INCIDENCE OF ADVERSE DRUG EVENTS IN COVID-19 PATIENTS ON ANTICOAGULANTS: A PHARMACOVIGILANCE STUDY

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INCIDENCE OF ADVERSE DRUG EVENTS IN COVID-19 PATIENTS ON ANTICOAGULANTS: A PHARMACOVIGILANCE STUDY

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ABSTRACT

Pharmacovigilance is a crucial component of today's health science studies that allows researchers to detect, assess, understand, to ultimately prevent any adverse event associated with drugs. Today, with the world struggling to get the COVID-19 pandemic under control, it is important to look at how this disease is affecting different patient populations. A common complication associated with this disease is thrombosis. A lower mortality rate in COVID-19 patients has been related to the use of the drug heparin, a widely used anticoagulant. The main objective of this study was to assess whether there were any adverse events associated with the administration of anticoagulants in patients known to have COVID-19. Thus, it was hypothesized that with study of different anticoagulant drugs, there would be no significant difference in the observed adverse events for these drugs.

Data for this study was obtained from a deidentified secondary database of COVID-19 positive patients from Truman Medical Center, Kansas City, MO and from the FDA's Adverse Event Reporting System (FAERS) Public Database. Chi-square test of association was performed to determine associations of race, sex and hospitalization rate with the adverse outcome variables. Proportional Reporting Ratios (PRR) and lower 95% confidence

intervals (Lower CI) were calculated for data from the FAERS database where the adverse events studied, mimicked COVID-19 symptoms.

It was found that there is a significant association between race and hospitalization rate for patients who were on anticoagulants and had COVID-19. Additionally, the study results suggested that patients who were put on the anticoagulant heparin were more likely to develop pneumonia compared to other anticoagulating drugs. However, no reportable adverse drug event was found for any other selected anticoagulant drugs. Given the findings, it would be important for the clinicians to use heparin with caution, especially in COVID-19 patients.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Medicine has examined this research proposal titled, “Incidence of Adverse Drug Events in COVID-19 Patients on Anticoagulants: A Pharmacovigilance Study” presented by Purva Patel, candidate for the Master of Science Degree, and certify that in their opinion it is worthy of acceptance.

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CHAPTER

1. INTRODUCTION

According to World Health Organization, as of May 17, 2021, there have been over 162 million cases of COVID-19 with more than 3.3 million fatalities worldwide[1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the known pathogen for causing the COVID-19 disease, can cause a rapid progression to acute respiratory distress syndrome (ARDS) in severe cases[2].

Many of those patients with the severest of COVID-19 that progressed to ARDS require mechanical ventilatory support. One of the major complications of having ARDS and being on a ventilator is developing blood clots. The process of formation of a blood clot is referred to as thrombosis. There are two types of thrombosis: venous and arterial thrombosis[3]. When formed in the leg, blood clots can cause Deep Vein Thrombosis (DVT). When a clot forms in the leg and then travels to the lungs it can cause a Pulmonary Embolism (PE). Venous thromboembolism is a term that is broadly used to address the disease PE and/or DVT. Additionally, incidence of ischemic stroke (due to a clot formed in heart with subsequent travel to the brain) is frequently observed in severe COVID-19 patients[4]. According to Zakeri et al., the risk of stroke in COVID-19 patients is high and the range of these patients having arterial thrombosis is from 2.8% to 3.8%. Due to this high rate of stroke risk, it is vital for researchers to find efficient and productive ways for managing anticoagulant drugs.

To manage and monitor drugs used in the healthcare system, conducting pharmacovigilance studies is crucial. As per the World Health Organization, pharmacovigilance is defined as "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem"[5]. Pharmacovigilance helps in studying whether a drug is effective and if it causes any major or minor adverse events in a population. According to FDA's (Food and Drug Administration) definition of adverse drug events, an adverse event can be defined as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related"[6]. In this study, adverse drug events considered were the conditions that mimicked symptoms of the disease COVID-19. As discussed above, thrombosis is a complication caused by COVID-19 and hence it is imperative to look at how different anticoagulant therapies affect patients with COVID-19 and whether they cause any adverse drug events or not in critically ill patients.

Mechanism of anticoagulant drugs

In this study, six anticoagulating drugs (heparin, warfarin, dabigatran, rivaroxaban, edoxaban, and apixaban) were included for assessment. These drugs directly affect the blood coagulation cascade. There are two mechanisms by which the coagulation cascade is activated: intrinsic and extrinsic. These two pathways contain a series of clotting factors. The intrinsic pathway includes factors I, II, IX, X, XI, and XII and the extrinsic pathway

includes factors I, II, VII, and X[7]. There is a pathway that is common to both mechanisms and it contains the clotting factors I, II, V, VIII and X[7]. As per Chaudhary, R. et al., "the intrinsic pathway is activated through exposed endothelial collagen, and the extrinsic pathway is activated through tissue factor (VII) released by endothelial cells after external damage"[7]. Low molecular weight heparins (LMWH), bind to AT3 (antithrombin 3), and have a higher proportional impact on factor Xa, inhibiting thrombin activation which in turn affects the intrinsic pathway[8]. Once thrombin is inhibited, it prevents the activation of fibrin from fibrinogen and thus the formation of cross-linked fibrin is arrested, preventing the formation of a clot. Warfarin is a vitamin K antagonist, meaning it binds to vitamin K and blocks the formation of the active forms of vitamin K-dependent clotting factors, namely, II, VII, IX and X[8]. Dabigatran binds directly to thrombin and inhibits fibrin formation, inhibiting intrinsic activity of thrombin[8]. Rivaroxaban, edoxaban and epixaban are factor Xa inhibitors and work by directly binding to the active site of factor Xa in the coagulation cascade, inhibiting free and clot-associated factor Xa[8].

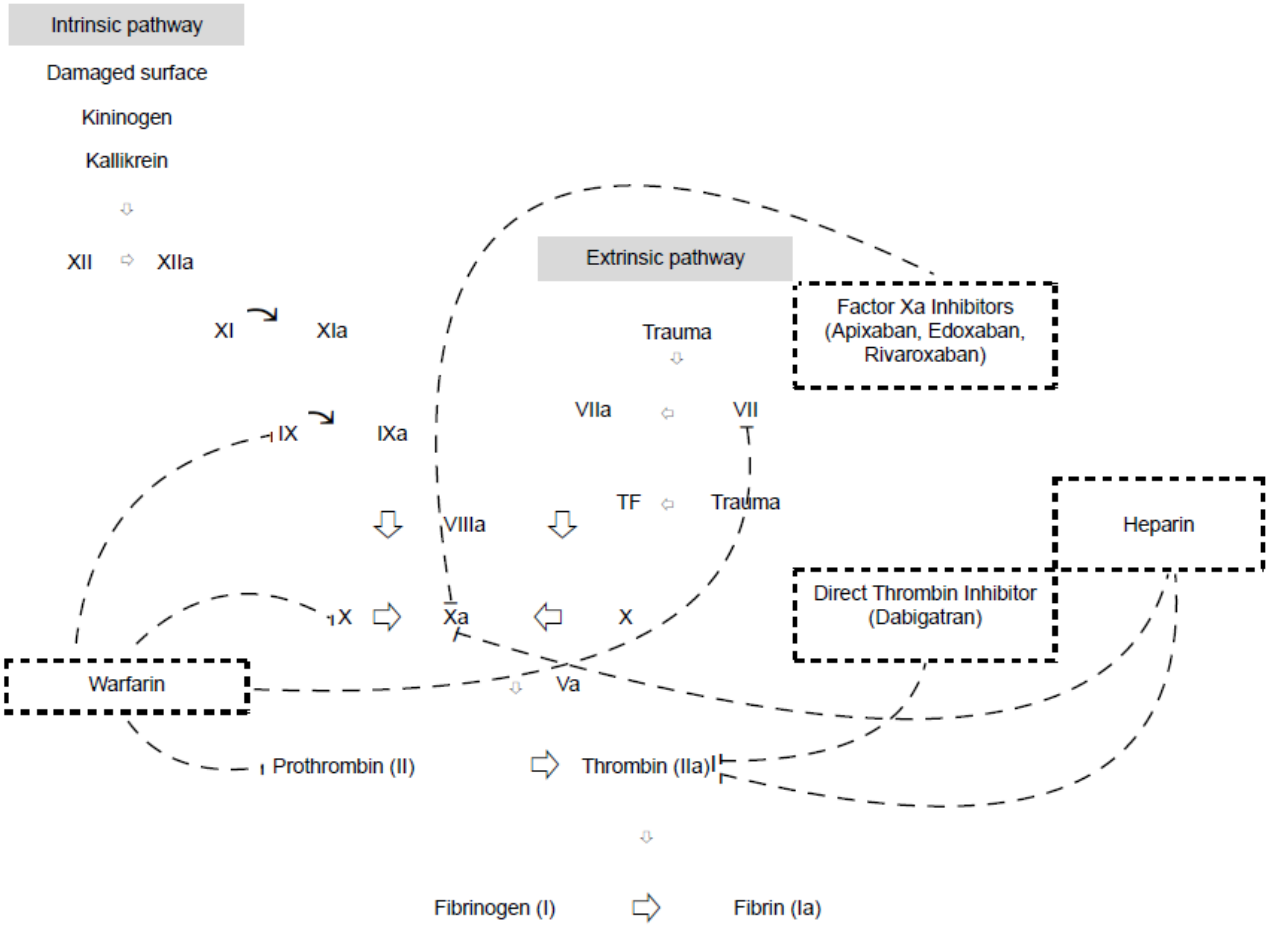
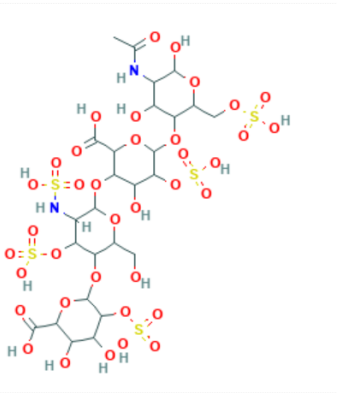
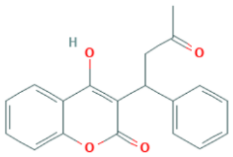
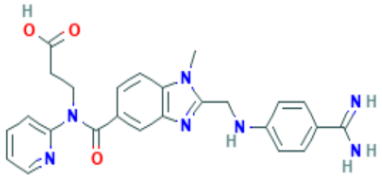


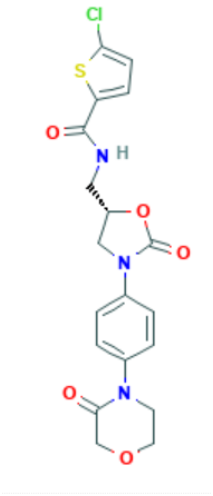
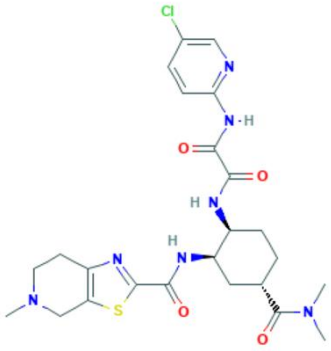
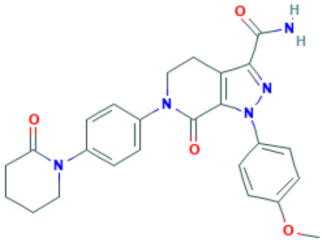
Figure 1. Normal coagulation cascade.
Diagram adapted from Perez-Puzol, S. et al. (2012)[9].

The diagram shown in Figure 1 includes both intrinsic and extrinsic pathways by which the coagulation cascade is activated. Here, it is important to note that factor X is a common factor that is present in both the pathways and thus, is not unique to any one pathway. Drugs like rivaroxaban, apixaban and edoxaban directly bind to the active site of

factor Xa and in turn inhibit both free and clot-associated factor Xa[8]. Anticoagulant drugs that inhibit the factor Xa act by decreasing the formation of fibrin polymers that ultimately lead to clotting of blood[10]. Table 1 below shows all the anticoagulant drugs used in the study with their action mechanism and chemical structures.

Table 1: Anticoagulant drugs[11]

Name of the drug	Mechanism of action	Affected pathway	Chemical structure
Heparin	Inhibits factor Xa and Thrombin IIa	Intrinsic	
Warfarin	Inhibits factor II, VII, IX and X	Extrinsic	
Dabigatran	Directly inhibits thrombin	Intrinsic	

Rivaroxaban	Inhibits factor Xa	Intrinsic and extrinsic	
Edoxaban	Inhibits factor Xa	Intrinsic and extrinsic	
Apixaban	Inhibits factor Xa	Intrinsic and extrinsic	

In an article by Clausen et al., researchers showed that heparan sulfate, a linear glycosaminoglycan polysaccharide present on the cell surface, acts as a coreceptor (along with ACE2), that helps in binding SARS-CoV-2 spike (S) protein onto the cellular surface[12]. Unique heparan sulfate chains are covalently bound to a core protein to form heparan sulfate proteoglycans (HSPG)[13]. Structural similarity between heparan sulfate glycosaminoglycan and heparin's glycosaminoglycan chains makes heparin an interesting drug to study. The work by Clausen and team suggests that competitive binding of heparin and heparan sulfate to the binding S protein of SARS-CoV-2 might prove to be inhibitory towards viral uptake by the cell and may offer therapeutic potential to control the transmission of SARS-COV-2[12]. Given this, it is of utmost importance that drugs like heparin and other anticoagulant drugs are studied in detail for COVID-19 disease.

CHAPTER
2. LITERATURE REVIEW

Heparin comes in two forms: unfractionated and fractionated (also known as LMWH). Unfractionated heparin is natural form of glycosaminoglycans (GAG) and is produced and purified from porcine intestine[14]. LMWH is one of the most widely used anticoagulant drugs in the healthcare industry due to its safety and conveniency of use[8]. This type of heparin is prepared by controlled chemical or enzymatic cleavage of unfractionated heparin into chains of molecular weight, varying from 5000 – 8000 Daltons[14]. The controlled process of breaking down unfractionated heparin into LMWH is the reason why LMWH has a more predictable course of action and is considered safer than unfractionated heparin[14]. In March of 2020, a study done in China with 449 patients showed that LMWH was associated with better prognosis in severe COVID-19 patients[15]. Similar results were obtained by Ayerbe et al. They showed that use of heparin in COVID-19 patients is associated with lower mortality rate compared to non-heparin users[16]. This study was conducted in Spain using clinical data obtained between the dates of 1st of March and the 20th of April 2020. Although, it included a large number of patients (n= 2075), one limitation of the study was that it was not a randomized control trial. Hence, such studies establish that more research needs to occur to recognize the best intervention and management of the anticoagulating drugs used with COVID-19 patients.

Another drug that has been highly used in the clinical setting as an anticoagulant therapy is warfarin, a synthetic vitamin K antagonist[17]. A major drawback of using warfarin in COVID-19 patients, is that the patient's International Normalized Ratio (INR) needs to be regularly monitored. This monitoring requires in-person visits to a lab, clinic, or hospital, thus increasing the risk for exposure to COVID-19[18]. However, it is important to look at this drug because it is commonly used due to its easy accessibility and low cost.

Newly emerged direct acting anticoagulants (DOACs) can be categorized into two classes: direct thrombin inhibitors and factor Xa inhibitors[19]. For this study, dabigatran a direct thrombin inhibitor, and rivaroxaban, edoxaban, and apixaban, factor Xa inhibitors, were chosen.

Dabigatran is a synthetic direct-thrombin inhibitor that is used in patients with atrial fibrillation (irregular or rapid heartbeat) to prevent stroke, due to its efficacy and safety profile related to hepatotoxicity[20]. As COVID-19 patients are more prone to developing atrial fibrillation[21] and hepatotoxicity, it is important to look at dabigatran's safety in COVID-19 patients. A study by Iturbe-Hernandez and team suggested that using dabigatran reduces the risk of ischemic stroke in patient population with atrial fibrillation and provides a better anticoagulation therapy alternative to vitamin K antagonist like warfarin[20].

Direct oral anticoagulants (DOACs) like factor Xa inhibitors, formed synthetically, are generally used in the prevention of venous thromboembolism and are seen as an effective treatment therapy in patients with pulmonary embolism and/or deep vein thrombosis[22]. As per Cabral and Ansell's randomized study, factor Xa inhibiting drugs

(rivaroxaban and edoxaban) are more effective and have more advantages over regular anticoagulants in treating venous thromboembolism[22]. Like dabigatran, factor Xa inhibitors are also thought to be better alternatives to warfarin[23]. Given this, it became important to learn about factor Xa inhibitors and how they might affect patients with COVID-19.

One of the factor Xa inhibitors, apixaban, has been shown to be related to lower mortality rate in COVID-19 patients (n= 2450) similar to the reported lower mortality rate (p= 0.047) associated with heparin[24]. Researchers used apixaban as a preferred DOAC in their study because of its superior safety profile in patients with renal failure. Renal failure has been reported as a common complication of COVID-19 disease[24].

As anticoagulant drugs are widely used to treat an array of thrombotic diseases and conditions, it is crucial to look at adverse events that may be caused by these drugs in COVID-19 patients. This research can help clinicians in making better decisions on how to administer and manage anticoagulant drug therapies in this population cohort. Therefore, in this study, on-going clinical trials that are using these specific drugs in patient population with COVID-19 disease were studied, along with COVID-19 positive patient population and general patient populations using these specific anticoagulant drugs. Thus, this study will identify whether any adverse events are associated with anticoagulant drugs of interest.

CHAPTER
3. METHODOLOGY

This research presents a retrospective analysis of data from two different database sources. Depending on the granularity of data available from these databases, appropriate statistical and mathematical tools were used for finding statistical significance and calculations. Primary outcomes for on-going clinical trials were also analyzed. In clinical studies, primary outcomes can be defined as an "outcome that an investigator considers to be the most important among the many outcomes that are to be examined in the study"[25]. Thirteen pulmonary adverse drug events (ADEs) that mimic COVID-19 symptoms are similar to ADE terminologies used by Medical Dictionary for Regulatory Activities (MedDRA) and were taken from previously published work on ADEs for other diseases[26]. According to MedDRA's hierarchy, these ADEs are grouped as preferred terms (PTs). In this study, the thirteen ADEs assessed were: pulmonary edema, dysphonia, nasopharyngitis, pleurisy, pleural effusion, cough, sinusitis, bronchitis, oropharyngeal pain, pneumonia, pneumonia aspiration, dyspnea, and emphysema. Terms used for recognizing drug indications associated with this drug class were ten frequent complications that occur with the use of these drugs.

Data collection

Information regarding current clinical trials was obtained from ClinicalTrials.gov website maintained by National Library of Medicine (NLM) by National Institutes of Health (NIH). Search criteria was adjusted for the fields: conditions or disease and other terms. COVID-19 was put in the condition or disease column and drug name of interest was put in other terms column for each search.

Data from 896 COVID-19 positive patients was obtained from a deidentified secondary data set containing electronic medical record clinical information for patients who were deemed to be positive for COVID-19 and were seen at Truman Medical Center (TMC). Data was collected during the time period, February 1, 2020 through January 31, 2021. Deidentification was accomplished via non-inclusion of Patient Health Information and randomized date shifting for all time and date stamps within the database. Demographic information provided included: age at encounter, sex, race, ethnicity, and payor status. Key information provided by the data set was whether the patient died, was hospitalized as well as the- presence of predefined comorbidities (ex., diabetes or hypertension) and most importantly, current drugs taken (by classification group). Classification groups of drugs included: Angiotensin converting enzyme (ACE), Angiotensin II receptor blocker (ARB), anti-hypertensives, anticoagulants, antiplatelets, aspirin, azithromycin, other-antibiotics, other-generals, pulmonary related, and statins.

The FDA's Adverse Event Reporting System (FAERS) was used to obtain curated information about the general patient population (n = 127,186) who were prescribed the drugs of interest. The data collected from this database represented information collected in the first quarter of the year 2020. While obtaining the information for the anticoagulant drugs from the database, the search query included not only the drug names but also the brand names for the drugs. Data extracted from this database was previously deidentified but much more granular and provided information about each of the six anticoagulant drugs with their reported adverse event and drug indication. Drug indications included the disease or condition for which that drug was prescribed. In this study, ten drug indications including thrombosis, deep vein thrombosis, pulmonary thrombosis, pulmonary embolism, hypercoagulation, acute myocardial infarction, embolism venous, pulmonary thromboembolism, embolism, and venous thrombosis were used.

Statistical analysis

Frequencies for various primary outcomes considered by researchers conducting clinical trials were calculated by the COUNTIF function in Microsoft Excel. Primary outcomes were consolidated into four major categories. A chart was created in Microsoft Excel to show the composition of primary outcomes that researchers are focusing on with regards to use of anticoagulant drugs in the clinical trials.

Using the dataset for COVID-19 patient population, the following statistics, in counts and percentages, were calculated in Microsoft Excel: patients prescribed anticoagulants, patients who died on anticoagulants, patients prescribed anticoagulants who were hospitalized and lastly, those of the hospitalized patients (on anticoagulants) who died. Another important aspect that was examined was hospital length of stay (days) for patients prescribed anticoagulants. Mean +/- SD were calculated for LOS for each drug class present in the dataset.

A chi-square test of association was performed to assess if there was any association between two categorical variables. This test was done for the variables; race, sex, and hospitalization to assess for association with presence or absence of an anticoagulant.

$$X^2 = \Sigma\ [(\text{Observed Frequency} - \text{Expected Frequency})^2/\text{Expected Frequency}]$$

The chi-square test of association uses the formula mentioned above to calculate chi-square test statistic. For the purposes of this study, the chi-square test statistic and p-values were calculated using a statistics calculator[27].

For the data obtained from FAERS database, frequencies of drug indications were calculated using Microsoft Excel. To study Adverse Drug Events (ADEs) of interest, Proportional Reporting Ratios (PRR) were calculated. The PRR is a method, proposed and implemented by the FDA, to analyze and identify the extent of reported disproportionality of

an adverse event for a drug and is compared to the same event for all other drugs in the database[28]. To calculate PRR, a contingency table was formed per event per drug.

Table 2: PRR contingency table[28]

	Drug of interest	All other drugs	Sum
Adverse event	a	b	a+b
All other adverse events	c	d	c+d
Sum	a+c	b+d	Total

Using the contingency table described above, PRR was calculated as:

PRR = [a/(a+c)]/[b/(b+d)] for each drug of interest and each adverse event of interest.

In the formula stated above:

a = all the reports for a specific adverse event for a particular drug,

b = all reports for all other drugs for that adverse event,

c = all reports for all other adverse events for a particular drug, and

d = all reports for all the other drugs for all other adverse events.

An adverse event is considered reportable if the PRR is greater than 2. Once the PRRs were calculated for the thirteen COVID-19 symptoms that mimicked pulmonary ADEs, the lower 95% confidence interval (CI) was calculated using following equation[29]:

Lower 95% CI = exp (ln PRR – 1.96(S))

Where S stands for standard deviation (27):

$$S = \sqrt{\left(\frac{c}{a*(a+c)} + \frac{d}{b*(b+d)}\right)}$$

Another criterion for a reportable adverse event is that the lower confidence interval value should be greater than 1. Pharmacovigilance greatly depends on statistical methods like PRR analysis to help identifying any possible statistical associations between a particular adverse event and a drug.

CHAPTER

4. RESULTS

Clinical trials

Below, Table 2 shows the breakdown of number of trials that were either recruiting, completed, not yet recruiting and active- not recruiting along with the very first column that shows total number of trials including that drug, as of April 29th, 2021. At the beginning of this study in August of 2020, there were a smaller number of clinical trials (CTs) that were studying anticoagulant drugs as used during treatment or COVID-19. For the drug heparin, there were only 36 trials recorded as of August 2020 compared to 87 clinical trials occurring recorded by April 29, 2020. This sudden increase in the number of clinical trials studying heparin as a drug of interest, especially factor Xa inhibitors, indicates the interest and concern for heparin use in the COVID-19 patient. This may be because of the lower mortality rate associated with heparin use in COVID-19 patients shown by studies done earlier in the pandemic. Also, heparin's known safety, wide-use and easy accessibility makes it a preferable anticoagulant drug to study.

Table 3: Number of COVID-19 clinical trials that includes anticoagulant drugs[30]

	Total trials	Recruiting	Completed	Not yet recruiting	Active, not recruiting
Heparin	91*	49	14	16	6
Warfarin	1		1		
Dabigatran	2	1	1		
Rivaroxaban	16	13	1	2	
Apixaban	10	6	2	1	1
Edoxaban	3	1	1	1	

*2 CTs is enrolling by invitation, 1 CT got terminated, and 3 CTs were withdrawn

Considering that there are many more registered clinical trials assessing heparin than other anticoagulants, including factor Xa inhibitors, it was essential to look at the primary outcomes that researchers/clinicians are interested in studying. Thus, a chart was created to depict the proportion of primary outcomes assessed by researchers who are studying the drug, heparin.

In figure 2, primary outcomes were generalized into four different categories: thrombotic events, mortality, hospitalization, and ventilation. Here, thrombotic events comprised of the conditions, venous thromboembolism, atrial thromboembolism, deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke. The primary outcome of mortality indicates whether the patient (enrolled in the CT) died during their enrollment during the clinical trial. For the category of hospitalization, primary outcomes of

hospitalization and ICU admission were combined, to indicate hospitalization. The category of ventilation included the primary outcomes that were described as ventilation or intubation and/or oxygen levels when supplemental oxygen was provided. Oxygen level was measured as the patient's PaO2/FiO2 ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen)[31].

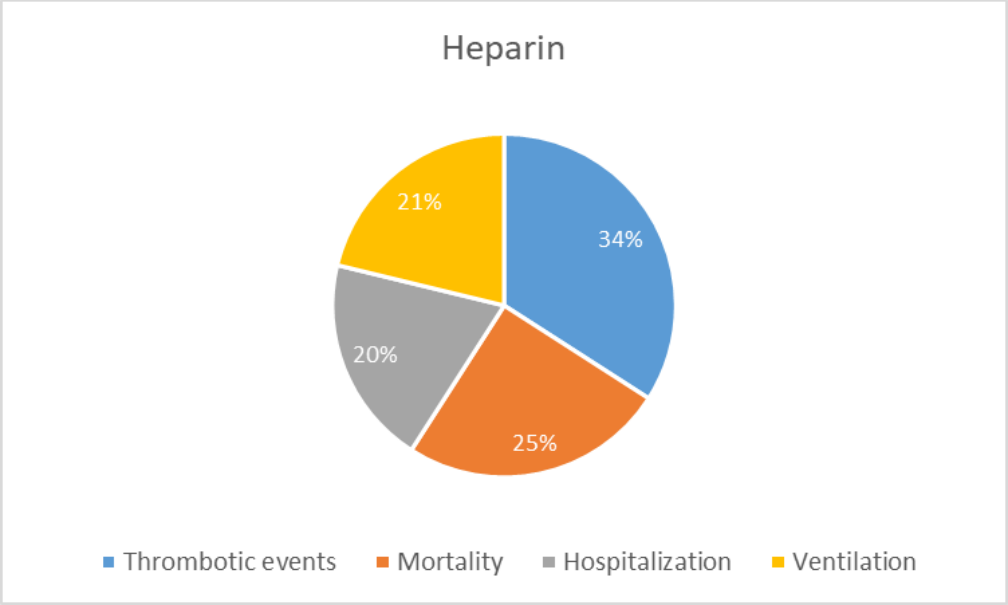


Figure 2: Breakdown of proportions of primary outcomes for the drug heparin

According to the chart, in the 87 clinical trials assessing heparin, 34% of reported primary outcomes are thrombotic events, 25% are mortality, 20% are hospitalization, and 21% are ventilation. This indicates that the plurality of the registered clinical trials is

focusing on clinical outcomes, including adverse thrombotic events occurring in the COVID-19 patients who are on heparin.

COVID-19 patients on anticoagulants

Data from the- Truman Medical Center's deidentified secondary database containing 896 COVID-19 positive patients showed that of these 896 patients, 455 (~51%) patients were prescribed anticoagulant drugs. Also, out of these 896 patients, 30 patients died, 25 of whom were reported to be prescribed an anticoagulant drug. This means that about 83% of patients who died were given anticoagulating drugs.

In addition, the data was assessed for associations in demographics for these patients. Chi-square test of association was performed for categorical variables such as race and sex for patients who were prescribed anticoagulant drugs. The assumptions about independence of observations and having minimum of five expected frequencies were fulfilled for the chi-square test.

Table 4: Race-wise classification of COVID-19 patients on anticoagulants or otherwise

	Anticoagulants	No anticoagulants
African American	197	167
White	104	157
Others	137	81

Out of 455 COVID-19 patients who were on anticoagulants, 197 were African Americans, 104 were whites and 137 patients identified themselves as “other” race. There were 17 patients (out of 455) who did not choose to identify their race and hence were not included in the chi-square test of association analysis. Out of 441 COVID-19 patients, who were not on anticoagulants, 167 were African Americans, 157 were whites and 81 patients identified themselves as other. 36 patients who did not receive any anticoagulant drugs chose not to identify their race. It was observed that there is statistically significant difference between different races who are given anticoagulants ($\chi^2 = 26.369$ and $p < 0.0001$).

Table 5: Division of COVID-19 patients on anticoagulants or otherwise between African Americans and other races

	Anticoagulants	No anticoagulants
African American	197	167
Total of white and others	241	238

A chi-square test of association was also done to assess if there was any significant association in the use of anticoagulant drugs in African Americans vs other races (total of patients who identified themselves as whites and others). Total number of patients from other races on anticoagulants was 241 and not on anticoagulants was 238. It was observed that there was no statistically significant difference between African Americans vs total of white and others who were given anticoagulants ($\chi^2 = 1.2$ and $p = 0.273$). Additionally, the odds ratio was calculated using an online calculator to compare the association[32]. The odds ratio was 1.165 with a 95% confidence interval lying between the values 0.887 and 1.531. This means that an African American patient is 1.165 times more likely to be on anticoagulants than patients from other races.

Table 6: Division of COVID-19 patients on anticoagulants or otherwise between African Americans and Whites

	Anticoagulants	No anticoagulants
African American	197	167
White	104	157

Furthermore, a chi-square test of association was also done to assess if there was any significant association in the use of anticoagulant drugs in African Americans vs whites. It was observed that there was a statistically significant difference between African Americans vs whites who were given anticoagulants ($\chi^2 = 12.41$ and $p = 0.0004$). The odds ratio was 1.781 with a 95% confidence interval lying between the values 1.290 and 2.458. This means that an African American patient is 1.781 times more likely to be on anticoagulants than a white patient.

Table 7: COVID-19 patients on anticoagulants or otherwise by sex

	Anticoagulant	No anticoagulant
Male	209	200
Female	245	240

Further, a chi-square test of association was performed for the categorical variable of sex for COVID-19 patients on anticoagulants. Out of 455 patients on anticoagulants, 209 were male and 245 were female. In the entire dataset, there were 2 patients who identified themselves as unknown and were left out from the chi-square test. The result of the test showed that there is no significant difference between the sex of the patients with COVID-19 and the use of anticoagulants ($\chi^2 = 0.0304$ and p-value = 0.862).

To assess the association between patients who were hospitalized and were given anticoagulant, a chi-square test of association was done.

Table 8: COVID-19 patients who were hospitalized on anticoagulants or otherwise

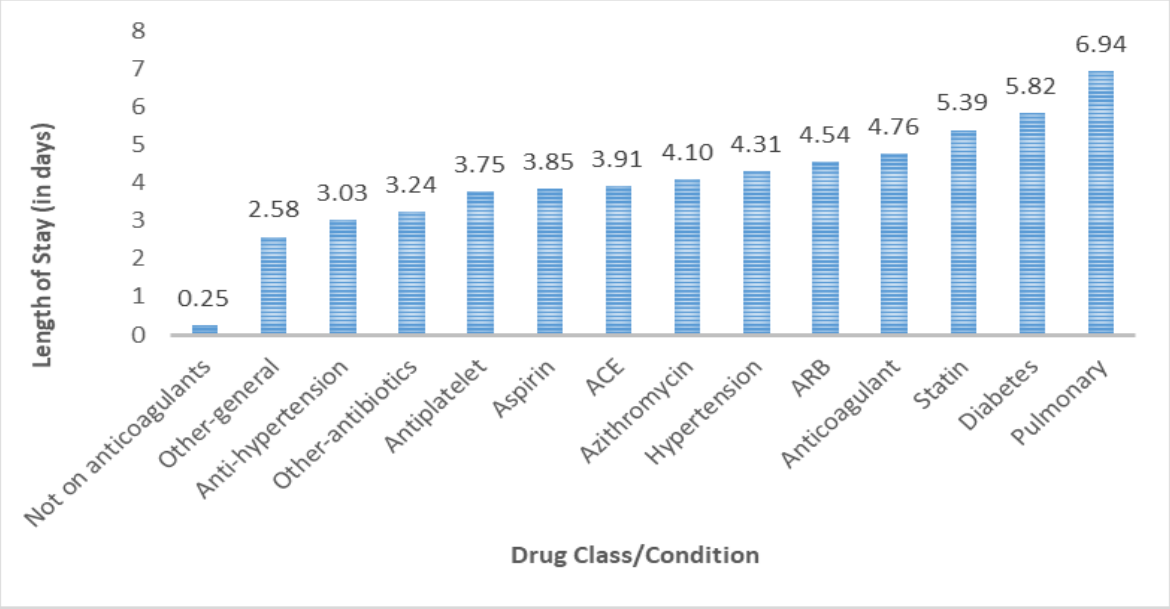
	Anticoagulant	No anticoagulant
Hospitalized	293	35
Not hospitalized	162	406

Out of 455 patients on anticoagulants, 293 were hospitalized and 162 were not hospitalized. The analysis indicates that there is significant difference between COVID-19 patients who were on anticoagulant and were hospitalized vs. patients who were on anticoagulant and were not hospitalized ($\chi^2 = 307.612$ and p-value < 0.0001). The odds ratio was 20.980 with a 95% confidence interval lying between the values 14.134 and 31.144. This shows that a hospitalized patient having COVID-19 is 21 times more likely to be on anticoagulants than a patient who is not hospitalized.

As discussed earlier, there were 30 patients who died, out of which 24 were hospitalized. It is important to note that out of these 24 patients, 23 were on varying anticoagulant drugs. This indicates that COVID-19 patients who are hospitalized are more likely to be prescribed an anticoagulant medication and those patients are more likely to die.

Given that there is an association between hospitalization rate and being prescribed on anticoagulant drug, the next assessment of interest is for hospital length of stay for these patients. It can be assumed that the longer the length of stay, the more severe the disease state. Further, it is hypothesized that these patients may be more likely to receive ventilatory support. Another possibility for longer length of stay at the hospital might suggest probable development of respiratory problems like pneumonia.

Table 9: Average length of hospital stay for COVID-19 patients



In the bar graph depicted above, average length of hospital stay for COVID-19 patients on various drug classes is shown. Hypertension and Diabetes are two conditions that are indicated in the data set and in the bar graph. For a COVID-19 patient who had either one of these conditions, the average length of stay was 4.31 and 5.82 days, respectively. As seen in the bar graph, the average length of stay for a COVID-19 patient who were given anticoagulants was 4.76 days which is relatively higher compared to average length of stay for patients who were not on anticoagulant (0.25 day). It is important to note here that average length of stay at hospital for a COVID-19 patient who was given drugs to treat pulmonary conditions was 6.94 days, highest compared to all the other drugs given. Use of pulmonary drugs in COVID-19 patients may indicate that a patient receiving these drugs were more likely to have ARDS and be on ventilatory support. It is also possible that these patients may have developed pneumonia, making their average hospital stay longer.

General patient population on anticoagulant drugs

Given the fact that clinical trials involving anticoagulant drugs are focusing on thrombotic events as their primary outcome, it became imperative to find anticoagulant drug indications, that include thrombotic events, in the general population. Data from the FAERS database was used to discover drug indications of interest.

As seen in the table 10, most drug indications for all the anticoagulant drugs of interest combined, are observed in thrombosis (67,240), deep vein thrombosis (36,342), and

pulmonary embolism (24,628) respectively. Further, it can be observed that out of all the drugs, rivaroxaban is prescribed more as compared to other drugs.

Table 10: Drug indications for anticoagulant drugs

Drug indication	13904	16012	92848	685	3896	12325	139670
	Heparin	Warfarin	Rivaroxaban	Edoxaban	Dabigatran	Apixaban	TOTAL
Thrombosis	7251	5762	47880	142	2362	3843	67240
Deep vein thrombosis	2690	5367	23275	263	743	4004	36342
Pulmonary thrombosis	31	180	633	1	13	47	905
Pulmonary embolism	2422	3672	14537	183	587	2867	24268
Hypercoagulation	86	151	156	1	13	15	422
Acute myocardial infarction	720	81	20	0	9	21	851
Pulmonary thromboembolism	0	1	1	0	0	0	2
Embolism venous	215	338	4833	76	76	1334	6872
Embolism	308	320	1251	8	72	141	2100
Venous thrombosis	181	140	262	11	21	53	668

Next, PRRs were calculated for 13 COVID-19 symptom mimicking ADEs that occurred in this patient population cohort. There were 4,453 adverse events reported for these drugs. According to the calculations (in table 11), most PRR values were relatively

similar to each other except for heparin (1.37) and edoxaban (1.09) for the symptom of pneumonia. Both the values (highlighted in the table) are higher than 1.0 and are relatively much higher than other calculated values.

Table 11: Proportional Reporting Ratios

PRR						
	APIXABAN	DABIGATRAN	HEPARIN	EDOXABAN	RIVAROXABAN	WARFARIN
PULMONARY OEDEMA	0.0600	0.1631	0.1236	0.0657	0.0609	0.1427
DYSPHONIA	0.0130	0.0531	0.0000	0.0000	0.0115	0.0000
NASOPHARYNGITIS	0.2139	0.1906	0.0338	0.0000	0.0681	0.1282
PLEURISY	0.0065	0.0000	0.0000	0.0000	0.0046	0.0289
PLEURAL EFFUSION	0.1801	0.2829	0.2915	0.0000	0.2466	0.1684
COUGH	0.1194	0.0811	0.0056	0.0653	0.0956	0.0440
SINUSITIS	0.1071	0.1091	0.0338	0.0000	0.1245	0.1333
BRONCHITIS	0.0327	0.0000	0.0331	0.0000	0.0161	0.0290
OROPHARYNGEAL PAIN	0.0658	0.1606	0.0000	0.0000	0.0371	0.0437
PNEUMONIA	0.6756	0.7233	1.3721	1.0850	0.6481	0.8738
PNEUMONIA ASPIRATION	0.0808	0.0549	0.0851	0.3318	0.1653	0.1092
DYSPNOEA	0.5050	0.3782	0.1735	0.7742	0.2990	0.2984
EMPHYSEMA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0289

Table 12: Lower 95% confidence interval (Lower CI)

LOWER CI						
	APIXABAN	DABIGATRAN	HEPARIN	EDOXABAN	RIVAROXABAN	WARFARIN
PULMONARY OEDEMA	0.0306	0.0737	0.0778	0.0095	0.0391	0.0934
DYSPHONIA	0.0027	0.0112	0.0000	0.0000	0.0031	0.0000
NASOPHARYNGITIS	0.1433	0.0917	0.0149	0.0000	0.0447	0.0832
PLEURISY	0.0008	0.0000	0.0000	0.0000	0.0010	0.0073
PLEURAL EFFUSION	0.1221	0.1568	0.2178	0.0000	0.1926	0.1184
COUGH	0.0712	0.0261	0.0008	0.0094	0.0608	0.0221
SINUSITIS	0.0639	0.0413	0.0150	0.0000	0.0861	0.0874
BRONCHITIS	0.0123	0.0000	0.0132	0.0000	0.0067	0.0116
OROPHARYNGEAL PAIN	0.0326	0.0698	0.0000	0.0000	0.0199	0.0210
PNEUMONIA	0.5564	0.5012	1.2229	0.7140	0.5705	0.7560
PNEUMONIA ASPIRATION	0.0452	0.0138	0.0503	0.1460	0.1178	0.0700
DYSPNOEA	0.3997	0.2283	0.1206	0.4761	0.2425	0.2290
EMPHYSEMA	0.0000	0.0000	0.0000	0.0000	0.0000	0.0289

After calculating PRRs, lower CIs were calculated, and their values are given in the table 12 (above). All the values for lower CI were relatively small compared to others, except of the value of heparin for the symptom of pneumonia (1.22). For any adverse event to be reportable, the 3 criteria that need to be followed are: there should be more than 3 reported incidences, PRR value should be greater than 2, and lastly, a PRR that is greater than the lower 95% confidence interval boundary, with the lower CI itself being over 1[25]. None of the values for any adverse event meet the criteria stated above, therefore, there is no reportable adverse event associated with the use of anticoagulant drugs.

CHAPTER 5. DISCUSSION

With each passing day during this pandemic, researchers and clinicians are finding new information about this novel SARS-COV-2 virus and are constantly looking for interventions and therapeutics to treat this disease in severe COVID-19 cases. As clinical studies show, there is great interest in exploring anticoagulants as a therapeutic intervention in battling COVID-19. With this, it is essential that pharmacovigilant studies like this are conducted to study the safety of these drugs. Although no reportable adverse event was found in this study, it is crucial to note that the PRR and lower CI values for heparin used associated with the adverse event of pneumonia has shown to be consistently higher compared to any other drug used in this study. This may indicate that COVID-19 patients who are participating in clinical trials for study of heparin need to be closely monitored for pneumonia or pneumonia-like symptoms because patients on heparin may be prone to develop pneumonia. Moreover, recent thromboembolic event complications seen with the use of Johnson and Johnson vaccine in response to heparin-resistance show that there might be a pneumonia-causing mechanism at play at a very cellular and molecular level regarding use of the drug heparin in COVID-19 patients.

In this study, we observed that COVID-19 patients on anticoagulants are more likely to be hospitalized and stay in the hospital for relatively longer period. Staying in the hospital for a longer time may be related to more complications in these patients and may make a

patient susceptible to developing pneumonia. Also, these hospitalized patients prescribed anticoagulants are more likely to die.

Based on these findings, more study using data pulled directly from the Electronic Health Records (EHRs) should be undertaken for the study of anticoagulant drug therapies and COVID-19. The more granular- EHR data could be used to look for various thrombotic events for specific anticoagulant drugs.

From the FEARS database it was observed that rivaroxaban was the drug that was most often prescribed in the year 2020 to treat various thrombotic events. This indicates that more clinical studies should be undertaken to test the safety and efficacy of factor Xa inhibitors in COVID-19 patients.

Knowing that use of heparin might result in some thrombotic complications in COVID-19 patients, it is important to shift the focus to new class of anticoagulant drugs i.e., factor Xa inhibitors. From the PRRs and lower CI calculations for these factor Xa inhibitors, it appears that rivaroxaban and apixaban are relatively safer to use. Lastly, based on the results of this study, there are no reportable adverse events for anticoagulant drugs of interest and hence, there is no statistically significant difference between any of these six anticoagulant drugs.

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VITA

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