ORIGINAL ARTICLE

Thromboprophylaxis with standard-dose vs. flexible-dose heparin for hospitalized COVID-19 patients: a target trial emulation

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Abstract

Objectives: To compare mortality of hospitalized COVID-19 patients under two low−molecular weight heparin (LMWH) thromboprophylaxis strategies: standard dose and variable dose (standard dose increased to intermediate dose in the presence of laboratory abnormalities indicating an increased thrombosis risk).

Study Design and Setting: Target trial emulation using observational data from 2,613 adults admitted with a COVID-19 diagnosis in Madrid, Spain between March 16 and April 15, 2020.

Results: A total of 1,284 patients were eligible. Among 503 patients without increased baseline thrombotic risk, 28-day mortality risk (95% confidence interval [CI]) was 9.0% (6.6, 11.7) under the standard dose strategy and 5.6% (3.3, 8.3) under the variable dose strategy; risk difference 3.4% (95% CI: −0.24, 6.9); mortality hazard ratio 1.61 (95% CI: 0.97, 2.89). Among 781 patients with increased baseline thrombotic risk, the 28-day mortality risk was 25.8% (22.7, 29.0) under the standard dose strategy and 18.1% (9.3, 28.9) under the intermediate dose strategy; risk difference 7.7% (95% CI: −3.5, 17.2); mortality hazard ratio 1.45 (95% CI: 0.81, 3.17). Major bleeding and LMWH-induced coagulopathy were rare under all strategies.

Conclusion: Escalating anticoagulation intensity after signs of thrombosis risk may increase the survival of hospitalized COVID-19 patients. However, effect estimates were imprecise and additional studies are warranted.   © 2022 Elsevier Inc. All rights reserved.

Keywords: Anticoagulants; COVID-19; COVID-19 drug treatment; Epidemiological methods; Low−molecular weight heparin; Target trial emulation

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1. Introduction

Coagulopathy and thrombotic complications are frequent and serious complications among hospitalized COVID-19 patients [1−5]. Therefore, most clinical guidelines recommend thromboprophylaxis with low−molecular weight heparin (LMWH), for example, 4,000 IU of enoxaparin subcutaneously daily for nonobese patients with normal renal function, for patients not previously on therapeutic anticoagulation and without thrombosis [6−12].

The optimal dose of LMWH, however, remains under debate [13,14] because evidence suggests some degree of heparin resistance especially in severe [15] and critical [16] COVID-19 patients. A recent randomized trial examined the role of therapeutic anticoagulation (e.g., 1 IU of enoxaparin subcutaneously twice per day or comparable dosage of dalteparin or tinzaparin) for thromboprophylaxis among

What is new?

Key findings
- In this target trial emulation including 1,284 hospitalized COVID-19 patients, a flexible thromboprophylaxis strategy that increases to a higher nontherapeutic dose (intermediate dose) after increased thrombotic risk is suspected was superior to the standard low dose strategy among patients without increased thrombotic risk at baseline.

What this adds to what was known?
- Therapeutic-dose heparin is known to reduce organ support-free days among hospitalized COVID-19 patients in comparison to standard low-dose heparin. This study expands existing evidence on thromboprophylaxis strategies for hospitalized COVID-19 patients by examining a widely-adopted and recommended dynamic thromboprophylaxis strategy where intermediate (non-therapeutic) doses of heparin are used only in presence of increased thrombotic risk.

What is the implication and what should change now?
- Standard-dose heparin should be escalated to intermediate (non-therapeutic) dose if signs of thrombosis risk are detected among COVID-19 hospitalized patients.

hospitalized COVID-19 patients. Compared with the standard prophylactic dose, therapeutic anticoagulation increased organ support-free days by 27% among noncritically ill patients [17] but was futile in critically ill counterparts [18] and increased risk of major bleeding two-fold. Some expert panels [19] and clinical guidelines [20,21] recommend intermediate doses of LMWH that are higher than the standard prophylactic dose but lower than the therapeutic dose. These intermediate doses are especially recommended in the presence of laboratory abnormalities that suggest increased thrombosis risk (e.g., elevated D-dimer level) [22,23].

In hospitalized COVID-19 patients, some observational studies found a lower risk of thrombotic complications [23,24] and death [23,25−27] for intermediate dose compared with standard-dose LMWH prophylaxis. However, a randomized trial in COVID-19 patients admitted to the intensive care unit found a similar risk of a composite outcome (including thromboembolic complications, treatment with extracorporeal membrane oxygenation, and 30-day mortality) in the intermediate-dose and standard-dose groups. The risks of severe thrombocytopenia and bleeding were slightly higher in the intermediate-dose group than in the standard-dose group [28].

Here we used electronic health records to emulate a (hypothetical) target trial that compares two LMWH thromboprophylaxis strategies for hospitalized COVID-19 patients: a standard dose strategy and a variable dose strategy based on standard dose that is increased after laboratory abnormalities suggesting an increased risk of thrombosis. We first specify the protocol of the target trial that would have answered the causal question of interest and then define the observational analysis that explicitly emulates this target trial.

2. Methods

2.1. Target trial specification

We specified the protocol of a target trial to estimate the effect of standard dose vs. variable dose of LMWH on the mortality of hospitalized COVID-19 patients. Table 1 summarizes the key protocol components. Briefly, the eligibility criteria include age $\geq$ 18 years, admission for $\geq$ 24 hours to La Paz University Hospital (a large teaching hospital in Madrid, Spain) between March 16 and April 15, 2020 with an RT-PCR−confirmed COVID-19 diagnosis, no active bleeding, no severe thrombocytopenia (platelet count <50,000/mL), no long-term use of anticoagulation, no thrombosis, and no baseline analytical abnormalities indicating an increased thrombotic risk (C-reactive protein >150 mg/dL, D-dimer >1,500 ng/mL, ferritin >1,000 μg/L, or lymphocyte count $\leq$ 800/mL).

Eligible individuals would be randomly assigned to either standard-dose or variable-dose thromboprophylaxis strategies with LMWH. Under the standard strategy, individuals would receive LMWH at a standard prophylactic dose (e.g., 4,000 IU of enoxaparin subcutaneously every 24 hours for a nonobese individual). Under the variable strategy, the initial standard dose will be increased to an intermediate prophylactic dose (e.g., 6,000 IU of enoxaparin subcutaneously every 24 hours for a nonobese individual), which does not reach therapeutic dose (e.g., > 9,000 IU of enoxaparin subcutaneously every 24 hours) within 48 hours of the recording of laboratory abnormalities indicating increased thrombotic risk. The choice of drug is left to the physician's discretion. Individuals are excused from following the assigned strategy after thrombosis (when anticoagulation treatment must be started) and after active bleeding or platelet count <50,000/mL (when anticoagulation must be discontinued). The causal contrasts of interest would be the intention-to-treat and the per-protocol effect.

2.2. Statistical analysis of the target trial

The intention-to-treat analysis is based on the comparison of 28-day survival curves and of mortality hazard ratios. The survival curves can be estimated using a nonparametric Kaplan−Meier estimator or a pooled logistic

Table 1. Outline of specification and emulation of a target trial of thromboprophylaxis in COVID-19 patients with no signs of increased thrombotic risk

Component	Target trial specification	Target trial emulation
Eligibility	• age ≥ 18 yr • admission for ≥ 24 hours to La Paz University Hospital between March 16 and April 15, 2020 • RT-PCR—confirmed COVID-19 diagnosis • no active bleeding, no severe thrombocytopenia (platelet count < 50,000/mL), no long-term use of anticoagulation, no thrombosis, no signs of increased thrombotic risk (C-reactive protein > 150 mg/dL, D-dimer >1,500 ng/mL, ferritin > 1,000 μg/L, or lymphocyte count ≤ 800/mL).	Same.
Treatment strategies	1. Standard dose: LMWH at standard prophylactic dose (i.e., 4,000–5,999 IU of enoxaparin or 2,500–3,999 IU of bemiparin for nonobese individuals and 4,000–7,999 IU of enoxaparin or 2,500–4,999 IU of bemiparin for obese individuals subcutaneously every 24 hours). 2. Variable dose: Same, except that dose is increased (i.e., 6,000–8,999 IU of enoxaparin or 4,000–7,499 IU of bemiparin for nonobese individuals and 8,000–8,999 IU of enoxaparin or 5,000–7,499 IU of bemiparin for obese individuals subcutaneously every 24 hours) within 48 hours if analytic abnormalities (C-reactive protein >150 mg/dL, D-dimer >1,500 ng/mL, ferritin >1,000 μg/L, or lymphocyte count <800/mL) are detected. Under both strategies, the choice of drug is left to the physician's discretion. Individuals are excused from following the assigned strategy after thrombosis (when anticoagulation treatment must be started) and after active bleeding or platelet count <50,000/mL (when anticoagulation must be discontinued).	Same.
Treatment assignment	Individuals are randomly assigned to one of the strategies. Individuals are aware of the strategy they are assigned to.	Individuals are assigned to the strategy their baseline data are compatible with.
Follow-up	For each individual, follow-up starts at the time of assignment to a strategy and ends at death, hospital discharge, or 28 days after hospitalization.	Same.
Primary end point	All-cause mortality at 28 days. We assume no deaths occurred after hospital discharge.	Same.
Causal contrast	Per-protocol effect. Intention-to-treat effect.	Observational analog of the per-protocol effect.
Statistical analysis	Intention-to-treat analysis: 28-day survival curves and hazard ratios are estimated using pooled logistic regression models. Individuals who are discharged are assumed to remain alive through day 28. Per-protocol analysis: Same as intention-to-treat analyses, with two exceptions. First, individuals are censored when their data stop being compatible with the strategy they are assigned to. Second, each individual receives a time-varying inverse probability weight to adjust for the potential selection bias introduced by censoring.	Same as per-protocol analysis except that, for individuals having treatment and laboratory data compatible with both strategies at baseline, we created two clones and assigned each clone to a different strategy.

regression model with an indicator for treatment group, a flexible time-varying intercept, and product terms between treatment group and time. The hazard ratios can be estimated using the same logistic model without the product terms [29]. Individuals who are discharged are assumed to remain alive through day 28.

The per-protocol analysis is the same as the intention-to-treat analysis with two exceptions. First, individuals are censored when they deviate from their assigned strategy. Individuals assigned to the standard-dose strategy are censored if/when they receive an intermediate dose. Individuals assigned to the variable dose strategy are censored if/when they receive an intermediate dose in the absence of analytic abnormalities or if they do not receive an intermediate dose within 48 hours of analytic abnormalities. Second, to adjust for the potential selection bias introduced by censoring, we would use nonstabilized inverse probability weights [30]

(Supplement) to adjust for baseline and time-varying covariates. Baseline covariates include age, gender, migration status, disability, high blood pressure, diabetes mellitus, dyslipidemia, chronic heart disease, chronic kidney disease, active oncological disease, active smoking, Charlson Comorbidity Index, CURB-65 score for pneumonia severity, and heart rate at admission. Time-varying variables include C-reactive protein, D-dimer, and lymphocyte count. The weights can be truncated at the 99th percentile to avoid undue influence of outliers. The validity of the per-protocol effect estimates require no unmeasured confounding given the above covariates and no model misspecification.

2.3. Target trial emulation

We emulated this target trial using observational data from La Paz University Hospital. Data on individuals'
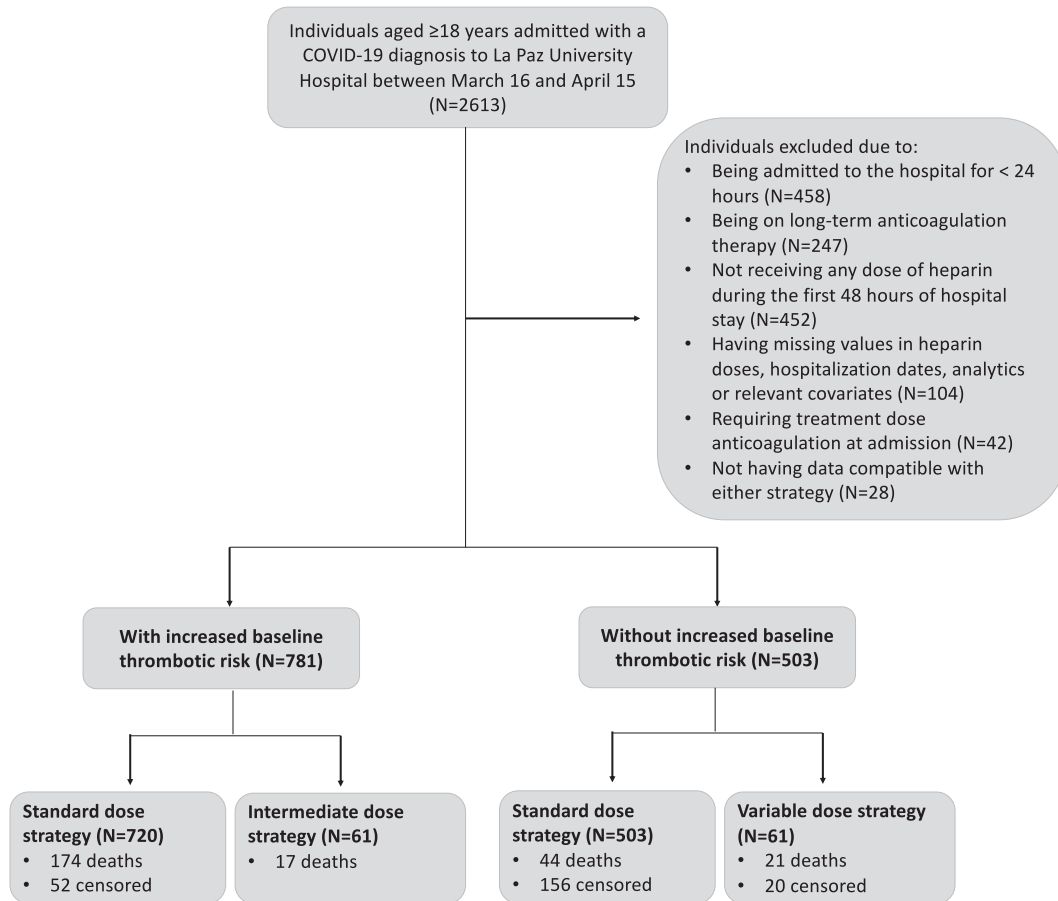
Fig. 1. Flowchart of eligible and included individuals for the emulation of a target trial of thromboprophylaxis in COVID-19 patients, Hospital Universitario La Paz, Madrid, Spain; March 16−April 15, 2020.

sociodemographic characteristics, previous medical history and regular medications, vital signs at admission and during hospitalization, comorbidity and pneumonia severity scales, treatments received during hospitalization, including start and stop dates, and clinical outcomes, including intensive care admission, mortality, hospital discharge, nonclinically significant coagulopathy (i.e., prothrombin time or international normalized ratio variations without clinical impact), clinically significant coagulopathy (i.e., prothrombin time or international normalized ratio variations and clinically compatible symptoms), and incident major bleeding (i.e., driving >2 g/dL drops in hemoglobin levels or requiring transfusion of blood or blood products) were retrieved from electronic health records by resident physicians or supervised last year medical students. For each individual, we linked these data with every laboratory determination performed during hospitalization. Ferritin was not monitored routinely in most individuals. We defined time zero as the hospitalization date.

To estimate the observational analog of the per-protocol effect, we conducted the statistical analysis described above with a difference: we created two copies (clones) of each eligible individual, one per strategy, and conducted the analysis in the expanded dataset [30]. We could not

estimate an observational analog of the intention-to-treat effect because individuals could not be assigned to a single strategy at time zero.

We also emulated a second identical target trial except that it was restricted to individuals with baseline laboratory abnormalities indicating increased thrombotic risk (C-reactive protein >150 mg/dL, D-dimer >1,500 ng/mL, ferritin >1,000 μg/L, or lymphocyte count ≤ 800/mL). These individuals have a worse prognosis than individuals without baseline laboratory abnormalities and thus need to be considered separately. In this second trial, both strategies are constant given that either the standard dose or the intermediate dose is assigned at baseline and the emulation does not require cloning because the strategy followed by each individual is known at baseline.

2.4. Sensitivity analyses

We conducted two sensitivity analyses. First, to assess the magnitude of the measured confounding, we conducted only age-adjusted and gender-adjusted analyses. Second, we repeated our analyses in COVID-19 patients who, at admission, had both increased thrombotic risk and severe COVID-19 pneumonia (as defined by the World Health Organization's guidelines [31]).

Table 2. Baseline characteristics of individuals eligible for the emulation of a target trial of thromboprophylaxis in COVID-19 patients, Hospital Universitario La Paz, Madrid, Spain; March 16—April 15, 2020

Variable	Increased baseline thrombotic risk[b]	
	Yes (*N* = 781)	No (*N* = 503)
Age (yr), median (IQR)	70 (59, 81)	61.0 (51.0, 76.0)
Gender (% Male)	60.2	47.1
Immigrant (%)	18.8	31.2
Disability (%)[a]	7.8	6.6
Suspected hospital acquisition (%)	15.1	16.7
Chronic heart disease (%)	16.3	14.11
High blood pressure (%)	52.1	42.1
Diabetes mellitus (%)	22.2	18.5
Obesity (%)	17.2	18.7
Dyslipidemia (%)	37.6	36.6
Active smoking (%)	7.4	4.4
Chronic kidney disease (%)	10.8	2.8
Malignant neoplasms (%)	11.1	5.9
Hematological disease (%)	52.5	6.2
Charlson Comorbidity Index, median (IQR)	3 (2, 5)	2 (1, 4)
CURB-65 score, median (IQR)	1 (0, 2)	1 (0, 1)
Heart rate at admission, bpm, median (IQR)	91 (80, 104)	91 (78, 105)
Admission before/after April 5 (%)	85.3	84.3
D-dimer at baseline	1,088.5 (609.5; 2,159.5)	540.0 (368.0, 802.0)

Abbreviations: IQR, interquartile range.
[a] Disability as indicated by a Katz Basic Activities of Daily Living Score ≤ 2.
[b] C-reactive protein >150 mg/dL, D-dimer $>1,500$ ng/mL, ferritin $>1,000$ µg/L, or lymphocyte count <800/mL.

Study procedures were approved by La Paz University Hospital's Institutional Review Board. Statistical analyses were programmed in R Studio. Study data are available on request from the corresponding author upon approval by the steering committee of the COVID@-HULP group. Analyses were finalized on July 15, 2021. All analyses were conducted using R version 3.6.2. The R code used in this manuscript is publicly available in: https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/.

3. Results

Of 2,613 individuals aged 18 years or more admitted with a COVID-19 diagnosis between March 16 and April
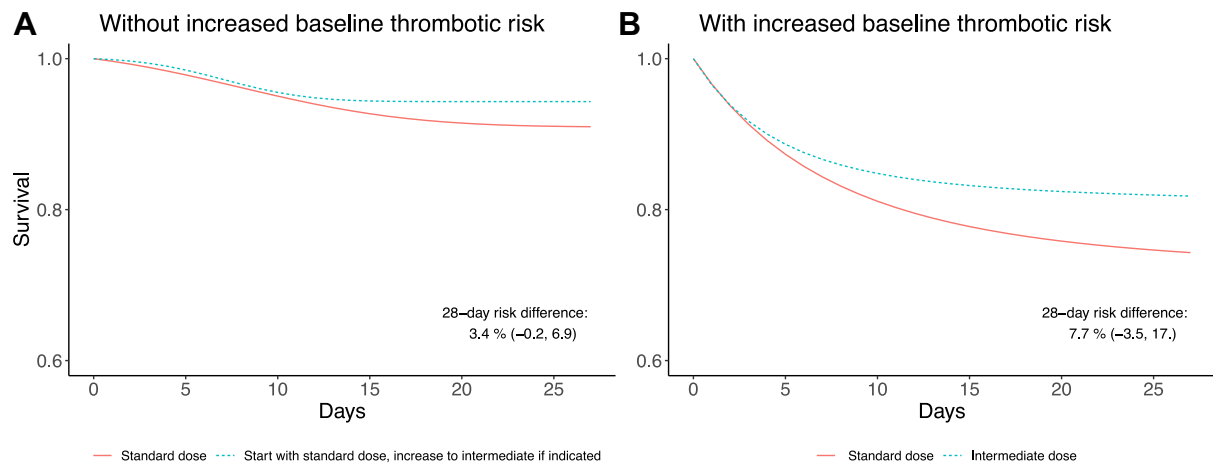

Fig. 2. Estimated survival curves under two thromboprophylaxis strategies for COVID-19 patients, Hospital Universitario La Paz, Madrid, Spain; March 16—April 15, 2020 for (A) individuals without increased baseline thrombotic risk and (B) individuals with increased baseline thrombotic risk.

Table 3. Estimated 28-day mortality risks under two thromboprophylaxis strategies for COVID-19 patients, Hospital Universitario La Paz, Madrid, Spain; March 16—April 15, 2020

	28-day mortality risk (No. deaths)		Risk difference[a] (95% CI)	Hazard ratio[a,b] (95% CI)
	Always standard dose	Start with standard dose, increase to intermediate dose if indicated		
No increased baseline thrombotic risk (*N* = 503)	8.7% (44)	4.2% (21)	3.4 (−0.2, 6.9)	1.58 (0.93, 2.88)
	Always standard dose	Always intermediate dose		
Increased baseline thrombotic risk (*N* = 781)	24.2% (174)	27.9% (17)	7.7 (−3.5, 17.2)	1.45 (0.81, 3.17)

Increased baseline thrombotic risk is indicated by presence of the following laboratory abnormalities at baseline: C-reactive protein >150 mg/dL, D-dimer >1,500 ng/mL, ferritin >1,000 μg/L, or lymphocyte count ≤ 800/mL.

[a] Adjusted for baseline confounders using inverse probability weighting: age, gender, migration status, disability, high blood pressure, diabetes mellitus, dyslipidemia, active smoking, Charlson Comorbidity Index, CURB-65 score for pneumonia severity, chronic heart disease, chronic kidney disease, malignant neoplasm, and heart rate at admission.

[b] Additionally adjusted for time-varying indicators using inverse probability weighting: C-reactive protein >150 mg/dL, D-dimer >1,500 ng/mL, and lymphocyte count <800/mL (only for individuals without an increased baseline thrombotic risk).

15, 1,284 (503 without increased baseline thrombotic risk and 781 with increased baseline thrombotic risk) were eligible (Fig. 1). Individuals with increased baseline thrombotic risk were on average 9 years older and more likely to be men, to be nonimmigrants, and to have comorbidities than those without increased thrombotic risk (Table 2).

3.1. Individuals without increased baseline thrombotic risk

The 28-day mortality risk was 9.0% (95% confidence interval [CI]: 6.6, 11.7) under the standard dose strategy and 5.6% (95% CI: 3.3, 8.3) under the variable dose strategy; risk difference 3.4% (95% CI: −0.24, 6.9). Figure 2 shows the survival curves. The mortality hazard ratio (95% CI) for the standard vs. the variable dose strategy was 1.58 (0.93, 2.88) (Table 3).

Overall, there were one episode of incident major active bleeding, five episodes of nonclinically significant coagulopathy, and two episodes of clinically significant coagulopathy.

3.2. Individuals with increased baseline thrombotic risk

The 28-day mortality risk was 25.8% (95% CI: 22.7, 29.0) under the standard-dose strategy and 18.1% (95% CI: 9.3, 28.9) under the intermediate-dose strategy; risk difference 7.7% (95% CI: −3.5, 17.2). Figure 2 shows the survival curves. The mortality hazard ratio (95% CI) for the standard-dose vs. intermediate-dose strategy was 1.45 (0.81, 3.17) (Table 3).

Under the standard-dose strategy, there were three episodes of incident major active bleeding, 25 episodes of nonclinically significant coagulopathy, and 11 episodes of clinically significant coagulopathy. Under the intermediate-dose strategy, there were no episodes of incident major active bleeding, three episodes of nonclinically

significant coagulopathy, and one episode of clinically significant coagulopathy.

3.3. Sensitivity analyses

When only adjusting the models for age and gender, the mortality hazard ratio (95% CI) was 1.70 (1.03, 3.0) for standard-dose vs. variable-dose strategies among individuals without increased baseline thrombotic risk and 0.91 (0.58, 1.58) for standard vs. intermediate dose among individuals with increased baseline thrombotic risk. The main confounders driving the difference between the hazard ratios for unadjusted and adjusted models for individuals with increased baseline thrombotic risk (0.91 unadjusted vs. 1.45 adjusted) were disability, diabetes mellitus, CURB-65 score for pneumonia severity, and heart rate at admission.

When restricting the analyses to patients with both increased thrombotic risk and severe COVID-19 pneumonia, the mortality hazard ratio (95% CI) was 1.25 (0.56, 3.07) for standard vs. intermediate dose.

4. Discussion

We used observational data from 1,283 hospitalized COVID-19 patients to emulate two target trials of thromboprophylaxis with LMWH. In individuals without signs of increased thrombotic risk at baseline, the estimated 28-day mortality risk was 3 percentage points higher under the standard prophylactic dose than under a strategy that increases to a higher nontherapeutic dose (intermediate dose) after increased thrombotic risk is suspected, with values between 0 and 7 percentage points being very compatible with our data. In individuals with signs of increased thrombotic risk, the difference was about 8 percentage points higher for standard dose compared with intermediate dose, with values between −4 and 17 percentage points being

very compatible with our data. There were no differences between strategies in terms of coagulopathy and major bleeding, which were overall rare.

Our findings are consistent with several observational studies of noncritical COVID-19 patients, which found a lower mortality among hospitalized patients receiving intermediate-dose LMWH than in those receiving standard-dose [23,25−27]. In contrast, when comparing standard-dose vs. intermediate-dose thromboprophylaxis among critical patients, one observational study did not find 14-day mortality differences [24] and the Intermediate vs Standard-Dose Prophylactic Anticoagulation in Critically-ill Patients With COVID-19 randomized trial found no clinically significant differences in a composite outcome including thromboembolic complications, treatment with extracorporeal membrane oxygenation, and 30-day mortality [28]. Similarly, a large randomized trial found that, in comparison with standard-dose thromboprophylaxis, therapeutic doses reduce organ support-free days in noncritical patients but not in critical patients [17,18]. In our study, analyses restricted to severely ill patients with increased baseline thrombotic risk yielded inconclusive results with very wide 95% CIs.

By examining a dynamic strategy in which the intermediate dose is only used after analytic signs of increased thrombotic risk, as empirically recommended by expert panels [17] and widely adopted clinical guidelines [18,19], our study expands existing evidence and generates estimates more relevant for clinical practice. Moreover, the explicit emulation of a target trial overcomes some common limitations of observational analyses [32,33] and enhances the clinical interpretability of results.

This study has limitations. First, as with any observational data study with a causal goal, we cannot rule out the possibility of residual confounding. However, we adjusted for key baseline and time-varying prognostic factors and the adjustment did not have a substantial impact of the effect estimates for patients without elevated thrombotic risk, which suggests that large residual confounding is unlikely. Second, by only examining in-hospital mortality, we may have somewhat underestimated mortality risk due to thromboembolic events [34,35] and other causes [36] following hospital discharge. However, we do not have reasons to believe that outpatient outcomes differed across treatment strategy groups. Third, we did not study anticoagulant agents (i.e., direct oral anticoagulants) other than LMWH [37] because the latter is the most frequently recommended agent for prophylactic anticoagulation in hospitalized COVID-19 patients, mostly because of their wide availability and extensive experience of use in hospitalized patients [38,39]. In addition, LMWH might possess anti-inflammatory [40] and antiviral [41] properties.

In conclusion, our results suggest that escalating the intensity of anticoagulation after detection of laboratory markers of thrombosis risk increases survival among noncritical hospitalized COVID-19 patients. However, our estimates were imprecise and additional studies are warranted.

Appendix A

Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2022.08.006.

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