

## ORIGINAL ARTICLE

# Thromboprophylaxis in people hospitalized with COVID-19: Assessing intermediate or standard doses in a retrospective cohort study

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## Abstract

**Background and Objectives:** Current clinical guidelines recommend thromboprophylaxis for adults hospitalized with coronavirus disease 2019 (COVID-19), yet it is unknown whether higher doses of thromboprophylaxis offer benefits beyond standard doses.

**Methods:** We studied electronic health records from 50091 adults hospitalized with COVID-19 in the United States between February 2020 and February 2021. We compared standard (enoxaparin 30 or 40 mg/day, fondaparinux 2.5 mg, or heparin 5000 units twice or thrice per day) versus intermediate (enoxaparin 30 or 40 mg twice daily, or up to 1.2 mg/kg of body weight daily, heparin 7500 units thrice per day or heparin 10 000 units twice or thrice per day) thromboprophylaxis. We separately examined risk of escalation to therapeutic anticoagulation, severe disease (first occurrence of high-flow nasal cannula, noninvasive positive pressure ventilation or invasive mechanical ventilation), and death. To summarize risk, we present hazard ratios (HRs)

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HCA Healthcare-affiliated entity. Data collection, analysis, interpretation of the data, and the writing of this article were performed independently by the authors. All authors had full access to all of the data in the study, including statistical reports and tables, and take responsibility for the integrity of the data and the accuracy of the data analysis. The views expressed in this publication represent those of the authors and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities

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with 95% confidence intervals (CIs) using adjusted time-dependent Cox proportional hazards regression models.

**Results:** People whose first dose was high intensity were younger, more often obese, and had greater oxygen support requirements. Intermediate dose thromboprophylaxis was associated with increased risk of therapeutic anticoagulation (HR, 3.39; 95% CI, 3.22-3.57), severe disease (HR, 1.22; 95% CI, 1.17-1.28), and death (HR, 1.37; 95% CI, 1.21-1.55). Increased risks associated with intermediate-dose thromboprophylaxis persisted in subgroup and sensitivity analyses varying populations and definitions of exposures, outcomes, and covariates.

**Conclusions:** Our findings do not support routine use of intermediate-dose thromboprophylaxis to prevent clinical worsening, severe disease, or death among adults hospitalized with COVID-19.

#### KEYWORDS

COVID-19, enoxaparin, heparin, pharmacoepidemiology, SARS-CoV-2

#### Essentials

- People who have coronavirus disease 2019 (COVID-19) have an increased risk of blood clots.
- People who are hospitalized with COVID-19 are given medications to prevent blood clots.
- In our study, higher doses of these medications did not help patients hospitalized with COVID-19.
- This work helps us understand how to best treat and manage patients with COVID-19 in the hospital.

## 1 | INTRODUCTION

Over 503 million infections and >6 million deaths have accrued worldwide from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as of April 15, 2022.<sup>1</sup> Coronavirus disease 2019 (COVID-19), the syndrome caused by SARS-CoV-2, is associated with an increased rate of thromboembolic events,<sup>2-5</sup> despite the routine use of thromboprophylaxis among hospitalized patients.<sup>6-9</sup> In response to rapidly evolving evidence, the Scientific Standardization Committee of the ISTH issued guidance in May 2020 for prescribers to consider intermediate-dose thromboprophylaxis, which provides a level of anticoagulation greater than standard prophylactic doses, yet less than therapeutic levels used to manage deep vein thrombosis or pulmonary embolism.<sup>10</sup> In November 2021, both the World Health Organization and National Institutes of Health (NIH) treatment guidelines stated that there is insufficient evidence to recommend for or against the use of intermediate-dose thromboprophylaxis.<sup>11,12</sup> In February 2022, the NIH guidelines were revised for adults requiring intensive care unit (ICU)-level care to state: "The Panel recommends against the use of an intermediate dose (eg, enoxaparin 1 mg/kg daily) or a therapeutic dose of anticoagulation for VTE [venous thromboembolism] prophylaxis, except in a clinical trial"; there was no change in recommendations pertaining to intermediate dosing in non-ICU hospitalized patients.

Several investigations compared therapeutic (full-dose) anticoagulation to standard thromboprophylaxis doses in hospitalized adult populations and settings. For example, there is evidence that therapeutic anticoagulation offers a benefit over standard thromboprophylaxis in noncritically ill patients hospitalized with COVID-19<sup>13,14</sup> but is not effective if started after the onset of critical illness.<sup>15-17</sup> Whether these findings extend to comparisons of standard- and intermediate-dose thromboprophylaxis is unclear.<sup>12,18-21</sup> A clinical trial of 562 patients in the ICU did not find significant differences in thrombosis, risk of extracorporeal membrane oxygenation (ECMO), or death between standard- and high-dose thromboprophylaxis; importantly, no differences in safety outcomes were noted.<sup>22</sup> Of note, this trial implemented differential dosing for persons with high body mass index (BMI), which limits the generalizability to centers that do not use weight-based thromboprophylaxis dosing. The role of standard- versus intermediate-dose thromboprophylaxis in non-ICU patients is unknown.

In addition to uncertainty as to optimal prophylactic doses, important questions remain regarding the effects of changes in intensity throughout the course of an inpatient stay. To date, studies have examined smaller data sets and have not considered the time-varying exposures that might bias intention-to-treat analyses.<sup>7,23-27</sup> We compared the real-world effectiveness of standard- versus intermediate-dose thromboprophylaxis in preventing the need for escalation to therapeutic anticoagulation, severe disease or death

among adults hospitalized with COVID-19 in the United States from February 2020 through February 2021.

## 2 | METHODS

### 2.1 | Study setting and population

Our analyses included individuals who received care at a facility affiliated with HCA Healthcare, a large health system with over 2000 sites of care including 186 hospitals across 20 states. We defined a COVID hospitalization as an adult with a positive SARS-CoV-2 test result and a clinical diagnosis of COVID-19. The COVID-19 Consortium of HCA Healthcare and Academia for Research Generation (CHARGE) is a group of 11 academic centers that have partnered with HCA Healthcare and the federal Agency for Health Research and Quality to learn from the clinical experience of HCA Healthcare. The data set has been previously described<sup>28,29</sup> and includes detailed information on demographics, clinical encounters, prescription drugs, vital signs, and laboratory measures.

### 2.2 | Inclusion and exclusion criteria

We used the CHARGE standard definition of a continuous COVID-19 clinical care episode (Table S1) and selected a person's first inpatient encounter for this analysis. We excluded people who were pregnant, had severe renal impairment, or who had a pulmonary embolism, cerebral infarction, or deep vein thrombosis at the time of admission, given the differential indications for anticoagulation in these populations. We also excluded people admitted to centers with no ICU beds, such as an inpatient psychiatric hospital or rehabilitation center, where the indication for admission is unlikely to be acute COVID-19. We required a positive SARS-CoV-2 test result no more than 21 days before their admission; to exclude nosocomial infections, positive tests could be no later than 5 days into their admission. Finally, we excluded people who did not receive any anticoagulation at any point in their stay, whose first anticoagulation strategy was therapeutic dosing, and people who were using anticoagulation before admission.

### 2.3 | Exposures

We used HCA's treatment protocols to define our exposure groups. We defined standard thromboprophylaxis doses as enoxaparin 30 or 40 mg once daily, fondaparinux 2.5 mg once daily or heparin 5000 units twice or thrice daily (Table S2). We defined intermediate-dose thromboprophylaxis as enoxaparin 30 mg or 40 mg twice daily or any enoxaparin dose >40 mg, which was up to 1.0 mg/kg/day plus 20% rounding factor; heparin 7500 units three times daily; or heparin 10 000 units two or three times daily.

Unlike previous work where we could reasonably employ time-fixed exposure definitions,<sup>30,31</sup> anticoagulation necessitates a time-varying exposure definition to allow for changes in intensity throughout the hospitalization. We defined follow-up time as beginning at the precise date and time of thromboprophylaxis administration. We considered people to be continuously exposed until 24 hours after the last administration, reflecting the relatively short-acting nature of thromboprophylaxis. If a person switched treatment intensity before the 24-hour washout period, we ended their prior exposure period the minute before the new exposure was first administered.

### 2.4 | Outcomes

First, based on clinical guidelines as well as expert opinion, we defined therapeutic anticoagulation as enoxaparin >1.2 mg/kg/day or intravenous heparin. While the effectiveness of thromboprophylaxis would be most clearly demonstrated with an absolute or relative reduction in risk of thrombotic events, we were not able to answer this question using these data. The CHARGE data set does not contain time stamps for recorded diagnosis codes, and given the time-varying nature of anticoagulation exposures during a hospitalization, we were unable to analyze the incidence of clots as a function of any given exposure strategy. We therefore considered the date and time of first therapeutic anticoagulation dose as a surrogate measure for clinical worsening or a suspected deep vein thrombosis or pulmonary embolism.

Second, we defined severe disease as the first occurrence of high-flow nasal cannula (HFNC), noninvasive positive pressure ventilation (NIPPV), or invasive mechanical ventilation (IMV). Third, we examined the risk of death, and included people who were discharged to hospice.

### 2.5 | Covariates

We adjusted for demographics, smoking status, overweight or obesity as defined by BMI, and select medications current at the time of admission (Table S3). We used the 2022 Elixhauser Comorbidity Index to summarize comorbidity burden.<sup>32</sup> We included abnormal values of laboratory measures and vital signs at the time of admission<sup>30,31,33-35</sup> to be relevant baseline confounders but not after initiation, as we considered these to be mediators rather than confounders of the causal effect (Figure S1).

### 2.6 | Statistical analyses

We calculated absolute standardized mean differences to compare people given the first strategy of anticoagulation they received, with >0.10 interpreted as a meaningful difference. We used time-dependent Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of each outcome of interest, while controlling for patient characteristics.

## 2.7 | Subgroup analyses

While HCA COVID-19 inpatient treatment protocols did not modify dosing for patients with increased body weight, it is possible that some facilities or prescribers made dosing adjustments that could affect our exposure definition. In subgroup analyses, intermediate doses in persons with class III obesity (BMI > 40 kg/m<sup>2</sup>) were instead considered standard thromboprophylaxis, as people with larger bodies may require higher doses to achieve similar anticoagulation effects.<sup>36</sup>

To evaluate whether effectiveness differed by baseline severity of disease, we also stratified analyses by oxygen support at the time of first dose, comparing people with no or low-flow oxygen requirements to those with advanced levels of respiratory support (HFNC, NIPPV, or IMV).

## 2.8 | Sensitivity analyses

First, we removed laboratory measures and vital signs from the time of admission from our set of adjusted covariates, given that these prognostic factors may be strongly associated with the outcomes of interest. Second, we implemented inverse probability of treatment weights in a marginal structural model framework to evaluate whether laboratory measures and vital signs exerted time-varying confounding.<sup>37</sup> Third, we calculated e-values, which are a form of quantitative bias assessment to estimate the strength of association that an independent unmeasured confounder would need to exert to change the interpretation of our findings.<sup>38</sup> Fourth, we excluded people who died within 48 hours of admission, to emulate the exclusion criteria for short life expectancy from several previous anticoagulation-related clinical trials.<sup>13,15,22</sup> Fifth, we added an indicator variable for each of the 186 facilities, to evaluate whether there were facility-level patterns influencing our results. Sixth, we excluded people who were hospitalized >7 days after their COVID diagnosis to more closely mimic antithrombotic clinical trial inclusion criteria.

Analyses were conducted using SAS software, version 9.4, of the SAS System for Windows (SAS Institute, Cary, NC, USA), and data visualizations were produced using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

## 2.9 | Patient and public involvement

Patients were not involved in the design or analysis of this study.

# 3 | RESULTS

## 3.1 | Characteristics at anticoagulation initiation

We identified 50091 adults hospitalized with confirmed SARS-CoV-2 infection who met inclusion and exclusion criteria (Figure S2). The median time from admission to first dose was 7 hours. People

whose first prophylaxis dose was high intensity were younger and more often obese (Table 1). At the time of the first dose, people with HFNC or NIPPV were more likely to receive intermediate rather than standard doses. No differences in preadmission medications for common chronic comorbidities were noted. Intermediate-dose thromboprophylaxis was more often chosen for people with elevated alanine aminotransferase and low albumin as well as abnormal vital signs (Table S4).

## 3.2 | Risk of outcomes from adjusted regression models

Overall, 14% of people changed from thromboprophylaxis to therapeutic anticoagulation, 18% progressed to severe disease, and 11% died within 10 days of their last prophylactic dose (Table 2). Adults who were receiving intermediate doses, as compared to standard doses, were more than three times as likely to switch to therapeutic anticoagulation (HR, 3.39; 95% CI, 3.22-3.57). Intermediate doses were also associated with an increased risk of severe disease (HR, 1.22; 95% CI, 1.17-1.28). We used a range of time points to define the relevant time window for the prophylaxis-associated risk of death, from 24 hours up to 10 days after the last dose, and found an increased risk of death for each (HR range, 1.37-1.41).

## 3.3 | Subgroup analyses

In analyses where we applied dose adjustment for people with class III obesity, HRs were slightly attenuated, but risks remained elevated (Table 3). In stratified analyses, we evaluated whether baseline disease severity modified the effect of intermediate-dose thromboprophylaxis (Table 4). In people with no or low-flow oxygen at the time of their first-ever prophylactic dose, the risk of therapeutic anticoagulation (HR, 3.78; 95% CI, 3.56-4.01) and death within 10 days (HR, 1.47; 95% CI, 1.38-1.57) for patients receiving intermediate-dose prophylaxis was larger than in the overall analyses. Conversely, in people with severe disease (high oxygen requirements), the risk of therapeutic anticoagulation (HR, 2.29; 95% CI, 2.06-2.55) and death (HR, 1.17; 95% CI, 1.07-1.29) was attenuated.

## 3.4 | Sensitivity analyses

Results from sensitivity analyses were consistent with main analyses. Laboratory measures and vital signs in the 24 hours before a switch from standard- to intermediate-dose prophylaxis are presented in Table S5. We further extend findings from the main analysis with e-values, as an unmeasured confounder would have to be associated with therapeutic anticoagulation by a risk ratio of >5.89-fold for the result to no longer be a statistically significant increased risk (Table S6). In sensitivity analyses to vary exposure, outcome, and covariate definitions, we continued to find statistically significant increases in

**TABLE 1** Characteristics at the time of first inpatient thromboprophylaxis dose

	Standard-dose prophylaxis n = 36060 (72%)	Intermediate-dose prophylaxis n = 14031 (28%)	Absolute standardized mean difference
Age, y	62.1 (16.8)	59.8 (16.3)	0.14
Male	18,895 (52)	7465 (53)	0.02
Self-identified race			
Asian	1295 (4)	379 (2)	0.05
Black	6114 (17)	2204 (16)	0.03
White	20,523 (57)	7967 (57)	0.01
Multiracial	328 (1)	112 (1)	0.01
Another race	6876 (19)	2979 (21)	0.05
Missing	924 (2)	390 (3)	0.02
Hispanic or Latinx ethnicity	11,281 (31)	4886 (35)	0.08
Current or former smoker	6327 (18)	2451 (17)	0.01
Body mass index			
Not overweight or obese	6423 (18)	1765 (13)	0.15
Overweight	9600 (27)	3260 (23)	0.08
Obese	14,263 (39)	7541 (54)	0.29
Missing	5774 (16)	1465 (10)	0.17
Highest level of oxygen support before anticoagulation initiation			
None	18,172 (50)	6256 (45)	0.12
Low-flow	14,472 (40)	5779 (41)	0.02
High-flow or noninvasive ventilation	2855 (8)	1689 (12)	0.14
Invasive mechanical ventilation	561 (2)	305 (2)	0.05
Medications current at the time of admission			
Antidiabetics	4501 (12)	1900 (14)	0.03
Antihypertensives	8940 (25)	3554 (25)	0.01
Antiplatelets	1753 (5)	609 (4)	0.02
Aspirin	5150 (14)	1849 (13)	0.03
Immunosuppression	1641 (5)	596 (4)	0.01
Inhaled corticosteroids	1542 (4)	672 (5)	0.02
Statins	7053 (20)	2649 (19)	0.02
Systemic glucocorticoids	1773 (5)	668 (5)	0.01

Note: Continuous variables are represented as mean (standard deviation), and categorical variables as count (percentage). There were two people for whom oxygen liters per minute value were outside plausible ranges and their oxygen support status could not be determined. For detailed definitions, see [Table S3](#).

the risk of therapeutic anticoagulation (HR range, 2.97-3.97), severe disease (HR range, 1.22-1.60) and death (HR range, 1.10-1.70) with intermediate-dose prophylaxis ([Tables S7-S11](#)). The risk of death was not statistically significant in marginal structural models.

## 4 | DISCUSSION

COVID-19 has been associated with an increased risk of venous and arterial thromboembolism, which may suggest intermediate-dose thromboprophylaxis as a treatment consideration, particularly in severe cases. Nevertheless, current treatment guidelines have not recommended routine use of intermediate-dose thromboprophylaxis

in non-ICU patients and have recently recommended against use in ICU patients. In this retrospective comparative effectiveness study, our findings do not support the use of intermediate-dose thromboprophylaxis to prevent clinical worsening, severe disease or death among adults hospitalized with COVID-19 in the United States. These findings are important, given that thromboprophylaxis plays a significant role in the inpatient management of COVID-19, and reflect one of several examples of evolving standards of care throughout the pandemic.<sup>39</sup>

These results persisted in a variety of subgroup and sensitivity analyses. Abnormal lab and vital signs were less common at the time of intensification than at standard prophylaxis initiation. These results do not support potential bias from confounding by indication,

**TABLE 2** Risk of specific severe outcomes from time-dependent Cox proportional hazards models

	Events	Person-days of follow-up	Event rate per 100 person-days	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Therapeutic anticoagulation					
Intermediate dose	4390	77,849	5.6	3.68(3.50-3.87)	3.39 (3.22-3.57)
Standard dose	2473	187,993	1.3	Reference	Reference
Severe disease					
Intermediate dose	3324	9632	34.5	1.59 (1.52-1.66)	1.22 (1.17-1.28)
Standard dose	5488	105,536	5.2	Reference	Reference
Death within 24 hours of last prophylaxis dose					
Intermediate dose	508	112,813	0.5	1.49 (1.32-1.68)	1.37 (1.21-1.55)
Standard dose	646	215,456	0.3	Reference	Reference
Death within 3 days of last prophylaxis dose					
Intermediate dose	1373	156,852	0.9	1.51 (1.41-1.63)	1.41 (1.31-1.52)
Standard dose	1698	295,626	0.6	Reference	Reference
Death within 7 days of last prophylaxis dose					
Intermediate dose	2100	242,248	0.9	1.53 (1.44-1.62)	1.38 (1.30-1.47)
Standard dose	2584	452,463	0.6	Reference	Reference
Death within 10 days of last prophylaxis dose					
Intermediate dose	2616	304,376	0.9	1.57 (1.49-1.65)	1.40 (1.33-1.48)
Standard dose	3120	568,045	0.5	Reference	Reference

Note: For a detailed list of covariates in the adjusted models, see [Table S3](#).

Abbreviations: CI, confidence interval; HR, hazard ratio.

	Events	Person-days of follow-up	Adjusted HR (95% CI)
Therapeutic anticoagulation			
Intermediate dose	3774	58,144	3.29 (3.13-3.46)
Standard dose	3089	207,698	Reference
Severe disease			
Intermediate dose	2499	5129	1.14 (1.09-1.20)
Standard dose	6313	110,040	Reference
Death within 24 h of last prophylactic dose			
Intermediate dose	427	86,900	1.38 (1.22-1.56)
Standard dose	727	241,368	Reference
Death within 3 days of last prophylactic dose			
Intermediate dose	1154	122,068	1.36 (1.26-1.46)
Standard dose	1917	330,409	Reference
Death within 7 days of last prophylactic dose			
Intermediate dose	1801	190,082	1.35 (1.27-1.43)
Standard dose	2883	504,629	Reference
Death within 10 days of last prophylactic dose			
Intermediate dose	2247	239,403	1.36 (1.29-1.44)
Standard dose	3489	633,018	Reference

**TABLE 3** Risk of specific severe outcomes, with dose adjustments for persons with body mass index >40 kg/m<sup>2</sup>

Note: There were 4113 persons with a body mass index >40 kg/m<sup>2</sup> with a total of 4607 person-periods, which were reclassified from intermediate-dose prophylaxis to standard-dose prophylaxis in this analysis. For a detailed list of covariates in the adjusted models, see [Table S3](#).

Abbreviations: CI, confidence interval; HR, hazard ratio.

**TABLE 4** Risk of specific severe outcomes, stratified by oxygen requirements at time of first dose

	No or low-flow oxygen at time of first dose			Severe disease at time of first dose		
	Events	Person-days	Adjusted HR (95% CI)	Events	Person-days	Adjusted HR (95% CI)
Therapeutic anticoagulation						
Intermediate dose	3365	64,817	3.78 (3.56-4.01)	1024	13025	2.29 (2.06-2.55)
Standard dose	1896	168,139	Reference	577	19854	Reference
Severe disease						
Intermediate dose	2662	22,375	1.21 (1.15-1.27)	...	...	...
Standard dose	4689	116,535	Reference	...	...	...
Death within 24 h of last prophylactic dose						
Intermediate dose	331	89,576	1.47 (1.26-1.71)	177	23229	1.11 (0.90-1.37)
Standard dose	422	186,383	Reference	224	29072	Reference
Death within 3 d of last prophylactic dose						
Intermediate dose	900	126,695	1.47 (1.34-1.61)	472	30147	1.21 (1.06-1.38)
Standard dose	1152	258,507	Reference	546	37119	Reference
Death within 7 d of last prophylactic dose						
Intermediate dose	1402	199,113	1.45 (1.35-1.56)	697	43121	1.16 (1.04-1.29)
Standard dose	1778	400,296	Reference	806	52167	Reference
Death within 10 d of last prophylactic dose						
Intermediate dose	1756	252,107	1.47 (1.38-1.57)	859	52252	1.17 (1.07-1.29)
Standard dose	2158	505,174	Reference	962	62871	Reference

where people could have been switched to intermediate doses due to worsening clinical status, which could have explained the increases risks reported. Further, the large *e*-values suggest that an unmeasured confounder would have to have a large magnitude of effect to change our findings to null or protective effects; importantly, this hypothetical variable would need to exert influence independently of each of the confounders already included in the adjustment set. An unmeasured confounder, such as high D-dimer, that would be strongly associated with preferential escalation to therapeutic anticoagulation would mean the effect estimates we present here are an underestimate, and adjustment for this confounder would strengthen reported associations. While the effect estimates we derived indicate statistically significant increases in risk associated with high-dose prophylaxis, we are unable to discern whether this is a true causal effect or due to residual confounding. Therefore, we conclude that our results are not consistent with reduced risk rather than clear evidence of increased risk.

Our findings add to a growing body of evidence that has failed to show benefits of intermediate-dose thromboprophylaxis among adults hospitalized with COVID-19.<sup>7,11,22-27</sup> A small clinical trial showed no difference in risk of thrombosis, ECMO, or death between standard and intermediate doses with weight-based adjustments.<sup>22</sup> In our subgroup analyses, where we applied weight-based adjustments, we again found increases in risk of therapeutic anticoagulation as a proxy for thrombosis, severe disease, and death. There are several potential explanations for the divergence of our findings from the earlier clinical trial. First, the definitions of the outcomes differed.

For example, our definition of severe disease used oxygen support devices more commonly used in the United States such as HFNC and IMV. Second, our observational analysis may suffer from residual confounding by indication, whereby patients with a worse prognosis were preferentially given intermediate doses, and the variables affecting those choices were not captured in our models. Third, the trial had 562 participants and our study had over 50000 people, and perhaps the increased statistical precision allowed for elucidation of effect.

One limitation of this work is the inability to quantify the incidence of thromboembolic events and treatment-associated major bleeds. We attempted to derive an algorithm consisting of discharge diagnosis codes and imaging procedure codes consistent with the presence of a thrombotic event and time stamps for the initiation of therapeutic anticoagulation. However, most patients had multiple imaging studies, and fewer than 1% of persons were identified with this strategy, whereas the literature suggests as many as 14% of hospitalized patients with COVID-19 develop venous thromboembolism during their stay.<sup>5,40-42</sup> Another limitation was the lack of model fit with the marginal structural model framework, precluding its use as the main analysis. The mean of the stabilized weights indicated remaining residual confounding, and there was a large amount of missingness of the single most important time-varying covariate, with >50% of people not having a D-dimer measure at baseline. It is also possible that some of the progressions to therapeutic anticoagulation reflect physician preference to use therapeutic doses for prophylactic purposes, particularly in early months of the pandemic where little was known

about the pathophysiology of the novel virus, rather than a true surrogate for thrombotic events.

Our conclusions are drawn from 186 hospitals in 20 states, and address facilities both with and without weight-based anticoagulation protocols. We examined the real-world experience, in consideration of time-varying treatment intensity changes, of >50000 hospitalized adults to directly address a knowledge gap identified by the National Institutes of Health's COVID-19 treatment guidelines.<sup>12</sup> The geographic diversity represented by HCA Healthcare includes many medium and large centers concentrated in the southern and western regions of the United States. An additional strength of this work is that nearly half of our cohort identified as a race other than White, and a third identified as Hispanic or Latinx, both of which are high-risk groups given the disproportionate burden of disease incidence and severity due to systemic racism and other factors.<sup>43</sup> The data period of February 2020 to February 2021 captures a relatively homogenous period in which there was not widespread vaccination nor the delta variant, each of which have important implications for disease presentation and severity.

Important questions remain unanswered. We could not answer questions about thromboembolic events, nor major bleeds, given data limitations. We did not consider groups whose anticoagulation protocols substantially differ from the general adult population. More work is needed to understand optimal thromboprophylaxis among people with chronic outpatient anticoagulation use, as well as among people who are pregnant or have severe renal impairment. The impact of center-level effects, such as clustering by local prescribing patterns or quality indicators of care, requires further understanding as well.

## 5 | CONCLUSION

This study of >50000 adults contributes to a growing body of evidence that does not support the use of higher than routine thromboprophylaxis doses in patients hospitalized with COVID-19.

### AUTHOR CONTRIBUTIONS

All authors contributed to study design. KMA, CSJ, HBM, JFB, and MLR derived the analytic cohort. KMA analyzed the data. CSJ reviewed all data reported in the manuscript for accuracy using direct output from the statistical programming software. All authors contributed to data interpretation. KMA, GCA, and BTG wrote the original draft of the manuscript. All authors contributed to the writing, review, and editing of the manuscript, and approved the final text.

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### RELATIONSHIP DISCLOSURE

CSJ, HBM, AMF, AG, CFL, MLR, YX, and DKN declare no conflicts of interest. After the completion of this work, KMA became a full-time employee of Pfizer, Inc. MBS has received research support from Janssen, NovoNordisk, Sanofi-Aventis, and Tremeau Pharmaceuticals; has consulted for Janssen and Pfizer; and has received continuing medical education lecture honoraria from Pfizer. JFB and RCB are entitled to equity and royalty payments from miDiagnostics. RCB is entitled to equity and royalty payments from emocha Health; and is a consultant for Merck & Co, Hologic, Wondros, and Hip Hop Public Health. GCA is a current member and past chair of the Food and Drug Administration's Peripheral and Central Nervous System Advisory Committee, is a cofounding principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a past member of OptumRx's National P&T Committee. BTG is a member of the Food and Drug Administration's Pulmonary and Asthma Drug Advisory Committee and has received consulting fees from Gilead Sciences, Inc., Janssen Research and Development, LLC, and Atea Pharmaceuticals, Inc. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict-of-interest policies.

### DATA AVAILABILITY STATEMENT

Data were made available by HCA Healthcare, and study-specific limited data sets were accessible for research via a secure platform hosted within a private virtual network. The data that support the findings of this study are available to people who have HCA approval for data access from the corresponding author (BTG) upon reasonable request. Authors of this manuscript are willing to share statistical programming code to people who have HCA approval for data access upon request.

### ETHICS STATEMENT

This research was deemed minimal risk with a waiver of consent by both Johns Hopkins Medicine (IRB00286926) as well as an external institutional review board (WIRB-Copernicus Group).

### TRANSPARENCY STATEMENT

The manuscript's guarantors (KMA, CSJ, GCA, and BTG) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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## REFERENCES

1. CSSE. COVID-19 dashboard by the center for systems science and engineering (CSSE) at Johns Hopkins University (JHU). Johns Hopkins University. 2020. Accessed April 15 2022. <https://coronavirus.jhu.edu/map.html>
2. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. 2020;136:489-500.
3. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. *Lancet Haematol*. 2020;7:e575-e582.
4. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost*. 2020;18:1738-1742.
5. Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. *Thromb Res*. 2020;191:148-150.
6. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46:1089-1098.
7. Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. *J Am Coll Cardiol*. 2020;76:1815-1826.
8. Kamel AM, Sobhy M, Magdy N, Sabry N, Farid S. Anticoagulation outcomes in hospitalized COVID-19 patients: a systematic review and meta-analysis of case-control and cohort studies. *Rev Med Virol*. 2021;31:e2180.
9. 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.
10. Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). *Blood Transfus*. 2020;18:167-169.
11. World Health Organization. COVID-19 clinical management: living guidance, 25 January 2021. World Health Organization. 2021. Accessed April 15 2022. <https://apps.who.int/iris/handle/10665/338882>
12. National Institutes of Health. Antithrombotic therapy in patients with COVID-19. COVID-19 Treatment Guidelines. Accessed April 15 2022. <https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/>
13. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. *N Engl J Med*. 2021;385:790-802.
14. Sholzberg M, Tang GH, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with COVID-19 admitted to hospital: RAPID randomised clinical trial. *BMJ*. 2021;375:n2400.
15. The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. *N Engl J Med*. 2021;385:777-789.
16. 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*. 2021;174:622-632.
17. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021;181:1612-1620.
18. Al-Samkari H. Finding the optimal thromboprophylaxis dose in patients with COVID-19. *JAMA*. 2021;325:1613-1615.
19. Godoy LC, Goligher EC, Lawler PR, Slutsky AS, Zarychanski R. Anticipating and managing coagulopathy and thrombotic manifestations of severe COVID-19. *CMAJ*. 2020;192:E1156-E1161.
20. ten Cate H. Surviving COVID-19 with heparin? *N Engl J Med*. 2021;385:845-846.
21. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST guideline and expert panel report. *Chest*. 2020;158:1143-1163.
22. INSPIRATION Investigators. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA*. 2021;325:1620-1630.
23. Billett HH, Reyes-Gil M, Szymanski J, et al. Anticoagulation in COVID-19: effect of enoxaparin, heparin, and apixaban on mortality. *Thromb Haemost*. 2020;120:1691-1699.
24. Ionescu F, Jaiyesimi I, Petrescu I, et al. Association of anticoagulation dose and survival in hospitalized COVID-19 patients: a retrospective propensity score-weighted analysis. *Eur J Haematol*. 2021;106:165-174.
25. Ferguson J, Volk S, Vondracek T, Flanigan J, Chernaik A. Empiric therapeutic anticoagulation and mortality in critically ill patients with respiratory failure from SARS-CoV-2: a retrospective cohort study. *J Clin Pharmacol*. 2020;60:1411-1415.
26. Daughety MM, Morgan A, Frost E, et al. COVID-19 associated coagulopathy: thrombosis, hemorrhage and mortality rates with an escalated-dose thromboprophylaxis strategy. *Thromb Res*. 2020;196:483-485.
27. Hozayen SM, Zychowski D, Benson S, et al. Outpatient and inpatient anticoagulation therapy and the risk for hospital admission and death among COVID-19 patients. *EClinicalMedicine*. 2021;41:101139.
28. Arnold Egloff SA, Junglen A, Restivo JS, et al. Convalescent plasma associates with reduced mortality and improved clinical trajectory in patients hospitalized with COVID-19. *J Clin Invest*. 2021;131:e151788.
29. Garibaldi BT, Wang K, Robinson ML, et al. Real-world effectiveness of Remdesivir in adults hospitalized with COVID-19: a retrospective, multicenter comparative effectiveness study. *Clin Infect Dis*. 2021;ciab1035. doi:10.1093/cid/ciab1035
30. Andersen KM, Mehta HB, Palamuttam N, et al. Association between chronic use of immunosuppressive drugs and clinical outcomes from coronavirus disease 2019 (COVID-19) hospitalization: a retrospective cohort study in a large US health system. *Clin Infect Dis*. 2021;73:e4124-e4130.
31. Andersen KM, Bates BA, Rashidi ES, et al. Long-term use of immunosuppressive medicines and in-hospital COVID-19 outcomes: a retrospective cohort study using data from the national COVID cohort collaborative. *Lancet Rheumatol*. 2021;4:E33-E41.
32. Elixhauser comorbidity software refined for ICD-10-CM v2022.1.
33. Garibaldi BT, Fiksel J, Muschelli J, et al. Patient trajectories among persons hospitalized for COVID-19. *Ann Intern Med*. 2020;174:33-41.
34. Wongvibulsin S, Garibaldi BT, Antar AAR, et al. Development of severe COVID-19 adaptive risk predictor (SCARP), a calculator to predict severe disease or death in hospitalized patients with COVID-19. *Ann Intern Med*. 2021;174:777-785.
35. Bowring MG, Wang Z, Xu Y, et al. Outcome-stratified analysis of biomarker trajectories for patients infected with severe acute respiratory syndrome coronavirus 2. *Am J Epidemiol*. 2021;190:2094-2106.

36. Sebaaly J, Covert K. Enoxaparin dosing at extremes of weight: literature review and dosing recommendations. *Ann Pharmacother.* 2018;52:898-909.
37. Robins JM, Hernán MÁ, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology.* 2000;11:550-560.
38. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med.* 2017;167:268-274.
39. Mehta HB, An H, Andersen KM, et al. Use of hydroxychloroquine, Remdesivir, and dexamethasone among adults hospitalized with COVID-19 in the United States: a retrospective cohort study. *Ann Intern Med.* 2021;174:1395-1403.
40. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Res Pract Thromb Haemost.* 2020;4:1178-1191.
41. Zhang L, Feng X, Zhang D, et al. Deep vein thrombosis in hospitalized patients with COVID-19 in Wuhan, China. *Circulation.* 2020;142:114-128.
42. Poissy J, Goutay J, Caplan M, et al. Pulmonary embolism in patients with COVID-19. *Circulation.* 2020;142:184-186.
43. Centers for Disease Control and Prevention. Risk for COVID-19 infection, hospitalization, and death by race/ethnicity. Accessed

April 15 2022. <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html>

## SUPPORTING INFORMATION

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

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