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Clinical outcomes and the impact of prior oral anticoagulant use in patients with COVID-19 admitted to hospitals in the UK – a multicentre observational study.

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Abstract

Coagulation dysfunction and thrombosis are major complications in patients with COVID-19. Patients on oral anticoagulants (OAC) prior to diagnosis of COVID-19 may therefore have better outcomes. In this multicentre observational study of 5883 patients (≥18 years) admitted to 26 UK hospitals between 1st of April to 31 July 2020, overall mortality was 29.2%. Incidences of thrombosis, major bleeding (MB) and multiorgan failure (MOF) were 5.4%,1.7% and 3.3% respectively. The presence of thrombosis, MB, or MOF were associated with a 1.8, 4.5 or 5.9-fold increased risk of dying, respectively.

Of the 5883 patients studied, 83.6% (n=4920) were not on OAC and 16.4% (n=963) were taking OAC at the time of admission. There was no difference in mortality between patients on OAC vs no OAC prior to admission when compared in an adjusted multivariate analysis (HR1.05(95%CI 0.93-1.19),P=0.15) or in an adjusted propensity score analysis (HR0.92(95%CI0.58-1.450, P=0.18). In multivariate and adjusted propensity score analyses, the only significant association of no anticoagulation prior to diagnosis of COVID-19 was admission to ICU (HR1.98[95%CI1.37-2.85]). Thrombosis, MB, and MOF were associated with higher mortality. Our results indicate that patients may have benefit from prior OAC use especially reduced admission to ICU, without any increase in bleeding.

Key words

coronavirus disease 2019; anticoagulation; bleeding; thrombosis; multiorgan failure; mortality

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Introduction

Coagulation dysfunction and thrombosis, primarily manifesting as pulmonary embolism (PE) or pulmonary thrombosis, are major complications in patients with coronavirus disease 2019 (COVID-19) (1). Low molecular weight heparin (LMWH) thromboprophylaxis within 24hrs of admission decreased the risk of 30-day mortality with no increased risk of major bleeding events (2). Furthermore, clinical benefit of treatment dose LMWH over prophylactic dose was found in patients with moderate COVID-19 disease, though not in patients with severe disease, in the multiplatform clinical trials (3). In addition to anticoagulant properties, heparin has both anti-inflammatory and anti-complement effects, and may also reduce viral cell entry (4). We hypothesised that if the anticoagulant effect was responsible, patients on oral anticoagulants (OAC) such as warfarin and direct acting oral anticoagulants (DOACs) prior to admission may have better outcomes compared to similar group of patients who were not on anticoagulants. Moreover, in the United Kingdom (UK), accurate multicentre data detailing the incidence and nature of thrombotic and bleeding complications in hospitalised patients with COVID-19 are lacking.

In this study, we assessed the 90-day mortality, incidence of thrombosis, major bleeding and, multiorgan failure (MOF) in patients with COVID-19 admitted to 26 UK National Health Service (NHS) Trusts as well as the impact of thrombosis, major bleeding, and MOF on their mortality. We estimated the effects of OAC prior to admission on clinically important outcomes: the development of thrombosis or multi-organ failure (MOF), requirement for Intensive Care Unit (ICU) admission and mortality, compared to a propensity matched cohort of patients not taking OAC prior to admission to the same hospitals during the same period.

Methods

This study is reported according to the strengthening the reporting of observational studies in epidemiology (STROBE).

Study design and Data collection

Coagulopathy associated with COVID-19 (CA-COVID-19) is a multicentre observational study across 26 UK NHS Trusts (listed in supplementary appendix page 1-2).

The study was approved by the Health Research Authority (HRA), Health and Care Research Wales (HCRW) and received local Caldicott Guardian support in Scotland (reference number: 20/HRA/1785). Data was collected both retrospectively and prospectively from patient clinical records by the treating medical team with no breach of privacy or anonymity by allocating a unique study number with no direct patient identifiable data; therefore, consent was waived by the HRA.

We included adult patients (≥18 years) admitted to hospital between 1st April 2020 and 31st July 2020. All patients had SARS-CoV-2 confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) on nasopharyngeal swabs or lower respiratory tract aspirates. Exclusion criteria included the absence of positive COVID-19 PCR test, parenteral anticoagulation with LMWH or Fondaparinux on admission and a history of a bleeding disorder.

Data collection

Data was entered directly by clinicians onto a bespoke standardised case report form (CRF) held on a central electronic database (Coagulopathy associated with COVID-19 [CA-COVID-19]), secure REDcap database (REDcap v10.0.10; Vanderbitt University, US) hosted by Imperial College London. Baseline patient demographics, comorbidities, haematology, and biochemical blood results on the day of admission and clinical outcomes until the day of discharge/death were collected. At the time of writing this paper, all patients had completed follow-up until day 90 post hospital admission or death.

Types and doses of oral anticoagulants prior to admission

Oral anticoagulants prior to admission included DOACs (Rivaroxaban 20mg, 15mg or 10mg daily, Apixaban 5mg or 2,5mg daily or Edoxaban 30mg or 60mg daily, Dabigatran 110mg bd or 150mg bd) or Warfarin. Patients on LMWH or fondaparinux before admission were specifically excluded in this study as the study aimed to assess the effect of oral anticoagulants on clinical outcomes in patients with COVID-19. LWMH or fondaparinux may have other effects in addition to the anticoagulation such as anti-inflammatory or anti-complement which may contribute to better outcomes in these patients.

Anticoagulation after admission to hospital

It is standard practice in the UK to give at least a prophylactic dose LWMH to all patients admitted to hospital with COVID-19 unless contraindicated for example presence of bleeding disorders, major bleeding, or platelet count <30x109/L, or to continue therapeutic anticoagulation if already on treatment dose anticoagulation. Of the 963 patients on OACs prior to admission, in 136 patients (14.1%) anticoagulation was changed to LMWH (71 enoxaparin, 31 Dalteparin and 30 Tinzaparin) on the day of admission and others continued the oral anticoagulation unless this was changed to LMHW or UFH later during admission if they developed thrombosis, admission to ICU or developed renal failure or other reason to withhold anticoagulation such as a bleeding event or invasive procedure.

Outcomes

The primary outcome was 90-day mortality. Secondary outcomes were thrombosis, major bleeding, the development of MOF, and ICU admission.

Definitions of clinical outcomes

All-cause mortality was classified as directly related to COVID-19, directly related to thrombosis, directly related to bleeding, or related to other causes as verified by two experts independently for the death certificate.

Thrombosis and bleeding complications

Thrombotic events were defined as radiologically confirmed pulmonary embolism (PE), deep vein thrombosis (DVT) or arterial thrombosis. Major bleeding events were defined according to International society on thrombosis and haemostasis (ISTH) classification (5) (table S1).

Multiorgan failure

This was defined as failure of two or more organ systems that require interventions to maintain homeostasis.

Admission to an intensive care unit

This was defined as patients who required continuous positive airway pressure ventilation (CPAP) or mechanical ventilation or required other organ support. Patients supported with

extracorporeal membrane oxygenation were excluded due to the associated risk of thrombosis and major bleeding.

Statistical analysis

To identify factors associated with the probability of survival, Kaplan-Meier curves were compared using the log-rank test. Factors found to be statistically significant at the $P<0.2$ level were then entered into a stepwise Cox regression analysis, to produce a final model that encompassed all independent prognostic factors significant at $P<0.05$. Identification of significant independent prognostic factors for the secondary outcomes of thrombosis, major bleeding, MOF, and admission to ICU, required the use of the cumulative incidence procedure with Gray's test to compare groups, and the Fine and Gray model for the multivariate setting. Death in the absence of the secondary outcome was considered the competing event. The effects of secondary outcomes on mortality were assessed by Cox proportional hazards models incorporating the secondary outcomes as time-dependent covariates.

The characteristics of patients who had received anticoagulants prior to admission were compared to those of patients who did not, using the Chi-squared or Chi-squared trend test. To reduce the effects of confounding, logistic regression was used to calculate individual propensity scores for treatment with anticoagulants prior to admission, using the covariates significantly associated with a given outcome. Propensity score matching was performed using the nearest neighbours method, with a desired ratio of 1:1 between untreated (not on oral anticoagulants on admission) and treated (on oral anticoagulants on admission) patients for each clinical outcome. Covariates used for propensity score matching are described in appendix page 4. An example of a love plot for propensity score matching to assess primary clinical outcome (mortality) is presented in Figure S1. The characteristics of the treated and untreated patients were summarised and compared using descriptive statistics.

The adherence to proportionality in the multivariate models was assessed by visual inspection of plots of cumulative hazards over time. Multiple imputation was used to account for missing laboratory values but not for comorbidities or clinical outcomes as there were no missing values. Multiple imputation by chained equation (MICE) technique with its regression imputation model was used for this imputation with ten iterative cycles (see appendix page 3 for full details). All tests were 2-sided, and the analyses were performed using either SPSS

version 27, R or Stata and open source software programming languages and libraries (Python, R, panda, numpy, scikit learn). Further details of statistical analysis are given in the appendix page 3).

Results

Overall, 5883 patients admitted to 26 NHS Trusts in the UK with COVID-19 between 1st of April and 31st of July 2020 were included in this analysis (Fig 1). Median age in the cohort was 74 years (interquartile range 56-84years) and 55.2 % (3247 /5883) were male. Patient and clinical characteristics are summarised in Table 1.

All patient group: Outcomes

Primary outcome: Mortality

Mortality at days 30 and 90 was 28.0% (1648 /5883) and 29.2% (1719/5883), respectively. In multivariate analysis, male sex (Hazard ratio [HR] 1.15 [95%CI 1.04-1.3]) , body mass index (BMI) >39.9 kg/m^2 (HR 1.49 [95% CI 1.1-2.0]), presence of diabetes (HR 1.24 (95% CI 1.1-1.4)) and lung disease (HR 1.12 [95%CI 1.01-1.25]) were independently associated with increased risk of death (Table 2). The effect of age is a gradual increase in mortality risk with advancing age of the patient with the highest HR for patients age >89 years (HR 17.8 [95%CI 9.4-33.7]) compared patients age <40 years (Table 2). Higher lactate, troponin I, activated partial thromboplastin time (APTT), C-reactive protein (CRP), white cell and lymphocyte counts, and lower platelet count on admission were also independently associated with an increased risk of death (Table 2).

Secondary outcomes

Thrombosis

In total, 320 patients developed venous or arterial thrombosis (320/5883, 5.5%), of which 241 (4.1%) were venous and 79 (1.3%) were arterial. The rates of venous thrombosis (VTE) in patients treated on ward and ICU were 119/5044 (2.4%) and 122/789 (15.5%), respectively. Arterial thrombosis rates in patients treated on ward and ICU were and 57/5044 (1.1%) and 22/789 (2.8%).

Of the venous thromboses, 202 (202/241, 84%) were PE, 24 were deep vein thrombosis (DVT) (24/241, 10%) and 15 were PE & DVT (15/241,6%). Of patients who developed arterial thrombosis, 49 patients (49/79, 62.0%) developed ischaemic strokes, 12 (12/79, 15.2%) developed acute coronary syndrome and 18 (18/79, 22.8%) developed arterial thrombosis elsewhere.

Major bleeding

In total 99 patients had major bleeding events (99/5883, 1.7%) of which 36/99 (36.4%) were fatal, with intracerebral haemorrhage (32/36 (88.9%)) being the predominant site. Rates of major bleeding in patients treated on ward and ICU were 43/5044 (1.01%) and 56/789 (7.1%) respectively. Of these major bleeds, 30% were intracerebral bleeding, irrespective of the patient's location.

Multiorgan failure (MOF)

A total of 194 patients developed MOF during the hospital admission equating to incidence of 3.3% (194/5883).

Impact of secondary outcomes on mortality in the overall study group

In multivariate analysis for mortality for the whole study group, which included all previously identified prognostic factors, and development of any thrombosis (venous or arterial) included as a time dependent covariate, patients with thrombosis had a 1.8 increased risk of mortality (95%CI 1.4-2.3) compared to patients with no thrombosis. Similarly, independent analyses also revealed increases in risk of mortality for patients with major bleeding (HR 4.5 [95%CI 3.2-6.3]) and MOF (HR 5.9 [95%CI 4.7-7.5])

Effects of oral anticoagulant prior to admission on clinical characteristics

Of the 5883 patients included in this study, 963(16.7%) were taking an OAC therapy prior to admission to hospital. Of the 963 patients on oral anticoagulant therapy prior to admission to hospital, most of them were taking Apixaban (410,42.6%) followed by Rivaroxaban (313, 32.5%), Warfarin (187, 19.4%), Edoxaban, (38,3.9%) and Dabigatran (15,1.6%). Of these 963 patients on OACs, 20.4% (196/963) were taking OACs for prevention of recurrent VTE, 61.5%

(592/963) for atrial fibrillation with or without history of stroke and 18.2% (175/963) for cardiovascular disease including valvular heart disease.

Table 3 summarises the baseline clinical and laboratory characteristics of the populations with and without the prescription of an OAC at the point of admission pre and post propensity matching.

Patients on OACs were older than those who were not on anticoagulation (p<0.001) and 57 % (550/963) versus vs 32 % (1593/4920) were ≥80 years. Patients on OACs more frequently had a history of VTE (196/ 963, 20.3% vs 134/4920, 2.7%, p<0.001). The incidence of other comorbidities (malignancy, hypertension, hypercholesterolaemia, heart disease, diabetes, lung disease and existing renal failure) were also higher in those on OACs (p<0.001, Table 3). Of note, a higher proportion of patients not on OACs were on antiplatelet therapy (1026/4920, 20.8% vs 67/963, 7.0 %, p <0.001).

Baseline laboratory characteristics of the entire population, comparing patients admitted with oral anticoagulants against those not on anticoagulants prior to admission.

There were significant differences in haemoglobin, lactate, troponin I, prothrombin time (PT), activated partial thromboplastin time (APTT), platelet count, alanine transferase (ALT), bilirubin, creatinine and C-reactive protein (CRP) levels between patients on OACs vs no OACs on admission to hospital (Table 3).

Baseline clinical and laboratory characteristics of propensity score-matched patients admitted with oral anticoagulants against those not on anticoagulants prior to admission.

Following propensity score-matching using covariates that were significantly associated with being on OACs, the only difference in the baseline clinical characteristics was a higher proportion of patients with a history of VTE in the OAC group [196/963 (20.35%) vs 104/963 (10.8%), p<0.001]. CRP and lactate levels also remained significantly higher in the no-anticoagulation group after propensity-score matching (Table 3). Furthermore, a higher

proportion of no-anticoagulant patients had raised white cell counts (p=0.001) and D-dimer measurements (p 0.002), which were not statistically significant prior to propensity score-matching (Table 3).

Effects of oral anticoagulants prior to admission on clinical outcomes

Mortality in patients on anticoagulation compared to no anticoagulation prior to admission.

Overall, 35.9% (346/963) of patients on OACs died, compared to 27.9% (1373/4920) of patients not on OACs prior to admission, equating to a 26% relative reduction in mortality (HR 0.74 (95%CI 0.65-0.83), P<0.0001) in the non-anticoagulated group (Figure 2A). However, there was no difference in mortality between the two groups when they were compared in an adjusted multivariate analysis (HR 1.05 (95%CI 0.93-1.19) P=0.15) or in an adjusted propensity score analysis (HR 0.92 (95%CI 0.58-1.450, P=0.18) (Figure 2B),

Thrombosis

Of the 320 patients who developed thrombosis, 28 (28/320, 8.8%) were on OACs at admission and 292 were not (292/320, 91.2%). In crude analysis of the unadjusted dataset, patients not on OACs at admission had an increased risk of 2.08 of developing thrombosis during hospital admission (95% CI1.42-3.06), compared to patients OACs. However, in multivariate analysis (HR 1.18 (95% CI 0.64-2.18)) and adjusted propensity score analysis (HR 1.38 (95% 0.33-1.62)) this was no longer significant.

Major bleeding

Of the 99 patients experiencing major bleeding events, 13/963 (1.3%) were on OACs and 86/4920 (1.7%) were not on OACs prior to admission. In crude analysis of the unadjusted dataset, patients not on OACs had an increased risk of 1.30 of developing major bleeding during admission, compared with those on anticoagulants, but this was not significant (95% 0.70-2.30). This finding was confirmed by adjusted multivariate analysis (HR 1.18 (95% CI 0.47-1.55) and adjusted propensity score analysis (HR 1.49 (95%CI 0.80-2.80).

Multiorgan failure

Of the 194 patients that developed MOF in the entire cohort of the study, 10/194 (5.2%) were on OACs and 184/194 (94.8%) were not on OACs, corresponding to a 3.64-fold risk (95% CI 1.93-6.90) in unadjusted analysis. Although patients not on OACs prior to admission remained at higher risk of developing MOF after adjusted multivariate analysis (HR 1.86 [95% CI 0.98-3.61]) and adjusted propensity score analysis (HR 1.53 (95% CI 0.70-3.33), the increases were no longer statistically significant.

Admission to intensive care unit

Of the total of 5883 patients included in this study, only patients aged <90 years (n= 5416) were included in the analysis of admission ICU as the patients age ≥90 were not considered to intensive care treatment. Propensity matched analysis was performed of the adjusted age and other comorbidities. Of the 789/5416 patients admitted to ICU, 45/789 (5.7%) were on OACs and 744/789 (94.3%) were not on OACs at admission. In crude analysis, patients not on OACs had a 3.11-fold (95%CI 2.30-4.20) increase in risk of going to ICU. This association remained significant in both adjusted multivariate analysis (HR 1.87 [95%CI 1.37-2.57]) and adjusted propensity score analysis (HR 1.98 [95%CI 1.37-2.85]).

Discussion

This is the largest study to date assessing the mortality, thrombosis, major bleeding, MOF, and admission to ICU in patients with COVID-19, comprising 5883 patients. Overall, 90-day mortality was 29.2%, incidence of thrombosis was 5.5%, with 4.1% and 1.3% of these being VTE and arterial thrombosis, respectively. The incidence of major bleeding events was 1.7% of which 36.4% were fatal, mainly due to intracerebral haemorrhage (88.9%).

There was no difference in mortality between patients on OACs vs no OACs prior to admission when compared in an adjusted multivariate analysis or in an adjusted propensity score analysis and the only significant association of no OACs prior to admission was treatment in intensive care unit (HR 1.98 [95% CI 1.37-2.85]). Additionally, patients on OACs prior to admission showed a reduced inflammatory response.

Overall mortality in this study was similar to the data from Hospital Episode Statistics in the UK which included 91,541 adult patients with COVID-19 and 28,200 (30·8%) deaths. Our data

are also in keeping with the multiplatform trial results to date(6). Our finding of the overall predictors of mortality of being male, increasing age, body mass index, diabetes mellitus and lung disease confirmed the findings from other larger studies(7). There is a very large variation in the reported rates of thrombosis and major bleeding complications in patients admitted to UK hospitals from small single centre cohort studies which were higher than the observed rates in this CA-COVID19 multicentre study (8-10) but similar to the study by Salisbury et al(11). A multicentre retrospective study in the USA with 400 hospital-admitted COVID-19 patients (144 critically ill) reported overall thrombotic complications in 9.5% (VTE rate was 4.8%) and major bleeding in 2.3%(1). In those admitted to ICU, VTE and major bleeding rates were 7.6% and 5.6% respectively. Although the overall thrombotic and the major bleeding rates were lower in our study, these events were higher in patients treated in ICU in our study compared to the US study(1). The observed difference in these complications are most likely due to patient selection for admission to ICU and the variation in anticoagulant practices between the two countries. In a meta-analysis of 102 studies including 64,503 patients, the overall frequency of VTE (14.7%) and arterial thrombosis (3.9%) were much higher than our study. Several studies have reported that thrombosis is associated with increased risk of death(12), and here we observe that the presence of thrombosis, major bleeding or MOF are associated with 1.8, 4.5 and 5.9-fold increased risk of dying respectively.

Crude mortality in hospital was higher amongst patients already taking anticoagulants at the time of admission. We expected that this may well be the case due to the underlying comorbidities and advancing age leading to the prescription of anticoagulant therapy. We therefore used multivariate analysis and propensity score-matching to correct for these confounding effects, after which the increase in mortality was lost. Notably there was no difference in bleeding between the groups, which might have offset any benefit from anticoagulation, in either the adjusted or unadjusted analyses.

The unadjusted risks for thrombosis and MOF were lower for patients on OACs. This is slightly surprising given the increase in mortality, but again these differences were not statistically significant in the adjusted and propensity score-matched analyses. This finding suggests that patients with identifiable risk factors may benefit from therapeutic anticoagulation, a question currently being studied in large platform trials(6). Data from these studies so far indicate that therapeutic anticoagulation may be beneficial for moderately ill patients and

reduce the need for organ support. Patients taking oral anticoagulants may therefore benefit from earlier anticoagulation but are frequently using anticoagulation for cardiovascular disorders which are themselves associated with poor outcomes from COVID-19. Moreover, these patients would require continuation of anticoagulation throughout their admission whilst the adaptive studies showed that for severely ill patients requiring organ support, therapeutic anticoagulation was associated with poorer outcomes associated with an excess of bleeding. Consequently, the balance of risk and benefit for these patients is unclear. Indeed, the only positive association remaining after adjustments and propensity-score matching is a reduced rate of admission to ICU, implying that this benefit is attributable to the anticoagulation itself. This is interestingly also borne out by the retained significantly reduced lab parameters such as C-reactive protein, white cell count and lactate levels that are associated with risk of adverse clinical outcomes in patients admitted with OACs (Table3).

Results from previous studies investigating the role of OACs prior to admission in patients with COVID-19 have varied(13-16). Table 4 summarised the some of the studies assessing the role of OACs in COVID-19. Variations in reported associations probably derive from the underlying disease state that required anticoagulation prior to diagnosis of COVID-19, covariates used for propensity matching when comparing with patients not on OACs, inclusion and exclusion criteria, and the OACs type and dose. Of note, many of these studies have propensity score-matched sample sizes of approximately 100 patients per arm and assessed only mortality as an outcome, with few considering thrombosis and bleeding(13-15). The largest of those studies included 4697 patients in total, with 559 per arm in its propensity score-matched analysis. However, unlike our study, they included patients on anticoagulants for atrial fibrillation only, and excluded patients < 65 years(16). In contrast to our study, admission to ICU was comparable between the patients on OACs and no OACs prior to admission, and all-cause mortality was significantly lower among patients on OACs (26.5% vs. 32.2%; HR 0.82 [95%CI 0.68–0.99]. However, in the time-to-event analysis all-cause mortality lost its statistical significance, (HR 0.8, 95%CI 0.65 – 1.01, p=0.054) which is similar to our findings.

Thrombosis and raised D-dimer levels in patients with COVID-19 were associated with increased risk of mortality(12, 17-19). Systemic inflammation, endotheliitis and activation of the complement system contribute to the prothrombotic state in COVID-19(20), and their

reduction by anticoagulants may be beneficial(2, 21, 22). This may be less so for oral anticoagulants than for heparin (21).

Although multiple clinical trials are in progress assessing the effects of various doses of heparin and DOACs in patients with COVID-19 admitted to hospitals(23) , none of these are able to assess the role of OACs prior to admission and prior to diagnosis of COVID-19 on clinical outcome. Therefore, our study provides the best possible evidence for the role of OACs prior to diagnosis of COVID-19 on mortality, thrombosis, major bleeding, MOF, and admission to ICU in patients admitted to hospitals.

This national report from the CA-COVID-19 is strengthened by its breadth, including 26 NHS Trusts across UK, using predefined electronic CRF to capture data. We used propensity score matching to mimic a hypothetical clinical trial including almost all covariates that can be associated with patients on oral anticoagulants.

Our study has important limitations. First, we were unable to externally validate the submitted data or confirm that all consecutive patients were recruited. Participating centres were self-selected and well-resourced which may have introduced bias. Data collection was both retrospective and prospective in nature, but the pre-designed eCRF preserved uniformity. Doses of oral anticoagulants and INR targets for patients on warfarin varied and these details were not collected. Although after propensity score matching the included covariates were fairly well balanced, confounders not included in the propensity score could lead to significant bias. Additionally, the commonest indications for anticoagulation prior to diagnosis COVID-19 were atrial fibrillation with or without stroke, history of VTE and mechanical heart valves, and it was not possible to do a complete matching for all these factors.

Conclusions

Our results provide real-world evidence that patients on OACs may continue to benefit from this therapy after admission especially with regards to reducing admission to ICU and with a trend towards improved survival. The benefit of being on oral anticoagulants in this group of patients is not offset by any increase in bleeding. Presence of thrombosis, major bleeding or MOF are associated with 1.8, 4.5 and 5.9-fold risk of mortality, respectively, in patients

admitted to hospital with COVID-19 irrespective of being on anticoagulant or not prior to the admission. This illustrates the fine balance between prevention of thrombosis and avoiding major bleeding and emphasises the need for the correct anticoagulant regimen in these patients.

Contributors

DJA conceptualised the study and acquired the funding acquisition and lead for the methodology, project administration, validation, visualisation, writing the original draft reviewing and editing the study as well as being involved in data curation. IR was involved with formal analysis, software and valuation of the study as well as supporting the review & editing of the paper. ZO was involved with data curation, formal analysis, software and valuation of the study as well as supporting the review & editing of the paper. PN supported the conceptualisation, project administration, resources and review of editing of this study and was involved with data curation, RS lead formal analysis of the study, was involved with software and validation and supported resources and review and editing of the study. MM supported Data curation, Project administration, resources, validation of the study and was involved in review and editing of the study. ML supported the conceptualisation, data curation, methodology of the study and was involved in its validation, review and editing. All other authors supported data curation, project administration, resources the review and editing of the study.

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Competing interest

DJA received funding from Bayer plc to setup the multicentre database of the study as an investigator-initiated funding and received research grant from Leo Pharma. ML received consultation and speaker fees from Astra-Zeneca, Sobi, Leo-Pharma, Takeda and Pfizer. PN received research grants from Novartis, Principia and Rigel, unrestricted grants from Sanofi, Chugai and Octapharma and honoraria from Bayer. RA received fees from Alexion, Bayer, BMS, Pfizer and Portola. SS has received meeting sponsorship, speaker fees and/or consultancy from Bayer, Pfizer, NovoNordisk, Sobi, Chugai/Roche and Shire/Takeda. SS receives funding support from the Medical Research Council (MR/T024054/1). The research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). SL has received speaker fees from Bayer, BMS and Pfizer. Others have no conflict of interests to declare.

References

1. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020;136(4):489-500.
2. Rentsch CT, Beckman JA, Tomlinson L, Gellad WF, Alcorn C, Kidwai-Khan F, 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.
3. Hunt BJ, De Paula EV, McLintock C, Dumantepe M. Prophylactic anticoagulation for patients in hospital with covid-19. Bmj. 2021;372:n487.
4. Mousavi S, Moradi M, Khorshidahmad T, Motamedi M. Anti-Inflammatory Effects of Heparin and Its Derivatives: A Systematic Review. Adv Pharmacol Sci. 2015;2015:507151.
5. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692-4.
6. ATTACC A-aaR-CRoIAJ, 2021. https://static1.squarespace.com/static/5cde3c7d9a69340001d79ffe/t/6013892709de942b53f6e3da/1611893037749/mpRCT+interim+presentation_v21slides+22+and+23+corrected.pdf (accessed May 10, 2021). .
7. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.
8. Desborough MJR, Doyle AJ, Griffiths A, Retter A, Breen KA, Hunt BJ. Image-proven thromboembolism in patients with severe COVID-19 in a tertiary critical care unit in the United Kingdom. Thromb Res. 2020;193:1-4.
9. Arachchillage DRJ, Shi C, Saliu D, Kozman P, Mi E, Buti N, et al. Efficacy Safety and of D-dimer, Weight, and Renal Function-Adjusted Thromboprophylaxis in Patients with Coronavirus Disease 2019 (COVID-19). Semin Thromb Hemost. 2021.
10. Mirsadraee S, Gorog DA, Mahon CF, Rawal B, Semple TR, Nicol ED, et al. Prevalence of Thrombotic Complications in ICU-Treated Patients With Coronavirus Disease 2019 Detected With Systematic CT Scanning. Crit Care Med. 2021;49(5):804-15.
11. Salisbury R, Iotchkova V, Jaafar S, Morton J, Sangha G, Shah A, et al. Incidence of symptomatic, image-confirmed venous thromboembolism following hospitalization for COVID-19 with 90-day follow-up. Blood Adv. 2020;4(24):6230-9.
12. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. EClinicalMedicine. 2020;29:100639.
13. Harrison RF, Forte K, Buscher MG, Jr., Chess A, Patel A, Moylan T, 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.
14. Chocron R, Galand V, Cellier J, Gendron N, Pommier T, Bory O, et al. Anticoagulation Before Hospitalization Is a Potential Protective Factor for COVID-19: Insight From a French Multicenter Cohort Study. J Am Heart Assoc. 2021;10(8):e018624.
15. Schiavone M, Gasperetti A, Mancone M, Curnis A, Mascioli G, Mitacchione G, et al. Oral anticoagulation and clinical outcomes in COVID-19: An Italian multicenter experience. Int J Cardiol. 2021;323:276-80.

16. Denas G, Gennaro N, Ferroni E, Fedeli U, Lorenzoni G, Gregori D, 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;329:266-9.
17. Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, et al. Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. Circulation. 2020;142(2):114-28.
18. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. Jama. 2020;324(8):799-801.
19. Shah S, Shah K, Patel SB, Patel FS, Osman M, Velagapudi P, et al. Elevated D-Dimer Levels Are Associated With Increased Risk of Mortality in Coronavirus Disease 2019: A Systematic Review and Meta-Analysis. Cardiol Rev. 2020;28(6):295-302.
20. Loo J, Spittle DA, Newnham M. COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. Thorax. 2021.
21. Buijsers B, Yanginlar C, Maciej-Hulme ML, de Mast Q, van der Vlag J. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. EBioMedicine. 2020;59:102969.
22. Hippensteel JA, LaRiviere WB, Colbert JF, Langouët-Astrié CJ, Schmidt EP. Heparin as a therapy for COVID-19: current evidence and future possibilities. Am J Physiol Lung Cell Mol Physiol. 2020;319(2):L211-l7.
23. Search on ClinicalTrials.gov hcgc, results?cond=COVID-19&term=anticoagulation.

Legends to tables and figures

Table 1. Personal and clinical characteristics of 5883 patients admitted to hospital with coronavirus disease 2019 (covid-19) included in the primary analysis

Table 2. Multivariate analysis assessing baseline clinical and laboratory characteristics and risk of mortality in the overall population studied (5883 patients)

Table 3 Baseline characteristics (clinical and laboratory) of the entire study population by anticoagulant use, and propensity matched no anticoagulant therapy at the admission to hospitals.

Figure 1. Flow chart of the patient selection and clinical outcomes of the study

Figure 2. Probability of death non-propensity matched patients admitted with oral anticoagulant vs no oral anticoagulants (A) and Probability of death for propensity matched patients admitted with oral anticoagulant vs no oral anticoagulants (B)

Table 1. Personal and clinical characteristics of 5883 patients admitted to hospital with coronavirus disease 2019 (covid-19) included in the primary analysis.

Clinical characteristics		**Total N=5883**	**Percentage**
Gender	Female	2636	44.81%
	Male	3247	55.19%
Age (years)	<40	332	5.64%
	40-49	415	7.05%
	50-59	746	12.68%
	60-69	916	15.57%
	70-79	1331	22.62%
	80-89	1590	27.03%
	>89	553	9.40%
Body Mass Index (Kg/m2)	<24.9	1665	28.30%
	25-29.9	2213	37.62%
	30-39.9	1751	29.76%
	>39.9	254	4.32%
Ethnicity	White	4330	73.60%
	Mixed multiple ethnic	34	0.58%
	Asian / Asian British	333	5.66%
	Black African/Caribbean	179	3.04%
	Other ethnic group	184	3.13%
	Unknown	823	13.99%
COMORBIDITIES			
Diabetes	No	4179	71.04%
	Yes	1704	28.96%
Antiplatelets prior to admission	No	4790	81.42%
	Yes	1093	18.58%
Autoimmune disease	No	5545	94.25%
	Yes	338	5.75%
Hypertension	No	3111	52.88%
	Yes	2772	47.12%
Hypercholesterolemia	No	4976	84.58%
	Yes	907	15.42%
Heart disease	No	4547	77.29%
	Yes	1336	22.71%
Liver disease	No	5672	96.41%
	Yes	211	3.59%
Lung disease	No	4439	75.45%
	Yes	1444	24.55%
Smoking	None	2258	38.38%
	Current smoker	283	4.81%
	Ex-smoker	1242	21.11%
	Unknown	2048	34.81%
Previous VTE	No	5553	94.39%
	Yes	330	5.61%

Existing renal failure	No	4806	81.69%
	Yes	1077	18.31%

VTE= venous thromboembolism.

Table 2. Multivariate analysis assessing baseline clinical and laboratory characteristics and risk of mortality in the overall population studied (5883 patients)

	Subgroup	N (%)	HR (95%CI)	P
Patient gender	Female	2636	1.00	
	Male	**3247**	**1.15 (1.04-1.3)**	**0.005**
Patient age (years)	<40	332	1.00	
	40-49	**415**	**3.85 (2.0-7.6)**	**<0.001**
	50-59	**746**	**5.62 (2.9-10.7)**	**<0.001**
	60-69	**916**	**7.26 (3.8-13.7)**	**<0.001**
	70-79	**1331**	**12.4 (6.6-23.3)**	**<0.001**
	80-89	**1590**	**16.1 (8.6-30.2)**	**<0.001**
	>89	**553**	**17.8 (9.4-33.7)**	**<0.001**
BMI	<24.9	1665	1.00	
	25-29.9	2213	1.04 (0.92-1.6)	0.56
	30-39.9	1751	0.93 (0.81-1.1)	0.31
	>39.9	**254**	**1.49 (1.1-2.0)**	**0.005**
Diabetes	No	4179	1.00	
	Yes	**1704**	**1.24 (1.1-1.4)**	**<0.001**
Lung disease	No	4439	1.00	
	Yes	**1444**	**1.12 (1.01-1.25)**	**0.033**
Lactate (mmol/L)	Normal (0.5-2.1)	4562	1.00	
	Above normal (>2.1)	1321	1.21 (1.08-1.35)	**0.001**
Troponin (ng/L)	Normal (<19.8)	1900	1.00	
	Above normal (>19.7)	**3983**	**1.19 (1.06-1.34)**	**0.004**
APTT (sec)	Normal (26-36)	4550	1.00	
	Below normal (<26.0)	586	1.05 (0.89-1.25)	0.55
	Above normal (>36.0)	**747**	**1.31 (1.06-1.61)**	**0.011**
Platelets (10^9/L)	Normal (150-400)	1001	1.00	
	Below normal (<150)	**4459**	**1.25 (1.10-1.42)**	**0.001**
	Above normal (>400)	423	0.86 (0.71-1.04)	0.13
WBC (10^9/L)	Normal (4.1-11.1)	542	1.00	
	Below normal (<4.1)	4018	1.17 (0.92-1.48)	0.21

	Subgroup	N (%)	HR (95%CI)	P
	Above normal (>11.1)	**1323**	**1.27 (1.14-1.42)**	**<0.001**
Lymphocytes (μL)	Normal (1.3-3.7)	279	1.00	
	Below normal (<1.3)	952	0.96 (0.70-1.32)	0.81
	Above normal (>3.7)	4652	**1.31 (1.08-1.58)**	**0.006**
CRP (mg/L)	Normal (0-10)	553	1.00	
	Above normal (>10)	**5330**	**2.00 (1.62-2.47)**	**<0.001**

The overall predictors of mortality are male, age, body mass index (BMI), diabetes mellitus (DM) and Lung disease. P values <0.05 are shown in bold. BMI= body mass index; VTE= venous thromboembolism; APTT= activated partial thromboplastin time; CRP= C-reactive protein

Table 3 Baseline characteristics (clinical and laboratory) of the entire study population by anticoagulant use, and propensity matched no anticoagulant therapy at the admission to hospitals.

	Subgroup	No anticoagulant therapy, N (%)	On anticoagulant therapy, N (%)	P[1]	Propensity matched no therapy, N (%)	P[2]
Overall		4920	963		963	
Patient gender	Male	2717 (55.2%)	530 (55.04%)	0.92	524 (54.41%)	0.78
	Female	2203 (44.8%)	433 (44.96%)		439 (45.59%)	
Patient age (years)	<40	323 (6.57%)	9 (0.93%)	**<0.001**	6 (0.62%)	0.15
	40-49	407 (8.27%)	8 (0.83%)		11 (1.14%)	
	50-59	710 (14.43%)	36 (3.74%)		47 (4.88%)	
	60-69	823 (16.73%)	93 (9.66%)		85 (8.83%)	
	70-79	1064 (21.63%)	267 (27.73%)		225 (23.36%)	
	80-89	1188 (24.15%)	402 (41.74%)		397 (41.23%)	
	>89	405 (8.23%)	148 (15.37%)		192 (19.94%)	
BMI	<24.9	1324 (26.91%)	341 (35.41%)	**<0.001**	324 (33.64%)	0.073
	25-29.9	1864 (37.89%)	349 (36.24%)		400 (41.54%)	
	30-39.9	1516 (30.81%)	235 (24.4%)		212 (22.01%)	
	>39.9	216 (4.39%)	38 (3.95%)		27 (2.8%)	
Ethnicity	White	3532 (71.79%)	798 (82.87%)	**<0.001**	780 (81%)	0.39
	Mixed multiple ethnic	31 (0.63%)	3 (0.31%)		6 (0.62%)	
	Asian / Asian British	315 (6.4%)	18 (1.87%)		21 (2.18%)	
	Black African/Caribbean	166 (3.37%)	13 (1.35%)		25 (2.6%)	
	Other ethnic group	167 (3.39%)	17 (1.77%)		16 (1.66%)	
	Unknown	709 (14.41%)	114 (11.84%)		115 (11.94%)	
Previous history of VTE	No	4786 (97.28%)	767 (79.65%)	**<0.001**	859 (89.2%)	**<0.001**
	Yes	134 (2.72%)	196 (20.35%)		104 (10.8%)	
Autoimmune disease	No	4648 (94.47%)	897 (93.15%)	0.11	904 (93.87%)	0.52
	Yes	272 (5.53%)	66 (6.85%)		59 (6.13%)	
Malignancy	No	4648 (94.47%)	824 (85.57%)	**<0.001**	817 (84.84%)	0.65
	Yes	272 (5.53%)	139 (14.43%)		146 (15.16%)	
Hypertension	No	2707 (55.02%)	404 (41.95%)	**<0.001**	395 (41.02%)	0.68
	Yes	2213 (44.98%)	559 (58.05%)		568 (58.98%)	
Hyper-cholesterolemia	No	4209 (85.55%)	767 (79.65%)	**<0.001**	786 (81.62%)	0.27
	Yes	711 (14.45%)	196 (20.35%)		177 (18.38%)	
Heart. Disease	No	4012 (81.54%)	535 (55.56%)	**<0.001**	541 (56.18%)	0.78
	Yes	908 (18.46%)	428 (44.44%)		422 (43.82%)	
Diabetes	No	3517 (71.48%)	662 (68.74%)	0.086	659 (68.43%)	0.88
	Yes	1403 (28.52%)	301 (31.26%)		304 (31.57%)	
	None	1940 (39.43%)	318 (33.02%)		334 (34.68%)	

	Subgroup	No anticoagulant therapy, N (%)	On anticoagulant therapy, N (%)	P[1]	Propensity matched no therapy, N (%)	P[2]
History of smoking**	Current smoker	242 (4.92%)	41 (4.26%)	**0.001**	39 (4.05%)	0.70
	Ex-smoker	1005 (20.43%)	237 (24.61%)		218 (22.64%)	
	Unknown	1695 (34.45%)	353 (36.66%)		365 (37.9%)	
Liver disease	No	4739 (96.32%)	933 (96.88%)	0.39	933 (96.88%)	1.00
	Yes	181 (3.68%)	30 (3.12%)		30 (3.12%)	
Lung disease	No	3751 (76.24%)	688 (71.44%)	**0.002**	702 (72.9%)	0.48
	Yes	1169 (23.76%)	275 (28.56%)		261 (27.1%)	
Existing renal failure	No	4122 (83.78%)	684 (71.03%)	**<0.001**	677 (70.3%)	0.73
	Yes	798 (16.22%)	279 (28.97%)		286 (29.7%)	
Antiplatelets prior to admission	No	3894 (79.15%)	896 (93.04%)	**<0.001**	887 (92.11%)	0.43
	Yes	1026 (20.85%)	67 (6.96%)		76 (7.89%)	
Ferritin (ug/L)	Below normal (<20)	15 (0.3%)	3 (0.31%)	0.85	2 (0.21%)	0.19
	Normal (20-186)	152 (3.09%)	42 (4.36%)		19 (1.97%)	
	Above normal (>186)	4753 (96.61%)	918 (95.33%)		942 (97.82%)	
Lactate (mmol/L)	Normal (0.5-2.1)	3859 (78.43%)	703 (73%)	**<0.001**	659 (68.43%)	**0.028**
	Above normal (>2.1)	1061 (21.57%)	260 (27%)		304 (31.57%)	
Haemoglobin* (g/L)	Below normal <130 (<115)	2618 (53.21%)	446 (46.31%)	**<0.001**	471 (48.91%)	0.34
	Normal 130-160 (115-150)	1963 (39.9%)	456 (47.35%)		443 (46%)	
	Above normal >160 (>150l	339 (6.89%)	61 (6.33%)		49 (5.09%)	
Troponin (ng/L)	Normal (<19.8)	1677 (34.09%)	223 (23.16%)	**<0.001**	212 (22.01%)	0.55
	Above normal (>19.7)	3243 (65.91%)	740 (76.84%)		751 (77.99%)	
LDH (IU/L)	Below normal (<266)	133 (2.7%)	23 (2.39%)	0.26	24 (2.49%)	0.43
	Normal (266-500)	2709 (55.06%)	773 (80.27%)		770 (79.96%)	
	Above normal (>500)	2078 (42.24%)	167 (17.34%)		169 (17.55%)	
Prothrombin Time (secs)	Below normal (<10.2)	69 (1.4%)	4 (0.42%)	**<0.001**	8 (0.83%)	**<0.001**
	Normal (10.2-13.2)	1340 (27.24%)	156 (16.2%)		217 (22.53%)	
	Above normal (>13.2)	3511 (71.36%)	803 (83.39%)		738 (76.64%)	
APTT (sec)	Below normal (<26.0)	531 (10.79%)	55 (5.71%)	**<0.001**	91 (9.45%)	**<0.001**
	Normal (26-36)	3808 (77.4%)	742 (77.05%)		776 (80.58%)	
	Above normal (>36.0)	581 (11.81%)	166 (17.24%)		96 (9.97%)	
Platelets (10^9/L)	Below normal (<150)	3760 (76.42%)	699 (72.59%)	**0.001**	734 (76.22%)	0.18
	Normal (150-400)	799 (16.24%)	202 (20.98%)		172 (17.86%)	
	Above normal (>400)	361 (7.34%)	62 (6.44%)		57 (5.92%)	
WBC (10^9/L)	Below normal (<4.1)	3338 (67.85%)	680 (70.61%)	**0.065**	624 (64.8%)	**0.001**
	Normal (4.1-11.1)	448 (9.11%)	94 (9.76%)		86 (8.93%)	
	Above normal (>11.1)	1134 (23.05%)	189 (19.63%)		253 (26.27%)	
Neutrophils (10^9/L)	Below normal (<2.1)	2571 (52.26%)	514 (53.37%)	0.55	482 (50.05%)	0.32
	Normal (2.1-6.7)	214 (4.35%)	35 (3.63%)		41 (4.26%)	

	Subgroup	No anticoagulant therapy, N (%)	On anticoagulant therapy, N (%)	P[1]	Propensity matched no therapy, N (%)	P[2]
	Above normal (>6.7)	2135 (43.39%)	414 (42.99%)		440 (45.69%)	
Lymphocytes (μL)	Below normal (<1.3)	792 (16.1%)	160 (16.61%)	0.92	153 (15.89%)	0.81
	Normal (1.3-3.7)	234 (4.76%)	45 (4.67%)		41 (4.26%)	
	Above normal (>3.7)	3894 (79.15%)	758 (78.71%)		769 (79.85%)	
Fibrinogen (g/L)	Below normal (<1.5)	117 (2.38%)	13 (1.35%)	0.052	19 (1.97%)	0.29
	Normal (1.5-4.5)	474 (9.63%)	108 (11.21%)		92 (9.55%)	
	Above normal (>4.5)	4329 (87.99%)	842 (87.44%)		852 (88.47%)	
ALT (IU/L)	Below normal (<8)	94 (1.91%)	29 (3.01%)	**<0.001**	26 (2.7%)	0.21
	Normal (8-40)	3284 (66.75%)	733 (76.12%)		704 (73.1%)	
	Above normal (>40)	1542 (31.34%)	201 (20.87%)		233 (24.2%)	
Bilirubin (μmol/L)	Normal (0-20)	4431 (90.06%)	847 (87.95%)	**0.049**	857 (88.99%)	0.48
	Above normal (>20)	489 (9.94%)	116 (12.05%)		106 (11.01%)	
Creatinine (μmol/L)	Below normal (<60)	736 (14.96%)	95 (9.87%)	**<0.001**	108 (11.21%)	0.60
	Normal (60-120)	2942 (59.8%)	539 (55.97%)		537 (55.76%)	
	Above normal (>120)	1242 (25.24%)	329 (34.16%)		318 (33.02%)	
CRP (mg/L)	Normal (0-10)	435 (8.84%)	118 (12.25%)	**0.001**	88 (9.14%)	**0.027**
	Above normal (>10)	4485 (91.16%)	845 (87.75%)		875 (90.86%)	
D-Dimer (ng/ml)	Normal (0-500)	361 (7.34%)	80 (8.31%)	0.30	47 (4.88%)	**0.002**
	Above normal (>500)	4559 (92.66%)	883 (91.69%)		916 (95.12%)	

P^1 refers to the comparison of the anticoagulant / no anticoagulant groups, whilst P^2 refers to the comparison of the anticoagulant group and the propensity matched no therapy group. P values <0.05 are shown in bold. BMI= body mass index; VTE= venous thromboembolism; LDH= lactate dehydrogenase; APTT= activated partial thromboplastin time; ALT =alanine transferase; CRP= C-reactive protein

Figure 1. Flow chart of the patient selection and clinical outcomes of the study

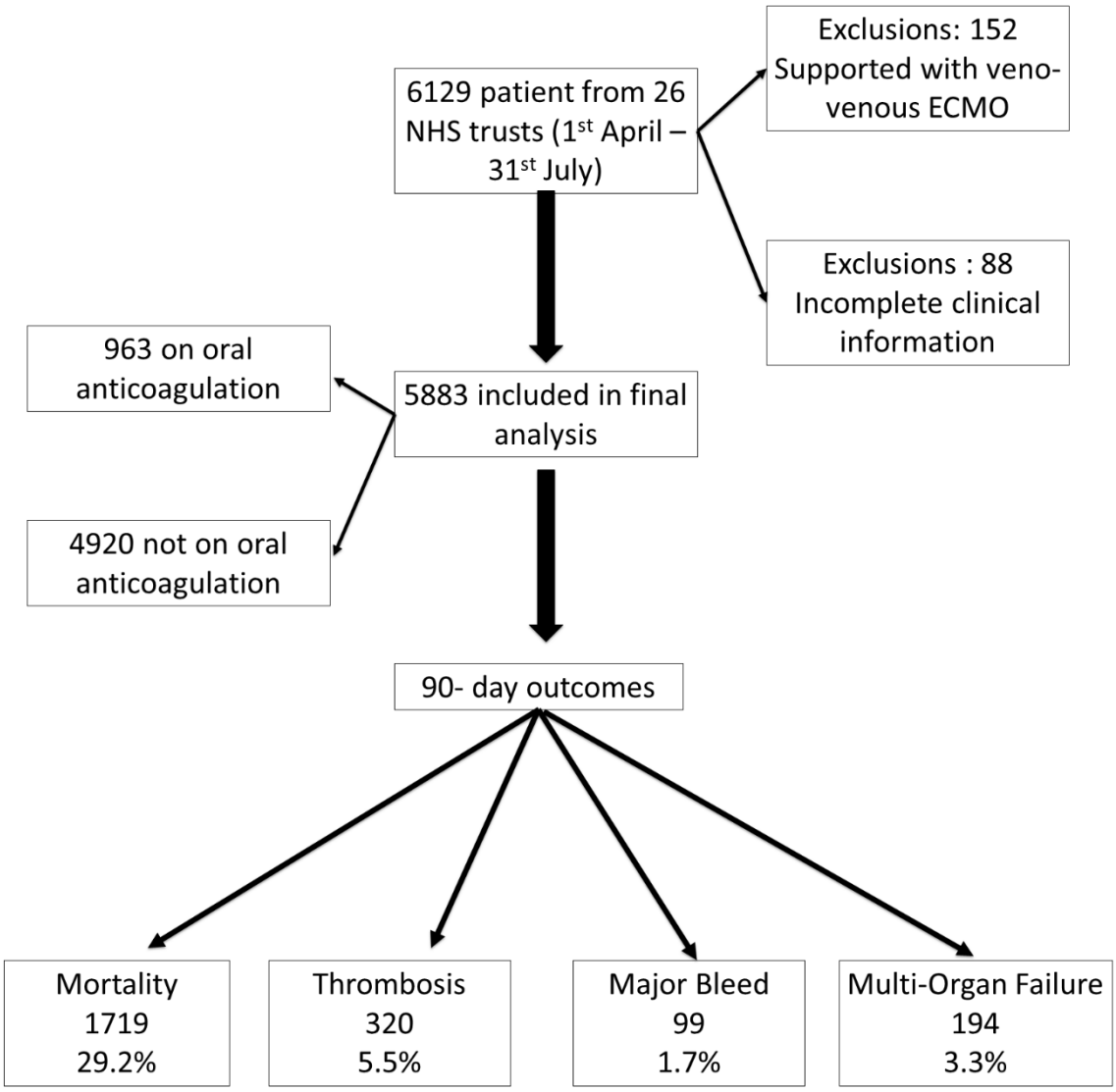

Figure 2A Probability of death non-propensity matched patients admitted with oral anticoagulant vs no oral anticoagulants.

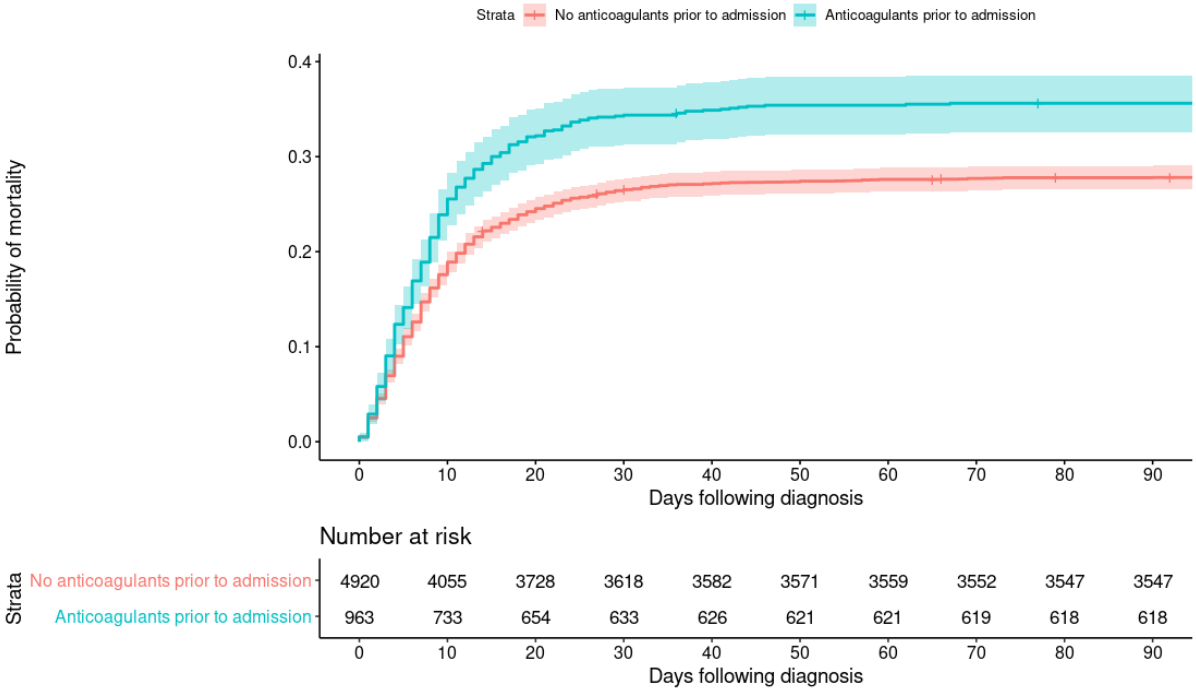

Figure 2B Probability of death for propensity matched patients admitted with oral anticoagulant vs no oral anticoagulants.