
Christopher Michael D'Amico

Follow this and additional works at: https://dc.uthsc.edu/himappliedresearch

Part of the Health and Medical Administration Commons, Health Information Technology Commons, Hemic and Lymphatic Diseases Commons, Investigative Techniques Commons, Therapeutics Commons, and the Virus Diseases Commons
Intermediate Anticoagulation Dosing in COVID-19 ICU Patients:
Evaluation Comparing Ventilated vs Non-Ventilated Populations

Christopher M. D’Amico, BS, PharmD Candidate
University of Tennessee Health Science Center
Master of Health Informatics and Information Management
Advisor: Sajeesh Kumar, PhD
November 19, 2021
Acknowledgements

I would like to thank Dr. Kyle Allmond for his devoted work and clinical guidance, Dr. Sajeesh Kumar for keeping me focused and on track to complete this study, my loved ones and family members for their never-ending support (especially my father who always believed in me), and lastly, I want to thank the University of Tennessee College of Pharmacy for placing me in this position to have the opportunity to achieve a PharmD and MHIIM.
Abstract

Surges of COVID-19 have been seen to place large numbers of patients into the ICU. Establishing standards of care is critical not only for patient care, but to also implement a baseline of therapy to build upon with future research. COVID-19 produces a hypercoagulable state resulting in higher occurrences of clotting such as deep vein thrombosis (DVT), and pulmonary embolism (PE). Anticoagulation medications thin the blood to combat this aspect of the disease from occurring but does so at the risk of increasing bleeding potential. The purpose of this study is to evaluate the risk/benefit of anticoagulation usage between ventilated and non-ventilated COVID-19 ICU patients as both bleeding and clotting are linked to worsened outcomes. A retrospective analysis reviewed 103 COVID (+) intensive care unit (ICU) patients with approved standardized COVID anticoagulation from August 2020 through January 2021 at a small community hospital. Patient data was obtained by navigating through Citrix Visual Apps including Pharmacy, NextGen EHR, and Paragon Clinician Hub. Pros and cons observed in EHR navigation were reflected upon in Chapter 5. Primary goal is to compare the endpoint of thrombotic events along with secondary outcomes of bleeding and overall mortality between ventilated and non-ventilated patients. Chi-square tests and two-sided t-tests were utilized in obtaining significance. Significance was defined as p<0.05 and confidence interval of 95%.

This study found ventilated patients experienced significantly more clotting (30 vs 15, p = 0.0003) in addition to higher bleeding rates (14 vs 5; p = 0.0138) and worse mortality (24 vs 11; p = 0.0016). There were no significant differences with number of prophylactic or intermediate anticoagulants given between groups. Treatment heparin was used significantly more in the ventilated group, but this was due to the higher rates of thrombosis being treated. Apixaban treatment and enoxaparin intermediate dosing resulted in the highest prevalence of thrombotic events (30.3%, 29.41% prospectively) while heparin treatment accounted for the highest prevalence of bleeding events (17.39%). Overall, this study displays a potential need for higher anticoagulation in COVID-19 ICU ventilated patients at the risk of bleeding. Future studies required include regression analysis on treatment heparin PTT and enoxaparin Xa levels and associated thrombosis/bleeding events in ventilated patients.
Table of Contents

Acknowledgements ................................................................. 2
Abstract ................................................................. 3
Definition of Terms & Acronyms ................................................. 5
List of Tables ................................................................. 6
List of Figures ................................................................. 6
Chapter 1: Introduction .......................................................... 7
  Background of the Problem ................................................. 9
  Thrombosis Risk Factors .................................................... 9
  Bleeding Risk Factors ...................................................... 10
  COVID-19 Biomarkers ..................................................... 11
  Purpose of the Study ...................................................... 12
  Significance of the Study ................................................. 13
Chapter 2: Literature Review .................................................... 14
  Methods ................................................................. 14
  Findings ................................................................. 15
  Conclusion ................................................................. 15
Chapter 3: Methods ............................................................... 17
  Research Design ........................................................ 17
Chapter 4: Results ............................................................... 19
Chapter 5: Conclusion ........................................................... 23
  Health Informatics Discussion ........................................... 24
  Limitations to Study ...................................................... 24
References ................................................................. 25
## Definition of Terms and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA81</td>
<td>Aspirin 81 mg; “Baby Aspirin”</td>
</tr>
<tr>
<td>CRP</td>
<td>C-Reactive Protein; COVID-19 inflammatory biomarker</td>
</tr>
<tr>
<td>DOAC</td>
<td>Direct-Acting Oral Anticoagulants</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep Vein Thrombosis</td>
</tr>
<tr>
<td>EHR</td>
<td>Electronic Health Record</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>Bleeding risk score assessment for patients on blood thinning medications for atrial fibrillation; Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history, Labile INR, Elderly, Drugs/Alcohol.</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act of 1996; patient consent and patient health information protection</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IT</td>
<td>Information Technology</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase; COVID-19 inflammatory biomarker</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low Molecular Weight Heparin</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
</tr>
<tr>
<td>PHI</td>
<td>Protected Health Information</td>
</tr>
<tr>
<td>PLT</td>
<td>Platelets</td>
</tr>
<tr>
<td>PPX</td>
<td>Prophylactic dosing</td>
</tr>
<tr>
<td>TX</td>
<td>Treatment dosing</td>
</tr>
<tr>
<td>UFH</td>
<td>Unfractionated Heparin</td>
</tr>
</tbody>
</table>
List of Tables

1) Anticoagulation Dosing Protocol .............................................................. 8
2) Risk factors with known association to thrombosis .................................. 10
3) Charted medications with known additive bleeding risk .......................... 11
4) Literature Review ..................................................................................... 16
5) Population Demographics and Admission Laboratory Values .................. 19
6) Thrombosis and Bleeding Risk Factors .................................................... 20
7) Endpoint Results and Anticoagulant Medication Usage ............................ 21

List of Figures

1) Patients Who Experienced Bleeding/Thrombosis While on Specific Anticoagulant ................................................................................................................. 22
Intermediate Anticoagulation Dosing in COVID-19 ICU patients:
Evaluation Comparing Ventilated vs Non-Ventilated Populations

Chapter 1: Introduction

The past year and a half has been shaped and defined by the pandemic of COVID-19. Healthcare around the world tested, and professionals seeking answers to deliver the highest quality of care possible. Even after over a year of COVID-19, there are still many questions that need to be confirmed. The nature of COVID-19 increases a patient’s blood to clot. A blood clot is a mass or clump of blood cells that blocks a blood vessel. The body will naturally make blood clots as a response to trauma to stop bleeding, but undesired clotting can lead to devastating outcomes including death. The exact mechanism of how COVID-19 increases coagulability of blood is not fully confirmed, but the theory is antibodies being produced as part of the immune response increases clotting activity leading to a higher chance to produce clots (Abou-Ismail, Diamond, Kapoor, Arafah, & Nayak, 2020). These clots can form in different places in the body including the lungs (leading to impaired breathing and lung function) and kidneys (impaired kidney function resulting in accumulation of toxins and drugs).

To help combat this higher coagulable state being produced in hospitalized patients, anticoagulants are prescribed. Anticoagulants are a class of medications that reduce the ability of the blood to coagulate and form a clot. Even in those without COVID-19, Chest Guidelines support anticoagulation in hospitalized patients with increased risk of thrombosis such as reduced mobility or history of VTE (Kahn, et al., 2012).

Typically seen medications include Unfractionated Heparin (UFH), Low Molecular Weight Heparins (LMWHs) such as Enoxaparin, and Direct-Acting Oral Anticoagulants (DOACs) such as Eliquis and Xarelto. The dosing of these are divided into prophylactic dosing and treatment dosing. Prophylactic dosing means the medication is given at a lower dose to help prevent a clot from forming. Treatment doses of anticoagulants are used in patients who have experienced a clot. Whether creating order sets, guidelines, or verifying prescriptions, it is
important to comprehend the differences in dosing as anticoagulants have different dosing based on desired effect and indication.

The American Thoracic Society (ATS) and American College of Chest Physicians first published guidelines regarding prevention of VTE in patients with COVID-19 in June 2020. Optimal strategies were noted to be sparse with little evidence-based guidelines in the COVID-19 population. Nonetheless, the expert panel suggested anticoagulant thromboprophylaxis over no anticoagulant. In critically ill population, low molecular weight heparins (LMWHs) were suggested over unfractionated heparin (UFH) in patients with CrCl > 30 mL/min. The reasoning behind this was to limit staff exposure as opposed to drug-disease correlation; LMWHs require once or twice a day dosing while UFH is dosed 3 times a day. During the study’s focused timeline, observational data displayed increased VTE risk in critically ill COVID-19 patients, there was not clear data regarding further VTE risk. A theorized intermediate dosing (shown in Table 1) was studied at Brigham Health, finding that ICU patients were at a 1.5-2 x higher relative risk for VTE compared to ward patients (Connors & Levy, 2020). These dosing protocols will be seen in this study as well, because at the time, this was the most up to date information regarding VTE prophylaxis. Current guidelines suggest using standard prophylaxis dosing of anticoagulants for thromboprophylaxis over intermediate or full treatment dosing for all COVID-19 patients.

**Table 1: Anticoagulation Dosing Protocol**

<table>
<thead>
<tr>
<th>Prophylaxis → Intermediate dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin (SQ):</td>
</tr>
<tr>
<td>Standard</td>
</tr>
<tr>
<td>Obese (&gt;40 BMI)</td>
</tr>
<tr>
<td>Underweight</td>
</tr>
<tr>
<td>Heparin (SQ):</td>
</tr>
<tr>
<td>Standard</td>
</tr>
<tr>
<td>Obese (&gt;40 BMI)</td>
</tr>
<tr>
<td>Treatment Dosing</td>
</tr>
<tr>
<td>Enoxaparin (SQ)</td>
</tr>
<tr>
<td>Heparin (IV)</td>
</tr>
</tbody>
</table>
Background of the Problem

Because both COVID-19 and critically-ill status increase thrombosis risk, clinicians have theorized the need for stronger anticoagulation dosing. At the small community hospital hosting the patient data for this study, an intermediate dosing guideline had been enabled for the majority of patients admitted to the ICU with COVID-19. As seen in Table 1, the intermediate dosing is designed to be a Goldilocks regimen between prophylactic and treatment dosing. As studies continue to be produced, the reviews on intermediate vs prophylactic dosing is mixed. Some studies have shown mortality benefit while others found no mortality benefit. Experts and hospital protocols are not standardized to a single guideline or protocol. Furthermore, guidelines on ventilated patients are not fully established either.

Thrombosis Risk Factors

Although COVID-19 is linked to higher DVT risk, there are baseline factors that need to be accounted for. Table 2 illustrates risk factors that are associated with an increase in thrombosis risk. Increasing age has mixed results as a risk factor. The question becomes if older age is the contributing factor to increasing DVT risk, or if increasing age means more comorbidities in addition to worsening progression of those comorbidities that influence DVT risk. Although patients can have many of these additive risk factors, anticoagulation is not added as a therapy. The exception is for the highlighted section in Table 2; patients who have a history of DVT/PE, Atrial Fibrillation, or Genetic dispositions are subject to chronic anticoagulation measures, typically with Direct-Acting Oral Anticoagulants (DOACs). Because of these additive risks, the study will document and analyze these risk factors to obtain the study population's overall baseline.

It would be remiss of this study to not discuss life-saving counseling points regarding clotting. For those that are experiencing a clot, the symptoms experienced alter based on location. If a clot forms in the legs or arms (DVT), the area around the clot will be painful, warm to touch, and begin to swell. If the clot forms in the lungs, also known as a pulmonary embolism, the patient will experience difficulty in breathing along with chest pain. Pulmonary embolisms elute similar symptoms compared to COVID-19. This is why imaging is important to help differentiate the two diagnoses. Lastly, if a clot forms in the brain (stroke), the patient will
complain of the worst headache they have ever had, impaired speech, and drooping of one side of the face. It is important as healthcare providers to educate patients on these signs and symptoms so that treatment can be provided as quickly as possible. Knowing the signs and symptoms clotting in patients also assist health professionals including IT to detect this dangerous event when analyzing patient histories.

**Table 2: Risk factors with known association to thrombosis**

<table>
<thead>
<tr>
<th>Thrombosis Risk Factors</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Smoking</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Obesity</td>
<td>Cancer</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>History of DVT/PE</td>
</tr>
<tr>
<td>Lung Disease</td>
<td>History of Atrial Fibrillation</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>Genetic Factors (ie. Factor V Leiden)</td>
</tr>
</tbody>
</table>

**Bleeding Risk Factors**

All this discussion about the dangers of thrombosis and its association with COVID, why not just give anticoagulants to everyone? Although a patient may have multiple factors that were discussed above to be treated for DVT prophylaxis, the risk of suffering a bleed may outweigh the benefit. Evaluating bleeding risk becomes highly important when discussing anticoagulation treatment for a patient. There are multiple scoring calculators that can be utilized to evaluate bleeding risk including HAS-BLED. The factors which HAS-BLED accounts for includes: age >65, hypertension, renal disease, liver disease, stroke history, previous history of bleeding, labile INR, additive medications (see Table 3), and excessive alcohol usage. Each point increases the patient’s risk for bleeding. A score of 3+ means the patient is at high risk of bleeding and may require alternatives to anticoagulation (Kooiman, et al., 2015).

Evaluation of bleeding determines the concerned adverse effect of anticoagulation. Because anticoagulation is thinning the blood, the patient becomes more susceptible to bleeding. Clinically important bleeding is associated with higher mortality and longer ICU stay (4-8 days) for those on the ventilator for > 48 hours (Cook, et al., 2001). The purpose of thinning the blood is to reduce the likelihood of a DVT/PE.
Table 3: *Charted medications with known additive bleeding risk*

<table>
<thead>
<tr>
<th>Medications with Additive Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiplatelets:</strong></td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>Aspirin, Ibuprofen, Meloxicam, Ketorolac, Naproxen</td>
</tr>
<tr>
<td>P2Y12 Inhibitors</td>
</tr>
<tr>
<td>Clopidogrel, Ticagrelor, Prasugrel</td>
</tr>
<tr>
<td><strong>Antidepressants:</strong></td>
</tr>
<tr>
<td>SSRIs</td>
</tr>
<tr>
<td>Citalopram, Escitalopram, Sertraline, Fluoxetine, Paroxetine</td>
</tr>
<tr>
<td>SNRIs</td>
</tr>
<tr>
<td>Duloxetine, Venlafaxine</td>
</tr>
</tbody>
</table>

Bleeding can also arise during or after thrombosis treatment. This is due to the stronger dosing utilized for treatment. Higher doses of anticoagulants will increase the bleeding risk even further. One example of this occurrence is a patient develops a DVT in one of the legs. Heparin drip is initiated to treat the DVT. After a couple days, the patient develops dark stools and is experiencing a gastric bleed. These situations are challenging to manage and are typically handled on a case-by-case basis. Nonetheless, gathering insight on how often this occurs may propose future studies in this area along with other precipitating factors that impact anticoagulation management.

**COVID-19 Biomarkers**

There are certain irregularities that continuously appear in COVID-19 patients. These include elevated lab values of CRP, LDH, Ferritin, D-Dimer, and Fibrinogen. Increases in CRP, D-Dimer, and LDH were associated with worse outcomes and more severe COVID. These biomarkers can guild the clinician on how severe a patient’s illness is beyond symptomology, thus were collected to assist in determining severity of COVID19 upon admission along with ventilation, pressor, and paralytic status.

C-reactive protein (CRP) is a biomarker produced by the liver typically seen with systemic inflammation. CRP levels in the serum rises rapidly with disease onset, and it plays a crucial step in part of immune complement activation. Multiple studies on CRP has shown association with worsening prognosis in COVID-19 patients. European Heart Journal published an article demonstrated patients with CRP levels higher than the study’s median (10.8 mg/dL) were significantly associated with VTE (8.3% vs 3.4%), acute-kidney injury (43% vs 28.4%),
critical illness (47.6% vs 25.9%), and mortality (32.2% vs 17.8%) when compared to patients with a CRP below the median (Smilowitz, et al., 2021). Based on these results the study will use 10 mg/dL as the comparative cutoff.

Lactate dehydrogenase (LDH) is a protein found in most cells involved with energy production. LDH is utilized as a biomarker for cell or tissue damage. When damage occurs, LDH will be released from the cells into the serum, resulting in elevated levels. Elevated LDH for the purpose of this study is defined as a value above 250 U/L. This reflects the pooled analysis from the American Journal of Emergency Medicine (Henry, et al., 2020). Their findings of elevated LDH in association to COVID-19 includes a 6-fold increase in odds of developing severe disease and a 16-fold increase in odds of mortality.

Another biomarker associated with the inflammatory response is ferritin, a protein that is used in the body to store iron and protect it from oxidation. Ferritin can be used as a predictor for cytokine storm as well as progression for critical illness (Lino, et al., 2021). Based off Lino’s study and cited meta-analysis on hyperferremia, a ROC curve analysis was conducted finding a cut off value of 1873 ng/mL.

Related to coagulability of COVID-19, D-Dimer and Fibrinogen are often elevated in patients presenting with COVID-19. D-dimer is a protein that is found after a blood clot undergoes degradation with fibrinolysis. Elevated values not only are corelated with the patient potentially experiencing a thrombosis, but also is associated with worse mortality and severity of illness. The Diabetes & Metabolic Syndrome: Clinical Research & Reviews published an article showing significantly worse mortality in hospitalized COVID-19 patients with D-Dimer levels > 2.01 equating a 4-fold increase (Soni, Gopalakrishnan, Vaishya, & Prabu, 2020).

**Purpose of the Study**

The focus of the study is to retrospectively evaluate the anticoagulation usage amongst ICU patients with COVID-19. As stated earlier, current guidelines suggest only prophylactic dosing of anticoagulation. This study will examine outcomes related to intermediate dosing amongst COVID-19 ICU ventilated and non-ventilated patients. Primary study questions to evaluate include:
1) In ICU patients who received anticoagulation, are there significant differences in primary & secondary outcomes between ventilated and non-ventilated patients?

2) Are there significant differences in COVID-19 admission biomarkers between ventilated and non-ventilated ICU patients?

3) Are there significant differences between different anticoagulants and associated primary & secondary outcomes?

These questions concentrate on both the safety and efficacy endpoints of anticoagulation. Questions related to ventilated vs non-ventilated will potentially distinguish differences in anticoagulation needs. Question 3 examines efficacy (thrombosis prevention) and adverse effects (bleeding) between different anticoagulation regimens and medications.

Understanding how to search through healthcare systems and collecting patient data from EHR is essential in practicing informatics in the healthcare setting as a pharmacist. Due to the nature of this study, it also serves as a platform to demonstrate learned skills in informatics coursework through health data collection, proper management of PHI abiding by HIPAA, and statistical analysis.

**Significance of the Study**

With the latest surge occurring with COVID-19, understanding drug regimens and therapies from the previous surge are critical in avoiding mistakes previously made in the medical community. Now that there is concrete data available with months of patient cases to analyze, a foundational therapy can be established and/or confirmed for the future. By reviewing previous literature and comparing to hospital protocols, there can be a discussion on the risk/benefit of anticoagulation along with differences in dosing (prophylactic vs intermediate vs treatment).
Chapter 2: Literature Review

COVID-19 has been highly scrutinized due to the shortcuts made with research and studies in order to find a treatment to save lives. The first blunder was seen with Hydroxychloroquine + Azithromycin as a treatment option. As the United States witnessed the healthcare system strained by COVID-19, with loved ones dying, emotional motivation pushed incomplete research and trials as temporary standards to give severe covid-19 cases a fighting chance. Ultimately, the reverse occurred; people were harmed with undesired side effects and unproven benefits to treating COVID-19. Now that the dust has settled, primary literature is being conducted more consistently and appropriately. That is why a proper literature review is required to understand current and updated standards being implemented regarding anticoagulation.

Method

The approach for this literature review included utilizing the University of Tennessee database library. The objective was to search for different journal articles that demonstrated bleeding risks, mortality, and/or benefit in anticoagulation usage not only in COVID-19 ICU patients, but ICU patients as well. Anticoagulation studies for ICU patients prior to COVID-19 provide a baseline for established guidelines, safety, and dosing. Three databases utilized were: PubMed, JAMA Network, and Cochrane Library. Terms used in the search engines included variations of MESH terms such as COVID-19, anticoagulation, ICU, bleeding, ventilated, and DVT. To account for differences in guidelines while adding validity to the review, search results were limited to 2 years for COVID-19 while limiting ICU anticoagulation articles to the past 5 years. Combination of MESH terms were utilized to narrow results to less than 100 articles. From there for each database, articles were chosen from the first 10-20 search results that yielded the highest relevancy to the study. Articles selected also needed to meet the following inclusion criteria:

1) Articles and studies written in English

2) Studies were conducted in the United States. Meta analysis studies require at least majority United States with rest still in developed countries
3) Scientific literature; not opinion-based, blogs, editorials

Table 4 outlines the articles reviewed. One additional article was included for review that was not randomized. The study “HOPE-COVID19” revealed mortality benefits for ventilated and respiratory failure patients, but not hospitalized and noninvasive ventilation patients (Santoro, et al., 2021). HOPE-COVID19 stood out as the closest and most recent evidence published regarding ICU ventilated patients.

Findings

Based on the results of the literature review, 3 articles included comparisons of prophylactic dosing vs intermediate or treatment dosing. These studies did not support the need for intermediate dosing as mortality benefit was not documented at the risk of having increased bleeding potential. The rates of thrombosis in the setting of COVID-19 did show increased thrombosis rates as well as elevated D-Dimer values. Older age and obesity was associated with worse outcomes. DVT and thrombosis rates varied greatly between institutions. Bleeding occurrences varied and occurred less, with the highest being 11%. The presence of meta-analysis on risk factors and associations with COVID were plentiful, but direct head-to-head studies on therapeutic agents were still being investigated. The standard of care for COVID-19 continues to evolve, which makes these types of trials hard to conduct or remain relevant to account for current standards.

Conclusion

The supporting evidence for the use of prophylactic dosing over intermediate matched current ATS thrombosis guidelines. The need for future head-to-head studies are needed to create a consistent care plan for the critically ill with COVID-19. Hasan et al. highlighted the need for individualized care as opposed to set guidelines and strict order sets. Considering how often guidance in COVID-19 patient care is changing, along with the need for individualized care, informatic pharmacists should promote order sets for physicians that are more rigorously updated than established treatments and provided the freedom to choose multiple different medications.
### Table 4: Literature Review

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Database</th>
<th>Objective, Comparative Groups</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flumignan et al.</td>
<td>Cochrane</td>
<td>Assess effects of prophylactic anticoagulants versus active comparator</td>
<td>Insufficient evidence from RCT reviews to determine risks/benefits of prophylactic hospitalized patients with COVID-19.</td>
</tr>
<tr>
<td></td>
<td>Library</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warrior et al.</td>
<td>Cochrane</td>
<td>Retrospective analysis comparing incidence of DVT in COVID-19 patients</td>
<td>10.9% of 1265 patients had thromboembolism from March 2020 – June 2020 at institute. Thrombosis resulted in significantly higher mortality (31.9% vs 10%, p&lt;0.001). No difference in mortality between prophylactic and treatment enoxaparin doses (40.5% vs 51.7% p = 0.3491).</td>
</tr>
<tr>
<td></td>
<td>Library</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pai et al. (2018)</td>
<td>Cochrane</td>
<td>PROTECT Trial subgroup analysis: ESRD patients and thromboprophylaxis</td>
<td>118 patients with dialysis dependent ESRD found no significant different in DVT (8.3% vs 8.6%, p = 0.76) or major bleeding (8.9% vs 11%, p = 0.66) between UFH and Dalteparin (LWMH).</td>
</tr>
<tr>
<td></td>
<td>Library</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bikdeli et al.</td>
<td>JAMA network</td>
<td>INSPIRATION trial results: intermediate-dose vs standard dose prophylaxis in COVID-19 ICU patients</td>
<td>562 patients; intermediate-dose did not reduce composite death, treatment with ECMO, or VTE at 90-day follow up when compared to standard-dose prophylaxis</td>
</tr>
<tr>
<td>Jimenez et al.</td>
<td>PubMed</td>
<td>VTE and Bleeding incidence amongst hospitalized COVID-19 patients</td>
<td>15 pooled studies: 17% VTE incidence; 7.8% Bleeding incidence. Highest bleeding reported for patients receiving intermediate or full dose anticoagulation (21.4%)</td>
</tr>
<tr>
<td>Hassan et al.</td>
<td>PubMed</td>
<td>Prophylactic or treatment anticoagulation in critically ill COVID-19 patients</td>
<td>Meta analysis including 12 studies. Overall resulted in high thromboprophylaxis failure, leading to individualized rather than protocolized VTE prophylaxis (pooled prevalence of VTE = 31%)</td>
</tr>
<tr>
<td>Gorlinger et al.</td>
<td>PubMed</td>
<td>COVID-19 Coagulopathy and Inflammatory Response</td>
<td>This article highlights COVID-19 characteristics and biomarkers. D-Dimer &gt; 1ug/mL and older age associated with in-hospital death. D-Dimer with &gt;3 ug/mL treated with UFH resulted in significant reduction in 28-d mortality (32.8% vs 52.4%, p = 0.017).</td>
</tr>
<tr>
<td>Santoro et al.</td>
<td>Online Clinical Investigation</td>
<td>[HOPE-COVID19]: ICU Ventilated and Non-Ventilated Anticoagulation</td>
<td>5838 patients with COVID-19; in those with respiratory failure, mortality was lower (32% vs 42%, p &lt; 0.01) in those with anticoagulation. Anticoagulation associated with lower mortality in ventilated patients (53% vs 64%, p = 0.05), but not in non-ventilated patients (35% vs 38%, p = 0.40)</td>
</tr>
</tbody>
</table>
Chapter 3: Methods

This study was approved by the small community hospital’s Institutional Board Review (IRB) under Exempt Review as no patient identifiers were used and minimal harm was possible to patients whose information was collected from the study. Compliance with HIPAA and respecting patient privacy is of upmost importance when conducting this study. All information that is collected will be deleted and/or shredded. All patient identifiers excluded from data collection.

Research Design

The study is constructed as a retrospective analysis. The base population of the study is based around patients who were admitted to the ICU and diagnosed with COVID-19 during the period of August 1\textsuperscript{st}, 2020 through January 31\textsuperscript{st}, 2021. Timeframe includes the largest peak of concurrent COVID-19 patients experienced at the hospital in December 2020; that record has since been lapsed in August 2021. Starting the study in August 2020 also gives enough time since the beginning of the COVID-19 pandemic to have established standards of care. Early months included mixed and poor science literature nationwide including the use of hydroxychloroquine + azithromycin in addition to inconsistent anticoagulation usage.

The patient list was generated by obtaining patents who had an active CPOE order set approved for COVID anticoagulation. Because COVID(+) patients outside the ICU were also receiving anticoagulation, the patient list was separated into intensive care and floor. For a brief moment in December, the ICU was expanded to a few select floor rooms to accompany the surge demand. These patients were handpicked and included. A total of 103 patients were selected to be analyzed. All data collected was put into an Excel sheet on an internal drive on the hospital network to ensure information security.

The primary health applications from Citrix Visual Apps include: Pharmacy, NextGen EHR, and Paragon Clinician Hub. Each application served as a means to obtain specific information. The Pharmacy application provided all medication orders along with times administered. This offered the most accurate illustration of when anticoagulants were started, switched, and/or discontinued along with noting additive bleeding risk medications. NextGen accesses the outpatient EHR. Not every patient has been previous admitted to the hospital. If the patient had previously visited the
same healthcare network, their documents would be viewable including their social history, ongoing treatments, home medications, and previous diagnoses. Lastly Paragon Clinician Hub contains all the in-patient documents, medical records, and lab values. Admission lab values assessed COVID-19 biomarkers and severity of illness. Imaging reports confirmed thrombosis events experienced by patients. The “Documents” tab contained the patient’s hospital course including Critical Care progress notes. Each application has their strengths, and collectively serve to better enhance the providers care of the patient.

The excel sheet database was constructed to include mostly binary answers. Answering “No” to a question or topic would receive the input of “0”, and as expected, answering “Yes” would result in a “1” being placed. Using 0/1 binary language allows for consistency, quicker input, and less error prone with analysis. If “Yes / No” were to be used, a spelling error could occur or perhaps a capitalization difference resulting in left out information (yes/YES would not register if the function line included =“Yes”). A legend was created for excel sheets “Anticoag_Meds_Before_Bleed” and “Anticoag_Meds_Before_Thrombosis” to continue a number system and avoid potential spelling errors. Anticoagulants and associated dosing were assigned different single digit numbers for input; zero was added if the patient did have previous anticoagulation. Reasons for not having anticoagulation on board include: active bleeding, pending surgery, severe thrombocytopenia (<50,000 platelets), or newly admitted patient with no home anticoagulant. Patients who were diagnosed with a thrombosis with 48 hours along with positive thrombosis imaging had their anticoagulation status reflect their anticoagulation status at home. Although most patients are not therapeutically anticoagulated at home, there are those could be anticoagulated prior to visiting the hospital with Apixaban or Xarelto due to history of atrial fibrillation, history of pulmonary embolism/deep vein thrombosis, or genetic predispositions.

Rstudio was utilized for analyzing data. Significance was determined by p < 0.05 with a confidence interval of 95%. Two-sided t-tests and chi square tests are the backbone of determining significance for this study. T-tests were selected for data that included independent, continuous, and normal data with little skew between two groups. The groups commonly being compared were ventilated and non-ventilated. Chi square tests were conducted when comparing the two independent groups that utilized nominal data (binary, yes/no).
Chapter 4: Results

Among the 103 patients, 47 required to be mechanically ventilated during their stay while 56 did not require mechanical ventilation. Table 5 displays demographic and admission laboratory values pertinent to COVID-19 biomarkers differences between these two groups. Age and sex is not significantly different. 96.4% of the population is white. Length of stay was significantly higher in the ventilated population (20.49 vs 12.59 days; \( p = 0.0031 \)). For admission labs, only elevated LDH was significantly higher in the ventilated group (37 vs 27; \( p = 0.0094 \)).

**Table 5: Population Demographics and Admission Laboratory Values**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Population</th>
<th>Ventilated Pts on Anticoagulation</th>
<th>Non-Ventilated Pts on Anticoagulation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>103</td>
<td>47</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>68.2</td>
<td>67.6</td>
<td>68.7</td>
<td>0.6579</td>
</tr>
<tr>
<td>Sex (Male), %</td>
<td>70 (67.9%)</td>
<td>37 (66.1%)</td>
<td>33 (70.2%)</td>
<td>0.8129</td>
</tr>
<tr>
<td>Length of Stay, avg days</td>
<td>16.19</td>
<td>20.49</td>
<td>12.59</td>
<td>0.0031</td>
</tr>
</tbody>
</table>

Lab values upon Admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Population</th>
<th>Ventilated Pts on Anticoagulation</th>
<th>Non-Ventilated Pts on Anticoagulation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte, %</td>
<td>9.36</td>
<td>11.89</td>
<td></td>
<td>0.1174</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.70</td>
<td>1.95</td>
<td></td>
<td>0.5517</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>13.74</td>
<td>11.57</td>
<td></td>
<td>0.1847</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>1430.60</td>
<td>802.87</td>
<td></td>
<td>0.0624</td>
</tr>
<tr>
<td>PLT, K/mcL</td>
<td>211.77</td>
<td>196.32</td>
<td></td>
<td>0.4415</td>
</tr>
<tr>
<td>Elevated LDH &gt;250 U/L, %</td>
<td>63</td>
<td>37</td>
<td>27</td>
<td>0.0094</td>
</tr>
<tr>
<td>D-Dimer &gt; 3x upper-normal limit (1500 ng/mL), %</td>
<td>74</td>
<td>23</td>
<td>22</td>
<td>0.6923</td>
</tr>
<tr>
<td>PCT &gt; 0.5 ng/mL, %</td>
<td>32</td>
<td>13</td>
<td>19</td>
<td>0.5083</td>
</tr>
</tbody>
</table>

Comparison of thrombotic and bleeding risk factors between ventilated and non-ventilated patients are illustrated in Table 6. These factors were previously discussed in their association to increase risk of having a thrombotic or bleeding event. Overall, most baseline characteristics and
past medical history were not significantly different, except smoking was significantly higher in the non-ventilated group (23 vs 8; p = 0.0149).

Table 6: Thrombosis and Bleeding Risk Factors

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Population</th>
<th>Ventilated Pts on Anticoagulation</th>
<th>Non-Ventilated Pts on Anticoagulation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT Risk Factors</td>
<td>103</td>
<td>47</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>53 (51.5%)</td>
<td>23 (48.9%)</td>
<td>30 (53.6%)</td>
<td>0.7865</td>
</tr>
<tr>
<td>Obesity (&gt;30 BMI)</td>
<td>52 (50.5%)</td>
<td>26 (55.3%)</td>
<td>26 (46.4%)</td>
<td>0.4833</td>
</tr>
<tr>
<td>History of Smoking</td>
<td>31 (30.1%)</td>
<td>8 (17.0%)</td>
<td>23 (41.1%)</td>
<td>0.0149</td>
</tr>
<tr>
<td>History of Lung Disease</td>
<td>38 (36.9%)</td>
<td>14 (29.8%)</td>
<td>24 (42.9%)</td>
<td>0.2443</td>
</tr>
<tr>
<td>History of Heart Disease</td>
<td>61 (59.2%)</td>
<td>27 (57.4%)</td>
<td>34 (60.7%)</td>
<td>0.8927</td>
</tr>
<tr>
<td>History of Cancer</td>
<td>13 (12.6%)</td>
<td>6 (12.8%)</td>
<td>7 (12.5%)</td>
<td>1</td>
</tr>
<tr>
<td>History of Atrial Fibrillation</td>
<td>20 (19.4%)</td>
<td>6 (12.8%)</td>
<td>14 (25%)</td>
<td>0.1891</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>10 (9.7%)</td>
<td>3 (6.4%)</td>
<td>7 (12.5%)</td>
<td>0.339</td>
</tr>
<tr>
<td>Genetic Predispositions</td>
<td>1 (0.9%)</td>
<td>1 (2.1%)</td>
<td>0</td>
<td>0.4563</td>
</tr>
</tbody>
</table>

Bleeding Risk Factors

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Population</th>
<th>Ventilated Pts on Anticoagulation</th>
<th>Non-Ventilated Pts on Anticoagulation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>30 (29.1%)</td>
<td>14 (29.9%)</td>
<td>16 (28.6%)</td>
<td>1</td>
</tr>
<tr>
<td>History of Bleeding</td>
<td>5 (4.9%)</td>
<td>3 (6.4%)</td>
<td>2 (3.6%)</td>
<td>0.8406</td>
</tr>
<tr>
<td>History of Liver Disease</td>
<td>13 (12.6%)</td>
<td>5 (10.6%)</td>
<td>8 (14.3%)</td>
<td>0.579</td>
</tr>
<tr>
<td>Previous Stroke</td>
<td>9 (8.7%)</td>
<td>4 (8.5%)</td>
<td>5 (8.9%)</td>
<td>0.941</td>
</tr>
</tbody>
</table>

Shared Risk Factors

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Population</th>
<th>Ventilated Pts on Anticoagulation</th>
<th>Non-Ventilated Pts on Anticoagulation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Renal Disease (CKD Diagnosis)</td>
<td>37 (35.9%)</td>
<td>13 (27.7%)</td>
<td>24 (42.8%)</td>
<td>0.163</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80 (77.7%)</td>
<td>41 (87.2%)</td>
<td>39 (69.6%)</td>
<td>0.0577</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>6 (5.8%)</td>
<td>3 (6.4%)</td>
<td>3 (5.4%)</td>
<td>1</td>
</tr>
<tr>
<td>DVT Risk Factors, avg</td>
<td>3.90</td>
<td>3.64</td>
<td>4.13</td>
<td>0.2084</td>
</tr>
<tr>
<td>Bleeding Risk Factors, avg</td>
<td>1.75</td>
<td>1.76</td>
<td>1.73</td>
<td>0.8764</td>
</tr>
</tbody>
</table>

The primary endpoint of thrombosis was significantly higher in ventilated patients (30 vs 15; p = 0.0003). Secondary endpoints of bleeding (14 vs 5; p = 0.0138) and mortality (24 vs 11; p = 0.0016)
were also found to be significantly higher in ventilated patients. Paralytics were utilized in 25/47 (53%) of ventilated patients. Table 7 outlines the differences in anticoagulant agents used between ventilated and non-ventilated patients. Prophylactic and intermediate anticoagulant dosed medications did not significantly differ between the two groups. Treatment heparin was used significantly more in the ventilated group (27 vs 19; \( p = 0.0284 \)).

**Table 7: Endpoint Results and Anticoagulant Medication Usage**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Population</th>
<th>Ventilated Pts on Anticoagulation</th>
<th>Non-Ventilated Pts on Anticoagulation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombosis</strong></td>
<td>45 (43.7%)</td>
<td>30 (63.8%)</td>
<td>15 (26.8%)</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>19 (18.4%)</td>
<td>14 (29.8%)</td>
<td>5 (8.9%)</td>
<td>0.0138</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>35 (33.9%)</td>
<td>24 (51.1%)</td>
<td>11 (19.6%)</td>
<td>0.0016</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>39 (37.8%)</td>
<td>20 (42.5%)</td>
<td>19 (33.9%)</td>
<td>0.4871</td>
</tr>
<tr>
<td><strong>Pressors</strong></td>
<td>47 (45.6%)</td>
<td>40 (85%)</td>
<td>7 (12.5%)</td>
<td>7.491e-13</td>
</tr>
<tr>
<td><strong>Anticoagulants:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin PPX</td>
<td>27</td>
<td>15</td>
<td>12</td>
<td>0.3269</td>
</tr>
<tr>
<td>Enoxaparin PPX</td>
<td>15</td>
<td>8</td>
<td>7</td>
<td>0.7132</td>
</tr>
<tr>
<td>Eliquis PPX</td>
<td>14</td>
<td>6</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Heparin Intermediate</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>0.81</td>
</tr>
<tr>
<td>Enoxaparin Intermediate</td>
<td>51</td>
<td>26</td>
<td>25</td>
<td>0.378</td>
</tr>
<tr>
<td>Heparin TX</td>
<td>46</td>
<td>27</td>
<td>19</td>
<td>0.0284</td>
</tr>
<tr>
<td>Enoxaparin TX</td>
<td>21</td>
<td>14</td>
<td>7</td>
<td>0.0544</td>
</tr>
<tr>
<td>Eliquis TX</td>
<td>33</td>
<td>14</td>
<td>19</td>
<td>0.8129</td>
</tr>
</tbody>
</table>

Further data was collected regarding differences between anticoagulant medications and dosing. Figure 1 displays percentages of thrombosis and bleeding events for number of patients who received that anticoagulation. For example: Apixaban TX was ordered in 33 different patients; a
thrombosis was developed in 10 patients who were on apixaban tx at the time of diagnosis \((10/33 = 30.3\%)\).

**Figure 1: Patients Who Experienced Bleeding/Thrombosis While on Specific Anticoagulant**

Lastly, there were patients in the study deemed to have no anticoagulation at the time of their event. 13 patients suffered a thrombosis without prior anticoagulation. Majority of these patients were admitted within 48 hours and were not taking anticoagulants at home. 1 patient bled with no active anticoagulation medications.
Chapter 5: Conclusion

This study confirms many previously seen associations of ventilated patients including higher length of stay, higher thrombotic risk, and worse associated bleeding. Anticoagulants did not significantly differ between the two populations outside of treatment heparin (primary treatment medication for acute thrombosis). Because ventilated patients were experiencing more thrombotic events, stronger anticoagulation would be utilized to treat.

Prophylactic Enoxaparin resulted in no bleeding and no thrombotic events. This is most likely contributed to the fact that patients who are originally on the floor are started on a prophylactic regimen. These people are generally not as sick as they are either progressing to the ICU or are coming out of the ICU and deescalating anticoagulant therapy. Interestingly enough, treatment Apixaban dosing had the highest percentage of thrombotic events (30.3%) followed by intermediate enoxaparin (29.41%), which may lead to the thought of this patient population requiring stronger anticoagulant measures. However, Figure 1 confirms the risk of higher bleeding rates seen in treatment dosing as opposed to prophylactic and intermediate dosing. Overall, these trends confirm the currents thought of increasing anticoagulant may reduce thrombotic events, but in turn may increase bleeding potential, thus questioning the beneficial effect of the therapeutic change.

This study showed an overall insignificant difference in DVT and Bleeding risk factors. These lack of differences in baseline past medical history could be contributed providers potentially not being able to fully assess a thorough patient history. There are patients who came in abruptly with no outpatient documentation with the patient being admitted straight to the ICU, and under this situation it can be hard to obtain a complete patient history.

Overall, evidence is present that COVID-19 ICU ventilated patients experienced more thrombotic events. Logical progression would indicate that ventilated patients would require a stronger anticoagulation than floor or ICU non-mechanically ventilated patients. Although current guidelines state against using treatment anticoagulation, this study proposes the need for future investigations as to specific monitoring of treatment anticoagulant dosing parameters and associated bleeding thresholds in ICU ventilated patients. Consistent Xa level monitoring with enoxaparin tx and PTT with heparin tx.
Health Informatics Discussion

From an informatics perspective, one major takeaway from navigating EHR databases to obtain historical information is the need for a universal EHR or improvement to patient history documentation. Communication between professions and between facilities is still a primary weak spot in the US healthcare system. At times, patient data record was found to be highly time consuming to gather as well as points of inconsistency. This is natural as not every patient recollects their history the same way to providers, patients may not be available to provide accurate histories (encephalopathy or dementia), and given the current physician and healthcare shortages, extensive complete histories are not always available. Inefficiencies arise in obtaining and navigating through patient histories unless a patient consistently sees the same provider (or stays in the same network).

The largest downside outside of the astronomical cost and resource power required to create a universal EHR between all providers and facilities, patient data most certainly would be at a higher risk to unauthorized access and more vulnerable to cyber-attacks. Healthcare facilities have standardized forms for general histories as a patient visits, but possibly an improvement could be a “Patient History” document that is continuously updated, including all recorded history and significant care received with time marks. This document would be pinned somewhere that is easily accessible on a facility’s interface in a relevant area near the documentation section (or pinned as the first line to the top of the documentation section).

Limitations of Study

Multiple limitations are acknowledged in this study. Because patients were not identified nor contacted, 30-day follow up mortality was not plausible. The eleven thrombosis risk factors evaluated in addition to the unmeasurable hypercoagulable state of COVID19 creates variance between cases. Each risk factor is not equivalent to each other in terms of perceived risk either. For example, a history of hypertension is not a reason to initiate anticoagulation, but a history of atrial fibrillation does. Patient size was 103 can contribute to a larger study size, but overall does not carry the weight of large-scale studies with thousands of participants.
References


