Title: Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19

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**ABSTRACT**

**Background:** Thrombotic complications occur at high rates in hospitalized patients with COVID-19. We examined the impact of intermediate-dose anticoagulation and aspirin in a large observational study of hospitalized patients with COVID-19 treated under a hospital-wide antithrombotic algorithm.

**Methods:** We analyzed clinical data from 2785 hospitalized patients with COVID-19 and established two separate propensity score-matched, nested cohorts including patients (1) who received intermediate- or prophylactic-dose enoxaparin or heparin during their hospitalization (N = 382), or (2) who were not on home antiplatelet therapy and received either in-hospital aspirin or no antiplatelet therapy during their admission (N = 638). The primary outcome was in-hospital death.

**Findings:** Compared to prophylactic-dose anticoagulation, intermediate-dose anticoagulation was associated with significantly lower odds of in-hospital death (odds ratio (OR 0.460 [95% confidence interval 0.241-0.857]) and a lower cumulative incidence of in-hospital death in a time-to-event competing risks model (hazard ratio (HR) 0.518 [0.308-0.872]). Similarly, use of in-hospital aspirin compared to no antiplatelet therapy was associated with significantly lower odds of in-hospital death (OR 0.521 [0.305-0.880]) and a lower cumulative incidence of in-hospital death in a time-to-event competing risks model (HR 0.522 [0.336-0.812]).

**Interpretation:** In a large, observational study of hospitalized patients with COVID-19, intermediate-dose anticoagulation and aspirin use were associated with a lower risk of in-hospital death.

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**RESEARCH IN CONTEXT**

**Evidence before this study:** We searched PubMed for articles published from inception up to October 30, 2020, using the keywords “(‘coronavirus’ OR ‘COVID-19’) AND (‘anticoagulation’ OR ‘aspirin’)”, with no language restrictions. Due to concerns about increased thrombosis risk in COVID-19, it has become a common worldwide practice to treat hospitalized COVID-19 patients with escalated-intensity (i.e., intermediate- or therapeutic-dose) anticoagulation. However, there have been minimal data to guide such approaches. Some studies suggest an improvement in mortality with therapeutic-dose anticoagulation, although reports have conflicted. No study has compared mortality with intermediate-dose anticoagulation to that observed with prophylactic-dose anticoagulation. The major societies and consensus groups, reflecting these uncertainties, have varied in their recommendations for anticoagulation dose intensity in the treatment of hospitalized COVID-19 patients. A potential benefit of aspirin has also been proposed, with support from one small case-control study and one observational study with limited ability to control for severity of illness.

**Added value of this study:** To the best of our knowledge, our large, observational study is the first to provide strong evidence that intermediate-dose anticoagulation, compared to prophylactic-dose anticoagulation, is associated with a significant reduction in the risk of in-hospital mortality in hospitalized patients with COVID-19. We also find that in-hospital aspirin, compared to no antiplatelet therapy, is associated with a reduced risk of in-hospital mortality. Unlike many other observational studies, our analysis makes use of careful propensity score matching to adjust for patient heterogeneity and treatment biases, allowing for treatment groups with balanced covariates to be reliably compared. In addition, we determine that in-hospital mortality may be accurately predicted at the time of hospital admission using the Rothman Index, a real-time score composed of clinical, laboratory, and nursing assessment variables, and we incorporate this and other measures of illness severity into our matching and multivariable regression models.

**Implications of all the available evidence:** Our study suggests that intermediate-dose anticoagulation and aspirin may have a beneficial role in the treatment of hospitalized patients with COVID-19, and that the Rothman Index calculated on admission may be a useful prognostic marker in evaluating the risk of in-hospital mortality. Future results of clinical trials will be needed to further guide these treatment decisions.

**INTRODUCTION**

Thrombosis is among the most devastating complications of COVID-19. Venous thromboembolism (VTE), arterial thrombosis, and microvascular thrombosis have been described in numerous studies of COVID-19.1-6 VTE rates in the range of ≥ 30-40% have been reported among critically ill patients with COVID-19, despite the use of prophylactic anticoagulation.7 Meanwhile, the high burden of pulmonary microvascular thrombosis may be central to the pathogenesis of COVID-19 in the lungs.5

A common global practice has been to administer escalated intensities of antithrombotic therapy beyond standard prophylactic-dose anticoagulation in hospitalized patients with COVID-19.8-10 To date, there has been little evidence to guide these practices. Some retrospective studies have observed lower mortality rates in COVID-19 patients on therapeutic-dose anticoagulation compared to either prophylactic-dose or no anticoagulation, while other studies comparing therapeutic- and prophylactic-dose anticoagulation have found no mortality difference.11-15 The use of therapeutic-dose anticoagulation also comes with a well-established increase in bleeding risk, prompting many hospital systems to implement intermediate-dose anticoagulation for COVID-19 patients, in the absence of strong evidence to guide this decision.7,11,12,14-17

To date, no study has compared the effects of intermediate- versus prophylactic-dose anticoagulation on mortality in hospitalized patients with COVID-19. A potential role for aspirin or other antiplatelet therapies has also been proposed, with encouraging findings in a few reports.18,19

A major limitation of retrospective studies is patient heterogeneity and bias in the likelihood of patients to receive the treatment of interest. To address these issues, propensity score matching has been used in some landmark observational studies of COVID-19, yielding key insights about interventions by enabling treatment groups with balanced covariates to be reliably compared and allowing more accurate estimates of potential treatment effects.20,21 We conjectured that the Rothman Index (RI), a real-time score composed of clinical, laboratory, and nursing assessment variables, might offer a tool for evaluating disease severity in COVID-19, both for clinical care and for the purposes of propensity score matching.22 In this study, we analyzed a large, multisite cohort of hospitalized COVID-19 patients and found a novel prognostic role for the admission RI in predicting clinical outcomes. Using a combination of propensity score matching and multivariable regression incorporating RI and other patient variables, we observed significant reductions in in-hospital mortality among hospitalized COVID-19 patients treated with either intermediate-dose anticoagulation or aspirin.

**METHODS**

Patients, data collection, and definitions of variables

Institutional Review Board approval was obtained for this study; an approved Data Use Agreement between institutions permitted analysis. From March through June, 2020, our hospital’s Joint Data Analytics Team (JDAT) identified 4150 hospital encounters in the Yale-New Haven Health System with a diagnosis of COVID-19 established via a nasopharyngeal polymerase chain reaction test. Patients were excluded if they were < 18 years of age (N = 35 patients), were transferred from one hospital to another within our health system or had multiple inpatient hospital encounters (N = 1247), or had missing data (N = 83), yielding an overall study cohort size of 2785 patients.

Data was extracted from each patient’s medical record by JDAT. Established population health registries were used for diabetes mellitus, hypertension, coronary artery disease (CAD), and congestive heart failure (CHF). Inclusion into a population health registry required an encounter diagnosis of the referenced disease state and at least a single, non-abstract patient encounter within the health system in the preceding three years (Supplemental Table 1); in addition, either the patient problem list was required to contain the referenced diagnosis, or the patient had to have a minimum of two face-to-face encounters within the previous 12 months. For disease states without established population health registries, ICD-10 codes were used for patient classification.

We defined cardiovascular disease as any of the following: hypertension, diabetes, CAD, myocardial infarction, CHF, atrial fibrillation, stroke, or transient ischemic attack. We categorized body mass index (BMI) according to the U.S. Centers for Disease Control definitions. We categorized the first RI on admission into four quartiles (quartile 1, RI -33 to 43; quartile 2, RI 43 to 65; quartile 3, RI 65 to 79; quartile 4, RI 79 to 99), with the lowest and highest quartiles representing patients with the greatest and least illness severities, respectively.

Outcomes

The primary outcome in this study was in-hospital death. The secondary outcome was cumulative incidence of in-hospital death and discharge evaluated as competing risks. We did not examine VTE rates, as only a small percentage of patients in our hospital system underwent VTE-specific imaging.

Overview of antithrombotic treatment algorithm

In March of 2020, a hospital system-wide antithrombotic treatment algorithm was established to guide clinicians in our health system in making choices about antithrombotic therapy in the management of hospitalized patients with COVID-19 (Supplemental Table 2). Overall provider adherence to the algorithm was variable, which provided the basis for us to examine the relative effects of different antithrombotic treatments in comparable, propensity score-matched patients.

Definitions of anticoagulation intensity

For our analysis, each patient was assigned to one anticoagulant group using the following criteria. First, the maximum dose of enoxaparin or heparin received during each patient’s admission was determined. Next, patients who received a maximum enoxaparin dose of 30-40 mg at a weight-adjusted concentration of < 0.7 mg/kg every 24 hours, enoxaparin 30-40 mg at a weight-adjusted concentration of < 0.4 mg/kg every 12 hours, subcutaneous unfractionated heparin (UFH) 5000 units at any frequency, or subcutaneous UFH 5000 or 7500 units at any frequency with a BMI ≥ 40 kg/m2, and who did not receive any other type of documented anticoagulant during their hospitalization, were categorized as prophylactic-dose anticoagulation (PPX). Patients who received a maximum enoxaparin dose of ≥ 0.4 and < 0.7 mg/kg every 12 hours or subcutaneous UFH 7500 U at any frequency with a BMI < 40 kg/m2, and who did not receive any other type of anticoagulant during their hospitalization, were categorized as intermediate-dose anticoagulation (INT). Patients who received a maximum enoxaparin dose ≥ 0.7 mg/kg every 12 hours, enoxaparin ≥ 0.7 mg/kg every 24 hours with creatinine clearance < 30 mL/min, enoxaparin ≥ 1.4 mg/kg every 24 hours, intravenous UFH, or intravenous bivalirudin were categorized as therapeutic-dose anticoagulation (TX). Patients who received any other dose of enoxaparin and who did not receive a direct oral anticoagulant (DOAC) or any other therapeutic-dose anticoagulant were categorized as “Alternative enoxaparin dose”. Patients who received a DOAC and no other type of therapeutic-dose anticoagulation were categorized as “DOAC”. All other patients were categorized as “No documented anticoagulation”. Manual chart review was performed in cases with ambiguous data regarding anticoagulation dosing.

Statistical analyses

Univariable and multivariable logistic regression models were used in all cohorts to estimate associations of in-hospital death with admission RI quartiles, INT versus PPX, in-hospital aspirin use versus no antiplatelet therapy, and other variables, reported as odds ratios (OR). Multivariable regression models included demographic factors (age > 60 years, male sex, BMI ≥ 30 kg/m2, African-American race), medical history (cardiovascular disease, home antiplatelet therapies), and clinical and laboratory features reflecting disease severity (admission RI quartiles, maximum D-dimer level during hospitalization (DDmax)). Cumulative incidence curves were estimated for nonparametric visualization of in-hospital death and discharge events and tested using Gray’s test.23 Univariable and multivariable regression modeling of subdistribution hazard functions in competing risks regression of in-hospital death and discharge was performed for INT versus PPX, and for in-hospital aspirin versus no antiplatelet therapy, reported as hazard ratios (HR).24

Propensity score matching was performed to achieve balance in covariates between the different treatment groups. Propensity scores were calculated using multivariable logistic regression models with covariates that were unbalanced between treatment groups before matching. The best-matched cohort was identified as the one that demonstrated the most balanced distribution of covariates between the two treatment groups in 1:1 nearest-neighbor matching, either with a caliper width of 0.25 (anticoagulation cohort) or without a caliper (aspirin cohort). The best-matched anticoagulation cohort was propensity score-matched on age, DDmax, RI, BMI, and race, while the best-matched aspirin cohort was propensity score-matched on age, DDmax, RI, and sex; the best-matched aspirin cohort admitted after May 18, 2020, was propensity score-matched on age, DDmax, and RI. Associations between treatment groups and different endpoints were assessed using the same univariable and multivariable regression models. All statistical analyses were performed using R (version 3.6.3).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data and the final responsibility to submit for publication.

**RESULTS**

Predictors of mortality and critical illness in the overall study cohort

Patient characteristics in the overall study cohort (N = 2785) are shown in Supplemental Table 3. About half of patients were male (50.1%; N = 1396). The majority were over 60 years old (58.4%; N = 1627). Among all patients, 13.8% (N = 383) died in the hospital, 83.7% (N = 2330) were discharged alive, and 2.6% (N = 72) remained in the hospital at the time of data abstraction. In multivariable analyses, we observed a novel association of low admission RI quartile with increased in-hospital death and cumulative incidence of in-hospital death in a time-to-event competing risks model (Table 1). Age > 60, male sex, obesity, and DDmax were also significantly associated with in-hospital death, in keeping with prior studies.25,26

Intermediate- versus prophylactic-dose anticoagulation

To study the potential impact of intermediate- versus prophylactic-dose anticoagulation, we created the “anticoagulation cohort”, a nested cohort of patients from the overall study cohort who were anticoagulated with either a maximum of prophylactic-dose enoxaparin or unfractionated heparin (PPX) or a maximum of intermediate-dose enoxaparin or unfractionated heparin (INT) (N = 1624). We performed propensity score matching for age, BMI, DDmax, admission RI score, and African-American race. The final propensity score-matched group of 382 patients from the anticoagulation cohort was well-balanced between PPX versus INT with respect to all matched and unmatched variables except for DDmax, which was higher among INT compared to PPX patients, as expected (Supplemental Table 4).

On univariable and multivariable analyses of propensity score-matched patients in the anticoagulation cohort, treatment with INT compared to PPX was associated with a significant improvement in odds of in-hospital death (OR 0.460 [95% confidence interval 0.241-0.857]; Table 2A) and a lower cumulative incidence of in-hospital death in a time-to-event competing risks model (HR 0.518 [0.308-0.872]; Table 2B and Figure 1). Male sex, obesity, advanced age, higher DDmax, lower RI quartile, and home antiplatelet agent use were all independent adverse risk factors for in-hospital death and cumulative incidence of in-hospital death in a time-to-event competing risks model.

In-hospital aspirin versus no antiplatelet therapy

Next, we explored the effects of in-hospital aspirin use. For this analysis, we established the “aspirin cohort”, a nested cohort of patients from the overall study cohort who were not on home antiplatelet therapy prior to admission and received either aspirin or no antiplatelet therapy during their hospitalization (N = 1956). Within the aspirin cohort, we performed propensity score matching for age, DDmax, male sex, and admission RI. The final propensity score-matched group of 638 patients from the aspirin cohort was well-balanced between aspirin- and non-aspirin-treated patients with respect to most variables, although fewer patients in the aspirin group received standard prophylactic-dose anticoagulation (Supplemental Table 5).

On multivariable analyses of propensity score-matched patients in the aspirin cohort, the use of in-hospital aspirin was associated with lower odds of in-hospital death (OR 0.521 [0.305-0.880]; Table 3A) and lower cumulative incidence of in-hospital death in a time-to-event competing risks model (HR 0.522 [0.336-0.812]; Table 3B). Once again, higher DDmax, low RI quartile, and advanced age were independent adverse risk factors for in-hospital death. Cardiovascular disease did not have a significant impact in our multivariable analyses on any outcome measured.

The initial version of our hospital system’s COVID-19 treatment algorithm did not include aspirin, while on May 18, 2020, the treatment algorithm added a recommendation that aspirin be administered to all hospitalized COVID-19 patients (Supplemental Table 2). Based on this, we separately analyzed outcomes of patients in the aspirin cohort who were admitted after May 18, applying propensity score matching for age, DDmax, and admission RI score. The final group of 140 propensity score-matched patients was well-balanced between aspirin- and non-aspirin-treated patients with respect to all variables except BMI (Supplemental Table 6). Once again, the use of in-hospital aspirin was associated with significant improvement in odds of in-hospital death (Supplemental Table 7A), and a lower cumulative incidence of in-hospital death in a competing risks model (Supplemental Table 7B; Figure 2).

**DISCUSSION**

Concern regarding the heightened risks of venous, arterial, and microvascular thrombotic complications in COVID-19 has prompted widespread implementation of aggressive pharmacologic thromboprophylaxis strategies at many institutions around the world. While some retrospective studies have reported a possible mortality benefit with therapeutic- compared to prophylactic-dose anticoagulation at the expense of a likely increase in bleeding risk, only two small studies have examined the effects of intermediate- compared to prophylactic-dose anticoagulation, specifically focusing on VTE rates, with conflicting results.7,11,12,14-17 A potential role for antiplatelet therapy has also been proposed, with a few studies suggesting a possible benefit.18,19

In our large, observational study of hospitalized patients with COVID-19, we report, for the first time, a significantly lower risk of in-hospital death among patients receiving intermediate- versus prophylactic-dose anticoagulation. At present, expert opinion and consensus recommendations about anticoagulation dosing from the major professional societies vary widely, highlighting the uncertainty that exists regarding the use of escalated-intensity anticoagulation in COVID-19.27-29 Our analysis suggests that there may be a beneficial role for intermediate-dose anticoagulation in the treatment of hospitalized patients with COVID-19.

We also observe a lower risk of in-hospital death in patients receiving in-hospital aspirin versus no antiplatelet therapy. This finding is in keeping with another recently-reported retrospective study, although the methodologic approaches between the two studies differ, in part based on our use of propensity score matching to account for differences in illness severity among patients, and the restriction of our analysis to patients not on home aspirin in order to minimize confounding effects from underlying cardiovascular disease.18 On an individual patient level, a potential mortality benefit with either antiplatelet therapy or escalated-intensity anticoagulation must be weighed against the risk of bleeding, taking into account additional factors such as critical illness, renal impairment, thrombocytopenia, and other patient comorbidities. Data from ongoing clinical trials will further guide clinical decision-making with respect to these strategies.

Additionally, our analysis reveals a novel role for the admission RI as a prognostic tool for evaluating in-hospital mortality in COVID-19. The existing spectrum of prognostic markers in COVID-19 includes a number of different patient-specific factors and laboratory tests.1,25,26,30 The RI is unique in that it synthesizes multiple clinical, laboratory, and nursing assessment variables into a single score and is universally accessible, enabling its use in real-time clinical decision-making.22

Our study has several limitations, beyond its retrospective nature. Overall provider adherence to the COVID-19 treatment algorithm varied and was subject to provider preference, although many of the confounding factors that would have resulted from such bias were accounted for through our use of propensity score matching and multivariable regression. Heterogeneity in the number of doses of intermediate-dose anticoagulation or aspirin that each patient received during their hospitalization likely biased our analysis against the detection of some significant associations by including patients in the intervention group who received limited exposure to the intervention. Also, we did not account for differences in other COVID-19 therapies that patients may have received, nor did we assess thrombosis or bleeding rates in this study.

In summary, in our large, observational study of hospitalized patients with COVID-19, using propensity score matching, multivariable regression, and competing risks analyses, we observed a mortality benefit with intermediate- compared to prophylactic-dose anticoagulation, and with aspirin compared to no antiplatelet therapy. Our findings suggest that increased-intensity anticoagulation and antiplatelet therapy may be beneficial in the treatment of COVID-19. We await the results of several randomized clinical trials to more definitively elucidate the impact of these therapies in COVID-19.

**Contributors**

M.L.M., G.G., Yiwen Liu, R.F., D.S.N., K.A.O., and A.I.L. designed the study. M.L.M., R.F., K.A., E.C., N.D., C.K., and Yuxin Liu performed chart abstractions. M.M., D.M., S.W., C.P., R.D.B., C.I.O.C., H.J.C., and A.B.P. contributed valuable ideas. M.L.M., G.G., Yiwen Liu, R.F., D.S.N., K.A.O., and A.I.L. wrote the manuscript, and all authors participated in editing the manuscript. M.L.M., G.G., Yiwen Liu, and R.F. contributed equally as first authors. D.S.N., K.A.O., and A.I.L. contributed equally as senior investigators.

**Declaration of interests**

No author in this study had any competing interests to declare.

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**(A)**

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| --- | --- |
|  | **In-hospital death** |
|  | **OR** | **CI** | **P value** |
| **Age > 60 years** | **4.379** | **3.118-6.261** | **< 0.001** |
| **Male sex** | **1.433** | **1.122-1.834** | **0.004** |
| **Obesity** | **1.489** | **1.154-1.921** | **0.002** |
| **Cardiovascular disease** | 1.039 | 0.79-1.373 | 0.785 |
| **African-American**  | 0.811 | 0.608-1.074 | 0.147 |
| **DDmax** | **1.060** | **1.047-1.074** | **< 0.001** |
| **RI on admission** | **Quartile 1** | **8.201** | **5.896-11.601** | **<0.001** |
| **Quartile 2** | **2.841** | **1.967-4.147** | **<0.001** |
| **RI on admission** | **Quartile 1** | **6.807** | **4.919-9.507** | **< 0.001** |
| **Quartile 2** | **2.416** | **1.692-3.455** | **< 0.001** |

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| --- | --- |
|  | **In-hospital death or discharge****(competing risks model)** |
|  | **HR for death** | **CI** | **P value** |
| **Age > 60 years** | **3.545** | **2.599-4.836** | **< 0.001** |
| **Male sex** | **1.315** | **1.070-1.618** | **0.009** |
| **Obesity** | **1.356** | **1.101-1.670** | **0.004** |
| **Cardiovascular disease** | 1.014 | 0.799-1.286 | 0.91 |
| **African-American**  | 0.850 | 0.670-1.077 | 0.18 |
| **DDmax** | **1.040** | **1.030-1.051** | **< 0.001** |
| **RI on admission** | **Quartile 1** | **6.713** | **4.860-9.274** | **< 0.001** |
| **Quartile 2** | **2.764** | **1.958-3.903** | **< 0.001** |

**(B)**

**Table 1. Multivariable analyses of outcomes in the overall study cohort. (A) Logistic regression evaluating in-hospital death. (B) Hazard ratios for in-hospital death in a competing risks model evaluating cumulative incidence of in-hospital death and discharge.** For maximum D-dimer level, odds ratios describe increase per mg/L fibrinogen equivalent units. Abbreviations: CI, 95% confidence interval; DDmax, maximum D-dimer level during hospitalization; HR, hazard ratio; OR, odds ratio; RI, Rothman Index.

 **(A)**

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| --- | --- |
|  | **In-hospital death** |
|  | **OR** | **CI** | **P value** |
| **INT (compared to PPX)** | **0.460** | **0.241-0.857** | **0.016** |
| **In-hospital aspirin** | **0.302** | **0.121-0.708** | **0.0075** |
| **Home antiplatelet agent use prior to hospitalization** | **2.573** | **1.098-6.297** | **0.033** |
| **Age > 60 years** | **4.007** | **1.852-9.387** | **< 0.001** |
| **Male sex** | **2.599** | **1.350-5.142** | **0.005** |
| **Obesity** | **2.346** | **1.233-4.564** | **0.010** |
| **Cardiovascular disease** | 1.893 | 0.934-3.974 | 0.083 |
| **African-American**  | 0.552 | 0.277-1.067 | 0.083 |
| **DDmax** | **1.070** | **1.033-1.110** | **< 0.001** |
| **RI on admission** | **Quartile 1** | **14.723** | **5.384-52.410** | **< 0.001** |
| **Quartile 2** | **7.223** | **2.429-26.869** | **< 0.001** |
|  |

**(B)**

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| --- | --- |
|  | **In-hospital death or discharge****(competing risks model)** |
|  | **HR for death** | **CI** | **P value** |
| **INT (compared to PPX)** | **0.518** | **0.308-0.872** | **0.013** |
| **In-hospital aspirin** | **0.311** | **0.153-0.634** | **0.001** |
| **Home antiplatelet agent use prior to hospitalization** | **2.663** | **1.335-5.313** | **0.006** |
| **Age > 60 years** | **3.269** | **1.694-6.310** | **< 0.001** |
| **Male sex** | **2.255** | **1.283-3.963** | **0.005** |
| **Obesity** | **2.096** | **1.217-3.608** | **0.008** |
| **Cardiovascular disease** | 1.588 | 0.886-2.846 | 0.12 |
| **African-American**  | 0.674 | 0.392-1.160 | 0.15 |
| **DDmax** | **1.050** | **1.021-1.080** | **< 0.001** |
| **RI on admission** | **Quartile 1** | **10.842** | **4.148-28.341** | **< 0.001** |
| **Quartile 2** | **6.518** | **2.394-17.751** | **< 0.001** |

**Table 2. Multivariable analyses of outcomes in the propensity-score matched anticoagulation cohort. (A) Logistic regression evaluating in-hospital death. (B) Hazard ratios for in-hospital death in a competing risks model evaluating cumulative incidence of in-hospital death and discharge.** Patients were propensity score matched for age, maximum D-dimer level, admission Rothman Index score, body mass index, and African-American race using a random number seed and a caliper width of 0.25. For maximum D-dimer level, odds ratios describe increase per mg/L fibrinogen equivalent units. Abbreviations: CI, 95% confidence interval; DDmax, maximum D-dimer level during hospitalization; HR, hazard ratio; OR, odds ratio; RI, Rothman Index.

**(A)**

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| --- | --- |
|  | **In-hospital death** |
|  | **OR** | **CI** | **P value** |
| **In-hospital aspirin** | **0.521** | **0.305-0.880** | **0.016** |
| **Anticoagulation: INT, TX, DOAC, or other** | **2.209** | **1.121-4.556** | **0.026** |
| **ICU** | **4.014** | **2.189-7.555** | **< 0.001** |
| **Age > 60 years** | **5.080** | **2.667-10.177** | **< 0.001** |
| **Male sex** | 1.323 | 0.774-2.305 | 0.309 |
| **Obesity** | 1.366 | 0.793-2.350 | 0.259 |
| **Cardiovascular disease** | 1.242 | 0.710-2.192 | 0.450 |
| **African-American**  | 0.521 | 0.262-0.994 | 0.054 |
| **DDmax** | **1.034** | **1.007-1.063** | **0.014** |
| **RI on admission** | **Quartile 1** | **3.885** | **1.998-7.869** | **< 0.001** |
| **Quartile 2** | **2.19** | **1.067-4.610** | **0.035** |

**(B)**

|  |  |
| --- | --- |
|  | **In-hospital death or discharge****(competing risks model)** |
|  | **HR for death** | **CI** | **P value** |
| **In-hospital aspirin** | **0.522** | **0.336-0.812** | **0.004** |
| **Anticoagulation: INT, TX, DOAC, or other** | **2.034** | **1.016-4.074** | **0.045** |
| **ICU** | **3.207** | **1.691-6.080** | **< 0.001** |
| **Age > 60 years** | **3.894** | **2.196-6.904** | **< 0.001** |
| **Male sex** | 1.227 | 0.777-1.938 | 0.38 |
| **Obesity** | 1.342 | 0.873-2.063 | 0.18 |
| **Cardiovascular disease** | 1.285 | 0.803-2.056 | 0.3 |
| **African-American**  | **0.525** | **0.298-0.926** | **0.026** |
| **DDmax** | 1.022 | 0.998-1.047 | 0.069 |
| **RI on admission** | **Quartile 1** | **3.333** | **1.774-6.264** | **< 0.001** |
| **Quartile 2** | **2.022** | **1.048-3.901** | **0.036** |

**Table 3. Multivariable analyses of outcomes in the propensity-score matched aspirin cohort. (A) Logistic regression evaluating in-hospital death. (B) Hazard ratios for in-hospital death in a competing risks model evaluating cumulative incidence of in-hospital death and discharge.** Patients were propensity score matched for age, maximum D-dimer level, admission Rothman Index score, and male sex. For anticoagulation dose group, “INT, TX, DOAC, or other” refers to the combination of intermediate-dose enoxaparin or heparin, therapeutic-dose anticoagulation, direct oral anticoagulants, alternative enoxaparin dose, and no documented anticoagulation, as defined in the Materials and Methods. For maximum D-dimer level, odds ratios describe increase per mg/L fibrinogen equivalent units. The analysis of in-hospital death included intensive care unit stay as one of the variables analyzed, while the analyses of mechanical ventilation and intensive care unit admission as outcomes did not. Abbreviations: BMI, body mass index; DDmax, maximum D-dimer level during hospitalization; DOAC, direct oral anticoagulant; FEU, fibrinogen equivalent units; INT, intermediate-dose enoxaparin or heparin; PPX, prophylactic-dose enoxaparin or heparin; RI, Rothman Index; TX, therapeutic-dose enoxaparin, intravenous heparin, or bivalirudin.

PPX

INT

Discharge

P = 0.272

PPX

INT

In-hospital death

P = 0.037

Probability

Days

**Figure 1. In-hospital death and discharge as competing risks in the anticoagulation cohort, comparing propensity score-matched patients who received a maximum of intermediate (INT)- vs. prophylactic (PPX)-dose anticoagulation.** Patients were propensity score matched for age, maximum D-dimer level, admission Rothman Index score, body mass index, and African-American race using a random number seed and a caliper width of 0.25. P values from Gray’s test describe differences in cumulative incidence function between intermediate- and prophylactic-dose anticoagulation groups. Abbreviations: INT, intermediate-dose enoxaparin or heparin; PPX, prophylactic-dose enoxaparin or heparin.

Aspirin

No aspirin

Discharge

P = 0.265

In-hospital death

P = 0.001

Aspirin

No aspirin

Probability

Days

**Figure 2. In-hospital death and discharge as competing risks among propensity score-matched patients in the aspirin cohort admitted after May 18, 2020.** Patients were propensity score matched for age, maximum D-dimer level, and admission Rothman Index score. P values from Gray’s test describe differences in cumulative incidence function between patients who received in-hospital aspirin and those who did not.

|  |  |
| --- | --- |
| **Population** | **Exclusions related to disease diagnosis** |
| Congestive heart failure | * Hypertensive heart failure
* Cor pulmonale
* Neonatal cardiovascular disorder
* Cardiac complication of procedure
* Cardiorenal syndrome
* Right heart failure due to pulmonary hypertension
* Hypertensive heart disease
* Complication of pregnancy, childbirth and/or the puerperium
 |
| Coronary artery disease | * None
 |
| Diabetes Mellitus | * Diabetes mellitus during pregnancy, childbirth, and the puerperium
* Fetal hypertrophic cardiomyopathy
* Gestational diabetes mellitus, controlled
* Steroid-induced diabetes
 |
| Hypertension | * Pregnancy, childbirth and puerperium finding
* Complication of pregnancy
* Pre-existing hypertension in obstetric context
* Chronic hypertension in obstetric context
* Essential hypertension in obstetric context
* Labile hypertension due to being in a clinical environment
* Transient hypertension
* Neonatal hypertension
* Postoperative hypertension
 |

**Supplemental Table 1. Registry exclusions.**

|  |  |  |  |
| --- | --- | --- | --- |
| **D-dimer range** | **Anticoagulation intensity** | **BMI < 40 kg/m2** | **BMI ≥ 40 kg/m2** |
| **< 5 mg/L FEU** | **Prophylactic** | **CrCl, mL/min** | **CrCl, mL/min** |
| **< 30** | **≥ 30** | **< 30** | **≥ 30** |
| Enoxaparin 30 mg SC QDUFH 5000 U SC BID-TID | Enoxaparin 40 mg SC QD | Enoxaparin 40 mg SC QDUFH 7500 U SC BID-TID | Enoxaparin 40 mg SC BID |
| **Prior to April 13, 2020:****≥ 10 mg/L FEU****April 13, 2020, and after:****≥ 5 mg/L FEU** | **Intermediate** | Enoxaparin 0.5 mg/kg SQ BIDUFH 7500 U SC BID-TID | Enoxaparin 0.5 mg/kg SC BID | Enoxaparin 0.5 mg/kg SC BID | Enoxaparin 0.5 mg/kg SC BID |
| **Suspected or radiologically confirmed VTE** | **Therapeutic** | Enoxaparin 1 mg/kg SC QDDOACUFH GTT | Enoxaparin 1 mg/kg SC BIDDOAC | Enoxaparin 1 mg/kg SC QDDOACUFH GTT | Enoxaparin 1 mg/kg SC BIDDOAC |
| **May 18, 2020, and after:****Aspirin 81 mg** **(all patients)** |

**Supplemental Table 2. Hospital algorithm for anticoagulation and antiplatelet therapy.** Prior to April 3, 2020, all patients were recommended for prophylactic-dose anticoagulation, except for those with suspected or radiologically confirmed venous thromboembolism, who were recommended for therapeutic-dose anticoagulation. From April 3-12, 2020, patients with D-dimer ≥ 10 mg/L FEU were recommended for intermediate-dose anticoagulation. On April 13, 2020, the D-dimer threshold for intermediate-dose anticoagulation was changed to 5 mg/L FEU. Starting on May 18, 2020, aspirin 81 mg was recommended for all patients. Abbreviations: BID, twice daily; BMI, body mass index; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; FEU, fibrinogen equivalent units; GTT, drip; QD, daily; SC, subcutaneous; TID, three times a day; UFH, unfractionated heparin.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total** | **Alive** | **Dead** | **P value****(Alive vs. dead)** |
| **Number of patients** | 2785 | 2402 (86.2%) | 383 (13.8%) |  |
| **Age in years (%)** | **18 to 40** | **359** | **356 (99.2%)** | **3 (0.8%)** | **< 0.001** |
| **> 40 to 50** | **298** | **285 (95.6%)** | **13 (4.4%)** |
| **> 50 to 60** | **501** | **467 (93.2%)** | **34 (6.8%)** |
| **> 60 to 70** | **553** | **499 (90.2%)** | **54 (9.8%)** |
| **> 70 to 80** | **492** | **389 (79.1%)** | **103 (20.9%)** |
| **> 80 to 90** | **421** | **301 (71.5%)** | **120 (28.5%)** |
| **> 90 to 110** | **161** | **105 (65.2%)** | **56 (34.8%)** |
| **RI on admission (%)** | **Quartile 1** | **732** | **494 (67.5%)** | **238 (32.5%)** | **< 0.001** |
| **Quartile 2** | **696** | **601 (86.4%)** | **95 (13.6%)** |
| **Quartile 3** | **676** | **635 (93.9%)** | **41 (6.1%)** |
| **Quartile 4** | **681** | **672 (98.7%)** | **9 (1.3%)** |
| **Sex (%)** | **Male** | 1396 | 1190 (85.2%) | 206 (14.8%) | 0.12 |
| **Female** | 1389 | 1212 (87.3%) | 177 (12.7%) |
| **BMI (%)** | **Underweight or normal** | **775** | **645 (83.2%)** | **130 (16.8%)** | **0.008** |
| **Overweight**  | **858** | **759 (88.5%)** | **99 (11.5%)** |
| **Obese**  | **1152** | **998 (86.6%)** | **154 (13.4%)** |
| **Race (%)** | **Caucasian** | **1300** | **1074 (82.6%)** | **226 (17.4%)** | **< 0.001** |
| **African-American** | **746** | **650 (87.1%)** | **96 (12.9%)** |
| **Asian-American** | **62** | **51 (82.3%)** | **11 (17.7%)** |
| **Other or not listed** | **677** | **627 (92.6%)** | **50 (7.4%)** |
| **Cardiovascular disease (%)** | **1683** | **1406 (83.5%)** | **277 (16.5%)** | **< 0.001** |
| **Home antiplatelet agent prior to hospitalization (%)** | **804** | **650 (80.8%)** | **154 (19.2%)** | **< 0.001** |
| **In-hospital aspirin use (%)** | **964** | **811 (84.1%)** | **153 (15.9%)** | **0.021** |
| **Anticoagulation during hospitalization (%)** | **PPX** | **1395** | **1291 (92.5%)** | **104 (7.5%)** | **< 0.001** |
| **INT** | **229** | **189 (82.5%)** | **40 (17.5%)** |
| **TX** | **531** | **386 (72.7%)** | **145 (27.3%)** |
| **Alternative enoxaparin dose** | **162** | **141 (87.0%)** | **21 (13.0%)** |
| **DOAC** | **233** | **206 (88.4%)** | **27 (11.6%)** |
| **No documented anticoagulation** | **235** | **189 (80.4%)** | **46 (19.6%)** |
| **DDmax, mg/L FEU (range)** | **-** | **2 (0-35)** | **5 (0-35)** | **< 0.001** |
| **Hospital LOS, days (range)** | - | 8 (1-111) | 10 (1-65) | 0.051 |
| **ICU (%)** | **945** | **680 (72.0%)** | **265 (28.0%)** | **< 0.001** |
| **Mechanical ventilation (%)** | **385** | **232 (60.3%)** | **153 (39.7%)** | **< 0.001** |

**Supplemental Table 3. Patient characteristics in overall study cohort.** Patient categorization for “Anticoagulation during hospitalization” is based upon the maximum intensity of anticoagulation that the patient received during the hospitalization, such that each patient falls into one category (as described in detail in the Materials and Methods). “Alternative enoxaparin dose” refers to a maximum dose of enoxaparin that was not able to be categorized as prophylactic, intermediate, or therapeutic. “No documented anticoagulation” refers to patients who did not receive enoxaparin, heparin, bivalirudin, or a direct oral anticoagulant during hospitalization. Abbreviations: BMI, body mass index; DDmax, maximum D-dimer level during hospitalization; DOAC, direct oral anticoagulant; FEU, fibrinogen equivalent units; ICU, intensive care unit; INT, intermediate-dose enoxaparin or subcutaneous heparin; LOS, length of stay, expressed as median; PPX, prophylactic-dose enoxaparin or subcutaneous heparin; TX, therapeutic-dose enoxaparin, intravenous heparin, or bivalirudin. RI, Rothman Index.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total** | **PPX** | **INT** | **P value** |
| **Number of patients** | 382 | 191 | 191 | - |
| **Age** | **≤ 60 years** | 148 | 73 | 75 | 0.83 |
| **> 60 years** | 234 | 118 | 116 |
| **RI on admission** | **Quartile 1** | 145 | 78 | 67 | 0.40 |
| **Quartile 2** | 91 | 46 | 45 |
| **Quartiles 3 and 4** | 146 | 67 | 79 |
| **Sex** | **Male** | 195 | 96 | 99 | 0.76 |
| **Female** | 187 | 95 | 92 |
| **BMI** | **Obese** | 181 | 82 | 99 | 0.082 |
| **Other**  | 201 | 109 | 92 |
| **Race** | **African-American** | 145 | 74 | 71 | 0.75 |
| **Other** | 237 | 117 | 120 |
| **Cardiovascular disease** | 237 | 113 | 124 | 0.25 |
| **Home antiplatelet agent prior to hospitalization** | 127 | 63 | 64 | 0.91 |
| **In-hospital aspirin** | 149 | 69 | 80 | 0.29 |
| **DDmax, mg/L FEU (range)** | - | **4 (0-34)** | **6 (0-35)** | **0.003** |

**Supplemental Table 4. Patient characteristics in the propensity score-matched anticoagulation cohort.** Patients were propensity score matched for age, maximum D-dimer level, admission Rothman Index score, body mass index, and African-American race using a random number seed and a caliper width of 0.25. P values describe differences between prophylactic- and intermediate-dose anticoagulation groups. Abbreviations: BMI, body mass index; DDmax, maximum D-dimer level during hospitalization, expressed as median; FEU, fibrinogen equivalent units; INT, maximum anticoagulation level of intermediate-dose enoxaparin or heparin; PPX, maximum anticoagulation level of prophylactic-dose enoxaparin or heparin; RI, Rothman Index.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total** | **No in-hospital aspirin** | **In-hospital aspirin** | **P value** |
| **Number of patients** | 638 | 319 | 319 | - |
| **Age** | **≤ 60 years** | 346 | 146 | 146 | > 0.99 |
| **> 60 years** | 292 | 173  | 173  |
| **RI on admission** | **Quartile 1** | 161 | 72 | 89 | 0.18 |
| **Quartile 2** | 158 | 87 | 71 |
| **Quartiles 3 and 4** | 319 | 160 | 159 |
| **Sex** | **Male** | 404 | 202 | 202 | > 0.99 |
| **Female** | 234 | 117 | 117 |
| **BMI** | **Obese** | 269 | 138 | 131 | 0.57 |
| **Other**  | 369 | 181 | 188 |
| **Race** | **African-American** | 149 | 69 | 80 | 0.30 |
| **Other** | 489 | 250 | 239 |
| **Cardiovascular disease** | 351 | 174 | 177 | 0.81 |
| **Anticoagulation dose group** | **PPX** | **288** | **163** | **125** | **0.003** |
| **INT, TX, DOAC, or other**  | **350** | **156** | **194** |
| **DDmax, mg/L FEU (range)** | - | 2 (0-35) | 3 (0-34) | 0.18 |

**Supplemental Table 5. Patient characteristics in the propensity score-matched aspirin cohort.** Patients were propensity score matched for age, maximum D-dimer level, admission Rothman Index score, and male sex. P values describe differences between in-hospital aspirin and no in-hospital aspirin groups. For anticoagulation dose group, “INT, TX, DOAC, or other” refers to the combination of intermediate-dose enoxaparin or heparin, therapeutic-dose anticoagulation, direct oral anticoagulants, alternative enoxaparin dose, and no documented anticoagulation, as defined in the Materials and Methods. Abbreviations: BMI, body mass index; DDmax, maximum D-dimer value during first 30 days of hospitalization, expressed as median; DOAC, direct oral anticoagulant; FEU, fibrinogen equivalent units; INT, intermediate-dose enoxaparin or heparin; PPX, prophylactic-dose enoxaparin or heparin; RI, Rothman Index; TX, therapeutic-dose enoxaparin, intravenous heparin, or bivalirudin.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total** | **No in-hospital aspirin** | **In-hospital aspirin** | **P value** |
| **Number of patients** | 140 | 70 | 70 | - |
| **Age** | **≤ 60 years** | 78 | 35 | 43 | 0.17 |
| **> 60 years** | 62 | 35 | 27 |
| **RI on admission** | **Quartile 1** | 41 | 21 | 20 | 0.75 |
| **Quartile 2** | 27 | 15 | 12 |
| **Quartiles 3 and 4** | 72 | 34 | 38 |
| **Sex** | **Male** | 72 | 31 | 41 | 0.091 |
| **Female** | 68 | 39 | 29 |
| **BMI** | **Obese** | **66** | **27** | **39** | **0.042** |
| **Other**  | **74** | **43** | **31** |
| **Race** | **African-American** | 43 | 18 | 25 | 0.20 |
| **Other** | 97 | 52 | 45 |
| **Cardiovascular disease** | 74 | 34 | 40 | 0.31 |
| **Anticoagulation dose group** | **PPX** | 62 | 31 | 31 | > 0.99 |
| **INT, TX, DOAC, or other**  | 78 | 39 | 39 |
| **DDmax, mg/L FEU (range)** | - | 2 (0-34) | 3 (0-32) | 0.083 |

**Supplemental Table 6. Patient characteristics in the aspirin cohort admitted after May 18, 2020, with propensity score matching.** Patients in the aspirin cohort who were admitted after May 18, 2020 were propensity score matched for age, maximum D-dimer level, and admission Rothman Index score. P values describe differences between in-hospital aspirin and no in-hospital aspirin groups. For anticoagulation dose group, “INT, TX, DOAC, or other” refers to the combination of intermediate-dose enoxaparin or heparin, therapeutic-dose anticoagulation, direct oral anticoagulants, alternative enoxaparin dose, and no documented anticoagulation, as defined in the Materials and Methods. Abbreviations: BMI, body mass index; DDmax, maximum D-dimer level during hospitalization; DOAC, direct oral anticoagulant; FEU, fibrinogen equivalent units; INT, intermediate-dose enoxaparin or heparin; PPX, prophylactic-dose enoxaparin or heparin; RI, Rothman Index; TX, therapeutic-dose enoxaparin, intravenous heparin, or bivalirudin.

**(A)**

|  |  |
| --- | --- |
|  | **In-hospital death** |
|  | **OR** | **CI** | **P value** |
| **In-hospital aspirin** | **0.033** | **0.001-0.258** | **0.007** |
| **Anticoagulation: INT, TX, DOAC, or other** | **14.125** | **1.768-235.671** | **0.031** |
| **Age > 60 years** | 1.011 | 0.165-6.614 | 0.991 |
| **Male sex** | 4.224 | 0.678-39.287 | 0.15 |
| **Obesity** | 0.542 | 0.095-2.585 | 0.455 |
| **Cardiovascular disease** | 1.711 | 0.396-8.288 | 0.48 |
| **African-American**  | 1.210 | 0.179-7.018 | 0.834 |
| **DDmax** | 0.973 | 0.855-1.069 | 0.606 |
| **RI on admission** | **Quartile 1** | **12.393** | **1.706-140.703** | **0.021** |
| **Quartile 2** | 1.213 | 0.100-14.467 | 0.874 |

**(B)**

|  |  |
| --- | --- |
|  | **Time to in-hospital death or discharge****(competing risks model)** |
|  | **HR for death** | **CI** | **P value** |
| **In-hospital aspirin** | **0.037** | **0.002-0.576** | **0.018** |
| **Anticoagulation: INT, TX, DOAC, or other** | **10.879** | **1.965-60.237** | **0.006** |
| **Age > 60 years** | 1.278 | 0.357-4.576 | 0.71 |
| **Male sex** | 4.132 | 0.762-22.403 | 0.1 |
| **Obesity** | 0.552 | 0.129-2.364 | 0.42 |
| **Cardiovascular disease** | 0.936 | 0.227-3.858 | 0.93 |
| **African-American**  | 1.280 | 0.336-4.870 | 0.72 |
| **DDmax** | 0.989 | 0.916-1.068 | 0.78 |
| **RI on admission** | **Quartile 1** | **9.413** | **1.435-61.736** | **0.019** |
| **Quartile 2** | 1.159 | 0.184-7.301 | 0.88 |

**Supplemental Table 7. Multivariable analyses of outcomes for patients in the aspirin cohort admitted after May 18, 2020, with propensity score matching. (A) Logistic regression evaluating in-hospital death. (B) Hazard ratios for in-hospital death in a competing risks model evaluating cumulative incidence of in-hospital death and discharge.** Patients were propensity score matched for age, maximum D-dimer level, and admission Rothman Index. For maximum D-dimer level, odds ratios describe increase per mg/L fibrinogen equivalent units. For anticoagulation dose group, “INT, TX, DOAC, or other” refers to the combination of intermediate-dose enoxaparin or heparin, therapeutic-dose anticoagulation, direct oral anticoagulants, alternative enoxaparin dose, and no documented anticoagulation, as defined in the Materials and Methods. Abbreviations: BMI, body mass index; DDmax, maximum D-dimer value during first 30 days of hospitalization, expressed as median; DOAC, direct oral anticoagulant; FEU, fibrinogen equivalent units; INT, intermediate-dose enoxaparin or heparin; PPX, prophylactic-dose enoxaparin or heparin; RI, Rothman Index; TX, therapeutic-dose enoxaparin, intravenous heparin, or bivalirudin.