

INFLUENCE OF REGIONAL DIFFERENCES AND HOSPITAL CHARACTERISTICS ON
HEALTH OUTCOMES FOR INPATIENT HOSPITALIZATION OF VENOUS
THROMBOEMBOLISM PATIENTS IN THE UNITED STATES

by

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(Under the Direction of Jack E. Fincham)

ABSTRACT

Venous thromboembolism (VTE) results in a tremendous health economic burden. Objectives: To determine if there is a significant association between: 1) hospital census region, teaching status, location, bedsize, and health outcomes for VTE, 2) mortality and race, gender, and payer status respectively. Methods: A retrospective database analysis was done using the Healthcare Cost & Utilization Project, Nationwide Inpatient Sample 2003 data of hospital discharges in the US. Multiple and logistic regression models were employed to study the possible associations. Results: Unlike previous analyses, this study found that Northeast has the highest mean charge per discharge, greater than that in the West, and hospital census region is not a significant predictor of mortality for VTE hospitalizations. Rural location, non-teaching status, small and medium size hospitals are associated with lesser total charge. Medicare and private insurance were positively associated with increased length of stay. Conclusion: Hospital characteristics influence health outcomes for VTE.

INDEX WORDS: Venous thromboembolism, hospital census regions, hospital characteristics, health outcomes, length of stay, expenditures, mortality

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DEDICATION

To my aunt Kalpana Mavshi; my parents Aayee and Baba; and my grandmother Tae Aaji.

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CHAPTER ONE

INTRODUCTION

Venous thromboembolism (VTE) results in a tremendous health economic burden accounting for approximately 500 million dollars per year in the United States (Hawkins, 2004a). The condition of VTE includes deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Venous thromboembolism (VTE) is the cause of significant morbidity and mortality and may lead to complications, including recurrent VTE and long-term post-thrombotic syndrome (Hawkins, 2004a). A recent study indicated that more than 600,000 people in the United States suffer from non-fatal VTE events each year (DVT, N=376,365; PE, N=237,058). There are almost 300,000 fatal VTE events each year (296,370) (Heit et al. 2005). Only 7% percent of patients with VTE who died were diagnosed and treated. Sixty percent of the fatal events followed undetected VTE (174,115). Approximately one-third of VTE events were unrelated to extended in-hospital immobilization, while two-thirds were due to extended in-hospital immobilization (Heit et al. 2005). This study is the US arm of the larger global study The VTE Impact Assessment Group in Europe (VITAE) study, which is attempting to establish the actual burden in terms of morbidity, mortality, complications, and costs of VTE across the European Union and the United States (Heit et al. 2005).

Previous research findings have suggested that regional (geographic regions as classified by the US census bureau into Northeast, Midwest, South and West) differences exist in the United States in the incidence, methods of diagnosis and treatment, and hospitalization charges for VTE (Proctor et al. 2004).

According to Allison et al. (2000), the issues of cost and quality are gaining importance in the delivery of medical care. Teaching hospitals may provide care that is of higher quality, but more costly when compared with non-teaching hospitals (Boscarino, 1992, Kassirer, 1999). It is important to know whether the clinical and economic outcomes for VTE differ significantly with teaching/non-teaching status of hospitals, so that the possible mechanisms that may lead to better health outcomes can be identified, and best practices that ensure efficient use of healthcare resources can be implemented. According to Taylor et al. (1999) admission to a major teaching hospital may be associated with increased costs to the Medicare program. However, overall survival for patients with the common conditions such as, hip fracture, stroke, coronary heart disease, and congestive heart failure was better in teaching hospitals (Taylor et al. 1999).

Managed care plans have been actively involved in containing healthcare cost inflation (Berg and Chattopadhyay, 2004). However, cost-cutting strategies of these plans aimed at restricting the hospital length of stay have been the focus of much criticism (Berg and Chattopadhyay, 2004). Patients diagnosed with VTE can consume a lot of resources (Geerts et al. 2004).

The Nationwide Inpatient Sample (NIS) is a powerful database of hospital inpatient stays, developed as part of the Healthcare Cost and Utilization Project (HCUP) (Agency for Healthcare Research and Quality, "Nationwide Inpatient Sample (NIS)," 2003 <http://www.hcup-us.ahrq.gov/nisoverview.jsp>).

Researchers and policymakers have used the HCUP NIS to identify national trends in health care utilization, access, charges, quality, and outcomes. These administrative data can be of great use in identifying trends, which is relevant for public health issues. Studies that assess

large number of hospitals in multiple states or regions are useful for guiding policy (Ayanian and Weisman, 2002).

To date, there has not been a study using the 2003 NIS data sample, comparing the clinical and economic outcomes, namely length of hospitalization, mortality, and expenditures of in-patient hospitalization for VTE in the different geographic locations of the U.S. for the post-2000 period. Also, no study has examined the relationship between the teaching/non-teaching hospital status and the above-mentioned VTE outcomes. Finally, there has been no study in the past that has examined the relationship between types of health insurance plans and mortality for VTE.

Therefore, in order to help fill the gaps in the literature, this study will be conducted to help determine if geographic and hospital characteristics result in differences in clinical and economic outcomes of the length of hospital stay, mortality, and expenditures for in-patient hospitalization for VTE. Secondly, this study will determine if the type of health insurance plan is a predictor of mortality for in-patient hospitalization for VTE. Lastly, this study will examine if race and gender are predictors of mortality for in-patient hospitalization for VTE.

The results of the current study may lead to further research to determine the causal pathways to better practices for in-patient management of VTE in a particular type of hospital setting.

CHAPTER TWO

BACKGROUND

This chapter will focus on the venous thromboembolism (VTE) epidemiology, cost considerations, etiology, pathophysiology, diagnosis, medical management, anticoagulation clinics, pharmacoeconomic studies, invasive management, and therapy practices, and current issues in therapy practice of VTE.

2.1 Epidemiology

The average annual incidence of VTE is more than 100 cases per 100,000 population (Silverstein et al. 1998). According to a systematic review, the incidence of deep vein thrombosis (DVT) in the general population was 0.5 per 1000 person-years (Fowkes et al. 2003). The incidence in the population aged 65-69 was 1.8 per 1000 person-years and that in the population aged 85-89 was 3.1 per 1000 person-years (Kniffin et al. 1994). A large number of silent events are detected at the time of autopsy (Havig 1977; Lindblad et al. 1991) leading to estimates of 2 million DVT cases and upto 200,000 deaths from pulmonary embolism (PE) annually (Hirsh and Hoak, 1996). Venous thromboembolism accounts for about 10% of the in-hospital deaths, and the long-term case-fatality rates were 19%, 25%, and 30% at 1, 2, and 3 years after hospital discharge (Anderson et al. 1991).

According to Stein et al. (2002) the prevalence of DVT seen in a retrospective hospital discharge database analysis was 0.69 in the black population and 0.84 in the white population. According to a British study, 23% blacks and 22% whites with suspected thrombosis were

confirmed to have the disease (Patel et al. 2004). The prevalence of PE/DVT in the Asian population is low (Klatsky et al. 2000).

2.2 Costs Considerations for Venous Thromboembolism

O'Brien and Caro (2002) studied the costs for the inpatient and the outpatient management of DVT. They found that the mean cost of hospital stay was US \$5779 per patient (range \$780 to \$254,520; median US \$4,152). The mean length of stay was 5.8 days. The mean cost per day was US \$1036 per patient (range US \$202 to US \$18,025; median US \$824). Case fatality rate was 1%, but the mean cost for those who died was three times of those who were discharged alive (US \$16,306 versus US \$5,694 respectively). Medicare was the primary payer for 56% of the discharges. Discharges with none of the complications of PE: major bleed, minor bleed, and drug-induced thrombocytopenia constituted 93% of all the DVT discharges. The mean hospital stay for this group was US \$5,561 per patient (range US \$769 to US \$250,953; median = 4,100) with an average cost per day of US \$1,020 patient (range US \$202 to US \$17,830; median = 814). Those having a major bleed had the highest average cost US \$11,189 per patient (range US \$1,258 to US \$80,480; median US \$9,065). The referral rate for additional services was highest for this group. Only 49% of the survivors were discharged, 32% required sub-acute inpatient care and 13% were referred to home healthcare services. On an average for PE, minor bleeds, and drug-induced thrombocytopenia, US \$3,915, US \$2,419, and US \$3,118 are to be added to the cost of hospital stay for DVT respectively. Uncomplicated DVT was defined as patients with a principal diagnosis of DVT, who survived the stay and were discharged home. Also, they had no comorbid conditions or any documented complications, nor any procedures other than venogram, or duplex sonography. For these patients the mean hospital cost was estimated to be US \$3,486 per patient (range US \$870 to US \$9,196; median = US \$3,204) with

an average cost per day of US \$820 patient (range US \$358 to US \$3,601; median = US \$714). Their mean length of stay was 4.5 days.

According to O'Brien and Caro (2002) in the outpatient scenario with treatment at home with a registered nurse giving low molecular weight heparins (LMWHs) injections, the cost was US \$1,707 for daily injections to US \$2,390 for twice daily therapy. For self-injected therapy, the cost was US \$1,415 for daily injections to US \$1,734 for twice daily therapy. Patients in an outpatient-program where an overnight stay was included incurred a cost of US \$2,267.

For patients who received injections on a continuing basis in a clinic setting had an estimated program cost of US \$1,520 for daily injections and US \$2,015 for twice-daily injections (O'Brien and Caro, 2002). The 6-month post-acute care management cost was US \$979.

2.3 Etiology

Virchow (1856) postulated that the famous triad of the causes of thrombosis namely, damage to the blood vessel wall, alterations in the flow, and hypercoagulability of the blood (Brotman et al. 2004).

Anderson and Spencer (2003) classify the risk factors for VTE as strong risk factors (with an odds ratio greater than 10), moderate risk factors (with an odds ratio of 2-9), and weak risk factors (with an odds ratio less than 2). The strong risk factors are fracture hip or leg, hip or knee replacement, major general surgery, major trauma, and spinal cord injury. The moderate risk factors are arthroscopic knee surgery, central venous lines, chemotherapy, congestive heart or respiratory failure, hormone replacement therapy, malignancy, oral contraceptive therapy, paralytic stroke, pregnancy/puerperium, previous venous thromboembolism, and thrombophilia. The weak risk factors include bed rest greater than 3 days, immobility due to sitting (such as,

prolonged air travel), laproscopic surgery, obesity, varicose veins, and increased age (Anderson and Spencer, 2003). The annual incidence of first time VTE rises from 5 cases per 100,000 population that is less than 20 years of age to 500 in population 80 years or older (Heit et al. 2001). Smoking is also a risk factor for venous thromboembolism (Hansson et al. 1999). Past history of DVT is also a risk factor, and the annual likelihood of recurrence is 5–15%, with a cumulative recurrence rate of about 25% after 4 years in patients with first spontaneous DVT (Prandoni et al. 1996).

Other risk factors include drugs, such as, anti-psychotics and thalidomide, superficial vein thrombosis, inflammatory bowel disease, antiphospholipid syndrome, dyslipoproteinaemia nephrotic syndrome, paroxysmal nocturnal haemoglobinuria, myeloproliferative diseases, Behçet's syndrome, congenital venous malformation, chronic care facility stay, heparin-induced thrombocytopenia (HIT), inferior vena cava filters, and drug abuse (Hagg and Spigset, 2002; Orth and Ritz, 1998; Bernstein et al. 2001; Ginsburg et al. 1992; Kyrle and Eichinger, 2005). These act mostly by increasing the coagulability of the blood; all presently known risk factors are thought to be involved in the development of at least one of the components of the Virchow's triad (Kaushal et al. 2004). The thrombophilias that are risk factors for DVT include Factor V Leiden, factor II G20210A, natural inhibitor deficiency, high factor VIII, factor IX, or factor XI, lupus anticoagulant, high thrombin activatable fibrinolysis inhibitor, hyperhomocysteinaemia, dysfibrinogenaemia or hyperfibrinogenaemia, and plasminogen deficiency (Kyrle and Eichinger, 2005; Meijers et al. 2000; van Tilburg, 2000; den Heijer et al. 1996; Turpie et al. 2002). Therefore, the incidence of VTE in different regions will be influenced by the epidemiology of the above-mentioned conditions.

2.4 Pathophysiology

Thrombi are formed when there is low flow and low shear stress in the vessel walls (Kyrle and Eichinger, 2005). They consist mainly of fibrin threads, red blood cells, and platelets (Kyrle and Eichinger, 2005). Thrombi mostly form in the valve pockets of calf veins and extend into the proximal veins (Nicolaidis et al. 1971). Due to the increase in the venous and capillary pressure, there is an increase in the trans-capillary filtration rate that results in edema (Kyrle and Eichinger, 2005). Generally, in 50% of the patients, the venous outflow obstruction subsides within 3 months by thrombus lysis and recanalization (Killewich et al. 1989). Patients with early edema are more likely to have residual thrombosis and late edema often results in valvular incompetence (Killewich et al. 1989).

2.5 Diagnosis

Accurate diagnosis of VTE maybe challenging due to atypical or absent symptoms (Jaffer et al. 2005). Also, non-invasive diagnostic tests have imperfect accuracy (Jaffer et al. 2005). Therefore, serial non-invasive diagnostic tests are used (Jaffer et al. 2005). They include D-dimer (a break-down product of cross-linked fibrin formed as a result of plasmin-mediated, proteolytic degradation; D-dimer levels increase in pathologic conditions that cause thrombosis {both venous and arterial}) and in disseminated intravascular coagulation) testing, compression ultrasonography, helical computed tomography (CT) of the chest, and nuclear lung scans. The cornerstone of the diagnosis is pretest clinical probability (Jaffer et al. 2005). Wells et al. (1995) have used a scoring model to stratify patients with suspected DVT into 3 distinct clinical pretest probabilities: low, moderate, or high. Presence of active cancer, (treatment ongoing or within previous 6 months or palliative) paralysis, paresis, or recent plaster immobilization of the lower extremities, recently bedridden for more than 3 days, or major surgery within 4 weeks, localized

tenderness along the distribution of the deep venous system, entire leg swollen, calf swelling by greater than 3 centimeter when compared with the asymptomatic leg (measured 10 centimeter below tibial tuberosity), pitting edema (greater in the symptomatic leg), and collateral superficial veins (non-varicose) each corresponded to a score of 1. If there was an alternative diagnosis as likely as or greater than that of deep-vein thrombosis then the final score was reduced by 2. A high score was three or more, a moderate score was one or two, and a low score was zero or less (Wells et al. 1995). Diagnosis of VTE can be secured or excluded when the pretest clinical probability is concordant with an appropriate diagnostic test (McGee, 2002). A high pre-test clinical suspicion with a high probability lung scan is adequate to confirm the diagnosis {greater than 95% certainty} (Jaffer et al. 2005). A low pre-test clinical suspicion with a negative D-dimer can exclude the diagnosis (Jaffer et al. 2005). When the clinical suspicion is discordant with the diagnostic result, further investigation is required (Jaffer et al. 2005). The gold-standard investigation has been pulmonary angiography, with even further diagnostic yield since the implementation of digital subtraction technology (Srivastava et al. 2004). This is an invasive procedure, however, the incidence of major complications is low. Spiral computed tomography (CT) contrast angiography is a promising imaging modality for the diagnosis of PE. A combination of a negative spiral CT contrast angiography scan and normal venous ultrasound imaging safely excludes the diagnosis of pulmonary embolism in the emergency department setting (Anderson et al. 2005). When positive, a helical CT or high probability lung scan in the context of a low pretest suspicion for PE does not rule in the diagnosis of PE. It is reasonable to order a pulmonary arteriogram in such cases (the PIOPED investigators, 1990; Rosen and McArdle, 1997).

2.6 Treatment

Goals of therapy for DVT include diminution of the duration and severity of the lower extremity symptoms, prevention of pulmonary embolism, minimization of the risk of recurrent venous thrombosis and prevention of post-thrombotic syndrome (Augustinos and Ouriel, 2004). Post-thrombotic syndrome occurs due to venous valvular incompetence, venous hypertension, and stasis that occur after an episode of DVT (Kearon, 2003). The symptoms includes chronic leg heaviness, leg aching, venous claudication, edema, varicosities, hyperpigmentation, and non-healing ulcers (Kahn, 2002).

Anticoagulants are used to prevent thrombus propagation, pulmonary embolism, and recurrent venous thrombosis, however they do not dissolve the occluding thrombus or reduce venous outflow obstruction (Augustinos and Ouriel, 2004). Therefore therapies have evolved to remove occlusive thrombi, preserve valvular competence, and reduce venous obstruction. These therapies include open surgical thrombectomy, pharmacological thrombolysis, percutaneous mechanical thrombectomy, adjuvant venous angioplasty and stenting, and inferior vena cava filters (Augustinos and Ouriel, 2004).

2.7 Medical Management of Venous Thromboembolism

Anticoagulants form the mainstay of medical management of the treatment and prophylaxis of venous thromboembolism (Kearon, 2003). The four major classes of anti-coagulants available in the United States include vitamin K antagonists (warfarin), indirect thrombin inhibitors (unfractionated heparin (UFH) and LMWH), direct thrombin inhibitors (DTIs), and factor Xa inhibitors (Nutescu et al. 2005). Thrombolytic agents such as, streptokinase, urokinase, and tissue-type plasminogen activator (tPA) have been approved by the FDA for the treatment of pulmonary embolism (Almoosa, 2002).

Vitamin K antagonists (VKAs) were developed in the early 1940s. Two classes of VKAs have been approved by the US FDA; the coumarins (warfarin) and the indandiones (anisindione). Warfarin is the anticoagulation of choice when long-term anticoagulation is indicated (Nutescu et al. 2005). The efficacy of VKA has been demonstrated for the primary and secondary prevention of VTE, prevention of systemic VTE in patients with atrial fibrillation, or prosthetic heart valves, prevention of thromboembolic stroke, and primary and secondary prevention of acute myocardial infarction (AMI). (Ansell, et al. 2004). Warfarin inhibits the activation of the vitamin K-dependent clotting factors II, VII, IX, and X and the anticoagulant proteins C and S. When warfarin therapy is initiated, the attainment of complete antithrombotic effect is delayed owing to the different half-lives of the clotting factors (6-72 hours) (Nutescu et al. 2005). Protein C and S are inhibited more rapidly due to their shorter half-lives, so there may be a paradoxical procoagulant state during the initial days of therapy (Nutescu et al. 2005). Therefore, patients with acute thrombosis should receive a parenteral anticoagulant, while transitioning to therapeutic doses of warfarin (Ansell et al. 2004; Schulman, 2003).

Disadvantages with warfarin therapy include frequent monitoring with the international normalized ratio (INR), large inter-individual dosing differences, narrow therapeutic index, slower onset and offset of action, drug interactions (e.g., with salicylate containing agents), drug-disease interactions, genetic variations in the response, and the need for dose adjustments, patient education, strict compliance, and frequent follow-up (Nutescu et al. 2005).

Unfractionated heparin, commercially isolated from porcine or bovine mucosa was discovered in the early twentieth century. Heparin acts via the plasma cofactor antithrombin III. The binding of the UFH antithrombin III complex to factor Xa causes a conformational change leading to inactivation of factor Xa. Unfractionated heparin can also bind to and inactivate factor

II (thrombin). This process requires simultaneous binding of the UFH-antithrombin III complex with thrombin. This process requires that the UFH be at least 18 saccharide units (Quader et al. 1998). The longer saccharide units (18 units) comprise less than 50% of the total fraction of LMWHs (Quader et al. 1998). Until 1996, when the LMWHs were approved by the US FDA, patients with DVT were generally treated in the hospital with UFH. Weight based nomograms dosing (bolus of 80 U/kilogram of ideal body-weight followed by IV infusion of 18 U/kg/hr) decreases the rate of recurrent thromboembolism in patients with VTE (Raschke et al. 1993). Therefore, in summary, UFH by virtue of its chemistry and biological activities has several disadvantages.

Fractionated or LMWHs are obtained by chemical or enzymatic depolymerization of UFH (Nutescu et al. 2005). This results in shorter heparin chains that have an enhanced affinity for inhibiting factor Xa relative to thrombin (Nutescu et al. 2005). Therefore, LMWHs have a relatively higher anti-factor Xa and lower anti-factor II activity compared to UFH. The potency of LMWH is reflected by the ratio of anti-factor Xa to antifactor IIa activity {Xa: IIa ratio} (Quader et al. 1998). The LMWHs available in the US are dalteparin, enoxaparin, and tinzaparin (Weitz, 1997).

Thus, even though UFH was the gold standard for anticoagulation for more than 60 years, its role is now challenged by the LMWHs, which have demonstrated at least comparable safety and efficacy, an improved side-effect profile, and more convenient dosing (Nutescu, et al. 2005).

Disadvantages with UFH are decreased bioavailability and inter-patient variability in the anticoagulant response {due to non-specific binding to several plasma and cellular proteins} (Nutescu et al. 2005). Unfractionated heparin requires frequent laboratory monitoring of activated partial thromboplastin time (aPTT) (Hirsh and Raschke, 2004).

Advantages of LMWHs are that they have improved pharmacodynamic and pharmacokinetic properties compared with UFH. They exhibit less binding to plasma and cellular protein resulting in a more predictable anticoagulant response (Wu and Matijevic-Aleksic, 2005; Nutescu et al. 2005). Therefore routine monitoring and dose adjustments are not required (Wu and Matijevic-Aleksic, 2005; Nutescu et al. 2005). The LMWHs have a long half-life resulting in once or twice daily administration as against UFH, which requires a twice or thrice daily regimen. The LMWHs have improved subcutaneous bioavailability and dose independent renal clearance (Nutescu et al. 2005). Therefore they can be given on an outpatient basis (Nutescu et al. 2005). They also have a more favorable side effect profile including a lower incidence of HIT and osteopenia (Nutescu et al. 2005). Therefore LMWHs are competing with UFH in all therapeutic and surgical interventions requiring anticoagulation (Nutescu et al. 2005; Hirsh and Raschke, 2004; Geerts et al. 2001)

The disadvantages of the LMWHs are higher acquisition costs, limited data on their use in high-risk populations, such as, obese, pregnant, and pediatric patients (Nutescu et al. 2005). Also, they are only partially reversible with protamine (Nutescu et al. 2005). Also, dosage adjustments are required in patients with renal elimination (Duplaga et al. 2001). The LMWHs cross-react with heparin and should not be given to patients with documented HIT (Carrasco, 2002; Hoppensteadt et al. 2003).

Factor Xa inhibitors are a novel class of anticoagulant agents. The first agent was approved by the FDA in late 2001. They are the synthetic versions of the five sugar sequence of heparin and are hence referred to as pentasaccharides. Due to their small molecular size they exert their action specifically on the activated factor Xa and have no effect on IIa. Pentasaccharides can inhibit factor Xa directly or indirectly. The direct inhibitors bind to Xa

without a cofactor. Agents in this class currently under development include tick anticoagulant peptide, YM-60828, and DX-9065a. The indirect inhibitors bind to antithrombin with high affinity, leading to a conformational change in antithrombin and increasing its rate of factor Xa inhibition (Nutescu et al. 2005). Thus, thrombin generation is reduced without affecting the circulating thrombin (Nutescu et al. 2005). Fondaparinux is the only commercially available factor Xa inhibitor in the United States. Idraparinux and razaxaban are undergoing clinical trials. Fondaparinux and Idraparinux are administered subcutaneously, while razaxaban is administered orally (Nutescu and Helgason, 2004a; Kaiser, 2003; Ansell, 2004; Davidson, 2003).

Advantages of synthetic factor Xa inhibitors include: no risk of animal pathogen transfer, batch-to-batch consistency, and unlimited sourcing (Nutescu et al. 2005). There is a predictable dose-response relationship, a quicker time to achieve maximum concentration and a long half-life (Nutescu et al. 2005). Factor Xa inhibitors do not require routine coagulation and dose monitoring (Nutescu et al. 2005). The half-life of fondaparinux is 17–21 hours, which allows once daily dosing. Idraparinux, an extended release formulation is being developed for once a week administration. These drugs are not metabolized in the liver, so there are fewer drug interactions (Nutescu et al. 2005). Factor Xa inhibitors do not affect platelet function and also do not react with the heparin-platelet factor 4 (PF4) antibodies (Ansell, 2004; Davidson, 2003; Turpie et al. 2004; Dager et al. 2004a). Therefore, there is lesser risk of HIT. There is no in-vitro cross-reactivity with fondaparinux and antibodies to the heparin-PF4 complex, therefore, this drug might be useful for treatment of patients with HIT and in the prophylaxis of patients with a HIT (Ansell, 2004; Davidson, 2003; Turpie et al. 2004; Dager et al. 2004a).

Fondaparinux is indicated for prophylaxis of venous thrombosis in patients undergoing hip and knee replacement and hip fracture surgery (Nutescu and Helgason, 2004a). It is also

approved by the FDA for the treatment of acute deep vein thrombosis and pulmonary embolism (Nutescu and Helgason, 2004a).

A drawback of these long acting agents is that there is no antidote if the patient bleeds or requires an invasive procedure (Dager et al. 2004a; Gerotziafas et al. 2004). In case of clinically significant bleeding, fresh frozen plasma or recombinant Factor VIIa maybe required to minimize the bleeding (Nutescu et al. 2005; Gerotziafas et al. 2004). Recombinant Factor VIIa is very expensive and can also increase the risk of thrombosis (Gerotziafas et al. 2004). Also, due to renal route of elimination, fondaparinux is contraindicated in patients with severe renal impairment {creatinine clearance less than 30 mL/min} (Tran and Lee, 2003).

The last group of drugs for VTE is the DTIs that bind with thrombin to prevent an interaction between the enzyme and substrate. The parenteral agents in this class of drugs include lepirudin, bivalirudin, argatroban, and desirudin (Nutescu and Wittkowsky, 2004b; Fritsma, 2004). Ximelagatran is a small molecule prodrug that is administered orally (Gustafsson and Elg, 2003). Large phase clinical trials of ximelagatran, in different clinical settings of stroke prevention in patients with atrial fibrillation, VTE prevention after major joint replacement, acute VTE treatment and secondary prevention of VTE, and secondary prevention of myocardial infarction showed that the drug can be used in these settings (Weitz, 2004; Schulman et al. 2003; Olsson, 2003; Dager et al. 2004b). The FDA has recently refused to approve ximelagatran due to concerns of liver toxicity

http://www.thepinksheet.com/FDC/AdvisoryCommittee/Committees/Cardiovascular+and+Renal+Drugs/091004_Exanta/091004_ExantaR.htm

Advantages of DTIs include specificity for thrombin, ability to inactivate the clot-bound thrombin, and absence of plasma protein and platelet interactions (Nutescu et al. 2005; Katira et

al. 2005). The DTIs produce a predictable anticoagulant effect and the variability of patient response is low (Nutescu and Wittkowsky, 2004b; Fritsma, 2004). Lepirudin is approved for use in patients with HIT and related thrombosis (Tran and Lee, 2003; Nutescu and Wittkowsky, 2004b; Fritsma, 2004). Bivalirudin is approved for use in patients undergoing percutaneous transluminal coronary angioplasty (Tran and Lee, 2003; Nutescu and Wittkowsky, 2004b; Fritsma, 2004). Argatroban is approved for the prevention and treatment of thrombosis in patients with HIT and in patients with HIT undergoing percutaneous coronary intervention (PCI) (Nutescu and Wittkowsky, 2004b; Fritsma, 2004; Warkentin, 2004). Desirudin is the first subcutaneously administered DTI and is the first DTI approved for the prevention of VTE after hip replacement surgery. However, it is not commercially available in the United States (Nutescu and Wittkowsky, 2004b). Advantages of ximelagatran over warfarin include: a predictable dose response that does not require dose adjustment or coagulation monitoring, a wider therapeutic index, a rapid onset and offset of action, lack of interaction with drugs metabolized by the CYP450 isoenzyme systems (Gustafsson and Elg, 2003; Crowther and Weitz, 2004).

2.8 Anticoagulation Clinics

Anticoagulation clinics represent the gold standard for long-term warfarin therapy (Macik, 2003). They typically provide structured environment for patient education and counseling, ordering and review of INR results, dosing adjustments, consultation to issues, strategies for long-term oral anticoagulation management such as, patient self-testing with home capillary blood monitors (Wittkowsky, 2004). Chiquette et al. (1998) compared hospitalization and emergency department costs of hypothetical patients in an anticoagulation clinic with anticoagulated patients receiving usual medical care. They found that anticoagulation clinics saved \$1,620 per patient per year, largely owing to fewer hemorrhages & thromboembolic

events. Lafata et al. (2000) compared usual care, care in an anticoagulation clinic, and patient self-testing. In this study they assumed that patients would be in therapeutic INR range 50% of the time with usual care, 65% of the time with anticoagulation clinic care, and 89% of the time with self-testing. The authors concluded that events changing from usual care to an anticoagulation clinic were cost-saving from the individual provider perspective. Changing to patient self-testing was cost-effective from the individual patient perspective. A large health maintenance organization (HMO) in Georgia calculated the per member/ per month cost for outpatient pharmacy anticoagulation service to be \$ 62 (Anderson, 2004).

2.9 Pharmacoeconomic Studies

Thomson et al. (2000) conducted a decision analysis and found that warfarin led to both quality adjusted life years (QALY) gains and lower costs compared with no therapy in patients at high stroke risk. Gage et al. (1995) compared warfarin, aspirin, and no therapy in a hypothetical cohort of 65-year-olds with chronic atrial fibrillation. They found that in high-risk patients (annual stroke rate of 4.9% to 17.6%), warfarin was more effective and more cost-saving than either aspirin or no therapy. In medium risk patients (annual stroke rate of 2.6% to 4.6%), warfarin was better than aspirin in terms of quality-adjusted survival, but cost greater than aspirin, incurring an additional \$8,000 per QALY saved. In the patients with a low risk of stroke, warfarin and aspirin were comparable in terms of quality-adjusted survival (and both were better than no therapy), but warfarin cost an additional \$370,000 per QALY saved in the base case. Hawkins et al. (1998) found that in a LMWH vs. warfarin decision analyses of short-term prophylaxis (4 to 15 days), the balance for favorable results was towards enoxaparin. The expected cost per VTE event avoided was \$2,525 less and \$87,201 less with enoxaparin than with warfarin for each DVT and PE prevented, respectively (Hawkins et al. 1998). In a cost-

effectiveness analysis Garcia-Zozaya¹ et al. (1998) found that the overall cost of care for 15 days of prophylactic therapy in joint replacement patients was lower with enoxaparin than with warfarin. In a Canadian decision analysis, Dranitsaris et al. (2004) found that fondaparinux in hip or knee surgery would prevent an additional 16 VTE events/1,000 patients compared with enoxaparin, resulting in a cost savings of \$55 (Canadian dollars) per patient. In a cost effective analysis, Spruill et al. (2004) found that prophylactic fondaparinux led to an incremental cost savings of \$1,081 per VTE event avoided compared with enoxaparin 30 mg twice daily; the incremental cost per life-year gained was \$5,437 and \$4,925 for enoxaparin and fondaparinux respectively. In a decision analysis by Gordois et al. (2003) fondaparinux prophylaxis was less costly overall than enoxaparin, largely owing to fewer VTE events and fewer VTE-related deaths in joint replacement and hip fracture patients (Gordois et al. 2003). According to a cost- effective analysis by Gould et al. (1999) LMWHs are highly cost-effective for inpatient management of venous thrombosis when compared with usual (i.e. inpatient) care with UFH.

Cost effectiveness of anticoagulation agents depends on stroke risk, bleeding risk, patient preferences, patient age, rates of appropriate use, and local costs of anticoagulation management (Bushnell and Matchar 2004; Gustafsson et al. 1992).

2.10 Invasive Management of VTE

The invasive treatment for deep vein thrombosis includes pharmacological thrombolysis, open surgical thrombectomy, percutaneous mechanical thrombectomy and stenting, adjuvant venous angioplasty and stenting, and inferior vena cava (IVC) filters (Augustinos and Ouriel, 2004).

The National Venous Thrombolysis Registry, the largest published experience with catheter-based local infusion of urokinase to enhance clot dissolution with minimum bleeding

showed that it is a safe and effective treatment of symptomatic iliofemoral DVT (Semba and Dake, 1994). The study by Comerota et al. (2000) demonstrated better quality of life and functioning in patients with iliofemoral DVT treated by catheter-directed thrombolysis compared with the patients treated with anticoagulants alone. According to a pooled analysis by Goldhaber et al. (1984) of randomized trials of streptokinase and heparin in patients with acute DVT, six studies showed that thrombolysis was achieved 3.7 times more often among patients treated with streptokinase than among patients treated with heparin (95 percent confidence limits 2.5, 5.7; p less than 0.0001). The three studies that allowed comparison for major bleeding complications, showed that bleeding complications were 2.9 times greater with streptokinase than with heparin (95 percent confidence limits 1.1, 8.1; $p = 0.04$). Thus, streptokinase-treated patients achieved thrombolysis, but seemed to experience major bleeding complications more frequently than those assigned at random to receive heparin. The contraindications to thrombolytic therapy include increased risk of bleeding complications, such as surgery, stroke, or gastrointestinal bleeding (Augustinos and Ouriel, 2004).

Surgical thrombectomy is reserved for patients with contraindications to pharmacological thrombolysis or in those patients in whom other modalities have failed (Augustinos and Ouriel, 2004). Surgical venous thrombectomy can play a role in patients with acute proximal DVT (Augustinos and Ouriel, 2004). Percutaneous mechanical thrombectomy is logical extension of open surgical thrombectomy and offers the advantage of rapid clearance of thrombus from occluded venous segments (Frisoli and Sze, 2003; Sharafuddin et al. 2003). Motorized thrombectomy devices include rotational thrombectomy and hydrodynamic or rheolytic recirculation devices (Augustinos and Ouriel, 2004). The rotational devices use a high speed rotating impeller to fragment the thrombus, while the hydrodynamic or rheolytic circulation

devices are based on Venturi effect created by high-speed saline jets directed retrograde (Delomez et al. 2001; Augustinos and Ouriel, 2004; Kasirajan et al. 2001). These devices are used in conjunction with pharmacological thrombolysis, except in patients with bleeding diathesis (Kasirajan et al. 2001). The May-Thurner syndrome (left common iliac vein stenosis), often responsible for high rate of re-thrombosis following open surgical venous thrombectomy (Vedantham et al. 2002) usually identified by post-intervention angiography can be treated with percutaneous venoplasty and stenting (Patel et al. 2000; Lamont et al. 2002).

The use of IVC filters has increased in patients with PE, patients with DVT alone, and at-risk patients who have neither PE or DVT (Stein et al. 2004f). Inferior vena cava filters were designed to protect against fatal PE. More than 90% of PEs are secondary to DVT (O'Sullivan et al. 2000). Patient with a contraindication to anticoagulants or those who sustained a complication of anticoagulants should be treated with IVC filters (Augustinos and Ouriel, 2004). Patients with severe cardiopulmonary disease and large free-floating ilio-caval thrombi may benefit from a combination of IVC filters and anticoagulations (Gardner et al. 1974) Contraindications to IVC filters include complete thrombosis and inability to gain access to the IVC (Augustinos and Ouriel, 2004). The IVC filters should be reserved for patients with contraindications to anticoagulation or developing thromboembolic disease despite anticoagulant therapy (Kinney, 2003).

Massive pulmonary embolism is a life-threatening event and requires prompt and aggressive management (Augustinos and Ouriel, 2004). The initial manifestations of PE are followed by mortality in 10% of cases and amongst the survivors, without prompt diagnosis, mortality occurs in 30% of the patients (Augustinos and Ouriel, 2004). When therapy is begun in a timely manner, mortality decreases to 10%. This explains why the mortality rate associated

with PE has not changed over the past 3 decades (Molgaard et al. 1992; Dalen and Alper, 1975). Indications for minimally invasive procedures for pulmonary embolism are arterial hypotension, systemic hypoperfusion and hypoxaemia, need for cardiopulmonary resuscitation, right ventricular failure and or pulmonary hypertension, arterial oxygen-alveolar gradient greater than 50 torr, and contraindications to anticoagulation (Barritt and Jordan, 1960; Konstantinides et al. 1997). Systemic intravenous infusions of thrombolytic agents have proved to be superior to anticoagulation for the PE treatment (Uflacker et al. 1996). Infusion of lytic agents directly into the pulmonary arteries accelerates clot lysis and causes rapid restoration of pulmonary circulation in selected patients with massive PE (Molina et al. 1992; Gonzales-Juanatey et al. 1992). Percutaneous embolectomy and thrombectomy are the minimally invasive options when thrombolytic therapy fails or is contraindicated (Augustinos and Ouriel, 2004). These devices remove, fragment, macerate, or aspirate the embolus, forming smaller particles that finally migrate to the periphery of the pulmonary circulation improving central hemodynamics (Goldhaber et al. 1986). Aklog et al. (2002) and Yalamanchili et al. (2004) have demonstrated that open pulmonary embolectomy can be performed in patients with minimum mortality and morbidity and that it should not be reserved only in patients who are hemodynamically unstable, or in whom thrombolysis has failed. Lastly, endovascular stents in the proximal main pulmonary artery provide relief of cardio-pulmonary compromise in patients with profound arterial hypoxemia, right heart failure and hypotension (Koizumi et al. 1998; Schmitz-Rhode et al. 1998).

2.11 Therapy Practices & Current Issues in Therapy Practice of VTE

There have been encouraging trends in the proper utilization of warfarin in stroke prevention as seen following the publication of major trials with warfarin and the treatment

guidelines based on the trials (Wittkowsky, 2004). The outpatient use of warfarin has increased from below 10% in the early 80s to as high as 50% in the mid-90s (Smith et al. 1999). Despite these findings, current problems with anticoagulation practice are underutilization of anticoagulants and undercoagulation with warfarin (Wittkowsky, 2004). Only half of eligible atrial fibrillation patients receive anticoagulation (Buckingham and Hatala, 2002). A review of 9 studies showed that warfarin use in eligible high risk patients ranged from 22% to 79% (Bushnell and Matchar, 2004). Upto 60% of those receiving warfarin had INRs below the recommended therapeutic range (Bushnell and Matchar, 2004). The DVT FREE Registry conducted at 183 different clinical sites around the US, prospectively evaluated 5451 DVT patients. Of the 2726 patients diagnosed with DVT in the hospital, only 1147 (42%) had received prophylaxis in the past 30 days (Goldhaber et al. 2004). The National Anticoagulation Benchmark and Outcomes Report (NABOR), which is a retrospective analysis of 38 US hospitals shows in its 3 years of data from 2000-2003 in 3778 patients of atrial fibrillation (AF), VTE, acute myocardial infarction, and orthopedic surgery, showed that 55% of AF of high stroke risk were on warfarin, 21% were on no treatment, and 14% of orthopedic surgery patients had no anticoagulation (Tapson et al. 2005).

The widely accepted goal for INR in atrial fibrillation is 2.0–3.0, which is a range aimed at preserving the efficacy, while preventing hemorrhage (Wittkowsky, 2004). An INR less than 2 will lead to stroke, while an INR greater than 4 will lead to intra-cranial bleed (Fuster et al. 2001; Hylek et al. 2003). The slope of the bleeding risk with INR greater than 3 is not as steep as the slope of increased stroke risk with INR less than 2 (Hylek et al. 1994; Hylek et al. 1996). The INRs greater than 2 reduce the frequency of stroke in patients with atrial fibrillation, and also reduce stroke severity and stroke related mortality (Hylek et al. 2003). The NABOR report

showed that 61% patients of AF with high stroke risk were discharged on bridge therapy without a therapeutic INR (Tapson et al. 2005).

Summary

Thus the review of the studies above, throws light on the disease, its epidemiology, costs and treatment options. These studies may help explain causes of any differences in the health outcomes of VTE observed among different populations.

CHAPTER THREE

LITERATURE REVIEW

This literature review will focus on previous publications examining variables that have been included in this study of the relationship between hospital type, geographic locations and insurance type and each of the three outcomes of length of inpatient stay, expenditure, and mortality in venous thromboembolism (VTE).

There are several variables (some known and some unknown) that may modify this relationship (if it exists), as each one of them may impact the outcomes studied. In this review, the focus will be on studies published describing the relationship between the three outcomes mentioned earlier and the following variables: teaching status of hospitals, comorbidity, geographic distribution, gender, payer status, length of stay, gender, investigations and procedures, age, race, and admission type. For some variables, there are no previous publications looking at the relationship between these variables and these three outcomes for VTE. For these variables, studies will be reviewed to see how these variables impact the outcomes in different disease settings.

3.1 Teaching Hospitals

There have been no studies conducted in the past comparing the outcomes of VTE in teaching and non-teaching hospitals. Therefore, studies done in the past that compare the performance for outcomes between teaching and non-teaching hospitals in other diseases will be reviewed. Teaching hospitals may provide care that is more costly and of higher quality as compared to non-teaching hospitals (Allison et al. 2000). According to Donabedian (1966), the

quality measures in general use are principally of three types: structure, process, and outcome. Kupersmith (2005), using Pub Med [a service developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM), located at the National Institute of Health (NIH) that includes over 16 million citations from MEDLINE (NLM's premier bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and the preclinical sciences) and other life science journals for biomedical articles back to the 1950s and includes links to full text articles and other related resources; <http://www.pubmed.gov/>] conducted a literature review of 23 studies published from 1989 to 2004 that compared the quality of care in teaching hospitals with that in non-teaching hospitals. In most of these studies, the outcome measures included mortality, preventable adverse events, survey of patient safety, patient satisfaction and post-surgical complications. The process measures that were used in these studies included use of medications, monitoring, consultations, and procedures. The results of this review showed that although the measures of quality were not at the target level for all the hospitals, teaching hospitals studied had better quality measures than did non-teaching hospitals in majority of these studies.

3.11 Process Measures Comparisons between Teaching and non-Teaching Hospitals

Process measures of quality were mostly better in teaching hospitals in seven of the eight studies in the review (Kupersmith, 2005). These seven studies included clinical studies on pharmacologic therapy in acute myocardial infarction (AMI) (Allison et al. 2000), peer review organization analysis (Kuhn et al. 1991), monitoring and therapy in pediatric (Pollack et al. 1994), adult (Zimmerman et al. 1993) and intensive care units (ICU) (Pollack et al. 1994; Zimmerman et al. 1993), and use of invasive cardiac procedures in patients with AMI, congestive heart failure (CHF) and cerebrovascular accident (CVA) (Polanczyk et al. 2002). The

one process study, which showed equal results for teaching and non-teaching hospital was on patients with community-acquired pneumonia (Whittle et al. 1998).

3.12 Process and Outcome Comparisons between Teaching and non-Teaching Hospitals

Six studies analyzed both outcome (adjusted mortality) and process measures (Allison et al. 2000; Keeler et al. 1992; Polanczyk et al. 2002; Whittle et al. 1998; Zimmerman et al. 1993). Five of these studies, except the one by Whittle et al. (1998) favored teaching hospitals and the process and outcome comparisons were consistent with each other. The study by Whittle et al. (1998) showed generally equal results for the care of patients with community-acquired pneumonia. In one of these studies, mortality differences were eliminated, when process measures related to medication were adjusted for, thus implying to a better relationship to process and care (Allison et al. 2000). In the pediatric ICU study the better process measures in teaching hospitals in teaching hospitals, better process measures (higher use of intraarterial and urinary catheters, mechanical ventilation, and vasoactive drugs) did not match the outcome of adjusted mortality (Pollack et al. 1994).

3.13 Structure, Length of stay, and Cost Comparisons between Teaching and non-Teaching Hospitals

Structural features such as, percentage of specialty-board-certified physicians, nurse/patient ratios, and high-tech equipment were better in the teaching hospitals (Kupersmith, 2005). Risk-adjusted length of stay was greater in teaching hospitals in one study (Zimmerman et al. 1993); depended on diagnosis, in the study by Polanczyk et al. (2002), while it was shorter in teaching hospitals in a third study by Rosenthal et al. 1997. Adjusted costs were higher in teaching hospitals in three studies (Polanczyk et al. 2002; Taylor et al. 1999; Zimmerman et al. 1993).

3.2 Risk Adjustment

Teaching hospitals are known to care for sicker patients (Kupersmith et al. 2005). Therefore, risk adjustments are very essential, otherwise an increased mortality related to intrinsic disease in a sicker patient may be misinterpreted to be related to the quality of care (Kupersmith et al. 2005). As per the review by Kupersmith et al. (2005) adjustments are generally made on the basis of severity of illness, comorbidity, demographics such as, age, sex, socioeconomic status, and location in the hospital such as intensive care unit (ICU). Severity of illness was higher in teaching hospitals (Kupersmith, 2005).

Risk-adjusted mortality was lower in teaching hospitals in 9 out of 15 studies where adjusted mortality was studied (Allison et al. 2000; Hartz et al. 1989; Keeler et al. 1992; Kuhn et al. 1991; Polanczyk et al. 2002; Rosenthal et al. 1997; Silber et al. 1995, Taylor et al. 1999; Zimmerman et al. 1993). Patients in these studies had different diagnoses such as, myocardial infarction, congestive heart failure (CHF), pneumonia, cerebrovascular accident, obstructive lung disease, hip fracture, gastrointestinal hemorrhage, bypass graft patients and ICU patients. There were no significant differences between teaching and non-teaching hospitals for this variable in five of the studies (Cunningham et al. 1999; Fleming et al. 1991; Rogowski et al. 2004; Schultz et al. 1999; Whittle et al. 1998). The patients in these studies had various diagnoses such as, acquired immunodeficiency syndrome (AIDS), low-birth-weight infants, AMI, and pneumonia. Risk-adjusted mortality was significantly lower in non-teaching hospitals in one study by Pollack et al. (1994) in pediatric intensive care units, despite the teaching hospital having a better process of care.

3.3 Hospital Size

Kupersmith (2005) in his review noted that hospitals were further divided as major and minor on the basis of their resident/bed ratios (Allison et al. 2000; Ayanian et al. 1998; Taylor et al. 1999). In seven of eight studies comparing major and minor teaching hospitals, the major hospitals had better outcome end points than did the minor and others (Allison et al. 2000; Ayanian et al. 1998; Taylor et al. 1999; Brennan et al. 1991; Polanczyk et al. 2002; Rosenthal et al. 1997; Taylor et al. 1999; Thomas et al. 2000). According to the review by Kupersmith, 2005, the endpoint gradient rose stepwise from non-teaching to minor or affiliated teaching hospitals to major teaching hospitals (Allison et al. 2000; Ayanian et al. 1998; Brennan et al. 1991). The resident/bed cutoff over which teaching hospitals had better outcomes was .062 (Keeler et al. 1992).

3.4 Other Observations

According to the review by Kupersmith, 2005 hospitals with higher volume, increased occupancy rate, increased proportion of board-certified physicians, and increased technical sophistication (Hartz et al. 1989; Keeler et al. 1992; Kuhn et al. 1991; Kuhn et al. 1994; Pearce et al. 1999; Schultz et al. 1999; Silber et al. 1995) generally had better process and outcome measures irrespective of the teaching status. This observation was not seen in the study conducted by Rogowski et al. (2004).

3.5 Comorbidity

Restrictive criteria during selection help decrease the confounding effect of comorbid diseases (Charlson and Horwitz, 1984; Sackett and Gent, 1979). However, eliminating patients without comorbid diseases limits the generalizability of the study (Charlson and Horwitz, 1984;

Sackett and Gent, 1979). Comorbidity and severity by their confounding effect will obscure the relationship between the independent and the dependent variables. Comorbidity is a major risk factor for short term mortality (Greenfield et al. 1988; Jencks et al. 1988; Iezzoni et al. 1994). Therefore risk adjustment is essential in any study comparing outcomes, especially in conditions where patients are not randomly assigned to different treatments (Iezzoni et al. 1992).

Charlson et al. (1987) devised a method for classifying comorbidity, for estimating the risk of death from comorbid disease that can be used in longitudinal studies. Charlson et al. (1987), described a method of classifying comorbidities according to their prognostic significance. The original comorbidity index was developed based on the 1-year mortality from an inception cohort study of 604 patients admitted to the medical service at New York Hospital during one month in 1884. This comorbidity index was validated for its ability to predict risk of death from comorbid disease in breast cancer patients. The method worked well in identifying patients, especially low to high risk of subsequent comorbid death (Charlson et al. 1987).

Romano et al. (1993) adapted the Charlson comorbidity index for use with International Classification of Disease-9-Clinical Modification (ICD-9CM) for administrative data. Of the thirty clinically important comorbidities identified by Charlson et al. (1987) nineteen had adjusted relative risks of 1-year mortality greater than 1.2 from a proportions hazard model (Romano et al. 1993). Each of these predictors was assigned a weight of 1, 2, 3, or 6 based on the magnitude of the adjusted relative risk. These weights were added up to produce a total comorbidity score for the patient (Romano et al. 1993).

D'Hoore et al. (1996) used the Charlson's comorbidity score and adapted it to ICD-9 codes. The main feature of this adaptation was that the authors used only the first 3 digits of the ICD-9 codes. Secondly, codes related to the procedures could not be used as the authors used the

ICD-9 code and not the ICD-9-CM classification. The Charlson index is strongly associated with inpatient death. (D’Hoore et al. 1996).

3.6 Geographic Locations

Proctor et al. (2004) studied the incidence of VTE and its associated mortality using the Nationwide Inpatient Sample (NIS) data between 1993 and 2000. They stratified the variables according to the United States census regions (Northeast, Midwest, South, and West) to test for geographic differences. Proctor et al. (2004) found that regions differed with respect to incidence, mortality, comorbidity score, methods of diagnosis, (phlebography, duplex ultrasonography, ventilation perfusion {V/Q scan}, and pulmonary angiography), treatment (heparin and inferior vena cava filters {IVC} filters) and hospitalization charge. All comparisons were statistically significant with p less than 0.001. The incidence of VTE was highest in the Midwest (1030.5 per 100,000 discharges). It was lowest in the West (817.4 per 100,000 discharges). Incidence of phlebography as a diagnostic tool was highest in the Northeast (7%) and lowest in the West (4.1%). The frequency of Duplex ultrasonography was highest in the West (38.9%) and lowest in the South (11.9%). Mortality in VTE patients varied from 6.3% in the Midwest to 7.9% in the Northeast. The Charlson Romano comorbidity index was associated with a difference in the regional mortality. The Midwest had the lowest comorbidity score 0.48 and the lowest mortality rate. The Northeast had the highest comorbidity score (0.54) and the highest mortality rate (7.9%). The authors also observed that the incidence of DVT has been stable over a 12-year period, suggesting that the current prophylactic studies have not been successful. Age was an important factor associated with mortality, and age greater than 65 years had an odds ratio of 1.84 (confidence interval: 1.79 – 1.89). Comorbidities were associated with a greater risk of mortality; there being a fourfold increased risk (odds ratio 3.62, confidence

interval: 3.01-3.16) with 3 or more comorbidities. A diagnosis of PE was associated with increased mortality (odds ratio 3.08, confidence interval: 3.01 – 3.16). White race (odds ratio 0.82), female gender, (odds ratio 0.9) and an admitting diagnosis of venous sufficiency (odds ratio 0.32) had a protective effect.

Proctor et al. (2004) explained that in the South, patients may undergo diagnostic testing before hospital admission, therefore the coding does not appear in the NIS database. In the West, patients undergo diagnostic testing as a part of hospitalization (Proctor et al. 2004). Mortality and the use of vena cava filters in the West region are low when compared with the Northeast. The use of imaging studies in the West is the highest in the four regions. According to Proctor et al. (2004), there maybe a high level of suspicion of VTE and therefore a lower mortality rate in the West. As outpatient treatment of VTE has gained wide acceptance, Proctor et al. (2004) expect a change in the rate of discharges related to VTE in the future.

The economic data also demonstrated regional differences. The Western region had the highest mean charge \$31,380 per discharge, followed by the Northeast (\$26,037) per discharge. The Midwest and South were lower at (\$19,767) per discharge and (\$20,873) per discharge. There was no statistical association between the Charlson comorbidity score and the charge. Proctor et al. (2004) suggest that the charges maybe due to different practice patterns in the four regions, as observed by a threefold greater use of duplex imaging and pulmonary angiography in the West compared with the South.

The length of stay was consistent in the 4 regions, with a mean hospitalization of 6.5 days (range being 6-7 days). The West had the highest charge, the shortest length of stay, a low comorbidity score, and a low mortality rate.

Doppler ultrasound was being increasingly accepted as the standard for diagnosis and was the most frequently used means of diagnosing DVT. Also, pulmonary angiography was being increasingly used as against V/Q scan, and was the preferred method for the diagnosis of pulmonary embolism. There was an increasing trend towards acceptance of IVC filters. This was seen due to expansion of the filter use indications to include prophylaxis. Regional differences existed in the rate of acceptance of IVC and ultrasonography diagnosis of VTE. The Northeast had the highest use phlebography (7%) and of IVC filter usage (33.7%). The West region had the highest use of Duplex ultrasonography (38.9%) for the diagnosis of VTE and the use of pulmonary angiography for PE (31.9%).

Stein et al. (2004a) evaluated the rates of diagnosis of DVT, PE, and VTE (PE and/or DVT) and the mortality rate of PE in hospitalized patients in 4 regions of the United States using the data from the National Hospital Discharge Survey and the United States Bureau of the Census. The authors observed that the western region of the United States showed a lower rate of diagnosis of DVT and VTE and a lower mortality rate of PE than any other region.

Lilienfeld and Godbold (1992) investigated the geographic distribution of PE mortality rates in the United States from 1980 to 1984. The authors found that men had greater PE mortality rates than women in most regions, and nonwhites had greater PE mortality rates than whites for age groups 40 to 64 and greater than 65. For the age group less than 40, men had equal mortality rate, as did women for the white population and most of the non-white population. The PE mortality rates for the non-whites were 2 to 3 times those for whites. The Pacific region was an exception to this pattern and all the age and gender groups had the same PE mortality rates. The PE mortality rate in the Pacific was lower than rates in all other parts of the country, particularly among nonwhites. Also, in the mountain region, the PE mortality rate was lower for

non-white women compared to white women in all the age groups. The higher proportion of Asians and Hispanics in the Pacific region may have affected these results. The increased risk of atherosclerosis and thrombogenesis in the Hispanics may be offset by the lower risk of atherosclerosis among Asian-Americans (Lilienfeld and Godbold, 1992).

Asians-Americans appear to be more sensitive to warfarin than whites (Takahashi and Echizen, 2003). The target range of the international normalized ratio in the Japanese patients with nonvalvular atrial fibrillation is 1.5 to 2.1 and for mechanical prosthetic valves is 1.5 to 2.5 as against 2-3 for most indications seen in North America (Matsuyama et al. 2002; Hirsh et al. 2001). This may suggest a more ready attainment of an anticoagulant state (Klatsky et al. 2000). Thus, there is literature suggesting that racial differences do exist in the epidemiology of VTE.

3.7 Payer Status

There is no literature in the past that describes the relationship between health insurance status and the length of stay, total charges and mortality for VTE hospitalizations. Studies have been conducted in the past looking at the relationship between the payer status and resource utilization for other diseases, such as myocardial infarction. A few studies will be reviewed here to see how payer status influences outcomes in different disease settings.

Sada et al. (1998) analyzed the National Registry of Myocardial Infarction (NRMII) data and concluded that patients with commercial insurance were more likely to undergo coronary arteriography than patients who were uninsured or who had Medicaid or health maintenance organization (HMO) insurance. Also, there was a higher in hospital mortality in the Medicaid cohort according to Sada et al. (1998).

Canto et al. (2000) compared a national cohort of 332,221 patients with AMI (from 1994 to 1996) within 5 payer groups to study the influence of payer status on hospital resource

allocation for AMI in the United States. They found that Medicare comprised the largest proportion (56%), followed by commercial insurance (25%), HMO (10%), uninsured (6%), and Medicaid (3%). They also observed that compared with commercially insured patients, Medicare and Medicaid patients received fewer reperfusion therapies, underwent fewer invasive cardiac procedures, and had longer hospitalizations. Medicare recipients were as likely as commercially insured patients to receive acute reperfusion therapies or any invasive cardiac procedure after adjusting for differences in clinical characteristics. Canto et al. (2000) concluded that uninsured and HMO patients tended to utilize hospital resources with intermediate frequency. According to the study, Medicare recipients aged 65 years or older and the HMO group had similar hospital mortality rates compared with the commercial group (Odds Ratio 1.07; 95% confidence interval [CI], 0.96-1.20 and OR, 0.93; 95% confidence interval, 0.83-1.04, respectively), but Medicaid and uninsured groups had higher hospital mortality rates compared with the commercial group (Odds Ratio, 1.30; 95% confidence interval, 1.14-1.48 and Odds Ratio, 1.29; 95% confidence interval, 1.12-1.48, respectively).

Young and Cohen (1992) compared the process and outcome measures of hospital care for Medicaid versus privately insured hospital patients. They studied 4,033 emergency patients admitted with a principal diagnosis of AMI to hospitals in Massachusetts in 1987. After adjusting for clinical, demographic characteristics, and the type of hospital where treatment occurred, they found that the Medicaid patients had longer hospital stays, but were less likely to receive selected coronary procedures. Also, the risk of death for Medicaid patients was almost twice as high as for privately insured patients.

Hadley et al. (1991) analyzed discharge abstracts for 592,598 patients hospitalized in 1987 in a national sample of hospitals. They found that that the condition of individuals on

admission to the hospital, resource utilization during hospitalization, and the likelihood of in-hospital death depended on whether the individual had health insurance. The actual in-hospital death rate was 1.2 to 3.2 times greater among uninsured patients in 11 of the 16 cohorts studied. The uninsured were 29% to 75% less likely to undergo high-cost procedures, and 50% less likely to have normal results on the tissue pathology reports for biopsies performed. Hadley et al. (1991) concluded that insurance status is associated with a several aspects of hospital care. Thus previous literature suggests a relationship between the payer status and outcomes.

3.8 Length of stay

Length of stay is an important determinant of total cost of care (Lave and Leinhardt, 1976). Knight et al. (2005) analyzed the Premier Healthcare Informatics, a large administrative hospital database for the period January 1999 and December 2000 to assess utilization of health care resources, and hospital costs associated with various treatments during inpatient care for VTE. They identified 953 primary DVT and 3933 primary PE admissions. Most admissions involved treatment with unfractionated heparin (UFH) and vitamin K antagonist (VKA) (UFH/VKA, 64.2% of admissions), followed by UFH with VKA and low-molecular-weight (LMWH) heparin (UFH/LMWH/VKA, 14.4%), and LMWH/VKA (12.9%). Compared with those treated with UFH/VKA, patients treated with LMWH/VKA experienced higher anticoagulant costs (\$540 versus \$106), but lower total hospital costs (\$5,198 versus \$5,977) and shorter lengths of stay (4.4 versus 5.7 days for those without PE and 5.7 vs. 6.7 days). The authors concluded that despite the higher medication cost, treatment with LMWH/VKA was associated with significantly shorter hospital stays and lower total hospitalization costs, compared with UFH/VKA (Knight et al. 2005).

Increase in the length of stay conflicts with the cost-reduction pressures of managed care (Shwartz et al. 1997). The cost-cutting strategies of managed care aimed at restricting the volume and mix of services has been the focus of much criticism (Berg and Chattopadhyay, 2004).

De Jong et al. (2004) examined the influence of type of insurance and the influence of managed care for seven Diagnosis Related Groups (DRGs): two medical (chronic obstructive pulmonary disease and congestive heart failure), one surgical (hip replacement) and four obstetrical (hysterectomy with and without complications and Cesarean section with and without complications using the New York Statewide Planning and Research Cooperative System (SPARCS) data for the years 1999, 2000 and 2001. They found that the average length of stay did not differ between managed and non-managed care patients, and they concluded that the type of insurance does not affect length of stay.

Managed care insurers use various utilization management strategies to decrease the health care costs (de Jong et al. 2004). Physician performance is judged on the length of stay among other things (de Jong et al. 2004). Methods employed to reduce costs include using the primary care physician as a gatekeeper, reducing the length of stay, and negotiating reduced payments to providers for services (Fairfield et al. 1997a; Fairfield et al. 1997b). Patient insurance significantly affects the hospital length of stay (Shi, 1996).

Bradbury et al. (1991) compared the length of hospital stay for 10 most frequently occurring DRGs in Independent Practice Association (IPA), HMOs and traditional insurance programs. Hospital admissions from 10 IPAs were compared with admissions to the same hospital of persons covered by Blue Cross and Blue Shield Plans or commercial insurance programs. All 10 IPAs exhibit shorter lengths of stay as indicated by negative beta coefficients, and in 6 of the 10 IPAs, this coefficient is statistically significant (p less than .05).

A review carried by Miller and Luft (1994) reported that the length of stay was 1% to 20% shorter for patients in Health Maintenance Organizations in 15 out of 16 observations from 13 studies carried out from 1980 forward.

There have been studies for other diagnoses, such as congestive heart failure where hospital characteristics and insurance types have been associated with the mortality, length of stay, and expenditure (Joshi et al. 2004).

3.9 Gender

Stein et al. (2003a) conducted a study to assess whether there is a sex disparity in the diagnostic tests used for detecting DVT or PE. They analyzed the cross-sectional samples of non-institutional hospitals in the 50 states and the District of Columbia from 1979 through 1999 using data from the National Hospital Discharge Survey. They found that the age-adjusted rates of the diagnosis of PE and DVT, utilization of ventilation-perfusion lung scans, venous ultrasonography of the lower extremities, contrast venography, and duration of hospitalization for PE or DVT were comparable in men and women.

3.10 Trends in Investigations and Procedures

Stein et al. (2003b) analyzed the practice trends in the diagnostic testing of DVT and PE using the National Hospital Discharge Survey (NHDS) database from the period 1979 -1999. They studied the procedure fields of the NHDS discharge data of patients having DVT or PE, who underwent venography, arteriography of the pulmonary arteries, pulmonary scintigraphy, or DVT ultrasonic scanning. The authors searched the EMBASE, MEDLINE, and the American Thoracic Society guidelines, and compared trends in procedure use in VTE using these guidelines. Changes in the diagnostic tests correlated over time with the publication of

prospective, randomized studies. Results for DVT showed an initial marked increase in the use of venography followed by a rapid decline that coincided with increased use of Doppler ultrasonography. Results for PE showed an initial marked increase in lung scanning followed by a rapid decline, while the use of ultrasonography increased considerably and pulmonary angiography increased modestly.

Stein et al. (2004b) assessed the proportion of imaging tests for PE, by computed tomography (CT), ventilation perfusion (VQ) lung scan, pulmonary angiography, and venous ultrasound from 1979 to 2001, using the National Hospital Discharge Survey. The authors found that by 2001, there were a higher proportion of imaging tests with CT than VQ scans (36% vs. 32%). Also, a large proportion of patients continued to have VQ scans (Stein et al. 2004b).

Lilienfeld et al. (1990b) examined hospital discharge data for all acute care facilities (except for the Veterans Administration Medical Center) in the Minneapolis- St. Paul metropolitan area in each year from 1979 to 1984 for persons aged 30 to 74 years. They found that with the exception of men younger than 55 years of age, all groups experienced significant decline in the pulmonary embolism discharge rate. No significant temporal changes were observed in any of the case fatality rates. Lilienfeld et al. (1990b) suggest that these patterns might reflect improved ascertainment of cases and better prevention of disease.

3.11 Age

Stein et al. (2004c) analyzed the practice trends in the diagnostic testing of deep vein thrombosis and pulmonary embolism using the National Hospital Discharge Survey (NHDS) database from the period 1979–1999 in the elderly. The rate of diagnosis for DVT in elderly (greater than 70 years) was constant from 1979 to 1990 but increased markedly from 1990 to 1999. Rate ratios (ratio of the rate of diagnosis for elderly to the rate of diagnosis for younger

patients) were used for comparisons. The rate of DVT diagnosis was higher for elderly patients (age greater than 70 years) than for younger patients (20-69 years old) (rate ratio, 4.72; 95% confidence interval, 4.30-5.14; p less than .001). The rate of PE diagnosis was greater among elderly patients (age greater than 70 years) than among younger patients (20-69 years old) (rate ratio 6.20; 95% confidence interval, 5.74-6.65; p less than .001). The rate of PE diagnosis decreased from 370 per 100,000 population in 1979 to 254 per 100,000 population in 1990. From 1990 to 1999, the rate was constant among those 70 years or older. The younger patients (20-69 years old) showed a slight but significant decline in the PE rate between 1979 and 1990 (p less than .001). This was followed by an increase in the rate from 1990 and 1999 (p less than .001). In all age groups the rate of diagnosis of PE significantly decreased from 1979 to 1990 (p less than .001). From 1990 to 1999, the rates remained constant in all age groups except in the 20- to 39-year-old age group, whose rate increased slightly. Contrast venography use was higher in elderly than in younger patients (p less than .001). Between 1989 and 1999, more venous ultrasound tests of the lower extremities were performed in the elderly population (less than 70 years) than in the younger population (20-69 years old) (p less than .001). The rate of use of lung scans for the 21-year study period was highest in elderly patients (p less than .001). However, lung scan use declined in all age groups as Doppler ultrasonography became common. The rate of pulmonary angiography for the 21-year study period was higher in elderly than in younger patients (p less than .001). Pulmonary angiography use increased from 1979 to 1999 for both elderly and younger patients. Patients aged 30 to 39 years have almost a 2-fold increase in the risk of DVT or PE compared with younger patients. The elderly are at the greatest need for thromboprophylaxis as supported by a 18 to 28 fold increase in the risk for DVT or PE in patients 70 years or older compared with those aged 20 to 29 years (Stein et al. 2004c).

3.12 Race

The incidence of deep vein thrombosis in hospitalized adults in the African-Americans was 0.9/100 hospitalizations, and 1/100 hospitalization in the white race (Stein et al. 2004d). The incidence of PE in hospitalized adults (age greater than or equal to 20) in the African-Americans and whites was 0.4 % (Stein et al. 2004d). Stein et al. (2004d) examined the data for VTE for the period 1990 through 1999 from the National Hospital Discharge Survey. They found that the rates of diagnosis of deep venous thrombosis, pulmonary embolism, and venous thromboembolism; incidences in hospitalized patients; and the mortality rate from pulmonary embolism were markedly lower in Asians/Pacific Islanders than in whites and African Americans.

Stein et al. (2004e) studied the rate of diagnosis of DVT and PE in American Indians and Alaskan Natives using the combined data from the National Hospital Discharge Survey (nonfederal hospitals) and the Indian Health Service (federal hospitals) from 1996 through 2001. The rate ratio comparing the rate of diagnosis of VTE in American Indians and Alaskan Natives with African Americans was 0.46 (95% confidence interval, 0.45-0.47) and comparing American Indians and Alaskan Natives with whites was 0.54 (95% confidence interval, 0.53-0.55). Stein et al. (2004e), suggest that this maybe due to the lower prevalence of factor V Leiden in American Indians and Alaskan Natives as observed by Ridker et al. (1997) an explanation also offered by White et al. (1998).

Klatsky et al. (2000) prospectively studied PE/DVT hospitalizations in 128,934 persons in relation to traits determined at health examinations in 1978 to 1985. Through 1994, 337 persons were subsequently hospitalized for PE and/or DVT (for PE first, N = 206). Cox proportional-hazards models with 9 covariates were used. In multivariate models, the following

relative risks (RRs) (95% confidence intervals) were found for PE/DVT combined: black/white = 1.1 (0.4 to 1.4); Hispanic/white = 0.7 (0.3 to 1.5); and Asian/white = 0.2 (0.1 to 0.5; $p = 0.002$). The lower risk of Asians was present in both sexes and for persons, first hospitalized for either PE or DVT. Covariates with significant positive relations to risk were age, male sex, body mass index, and a composite coronary disease risk/symptom variable; covariates not significantly related were education, marital status, smoking, and alcohol. These data suggest that Asians have very low risk of PE/DVT, which may account for US geographic variations in white/non-white risk differences. Possible explanations include the absence of hazardous mutations or unspecified PE/DVT protective traits in Asians (Klatsky et al. 2000).

White et al. (1998) analyzed the California Patient Discharge Data Set from 1991 to 1994 to determine the incidence of deep venous thrombosis among ethnic groups. They found that the for the annual incidence of idiopathic deep venous thrombosis per 1,000,000 persons older than 18 years of age was higher for the African Americans (rate ratio, 1.27 [95% confidence interval, 1.07 to 1.51]), lower for Hispanic persons (rate ratio, 0.60 [CI, 0.54 to 0.67]), and for Asians and Pacific Islanders (rate ratio, 0.26 [CI, 0.22 to 0.30]) compared with whites.

Lilienfeld et al. (1990a) reviewed the mortality for PE in the United States from 1962 to 1984. They found that the age-adjusted PE mortality increased by 67 to 100 percent between 1962 and 1974 for white and non-white men and women. It declined by 20 to 28 percent from 1975 to 1984. The non-white PE mortality was greater than white PE mortality and men had a greater risk of PE death than women.

Kniffin et al. (1994) analyzed all Medicare claims during the period 1986 through 1989 from a random 5% sample of US Medicare enrollees. They identified cases of PE and DVT and analyzed the cohorts to provide incidence by age, race, sex, and geographic location. They

observed that the annual incidence rates per 1000 for PE and DVT increased from 1.3 and 1.8, respectively at age 65 to 69 years to 2.8 and 3.1 respectively by age 85 to 89 years. For PE, women had lower rates than men (adjusted relative risk, 0.86; 95% confidence interval, 0.82 to 0.90), and blacks had higher rates than whites (adjusted relative risk, 1.25; 95% confidence interval, 1.15 to 1.36). For DVT, the associations with gender and race were weaker and in the opposite direction. The in-hospital mortality associated with PE and DVT was 21% and 3%, respectively.

3.13 Admission Type and Length of stay

Emergency room admission with a VTE diagnostic code was associated with 65% increased mortality in the study conducted by Proctor et al. (2004). Furthermore, Liew et al. (2003) observed that emergency department length of stay correlates strongly with the inpatient length of stay, and predicted whether length of stay exceeds the state average inpatient length of stay for the relevant diagnosis-related group.

Summary

Thus after reviewal of the studies above, there appears to be a gap in the reported literature. Thus, this study will be conducted to determine the relationship between geographic locations, hospital characteristics and insurance type on the outcomes of length of in-patient stay, mortality, and expenditure in VTE. The findings of this study will be interpreted in the light of previous literature.

CHAPTER FOUR

RESEARCH OBJECTIVES AND HYPOTHESES

There are studies in the past that have investigated the influence of geographic location and the clinical and economic outcomes of venous thromboembolism (VTE) (Proctor et al. 2004; Lilienfeld et al. 2004a; Lilienfeld et al. 2004b; Lilienfeld and Godbold 1992). However, there is no current study examining the influence of hospital characteristics and geographic region (as per the United States Census Bureau) at the national level, using the 2003 Nationwide Inpatient Sample dataset on the clinical and economic outcomes of VTE.

The main purpose of this study is to investigate the impact of hospital characteristics and geographic locations on the clinical and economic outcomes of VTE. The objectives of this study are: (1) to compare the mortality, length of hospital stay and expenditures for inpatient hospitalization for VTE patients from hospitals with different characteristics, and from different geographic regions using the 2003 HCUP nationwide inpatient sample. (2) Secondly, this study will also examine the relationship between the type of health insurance plan and mortality for inpatient VTE hospitalization. The specific hypotheses to be tested are:

Hypothesis 1

After adjusting for other independent variables (see below for details), the variables hospital census region, hospital teaching status, and hospital bed size in patients with VTE are not significant for explaining differences in length of stay.

Multilinear regression will be used to test this relationship after controlling for the variables: age, gender, race, payer status, total number of diagnoses, total number of procedures,

admission type, and comorbidities. Many of these variables have been established as predictors of health outcomes in VTE. (Stein et al. 2004; Stein et al. 2004; Kniffin et al. 1994; Klatsky et al. 2000).

The adapted Charlson Comorbidity index as described by D’Hoore et al. (1996) will be used to determine the comorbidity index. This adapted Charlson index assigns a weighted index and is commonly used with administrative databases to evaluate patient’s comorbidities.

Hypothesis 2

After adjusting for other independent variables (see below for details), the variables hospital census region, hospital teaching status, and hospital bed size in patients with VTE are not significant for explaining differences in total charge.

Multilinear regression will be used to test this relationship controlling for length of stay, age, gender, race, payer status, total number of diagnoses, total number of procedures, admission type, and comorbidities.

Hypothesis 3

After adjusting for other independent variables (see below for details), the variables hospital census region, hospital teaching status, and hospital bed size in patients with VTE are not significant for explaining differences in mortality.

Logistic regression will be used to test this relationship, after controlling for length of stay, age, gender, race, payer status, total number of diagnoses, total number of procedures, admission type, and comorbidities.

Hypothesis 4

After adjusting for other independent variables (see below for details), the variable payer status in patients with VTE is not significant for explaining differences in mortality.

Logistic regression will be used to test this relationship, after controlling for length of stay, age, gender, race, total number of diagnoses, total number of procedures, admission type, hospital census region, hospital teaching status, and hospital bed size, and comorbidities.

Hypothesis 5:

After adjusting for other independent variables (see below for details), the variables race and gender in patients with VTE are not significant for explaining differences in mortality. Logistic regression will be used to test this relationship after controlling for length of stay, age, payer status, total number of diagnoses, total number of procedures, admission type, hospital census region, hospital teaching status, and hospital bed size, and comorbidities.

CHAPTER FIVE

METHODS

This chapter contains the description of the data sources, the data files used for the analysis, the exclusion and inclusion criteria, variables used in this study, the descriptive analysis for the expenditure, length of stay, and mortality for VTE, and the statistical methods employed for the explanatory analysis using multiple regression model for the expenditure, and length of stay, and the logistic regression model for the mortality for venous thromboembolism (VTE).

5.1 Data Sources:

The data was drawn from the Nationwide Inpatient Sample, (NIS) 2003, which is a part of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS is a database of hospital inpatient stays. It is used by researchers and policymakers to identify and analyze national trends in healthcare utilization, access, charges, quality, and outcomes.

The NIS is the largest all-payer inpatient care database that is publicly available in the United States. The NIS contains data from 5 to 8 million hospital stays from about 1,000 hospitals sampled to approximate a 20-percent stratified sample of U.S. community hospitals. The NIS contains all-payer data on hospital inpatient stays and has patient-level clinical and resource use information included in a typical discharge abstract. All discharges from sampled hospitals are included in the NIS database. The NIS is the only national hospital database with charge information on all patients, regardless of payer, including people covered by Medicare, Medicaid, private insurance, and the uninsured.

The NIS is designed to approximate a 20-percent sample of U.S. community hospitals, defined by the American Hospital Association (AHA) to be “all nonfederal, short-term, general, and other specialty hospitals, excluding hospital units of institutions.”(Agency for Healthcare Research and Quality, "Nationwide Inpatient Sample (NIS)," September 2003, <http://www.hcup-us.ahrq.gov/nisoverview.jsp> p6). The community hospitals include specialty hospitals such as obstetrics-gynecology, ear-nose-throat, short-term rehabilitation, orthopedic, pediatric institutions, public hospitals, and academic medical centers. Excluded from the NIS are short-term rehabilitation hospitals (beginning with the 1998 data), long-term hospitals, psychiatric hospitals, and alcoholism/chemical dependency treatment facilities.

This universe of U.S. community hospitals is divided into strata using five hospital characteristics: ownership/control, bed size, teaching status, urban/rural location, and U.S. region. The NIS is a stratified probability sample of hospitals in the frame, with sampling probabilities proportional to the number of U.S. community hospitals in each stratum.

The data files in NIS include four types of fixed-width ASCII formatted files. They are as follows:

5.1.1 Inpatient Core File:

This inpatient discharge-level file contains data for 100% of the discharges from a sample of hospitals in participating states. The unit of observation is an inpatient stay record.

5.1.1.1. Subsample Inpatient Core Files:

Each of these discharge-level files contains all data elements from the Core File for a 10% subsample of discharges from the NIS. The unit of observation is an inpatient stay record.

5.1.2 Hospital Weights File:

This hospital-level file contains one observation for each hospital included in the NIS and contains linkage data elements. The unit of observation is the hospital. The HCUP hospital identifier (HOSPID) provides the linkage between the NIS Inpatient Core files and the Hospital Weights file. The hospital universe is defined by all hospitals that were open during any part of each calendar year and were designated as community hospitals in the AHA Annual Survey of Hospitals. Five hospital sampling strata have been defined based on hospital characteristics contained in the AHA Annual Survey of Hospitals. The stratification variables are:

1) Geographic Region: Northeast, Midwest, West, or South, as defined by the U.S. Census bureau.

2) Location: urban or rural. A metropolitan statistical area is considered urban.

3) Teaching Status: teaching or non-teaching. A hospital is considered to be a teaching hospital if it has an American Medical Association approved residency program, is a member of the Council of Teaching Hospitals (COTH) or has a ratio of full-time equivalent interns and residents to beds of .25 or higher. Rural hospitals were not split according to teaching status, because rural teaching hospitals were rare.

4) Control: government nonfederal (public), private not-for-profit (voluntary) or private investor-owned (proprietary). When there were enough hospitals of each type to allow it (southern rural, southern urban non-teaching, and western urban non-teaching), hospitals were stratified as public, voluntary, and proprietary. For smaller strata (mid western rural and western rural hospitals) a collapsed stratification of public versus private was used with the voluntary and proprietary hospitals combined to form a single 'private' category. For all other combinations of region, location and teaching status, no stratification based on control was advisable given the number of hospitals in these cells.

5) Bed size: small, medium, or large. Bed size categories are based on hospital beds, and are specific to the hospital's location and teaching status. Bed size cut -off points were chosen so that approximately one-third of the hospitals in a given region and location/teaching combination would be in each bed size category (small, medium, or large).

To ensure geographic representativeness, implicit stratification variables included state and three-digit zip code (the first three digits of the hospital's five digit zip code). The hospitals were sorted according to these variables prior to systematic random sampling.

5.1.3 Disease Severity Measures Files:

These discharge-level files contain information from four different sets of disease severity measures. The unit of observation is an inpatient stay record. The HCUP unique record identifier (KEY) provides the linkage between the Core files and the Disease Severity Measures files.

For this study, the two Subsample Inpatient Core Files were combined to create a 20% NIS subsample of discharges. This dataset containing the 20% NIS subsample of discharges was merged with the Hospital Weights File with. The HCUP hospital identifier (HOSPID) provided the linkage between the two files.

5.2 Exclusion and Inclusion Criteria:

This was a cross-sectional retrospective cohort study. The NIS 2003 database was used to compare the length of stay, expenditures, and mortality in venous thromboembolism (VTE) between hospital census location, hospital teaching status, hospital bedsize and hospital region. Patients of venous thromboembolism were identified using the following International Classification of Disease-9-Clinical Modification (ICD- 9CM codes):

415.1 Pulmonary embolism and infarction

415.11 Iatrogenic Pulmonary embolism

415.19 Other pulmonary embolism

451.1 Phlebitis and thrombophlebitis of deep vessels of lower extremities

451.11 Phlebitis and thrombophlebitis of femoral vein (deep)

451.19 Phlebitis and thrombophlebitis of deep vessels of lower extremities: Other
(Femoropopliteal vein Popliteal vein tibial vein)

451.81 Phlebitis and thrombophlebitis of other sites: Iliac vein

453.2 Other venous embolism and thrombosis, of vena cava

453.8 Other venous embolism and thrombosis of other specified veins

5.3 Data Analysis

The dependent variables were as follows:

Length of stay

Expenditure

Mortality

The independent variables of interest for the outcomes, length of stay and expenditure were hospital census region, hospital teaching status, and hospital bed size. This is an important stratifier for this study since practice patterns have been shown to vary substantially by region (Agency for Healthcare Research and Quality, "Nationwide Inpatient Sample (NIS)," 2003, NIS, 2003 documentation). **Table 3** gives the list of the independent categorical variables. The variable for the hospital region HOSP_REGION was coded as '1' Northeast '2' Midwest '3' South and '4' West. The variable for hospital location, HOSP_LOCATION was considered as '0' for rural and '1' for urban.

Bedsizes categories are based on hospital beds, and are specific to the hospital's location and teaching status. Bedsizes assesses the number of short-term acute beds in a hospital. Rural hospitals were not split according to teaching status, because rural teaching hospitals were rare. The variable for hospital location, HOSP_BEDSIZE was considered as '1' small '2' medium and '3' large as shown in **Table 1**. The variable for hospital teaching status, HOSP_TEACH was coded as '0' for non-teaching and '1' for teaching status.

Table 1 Categories of Bedsizes

BEDSIZE CATEGORIES (Beginning in 1998)			
Location and Teaching Status	Hospital Bedsizes		
	Small	Medium	Large
NORTHEAST REGION			
Rural	1-49	50-99	100+
Urban, nonteaching	1-124	125-199	200+
Urban, teaching	1-249	250-424	425+
MIDWEST REGION			
Rural	1-29	30-49	50+
Urban, nonteaching	1-74	75-174	175+
Urban, teaching	1-249	250-374	375+
SOUTHERN REGION			
Rural	1-39	40-74	75+
Urban, nonteaching	1-99	100-199	200+
Urban, teaching	1-249	250-449	450+
WESTERN REGION			
Rural	1-24	25-44	45+
Urban, nonteaching	1-99	100-174	175+
Urban, teaching	1-199	200-324	325+

Reference p24: http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2003_v7.pdf

Age, gender, race, payer status, total number of diagnoses, total number of procedures, admission type, and comorbidities were included as independent variables and used to control for differences in the length of stay. Besides, all these above mentioned variables, logarithm of length of stay was used to control for expenditures.

Age was treated as a continuous variable. Gender was treated as a dichotomous variable and coded as '0' for male and '1' for female. Race was treated as classificatory variable and coded as '1' White, '2' Black, '3' Hispanic, '4' Asian or Pacific Islander, '5' Native American, '6' Other. Payer status was treated as classificatory variable (PAY1) and indicates the expected primary payer (Medicare, Medicaid, private insurance, etc.). Payer 1 was coded as PAY1=1 for Medicare and PAY1 = 2 for Medicaid patients. Private insurance (PAY1=3) includes Blue Cross, commercial carriers, and private Health Maintenance Organizations (HMO) and Preferred Provider Organizations (PPO). Other (PAY1=6) includes Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs. No charge i.e. (PAY1 = 5) i.e. the observations representing indigent patients have been deleted from the data used for analysis. The variable PAY2 indicates the expected secondary payer (Medicare, Medicaid, private insurance, etc.). The interaction between the terms PAY1 and PAY2 was found to be insignificant in the regression analysis and hence PAY1 and PAY2 were retained as separate terms without including the interaction. Also, for several states the variable PAY2 was missing. For a missing value of PAY2, a new level was created PAY2 = -1, so as to keep the level PAY1 = Medicare and PAY2 = missing, separate from the level PAY1 = Medicare and PAY2 = any value other than missing, and so on and so forth for other combinations of PAY1 and missing PAY2. The number of diagnoses is a continuous variable NDX. The variable NDX indicates the total number of diagnoses coded on the discharge record. A maximum of 15 diagnoses has been

retained on a NIS inpatient record. While a maximum of 15 diagnoses have been retained on a NIS inpatient record, NDX may take the value from 0-30. The total number of procedures is a continuous variable NPR. The variable NPR indicates the total number of ICD-9-CM procedures coded on the discharge record. While a maximum of 15 procedures have been retained on a NIS inpatient record, NPR may take the value from 0-30. The variable ATYPE is a classificatory variable and indicates the type of admission (emergency, urgent, elective, etc.) and is coded as '1' = emergency, '2' = Urgent, '3' = Elective, '4' = Newborn, '5' = Trauma Center, '6' = other. The adapted Charlson index as interpreted by D'Hoore et al. 1996 was used to determine comorbidity index. Only the first 3 digits of the ICD-9 codes were used to determine comorbidity. Mortality was coded by the variable DIED. The variable DIED =1 indicates the patient died during hospitalization and DIED =0 indicates the patient did not die during hospitalization.:

Table 2 Adapted Charlson Comorbidity Index

Weights	Conditions	ICD-9 codes
1	Myocardial infarct	410, 411
	Congestive heart failure	398, 402, 428
	Peripheral vascular disease	440-447
	Dementia	290, 291, 294
	Cerebrovascular disease	430-433, 435
	Chronic pulmonary disease	491-493
	Connective tissue disease	710, 714, 725
	Ulcer disease	531-534
	Mild liver disease	571, 573
2	Hemiplegia	342, 434, 436, 437
	Moderate or severe renal disease	403, 404, 580-586
	Diabetes	250
	Any tumor	140-195
	Leukemia	204-208
	Lymphoma	200, 202, 203
3	Moderate or severe liver disease	070, 570, 572
6	Metastatic solid tumor	196-199

Reference: D'Hoore et al 1996, p 1430.

5.4 Explanatory Analysis of the Length of stay and Total Charge

The dependent variables are length of stay and expenditure. While running the multiple regression, one of the assumptions is that the data should be normally distributed. However since the distribution for the variable for total charges (TOTCHG) is highly skewed, the expenditure variable was transformed into its natural logarithm term. The distribution for the variable for length of stay (LOS) is also highly skewed. Hence, the variable for the length of stay was also transformed into its natural logarithm term. As recommended by the Box- Cox et al. (1964) method of transformation, the variables were transformed into their natural logarithms. The residual plots showed much improvement and normal distribution of the transformed variables. Joshi et al. (2004) carried out a similar transformation due to the skewed nature of the dependent variables, length of stay and hospital charges.

The regression models are as follows:

The multiple regression models are as follows:

$$\begin{aligned} \text{LOG(LENGTH OF STAY)} = & \beta_0 + \beta_1 \text{AGE} + \beta_{\text{ATYPE(A)}} + \beta_{\text{RACE(I)}} + \beta_{\text{FEMALE(J)}} + \\ & \beta_5 \text{NDX} + \beta_6 \text{NPR} + \beta_{\text{PAY1(K)}} + \beta_{\text{PAY2(L)}} + \beta_9 \text{COMORBIDITY_INDEX} + \beta_{\text{HOSP_BEDSIZE (M)}} \\ & \beta_{\text{HOSP_LOCATION(N)}} + \beta_{\text{HOSP_TEACH(O)}} + \beta_{\text{HOSP_REGION (P)}} + \text{ERROR}(\epsilon) \end{aligned}$$

$$\begin{aligned} \text{LOG(TOTAL CHARGE)} = & \beta_0 + \beta_1 \text{LOG(LOS)} + \beta_2 \text{AGE} + \beta_{\text{ATYPE(A)}} + \beta_{\text{RACE(I)}} + \\ & \beta_{\text{FEMALE(J)}} + \beta_6 \text{NDX} + \beta_7 \text{NPR} + \beta_{\text{PAY1(K)}} + \beta_{\text{PAY2(L)}} + \beta_{10} \text{COMORBIDITY_INDEX} + \\ & \beta_{\text{HOSP_BEDSIZE (M)}} \beta_{\text{HOSP_LOCATION(N)}} + \beta_{\text{HOSP_TEACH(O)}} + \beta_{\text{HOSP_REGION (P)}} + \text{ERROR}(\epsilon) \end{aligned}$$

$$\begin{aligned} \text{LOG(ODDS OF MORTALITY)} = & \beta_0 + \beta_1 \text{LOS} + \beta_2 \text{AGE} + \beta_{\text{ATYPE(A)}} + \beta_{\text{RACE(I)}} + \\ & \beta_{\text{FEMALE(J)}} + \beta_6 \text{NDX} + \beta_7 \text{NPR} + \beta_{\text{PAY1(K)}} + \beta_{\text{PAY2(L)}} + \beta_{10} \text{COMORBIDITY_INDEX} + \\ & \beta_{\text{HOSP_BEDSIZE (M)}} + \beta_{\text{HOSP_LOCATION(N)}} + \beta_{\text{HOSP_TEACH(O)}} + \beta_{\text{HOSP_REGION(P)}} + \text{ERROR}(\epsilon) \end{aligned}$$

Where:

$\beta_{\text{ATYPE(1)}} \dots \beta_{\text{ATYPE(6)}}$ are the parameters that correspond to the six levels for the variable Admission type

$\beta_{\text{RACE(1)}} \dots \beta_{\text{RACE(6)}}$ are the parameters that correspond to the six levels for the variable Race

$\beta_{\text{FEMALE(1)}}$ and $\beta_{\text{FEMALE(2)}}$ are the parameters that correspond to the two levels for the variable Gender

$\beta_{\text{PAY1(1)}} \dots \beta_{\text{PAY1(6)}}$ are the parameters that correspond to the six levels for the variable expected primary payer

$\beta_{\text{PAY1(-1)}} \dots \beta_{\text{PAY1(6)}}$ are the parameters that correspond to the seven levels for the variable expected secondary payer

$\beta_{\text{HOSP_BEDSIZE (1)}} \dots \beta_{\text{HOSP_BEDSIZE (3)}}$ are the parameters that correspond to the three levels for the variable hospital bedsize

$\beta_{\text{HOSP_LOCATION (1)}}$, $\beta_{\text{HOSP_LOCATION (2)}}$ are the parameters that correspond to the two levels for the variable hospital location

$\beta_{\text{HOSP_TEACH (1)}}$, $\beta_{\text{HOSP_TEACH (2)}}$ are the parameters that correspond to the two levels for the variable hospital teaching status

$\beta_{\text{HOSP_REGION (1)}} \dots \beta_{\text{HOSP_REGION (3)}}$ are the parameters that correspond to the four levels for the variable hospital region

5.5 Explanatory Analysis of Mortality

Mortality being a binary response variable, logistic regression was used to determine whether the variables hospital census region, hospital teaching status, hospital bed size, payer status, race, and gender were significant factors predicting mortality. A dummy variable was created for mortality. Age, gender, race, length of stay, payer status, total number of diagnoses, total number of procedures, admission type, and comorbidities were included as independent variables and used to control for mortality. Dummy variables were created to code for different levels of the classificatory variables. For gender, race, hospital location, and hospital teaching status, 1 dummy variable was coded to control for each of these variables. For admission type, 2 dummy variables were coded for admission type = emergent, admission type = urgent, and admission type = elective. For race and payer status (PAY1) 4 dummy variables were coded for different levels of these variables; for payer status (PAY2) 5 dummy variables were coded.

5.6 Descriptive Analysis of Expenditure and Length of stay

Frequency analysis of the categorical variable DIED and each of the independent categorical variables was carried out to describe the number of patients who died and who did not for each level of the categorical variables. The variables of interest were payer status (PAYER1, PAYER2), hospital census region, hospital teaching status, hospital bed size, payer status, race, and gender.

As the data was unbalanced, and there were several covariates the least square means (lsmeans) for logarithm of length of stay and logarithm of expenditure for the different levels of hospital census region, hospital teaching status, and hospital bed size were determined after having adjusted for all the covariant variables used in the general linear model. The differences in the lsmeans of log (length of stay) and log(total charges) were determined using Bonferroni's

significant difference (BSD) for multiple comparisons that controls for experiment wise error rate.

5.7 Statistical Analyses

All analyses were accomplished with the SAS (Release 9.1. SAS Institute Inc.,Cary, NC) statistical software. The level of significance was set at 0.05 levels. Multiple regression was used to test the hypotheses related to the continuous dependent variables: length of stay, and total charges. Logistic regression was used to test the hypotheses related to the dichotomous dependent variable mortality.

The study was conducted as a retrospective database analysis as described above. Parametric methods were used as for analysis as described above. The next chapter describes the results of the analysis.

Table 3 Independent Categorical variables

Variable	Description	Value	Value Description
ATYPE	Admission type	1	Emergency
		2	Urgent
		3	Elective
		4	Newborn
		5	Delivery (coded in 1988-1997 data only)
		6	Trauma Center (beginning in 2003)
PAY1	Expected primary payer	1	Medicare
		2	Medicaid
		3	Private insurance
		4	Self-pay
		5	No charge

		6	Other
FEMALE	Indicator of sex	0	Male
		1	Female
RACE	Indicator of race	1	White
		2	Black
		3	Hispanic
		4	Asian or Pacific Islander
		5	Native American
		6	Other
HOSP_LOCATION	Location (urban/rural) of hospital	0	Rural
		1	Urban
HOSP_REGION	Region of hospital	1	Northeast
		2	Midwest
		3	South
		4	West
HOSP_TEACH	Teaching status of hospital	0	Nonteaching
		1	Teaching

CHAPTER SIX

RESULTS

The first part of this chapter contains the description of the characteristics of the study sample in terms of the relevant variables on which the information was collected. This is followed by the results of the multiple regression models that demonstrate whether the variables of interest, hospital bedsize, hospital location, hospital teaching status, and hospital region are significant predictors of the log transformed response variables, logarithm of length of stay and logarithm of total expenditure. Next is the description of the frequency analysis of the dichotomous response variable, mortality for different levels of the categorical variables. Frequency analysis was done to review number of observations that appear in the various levels of each predictor variable to see if there is any pattern that would indicate some relationship between the mortality and predictor variables. Finally, the results of the logistic regression model are presented, which has been fitted to predict the probability of mortality, after adjusting for other possible predictors. As the logistic regression model considers all the predictors simultaneously, it provides reliable information whether the variables of interest hospital bedsize, hospital location, hospital teaching status, and hospital region are significant predictors of the response variable mortality. Therefore the Wald chi-square results of the analysis of maximum likelihood estimates for different levels of the predictor variables will be used to determine whether their association with mortality is statistically significant or not.

6.1 Descriptive Analysis of Study Sample

The study sample contained 14,080 patients that satisfied the inclusion criteria. The median age was 67 years. The number of diagnoses per patient ranged from 1 to 30. The median number of diagnoses per patient was 8. The number of procedures per patient ranged from 0 to 25. The median number of procedures per patient was 1 and the 90th quantile for the number of procedures per patient was 6.

Tables 4 to 12 depict the characteristics of the study sample. Emergency admission type was the most frequent admission type followed next by urgent type and then elective types. Whites accounted for the largest sample segment, followed by African-Americans, and then Hispanic-Americans. The percentage of females was marginally greater than that of males. Medicare constituted the most frequent primary payer followed by private insurance. Secondary payer status was missing for 55% of the data. The bedsize category, large constituted the largest percent (63.19%) of the bedsize types. Majority (88.24%) of the patients were from the urban hospitals. The percentage of non-teaching hospitals was marginally greater than that of the teaching hospitals (53% versus 46%). The largest percentage of the patients was from the South (49%), followed by the Northeast (30.39%). The smallest percent of patients was from the West.

Table 4 Frequency Analysis of Admission Type

Admission type	Frequency	Percent
Emergency	8273	58.76
Urgent	3192	22.67
Elective	2600	18.47
Newborn	2	0.01
Trauma	2	0.01
Other	11	0.08

Table 5 Frequency Analysis of Race

Race	Frequency	Percent
White	10399	73.86
African-American	2426	17.23
Hispanic-American	905	6.43
Asian/Pacific Islander	87	0.62
Native American	8	0.06
Other	255	1.81

Table 6 Frequency Analysis of Gender

Gender	Frequency	Percent
Female	7973	56.63
Male	6107	43.37

Table 7 Frequency Analysis of Primary Payer

Primary expected payer	Frequency	Percent
Medicare	8164	57.98
Medicaid	1252	8.89
Private	3972	28.21
Self	369	2.62
Other	323	2.29

Table 8 Frequency Analysis of Secondary Payer

Secondary expected payer	Frequency	Percent
Missing	7692	54.63
Medicare	1454	10.33
Medicaid	1012	7.19
Private	2776	19.72
Self	911	6.47
Other	235	1.67

Table 9 Frequency Analysis of Hospital Bed Size

Hospital Bedsize	Frequency	Percent
Small	1559	11.07
Medium	3624	25.74
Large	8897	63.19

Table 10 Frequency Analysis of Hospital Location

Hospital Location	Frequency	Percent
Rural	1656	11.76
Urban	12424	88.24

Table 11 Frequency Analysis of Hospital Teaching Status

Hospital Teaching status	Frequency	Percent
Non-teaching	7469	53.05
Teaching	6611	46.95

Table 12 Frequency Analysis of Hospital Region

Hospital Region	Frequency	Percent
Northeast	4279	30.39
Midwest	2202	15.64
South	6883	48.88
West	716	5.09

6.2 Results of Explanatory Analysis for Continuous Variables

6.21 Regression Model for Logarithm of Length of stay

The results of the multiple regression analysis are presented in **Table 13**. Since the distribution of length of stay is highly skewed the variable was transformed into its natural

logarithm (as suggested by Box Cox method of transformation). In this model ($R^2 = 0.3749$), the results (Type III sum of squares) indicate that the admission type ($p = 0.0347$), race (p less than 0.0167), gender (p less than 0.0001), number of diagnoses (p less than 0.0001), number of procedures (p less than 0.0001), primary payer status ($p = 0.0007$), secondary payer status (p less than 0.0001) and the comorbidity score ($p = 0.0135$) were found to be significant predictors of the length of stay. The variables of interest hospital location, hospital bedsize, hospital teaching status, and hospital region were all found to be statistically significant predictors of the response variable, length of stay (p less than 0.0001). The interaction between age and gender and between age and race were found to be statistically significant (p less than 0.0001 and $p = 0.0427$ respectively). **Table 13** gives the parameter estimates of the predictor variables (continuous and categorical) and the comparison of the parameter estimate for each level of the categorical variable with the last level.

Table 13 Results of the Multiple Regression Model for Logarithm of Length of stay

Parameter	Level	Estimate	Error	t	Pr > t
Intercept		0.90	0.218	4.14	<.0001**
AGE		-0.0007	0.001	-0.40	0.6895
ATYPE	Emergency	0.284	0.177	1.61	0.1076
ATYPE	Urgent	0.310	0.176	1.75	0.0796
ATYPE	Elective	0.295	0.176	1.67	0.0952
ATYPE	Newborn	0.690	0.463	1.49	0.1363
ATYPE	Trauma	1.121	.449	2.49	0.0127**
ATYPE	Other	0.0000	.	.	
Race	White	0.129	0.119	-1.09	0.2771
Race	African-American	0.005	0.123	-0.04	0.9684
Race	Hispanic	0.203	0.135	-1.50	0.1328
Race	Asian/Pacific Islander	0.392	0.226	-1.74	0.0824
Race	Native American	0.732	0.681	1.08	0.2822

Race	Other	0.00	.	.	.
Gender	Male	0.152	0.037	4.04	<.0001**
Gender	Female	0	.	.	.
No of diagnoses		0.057	0.001	31.2	<.0001**
No of procedures		0.13	0.002	59.2	<.0001**
Primary payer	Medicare	-0.001	0.035	-0.04	0.9684
Primary payer	Medicaid	0.028	0.037	0.78	0.4359
Primary payer	Private	0.045	0.034	-1.34	0.1802
Primary payer	Self	0.013	0.045	0.29	0.7703
Primary payer	Other	0	.	.	.
Secondary payer	Missing	0.089	0.039	2.29	0.0223**
Secondary payer	Medicare	0.081	0.041	1.98	0.0478**
Secondary payer	Medicaid	0.135	0.043	3.18	0.0015**
Secondary payer	Private	0.084	0.040	2.13	0.0328**
Secondary payer	Self	-0.007	0.043	-0.17	0.8685
Secondary payer	Other	0.0	.	.	.
Comorbidity		-0.003	0.001	-2.47	0.0135**
Hosp_Bedsize	Small	-0.067	0.016	-4.16	<.0001**
Hosp_Bedsize	Medium	-0.067	0.011	-5.86	<.0001**
Hosp_Bedsize	Large	0.0	.	.	.
Hosp_location	Rural	-0.083	0.016	-5.03	<.0001**
Hosp_location	Urban	0.0	.	.	.
Hosp_teach	Non-teaching	0.041	0.010	3.82	0.0001**
Hosp_teach	Teaching	0.0	.	.	.
Hosp_region	Northeast	0.168	0.024	6.80	<.0001**
Hosp_region	Midwest	0.053	0.026	2.08	0.0373**
Hosp_region	South	0.165	0.023	7.04	<.0001**
Hosp_region	West	0.0	.	.	.
Age*Gender	Male	-0.002	0.0005	-4.46	<.0001**
Age*Gender	Female	0.0	.	.	.
Age*Race	Race: White	0.002	0.001	1.12	0.2634
Age *Race	African-American	0.001	0.001	0.68	0.4970
Age *Race	Hispanic-American	0.004	0.002	1.93	0.0540
Age *Race	Asian/Pacific Islander	0.008	0.004	2.17	0.0297**
Age *Race	Native-American	-0.013	0.013	-1.10	0.2708
Age *Race	Other	0	.	.	.

Using the Bonferroni's significant difference (BSD) (Bland, and Altman, 1995) for multiple comparisons, statistically significant differences were seen in the length of stay for different levels of the variables of interest as described below. The mean value for the response

variable in the model, logarithm of length of stay for bedsize category large (2.145) was significantly greater than that for bedsize small (2.078) and medium (2.079). The logarithm of length of stay for urban hospital location (2.143) was significantly greater than that for rural location (2.059). The logarithm of length of stay for teaching hospitals (2.079) was significantly less than that for the non-teaching hospitals (2.122). The logarithm of length of stay for hospitals in the Northeast census region (2.173) was significantly greater than that for the hospitals in the Midwest (2.057) and West (2.003) census regions. The logarithm of length of stay for hospitals in the South (2.169) was significantly greater than that for the hospitals in the Midwest (2.057) and West (2.003) census regions. The effect of age (after adjusting for gender, race, payer status, total number of diagnoses, number of diagnoses, admission type, comorbidities, hospital census region, hospital teaching status, hospital bedsize, and hospital location) on the length of stay depends on the level of the race. Also, significant interaction was seen between age and gender. The change in the length of stay for every one unit increase in age when race was Asian (slope = 0.007232) was greater than that when race was African-American (slope = 0.00058) and when race was Other (slope = -0.00075). The change in the length of stay for every one unit increase in age when race was Hispanic (slope = 0.0033) was greater than that when race was African-American (slope = 0.00058). The change in the length of stay for every one unit increase in age when gender was Male (slope = 0.1497) was greater than that when gender was Female (slope = -0.002) and this was found to be statistically significant.

The corresponding lengths of stay values have also been provided in the **Table 14**. Since the values for the length of stay appear to be consistent across different levels of the categorical variable of interest this finding of statistical significance may not be relevant point of view of

healthcare administration, as the large sample size may have led to statistical significance. The least square means are presented in **Table 14**.

Table 14 Least Square Means of Logarithm of Length of stay and their Corresponding Length of stay

Variable	Least square means	95% Confidence Intervals		Corresponding Antilogarithm
Bedsizes				
Small	2.07	1.86	2.29	7.98
Medium	2.07	1.86	2.29	7.99
Large	2.14	1.93	2.35	8.54
Hospital location				
Rural	2.05	1.844	2.27	7.83
Urban	2.143	1.929	2.35	8.52
Hospital teaching				
Non-teaching	2.12	1.90	2.33	8.35
Teaching	2.07	1.86	2.29	8.00
Hospital region				
Northeast	2.17	1.96	2.38	8.79
Midwest	2.05	1.84	2.72	7.82
South	2.17	1.95	2.38	8.75
West	2.0	1.78	2.22	7.41

6.2.2 Regression Model for Logarithm of Total Charges

The results of the multiple regression analysis are presented in **Table 15**. Since the distribution of total charges is highly skewed the variable was transformed into its natural logarithm (as suggested by Box Cox method of transformation). Based on model ($R^2 = 0.7348$), results for the Type III sum of squares indicate that logarithm of length of stay (p less than 0.0001), age ($p = 0.0049$), admission type (p less than 0.0001), race ($p = 0.0085$), number of diagnoses (p less than 0.0001), number of procedures (p less than 0.0001), primary payer status (p less than 0.0021),

secondary payer status (p less than 0.0001) were found to be significant predictors of the total charges. Variables of interest hospital location (p less than 0.0001), hospital bedsize (p less than 0.0001), hospital teaching status (p less than 0.0352), and hospital region (p less than 0.0001), were all found to be statistically significant predictors of the response variable, total charges. **Table 15** depicts the parameter estimates of the predictor variables (continuous and categorical) and compares the parameter estimate for each level of the categorical variable with its last level.

The effect of age (after adjusting for gender, race, payer status, total number of diagnoses, number of diagnoses, admission type, comorbidities, hospital census region, hospital teaching status, hospital bedsize, and hospital location) on the total charge was dependent on the level of the race. An interaction was seen between age and race that was statistically significant. The change in the total charge for every one unit increase in age when race was Native American (slope = -0.0286) was lesser than that when the levels for race were American-White (slope = -0.001), African-American (slope = -0.0009), Hispanic-American (slope = 0.001) and Other (slope = -0.00219). The change in the total charge for every one unit increase in age, when race was Hispanic-American (slope = 0.001) was greater than that when the levels for race were American-White (slope = -0.0012) and Asian/Pacific Islander (slope = -0.007) respectively. The corresponding values of total charges have also been provided in the table below.

Table 15: Results of the Multiple Regression Model for Logarithm of Total Charge

Parameter	Level	Estimate	Error	t	Pr > t
Intercept		6.856	0.21	31.83	<.0001**
ILOS2		0.908	0.008	109.11	<.0001**
AGE		-0.002	0.001	-1.18	0.2375
ATYPE	Emergency	0.857	0.174	4.92	<.0001**

ATYPE	Urgent	0.767	0.174	4.39	<.0001**
ATYPE	Elective	0.8140	0.174	4.66	<.0001**
ATYPE	Newborn	0.4597	0.457	1.00	0.3150
ATYPE	Trauma	1.5614	0.4442	3.51	0.0004**
ATYPE	Other	0.000	.	.	.
Race	White	-0.068	0.117	0.58	0.5629
Race	African-American	-0.023	0.1220	-0.19	0.8497
Race	Hispanic	0.0589	0.1333	0.44	0.6585
Race	Asian/Pacific Islander	0.3981	0.22	1.78	0.0745
Race	Native American	1.656	0.672	2.46	0.0137**
Race	Other	0.00	.	.	.
Gender	Male	-0.010	0.0372	-0.27	0.7850
Gender	Female	0.000	.	.	.
No of diagnoses		0.0165	0.002	8.84	<.0001**
No of procedures		0.119	0.0024	48.16	<.0001**
Primary payer	Medicare	0.1067	0.034	3.10	0.0019**
Primary payer	Medicaid	0.0390	0.036	1.07	0.2838
Primary payer	Private	0.0672	0.033	2.00	0.0455**
Primary payer	Self	0.0677	0.044	1.53	0.1249
Primary payer	Other	0.000	.	.	.
Secondary payer	Missing	0.26	0.038	6.73	<.0001**
Secondary payer	Medicaid	0.179	0.040	4.41	<.0001**
Secondary payer	Private	0.0949	0.042	2.25	0.0242**
Secondary payer	Self	0.0273	0.039	0.70	0.4859
Secondary payer	Other	-0.079	0.042	-1.85	0.0649
Secondary payer	Missing	0.000	.	.	.
Comorbidity		0.0007	0.001	0.56	0.5742
Hosp_Bedsize	Small	-0.20	0.016	-12.73	<.0001**
Hosp_Bedsize	Medium	-0.135	0.011	-11.83	<.0001**
Hosp_Bedsize	Large	0.000	.	.	.
Hosp_location	Rural	-0.30	0.016	-18.56	<.0001**
Hosp_location	Urban	0.00	.	.	.
Hosp_teach	Non-teaching	-0.02	0.010	-2.11	0.0352**
Hosp_teach	Teaching	0.00	.	.	.
Hosp_region	Northeast	0.155	0.024	6.35	<.0001**
Hosp_region	Midwest	-0.163	0.025	-6.40	<.0001**
Hosp_region	South	-0.062	0.023	-2.70	0.0068**
Hosp_region	West	0.000	.	.	.
Age*Gender	Male	0.0007	0.0005	1.40	0.1603
Age*Gender	Female	0.00	.	.	.
Age*Race	Race: White	0.000	0.0018	0.54	0.5919
Age *Race	African-American	0.0012	0.001	0.66	0.5113
Age *Race	Hispanic-American	0.0032	0.002	1.55	0.1207
Age *Race	Asian/Pacific Islander	-0.004	0.003	-1.35	0.1768
Age *Race	Native-American	-0.26	0.0124	-2.12	0.0338**

Age *Race	Other	0	.	.	.
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According to this model, the total charges decreased with rural hospital location, non-teaching status, small and medium size hospitals, and Midwest and South census regions (provided the values of all other variables besides the variable with the negative coefficients were kept constant). Using the Bonferroni's significant difference (BSD), multiple comparison method, statistically significant differences were seen in the logarithm of the total charges for different categories of the variables of interest as shown in **Table 16**. The following comparisons were statistically significant. The least square mean logarithm of total charges for bedsize category small (9.581) was significantly less than that for bedsize medium (9.651) and large (9.786). The least square mean logarithm of total charges for urban hospital location (9.824) was significantly greater than that for rural location (9.522). The least square mean logarithm of total charges for teaching hospitals (9.684) was significantly greater than that for the non-teaching hospitals (9.662). The least square mean logarithm of total charges for hospitals in the Northeast census region (9.845) was significantly greater than the logarithm of total charges for the hospitals in the Midwest (9.527), South (9.628), and West (9.691) census regions. The least square mean logarithm of total charges for hospitals in the Midwest was significantly less than that in the South and West. The least square mean logarithm of total charges for hospitals in the South was significantly less than that for the hospitals in the West.

Table 16 Least Square Means of Logarithm of Total Charge and their Corresponding Total Charge

Variable	Least square means	95% Confidence Intervals		Corresponding Antilogarithm
Bedsizes				
Small	9.58	9.36	9.79	14,498
Medium	9.65	9.44	9.86	15,547
Large	9.79	9.58	9.99	17,795

Hospital location				
Rural	9.52	9.31	9.73	13,661
Urban	9.82	9.61	10.03	18,479
Hospital teaching				
Non-teaching	9.66	9.45	9.87	15,715
Teaching	9.68	9.47	9.89	16,063
Hospital region				
Northeast	9.84	9.63	10.05	18,876
Midwest	9.52	9.31	9.73	13,735
South	9.62	9.41	9.83	15,196
West	9.69	9.47	9.9	16,175

6.3 Frequency Analysis for Mortality

The sample can be characterized for mortality data using the categorical variables as shown in **Tables 17 to 25**.

Table 17 Proportion of those who died by Admission Type

Admission type	Proportion of those who died	Percent
Emergency	610/924	66.02
Urgent	181/924	19.59
Elective	133/924	14.33

Table 18 Proportion of those who died by Race

Admission type	Proportion of those who died	Percent
American-White	647/924	70.02
African-American	185/924	20.02
Hispanic American	67/924	7.25
Asian/Pacific Islander	7/924	0.76
Native American	0/924	0

Other	18/924	1.95
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Table 19 Proportion of those who died by Gender

Gender	Proportion of those who died	Percent
Female	414/924	44.81
Male	510/924	55.19

Table 20 Proportion of those who died by Primary Payer

Primary payer	Proportion of those who died	Percent
Medicare	624/924	67.53
Medicaid	78/924	8.44
Private	187/924	20.24
Self	19/924	2.06
Other	16/924	1.73

Table 21 Proportion of those who died by Secondary Payer

Secondary payer	Proportion of those who died	Percent
Missing	423/924	45.78
Medicare	116/924	12.55
Medicaid	75/924	8.12
Private	234/924	25.32
Self	62/924	6.71
Other	14/924	1.52

Table 22 Proportion of those who died by Hospital Bed Size

Hospital Bedsize	Proportion of those who died	Percent
Small	83/924	8.98
Medium	250/924	27.06
Large	591/924	63.96

Table 23 Proportion of those who died by Hospital Location

Hospital Location	Proportion of those who died	Percent
Rural	92/924	9.96
Urban	832/924	90.04

Table 24 Proportion of those who died by Hospital Teaching Status

Hospital Teaching status	Proportion of those who died	Percent
Non-teaching	441/924	47.73
Teaching	483/924	52.27

Table 25 Proportion of those who died by Hospital Region

Hospital Region	Proportion of those who died	Percent
North-East	327/924	35.39
Mid-West	118/924	12.77
South	436/924	47.19
West	43/924	4.65

6.4 Logistic Regression model for Mortality

The results of logistic regression model are shown in **Table 26**. Therefore length of stay (p less than 0.0001), age (p less than 0.0001), number of diagnoses (p less than 0.0001), number of procedures (p less than 0.0001) and comorbidity score (p less than 0.0001) were statistically significant predictors of mortality.

Table 26 Results of Logistic Regression Model for Mortality

Variable	Estimate	CHI-square	Pr > ChiSq	Odds ratio	95% confidence interval for odds ratio	
Intercept	-6.12	123.8696	<.0001**			
Length of stay	-0.009	7.4777	0.0062**	0.99	0.98	0.997
Age	0.02	64.3107	<.0001**	1.02	1.020	1.033
No of diagnoses	0.11	77.3276	<.0001**	1.11	1.09	1.14
No of procedures	0.21	226.3778	<.0001**	1.23	1.20	1.27
Comorbidity score	0.07	111.0879	<.0001**	1.07	1.06	1.09
Female	-0.12	2.9477	0.0860	0.88	0.77	1.01
Race: White	-0.09	0.1204	0.7286	0.91	0.54	1.54
African-American	0.08	0.0915	0.7623	1.09	0.63	1.87
Hispanic-American	0.02	0.0062	0.9372	1.02	0.57	1.83
Asian/Pacific Islander	0.19	0.1593	0.6898	1.22	0.46	3.22
Native American	-10.72	0.0022	0.9624	<0.001	<0.001	>999.999
Admission type:						
Emergency	0.37	2.6065	0.0004**	1.45	1.18	1.79
Urgent	0.19	2.3066	0.1288	1.2	0.94	1.54
Primary payer:						
Medicare	-0.20	0.6101	0.4347	0.82	0.49	1.36
Medicaid	0.006	0.0005	0.9827	1.00	0.58	1.73
Private	0.04	0.0237	0.8777	0.96	0.58	1.59
Self	0.19	0.3079	0.5790	1.21	0.61	2.39
Secondary payer:						
Medicare	0.17	0.3147	0.5748	1.18	0.65	2.16
Medicaid	0.25	0.6435	0.4225	1.29	0.69	2.40
Private	0.34	1.3064	0.2530	1.40	0.78	2.52
Self	0.03	0.0084	0.9269	1.03	0.54	1.95
Bedsizesmall	-0.09	0.4812	0.4879	0.915	0.713	1.175
Medium	0.06	0.4378	0.5082	1.057	0.897	1.245
Large	-0.18	2.1038	0.1469	0.832	0.649	1.067
Hospital teaching	-0.02	0.0836	0.7724	0.977	0.837	1.141

Hospital region Northeast	0.04	0.0459	0.8304	1.042	0.718	1.512
Midwest	-0.40	3.8323	0.0503	0.671	0.450	1.000
South	0.13	0.5517	0.4576	1.144	0.802	1.631

Thus the results of the descriptive and explanatory analysis were obtained using the methods described earlier. The next chapter will describe the findings with respect to past literature and future research.

CHAPTER SEVEN

DISCUSSION AND CONCLUSION

7.1 Discussion of Study Results

7.11 Hospital Characteristics, Geographic Location and Health Outcomes

Venous thromboembolism (VTE) presents a tremendous clinical and economic burden to society. The goal of this study was to identify if hospitals with specific characteristics such as, hospital size, hospital location, hospital teaching status, hospital census regions have optimal/superior results for health outcomes of VTE when compared with other hospital types. This is a preliminary step to see if the existing data are able to map hospitals with better outcomes for VTE. Further in-depth study of the standard operating procedures in hospitals with specific profiles may give more insight in the identification of best practices for the management of VTE. Due to limited resources and to ensure maximal efficiency of existing resources, it is important to identify the most effective and efficient practices for the management of VTE and thus help in the standardization of best practices once they are identified

This chapter summarizes the conclusions drawn from the study. Specifically, the chapter contains how the findings of this study are to be interpreted and can be used as a foundation for future research in this area.

Of the 14,080 patients of VTE in the current study sample from the 20% sample of NIS 2003, 4279 (30.39%) were from the Northeast, 2202 (15.64%) were from Midwest, 6883 (48.88%) were from South and 716 (5.09%) were from the West. Thus the highest percentage of patients was from the South. The descriptive analysis for mortality showed that out of the 924

patients that died, 35.39% were from the Northeast, 12.77% were from Midwest, 47.19% were from South and 4.65% were from the West. Therefore, a logistic regression was conducted to find if the association between hospital regions and mortality was significant after controlling for other covariates. Sufficient evidence was not found to suggest that the variables of interest, hospital census region, hospital teaching status, hospital bed size, payer status, race and gender are significant predictors of mortality; hence the null hypothesis that the coefficients of estimates for these variables in the maximum likelihood test are zero is not rejected. Also, in the current study, length of stay, age, number of diagnoses, number of procedures, Charlson's comorbidity scores, and emergency admission type were important predictors of mortality.

Mean total hospital charges varied significantly for different hospital census regions. In the current study, it was found that highest total charge was for hospitals in the Northeast census region (18,876), which was significantly greater than the total charge for the hospitals in the Midwest (13,735) South (15,196) and West (16,175) census regions. The total charge for hospitals in the Midwest was significantly less than that in the South and West and total charge for hospitals in the South was significantly less than that for the hospitals in the West. A multiple regression was conducted to find if the association between hospital regions and total charge was significant after controlling for other covariates.

According to the model used in the current study, the total charges decreased with rural hospital location, non-teaching status, small and medium size hospitals and Midwest and South census regions. The effect of age on the total charge was dependent on the level of the race. And this was found to be statistically significant. Although the comparisons showed that the length of stay for large hospitals was greater than that for small and medium sized hospitals, length of stay for urban hospitals was greater than that for rural hospitals, length of stay for hospitals in the

Northeast was greater than that for hospitals in other geographic locations, and length of stay for hospitals in the South was greater than that for hospitals in Midwest and West, these observations do not seem relevant from an administrative point of view because the length of stay in the current study for VTE varied from 7.41 to 8.79. The statistical significance obtained may be attributable to the large sample size. A multiple regression was conducted to find if the association between hospital regions and length of stay was significant after controlling for other covariates. In the current study the admission type, number of diagnoses, number of procedures, Charlson comorbidity score, hospital bedsize, hospital location, hospital teaching status, and hospital region were found to be significant predictors of length of stay. The effect of age on the length of stay depends on the level of the race. Also, significant interaction was seen between age and gender, and the change in the length of stay for every one unit increase in age when gender was Male (slope = 0.1497) was greater than that when gender was Female (slope = -0.002). Medicare comprised the largest proportion of primary insurance coverage (58%), followed by private (25%), and next by Medicaid (8.89%). No association was found between the payer status and mortality or payer status.

7.12 Race, Gender and Health Outcomes of Venous Thromboembolism

No association was found between the mortality and race. Also, no association was seen between mortality and race. Therefore, in this study race and gender were not found to be significant predictors of mortality.

While Proctor et al. (2004) found that the mortality rate in the Midwest, South, and West was significantly lower compared with the mortality rate in the Northeast (Odds Ratio 0.84, 0.84, 0.76) respectively, {the mortality being highest in the Northeast (7.9%), followed by South (6.8%), West (6.4%), and then Midwest (6.3%)}. The NIS 2003 sample suggests that hospital

census regions are not significant predictors of mortality. In the study by Proctor et al. (2004) the West had the highest mean charge per discharge, followed by the Northeast, then the South and lastly Midwest. The findings of the current study corroborate the previous literature that cites age and emergency room admission as a risk factor for VTE mortality (Stein et al. 2004c; Proctor et al. 2004).

There can be several mechanisms by which outcomes for VTE differ in different hospital settings or hospital census region. Lower costs in a particular region and elimination of disparity in the mortality comparisons may suggest higher level of adoption of anticoagulation clinics and adherence to the guidelines provided by these clinics, which represent the gold standard for long-term warfarin therapy. This may explain fewer hospitalizations and mortality.

Differences in the practice patterns for VTE may be responsible for disparity in the health outcomes for patients admitted to hospitals with different characteristics. Doppler ultrasound and pulmonary angiography are being increasingly used compared with phlebography and ventilation perfusion scanning as the preferred method for the diagnosis of DVT and PE (Proctor et al. 2004) respectively. Incidence of phlebography as a diagnostic tool was highest in the Northeast (7%) and lowest in the West (4.1%) (Proctor et al. 2004). The frequency of Duplex ultrasonography was highest in the West (38.9%) and lowest in the South (11.9%) (Proctor et al. 2004). Proctor et al. (2004) suggested that in the South, patients may undergo diagnostic testing before hospital admission; therefore the coding does not appear in the NIS database. In the West, patients undergo diagnostic testing as a part of hospitalization (Proctor et al. 2004). The West region had the highest use of Duplex ultrasonography (38.9%) for the diagnosis of VTE and the use of pulmonary angiography for PE (31.9%).

Mortality and the use of vena cava filters in the West region are low when compared with the Northeast. According to Proctor et al. (2004) there may be a high level of suspicion of VTE and therefore a lower mortality rate in the West.

Another possible explanation for the difference in the costs may have been due to prophylactic and therapeutic use of more cost-effective anticoagulants, such as fondaparinux and enoxaparin as against the less cost-effective anticoagulants, such as unfractionated heparin.

7.2 New Findings from this Study

1. Hospital census region is not a significant predictor of mortality for inpatient hospitalization VTE.
2. The Northeast has the highest mean charge per discharge for VTE in-patient hospitalization overtaking the West as seen in previous literature.
3. Rural hospital location, non-teaching status, and small and medium size hospitals are associated with lesser total charge for VTE in-patient hospitalization.
4. Medicare and private insurance were found to be positively associated with the length of stay.

7.3 Strength of this Study

1. Since the nation-wide sample was used, the findings of this study are representative for practice outcomes of venous thromboembolism in the hospitals all over the nation. The sample includes all types of institutional settings, major academic centers as well as small community hospitals.
2. There have been no studies conducted in the past comparing the outcomes of VTE in teaching and non-teaching hospitals. Hence the results in the current study would provide

more information than the previous research. Therefore this study is unique in that it suggests practice differences in the teaching and non- teaching hospitals for the management of VTE.

7.4 Limitations of the Study

1. It is not possible to determine whether thromboembolism prophylaxis was used and if so, which method was employed. So, data needs to be captured to identify if the problem lies in the method of prophylaxis.
2. Information in the NIS data is based on the ICD-9- CM coding. Such coding is susceptible to errors due to failure to identify cases and inclusion of false positive cases. These errors may differ according to states, hospitals within states, geographic locations, and hospital characteristics.
3. Since NIS data does not provide information on medications, drug dosages, and adverse events it is not possible to adjust for variation due to different anticoagulants options for venous thromboembolism.
4. The ICD-9 CM code limits the detection of new application of existing technology. Also, an investigation such as, pulmonary computed tomography scan cannot be specifically identified for the diagnosis of pulmonary embolism. Hence it was not possible to identify which investigations were specific for the diagnosis of VTE.
5. Like in all retrospective analyses, since the subjects are not randomly allocated to treatment options, the potential selection bias is inevitable.
6. Information on the variable race was missing for several states. Also the secondary payer status was missing for several states. The admission type was missing for the state of

California. Therefore these observations had to be deleted from the study sample. Hence, this would impact the observed frequencies from the different geographic locations.

7.5 Conclusion and Implications

This study used NIS 2003 sample to explore the relationship between hospital characteristics, geographic locations and health outcomes, length of stay, total charge, and mortality in VTE. The study identified statistically significant relationship between geographic locations and total charge, and hospital characteristics and total charge for venous thromboembolism. This suggests there are disparities in the operating procedures for the inpatient management of patients of VTE in different hospital types. Further studies directly comparing the specific management of inpatient VTE hospitalizations and comparing the VTE management history prior to hospitalization episode will help throw light on the best practices and perhaps the method of implementation of the best practices. Standardization of the best practices across the country could yield to greater return on investment of resources.

7.6 Future Research

Future research that compares the regions and hospital characteristics directly in terms of management of anticoagulation clinics, practice patterns in terms of diagnostic, prophylactic, and treatment (pharmacotherapy and surgical including the use of IVC filters) protocols, should be conducted to probe further into the possible explanation for differences in the health outcomes.

The ultimate aim is to learn from smaller hospital models that have the most efficient operating procedures and implement them on a national scale. Datasets that also include disease

management details (such as details of prophylaxis) prior to hospitalization will be very useful to compare the continuum of VTE management for patients admitted in different hospital types.

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Appendix A: Census Bureau Regions and Divisions with State FIPS Code

http://www.census.gov/geo/www/us_regdiv.pdf

North East	
Division 1	Division 2
New England	Middle Atlantic
Connecticut (09)	New Jersey (34)
Maine (23)	New York (36)
Massachusetts (25)	Pennsylvania (42)
New Hampshire (33)	
Rhode Island (44)	
Vermont (50)	

Midwest	
Division 3	Division 4:
East North Central	West North Central
Indiana (18)	Iowa (19) Nebraska (31)
Illinois (17)	Kansas (20) North Dakota (38)
Michigan (26)	Minnesota (27) South Dakota (46)
Ohio (39)	Missouri (29)
Wisconsin (55)	

South		
Division 5:	Division 6	Division 7
South Atlantic	East South Central	West South Central
Delaware (10)	Alabama (01)	Arkansas (05)
District of Columbia (11)	Kentucky (21)	Louisiana (22)
Florida (12)	Mississippi (28)	Oklahoma (40)
Georgia (13)	Tennessee (47)	Texas (48)
Maryland (24)		
North Carolina (37)		
South Carolina (45)		
Virginia (51)		
West Virginia (54)		

West	
Division 8	Division 9
Mountain	Pacific
Arizona (04)	Alaska (02)
Colorado (08)	California (06)
Idaho (16)	Hawaii (15)
New Mexico (35)	Oregon (41)
Montana (30)	Washington (53)
Utah (49)	
Nevada (32)	
Wyoming (56)	

Appendix B: Census Regions and Divisions of the United States

http://www.census.gov/geo/www/us_regdiv.pdf

