Anticoagulation, Mortality, Bleeding and Pathology Among Patients Hospitalized with COVID-19: A Single Health System Study

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PII: S0735-1097(20)36408-1

DOI: https://doi.org/10.1016/j.jacc.2020.08.041

Reference: JAC 27631

To appear in: *Journal of the American College of Cardiology*

Received Date: 3 August 2020

Revised Date: 20 August 2020

Accepted Date: 20 August 2020

Please cite this article as: Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno P, Pujadas E, Arvind V, Bose S, Charney AW, Chen MD, Cordon-Cardo C, Dunn AS, Farkouh ME, Glicksberg B, Kia A, Kohli-Seth R, Levin MA, Timsina P, Zhao S, Fayad ZA, Fuster V, Anticoagulation, Mortality, Bleeding and Pathology Among Patients Hospitalized with COVID-19: A Single Health System Study, *Journal of the American College of Cardiology* (2020), doi: https://doi.org/10.1016/j.jacc.2020.08.041.

Anticoagulation, Mortality, Bleeding and Pathology Among Patients Hospitalized with COVID-19: A Single Health System Study

Short Title: Anticoagulation and COVID-19

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Conflicts of Interest: Dr. Nadkarni reports grants, personal fees and non-financial support from Renalytix AI, non-financial support from Pensieve Health, personal fees from AstraZeneca,

personal fees from AstraZeneca, personal fees from BioVie, personal fees from GLG Consulting, from outside the submitted work. Dr. Lala reports personal fees from Zoll, outside the submitted work. Dr. Dunn reports grants from Pfizer, personal fees from BMS, outside the submitted work. Dr. Farkouh reports grants from Amgen, Novo Nordisk and Novartis, outside the submitted work. Dr. Fayad reports grants from Daiichi Sankyo, grants from Amgen, grants from Bristol Myers Squibb, from Siemens Healthineers, personal fees from Alexion, personal fees from GlaxoSmithKline, personal fees from Trained Therapeutix Discovery, outside the submitted work. In addition, Dr. Fayad has patents licensed to Trained Therapeutix Discovery. The other authors have nothing to disclose.
Funding: U54 TR001433-05, National Institutes of Health. The funding source had no role in the writing of the manuscript or the decision to submit it for publication. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgements: To all the nurses, physicians, and providers who contributed to the care of these patients. To the patients and their family members who were affected by this pandemic.

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ABSTRACT:
Background: Thromboembolic disease is common in coronavirus disease-19 (COVID-19). There is limited evidence on association of in-hospital anticoagulation (AC) with outcomes and postmortem findings.
Objective: To examine association of AC with in-hospital outcomes and describe thromboembolic findings on autopsies.
Methods: A retrospective analysis examining association of AC with mortality, intubation and major bleeding. We also conducted sub-analyses on association of therapeutic vs prophylactic AC initiated ≤48 hours from admission. We describe thromboembolic disease contextualized by pre-mortem AC among consecutive autopsies.
Results: Among 4,389 patients, median age was 65 years with 44% female. Compared to no AC (n=1530, 34.9%), therapeutic (n=900, 20.5%) and prophylactic AC (n=1959, 44.6%) were associated with lower in-hospital mortality (adjusted hazard ratio [aHR]=0.53; 95%CI: 0.45-0.62, and aHR=0.50; 95%CI: 0.45-0.57, respectively), and intubation (aHR 0.69; 95%CI: 0.51-0.94, and aHR 0.72; 95% CI: 0.58-0.89, respectively). When initiated ≤48 hours from admission, there was no statistically significant difference between therapeutic (n=766) vs. prophylactic AC (n=1860) (aHR 0.86, 95%CI: 0.73-1.02; p=0.08). Overall, 89 patients (2%) had major bleeding adjudicated by clinician review, with 27/900 (3.0%) on therapeutic, 33/1959 (1.7%) on prophylactic, and 29/1,530 (1.9%) on no AC. Of 26 autopsies, 11 (42%) had thromboembolic disease not clinically suspected and 3/11 (27%) were on therapeutic AC.
Conclusions: AC was associated with lower mortality and intubation among hospitalized COVID-19 patients. Compared to prophylactic AC, therapeutic AC was associated with lower mortality, though not statistically significant. Autopsies revealed frequent thromboembolic disease. These data may inform trials to determine optimal AC regimens.

CONDENSED ABSTRACT: An increased incidence of thromboemboli has been reported in COVID-19. We explored the association of in-hospital anticoagulation at prophylactic and therapeutic doses with in-hospital outcomes and described thromboemboli in consecutive autopsies. Compared to no anticoagulation, both prophylactic and therapeutic anticoagulation, was associated with decreased mortality and intubation. In those who began anticoagulation <48 hours of admission, there was no statistically significant difference between therapeutic vs. prophylactic anticoagulation. Bleeding rates were low, but higher with therapeutic anticoagulation. In consecutive autopsies, thromboemboli were common, mostly in patients not on therapeutic anticoagulation. These data may inform clinical trials of anticoagulation regimens in COVID-19.

Keywords: COVID-19, Anticoagulation, Mortality, Intubation

Abbreviations:
COVID-19: Coronavirus Disease-19
EHR: Electronic Health Record
AC: Anticoagulation
ICD-10: International Classification of Diseases-10
PRBC: packed red blood cell
BMI: body mass index
IPTW: Inverse probability treatment weighted

HR: hazard ratios
CI: 95% confidence intervals
LMWH: low molecular weight heparin
NOACs: novel anticoagulants
UFH: unfractionated heparin

INTRODUCTI ON

Coronavirus disease-19 (COVID-19) has led to >22 million affected, (1) and > 784,000 deaths worldwide. Among hospitalized patients, new thromboembolism has emerged as an important disease manifestation.(2-5) Autopsy studies have corroborated these observations by demonstrating a high incidence of macro and microthrombi. (6-8) Accordingly, it has been hypothesized that inflammation associated with SARS-CoV2 infection leads to a "COVID-19 related coagulopathy", (9) resulting in increased thrombosis.(6)

Observational analyses have suggested potential benefit for in-hospital use anticoagulation (AC) in COVID-19 treatment. (10,11) Yet, practice patterns vary significantly due to lack of rigorous evidence for optimal regimens. Specifically, anticoagulant choice, dosing, and treatment duration are not well understood. In a preliminary analysis of 2700 patients admitted to the Mount Sinai Health System (MSHS) in New York, we found an association between in-hospital therapeutic AC and lower mortality compared to patients on no/prophylactic AC. (10) The present analysis expands upon those results in a larger cohort to explore the impact of therapeutic and prophylactic AC, as well as choice of agent, on survival, intubation, and major bleeding compared to no AC. We also review the first consecutive autopsies performed at our institution and describe their pre-mortem management as related to AC.

METHODS

Data Sources

Data were retrieved from the electronic health record (EHR). Variables collected included demographics, laboratory measurements, vital signs, disease diagnoses, comorbidities, procedures, and outcomes (death, intubation, and hospital discharge). The Mount Sinai Institutional Review Board approved this study.

Study Design and Participants

We included all patients >18 years old admitted with laboratory confirmed SARS-CoV-2 infection between March 1st -April 30th, 2020 to five New York City hospitals. Patients who left the hospital within 24 hours of admission as well as those patients treated with both therapeutic and prophylactic regimens of AC during their hospitalization were excluded. If treated for <48 hours total with a therapeutic or prophylactic dose, they were conservatively categorized as "not treated with AC" unless AC was stopped due to major bleeding. **(Supplemental Figure 1).** Details on how patients were categorized into therapeutic/ prophylactic AC are in the **Supplemental Appendix.**

Exposures

The primary exposure of interest was therapeutic or prophylactic AC compared to no AC. We also conducted a sub-analysis of patients initiated therapeutic or prophylactic anticoagulants within 48 hours of admission.

Outcomes

The primary endpoint was in-hospital mortality. Secondary endpoints were intubation and major bleeding. Consistency checks were performed to properly align these data tables and minimize missing data. If the amount of missing data was less than 1% patient was considered as not having the condition (e.g. for comorbidities). Missing values were mostly present for the vitals and the labs for which we used a "missing" category in the propensity score models to account for the missing data. (**Supplemental Appendix**) Major bleeding was defined using International Classification of Diseases-10 (ICD-10) codes (**Supplemental Table 1**) or receiving ≥2 packed red blood cell (PRBC) transfusions within 48 hours. Two physicians (GN/SZ) reviewed bleeding cases (n=153) to adjudicate major bleeding. Disagreements were resolved by

consensus discussion with an independent physician (VF). Criteria for confirmation of major bleeding included; a) Physician documentation of an active source of bleeding; b) Confirmatory imaging or other evidence (neuroimaging for intracranial bleed); c) Bleeding necessitating ≥2 PRBC transfusion within 48 hours or d) Suspected bleeding without confirmation of an active bleeding source. PRBCs transfused for other reasons included a) Chronic anemia (dialysis or other reasons like cancer); b) Maintenance of hemoglobin over 7g/dL and c) Other reasons (perioperative or symptom improvement). We also ascertained the bleeding site.

Autopsy Data

Autopsies were performed at the Mount Sinai Hospital after obtaining appropriate consent and verifying SARS-CoV-2 infection status by nasopharyngeal swab unless already appropriately documented. Examinations were carried out in a negative pressure room with enhanced airborne precautions. Histological processing of tissue blocks was performed in standard fashion after extended formalin-fixation. Slides were reviewed by a team of pathology subspecialists.

Statistical Analysis

General characteristics of the sample were summarized using appropriate descriptive statistics for continuous and categorical variables. Some continuous variables (e.g. body mass index [BMI], age, D-dimer, respiratory rate and oxygen saturation) were categorized using clinically meaningful cut-points to improve interpretability. Patients were divided into three groups according to whether they were treated with a therapeutic or prophylactic regimen, or no anticoagulant. Patients receiving both therapeutic and prophylactic anticoagulants were excluded.

Inverse probability treatment weighted (IPTW) models, were used to correct for the potential bias brought about by AC indication. A multinomial logistic model was fit with therapeutic, prophylactic or no use of AC during the hospitalization as the dependent variable, and age, sex, race and ethnicity, BMI, history of hypertension, atrial fibrillation, heart failure, chronic kidney disease or renal failure, use of anticoagulants or antiplatelet agents prior to hospitalization, month of admission, intubation during hospitalization, time of implementation of institutional guidelines for AC at Mount Sinai, respiratory rate, oxygen saturation and D-dimer at admission as the predictors. These predictors were chosen based on clinical judgment and model fit. We derived stabilized inverse IPTW by multiplying the inverse of the predicted probability of treatment from the propensity score model by the observed probability of treatment. The IPTW approach was used in all analyses. A robust variance was estimated in all models to account for the clustering effect resulting from IPTW. Standardized differences were calculated to determine the level of adjustment induced by the IPTW. To account for residual confounding, all models were adjusted for variables with absolute standardized differences greater than 0.2 (**Supplemental Figure 1**). Regarding missing data, if the amount of missingness was less than 1%, a patient was considered as not having the condition (e.g., for comorbidities). Missing values were mostly in vitals and labs (e.g., D-dimer) for which we used a "missing" category in the propensity score models to account for the missing data.

The primary analysis used IPTW Fine and Gray's sub-distribution hazard models to determine AC association with in-hospital mortality. (12) Survival in days was calculated as time from hospital admission to in-hospital death, discharge, or the date of dataset lock (May 7th, 2020). Patients who were still hospitalized at the time of the data lock were censored. Discharge alive was considered a competing risk. To minimize immortal time bias, therapeutic or

prophylactic AC use were entered in the model as time dependent variables and similarly for intubation status. The multivariable model also accounted for admission respiratory rate and oxygen saturation.

For the time to intubation analysis, the time between hospital admission and intubation was considered in IPTW competing risk models using the method of Fine and Gray. Death and hospital discharge were considered competing events and patients who were in hospital but not intubated at the time of data lock were censored. AC use was entered as time dependent variables with the same covariate adjustment made previously. The hazard ratios (HR) and their respective 95% confidence intervals (CI) are reported for all time-to-event models. Frequency tables were used to describe the association between AC use and bleeding events. A similar approach was used for the subgroup of patients treated with therapeutic or prophylactic anticoagulants within 48 hours of admission.

Landmark analyses were considered at 3 different timepoints: days 2, 3 and 4 after hospital admission (**Supplemental Appendix)**. All analyses were conducted using SAS 9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Patient and Hospital Presentation Characteristics

A total of 4,389 patients met inclusion criteria for analysis **(Supplemental Figure 2**). The median age was 65 (IQR, 53 to 77 years), 44% were female, 26% self-identified as African American and 27% as Hispanic/Latino. **Table 1** shows baseline characteristics and laboratory values stratified by therapeutic AC (n=900), prophylactic AC (n=1,959), and no AC (n=1,530). Pre-hospital medications of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers, prior AC and antiplatelet therapy by group are also shown in **Table 1**.

Approximately one-tenth of the total cohort were on AC or antiplatelet medications prior to admission (1.8% and 8.5% respectively). On hospital presentation, patients in the therapeutic AC group had higher blood pressures, faster heart and respiratory rates, and lower oxygen saturation **(Table 1)**. D-dimer concentrations were highest in the patients who received therapeutic AC (2.3; 1.2-5.8 μg/ml). Elevated inflammatory markers including ferritin, lactate dehydrogenase, and c-reactive protein increased progressively from the no AC to prophylactic AC and then therapeutic AC patient groups.

Mortality, Intubation and Outcomes

Overall 1,073 (24.4%) patients died during the study period, 2892 (65.9%) were discharged alive and 424 (9.7%) were still hospitalized by dataset freeze date. Among the no AC group, 931 (60.8%) patients were discharged alive; 392 (25.6%) expired in the hospital; and 207 (13.5%) were still hospitalized. In the prophylactic AC group, 1472 (75.1%) patients were discharged alive; 424 (21.6%) expired in the hospital; and 63 (3.2%) were still hospitalized. Finally, in the therapeutic AC group, 89 (54.3%) patients were discharged alive; 257 (28.6%) expired in the hospital; and 154 (17.1%) were still hospitalized. Therapeutic AC was associated with a 47% reduction in the hazard of in-hospital mortality (aHR=0.53; 95% CI: 0.45-0.62; p<0.001; **Figure 1A**) compared to no AC. Similarly, prophylactic AC was associated with a lower hazard of mortality (aHR=0.50; 95% CI: 0.45-0.57; p<0.001) compared to no AC. Overall, 467 (10.6%) patients required intubation and mechanical ventilation during hospitalization. Therapeutic AC was associated with a 31% reduction in the hazard of intubation (aHR 0.69; 95% CI: 0.51-0.94; p=0.02; **Figure 1B**) compared to no AC. Prophylactic AC was also associated with similarly reduced incidence of intubation (adjusted HR 0.72; 95% CI: 0.58-0.89, p=0.003)

compared to no AC. Landmark analyses showed similar associations (**Supplemental Tables 2 and 3**).

Therapeutic and Prophylactic Dose AC

We conducted a sub analysis for patients initiated on therapeutic (n=766) or prophylactic doses (n=1,860) of AC ≤48 hours of admission. Baseline characteristics are presented in **Supplemental Table 4**. Patients who received therapeutic AC were older, had more comorbid conditions and were more likely to be on an anticoagulant prior to admission compared to those receiving prophylactic AC. Patients on therapeutic AC also presented with more altered vital signs, and inflammatory markers, in particular D-dimer (2.4 vs. 1.4 μg/ml) compared to those receiving prophylactic AC. In adjusted analyses, therapeutic AC was associated with lower in-hospital mortality (aHR 0.86; 95% CI: 0.73-1.02; p=0.08; **Figure 2A**) although not statistically significant. There was no difference in incidence of intubation (aHR 0.94; 95% CI: 0.74-1.21); p=0.63; **Figure 2B**).

Bleeding Outcomes

A total of 153 patients met the prespecified definition of major bleeding. Of these, 89 either had a confirmed or suspected bleed **(Supplemental Figure 3)**. For patients on AC, bleeding was counted only if it occurred after initiation of treatment. The proportion of patients with bleeding events after initiation of AC treatment was highest in patients on therapeutic AC (27/900, 3.0%) as compared to patients on prophylactic AC (33/1959, 1.7%) and no AC (29/1530, 1.9%). (**Supplemental Table 5**) Among patients on a single therapeutic agent, bleeding rates were higher in those on low molecular weight heparin (LMWH) compared to novel anticoagulants (NOACs) (2.6% vs 1.3% respectively) and among those on a single prophylactic agent, bleeding rates were higher in those on unfractionated heparin (UFH)

compared to LMWH (1.7% vs. 0.7% respectively). The site of bleeding was determined in 67/89; 75%, with gastrointestinal being most common (50.7%), followed by mucocutaneous (19.4%), bronchopulmonary (14.9%) and then intracranial (6%).

Anticoagulation Agents

A sizable proportion of patients were on more than one AC agent over the course of their hospitalization preventing direct comparisons between anticoagulants. In a descriptive analysis, we present differences in cumulative incidence of mortality and intubation among individuals who were on a single anticoagulant received within 48 hours of admission. Among patients on therapeutic AC, differences in mortality and intubation between NOACs (n=178) vs. LMWH (n=211) are shown in **Supplemental Figures 4A and 4B,** respectively, and suggest that NOACs may be associated with better survival and lower intubation rates compared to patients on LMWH. Patients on UFH were not included due to the relatively small sample size of this group (n=35). Similarly, among patients on prophylactic dose AC, cumulative incidence of mortality and intubation for patients on UFH (n=941) and LMWH (n=445) are shown in **Supplemental Figure 4C and 4D** respectively. Patients on prophylactic NOACS are not shown due to limited sample size (n=34).

Autopsy Findings

Autopsies were performed on COVID-19 positive patients at MSHS starting on 3/20/2020, with 72 completed by 5/7/2020.[8] Of these, the first 26 sequential cases were evaluated microscopically by a team of subspecialty pathologists across organ systems. These cases are presented with a focus on thromboembolism and contextualized by pre-mortem AC regimens **(Table 2)**. Amongst 26 patients, 4 were on AC prior to admission due to atrial fibrillation (n=3) or prior DVT (n=1) (NOACs=3, warfarin=1). Of the remaining 22, 4 died

within 24 hours of presentation without ever receiving AC, 14 were placed on AC upon admission (prophylactic=13, therapeutic=1), and 4 received AC later during their hospital course (mean number of days post admission= 2.3 days).

In total, 11/26 (42%) had evidence of thromboembolic disease, including 4 pulmonary emboli (15%, **Figure 3A,B**), 2 cerebral infarctions (8%, **Figure 3C,D**) and 5 patients with microthrombi in multiple organs including the heart (n=4, **Figure 3E**), liver (n=1, **Figure 3F**), kidneys (n=2, not shown) and lymph nodes (n=2, not shown). The lungs were examined and revealed an extensive burden of fibrin thrombi visible on hematoxylin and eosin stain (15/26), however, this was not counted towards the thrombotic burden as it is an expected and frequently encountered finding in diffuse alveolar damage. Two of the four patients with pulmonary emboli were on prophylactic AC throughout, one was not on AC and one was given AC using UFH to treat disseminated intravascular coagulation but at subtherapeutic levels. More generally, 8/11 (73%) patients with thromboemboli were not on therapeutic AC. There was no pre-mortem suspicion of thromboemboli in 25/26 patients. There was only one major bleeding complication, which was a retroperitoneal bleed on presentation in a patient taking warfarin for atrial fibrillation prior to admission.

DISCUSSION

Thromboembolic disease has emerged as an important complication among hospitalized patients with COVID-19. In the present report of nearly 4,400 patients, we demonstrate the following (Central Illustration): first, AC is associated with lower hazards of in-hospital mortality and intubation compared to no AC after controlling for relevant clinical factors. Second, after restricting analysis to those in whom AC was initiated within 48 hours of admission, no statistically significant difference in in-hospital mortality or intubation for

therapeutic vs. prophylactic AC was observed. Third, overall rates of major bleeding were low. Finally, these observations were corroborated by autopsy findings, wherein 11/26 of patients had thromboembolic disease not otherwise suspected pre-mortem. The majority of these patients were not treated with therapeutic AC.

Mechanisms by which thrombotic disease may occur in the setting of COVID-19 infection include inflammation, hypoxia, and potentially pharmacotherapeutic interactions. (2,4,13,14) As such, the potential benefit of AC in the treatment of COVID-19 is based on the prevention and treatment of micro and macrovascular thrombosis. In addition, AC agents may exert antiviral and anti-inflammatory properties affording further benefit. (15,16)

In our cohort of patients hospitalized with COVID-19, a strong association of AC with approximately 50% reduced hazard of in-hospital mortality was observed (**Figure 1A**). Both therapeutic and prophylactic doses of AC were associated with better in-hospital survival compared to no AC. As mortality rates for patients with COVID-19 who undergo intubation for respiratory failure range from 30-80%, (17-19) we analyzed the association between AC and intubation. Both therapeutic and prophylactic AC were associated with an approximately 30% reduced hazard of intubation compared to patients on no AC (**Figure 1B**). Landmark analyses were performed to minimize immortal time bias and revealed similar associations (**Supplemental Tables 2, 3**).

Therapeutic Compared to Prophylactic Dose AC

Due to variation in timing of initiation and administration of AC across patients, a subanalysis to patients who received either therapeutic or prophylactic AC within 48 hours of admission, showed therapeutic AC was associated with a 14% reduction in hazard of mortality compared to

prophylactic AC that did not reach statistical significance (p=0.08). There was no difference in intubation risk between the two doses (**Figures 2A, B**).

In entirely descriptive analyses examining individual agents, potential benefit with prophylactic LMWH compared to UFH may exist for mortality but differences in intubation appear minimal. Therapeutic NOACs visually may be associated with lower mortality and intubation risk compared to LMWH (**Supplemental Figure 4**). No conclusions can be drawn from these purely descriptive comparisons however, and randomized trials comparing specific agents are needed to inform whether comparative benefit exists.

Bleeding

Bleeding rates were low overall, but as expected, slightly higher in the therapeutic AC group compared to the prophylactic and no AC groups (**Table 2**). In patients on a single therapeutic agent, the bleeding rates were higher in patients on LMWH vs. NOACs. Further studies and trials are required however to better understand this observation. As always, the benefit-risk tradeoff, here between AC and bleeding, needs to be evaluated on an individual basis and discussed as part of shared-decision making.

Autopsy findings

We show a high prevalence of thrombotic complications mostly occurring in patients receiving prophylactic/ no AC, consistent with a recent autopsy study demonstrating thrombotic burden in 58%. (6,20) Though lung microthrombi were not counted towards overall burden but rather as a feature of diffuse alveolar damage, it is worth noting that this finding emphasizes the endothelial dysfunction at play. Finally, in all except for one case of stroke, there was no clinical suspicion of thromboembolic disease prior to autopsy, suggesting that clinical estimates of thromboembolic disease may be under-estimating the actual burden.

Limitations

Our study has several limitations. As an observational study, there may have been confounders leading to differences in the outcomes for the treatment groups. Though we minimized their potential impact through IPTW modeling, unmeasured confounders and residual bias may have been present. Despite a two-physician manual review of different AC regimens for the purposes of categorizing patients, there may have been discrepancies between regimens of NOACs and LMWH wherein doses may not have accurately represented therapeutic and prophylactic AC. Patients who were on both therapeutic and prophylactic doses of AC were excluded due to an inability to definitively categorize them. Patients with hospital stay <24 hours were also excluded. Nonetheless, we adopted a conservative approach wherein individuals receiving <48 hours of AC were considered in "no AC" group. To minimize immortal time bias, we analyzed AC as a time dependent variable and conducted landmark sensitivity analyses. However, we cannot rule out residual bias even after using IPTW. We included UFH infusion in the therapeutic group, but patients may not be in the therapeutic aPTT range. Since manual validation of each outcome was not feasible in the whole sample size, there exists the possibility of misclassification of outcomes. We did not conduct analysis on novel antiviral treatments (Remdesivir, IL-1 antagonists) since these were still under investigation and administered in the context of clinical trials at our institution. The generalizability of the autopsy data may be limited due to small sample size and fact that these were not consecutive deaths. Finally, we may have encountered higher proportions of patients on AC due to the fact that Mount Sinai initiated a system-wide protocol wherein at least prophylactic AC was strongly encouraged with guidance provided for consideration of therapeutic AC based on various factors (**Supplemental Figure 5**).

CONCLUSIONS

Among patients hospitalized with COVID-19, AC was associated with lower adjusted risk of mortality and intubation vs. no AC. Rates of major bleeding were low. Consecutive autopsies revealed frequent thromboembolism, with most patients not on therapeutic AC. The results of randomized controlled trials evaluating different AC regimens for treatment for hospitalized patients with COVID-19 are needed.

Clinical Perspectives

Competency in Medical Knowledge: We conducted a retrospective observational study of patients hospitalized with COVID-19 within a large health system in New York City. Compared to no anticoagulation, we found a decreased hazard of mortality and intubation with anticoagulation (at both prophylactic and therapeutic doses) after adjustment for clinically relevant factors When restricting analyses to those who received either prophylactic or therapeutic anticoagulation within 48 hours of admission, there was no statistically significant difference between therapeutic over prophylactic regimens for mortality or intubation. Bleeding rates were generally low, but higher among patients on therapeutic anticoagulation. We also present descriptive analyses comparing patients on unfractionated heparin, novel oral anticoagulants, and low molecular weight heparin, at both therapeutic and prophylactic doses. Finally, in well annotated consecutive autopsy samples, the incidence of thromboembolism was high.

Translational Outlook: Anticoagulation may be associated with better survival and less frequent intubation with low rates of bleeding among patients hospitalized with COVID-19. These data from a large, diverse hospitalized cohort may help inform clinical trials as to appropriate anticoagulation regimens in patients with COVID-19.

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Figure Legends

Figure 1A. Association of Prophylactic/Therapeutic vs. No Anticoagulation for In-Hospital Mortality; Figure 1B. Association of Prophylactic/Therapeutic vs. No Anticoagulation for Intubation. Stabilized weight adjusted cumulative incidence curves for the effect of anticoagulation on in-hospital mortality with discharge as a competing risk. The estimates are adjusted for the inverse probability of treatment weighting (IPTW) using propensity scores. Hazard ratio (HR) and 95% confidence interval (CI) are based on stabilized IPTW Fine and Gray's sub-distribution hazard models with robust variance and discharge as a competing event. The multivariable model includes therapeutic and prophylactic anticoagulation as time-dependent variables and controls for the effect of time-varying intubation status and respiratory rate and oxygen saturation at admission. Stabilized weight adjusted cumulative incidence curves for the effect of anticoagulation on intubation with death and discharge as competing risks. The estimates are adjusted for the inverse probability of treatment weighting (IPTW) using propensity scores. Hazard ratio (HR) and 95% confidence interval (CI) are based on stabilized IPTW Fine and Gray's sub-distribution hazard models with robust variance and death and discharge as competing events. The multivariable model includes therapeutic and prophylactic anticoagulation as time-dependent variables and controls for the effect of respiratory rate and oxygen saturation at admission.

Figure 2A. Association of Prophylactic vs. Therapeutic Anticoagulation started within 48 hours of hospital admission on in-hospital mortality; Figure 2B. Association of Prophylactic vs. Therapeutic Anticoagulation started within 48 hours of hospital admission on intubation. Stabilized weight adjusted cumulative incidence curves comparing the effect of therapeutic vs. prophylactic anticoagulation (within 48 hours of hospital admission) on in-

hospital mortality with discharge as a competing risk. The estimates are adjusted for the inverse probability of treatment weighting (IPTW) using propensity scores. Hazard ratio (HR) and 95% confidence interval (CI) are based on stabilized IPTW Fine and Gray's sub-distribution hazard models with robust variance and discharge as a competing event. The multivariable model includes therapeutic and prophylactic anticoagulation as time-dependent variables and controls for the effect of time-varying intubation status. Stabilized weight adjusted cumulative incidence curves comparing the effect of therapeutic vs. prophylactic anticoagulation (within 48 hours of hospital admission) on intubation with deaths and discharge as competing risks. The estimates are adjusted for the inverse probability of treatment weighting (IPTW) using propensity scores. Hazard ratio (HR) and 95% confidence interval (CI) are based on stabilized IPTW Fine and Gray's sub-distribution hazard models with robust variance and death and discharge as competing events. The multivariable model includes therapeutic and prophylactic anticoagulation as time-dependent variables.

Figure 3. Thromboembolic Disease in autopsy specimens from 26 consecutive autopsies. (A) Pulmonary embolus with lines of Zahn and adherence to the pulmonary vasculature (H&E, 0.5x). (B) Pulmonary embolus near an intraparenchymal pulmonary lymph node, with lines of Zahn and adherence to the pulmonary vasculature (H&E, whole slide image). (C) Sequential gross sections of the right frontal lobe of the brain with peripheral infarcts (arrows) and surrounding hemorrhage (ruler shows dimensions in centimeters). (D) Microthrombus in an intraparenchymal brain vessel (H&E, 20x). (E) Microthrombus within the myocardium with lines of Zahn and adherence to the vascular wall (H&E, 4x). (F) Microthrombus in a portal venule in the liver (H&E, 20x).

Central Illustration: In Hospital Anticoagulation and Outcomes in COVID-19.

Thromboembolic disease is a complication of COVID-19. Prophylactic and therapeutic anticoagulation are associated with better outcomes in hospitalized patients with COVID-19. randomized controlled trials evaluating different AC regimens in COVID-19 are needed.

Table 1. Baseline Characteristics of Patients stratified by Therapeutic, Prophylactic and No Anticoagulation (n=4389)

	n	Total (n=4389)	Therapeutic Anticoagulation (n=900)	Prophylactic Anticoagulation (n=1959)	No Anticoagulation (n=1530)	P Value*
Age, median (IQR)	4389	65 (53-77)	70 (59-80)	65 (54-76)	61 (45-75)	<0.001
Female sex, n (%)	4389	1932 (44.0)	353 (39.2)	851 (43.4)	728 (47.6)	<0.001
Race/Ethnicity, n (%)	4389					0.01
Black		1152 (26.2)	228 (25.3)	567 (28.9)	357 (23.3)	
Hispanic		1172 (26.7)	222 (24.7)	523 (26.7)	427 (27.9)	
White		1060 (24.2)	234 (26.0)	432 (22.1)	394 (25.8)	
Asian		201 (4.6)	38 (4.2)	94 (4.8)	69 (4.5)	
Other		804 (18.3)	178 (19.8)	343 (17.5)	283 (18.5)	
Body Mass Index in kg/m2, median (IQR)	3940	28 (25-33)	29 (25-34)	28 (24-32)	28 (24-33)	<0.001
Current Smoking, n (%)	3405	184 (5.4)	29/687 (4.2)	92/1533 (6.0)	63/1185 (5.3)	0.23
Comorbid Conditions, n (%)						
Asthma	4377	274 (6.3)	59/896 (6.6)	137/1958 (7.0)	78/1523 (5.1)	0.07
Chronic Obstructive Pulmonary Disease	4377	216 (4.9)	61/896 (6.8)	102/1958 (5.2)	53/1523 (3.5)	<0.001
Type 2 Diabetes	4377	991 (22.6)	243/896 (27.1)	462/1958 (23.6)	286/1523 (18.8)	<0.001
Hypertension	4380	1526 (34.8)	362/898 (40.3)	706/1959 (36.0)	458/1523 (30.1)	<0.001
Coronary Artery Disease	4352	541 (12.4)	152/895 (17.0)	224/1950 (11.5)	165/1507 (10.9)	<0.001
Atrial Fibrillation	4352	298 (6.8)	158/895 (17.7)	49/1950 (2.5)	91/1507 (6.0)	<0.001
Heart Failure	4380	362 (8.3)	104/898 (11.6)	139/1959 (7.1)	119/1523 (7.8)	<0.001
Chronic Kidney Disease	4352	493 (11.3)	105/895 (11.7)	239/1950 (12.3)	149/1507 (9.9)	0.08
End Stage Kidney Disease	4286	291 (6.8)	56/835 (6.7)	144/1938 (7.4)	91/1513 (6.0)	0.26
Liver Disease	4286	69 (1.6)	9/835 (1.1)	38/1938 (2.0)	22/1513 (1.5)	0.2
Cancer	4377	340 (7.8)	78/896 (8.7)	160/1958 (8.2)	102/1523 (6.7)	0.14
HIV/AIDS	4377	73 (1.7)	9/896 (1.0)	39/1958 (2.0)	25/1523 (1.6)	0.56
Medications at Baseline, n (%)						

ACE inhibitor or ARB	4389	331 (7.5)	69 (7.7)	134 (6.8)	128 (8.4)	0.24
Anticoagulant	4389	79 (1.8)	43 (4.8)	7 (0.36)	29 (1.9)	<0.001
Antiplatelet agents	4389	374 (8.5)	69 (7.7)	174 (8.9)	131 (8.6)	<0.001
Initial vital signs-Median (IQR)						
Systolic blood pressure in mm of Hg	4347	138 (125-155)	143 (128-158)	140 (125-156)	136 (122-151)	<0.001
Diastolic blood pressure in mm Hg	4347	80 (72-89)	83 (75-91)	80 (72-89)	79 (72-87.5)	<0.001
Heart rate in beats/min	4354	99 (88-113)	102 (89-119)	99 (88-112)	98 (87-111)	<0.001
Oxygen saturation-%	4275	94 (90-96)	92 (88-95)	94 (91-96)	95 (92-97)	<0.001
Respiration in breaths/min	4354	20 (18-24)	22 (20-30)	20 (18-24)	20 (18-20)	<0.001
Initial laboratory tests — median (IQR)						
Hemoglobin g/dL	3557	12.7 (11.2-14.0)	12.6 (11.0-13.9)	12.8 (11.4-14.1)	12.6 (11.0-13.9)	<0.001
White blood cell count in cells/mm^3	4206	7.6 (5.5-10.6)	8.5 (6.0-11.9)	7.3 (5.3-10.0)	7.5 (5.6-10.5)	<0.001
Lymphocyte in %	3831	9.8 (6.0-15.5)	8.2 (5.2-13.0)	9.8 (6.1-15.2)	11.0 (6.6-17.8)	<0.001
Neutrophil in %	3831	66 (44.2-80.7)	75.6 (47.5-85.1)	56.9 (42.6-78.9)	67 (44.9-79.8)	<0.001
D-Dimer in µg/ml	3259	1.7 (0.9-3.6)	2.3 (1.2-5.8)	1.5 (0.8-2.9)	1.7 (0.8-3.7)	<0.001
Ferritin in ng/ml	3389	706 (317-1617)	830 (417-1969)	710 (316-1594)	601 (272-1437)	<0.001
Lactate dehydrogenase in U/liter	3268	414 (311-564)	484 (366-670.5)	402 (310-534)	380 (279-512)	<0.001
C-reactive protein in mg/liter	3524	108 (51-195)	141 (65-234)	106 (54-186)	90 (34-168)	<0.001
Procalcitonin in ng/ml	3124	0.2 (0.1-0.6)	0.2 (0.1-0.7)	0.2 (0.1-0.6)	0.1 (0.1-0.6)	<0.001
Albumin in g/dL	4033	3.1 (2.8-3.5)	3.0 (2.7-3.4)	3.2 (2.8-3.6)	3.1 (2.7-3.6)	<0.001

Total Bilirubin in mg/dL	2240	0.6 (0.4-0.8)	0.7 (0.5-1.0)	0.6 (0.4-0.8)	0.6 (0.4-0.8)	<0.001
Sodium in MeQ/L	4057	137 (134-140)	137 (134-140.5)	137 (134-140)	138 (135-141)	<0.001
Creatinine in mg/dL	4156	1.0 (0.8-1.6)	1.0 (0.8-1.6)	1.0 (0.8-1.5)	1.0 (0.7-1.6)	0.004
Prothrombin time in seconds	2604	13.7 (12.0-15.3)	14.7 (13.6-16.6)	13.4 (8.2-14.5)	13.7 (11.5-15.7)	<0.001
Partial thromboplastin time in seconds	2501	16.6 (13.8-31.3)	16.6 (14.3-31.0)	17.9 (13.7-32.0)	15.8 (13.5-30.5)	0.02
International normalized ratio (INR)	2743	1.1 (1.0-1.3)	1.2 (1.1-1.4)	1.1 (1.0-1.2)	1.1 (1.0-1.3)	<0.001
Platelet Count, in cells/mm^3	4129	211 (161-280)	227 (167-303)	207 (160-270)	210.5 (156-276)	<0.001

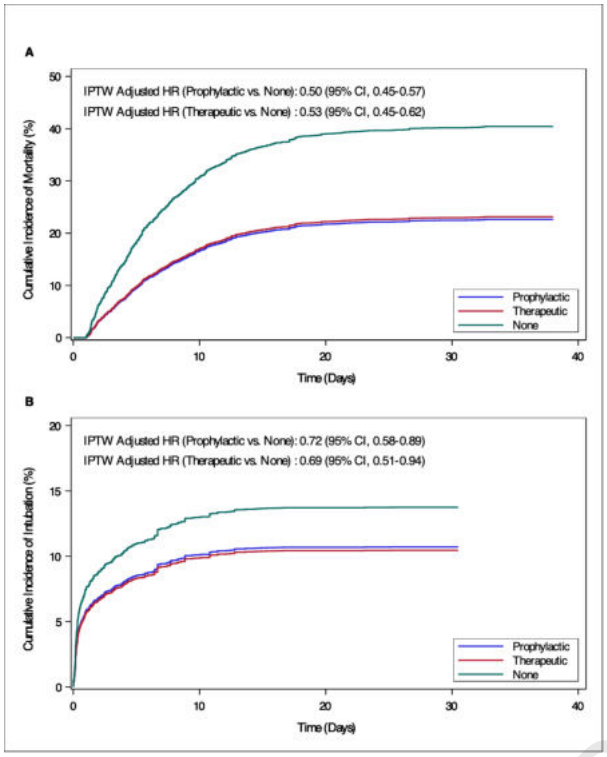
Abbreviations: IQR, interquartile range; ACE, Angiotensin Converting Enzyme, ARB, Angiotensin Receptor Blocker
Values at baseline are within 48 hours of admission
*Chi-squared test used for categorical variables. Kruskal-Wallis test used for continuous variables.

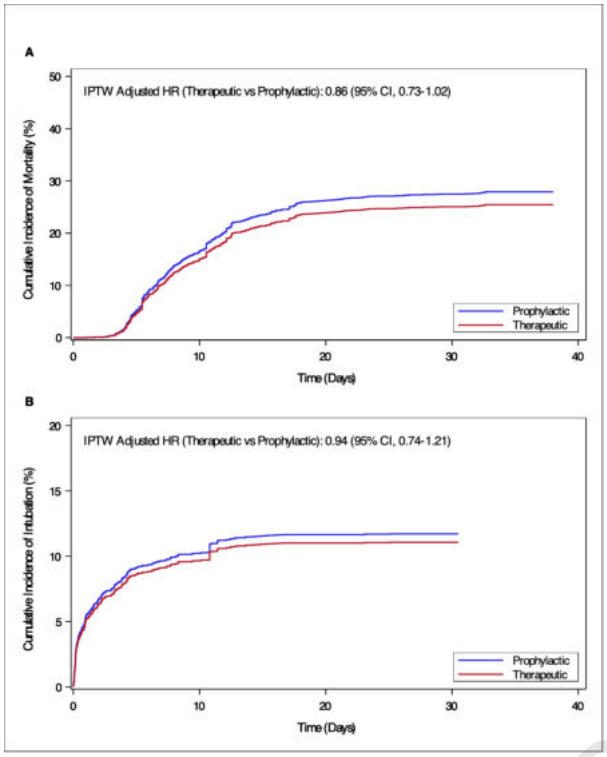
Table 2. Clinical and Pathological Features of Thromboembolic Disease in Sequential Autopsies (n=26)

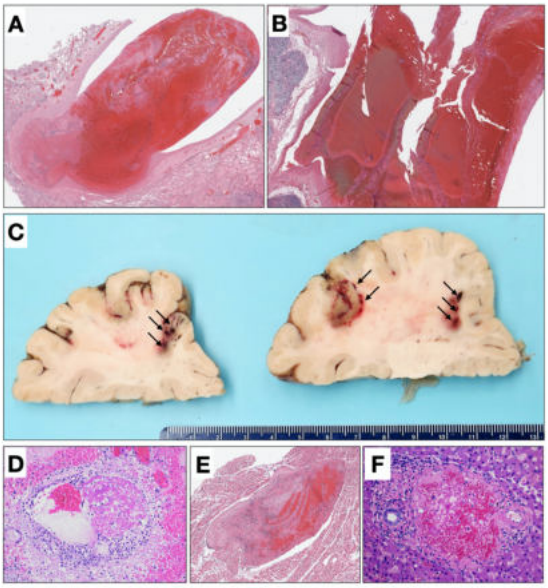
Age range	Sex	Prior indication	Type of Anticoagulation	Duration of death from admission in days	Duration of anticoagulation	Type (therapeutic/ prophylactic/ none)	Bleeding	Pulmonary Embolism	Microthrombi*	Suspicion of thrombosis before autopsy
50-59	M	NA	UFH	9	whole admission	Prophylactic		X	X	No
80-89	F	NA	UFH	11	whole admission	Prophylactic			X	No
60-69	M	Atrial Fibrillation	NOACs	4	whole admission	Therapeutic			X	No
<50	M	NA	LMWH	6	whole admission	Prophylactic		X	X	No
60-69	F	NA	None	0	NA	None				No
30-39	M	NA	LMWH	7	whole admission	Prophylactic				No
80-89	F	NA	UFH	10	whole admission	Prophylactic			X	No
70-79	M	NA	LMWH	10	whole admission	Prophylactic				No
<50	M	NA	None	0	NA	None				No
80-89	M	NA	None	0	NA	None				No
70-79	M	Atrial Fibrillation	Warfarin	1	whole admission	Therapeutic	Retro-peritoneal			No
<50	F	NA	UFH	3	whole admission	Prophylactic				No
80-89	F	NA	UFH	1	whole admission	Prophylactic				No
70-79	M	Deep Venous Thrombosis	NOACs	1	whole admission	Prophylactic			X	No
50-59	M	NA	UFH	4	1	Subtherapeutic**		X		No
50-59	M	NA	UFH, LMWH	5	whole admission	Prophylactic				No
60-69	M	NA	None	1	-	None		X		No
50-59	M	NA	UFH, LMWH	5	whole admission	Prophylactic				No
70-79	F	NA	LMWH	6	whole admission	Prophylactic				No

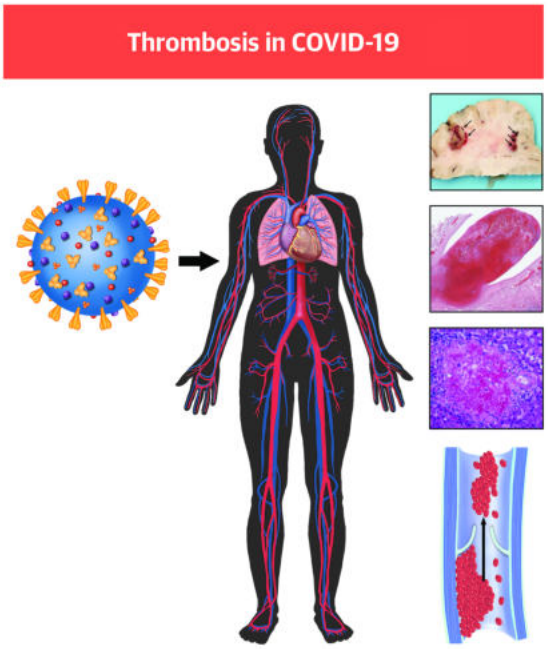
50-59	F	NA	UFH	4	whole admission	Prophylactic			X	No
70-79	F	Atrial Fibrillation	NOACs	5	whole admission	Therapeutic				No
50-59	F		UFH, LMWH	15	2	Therapeutic				No
80-89	F		LMWH	10	whole admission	Prophylactic				No
70-79	M		UFH	9	whole admission	Therapeutic				No
60-69	M		UFH	22	5	Therapeutic			X	No
<50	M		UFH	11	1	Subtherapeutic**			X	Yes

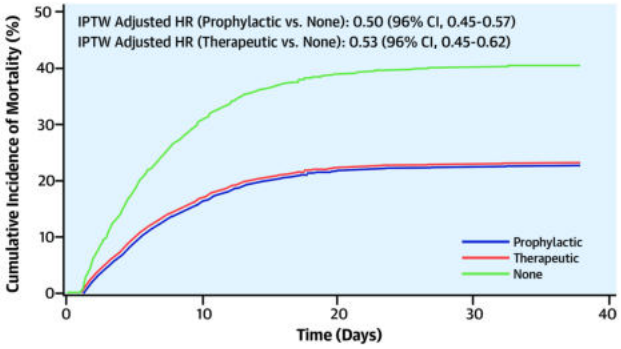
* Organs assessed for microthrombi in H&E include heart (found in 4/26), kidneys (found in 2/26), liver (found in 1/26), lymph nodes (found in 2/26) and brain (found in 2/26).
Microthrombi in the lungs are normally seen as part of diffuse alveolar damage and are discussed separately (see Results and Discussion).
** Anticoagulation in this case was intended to be therapeutic, however PTT never reached the therapeutic range
NA=Not Applicable, UFH= Unfractionated Heparin, LMWH= Low Molecular Weight Heparin, NOACs=Novel Anticoagulants











Anticoagulation Associated With Better Outcomes

Clinical Trial

Therapeutic vs. Prophylactic LMWH vs. NOAC?