVID-19 death analysis, and censoring any death for other outcomes analysis).

We used graphical methods and tests based on Schoenfeld residuals to explore violations of the proportional hazards assumption.

We constructed unadjusted models, models adjusted for age (using restricted cubic splines) and sex, and DAG adjusted model.

Quantitative Bias Analysis

We considered that OAC users may lower their COVID-19 risk through more risk-averse health behaviour (e.g. wearing face masks, avoiding close proximity to others) than, respectively, non-users. Given that health behaviour is not captured in databases, we conducted quantitative bias analyses (both the E-value and the Cornfield condition)²⁷ to assess the sensitivity of our results to this potential unmeasured confounder.

Sensitivity Analyses

Table 1 shows the list of sensitivity analyses.

Data management was performed using Python 3.8 and SQL, with analysis carried out using Stata 16.1. All study analyses were pre-planned unless otherwise stated. All code for data management and analyses are archived at <https://github.com/opensafely/oral-anticoagulant-covid-outcome>, in addition to the pre-specified protocol

(https://github.com/opensafely/anticoagulants-research/blob/master/protocol/Protocol_%20Anticoag%20OpenSAFELY_v3.docx).

Deviations from pre-specified protocol, with reasons were stated in the Supplementary Method 1 & Supplementary Table 1.

Results

Among 71,103 people with AF who had a CHA₂DS₂-VASc score of 2, we included 52,832 current OAC users and 18,271 non-users (Figure 2, Supplementary Table 2). Median age was 71 years (IQR:66–75) among current users and 69 years (IQR:63–74) among non-users.

Current OAC users were more likely to be men, obese, former smokers, and have a medical history of heart failure, chronic obstructive pulmonary disease, chronic kidney disease, but were less likely to have myocardial infarction, peripheral artery disease, venous thromboembolism, immunosuppression, and diabetes than non-users. Current users were less likely to have a prescription for oestrogen/oestrogen-like drugs, antiplatelets, non-steroidal anti-inflammatory drugs, and aspirin, but to have had more primary care consultations and flu vaccination than non-users.

Supplementary Figure 2 presents time to COVID-19 outcomes in adjusted cumulative incidence plots. A lower risk of testing positive for SARS-CoV-2 [480 events in 2,107,517 person-weeks; unadjusted HR: 0.75 (95%CI:0.62–0.91); DAG-aHR: 0.77 (95%CI:0.63–0.95)] was observed associated with current use, compared with non-use (Figure 3, Supplementary Table 3). Similarly, we observed a lower risk of COVID-19 related hospital admission with wide CI [226 events in 2,110,854 person-week; unadjusted HR: 0.89 (95%CI:0.67–1.19); DAG-aHR: 0.85 (95%CI:0.62–1.15)], and COVID-19 related deaths [185 events in 2,113,796 person-week; unadjusted HR: 0.81 (95%CI:0.59–1.11); DAG-aHR: 0.74 (95%CI:0.53–1.04)], comparing current use with non-use.

For negative control outcome, there was no difference in risk of being tested for SARS-CoV-2 comparing current use with non-use [11,190 events in 1,994,072 person-weeks; unadjusted HR: 0.95 (95%CI:0.91–0.99); DAG-aHR: 0.99 (95%CI:0.95–1.04)].

Sensitivity analyses

In the fully adjusted model, we observed a lower risk of COVID-19 related death comparing current OAC use with non-use [HR: 0.66 (95%CI:0.45–0.97)]. Results of all other sensitivity analyses were similar to those of the main analyses (Supplementary Table 4–6). Whilst there was no strong evidence of a different association between current use of OACs and testing positive for SARS-CoV-2 according to care home residence (Supplementary Table 7), this comparison was underpowered.

Quantitative bias analysis

To potentially fully explain the observed associations, either non-anticoagulant use would need to be associated with at least 1.29 increased risk of unmeasured risk-prone behaviour; or risk-prone behaviour would need to be associated with 1.29 times increased risk of each COVID-19 outcome. Alternatively, both non-use and each COVID-19 outcome would need to be associated with risk-prone behaviour by associations ranging from 1.05 (Supplementary Table 8).

Discussion

Summary

We observed a lower risk of testing positive for SARS-CoV-2 associated with current OAC use, versus non-use among people with AF and a low baseline risk of stroke. With small absolute numbers of COVID-19 related hospital admission and COVID-19 related deaths, we observed a marginally lower risk of these outcomes associated with current OAC use, compared with non-use. We observed no difference in risk of being tested for SARS-CoV-2 between current users and non-users, indicating that the lower risk of testing positive was unlikely due to the chance of being tested.

Consideration needs to be given to whether these associations are causal, or due to other differences between groups. There is no clear evidence that the current users were generally frailer in terms of their comorbidities than non-users. The inverse associations in OAC users were specific to COVID-19 outcomes, with no protective association seen against having a COVID-19 test, which would support a possible causal association. OAC users had a reduced risk of receiving a positive test and severe COVID-19 outcomes, suggesting a lower risk of acquiring test-detected infection in this group. An experimental study suggested that direct factor Xa inhibitors may prevent SARS-CoV entry to human cells by preventing the spike protein cleavage into the S1 and S2 subunits²⁸ but the clinical evidence is limited. Additionally, we considered that anticoagulation might inhibit the PCR for SARS-CoV-2^{29,30} but the evidence of a specific inhibitory effect of OACs on PCRs for SARS-CoV-2 is lacking. Notably, these results do not necessarily mean OACs reduce the risk of infection; in many instances the outcome of a positive COVID-19 test reflects both infection and symptom severity leading to test seeking. It is possible that anticoagulant activity lessens symptoms/severity, leading to a lower rate of infection detection. We also considered the non-causal explanation that risk behaviours may differ between OAC users and non-users and impact the probability of being infected with SARS-CoV-2 and severe COVID-19 outcomes. Although we cannot fully capture the behavioural differences between groups in the database, we observed that OAC users are less likely to be current smokers, had less hazardous alcohol use and more likely to have had flu vaccination than non-users but the differences were small. We further performed quantitative bias analyses and found that an unmeasured confounder would need to be of moderate strength to potentially explain the observed associations. Whilst this is always possible, notably the very wide range of well measured confounders we did have information on had little impact on our findings, suggesting confounding may not be a substantial problem. Nonetheless, further studies that can account for behavioural differences between groups are required to confirm the findings as we cannot rule this out as a possible contributor to our findings.

Strengths and limitations

The greatest strength of this study was the power enabling us to examine the association between OACs and various COVID-19 outcomes as our dataset included medical records from 24 million individuals. We also conducted quantitative bias analyses to explore the impact of unmeasured confounding to our observed results, complementing our interpretation. The breadth of data available in primary care allows us to account for a wide range of potential confounders.

We recognise possible limitations. First, as in any observational study, we cannot eliminate residual confounding. Further, there may be misclassification bias in measuring covariates, leading to incomplete adjustment for confounding. Although we attempted to reduce confounding by limiting the cohort to people who had a threshold CHA₂DS₂-VASc score to be prescribed anticoagulants, results may not be generalisable to all patients with AF. In particular, women and people with stroke, transient ischaemic attack or venous thromboembolism may be under-represented in this study given that these alone would have led to a CHA₂DS₂-VASc score of 2, so any additional risk factors would mean therefore would be excluded from the exposed group. Second, we do not know whether patients took the medications as prescribed. However, non-adherence of oral anticoagulant treatment would only bias the estimate towards null. Third, we are also not able to capture anticoagulant use (e.g. low molecular weight heparin or unfractionated heparin) during hospitalisation. However, this would tend to make our comparison groups more similar to each other during hospitalisation which would most likely lead to an underestimation of any effect of routine OAC use before hospitalisation. Fourth, there may be misclassification in ascertaining AF using diagnostic codes alone when deriving the study population. Some recorded AF might resolve at the study start and thus not require anticoagulants. However, this is considered to be less common³¹ and is unlikely to substantially bias our results. Fifth, some COVID-19 cases at the early pandemic may be missed due to limited testing capacity.

Importantly, the effect estimate in our analysis would not be biased assuming non-differential misclassification bias of outcome.

Comparison with existing literature

While the effects of COVID-19 may predispose patients to thromboembolic disease through severe illness, hypoxia or severe inflammatory response³², anticoagulation may have a role in preventing thrombotic events in patients with COVID-19. Recent studies investigating the potential effects of early initiation of anticoagulation resulted in conflicting findings^{3,8–15,33–37}. Seven studies^{8,9,13,14,16–18} focusing on prehospital use of anticoagulants and one study³⁴ focusing on therapeutic use of anticoagulants found no difference in risk of mortality, mechanical ventilation or acute distress respiratory syndrome. Notably, some were of small sample size^{8,16–18}, with unclear exposure definition⁹, classifying patients who initiated therapeutic anticoagulation on day 3 or later after ICU admission in the control group³⁴ or used composite outcomes with varying clinical importance^{13,14}, limiting the interpretation of the results. Two cohort studies showed a higher risk of admission to ICU, intubation, or death associated with anticoagulants in patients with COVID-19 disease, versus non-use without restricting to a study population with a specific OAC indication, but they were possibly due to confounding by indication^{12,36}. A cohort study with propensity score matching reported a lower risk of all-cause mortality associated with OACs in people with COVID-19 disease, compared with non-use, supporting our results¹⁹.

Implications for research and/or practice

Notably, this study was undertaken during the early pandemic before vaccines and COVID-19 treatments were available to prevent or treat severe COVID-19 disease. Future work is needed to confirm our findings of an inverse association between OACs and severe COVID-19 related outcomes in people with AF at the threshold for OAC treatment, and to establish causality; either randomised trials, or observational studies with detailed data on risk factors for COVID-19 infection. If confirmed to be a causal effect, this could be of significant clinical

importance, particularly as the older age and comorbidities in this group are independent risk factors of severe COVID-19 outcomes. Choice of routine anticoagulant therapy represents a complex balance of expected risks, benefits and patient preference; we do not recommend changes to ongoing anticoagulant therapy based on these results.

List of abbreviations

AF: atrial fibrillation;
DAG: Directed Acyclic Graph;
HR: Hazard ratio;
OACs: oral anticoagulants;

Declarations

Ethics approval and consent to participate

This study was approved by the Health Research Authority (REC reference 20/LO/0651) and by the LSHTM Ethics Board (reference 21863).

Consent for publication

Not applicable

Availability of data and materials

All data were linked, stored, and analysed securely within the OpenSAFELY platform. Detailed pseudonymised patient data are potentially re-identifiable and therefore not shared. We rapidly delivered the OpenSAFELY data analysis platform without previous funding to deliver timely analyses of urgent research questions in the context of the global COVID-19 health emergency: now that the platform is established, we are developing a formal process for external users to request access in collaboration with NHS England. Details of this process will be published in the near future on the OpenSAFELY website.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following: BG has received research funding from Health Data Research UK (HDRUK), the Laura and John Arnold Foundation, the Wellcome Trust, the NIHR Oxford Biomedical Research Centre, the NHS National Institute for Health Research School of Primary Care Research, the Mohn-Westlake Foundation, the Good Thinking Foundation, the Health Foundation, and the World Health Organisation; he also receives personal income from speaking and writing for lay audiences on the misuse of science. IJD has received unrestricted research grants and holds shares in GlaxoSmithKline (GSK). All other authors declare that they have no competing interests.

Funding

The OpenSAFELY data science platform is funded by the Wellcome Trust. OpenSAFELY work was jointly funded by UKRI [COV0076;MR/V015737/1], NIHR and Asthma UK-BLF and the Longitudinal Health and Wellbeing strand of the National Core Studies programme. TPP provided technical expertise and infrastructure within their data centre *pro bono* in the

context of a national emergency. BG's work on better use of data in healthcare more broadly is currently funded in part by: National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, NIHR Applied Research Collaboration Oxford and Thames Valley, the Mohn-Westlake Foundation, NHS England, and the Health Foundation; all DataLab staff are supported by BG's grants on this work. LS reports grants from Wellcome, MRC, NIHR, UKRI, British Council, GSK, British Heart Foundation, and Diabetes UK outside this work. AYSW holds a fellowship from BHF. JPB is funded by a studentship from GSK. AS is employed by LSHTM on a fellowship sponsored by GSK. KB holds a Sir Henry Dale fellowship jointly funded by Wellcome and the Royal Society (107731/Z/15/Z). HIM is funded by the NIHR Health Protection Research Unit in Immunisation, a partnership between Public Health England and LSHTM. RM holds a Sir Henry Wellcome fellowship. EW holds grants from MRC. ID holds grants from NIHR and GSK. HF holds a UKRI fellowship. The views expressed are those of the authors and not necessarily those of the NIHR, NHS England, Public Health England or the Department of Health and Social Care.

This research was funded in part by Wellcome, For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript (AAM) version arising from this submission.

Funders had no role in the study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Authors' contributions

Contributions are as follows:

Conceptualization LS BG ID;

Data curation CB JP JC SH SB DE PI CM;

Formal Analysis AYSW JB;

Funding acquisition BG LS;

Information governance AM BG CB;

Methodology ID AYSW LT AS EP WE KW KB CTR EW SJWE LS JB CM AJW BM SB RE BG;

Disease category conceptualisation and codelists AYSW LT WE BM CM AJW RC AS CTR PI SB DE CB JC HC KB AM ID HM RM HF RE;

Ethics approval HC EW LS BG;

Project administration AYSW BM CM AS AJW CTR WH CB SB AM LS BG;

Resources BG LS;

Software SB DE PI AJW CM CB JC;

Supervision ID BG;

Visualisation AYSW JB;

Writing (original draft) AYSW ID JB;

All authors were involved in design and conceptual development and reviewed and approved the final manuscript.

Acknowledgements

We are very grateful for all the support received from the TPP Technical Operations team throughout this work; for generous assistance from the information governance and database teams at NHS England / NHSX.

References

1. Fauvel C, Weizman O, Trimaille A, et al. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J*. Published online July 13, 2020. doi:10.1093/eurheartj/ehaa500
2. Paranjpe I, Fuster V, Lala A, et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. *J Am Coll Cardiol*. 2020;76(1):122-124.
3. Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, Mortality, Bleeding and Pathology Among Patients Hospitalized with COVID-19: A Single Health System Study. *J Am Coll Cardiol*. Published online August 24, 2020. doi:10.1016/j.jacc.2020.08.041
4. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099.
5. Lopes RD, de Barros E Silva PGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2021;397(10291):2253-2263.
6. Lacoïn L, Lumley M, Ridha E, et al. Evolving landscape of stroke prevention in atrial fibrillation within the UK between 2012 and 2016: a cross-sectional analysis study using CPRD. *BMJ Open*. 2017;7(9):e015363.
7. Inciardi RM, Adamo M, Lupi L, Metra M. Atrial fibrillation in the COVID-19 era: simple bystander or marker of increased risk? *Eur Heart J*. 2020;41(32):3094.
8. Russo V, Di Maio M, Attena E, et al. Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: A multicenter observational study. *Pharmacol Res*. 2020;159:104965.
9. Tremblay D, van Gerwen M, Alsen M, et al. Impact of anticoagulation prior to COVID-19 infection: a propensity score--matched cohort study. *Blood, The Journal of the American Society of Hematology*. 2020;136(1):144-147.
10. Chocron R, Galand V, Cellier J, et al. Anticoagulation prior to hospitalization is a potential protective factor for COVID-19: insight from a French multicenter cohort study. *J Am Heart Assoc*. Published online February 8, 2021:e018288.
11. Harrison RF, Forte K, Buscher MG Jr, et al. The Association of Preinfection Daily Oral Anticoagulation Use and All-Cause in Hospital Mortality From Novel Coronavirus 2019 at 21 Days: A Retrospective Cohort Study. *Crit Care Explor*. 2021;3(1):e0324.
12. Rivera-Caravaca JM, Núñez-Gil IJ, Vivas D, et al. Clinical profile and prognosis in patients on oral anticoagulation before admission for COVID-19. *Eur J Clin Invest*. 2021;51(1):e13436.
13. Ho G, Dusendang JR, Schmittiel J, Kavecansky J, Tavakoli J, Pai A. Association of chronic anticoagulant and antiplatelet use on disease severity in SARS-COV-2 infected patients. *J Thromb Thrombolysis*. Published online February 1, 2021. doi:10.1007/s11239-021-02383-w
14. Flam B, Wintzell V, Ludvigsson JF, Mårtensson J, Pasternak B. Direct oral

- anticoagulant use and risk of severe COVID-19. *J Intern Med*. 2021;289(3):411-419.
15. Fröhlich GM, Jeschke E, Eichler U, et al. Impact of oral anticoagulation on clinical outcomes of COVID-19: a nationwide cohort study of hospitalized patients in Germany. *Clin Res Cardiol*. Published online January 8, 2021. doi:10.1007/s00392-020-01783-x
 16. Rossi R, Coppi F, Talarico M, Boriani G. Protective role of chronic treatment with direct oral anticoagulants in elderly patients affected by interstitial pneumonia in COVID-19 era. *Eur J Intern Med*. 2020;77:158-160.
 17. Spiegelenberg JP, van Gelder MMHJ, Maas ML, et al. Prior use of therapeutic anticoagulation does not protect against COVID-19 related clinical outcomes in hospitalized patients: a propensity score-matched cohort study. *Br J Clin Pharmacol*. Published online April 25, 2021. doi:10.1111/bcp.14877
 18. Schiavone M, Gasperetti A, Mancone M, et al. Oral anticoagulation and clinical outcomes in COVID-19: An Italian multicenter experience. *Int J Cardiol*. 2021;323:276-280.
 19. Denas G, Gennaro N, Ferroni E, et al. Reduction in all-cause mortality in COVID-19 patients on chronic oral anticoagulation: A population-based propensity score matched study. *Int J Cardiol*. 2021;329:266-269.
 20. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125-e151.
 21. National Institute for Health and Care Excellence. Recommendations | Atrial fibrillation: management | Guidance. Accessed September 4, 2020. <https://www.nice.org.uk/guidance/cg180/chapter/1-Recommendations>
 22. In those patients with atrial fibrillation with a record of a CHA2DS2-VASc score of 2 or more, the percentage of patients who are currently treated with anticoagulation drug therapy | NICE Quality and Outcomes Framework indicator | Standards and Indicators | NICE. Accessed April 19, 2021. <https://www.nice.org.uk/standards-and-indicators/qofindicators/in-those-patients-with-atrial-fibrillation-whose-latest-record-of-a-cha2ds2-vasc-score-is-2-or-above-the-percentage-of-patients-who-are-currently-treated-with-anti-coagulation-drug-therapy>
 23. Williamson EJ, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature*. Published online July 8, 2020. doi:10.1038/s41586-020-2521-4
 24. Coronavirus (COVID-19): scaling up our testing programmes. Accessed May 5, 2021. <https://www.gov.uk/government/publications/coronavirus-covid-19-scaling-up-testing-programmes/coronavirus-covid-19-scaling-up-our-testing-programmes>
 25. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ*. 2019;364:k4810.
 26. Steinhubl SR, Eikelboom JW, Hylek EM, Dauerman HL, Smyth SS, Becker RC. Antiplatelet therapy in prevention of cardio- and venous thromboembolic events. *J Thromb Thrombolysis*. 2014;37(3):362-371.

27. Ding P, VanderWeele TJ. Sensitivity Analysis Without Assumptions. *Epidemiology*. 2016;27(3):368-377.
28. Du L, Kao RY, Zhou Y, et al. Cleavage of spike protein of SARS coronavirus by protease factor Xa is associated with viral infectivity. *Biochem Biophys Res Commun*. 2007;359(1):174-179.
29. Miyachi H, Masukawa A, Ohshima T, et al. Monitoring of inhibitors of enzymatic amplification in polymerase chain reaction and evaluation of efficacy of RNA extraction for the detection of hepatitis C virus using the internal control. *Clin Chem Lab Med*. 1998;36(8):571-575.
30. Kirstein LM, Mellors JW, Rinaldo CR Jr, et al. Effects of anticoagulant, processing delay, and assay method (branched DNA versus reverse transcriptase PCR) on measurement of human immunodeficiency virus type 1 RNA levels in plasma. *J Clin Microbiol*. 1999;37(8):2428-2433.
31. Ruigómez A, Johansson S, Wallander M-A, García Rodríguez LA. Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. *BMC Cardiovasc Disord*. 2005;5:20.
32. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;75(23):2950-2973.
33. Hanif A, Khan S, Mantri N, et al. Thrombotic complications and anticoagulation in COVID-19 pneumonia: a New York City hospital experience. *Ann Hematol*. 2020;99(10):2323-2328.
34. Al-Samkari H, Gupta S, Leaf RK, et al. Thrombosis, Bleeding, and the Observational Effect of Early Therapeutic Anticoagulation on Survival in Critically Ill Patients With COVID-19. *Ann Intern Med*. Published online January 26, 2021. doi:10.7326/M20-6739
35. Hsu A, Liu Y, Zayac AS, Olszewski AJ, Reagan JL. Intensity of anticoagulation and survival in patients hospitalized with COVID-19 pneumonia. *Thromb Res*. 2020;196:375-378.
36. Zhou J, Lee S, Guo CL, et al. Anticoagulant or antiplatelet use and severe COVID-19 disease: A propensity score-matched territory-wide study. *Pharmacol Res*. Published online 2021. <https://www.ncbi.nlm.nih.gov/pmc/articles/pmc7846462/>
37. Rentsch CT, Beckman JA, Tomlinson L, et al. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. *BMJ*. 2021;372:n311.

Table 1. List of sensitivity analyses

Sensitivity analysis	Justification
1. In addition to the covariates identified by DAG, other covariates based on prior evidence of likely confounders such as chronic obstructive pulmonary disease, other respiratory diseases, cancer, immunosuppression, chronic kidney disease, general practice attendance rate in the year prior to cohort entry, and A&E attendance rate in the year prior to cohort entry were also included in the fully-adjusted models (stratified by general practice).	To test the robustness of the covariate selection.
2. Additionally adjusted for ethnicity in DAG and fully-adjusted models. In the fully adjusted models, additional covariates included chronic obstructive pulmonary disease, other respiratory diseases (not including asthma), cancer, immunosuppression, chronic kidney disease, General Practice attendance rate in the year prior to cohort entry, and Accident & Emergency attendance rate in the year prior to cohort entry.	In the main analysis, we did not adjust for ethnicity as a sizable proportion of individuals with missing ethnicity (~23%). We undertook complete case analysis to address missing data.
3. Repeated main analysis excluding people prescribed antiplatelets 4 months before study start date	To explore the impact of use of antiplatelet which can reduce the risk of blood clots.
4. Limited the study cohort to people who aged 55 or above	To explore the impact of potential confounders at a young age, for example, pregnancy.
5. Stratified the cohort according to the care home residence for the outcome of testing positive for SARS-CoV-2 (<i>post-hoc</i> analysis)	To explore the impact of health behaviour as people living in care homes were less likely to have differences in behaviour.

Figure 1: Study diagram

Figure 2: Flowchart of inclusion of participants

Figure 3. Hazard ratios of the association between current use of oral anticoagulants and COVID-19 related outcomes, versus non-use in people with atrial fibrillation who had a CHA₂DS₂-VASc score of 2.