

Assigned PFRRID # _____

Date: 9/30/2015

Pharmacy Department Funds Request (\$1,000-\$10,000)

Principal Investigator

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Protocol Title: Effectiveness of Venous Thromboembolism Prophylaxis in Patients with Liver Disease

Project start date: 10/10/2015

Project end date: 6/26/2016

Amount Requested from PRC: \$5200

Total Project Cost:\$5200

Collaborating investigators:

Co-investigator	Department	Mail Code	Email
Dr. Sarah Welch	Pharmacy	Hb-65	welchs@ccf.org
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Please provide five Key Words that best describe your project:

1. Venous thromboembolism
2. Bleeding
3. Liver disease
4. Prophylaxis
5. Anticoagulant

Last Updated 12/24/13 at 1300 by H. Hoffmaster

Described clearly and concisely, in language readily understandable to a biomedical scientist who may not be a specialist in the research projects field the following:

Abstract:

Background: In patients with liver disease, synthetic function of most procoagulant factors is decreased, leading to abnormalities in laboratory tests of coagulation (e.g. INR)¹. In addition, platelet formation is also generally reduced in patients with liver disease¹. However, more recent studies have shown concomitant pro-hemostatic changes, and patients with liver disease may actually be at increased risk for VTE¹⁻⁴. Paradoxically, patients with liver disease are also at increased risk for bleeding, particularly of the GI tract¹. Because of this, no definitive conclusion has been made in regards to whether patients with liver disease benefit from pharmacologic VTE prophylaxis, whether they are harmed by it, or whether there is no difference in outcomes.

Objective: The main objective of this study is to determine the effects of pharmacological venous thromboembolism (VTE) prophylaxis on incidence of VTE and major bleeding in patients with liver disease in comparison with no pharmacological VTE prophylaxis.

Methodology: This study will be completed using retrospective chart review at the Cleveland Clinic main campus. Patients will be identified by using ICD-9 codes for liver disease. Patients will be included if their length of stay is at least 48 hours and if they are at least 18 years of age. Patients will be excluded if incident VTE occurs within 48 hours of admission, treatment with full dose anticoagulation occurs at any time during hospital stay other than for treatment of incident VTE, or if the patient has a history of congenital or acquired thrombophilia or hemophilia. Patients that received pharmacological VTE prophylaxis will be compared to patients that received no pharmacological VTE prophylaxis in regards to incidence of VTE and major bleeding as the composite primary endpoint.

Hypothesis:

Combined rate of venous thromboembolism (VTE) and major bleeding will be different in patients with liver disease treated with pharmacological VTE prophylaxis than in patients that receive no pharmacological VTE prophylaxis.

Specific Aims (Primary and secondary objectives):

Primary Objective:

- To compare the rate of VTE and major bleeding between hospitalized patients with liver disease that received pharmacological VTE prophylaxis versus those that did not

Secondary Objectives:

- To compare differences in the rate of modified Bleeding Academic Research Consortium (BARC) Type 2 bleeding (defined below) during hospital stay
- To compare differences in hospital length of stay (LOS) from admission to discharge
- To compare differences in in-hospital mortality
- To compare differences in the rate of 30-day mortality

Background and significance:

Last Updated 12/24/13 at 1300 by H. Hoffmaster

In the past, it was thought that patients with liver disease and elevated INR were protected from VTE through “autoanticoagulation” due to a reduction in procoagulant clotting factors¹. However, many recent studies have demonstrated that patients with liver disease are not only at risk for VTE, but may have a hypercoagulable state due to a reduction in proteins C and S and an increase in factor VIII and vWF¹⁻⁴. Unfortunately, practice guidelines make no recommendation in regards to pharmacological VTE prophylaxis in this patient population. Although several studies have demonstrated that patients with liver disease are at risk for VTE, few have examined the effectiveness of pharmacological prophylaxis in the prevention of VTE, and none have been adequately powered to show a treatment effect. Therefore, the aim of this study is to evaluate the safety and efficacy of pharmacological VTE prophylaxis in patients with chronic liver disease.

Experimental Methods and Data Analysis:

Patients with liver disease will be identified using ICD-9 codes. These patients will then be screened for exclusion criteria using ICD-9 codes. The remaining patients will form the study cohort. These patients will then be allocated to the “Pharmacological Prophylaxis” or “No Pharmacological Prophylaxis” groups based on their anticoagulant usage. Patients that are allocated will be matched by propensity scoring in regards to risk factors for venous thromboembolism and bleeding events. Patients will then be screened for incident venous thromboembolism development as well as for bleeding events using ICD-9 codes. Patients with a documented event will have that event verified by examination of the electronic medical record.

Study Design

Non-interventional, matched group, retrospective cohort study utilizing medical chart review

Inclusion and Exclusion Criteria:

- Inclusion
 - Patients with liver disease based on ICD-9 codes
 - Patients ≥18 years of age
 - LOS≥48 hours
 - Only a patient’s most recent admission will be included
 - Patients that receive a liver transplant will be included until 23:59:59 the day prior to transplantation
- Exclusion
 - Incident VTE within 48 hours of admission
 - Treatment with full dose anticoagulation at any time during hospital stay other than for treatment of incident VTE
 - Patients with congenital or acquired thrombophilia or hemophilia

Study Procedure:

- Patients that are included in the final cohort will be allocated to the appropriate group based upon the following criteria:
 - Patients will be allocated 2 patients to the “No Pharmacological Prophylaxis” group to 1 patient to the “Pharmacological Prophylaxis” group
 - Patients that have no incident VTE or bleeding event (defined below) during their hospital stay will be placed in the “Pharmacological Prophylaxis” group if they receive pharmacological prophylaxis for 50% or more of their hospital stay, and to the “No Pharmacological Prophylaxis” group if they receive pharmacological prophylaxis for less than 50% of their hospital stay
 - Patients that have incident VTE or extension of an existing VTE during their hospital stay will be placed in the “Pharmacological Prophylaxis” group if the VTE/extension of VTE occurs during pharmacological VTE prophylaxis or within 48 hours of discontinuing pharmacological VTE prophylaxis, and to the “No Pharmacological Prophylaxis” group if the VTE occurs more than 48 hours after discontinuing pharmacological VTE prophylaxis
 - Patients that have an incident bleeding event during their hospital stay will be placed in the “Pharmacological Prophylaxis” group if the bleeding event occurs during pharmacological VTE prophylaxis or within 24 hours after discontinuing pharmacological VTE prophylaxis, and will be placed into the “No Pharmacological Prophylaxis” group if the bleeding event occurs more than 24 hours after discontinuing pharmacological VTE prophylaxis
- Matching will be performed using propensity scoring based on the following criteria:
 - Active cancer
 - History of VTE
 - Surgery, fracture, or trauma within one month of admission
 - Use of mechanical VTE prophylaxis
 - Baseline MELD score
 - Baseline Child-Pugh score
 - Presence of esophageal varices at baseline
 - Bleeding event as admitting diagnosis
 - Age
 - Platelets at baseline
 - Presence of heart failure
 - Presence of chronic kidney disease
 - Presence of lung disease (COPD, asthma, or idiopathic pulmonary fibrosis)
 - Hospital LOS
 - Etiology of liver disease

Endpoints:

- Incident venous thromboembolism
- Incident bleeding event
- Death

- Hospital discharge

Data Collection:

Actual data points for the included cohort will be extracted from the electronic medical record using a computerized data pull for the following data points:

- Screening
 - Age (in years)
 - Length of stay from hospital admission to discharge
 - Presence of ICD-9 codes for non-alcoholic steatohepatitis, alcoholic cirrhosis, alcoholic fatty liver disease, chronic hepatitis, cirrhosis due to alpha-1 antitrypsin deficiency, primary sclerosing cholangitis, biliary cirrhosis, autoimmune hepatitis, and acute liver failure
 - Treatment with warfarin or other vitamin K antagonists, or anticoagulation with LMWH, UFH, fondaparinux, dabigatran, apixaban, rivaroxaban, edoxaban, or dabigatran
 - Presence of ICD-9 codes for factor V Leiden, anti-phospholipid syndrome, prothrombin G20210A, protein C or S deficiency, prothrombin mutation, anti-thrombin deficiency, and/or any type of hemophilia
- Patient Population Data
 - MRN/Study ID
 - Weight (kg)
 - Height (m)
 - BMI
 - Hospital admission and discharge dates
 - Sex
 - Presence of ICD-9 code(s) for VTE (all events will be verified in the electronic medical record)
 - Presence of ICD-9 code(s) for bleeding (all events will be verified in the electronic medical record)
 - Baseline INR
 - Baseline activated partial thromboplastin time (PTT)
 - Baseline serum albumin
 - Baseline serum total bilirubin
 - Baseline serum creatinine
 - Change in Hemoglobin $\geq 2\text{g/dL}$
 - Blood transfusions
 - Specific liver disease etiology
 1. Non-alcoholic steatohepatitis
 2. Alcoholic cirrhosis
 3. Alcoholic fatty liver disease
 4. Chronic hepatitis
 5. Cirrhosis due to alpha-1 antitrypsin deficiency
 6. Primary sclerosing cholangitis
 7. Biliary cirrhosis
 8. Autoimmune hepatitis
 9. Acute liver failure
 - Presence of varices at admission
 - Presence and degree of hepatic encephalopathy at admission

- Presence and degree of ascites at admission
- Thromboelastography
- Dialysis ≥ 2 times in the past 7 days
- Use and type of renal replacement therapy (if applicable)
- Active cancer
- Presence of CHF
- Presence of lung disease
 1. COPD
 2. asthma
 3. idiopathic pulmonary fibrosis
- Surgery within 1 month of admission
- Fracture/trauma within 1 month of admission
- History of VTE
- Platelets at admission and time of bleeding event (if applicable)
- MELD score at admission
- Child-Pugh score at admission
- Presence of mechanical VTE prophylaxis
- Date of death (if applicable)
- APACHE II score (if applicable)
- Highest VTE risk score
- Pharmacological prophylaxis
 - Medication administered
 - Dose
 - Dates therapy was administered
 - Percentage of doses received

Data Management:

Data will be collected and uploaded on to an Excel database with access limited to only the principal investigator and co-investigators. This electronic database is password protected and requires network access. De-identified data may be stored and transported in a password protected file within a secured and encrypted portable USB drive accessible only to the primary investigator.

Statistical and Analytical Plan:

Statistics

- Chi-square test or Fisher's exact test for categorical variables
- Student's paired t-test for parametric continuous variables or Mann-Whitney U test for non-parametric continuous variables
- Multivariable logistic regression in regards to major bleeding and VTE
- Analysis by stratification by MELD score, Child-Pugh score, and type of pharmacological VTE prophylaxis (LMWH or UFH)

References:

1. Tripodi A, Mannucci P. The coagulopathy of chronic liver disease. N Engl J Med [internet]. 2011 Jul 14 [cited 2015 Aug 16]; 365(2):147-56. Available from: <http://search.proquest.com/docview/876930406/fulltextPDF/BD3C492751414C89PQ/1?accountid=50452>
2. Søgaard KK, Horváth-Puhó E, Grønbaek H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. Am J Gastroenterol [internet]. 2009 Jan [cited 2015 Aug 16]; 104(1):96-101. Available from: <http://www.nature.com/ajg/journal/v104/n1/pdf/ajg200834a.pdf>
3. Northup PG, McMahon MM, Ruhl AP, Altschuler SE, Volk-Bednarz A, Caldwell SH, et al. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. Am J Gastroenterol [internet]. 2006 Jul [cited 2015 Aug 16]; 101(7):1524-8. Available from: <http://www.nature.com/ajg/journal/v101/n7/pdf/ajg2006286a.pdf>
4. Gómez Cuervo C, Bisbal Pardo O, Pérez-Jacoiste Asín MA. Efficacy and safety of the use of heparin as thromboprophylaxis in patients with liver cirrhosis: a systematic review and meta-analysis. Thromb Res [internet]. 2013 Oct [cited 2015 Aug 16]; 132(4):414-9. Available from: <https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0049384813003307>

Budget Request (Insert guidelines about how much how often etc. here): one-time expense

Budget Beginning Date: 10/10/2016 Budget End date: 6/26/2016

Itemized Project Costs

Type	Description	Cost in \$
Statistician Expenses	<p>Data Management (8 hours) Data will be imported from Excel to a statistical package. Formats for coded categorical factors will be created. Range checking will be performed and data summaries for the full sample will be calculated.</p> <p>Analysis (44 hours) A logistic regression model regression model will be fit to the full dataset predicting prophylaxis use. A greedy matching algorithm will be used to match those with and without prophylaxis use on several factors. Confirmation of the quality of the match will be evaluated by comparing standardized differences between matched groups (6 hours). For each outcome, logistic, Poisson, or linear regression modeling methods appropriate for matched/clustered data will be performed (20 hours). Repeated analyses will be performed by stratification factors (3 stratification factors x 6 hours each).</p> <p>Estimated Effort: 52 hours @ \$100/hour (\$5200)</p>	\$5200

Personnel Justification:

The services of a statistician will be required to perform propensity scoring to match patients appropriately between groups. Without this service, the study would be vulnerable to considerable selection bias, which would weaken the validity of the study.

Note: Fund request does not include travel expenses