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ORIGINAL PAPER

Impact of thromboprophylaxis on hospital acquired thrombosis following discharge in patients admitted with COVID-19: Multicentre observational study in the UK

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Abstract

Post-discharge thromboprophylaxis in patients admitted with COVID-19 remains controversial. We aimed to determine the impact of thromboprophylaxis on hospital acquired thrombosis (HAT) in patients (≥18 years) discharged following admission for COVID-19 in an observational study across 26 NHS Trusts in the UK (01.04.2020–31.12.2021). Overall, 8895 patients were included to the study: 971 patients were discharged with thromboprophylaxis and propensity score matched (PSM) with a desired ratio of 1:1, from patients discharged without thromboprophylaxis. Patients with heparin induced thrombocytopenia, major bleeding during admission and pregnant women were excluded. As expected from 1:1 PSM, no difference was observed in parameters between the two groups, including duration of hospital stay, except the thromboprophylaxis group had a significantly higher proportion who had received therapeutic dose anticoagulation during admission. There were no differences in the laboratory parameters especially D-dimers between the two groups at admission or discharge. Median duration of thromboprophylaxis following discharge from hospital was 4 weeks (1–8 weeks). No difference was found in HAT in patients discharged with TP versus no TP (1.3% vs. 0.92%, $p = 0.52$). Increasing age and smoking significantly increased the risk of HAT. Many patients in both cohorts had raised D-dimer at discharge but D-dimer was not associated with increased risk of HAT.

KEYWORDS
anticoagulants, COVID-19, D-dimer, hospital acquired thrombosis, Thromboprophylaxis, propensity matching

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization on March 11, 2020. COVID-19 progressed through several waves, each with distinct transmission and virulence characteristics. Severe COVID-19 is associated with an uncontrolled inflammatory response leading to an excess rate of thrombosis including pulmonary thrombosis.

Thromboprophylaxis is given to all in-patients without contraindications as early evidence from China demonstrated the efficacy of low molecular weight heparin (LMWH) in improving survival.[1,2] However, it had

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Complete list of "CA-COVID19 Investigators" given in Appendix.

become standard practice in the UK to perform risk assessment for venous thrombosis (VTE) in all patients admitted to hospital and offer thromboprophylaxis irrespective of COVID-19 even before the start of the pandemic. The dose of LMWH used in patients admitted with COVID-19 varied widely from standard dose to intermediate or therapeutic dose depending on the severity of the disease, including in the setting of the multiplatform REMAP-CAP study.[3,4] The thrombotic rate in patients admitted to a ward setting was around 6%–14% and this rate was much higher in patients treated in intensive care with reported rates of 22%–34%.[5,6]

Although thromboprophylaxis with LMWH or UFH became the standard practice during the hospital stay, the role of thromboprophylaxis to prevent post discharge hospital acquired thrombosis (HAT), which is defined as VTE up to 90 days following the hospital discharge, was not clear. In general, ~80% of all HATs occur within 6 weeks from hospital discharge in acutely ill medial patients especially in those who required ITU treatment, based on studies prior to COVID-19.[7,8] As COVID-19 is a highly prothrombotic disease, patients with COVID-19 may continue to have an increased risk of thrombosis following discharge especially if in a high-risk group (i.e., high D dimer, reduced mobility, prolonged hospital stay including ITU treatment etc).[6,9] Due to uncertainty over benefit, practice varied widely over the course of the pandemic from no post-discharge thromboprophylaxis to 7 days–45 days[10] of thromboprophylaxis with LWMH or direct acting oral anticoagulant.[11] ISTH guidelines suggested DOAC prophylactic dose to be considered in selected patients.[12] In a systematic review of National and International Clinical Guidance Reports on of Thromboprophylaxis in Patients with COVID-19 which included 33 guidance documents (20 published by national and 13 by international societies), extended pharmacological thromboprophylaxis was recommended for patients with high VTE risk after hospital discharge in 63% of documents.[11]

The study by Roberts et al, from King's College London assessed the post discharge VTE rate in patients admitted with COVID-19 compared to patients without COVID-19 discharged prior to the COVID-19 pandemic.[13] Both groups received thromboprophylaxis only during the hospital stay. Of the 1877 hospital discharges associated with COVID-19, 9 episodes of VTE were diagnosed within 42 days (4.8 per 1000 discharges) compared to 56 episodes of HA-VTE within 42 days in 18 159 discharges without COVID-19 (3.1 per 1000 discharges). The study concluded that COVID-19 hospitalization does not increase the risk of post discharge VTE compared with hospitalization with other acute medical illness.

Except the above study by Roberts et al, there are no large studies assessing the role of post-discharge thromboprophylaxis in patients with COVID-19 admitted to hospitals in the UK. Therefore, to complement the study of Roberts et al we aimed to determine the impact of thromboprophylaxis on hospital acquired thrombosis (HAT) in patients discharged following hospital admission with COVID-19 in the UK.

METHODS

This was a multicentre observational study across 26 NHS (national health service) Trusts in the UK. Data were collected both retrospectively and prospectively using a central Redcap database by clinicians directly involving the management of patients (Coagulopathy in COVID19—A Multi-Centre Observational Study in UK https://www.clinicaltrials.gov/ct2/show/NCT04405232). Adult patients (≥18 years) admitted with symptomatic COVID-19 between 1 April 2020 and 31 December 2021 were included. All patients had SARS-CoV-2 infection confirmed by RT-PCR positive nasal swabs or nasopharyngeal or lower respiratory tract aspirates. The study was approved by the Human Research Authority (HRA), Health and Care Research Wales and the local Caldicott Guardian in Scotland (20/HRA/1785). Data were collected 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. Details on data collection are summarized in Data S1 page 1. At the discharge from hospital, laboratory parameters and use of thromboprophylaxis (type of thromboprophylaxis, dose and the duration) were collected. Post discharge VTE up to 90 days from the hospital discharge and the readmission due to major bleeding events were documented.

Thromboprophylaxis during the hospital admission

It is standard practice in the UK to give at least prophylactic dose LMWH to all patients admitted to hospital with COVID-19 unless contraindicated for example by the presence of a bleeding disorder, major bleeding or a platelet count $<30 \times 10^9$/L, or to continue therapeutic anticoagulation if already on treatment dose anticoagulation.

Thromboprophylaxis following the hospital discharge

There was no standard approach to thromboprophylaxis across the study centres. The decision to discharge with thromboprophylaxis was based on local guidelines and this varied depending on the NHS trust and the timing of the pandemic.

Statistical analysis

Standard descriptive parameters were calculated for categorical and quantitative variables and presented as frequencies with percentages, or medians with a range. Two cohorts

of patients (1:1 propensity score-matched) for patients discharged with thromboprophylaxis and patients discharged without thromboprophylaxis were compared using either the two-tailed, *t*-test (numerical parameters), chi-squared test or chi-squared trend test (categorial data).

Logistic regression analyses were performed to assess the association between independent variables and development of HAT (yes or no) in the whole study group (both cohorts discharged with thromboprophylaxis and the cohort without thromboprophylaxis together) and the cohort discharged without thromboprophylaxis. Following univariate analyses to identify significant factors associated with development of HAT, multivariate analyses were performed. However, in the final logistic regression models, the following variables were included regardless of their univariate *p*-values in the univariate analyses: age, body mass index, IMPROVE-DD VTE score, use of thromboprophylaxis, and D-dimer >4 to 6 times the ULN (upper limit of normal) or >6 times the ULN, history of VTE prior to admission, coronary artery disease, chronic renal disease, lung disease, ethnicity, mechanical ventilation and ICU admission. Variables with univariate *p* values <0.05 were also included in the final model. Results are reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Details on data management are provided in Data S1 page 1.

RESULTS

Overall, 8895 patients were included to the study. Of these 971 patients were discharged with thromboprophylaxis and propensity score matching (PSM) was performed using the nearest-neighbours method, with a desired ratio of 1:1, from patients discharged without thromboprophylaxis (Figure 1). Patients who had thrombosis, heparin induced thrombocytopenia or major bleeding (defined according to International Society on Thrombosis and Haemostasis (ISTH) classification[14]) during admission and pregnant women were excluded (Figure 2). Comparison of demographics and comorbidities between the propensity matched cohort of patients discharged with thromboprophylaxis versus the no thromboprophylaxis group is presented in Table 1.

As expected, there were no differences in the age, gender, demographics or comorbidities between the propensity matched cohorts. Comparison of the laboratory parameters between the two cohorts is summarized in Table 2. Although there were no differences in the inflammatory markers including C-reactive protein and the D-dimer levels between the two cohorts, a large majority of patients in both cohorts had raised C-reactive protein and D-dimer levels at discharge (83.5% [811/971] vs. 87.3% [848/971] $p = 0.79$ for D-dimers and 75.2% [730/971] vs. 77.1% [749/971] $p = 0.61$
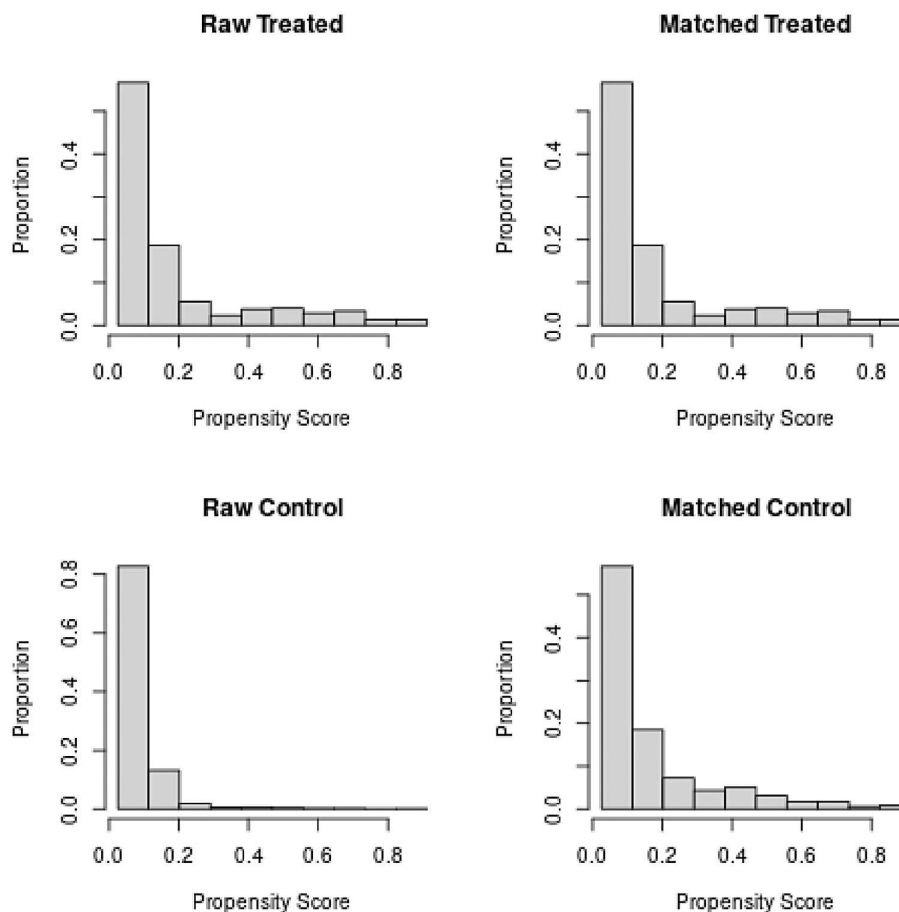

FIGURE 1 1:1 propensity matching for the patients discharged with thromboprophylaxis versus no thromboprophylaxis.
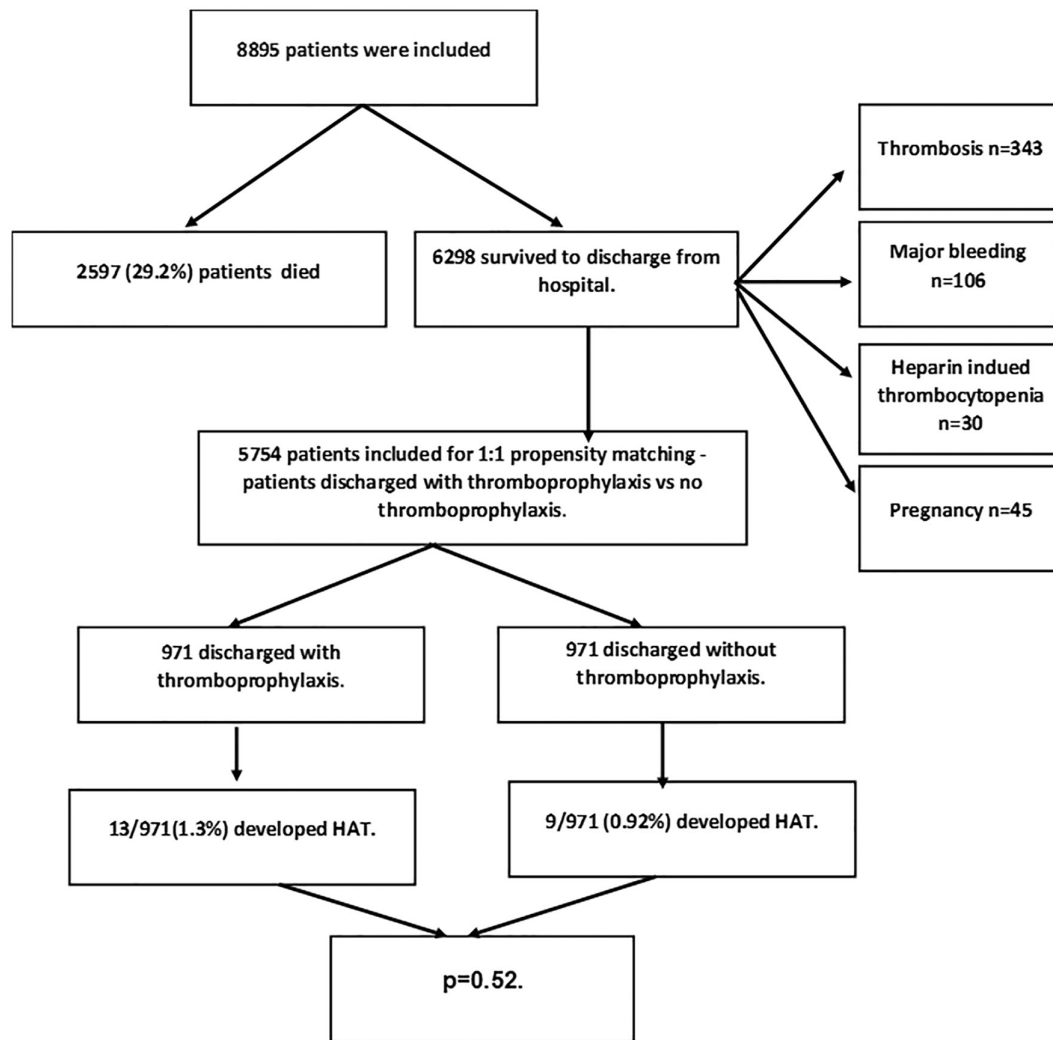
FIGURE 2 Study population and outcomes.

for C-reactive protein for patients discharged with or without thromboprophylaxis). No differences in the laboratory parameters were observed between the two cohorts of patients. Table 3 summarizes the interventions and the events during the hospital stay comparing the patients discharged with thromboprophylaxis versus patients discharged without thromboprophylaxis. Except for the higher proportion of patients discharged with thromboprophylaxis who received treatment dose anticoagulation (with no history of thrombosis) (355/971, 36.5%) compared to patients discharged without thromboprophylaxis (182/971, 18.7%), $p < 0.0001$, there were no differences in the two cohorts including the duration of the duration of the hospital stay (Table 3).

Thromboprophylaxis following hospital discharge

The majority of these patients were discharged with a direct acting oral anticoagulant (DOACs) (496/971, 51.1%)

as thromboprophylaxis followed closely by low molecular weight heparin (LMWH) (475/971, 48.9%). Rivaroxaban was the most frequently used DOAC (262/496, 52.8%) followed by apixaban (224/496, 45.2%) and rest of the patients were discharged with dabigatran (10/496, 2.0%).

Thrombotic events following discharge from hospital (HAT)

Of patients discharged with thromboprophylaxis, 13/971 (1.3%) developed HAT compared to nine patients discharged without thromboprophylaxis (0.92%, 9/971), $p = 0.52$. Of the 13 patients who developed HAT following discharge with thromboprophylaxis, five patients (38.5%) developed pulmonary embolism (PE) and the remainder (61.5%) developed deep vein thrombosis (DVT) of the lower limbs. Nine patients developed HAT when discharged without thromboprophylaxis, three patients (33.3%) developed PE and other 6 patients (66.4%) developed DVT. None of the patients in either group

TABLE 1 Demographics and baseline clinical characteristics of the patients discharged with no thromboprophylaxis versus patients discharged with thromboprophylaxis at admission and discharge.

Demographics	No thromboprophylaxis at discharge	Thromboprophylaxis at discharge	p value
Gender			
Men	536	547	0.64
Women	435	424	
Age (years)			
0–29	22	20	0.98
30–49	116	118	
50–69	284	283	
70–89	470	470	
90+	79	80	
BMI (Kg/m^2)			
0–18.5	18	18	0.39
18.6–24.9	248	238	
25–29.9	363	349	
30–39.9	299	326	
40+	43	40	
Ethnicity			
White	751	748	0.49
Mixed multiple ethnic	8	2	
Asian/Asian British	46	40	
Black African/Caribbean	25	24	
Other ethnic group	25	33	
Unknown	116	124	
Patients on antiplatelet treatment prior to admission			
No	814	814	1
Yes	157	157	
Patients was on anticoagulation prior to admission			
No	841	849	0.58
Yes	130	122	
History of VTE prior to admission			
No	931	921	0.2755
Yes	40	50	
History of autoimmune disease			
No	898	896	0.8649
Yes	73	75	
History of malignancy in the past 6 months prior to admission			
No	863	859	0.7775
Yes	108	112	
Hypertension			
No	589	579	0.6092
Yes	382	392	
Hypercholesterolemia			
No	840	851	0.4596
Yes	131	120	
Ischaemic heart disease			
No	784	775	0.6054

(Continues)

TABLE 1 (Continued)

Demographics	No thromboprophylaxis at discharge	Thromboprophylaxis at discharge	p value
Yes	187	196	
Diabetes mellitus			
No	699	696	0.877
Yes	272	275	
History of smoking			
None	373	371	0.8907
Current smoker	93	100	
Ex-smoker	212	186	
Unknown	293	314	
History of liver disease			
No	941	931	0.2115
Yes	30	40	
History of lung disease			
No	750	737	0.4778
Yes	221	234	

presented to hospital with major bleeding events following discharge.

Factors associated with HAT

Factors that can be associated with HAT were assessed separately in the whole study group and in the cohort of patients discharged without thromboprophylaxis. In univariate analysis, age, history of no smoking and D-dimer >6 times ULN were significantly associated with development of HAT in the overall cohort but only age was significantly associated with developing HAT in the group of patients discharged without thromboprophylaxis.

In multivariate analysis increasing age (odds ratio [OR] 1.08 [95% CI 1.01–1.12], $p = 0.017$) and history of no smoking (OR 0.68 [95% CI 0.47–0.95], $p = 0.031$) were the only significant factors linked with increased risk of HAT in the overall cohort whilst age was the only significant factor associated with HAT in patients discharged without thromboprophylaxis (OR = 1.09 [95% CI 1.03–0.1.13], $p = 0.013$). D-dimer was not associated with the development of HAT in the multivariate analysis in either group. The distribution of D-dimer was not normal; hence, we assessed the D dimer as a categorical variable. However, analysis was performed as continuous variable as well which did not show a significant association with HAT. Furthermore, IMPROVE-DD VTE score (OR 1.5 [95% CI 0.89–2.7]) and D-dimer >4 to 6 times the ULN (upper limit of normal) (OR 1.7 [0.9–2.1]) or >6 times the ULN (OR 1.9 [0.8–2.3]) at discharge were not associated with increased risk of HAT events. Table 4 summarizes the IMPROVE VTE scores between the two groups. An analysis was performed to assess whether including the highest D dimer value during the hospital stay would change the IMPROVE-DD scores between the groups and the final multivariate model, but it was not altered.

DISCUSSION

In this large multicentre observational study assessing the role of thromboprophylaxis on the development of thrombosis (HAT) in patients admitted with COVID-19, it was found that the rate of HAT is low in patients discharged following COVID-19, and thromboprophylaxis at discharge did not have a significant impact. In the 1:1 propensity matched cohort of patients discharged without thromboprophylaxis, except for the higher proportion of patients discharged with thromboprophylaxis receiving treatment dose anticoagulation during admission (with no history of thrombosis), there were no differences in the two cohorts, including the duration of the duration of hospital stay. This suggests that if the patient received treatment dose thromboprophylaxis during hospital they were more likely to be also given post discharge thromboprophylaxis. This indicates that at some point these patients were assessed as being at higher risk. However, it was not possible to clarify how the clinicians came to that conclusion.

The median duration of thromboprophylaxis was 4 weeks with a range of 1–8 weeks, reflecting the variability of clinical practice across NHS Trusts regarding thromboprophylaxis. DOACs were the most frequently used anticoagulant as thromboprophylaxis closely followed by LMHW and rivaroxaban was the most prescribed DOAC. In multivariate analysis increasing age was significantly linked with increased risk of HAT whilst history of no smoking reduced the risk by 32% in the overall cohort whilst age was the only significant factors associated with HAT in patients discharged without thromboprophylaxis. It is possible that clinicians were able to correctly identify the lower-risk patients based on overall clinical impression at discharge although the propensity matching includes multiple measures of disease severity. In multivariate analysis

TABLE 2 Laboratory blood results of the patients discharged with no thromboprophylaxis versus patients discharged with thromboprophylaxis at admission and discharge.

Laboratory parameter	At admission			At discharge		
	No thromboprophylaxis at discharge	Thromboprophylaxis at discharge	p value	No thromboprophylaxis at discharge	Thromboprophylaxis at discharge	p value
Lactate (mmol/L)						
Normal (0.5–2.1)	879	907	0.72	745	744	0.29
Above normal (>2.1)	81	52		115	102	
Haemoglobin (g/L)[a]						
Below normal <130 (<115)	471	449	0.41	554	542	0.84
Normal 130–160 (115–150)	421	430		285	281	
Above normal >160 (>150)	48	67		23	25	
Lactate dehydrogenase (IU/L)						
Below normal (<266)	24	17	0.11	24	17	0.10
Normal (266–500)	523	510		472	454	
Above normal (>500)	422	434		388	396	
Troponin I (ng/L)						
Normal <19.8	270	241	0.40	259	246	0.48
Above normal >19.7	700	730		626	622	
Ferritin (µg/L)						
Below normal (<20)	3	0	0.65	2	0	0.74
Normal (20–186)	24	22		25	25	
Above normal (>186)	943	949		858	843	
Prothrombin time (s)						
Below normal (<10.2)	10	1	0.40	6	3	0.53
Normal (10.2–13.2)	192	170		200	164	
Above normal (>13.2)	747	778		662	681	
APTT (s)						
Below normal (<26.0)	86	61	0.82	84	56	0.15
Normal (26–36)	761	782		690	684	
Above normal (>36.0)	116	124		105	123	
White cell count (10^9/L)						
Below normal (<4.1)	79	94	0.16	71	73	0.52
Normal (4.1–11.1)	668	670		610	609	
Above normal (>11.1)	217	197		198	180	
Neutrophils (10^9/L)						
Below normal (<2.1)	37	47	0.35	40	44	0.72
Normal (2.1–6.7)	507	493		489	466	
Above normal (>6.7)	419	423		341	345	
Fibrinogen (g/L)						
Below normal (<1.5)	17	1	0.92	21	4	0.18
Normal (1.5–4.5)	72	114		84	120	
Above normal (>4.5)	874	845		769	735	
Creatinine (µmol/L)						
Below normal (<60)	136	140	0.42	221	200	0.76
Normal (60–120)	594	577		504	492	
Above normal (>120)	223	242		141	162	

(Continues)

TABLE 2   (Continued)

	At admission			At discharge		
Laboratory parameter	No thromboprophylaxis at discharge	Thromboprophylaxis at discharge	p value	No thromboprophylaxis at discharge	Thromboprophylaxis at discharge	p value
CRP (mg/L)						
Normal (0–10)	93	81	0.34	222	241	0.61
Above normal (>10)	873	882		749	730	
Platelets (10^9/L)						
Below normal (<150)	158	169	0.16	100	110	0.47
Normal (150–400)	728	724		732	737	
Above normal (>400)	79	73		139	124	
D-dimer (ng/mL)						
Normal (0–500)	51	64	0.66	123	160	0.71
>500–1000	166	150		413	402	
>1000–2000	249	268		289	272	
>2000–4000	274	250		120	112	
>4000	231	239		26	25	

Abbreviation: APTT, activated partial thromboplastin time.

[a]Values in brackets indicate normal reference range for female.

D-dimer on the day of the discharge from hospital was not associated with the development of HAT in either group as a categorical or continuous variable. Furthermore, including the highest D-dimer value during the hospital stay did not change the IMPROVE-DD scores between the groups or the results of the final multivariate model.

Hospital acquired VTE is a global health issue and a systematic approach in risk assessment and thromboprophylaxis during hospital admission has significantly reduced HAT and its related morbidity and mortality.[15] COVID-19 is associated with significantly higher risk of thrombosis due to multiple mechanisms including hyperinflammation and endothelial activation.[16,17] Open-label, adaptive, multiplatform, controlled trials in hospitalized, not critically ill, patients with COVID-19 demonstrated that therapeutic-dose anticoagulation with heparin had better survival and reduced use of organ support (cardiovascular or respiratory) compared to standard dose heparin thromboprophylaxis.[4] Trials on the use of extended thromboprophylaxis in medically ill patients without COVID-19 at discharge have demonstrated mixed results, either from not achieving their primary end point or having had an increase in major bleeding.[18] A meta-analysis of these trials revealed an overall 39% reduction of symptomatic VTE and VTE-related death but two-fold increase in major and fatal bleeding with no significant difference in VTE-related death.[19] However, the absolute rates of major bleeding are much lower in patients discharged following COVID-19, such that there may be a favourable number needed to treat (NNT) when compared to the number needed to harm (NNH).

CORE-19 is a large prospective registry from New York including 4906 consecutive adult, non- obstetric hospitalized COVID-19 patients from first the wave.[20]

Post discharge thromboprophylaxis was prescribed in 13.2% patients. The primary outcome of the study was a composite of adjudicated VTE, arterial thromboembolism (ATE) and all-cause mortality (ACM). The primary safety outcome was major bleeding. Rates of VTE, ATE and ACM were 1.55%, 1.71% and 4.83%, respectively. Major bleeding occurred in 1.73%. Composite primary outcome rate was 7.13% and was significantly associated with advanced age, prior VTE, intensive care unit (ICU) stay, chronic kidney disease, peripheral arterial disease, carotid occlusive disease, IMPROVE-DD VTE score ≥4 and coronary artery disease. Postdischarge thromboprophylaxis was associated with reduction in primary outcome by 46% (CI, 0.47%–0.81%). A meta-analysis of 18 949 patients with COVID-19 admitted to hospitals showed a pooled incidence of post-discharge VTE of 1.8% (95% CI: 0.8%–4.1%).[21] In comparison with the above studies, VTE rates following discharge in this study were lower (1.3% in the patients discharged with thromboprophylaxis versus 0.92% in patients discharged without thromboprophylaxis). Moreover, none of the patient presented with major bleeding in contrast to 1.73% patients with major bleeding in the CORE-19 registry.[20] However, the present study did not assess the all-cause mortality or ATE.

The MICHELLE trial was an open labelled multicentre randomized trial of post-discharge extended thromboprophylaxis in COVID-19 inpatients where 320 patients were randomized to receive rivaroxaban 10 mg daily for 35 days versus no anticoagulation (160 patients in each arm).[22] All patients received standard doses of heparin thromboprophylaxis during hospitalization. This study included a high thrombotic risk population (IMPROVE VTE score

TABLE 3 1:1 propensity matching and the comparison between patients discharged with thromboprophylaxis versus no thromboprophylaxis: Clinical interventions and events at or during the admission.

Interventions/events at or during admission	No thromboprophylaxis at discharge	Thromboprophylaxis at discharge	p value
Thromboprophylaxis on admission			
No	547	517	0.15
Yes	424	454	
Therapeutic anticoagulation during admission			
No	789	616	**<0.0001**
Yes	182	355	
Steroids during admission			
No	771	779	0.54
Yes	200	192	
Blood transfusion during admission			
No	844	835	0.51
Yes	127	136	
Development of renal failure during admission			
No	915	905	0.29
Yes	56	66	
Clinically significant non-major bleeding during admission[a]			
No	935	931	0.64
Yes	36	40	
Multiorgan failure during admission			
No	931	921	0.25
Yes	40	50	
Secondary infection during admission			
No	759	764	0.75
Yes	212	207	
Mechanical ventilation during admission			
No	822	810	0.36
Yes	149	161	
Requirement for intensive care unit admission			
No	759	753	0.67
Yes	212	218	
Duration of hospital stay			
Median (range)	32 (3–190)	32 (3–187)	0.98

Note: p values <0.05 are considered as significant and shown in bold.
[a]Defined as per ISTH criteria for clinically relevant non-major bleeding.[24]

TABLE 4 IMPROVE-VTE score in patients discharged with thromboprophylaxis versus no thromboprophylaxis.

IMPROVE-VTE score	No thromboprophylaxis at discharge	Thromboprophylaxis at discharge	p value
IMPROVE-VTE score of ≥4	226	223	0.91
IMPROVE-VTE score of 2–3 with D dimer >500 ng/mL[a]	541	560	0.40

[a]D dimer level at discharge.

of ≥4 or a score of 2–3 with D dimer >500 ng/mL). Only 159 patients in each arm of the study were included in the intention-to-treat primary analysis due to loss of follow-up.

Symptomatic or fatal VTE and/or arterial thrombosis occurred in 3% of rivaroxaban arm versus 9% of no anticoagulation (relative risk 0.33, 95% CI 0.12–0.90; $p = 0.029$).

No major bleeding occurred in either study group.[22] In contrast to the present study, in the MICHELLE trial there was a significant reduction in symptomatic VTE in patients who received rivaroxaban at discharge with no fatal VTE[22] (1/159 [0.63%] vs. 8/159 [5·03%] with 3/8 fatal events). Compared to the MICHELLE trial where rivaroxaban 10 mg was given for 35 days in the thromboprophylaxis group,[22] rivaroxaban, apixaban, dabigatran or LMWH were all used as thromboprophylaxis in the present study, and duration varied from 7 days to 56 days with a median 28 days. The MICHELLE trial concluded that inpatients with cardiovascular risk factors, advanced age, intensive care unit stay, or an IMPROVE VTE score of 4 or more or a score of 2 or 3 plus elevated D-dimers (>2X ULN) or an IMPROVE-DD VTE score of ≥4 are at high thrombotic risk in the post-discharge period and may benefit from post discharge thromboprophylaxis.[22] However, except increasing age and smoking status, we failed to identify other significant factors that are associated with increased risk of post discharge VTE. Interestingly, we did not find a link between raised D dimer and risk of post discharge VTE. At discharge 83.5% (811/971) and 87.3% (848/971) patients had raised D-dimer in the thromboprophylaxis and no thromboprophylaxis group respectively with no difference between the two. The elevated D- dimers suggest ongoing inflammatory response post-discharge in COVID-19 patients. This is further supported by the raised C reactive protein levels in 75.2% (730/971) versus 77.1% (749/971) in the two groups. Neither study found significant difference in the major bleeding rates in patients receiving thromboprophylaxis versus no thromboprophylaxis.[22]

The median length of stay in hospital for both groups was 32 days which is much longer than average length of 4.5 days in-hospital stay for non-COVID medical patients. Studies assessing the VTE risk in medically ill patients demonstrated that most of VTE events occur within 6 weeks of hospitalization.[7,8] The lower rates of HAT in patients may be attributed to a longer period of in-hospital prophylaxis. However, in-hospital rates of thrombosis were higher for COVID-19 and the raised D-dimer and CRP suggest that inflammation had not resolved at time of discharge. Similarly, patients with COVID-19 were kept in longer because they were ill longer. Therefore, their period of risk was longer and so not comparable to less ill medical patients with shorter admissions.

Some of the patients who were on anticoagulation prior to admission with COVID-19 were not discharged with thromboprophylaxis (Table 1). Reasons for discharging patients off anticoagulation when they were admitted on anticoagulation were not available. However, there was no difference in the number of patients who stopped their anticoagulant at discharge between the two groups and so the results of our study would not be affected by this. Furthermore, none of the patients who stopped anticoagulant developed HAT following discharge.

https://clinicaltrials.gov/ct2/show/NCT04650087 was an adaptive, prospective, randomized platform trial which compares the safety and efficacy of thromboprophylaxis (apixaban 2.5 mg bd) versus no thromboprophylaxis following hospitalization ≥48h for COVID-19. This study terminated early following the recruitment of 1217 participants due to lower event rates and decreasing COVID-19 hospitalizations. The incidence of the primary end point (30-day composite of death, arterial thromboembolism and venous thromboembolism) was 2.13% (95% CI, 1.14 to 3.62) in the apixaban group and 2.31% (CI, 1.27 to 3.84) in the placebo group. Similar to our study, the symptomatic VTE rates were low in both study arms (5/607, 0.82% in the placebo arm vs. 5/610, 0.82% in apixaban arm) with no difference. The primary safety end point (major bleeding) occurred in 2 (0.4%) and 1 (0.2%) apixaban-treated and placebo-treated participants, respectively.[23] The observed low rate of venous thrombosis and no difference in patients discharged with thromboprophylaxis versus no thromboprophylaxis are in keeping with the current study.

Our study has some important limitations. It is possible that not all VTE events were captured following hospital discharge although in the UK, there is robust system to assess the post discharge VTE from the ongoing quality improvement program incorporating root-cause analysis of hospital associated VTE. Even if the patient is not admitted to the same hospital with post discharge VTE, in root-cause analysis process this data is captured from the admission hospital. During the COVID-19 pandemic this may not have happened as expected due to reduced resources due to redeployment of the staff. Therefore, our data may underestimate the post-discharge VTE rate. However, this is applicable to both cohorts in the study. It is not possible to exclude the possibility that patients identified as high-risk for thrombosis were given more intense prophylaxis in-hospital as well as thromboprophylaxis post-discharge using some measure not captured by the propensity matching. ISTH criteria for defining the clinically relevant non-major bleeding may not be appropriate. However, the same criteria were applied to both groups and the number of patients who developed clinically relevant non-major bleeding in the two groups were comparable and very small (3.7% in the no thromboprophylaxis at discharge vs. 4.1% Thromboprophylaxis at discharge).

Additionally, this study did not have information on different coronavirus variants over the course of the pandemic which may affect the risk of thrombosis.

Despite the above limitations, this is the largest multicentre study to date assessing the role of post discharge thromboprophylaxis in patients with COVID-19 representing patients discharged from 26 NHS Trusts across the UK. By including a 1:1 propensity matched cohort of patients with COVID-19 discharged from the same hospitals with the study period, we have matched the comparator group in the best possible scenario outside a randomized control study. Furthermore, we included the use of steroids, blood transfusion, development of secondary infections, renal, respiratory failure and multiorgan failure which are all known risk factors for development of thrombosis in the propensity matching compared to other studies.[13,20,22]

In conclusion, the rate of HAT is low in patients discharged following COVID -19, and thromboprophylaxis at discharge did not have a significant impact on this. Although the majority of patients in both cohorts had raised D-dimer at discharge D-dimer was not associated with increased risk of HAT.

AUTHOR CONTRIBUTIONS

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FUNDING INFORMATION

CONFLICT OF INTEREST STATEMENT

DJA received funding from Bayer PLC to setup the multicentre database of the study as an investigator-initiated funding and received speaker fees. ML received speaker fees from Pfizer, Leopharma, Bayer PLC and consultancy fees from Pfizer. Other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, [DJA] upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

APPENDIX

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