Anticoagulation in COVID-19: Effect of enoxaparin, heparin and apixaban on mortality

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Running Title: AC in COVID-19

Research in context

Evidence before this study.
COVID-19 is recognized as a prothrombotic disease with a high mortality in hospitalized patients. Anticoagulation has been advocated by many guidelines as potentially beneficial in reducing mortality. The evidence to support this, however, has been sparse and it is unclear whether therapeutic anticoagulation, particularly in those with severe disease, is more beneficial than thromboprophylaxis. In addition, it has been difficult to adjust for potential comorbidities and get sufficient outcome measures within the short time span of disease.

Added value of this study
In a large cohort of 3625 hospitalized COVID-19 patients with known outcomes, we analyzed the results of anticoagulation with therapeutic intent in the first 48 hours of hospitalization on downstream mortality in an observational intention to treat analysis. We examined the use of both parenteral and oral medication and both prophylactic and therapeutic levels. We adjusted for known comorbidities and severity of illness as defined by D-dimer levels.

Implications of all the available evidence
Ours is the largest study investigating the effect of different types of anticoagulation intent and mortality outcome. Our data show that anticoagulation was associated with decreased mortality in patients with COVID-19. Therapeutic anticoagulation does not offer any increased benefit over prophylactic anticoagulation in patients with COVID-19, even in patients with high D-dimer levels.

Acknowledgments

We greatly appreciate the efforts of our fellow health care workers and support staff at the Montefiore Medical Center for providing outstanding patient care at considerable personal risk on the front lines of this pandemic. We express our support for our patients with COVID-19 and their families.

Abstract

Background: Mortality in coronavirus disease of 2019 (COVID-19) is associated with increases in prothrombotic parameters, particularly D-dimer levels. Many institutions have adopted anticoagulation guidelines, often adjusted for illness severity. We wanted to investigate whether anticoagulation improves survival in COVID-19 and if this improvement in survival is associated with disease severity.

Methods: To simulate an intention to treat clinical trial, we analyzed the effect on mortality of anticoagulation therapy chosen in the first 48 hours of hospitalization. We analyzed 3,625 COVID-19+ inpatients, controlling for age, GFR, oxygen saturation, ventilation requirement and time period, all determined during the first 48 hours.

Findings: Adjusted logistic regression analyses demonstrated a significant decrease in mortality with prophylactic use of apixaban (OR 0·52, p=0·005) and enoxaparin (OR=0·50, p=0·002). Therapeutic apixaban was also associated with decreased mortality (OR 0·63, p=0·025) but was not more beneficial than prophylactic use. UFH did not show the same benefit. Higher D-dimer levels were associated with increased mortality (p<0·0001). When adjusted for these same predictors within D-dimer strata, patients with D-dimer levels <1ug/ml did not appear to benefit from anticoagulation while patients with D-dimer levels >10ug/ml derived the most benefit. There was no increase in transfusion requirement with any of the anticoagulants used.

Interpretation: We conclude that COVID-19+ patients with moderate or severe illness benefit from anticoagulation and that apixaban has similar efficacy to enoxaparin in decreasing mortality in this disease.

Funding: There was no internal or external funding support for this study.

Word count 241

Background

Coronavirus disease of 2019 (COVID-19) is a heterogeneous disease, ranging from asymptomatic illness in some to rapid death in others. Trying to understand the manifestations of the disease, and whether these could be used both prognostically and therapeutically, has been a focus of intense work throughout the world. The Chinese were the first to report a COVID-19 coagulopathy, particularly among patients with severe forms of the illness.[1] There are now data that coagulation parameters, particularly D -Dimer levels, are prognostically significant for mortality in COVID-19 and that patients with COVID-19 are at increased risk of both arterial and venous thrombosis.[2–4]

There has been a suggestion that anticoagulation may be of benefit in these patients, either in reduced VTE rate or mortality, although the evidence is sparse and not all experts agree.[5,6] In Wuhan, 449 patients with severe COVID-19 were retrospectively analyzed regarding the potential benefit of AC.[7] All of these patients received antiviral and supportive therapy in addition to anticoagulation and all anticoagulation was grouped, prophylactic and therapeutic. Although the study was done at the early onset of COVID-19 and did not analyze for other variables, this was an early indication that anticoagulation might affect mortality. A similar beneficial outcome for anticoagulation was seen in a smaller retrospective analysis in New York grouping all types of anticoagulants.[8,9]

This is a data analysis of patients March–May 2020 during the COVID-19 pandemic. An optional anticoagulation algorithm was initiated as best clinical judgement April 4th and provided to all physicians. This included specific recommendations for surveillance monitoring of D-dimer levels as well as recommendations for prophylactic or therapeutic anticoagulation with either indirect or direct oral anticoagulants (DOAC). Since data have shown a benefit of DOACs in prophylaxis of high risk cancer patients, for medically ill patients with acute infectious diseases, and for patients undergoing orthopedic procedures, oral anticoagulation with a DOAC was offered to minimize direct nursing/patient exposure.[10–13] We understood that with the overwhelming onslaught of patients, the tripling in number of our medical "beds", the deployment to a medical floor of physicians who were not internal medicine trained, and the number of deaths at the maximum admission rate ~100/day, that not all aspects of the protocol would be followed.

It is with a potential survival benefit in mind that we thought it important to assess the relationship of both type and intensity of anticoagulation to mortality and severity of illness and whether there were objective parameters like D-dimer levels that might differentiate outcomes with specific regimens.

Methods

Study Population. All patients admitted to one of three Montefiore Medical Center Hospitals in the Bronx from March 1- April 26, 2020 and who tested positive for COVID-19 for the first time within 24 hours of admission were eligible for inclusion. These patients were followed until May 30th, 2020.

Data Collection. After obtaining Institutional Review Board approval from Albert Einstein College of Medicine, we (EB) queried Looking Glass, (CLG),[14,15]a user-friendly cohort building and outcome analysis software application with access to EMR data, for all positive COVID-19 tests performed by Montefiore Health System (MHS) between 3/1/2020-4/26/2020. We (EB, LS, KI, JS) then built cohorts qualified by laboratory test results and medications and followed those patients to the outcome of death or discharge as recorded in the EMR (all authors). Death or censorship was determined on 5/30/2020. Data validation by chart review was performed to ensure correct coding.

Cohort Creation and Outcome Analysis. Data collected included age, BMI, estimated glomerular filtration rate (eGFR), oxygen saturation as determined by pulse oximetry, vital signs, ventilator requirement, D-dimer level, and choice of anticoagulation within the first 48 hours of presentation. D-dimer level was categorized as <1, 1-<3, ≥3-10, ≥10 ug/ml; eGFR was categorized a 0-15, 15-30, 30-60, ≥60ml/min. The highest two eGFR categories were collapsed during analysis. Patients on IRB approved clinical trials were excluded from the survival analyses.

Physician intent to treat with a specific anticoagulation medication and style was established by last physician anticoagulation order in the first 48 hours of admission. This treatment assignment with downstream intention-to-treat analysis is the analogue of treatment assignment in a prospective clinical trial. Adjustment covariates were also collected only in the first 48 hours so as not to adjust for outcomes created by the 48-hour therapeutic choice. Death was evaluated on May 30th for all patients discharged by that date. Those who did not survive the first two days were excluded from consideration. Death was ascertained from the Electronic Medical Record (EMR). Logistic regression modeling was restricted to discharged patients with complete data.

We classified anticoagulation regimen intensity as therapeutic or prophylactic and noted route as shown in Supplementary Table S1. All dosages were reviewed individually (HHB), with particular attention to GFR, age and weight, to ensure correct designation. All intravenous unfractionated heparin (UFH) was deemed to have been given for therapeutic intent; anti-X_a levels were not monitored and PTT data were not considered reliable within the COVID-19 "coagulopathy". Patients on chronic anticoagulation were excluded, as were patients on other clinical trials. Cohorts were created recognizing four distinct time convenience periods in the COVID-19 influx of patient admissions: March 1- 31, April 1-11, April 12-26th and April 27th – May 30th and controlled for these time periods.

Statistical Method. Stata 16 (Stata Press, College Station Texas) was used for all statistical analyses. Univariate survival analysis was performed with the Kaplan Meier statistic and log rank test. Multivariate logistic regression modeling was performed on discharged patients (dead or alive) by May 30th. Patients that were still hospitalized by May 30th were censured.

Role of the funding source. There was no funding source for this study. All authors had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study Population. 4,234 patients who were found to be COVID-19 positive for the first time within 24 hours of admission were evaluated. 252 patients were participating in randomized clinical therapy trials and were excluded, leaving 3982 potentially evaluable patients for anticoagulation intent. A further 175 patients were eliminated due to lack of sufficient data or were under 18years of age. 182 patients were further eliminated because they were not discharged by study termination (22) or had died within the first 48 hours (160). This left 3625 patients as patients evaluable for the study (Supplementary Figure S1), of which 2450 had complete data sets. Demographics and initial 48-hour descriptors are summarized in Table 1.

Adjustments for Time. Adjustments were made for four time periods. The first corresponded to the initial wave of 21 days (March 11-31) with 759 patients or 36·1 COVID-19+ patients/day; time period 2 (April 1-11) was one of maximum surge and had 1666 COVID-19 admissions in 11 days or 151·5 COVID-19+ patients/day; period 3 (April 12-26) is where the "curve flattening" started to occur and 797 COVID-19+ patients were admitted in 15 days or 53·1 patients/day. Period 4 (April 27 – May 30) was when the admission rate decreased markedly (369 patients in 33 days or 11·2 patients/day), expertise was greater, and beds and supplies were sufficient. It was during the initial surge that an anticoagulation protocol (Supplementary Figure S2) was developed which stratified therapy according to D-dimer level. Survival in the third time period increased significantly (Figure 1). Since the later time periods (3&4) were associated with significantly decreased mortality that may or may not have been associated with choice of anticoagulant therapy, logistic models adjusted for time "wave".

Therapy Choice. Despite the protocol, at 48 hours, no orders for anticoagulation had been given for 17·6% of the admitted patients; 58·8% received standard thromboprophylaxis, 4·0% received high dose prophylaxis and 19·6% received therapeutic anticoagulation. For those who chose prophylaxis, UFH given subcutaneously either at the standard twice daily dose (bid) or the high, three times daily (tid) dose was preferred for prophylaxis (42·7%) while apixaban was the overall preferred therapeutic regimen (66·8%). For patients with D-dimer values <3ug/ml for whom thromboprophylaxis had been recommended by protocol, 13·2% received full therapeutic doses and 12·3% were not prescribed any anticoagulation. Similarly, for those patients with D-Dimer levels ≥3ug/ml for whom therapeutic dose had been recommended by protocol, 16·0% received thromboprophylaxis only and 5·5% were not prescribed any anticoagulation. Patients admitted on full dose anticoagulation were excluded from the logistic regression and mortality analysis. Anticoagulation choices are presented in full in Supplementary Table S2. Warfarin, rivaroxaban, argatroban and bivalirudin had few patients; these were grouped and classified as "other" and excluded from the logistic regression and mortality analyses.

Mortality outcome stratified by D-dimer level. Unadjusted Kaplan Meier survival analysis by first D-dimer level category for those patients not on clinical therapy trials confirmed the positive association of D-dimer level with mortality (Supplementary Figure S3; p <0·0001) and its value as a surrogate marker of severity.

Chosen therapy stratified by D-dimer level. We examined separately these therapies according to D-dimer level. Most patients had D-dimer levels drawn (69·7%) within 48 hours of admission. The distribution of D-dimer values for the patient population is shown in Supplemental Table S3. Choice of anticoagulation varied within the D-dimer levels. Patient on no anticoagulation were seen throughout the range of D-dimer levels. Of patients with a D-dimer level of <1 ug/ml, 74 (9·6%) were placed on therapeutic anticoagulation while 105 (13·5%) received no thromboprophylaxis. At a D-dimer level between 1 and <3 ug/ml, 162 (16·0%) received full therapeutic doses and 116 (11·5%) received no therapy. At a D-dimer value of ≥10 ug/ml, 38 (13·7%) received no thromboprophylaxis or therapy (Supplementary Table S3).

Comparisons of Efficacy of Therapy Regimens: Adjusted analysis. A logistic model for discharged patients is provided in Table 2 describing the impact of age, oxygen saturation, eGFR, D-dimer level, time period (wave), ventilation requirement, and anticoagulation med order and type, all as determined in the first 48 hours of admission on the odds of death (n=2450). BMI categorically defined as (<30, 30-35,>35) was not significant and was not included in the table. All other parameters were significant and were adjusted for. As expected, age, oxygen saturation <90%, decreased GFR, elevated D-dimer levels, and ventilator requirement were all significantly associated with increased mortality. The later time periods, collapsed into two levels and designated as time waves, were also significantly associated with a better prognosis.

When compared to no anticoagulation at baseline and after adjustment for the variables above, apixaban prophylaxis (OR 0·52, p=0·005), apixaban therapy (OR 0·63, p=0·025) and enoxaparin prophylaxis (OR 0·50, p=0·002) were all associated with a

significant decrease in mortality, as shown in Table 2. UFH was not associated with significant benefit, either as prophylaxis or therapy.

We then compared therapy for patients to a baseline of no anticoagulation stratified, rather than adjusted, by D-dimer values with adjustment for the other variables in stratum specific logistic regression models (Table 3). For D-dimer levels <1 ug/ml, there was no benefit associated with any of the treatments. At D-dimer levels 1 - <3 ug/ml, apixaban at both the prophylactic (OR 0·49, 95%CI: 0·25 – 0·94, p=0·033) and therapeutic (OR: 0·48, 95%CI: 0·23 – 0·97, p=0·041) dosing was associated with a significant decrease in mortality odds ratios as was enoxaparin prophylaxis (OR 0·5, 95%CI: 0·26 – 0·96, p=0·036) and UFH therapy (OR 0·22, 95%CI: 0·52 – 0·90, p=0·035). Enoxaparin therapy was not associated with better survival at any level but the number of patients on enoxaparin therapy was small. By contrast, UFH standard dose prophylaxis, with a larger number of patients, also did not appear to be beneficial at any level. At D-dimer levels >10ug/ml, both enoxaparin prophylaxis and apixaban therapy were associated with decreased mortality (OR 0·15, 95%CI: 0·04-0·62, p=0·008 and OR 0·26, 95% CI: 0·09 -0·70, p=0·008 respectively). Apixaban prophylaxis at the same decrease in odds ratio (0·26) did not reach statistical significance (p=0·061).

Transfusion Requirement. We were concerned about the possibility that certain anticoagulation choices, particularly intravenous heparin, might have been influenced by concern over increased bleeding. We reexamined our cohort for those patients requiring transfusion support that were contemporaneous with the anticoagulant order. For the transfusion risk analysis, we eliminated 106 patients who received a transfusion within the first 72 hours of admission since those who actually received a transfusion within the first 72 hours might have been suspected of requiring it at the 48-hour mark when the anticoagulation was chosen and therefore biasing the selection. 614 patients had a length of stay greater than 48 hours but less than 72 hours and were excluded from evaluation. 183 patients did not have a transfusion in the first three days but did have a transfusion from day three onwards. Logistic regression adjusted models, with same adjusters as in the mortality analysis, did not find any anticoagulant regimen with a likelihood of transfusion greater than for patients on no anticoagulant regimen (Table 4).

Discussion

Early in the course of COVID-19, The Shanghai Clinical Treatment Expert Group had suggested that anticoagulation may be of some benefit in COVID-19 patients.[7] Tang found no difference in 28-day mortality for the general population of heparin users and nonusers overall, but in patients with SIC score ≥4, those patients on heparin for ≥7 days had a lower mortality than those not on anticoagulation (40·0% vs 64·2%, P=0·029). This benefit was particularly seen in those with the highest D-dimer values, those with >6 fold of upper limit of normal (32·8% vs 52·4%, P=0·017). Although the study was done at the early onset of COVID-19 and did not analyze for other variables, nor did it differentiate between prophylactic and therapeutic dosing intensity, this was a hopeful outcome. Llitjos showed no difference in death between prophylactic (one of eight patients) and therapeutic (two deaths in 18 patients) anticoagulation but the small numbers precluded any meaningful conclusion.[16] Thachil has also suggested that perhaps higher than prophylactic doses should be used in patients with extremely high D-dimer values.[17]

Limitations. With all our care, this is still an observational study with potential confounders that we may not yet have adequately addressed but even in prospective studies, there may be confounders of which we are not initially aware. We cannot with certainty eliminate the possibility that certain clinicians who supervised care in the most acute intensive care areas did not have a predilection for one of the therapies, which could have created an artificial relationship between severity and therapy choice. We did not track how long individual patients received the ordered anticoagulation or whether anticoagulation choice was switched after the 48-hour timepoint. Again, this would be similar to an intention-to-treat setting. Although we used transfusion as a surrogate for significant bleeding, we understand that this does not take into account intracranial or critical site bleeds that would not necessarily entail transfusion support. We did not examine the benefit of the different types of anticoagulation regimens for thrombosis prevention, eventual ventilator requirement, eventual need for dialysis, nor the relationship of thrombosis to mortality. This is the subject of future analyses because of the intense medical record and image reviews required to ensure data accuracy.

The strengths of this paper are its large size and mature adjusted determination of baseline risk, establishing relevant variables in the first 48 hours. In addition, specific attention to medication type and dose adjusted to patient weight and creatinine clearance allowed us to establish anticoagulation therapeutic intent (prophylaxis or full therapy) prior to evaluating the impact of that intent on downstream mortality.

We examined the value of different regimens and types of anticoagulation in COVID-19+ patients, accepting as evidence of anticoagulation intent the last anticoagulant order chosen during the first 48-hour window after admission. Establishing intent prior to a search for outcome alleviates problems often seen in other studies where therapy choice is confounded with outcome. Anticoagulation begun later in the hospital stay may have been chosen as a response to patient deterioration but be misinterpreted as causal.[9] We sought to use an intention-to-treat- like model to preclude confounding by indication and falsely attribute bad outcome to "innocent therapy" added at the time of the patient's disease progression. An additional advantage of this model is that it obviates the "longevity" bias where the longer one survives in the hospital, the greater the chance the clinician might implement anticoagulation. Our careful attention to baseline intent obviates both biases and is a major strength of this analysis. Our very large numbers and our long follow-up, for this disease, allowed us to have a large number with actual outcomes, rather than many studies where, although the

initial numbers appear high, many patients are still hospitalized, leaving a question as to what happens to these patients. The exclusion of 160 (3·8%%) patients who died within the first 48 hours, necessary for our intent to treat construct, had the additional benefit of excluding immediately terminal patients who might not have lived long enough to gain a potential benefit from anticoagulation.

Implementation of the best practice anticoagulation protocol was confounded by an improved outcome over time, as has been noted previously in other studies[18,19] It could be argued that the improved outcome over time was secondary to reduced admissions in the later time period, improved staffing, and increased experience in managing these critically ill patients but may also have been associated with the acceptance of our anticoagulation protocol. To aggressively control for this potential bias, we included, in our logistic modelling, an adjustment for time period. It could be argued that this adjustment might hide the value of anticoagulation but, despite this adjustment, the association of anticoagulation with survival remained. We also eliminated from consideration all patients on a clinical trial whether given therapy or placebo, reducing our sample size but eliminating the possibility that some of the observed improvement might be due to the experimental interventions.

We adjusted for severity of illness both in the major logistic regression model and in the stratified model. Despite adjusting for vent requirement, GFR, age, oxygen saturation, time and D-dimer level, prophylactic anticoagulation with apixaban and enoxaparin were both significantly associated with decreased OR for mortality. Apixaban at full therapeutic levels did not improved survival in this model. It is interesting that the reduction in mortality is strikingly similar for both prophylactic therapies throughout the analyses. When stratified by D-dimer values, it appeared that there was no real benefit to any anticoagulation at the lowest D-dimer level <1ug/ml, but as the D-dimer values increased, anticoagulation became more important.

Research has examined the anti-inflammatory aspects of heparin. A hypothesis by Belen-Apak suggests that there might be a direct effect of UFH on the virus by blockage of host cell proteases.[20] UFHs have been associated with anti-inflammatory effects that may be beneficial to the cytokine storm associated with COVID-19, but again the true clinical value of this is uncertain.[21] There is also evidence suggesting that FXa exerts cellular effects that can contribute to inflammation.[22] Whether anti-inflammatory effects should be applicable to all anti-Xa therapies is unclear but studies of rivaroxaban have shown inhibition of apoptosis and inflammation, and our data do not appear to show a significant beneficial effect of unfractionated heparin.[23,24] This may be due to the majority of our patients receiving only twice daily UFH rather than thrice daily, which might be a better option for the hypercoagulable state that is COVID. Our data appear to show that apixaban is associated with approximately the same decrease in odds ratio and improvement in survival as the heparins, whether this is because of a similar anticoagulation effect or a similar anti-inflammatory effect is unknown at this point.

No other published studies have examined apixaban in these circumstances. The ability to use an oral drug that is less affected by renal function and has a generally low bleeding risk makes this drug advantageous in the setting of COVID-19, where longer and closer contact time between patient and nurse in the subcutaneous or the intravenous setting confers an increased transmission risk.

We report here a very large observational study which shows a survival benefit, after adjustment for age, ventilation requirement, oxygen saturation and time period, with anticoagulation for patients with COVID-19. We conclude that COVID-19+ patients with moderate or severe illness benefit from D-dimer level-dependent anticoagulation and that apixaban has similar efficacy to the heparins in decreasing mortality in this disease. Although benefit with therapeutic levels of anticoagulation was also seen, therapeutic dosing offered no further benefit seen over thromboprophylaxis.

While these data suggest that anticoagulation improves survival in COVID-19+ patients, randomized controlled studies are needed and many are underway. In the interim, it would seem appropriate to treat hospitalized COVID-19+ patients with D-dimer levels >1ug/ml with anticoagulation.

Contributors

Henny H. Billett originated the concept, helped in the analysis and wrote the manuscript. She declares no competing conflict of interest.

Morayma Reyes Gil helped originate the concept, helped in the analysis and reviewed and edited the manuscript. She declares no competing conflict of interest.

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Eran Bellin developed the CLG program, developed the cohorts, performed the statistical analyses, and reviewed and edited the manuscript. He declares no competing conflict of interest..

Declaration of interests

HHB has received research or advisory funding from Bristol Myers Squibb, Janssen Pharmaceuticals, Bayer, and Kedrion Pharmaceuticals. MK has received research or advisory funding from Bristol Myers Squibb and Janssen Pharmaceuticals. All other authors declare no competing interests.

Data sharing

For original data, please contact HBILLETT@montefiore.org.

Word Count 3428

References

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;**395**:507-513.

2. Middeldorp S, Coppens M, van Haaps TF et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020;**18**:1995-2002.

3. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;**191**:9-14.

4. Helms J, Tacquard C, Severac F et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;**46**:1089-1098.

5. Liu XL, Wang XZ, Liu XX, et al. Low-dose heparin as treatment for early disseminated intravascular coagulation during sepsis: A prospective clinical study. Exp Ther Med 2014;**7**:604–608.

6. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020; **135**:2033-2040.

7. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;**18**:1094-9.

8. Hanif A, Khan S, Mantri N, et al. Thrombotic complications and anticoagulation in COVID-19 pneumonia: a New York City hospital experience [published online ahead of print, 2020 Aug 17]. Ann Hematol 2020; 10.1007/s00277-020-04216-x. doi:10.1007/s00277-020-04216-x

9. Paranjpe I, Fuster V Lala A,et al. Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19. J Am Coll Cardiol 2020; **76**:122-9.

10. Cohoon KP, De Sanctis Y, Haskell L, McBane RD, Spiro TE. Rivaroxaban for thromboprophylaxis among patients recently hospitalized for acute infectious diseases: a subgroup analysis of the MAGELLAN study. J Thromb Haemost 2018;**16**:1278-1287.

11. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N Engl J Med 2019;**380**:720-728.

12. Yoshida Rde A, Yoshida WB, Maffei FH, El Dib R, Nunes R, Rollo HA. Systematic review of randomized controlled trials of new anticoagulants for venous thromboembolism prophylaxis in major orthopedic surgeries, compared with enoxaparin. Ann Vasc Surg 2013;**27**:355-369.

13. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. N Engl J Med 2019; **380**:711-719.

14. Bellin E, Fletcher DD, Geberer N, Islam S, Srivastava N. Democratizing information creation from health care data for quality improvement, research, and education-the Montefiore Medical Center Experience. Acad Med 2010; **85**:1362-1368.

15. Bellin E. Missing Management: Health-Care Analytic Discovery in a Learning Health System. South Carolina: Kindle direct publishing; 2019.

16. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020; **18**:1743-1746.

17. Thachil J. The versatile heparin in COVID-19. J Thrombos Haemost 2020;**18**:1020-1022.

18. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966. Published 2020 May 22. doi:10.1136/bmj.m1966

19. Wang M, Zhang J, Ye D, et al. Time-dependent changes in the clinical characteristics and prognosis of hospitalized COVID-19 patients in Wuhan, China: A retrospective study [published online ahead of print, 2020 Jul 6]. Clin Chim Acta. 2020;S0009-8981(20)30315-6. doi:10.1016/j.cca.2020.06.051

20. Belen-Apak FB, Sarialioglu F. The old but new: Can unfractionated heparin and low molecular weight heparins inhibit proteolytic activation and cellular internalization of SARS-CoV2 by inhibition of host cell proteases? Med Hypotheses 2020;**142**:109743.

21. Allen KS, Sawheny E, Kinasewitz GT. Anticoagulant modulation of inflammation in severe sepsis. World J Crit Care Med 2015; **4**:105-15.

22. Papadaki S, Tselepis AD. Nonhemostatic Activities of Factor Xa: Are There Pleiotropic Effects of Anti-FXa Direct Oral Anticoagulants? Angiology 2019;**70**:896-907.

23. Al-Harbi NO, Imam F, Alharbi MM, et al. Role of rivaroxaban in sunitinib-induced renal injuries via inhibition of oxidative stress-induced apoptosis and inflammation through the tissue necrosis factor-α induced nuclear factor-κappa B signaling pathway in rats. J Thromb Thrombolysis 2020; **50**:361-370.

Table 1. Characteristics of the Study Population

	n	%
Race (n=3625)		
Black	1359	37·5%
White	347	9·6%
Other	1919	52·9%
Ethnicity (n=3625)		
Hispanic	1361	37·5%
Age,yrs (n=3625)		
<50	708	19·5%
50-60	671	18·5%
60-70	836	23·1%
70-80	820	22·6%
>80	590	16·3%
Gender (n=3625)		
F	1719	47·4%
M	1905	52·6%
Not given	1	0·0%
Survival Status (n=3625)		
Survived	2832	78·1%
Died >48hrs	793	21·9%
eGFR, ml/min (n=3538)		
30-120	2778	78·5%
15-30	366	10·3%
0-15	394	11·1%
D-dimer Value, ug/ml (Initial 48 hrs, n=2527)		
<1	779	30·8%
1-<3	1013	40·1%
3-<10	457	18·1%
≥10	278	11·0%
Oxygen Saturation (%) by Pulse Oximetry (n=3599)		
95%	2127	59·1%
90-95%	875	24·3%
<90%	597	16·6%
Ventilator Required Initial 48 hrs (n=3625)		
No	3312	91·4%
Yes	313	8·6%

Table 2. Logistic regression analysis of variables: Adjusted Odds ratios for mortality outcome (n=2450)

Variable	Odds Ratio	95% Confidence Interval	p
Age, yrs			
<50	1.00		
50 to 60	2·55	1·44 – 4·52	0·001
60 to 70	3·87	2·53 – 6·66	<0·001
70 to 80	5·71	3·32 – 9·84	<0·001
≥80	8·77	5·04 - 15·28	<0·001
Oxygen Saturation, %			
>95%	1.00		
90 – 95%	1·62	1·22 – 2·15	0·001
<90%	2·83	2·12 - 3·79	<0·001
eGFR ml/min			
>60	1.00		
≥30-60	1·77	1·32 – 2·38	<0·001
15-30	2·68	1·87 - 3·85	<0·001
0-15	1·92	1·31 – 2·81	<0·001
D-dimer, ug/ml			
<1	1.00		
1 to 3	1·61	1·15 – 2·26	0·005
3 to 10	1·99	1·35 - 2·92	<0·001
≥10	2·65	1·74 – 4·04	<0·001
Time Period			
First Time Period	1.00		
Wave	0·59	0·45 - 0·76	<0·001
Ventilator Needed first 48 hours			
No Ventilator Needed	1.00		
Ventilator Needed	10·34	6·86 - 15·61	<0·001
Medication and Regimen, Intent Type			
No Anticoagulation	1.00		
Apixaban Prophylaxis	0·52	0·33 - 0·82	0·005
Apixaban Full Therapy	0·63	0·42 – 0·94	0·025
Enoxaparin Prophylaxis	0·50	0·33 – 0·77	0·002
Enoxaparin Full Therapy	0·96	0·50 – 1·82	0·90
UFH Prophylaxis bid	0·82	0·55 - 1·23	0·34
UFH Prophylaxis tid	0·84	0·44 – 1·61	0·60
UFH Full Therapy	0·66	0·33 – 1·34	0·25

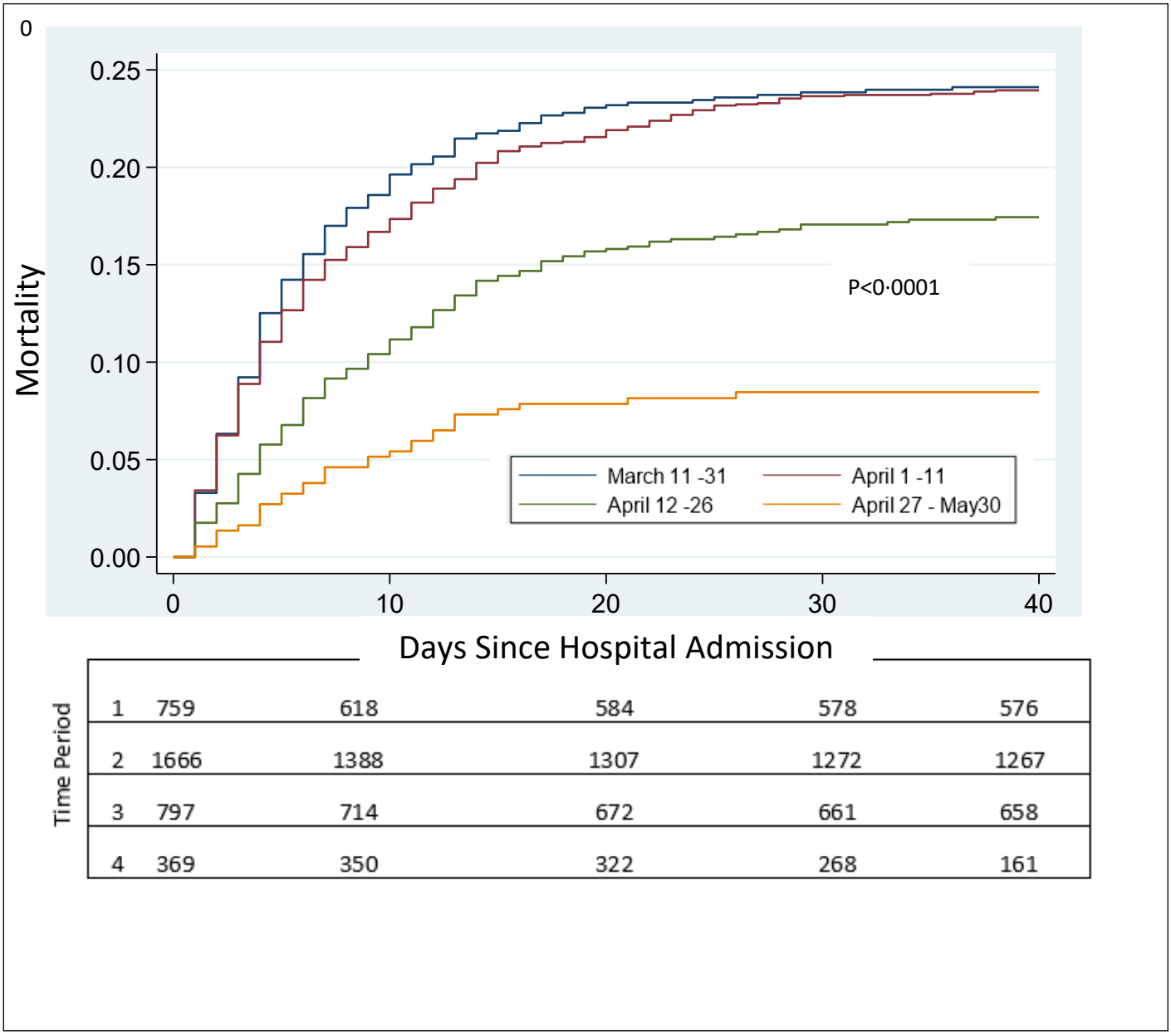
Table 3. Adjusted mortality per therapeutic modality, stratified by D-dimer (DD): Odds ratios and confidence intervals (n=2450)

n=2450	Apixaban Prophylaxis	Apixaban Therapy	Enoxaparin Prophylaxis	Enoxaparin Therapy	UFH Prophylaxis	UFH High Dose Prophylaxis	UFH Therapy
DD<1 (n=751)	0·87 95%CI: 0·26-2·88 p=0·82	1·72 95%CI: 0·51-5·79 p=0·38	0·93 95%CI: 0·31-2·81 p=0·89	5·78 95%CI: 0·49-68·2 p=0·16	2·20 95%CI: 0·76 - 6·38 p=0·15	1·71 95%CI:0·27-10·86 p=0·57	2·50 95%CI:0·32-19·73 p=0·38
DD 1-<3 (n=991)	**0·49** **95%CI: 0·25 - 0·94** **p=0·033**	**0·48** **95%CI: 0·23 - 0·97** **p=0·041**	**0·5** **95%CI: 0·26 - 0·96** **p=0·036**	0·95 95%CI: 0·27-3·30 p=0·93	0·66 95%CI: 0·35-1·23 p=0·19	0·76 95%CI:0·28-2·03 p=0·59	**0·22** **95%CI: 0·05-0· 90** **p=0·035**
DD 3-<10 (n=439)	0·44 95%CI: 0·11 – 1·68 p=0·23	0·78 95%CI: 0·36 – 1·72 p=0·54	0·45 95%CI: 0·17 – 1·21 p=0·11	0·88 95%CI: 0·26-3·02 p=0·84	0·81 95%CI: 0·32-2·07 p=0·66	1·02 95%CI: 0·28-3·76 p=0·97	0·36 95%CI: 0·73-1·72 p=0·20
DD ≥10 (n=269)	0·25 95%CI: 0·06 – 1·07 p=0·061	**0·26** **95%CI: 0·09 - 0·70** **p=0·0080**	**0·15** **95%CI: 0·04 - 0·62** **p=0·0080**	0·74 95%CI: 0·22-2·45 p=0·62	0·59 95%CI: 0·21-1·70 p=0·33	0·36 95%CI: 0·29-4·44 0·43	0·89 95%CI: 0·25-3·08 p=0·85

Table 4. Logistic Regression for Transfusion Requirement by Treatment Choice

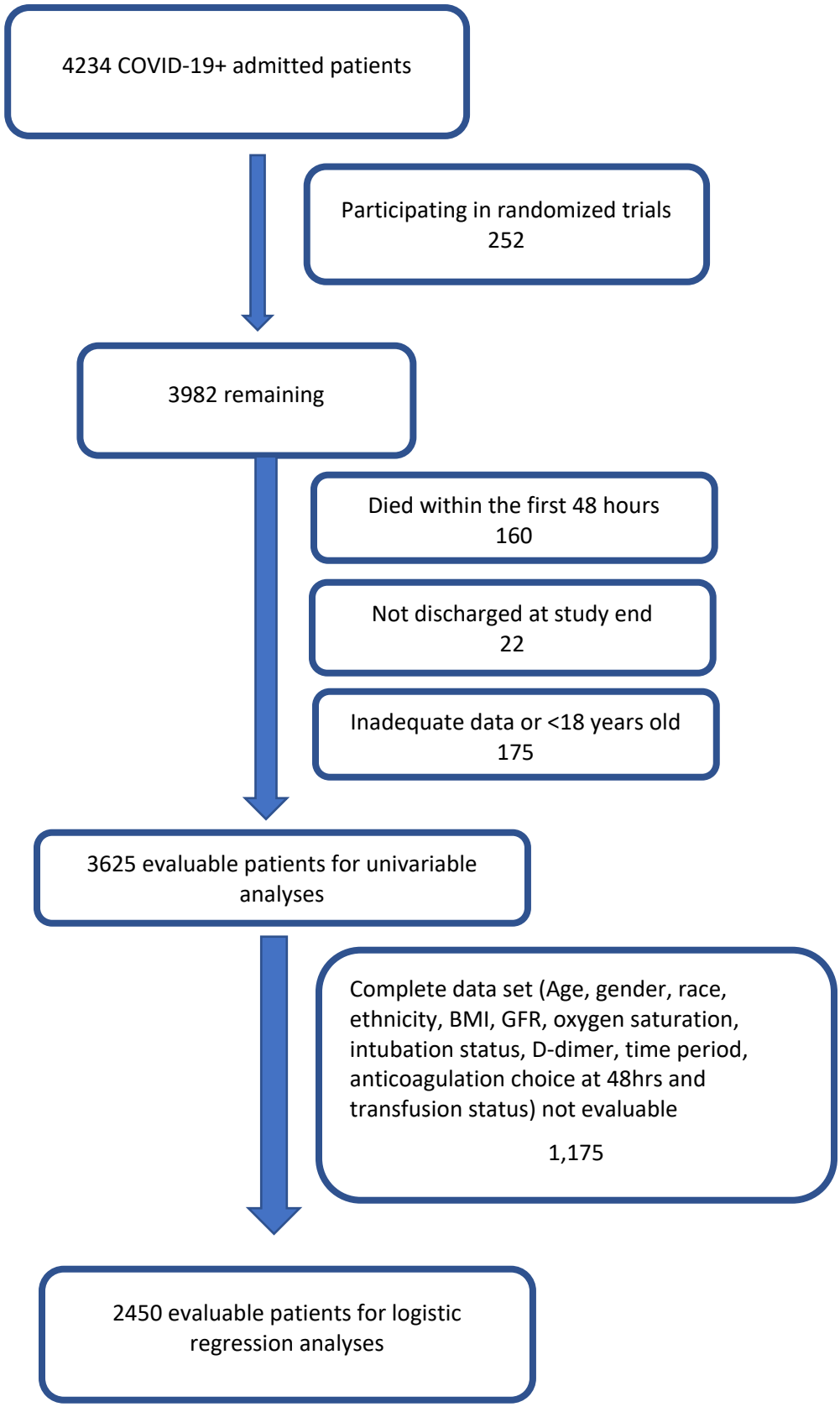
Bleeding as Defined by Transfusion Requirement			
	OR	95%CI	p
None	1.00		
Apixaban Prophylaxis	0·68	0·31 - 1·50	0·34
Apixaban Full Therapy	0·79	0·40 - 1·57	0·51
Enoxaparin Prophylaxis	0·68	0·32 - 1·44	0·31
Enoxaparin Full Therapy	1·31	0·51 - 3·36	0·58
UFH Std Prophylaxis	0·87	0·43 - 1·74	0·69
UFH High Prophylaxis	0·69	0·26 - 1·79	0·45
UFH Full Therapy	1·01	0·40 - 2·53	0·99

Figure 1. Cumulative mortality according to time period on presentation

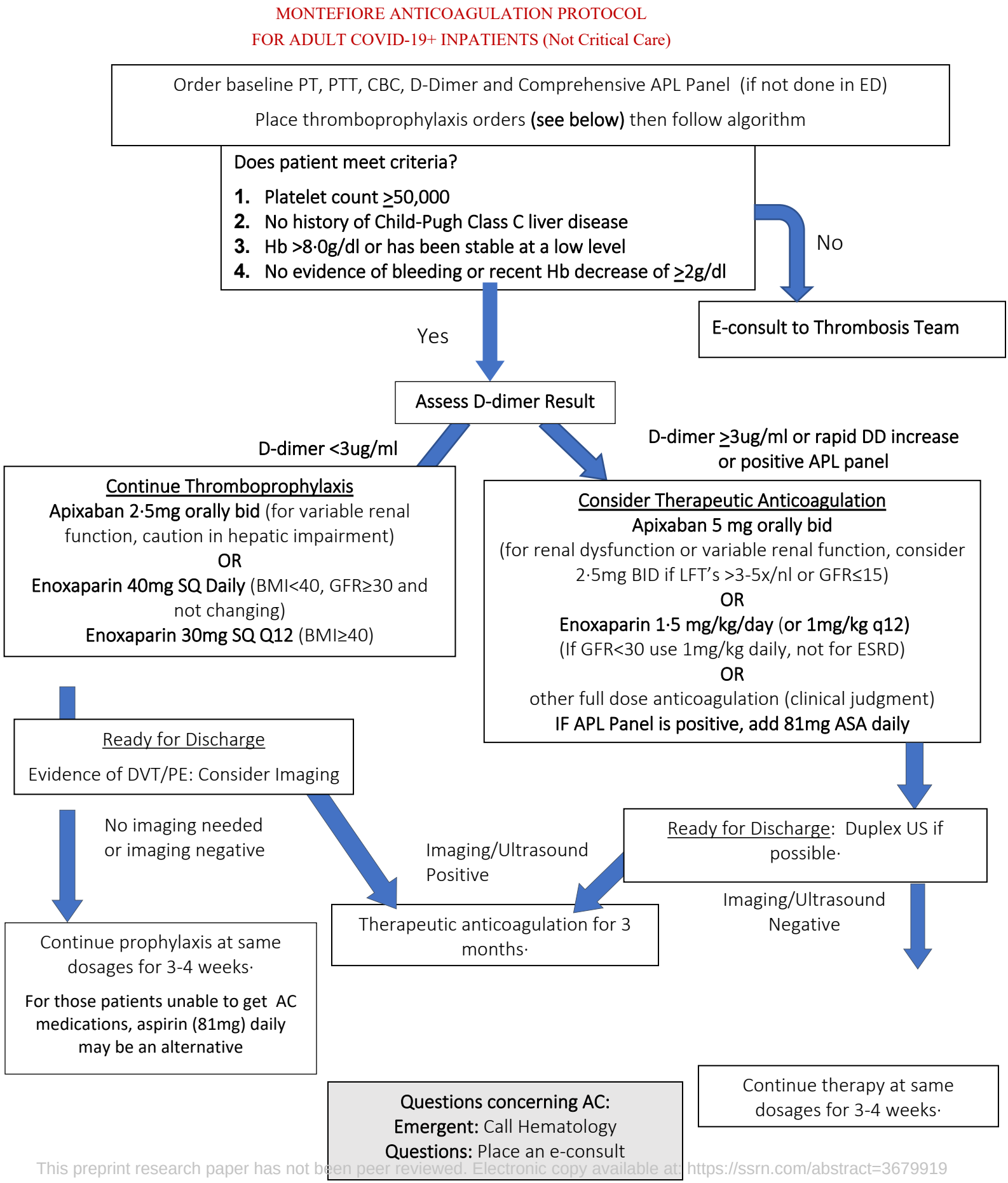


Time Period					
1	759	618	584	578	576
2	1666	1388	1307	1272	1267
3	797	714	672	661	658
4	369	350	322	268	161

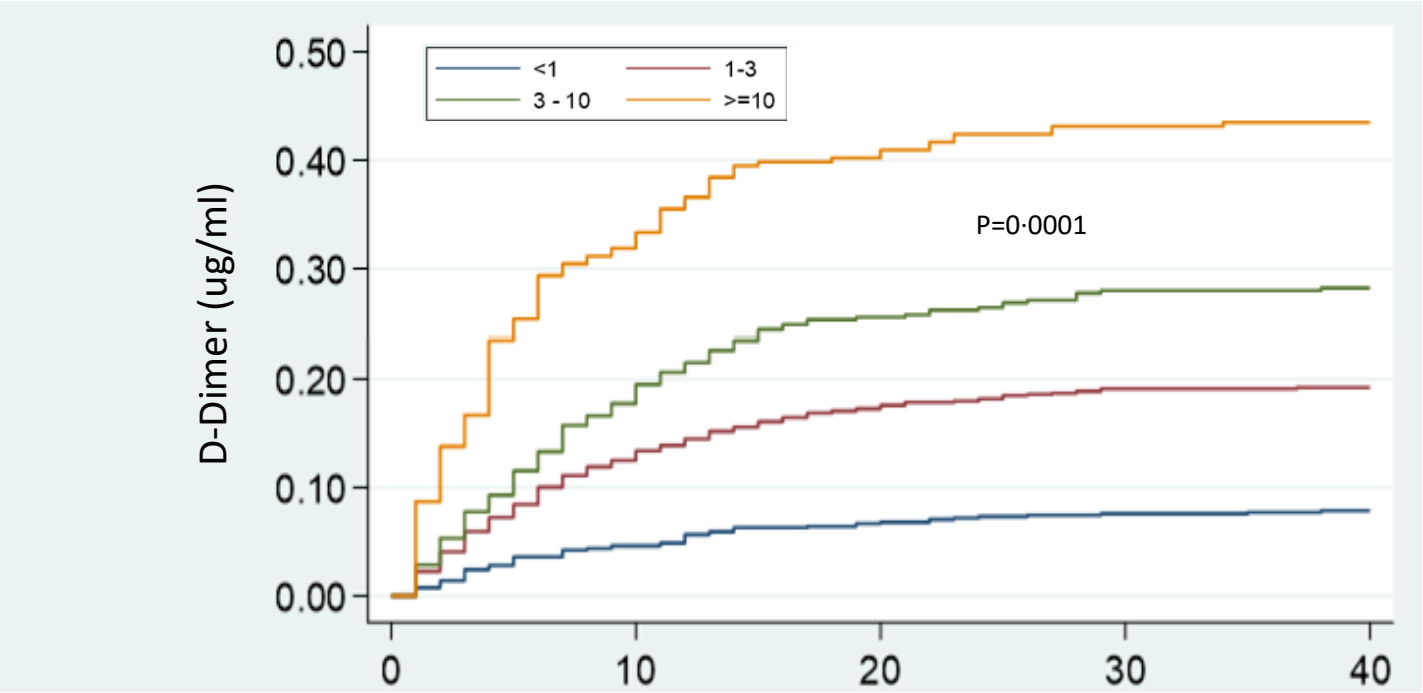
Supplementary Figure S1: Consort diagram for study



Supplemental Figure S2. Anticoagulation Protocol



Supplemental Figure S3· Cumulative mortality according to initial D-dimer value



D-dimer (ug/ml)						
	<1	778	742	722	699	661
	1-<3	1008	882	823	781	745
	3-<10	451	371	335	320	304
	>10	276	188	165	155	149

Supplementary Table S1· Classification of anticoagulation regimens

Route	Drug	Prophylactic dosing	Therapeutic dosing
Oral	Warfarin	None#	any dose#
	Rivaroxaban	10 mg daily#	10 mg bid,15 mg daily, 15mg bid, 20 mg bid#
	Apixaban (GFR≥30)	2·5 mg bid	5 mg bid
	Apixaban (GFR<30)	2·5 mg bid	2·5 mg or 5mg bid
SC	Enoxaparin (GFR≥30)	≤0·5mg/kg bid or ≤1·0 mg/kg daily	≥1mg/kg bid or ≥1·5mg/kg daily
	Enoxaparin (GFR<30)	≤0·35mg/kg bid or ≤0·7 mg/kg daily	≥ 0·7mg/kg bid or ≥1 mg/kg daily
	Enoxaparin no weight adjustment	30-60 mg daily	none
	UFH	4,000 IU - 10,000 units bid or tid	none
IV	UFH	none	any dose
	Bivalirudin	none	any dose
	Argatroban	none₸	any dose₸
	TPA (tissue plasminogen activator)	none₸	any dose₸
	Desirudin	none₸	any dose₸

Too few patients in each category - all collapsed into therapeutic category with warfarin as "Rivwarf" and excluded from most analyses·
₸ Deleted due to fewer than 5 patients

Supplementary Table S2· Drug choice and indication

Therapy	No Anticoagulation	Prophylaxis Standard Dose	Prophylaxis High Dose	Therapy	Total
Apixaban	0	554	0	474	1028 (28·4%)
Enoxaparin	0	748	0	84	832 (23·0%)
Heparin Standard	0	796	0	0	796 (22·0%)
Heparin High Dose	0	0	176	0	176 (4·9%)
IV Heparin	0	0	0	79	79 (2·2%)
Other	0	2	0	73	75 (2·1%)
No Anticoagulation	639	0	0	0	639 (17·6%)
Total	639 (17·6%)	2100 (57·9%)	176 (4·9%)	710 (19·6%)	3625 (100%)

Supplemental Table S3· Chosen therapy by first D-dimer within 48 hours of admission

	D-dimer Level (ug/ml)					
	<1	1-3	>3-10	>10	No D-dimer obtained	Total
No therapy	105 (13·5%)	116 (11·5%)	57 (12·5%)	38 (13·7%)	323 (29·4%)	639 (17·6%)
Apixaban Prophylaxis	211 (27·1%)	264 (26·1%)	26 (5·7%)	17 (6·1%)	36 (3·3%)	554 (15·3%)
Apixaban Therapy	59 (7·6%)	128 (12·6%)	166 (36·3%)	77 (27·7%)	44 (4·0%)	474 (13·1%)
Enoxaparin Prophylaxis	223 (28·6%)	222 (21·9%)	67 (14·7%)	27 (9·7%)	209 (19·0%)	748 (20·6%)
Enoxaparin Therapy	6 (0·8%)	17 (1·7%)	32 (7·0%)	25 (9·0%)	4 (0·4%)	84 (2·3%)
UFH Prophylaxis	122 (15·7%)	193 (19·1%)	57 (12·5%)	55 (19·8%)	369 (33·6%)	796 (22·0%)
UFH HD Prophylaxis	26 (3·3%)	44 (4·3%)	22 (4·8%)	6 (2·2%)	78 (7·1%)	176 (22·0%)
UFH Therapy	9 (1·2%)	17 (1·7%)	17 (3·7%)	28 (10·1%)	8 (0·7%)	79 (2·2%)
Other	18 (2·3%)	12 (1·2%)	13 (2·8%)	5 (1·8%)	27 (2·5%)	75 (2·2%)
Total for D-dimer Category	779	1013	457	278	1098	3625
% of Total	21·5%	27·9%	12·6%	7·7%	30·3%	100·0%