Direct Thrombin Inhibitors: Use and Consequences in Patients with Heparin-Induced Thrombocytopenia

BY

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THESIS

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Contribution of Authors

Chapters 2, 3 and 4 are the three studies that comprise this dissertation. I am the primary author of these three studies, and designed the studies, analyzed the data and wrote the first drafts of the manuscripts. All co-authors provided guidance in the design, analysis and interpretation of the results. In addition, Dr. William L. Galanter and Dr. Edith A. Nutescu ascertained the disease status of patients for the conduct of the first study. All co-authors contributed to the writing of the three studies.

Yash J. Jalundhwala, MS, of the Department of Pharmacy Systems, Outcomes and Policy abstracted data from electronic medical records of 10% of random sample of patients, and Yee M. Lee, PharmD, of the Department of Pharmacy Practice ascertained heparin-induced thrombocytopenia in six patients.

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LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
AHA/ACC	American Heart Association/American College of Cardiology
APPROVE	Angiomax Peripheral Procedure Registry of Vascular Events Trial
aPTT	Activated partial thromboplastin time
CABG	Coronary artery bypass graft
CCTS	Center for Clinical and Translational Science
CDB/RM	Clinical Database/Resource Manager
CI	Confidence interval
DTI	Direct thrombin inhibitor
DVT	Deep vein thrombosis
ELISA	Enzyme-linked immunosorbent assay
EMR	Electronic medical records
FDA	Food and Drug Administration
HIPA	Heparin-induced platelet aggregation
HIT	Heparin-induced thrombocytopenia
HR	Hazard ratio
ICC	Intraclass correlation coefficient
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICH	Intracranial hemorrhage

LIST OF ABBREVIATIONS (continued)

INR	International Normalized Ratio
IQR	Interquartile range
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
LMWH	Low-molecular-weight heparin
LOS	Length-of-stay
MI	Myocardial infarction
NPV	Negative predictive value
PCI	Percutaneous coronary intervention
PH	Proportional hazard
POA	Present on admission
PPI	Percutaneous peripheral intervention
PPV	Positive predictive value
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomized clinical trial
REDCap	Research Electronic Data Capture
SRA	Serotonin release assay
UA	Unstable angina
UFH	Unfractionated heparin
UHC	University HealthSystem Consortium
UIC	University of Illinois at Chicago

SUMMARY

This dissertation examines the off-label use and consequence of direct thrombin inhibitor (DTI) treatment in patients with suspected heparin-induced thrombocytopenia (HIT). Three separate studies were undertaken to develop algorithms to identify patients with suspected HIT, compare the effectiveness and safety of DTIs, and examine the factors associated with the off-label use of DTIs.

The first chapter introduces HIT, problems with current evidence and the conceptual framework that provides an understanding of the interrelationship between heparin, and DTI exposure, incidence of HIT, outcomes and confounders. For the first study, the conceptual framework shows the subgroups that differ in the incidence of HIT. Variation in the incidence of HIT in subgroups of at-risk patients (i.e. exposed to heparin) may influence the positive predictive value of the algorithms. Subgroup analysis would help in examining the trade-off between improvement in the performance of algorithms and restriction of patients to subgroups in future studies. For the second and third studies, the conceptual framework shows the relationship between DTI treatment, outcomes, and variables that are associated with the preference for a DTI and are risk factors for events such as thrombosis, major bleeding, amputation and mortality.

The purpose of the first study was to develop and compare the performance of algorithms for identifying HIT using gold standard measures of clinically suspected and actual HIT. The general rationale for these algorithms was based on treatment guidelines. Pharmacy orders, diagnostic test orders and diagnostic codes were used to define the algorithms. Electronic medical records (EMRs) of admissions involving heparin exposure from April 1, 2006 to March 31, 2011 at the University of Illinois Hospital and Health Sciences System were used to identify patients who met the definitions

of algorithms. Positive predictive values (PPV), negative predictive value (NPV), sensitivity and specificity were calculated based on the ascertainment of HIT status by expert clinicians (gold standard) to identify the best performing algorithm. Omnibus Fisher's exact tests were used to detect statistically significant differences in the PPV and sensitivity between algorithms.

The second study examined the differences in the rate of thrombosis, major bleeding, amputation and mortality between argatroban and bivalirudin groups. Using a retrospective cohort study design and the Clinical Database/Resource Manager (CDB/RM) data from 2009 to 2012 from the University HealthSystem Consortium, patients were followed up to 30 days after the initiation of DTI treatment. Propensity score matching between patients in the two treatment groups was used to adjust for confounding. The differences in safety and effectiveness of the DTI treatments were examined by hazard ratios generated from Cox proportional hazard regression models.

The third study examined the hospital, physician, visit and patient characteristics associated with the off-label use of bivalirudin. Data on the off-label use of DTIs is limited. Bivalirudin is indicated for percutaneous coronary intervention. However, the off-label use of bivalirudin for the treatment of suspected HIT has been observed at hospitals. The off-label use of argatroban was not examined in this study. The CDB/RM data for patients admitted to hospitals from 2010 to 2012 were used for this study. In this cross-sectional study, a hierarchical logistic regression model was used to identify the factors associated with off-label bivalirudin use, as there may be differences in patient mix and clinical practice between hospitals.

The fourth chapter provides an overall conclusion to the dissertation. The overall conclusion is that bivalirudin-treated patients are at a higher risk of experiencing major bleeding than argatroban-treated patients, and not all off-label prescriptions for bivalirudin are clinically justified. Although bivalirudin is preferred over argatroban at some hospitals due to the lower costs, higher

frequency of bleeding events may offset the savings. Current treatment guidelines need to be updated so that clinicians may reserve the use of bivalirudin in patients with severe hepatic impairment. Off-label prescriptions of bivalirudin should be scrutinized and local anticoagulation protocols need to be strengthened to limit the off-label use of bivalirudin without clinical justification. In addition, it is not feasible to identify actual HIT using claims data. The diagnosis of HIT is complex due to the multitude of risk factors for thrombocytopenia. Given the hypercoagulable nature of HIT, patients are often administered DTI at the time of clinical suspicion of HIT, regardless of confirmation by diagnostic tests at a later point in time.

1 INTRODUCTION

1.1 Background

Heparin is an anticoagulant used for the prevention of thrombosis in blood vessels.[1] Patients at-risk of experiencing thrombosis include those who undergo surgery or have medical conditions such as heart failure and myocardial infarction.[1] An estimated 12 million hospitalized patients are administered heparin in the United States each year.[2-4] However, 0.5-5% of patients administered heparin experience an acute immunologic reaction called heparin-induced thrombocytopenia (HIT).[5-8] HIT is characterized by a drop in platelet count.[9] This drop in platelet count is an intermediary step in a sequence of events that lead to the coagulation of blood after heparin administration.[9] Twenty-four percent of patients with HIT develop potentially fatal thrombosis in blood arteries and veins.[10] In addition to the clinical burden of HIT, the cost of treatment per HIT case was $14,384 in 2004 at a large tertiary care hospital in the United States.[11]

Direct thrombin inhibitors (DTI) such as argatroban and bivalirudin are the preferred medications for the treatment of HIT. The Food and Drug Administration (FDA) approved both DTIs in 2000.[2] Argatroban was approved for the treatment of HIT while bivalirudin was approved for anticoagulation during a percutaneous coronary intervention, regardless of HIT status.[12-14] However, literature suggests that bivalirudin is used for the treatment of HIT as an off-label indication.[2,5,15,16] Reasons for the off-label use of bivalirudin may be disease and drug class similarities,[17] and lower per day cost of bivalirudin than argatroban ($891 vs. $1,100 in 2014).[18]

The absolute risk of thrombosis due to treatment with argatroban reduces by 18%.[10] However, DTI treatment leads to major bleeding in 6% of patients.[10] Thus, DTIs are both protective and harmful. Head-to-head trials of argatroban and bivalirudin have not been conducted. Current American College of Chest Physicians (ACCP) guidelines recommend argatroban for the

treatment of HIT.[6] Bivalirudin has not been included in the recommendation due to the lack of evidence on efficacy and safety.

Of note, patients with suspected HIT are of interest in studies that compare the clinical and economic outcomes of DTIs. Due to the hypercoagulable nature of HIT and multitude of factors that can cause thrombocytopenia, the guidelines recommend the initiation of DTI at the time of clinical suspicion of HIT, regardless of confirmation by diagnostic tests at a later point in time.[19]

1.2 Problem Statement

The 2012 American College of Chest Physicians (ACCP) guidelines for the treatment of HIT does not provide recommendations on the preference of one DTI over another due to the lack of comparative evidence on clinical outcomes. Clinical trials have only examined argatroban against placebo for the treatment of HIT.[10,20] Although bivalirudin is commonly used in current clinical practice,[2,5,16] the benefit and harm of bivalirudin relative to argatroban has not been extensively studied. Bivalirudin may be preferred over argatroban in patients with liver dysfunction, as liver mainly eliminates argatroban.[2] However, other reasons for the use of bivalirudin over argatroban may include lower drug cost,[5] widespread use by cardiologists for surgeries[15,21] and drug class similarity.[2] Comparative effectiveness research that examines therapeutic alternatives in a real-world clinical setting can provide the evidence needed to develop treatment guidelines.[22] In addition, no previous study has examined the factors associated with the off-label use of bivalirudin in patients with suspected HIT. Well-designed observational studies using data from multiple hospitals can be useful to address this gap in evidence. Of note, the conduct of the above mentioned observational studies using electronic medical records (EMRs) may be time consuming and expensive.[23] Administrative claims data is a potential alternative to EMRs. However, criteria to identify patients with suspected HIT in retrospective administrative claims data have not been developed and validated.

1.3 Significance

Development and validation of criteria to identify suspected HIT in claims data is valuable for two reasons. Validated criteria may enable the use of claims data for observational studies, and decrease the resources needed to conduct future studies. In addition, the performance of criteria based on diagnostic codes may shed light on the extent of overtreatment in clinical practice due to false positive diagnosis. Studying the off-label use of bivalirudin and relative effectiveness and safety of DTIs is important for several reasons. First, findings may be useful to strengthen guidelines and help clinicians make treatment decisions based on both clinical outcomes and drug costs. It will shed light on the benefits and risk of harm from the off-label use of bivalirudin. Second, study results may serve as preliminary evidence for a much larger clinical trial. Third, the findings on factors associated with off-label use of bivalirudin may help develop and strengthen hospital anticoagulation protocols. It may further stimulate scrutiny of patient records to assess the clinical necessity of using bivalirudin over argatroban.

1.4 Research Objectives

The objectives of this dissertation were to: (1) develop and compare the sensitivity, specificity, positive predictive value and negative predictive value of algorithms based on pharmacy orders, diagnostic test orders and diagnostic codes to identify patients with actual and suspected HIT; (2) compare the rates of thrombosis, major bleeding, amputation and mortality between argatroban and bivalirudin groups in patients with suspected HIT; and (3) identify the hospital, visit, physician and patient characteristics associated with the off-label use of bivalirudin in patients with suspected HIT.

1.5 Conceptual Framework

Figure 1 provides a conceptual framework for understanding the relationship between heparin, HIT, DTI, clinical outcomes and confounders. Patients at-risk of developing thrombosis are commonly administered unfractionated heparin or low-molecular weight-heparin (LMWH) during their hospitalization.[1-4] More than four days after exposure to heparin, the patient may develop an immunologic reaction called HIT.[24] Given the hypercoagulable nature of HIT and complexity in diagnosis,[6,25] clinicians typically initiate a DTI treatment at the time of clinical suspicion of HIT.[19] DTI treatment may decrease the risk of potentially fatal thrombosis at the cost of an increase in the risk of major bleeding.[10]

The objective of the first study was to develop and validate algorithms to identify actual and suspected HIT. In addition, improvement in the performance of algorithms in patient subgroups with a high incidence of HIT was examined in this study. For example, surgical patients (1-3%) are more likely to develop HIT compared to medical patients (≤ 1%).[6] Figure 1 provides a list of such subgroups. The objective of the second study was to compare the effectiveness and safety of DTIs. Risk factors for thrombosis, major bleeding, amputation and mortality were identified from the literature. These risk factors were confounders if they were also associated with the choice of one DTI over another. For example, patients with hepatic impairment may be more likely to receive bivalirudin but less likely to experience thrombosis than patients with normal liver function.[26] Adjusted analyses were conducted to avoid a distortion in the observed relationship between DTIs and clinical outcomes. These confounders were examined again in the third objective to identify the hospital, visit, physician and patient characteristics associated with the off-label use of bivalirudin. Patients who were initiated on a DTI for a percutaneous coronary intervention (PCI) were excluded for the third objective, as this would not be an off-label use of bivalirudin. Examples of confounders are shown in Figure 1.

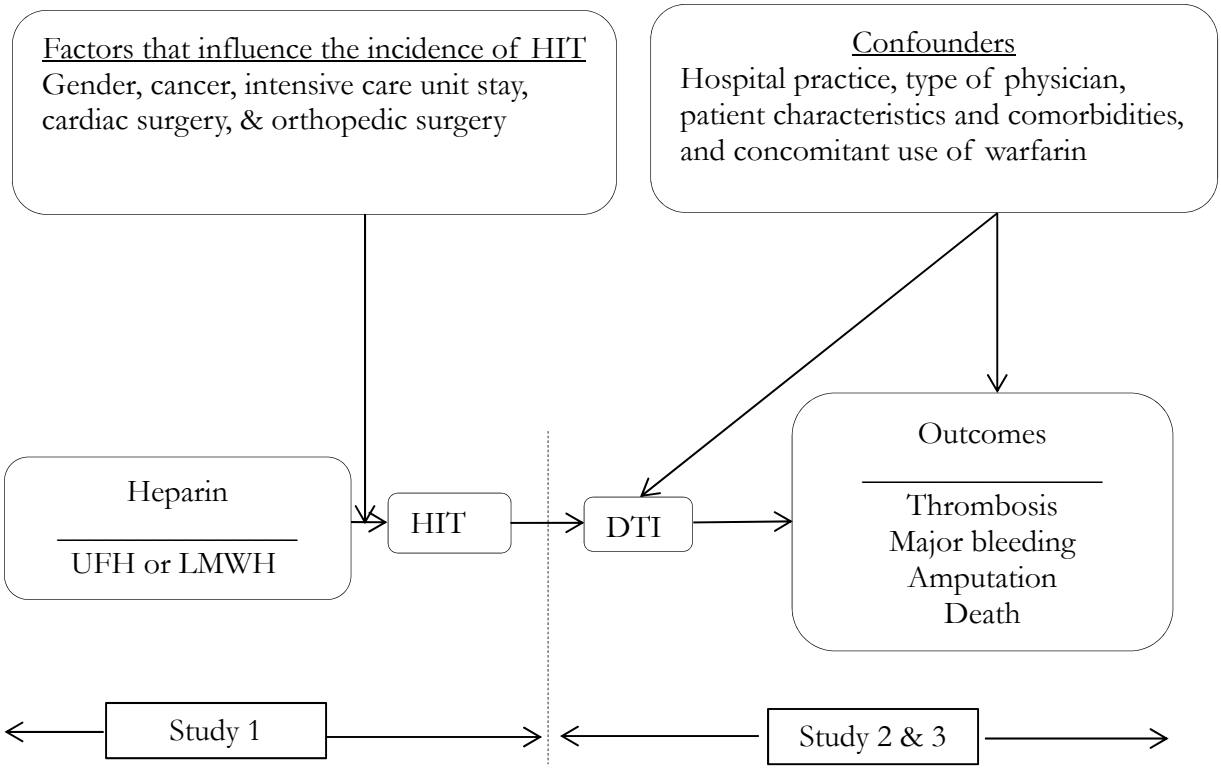

Figure 1. Conceptual framework depicting the interrelationship between heparin and direct thrombin inhibitor exposure, outcomes, and confounders.
HIT=heparin-induced thrombocytopenia; DTI=direct thrombin inhibitor; UFH=unfractionated heparin; LMWH=low-molecular weight-heparin

2 THE VALIDITY OF ALGORITHMS FOR IDENTIFYING SUSPECTED AND CONFIRMED HEPARIN-INDUCED THROMBOCYTOPENIA

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2.1 Preface

The abstract of this study was published in the *Journal of Thrombosis and Haemostasis* and titled "The validity of algorithms for identifying suspected and confirmed heparin-induced thrombocytopenia."[27] Copyright permission for the use of published abstract is described at http://onlinelibrary.wiley.com/journal/10.1111/%28ISSN%291538-7836/homepage/Permissions.html. This paper is the first of the three studies that comprise the dissertation research.

2.2 Abstract

Purpose: The aim of this study was to develop and compare three algorithms for identifying heparin-induced thrombocytopenia (HIT) using gold standard measures of clinically suspected and actual HIT.

Methods: We identified 45,096 inpatients exposed to heparin from 2006 to 2011 at an urban academic medical center. Three algorithms were examined: (A) initiation of direct thrombin inhibitor (DTI) treatment and a diagnostic test ordered more than 4 days after exposure to heparin; (B) algorithm A plus presence of ICD-9-CM code 287.4, 287.5, or 289.84; and (C) algorithm A plus presence of ICD-9-CM code 289.84. The data were collected from medical and billing records for patients (n=39) identified by algorithm A and a random sample (n=250) of patients who did not meet the algorithm's definition. Algorithms B (n=24) and C (n=6) were subsets of algorithm A. The

performance of the algorithms was computed based on the ascertainment of confirmed/suspected HIT by clinicians. Suspected HIT cases were tested for HIT antibodies and administered DTI to treat HIT.

Results: The positive predictive values (PPV) for confirmed HIT were 30.77%, 37.50% and 50% for algorithms A, B and C, respectively (P=0.547). However, the PPV was 100% for suspected HIT for all three algorithms. The differences in sensitivity between the algorithms A, B, and C for confirmed (100% vs. 75% vs. 50%; P=0.024) and suspected (100% vs. 61.54% vs. 40%; P<0.001) HIT were statistically significant.

Conclusions: These findings suggest that algorithms based on medical and billing records can be used to identify patients with suspected HIT.

2.3 Introduction

Heparin based anticoagulation is used in over 12 million patients admitted to hospitals in the United States annually.[2-4] Heparin-induced thrombocytopenia (HIT), a hypercoagulable state, is a potentially fatal immunologic response experienced by 0.5%-5% of patients administered heparin.[5-8] The incidence of life-threatening thrombosis and death among patients not treated for HIT has been reported to be 27% and 5%, respectively.[10] Several direct thrombin inhibitors (DTIs) such as argatroban, bivalirudin, and desirudin are currently available to treat HIT. Of these DTIs, only argatroban has been approved by the Food and Drug Administration for the treatment of HIT.[2] Argatroban was associated with an absolute risk reduction of 18% for thrombosis in comparison to historical controls.[10] The cost of treating a single case of HIT at a large tertiary care hospital in the US was estimated to be $14,387 in 2004.[11]

Accurate identification of HIT cases is needed in observational studies for comparing the effectiveness of treatment approaches (i.e. DTIs), estimating the incidence and burden of HIT, examining the compliance of laboratory testing with guidelines, and other epidemiological

investigations. The abstraction of data from medical records for such studies is time consuming and expensive.[23] The alternative is to use large administrative and claims data. Studies commonly use International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify the patients of interest in these databases. However, the reported ICD-9-CM codes are prone to errors by coders and physicians. In addition, the list of ICD-9-CM codes can be incomplete.[23,28] The ICD-9-CM code for HIT was introduced on Oct 1, 2008 and the extent to which hospitals subsequently altered their coding for HIT is not known.[29] Previous studies that had included patients before Oct 1, 2008 have used ICD-9-CM codes for secondary thrombocytopenia (287.4) or unspecified thrombocytopenia (287.5) to identify patients with HIT.[30-32] Moreover, there is a potential for misdiagnosis due to the high false positive rate (12%-19%) associated with the widely used enzyme-linked immunosorbent assay (ELISA) test.[6] Therefore, ICD-9-CM codes for HIT in observational databases can potentially indicate false positives, secondary thrombocytopenia or unspecified thrombocytopenia.

HIT is difficult to diagnose due to the presence of many other potential causes of thrombocytopenia (eg, surgery, bacteremia, medications, etc.).[6,25] Given that the diagnosis of HIT is challenging and complications costly, guidelines have recommended the initiation of DTI treatment when HIT is clinically suspected.[19] In addition, studies have evaluated the effectiveness of DTIs in patients with high clinical suspicion of HIT (intended population).[5,16] For these reasons, the identification of both clinically suspected and confirmed HIT cases is of interest for observational studies.

To the best of our knowledge, no previous study has developed algorithms and compared their accuracy for identifying patients with confirmed or clinically suspected HIT. Therefore, we developed and evaluated the validity of three algorithms (defined using pharmacy, laboratory, and ICD-9-CM data) for identifying confirmed and clinically suspected HIT. The gold standard was

diagnosis by expert clinicians based on review of the electronic medical records (EMR). In addition, we evaluated the performance of the algorithms across subgroups that may have higher or lower incidence of HIT.

2.4 Methods

2.4.1 Study Design and Data Source

A cross-sectional study was conducted to examine the validity of three algorithms for identifying HIT among at-risk patients. The study was based on EMR and billing data collected from the 495-bed University of Illinois Hospital and Health Sciences System (UI Health). The EMR contains detailed information on laboratory test results, diagnoses, procedures, discharge status, medications, and patient demographics while the billing data includes ICD-9-CM codes.

2.4.2 Inclusion and exclusion criteria

Based on prescription information from the EMR, patients exposed to unfractionated heparin or low-molecular-weight heparin during a hospitalization between April 1, 2006 and March 31, 2011 were included in this study. Patients were excluded if their age was < 18 years or if they were pregnant. Patients diagnosed with thrombocytopenia at admission or transferred from another facility were excluded because the ascertainment of HIT required information on anticoagulant exposure, laboratory test results, comorbidities and procedures. Admissions with a missing billing file that housed the ICD-9-CM data were excluded, as this information was required to assign patients to the algorithms. In addition, only the first admission was included for patients with multiple admissions.

2.4.3 General rationale for algorithms to identify HIT

HIT typically develops after four or more days of heparin treatment.[24] However, patients typically experience a drop in platelet count before the 5th day of heparin treatment due to reasons other than HIT such as surgery, bacteremia, and chemotherapy, among others. Therefore,

algorithms with a temporal element are required to avoid falsely including patients with a drop in platelet count due to reasons other than HIT.

2.4.4 Specific definitions of the algorithms

Table I shows the definitions of the three algorithms developed using information from American College of Chest Physicians (ACCP) guidelines and previous studies that could be matched with data elements from the EMR and billing data.[6,30-32] The algorithms are meant to identify HIT in patients receiving heparin. The initiation of a DTI therapy and an order for a HIT diagnostic test occurring more than 4 days after the initiation of heparin/LMWH were required criteria for all three algorithms.[7,24,33,34] Algorithm A was the least restrictive of the three algorithms and included simply the criteria mentioned above. Algorithm B was defined as a subset of algorithm A, including patients who met the basic criteria that also had at least one of the three ICD-9-CM codes for thrombocytopenia (secondary thrombocytopenia (ICD-9-CM 287.4), unspecified thrombocytopenia (287.5) and HIT (289.84)).[30-32] Of the patients identified by algorithm B, only the subset that had an ICD-9-CM code for HIT (289.84) were identified using algorithm C. Given that the ICD-9-CM code 289.84 was introduced on October 1, 2008, patients admitted to the hospital before October 1, 2008 were not considered for algorithm C. Algorithms B and C were designed to examine the improvement in accuracy when patients were restricted to those with HIT specific ICD-9-CM codes.

TABLE I. DEFINITIONS OF ALGORITHMS USED TO IDENTIFY SUSPECTED OR CONFIRMED HIT

Algorithm	**Criteria**			
	Pharmacy and laboratory testing data	**ICD-9-CM codes**		
	Initiation of a DTI therapy and a diagnostic test ordered (ELISA or HIPA or SRA) more than 4 days after the initiation of heparin therapy	**287.4** [31,32]	**287.5** [30]	**289.84** [29]
A	✓			
B	✓	✓	✓	✓
C	✓			✓

ICD-9-CM=International Classification of Disease, 9th version, Clinical Modification, DTI=direct thrombin inhibitor, ELISA=enzyme-linked immunosorbent assay, HIPA=heparin-induced platelet activation, SRA=serotonin release assay

Note: Algorithm C ⊂ algorithm B ⊂ algorithm A

2.4.5 Patient identification for testing the algorithms

The lead investigator (V.P.) abstracted data from the EMR records for all patients who met the inclusion criteria and definition of algorithm A (Figure 2). To calculate the accuracy of the algorithm, data were then abstracted for patients who did not meet the definition of algorithm A. Here a balance was struck between having a sufficient sample to identify controls with positive HIT and feasibility (given the limited resources) of being able to conduct the necessary chart reviews to apply the specific exclusion criteria and clinically identify those with HIT from those without HIT. First, five hundred patients were randomly sampled from the pool of 24,945 patients on heparin but not fitting algorithm A. Second, medical records were reviewed to determine the eligibility of these 500 patients. Last, data were abstracted for a random sample of 250 from the subset patients who met the inclusion criteria. Further, a second reviewer (Y.J.) abstracted data from a 10% random sample of the patients identified by algorithm A and a 10% sample of the 250 controls to identify errors by the lead investigator. The agreement in data collected by the two reviewers was high (>90%). Given that algorithms B and C were subsets of algorithm A, controls for these two algorithms included the 250 controls of algorithm A plus the patients identified by algorithm A that did not meet the definition of algorithms B and C.

The following data elements were collected and entered in REDCap (Research Electronic Data Capture) hosted at the University of Illinois at Chicago (UIC) Center for Clinical and Translational Science (CCTS):[35] patient demographics, heparin/LMWH and DTI treatment, laboratory tests, diagnoses, procedures, admission date, discharge date, discharge status, insurance status (uninsured vs. insured) and presence of other causes of thrombocytopenia.[6,25,36] Baseline platelet count was defined as the count immediately before heparin exposure during the inpatient stay. When baseline platelet count was not available, we selected the most recent platelet count

during the previous 12 months. If this information was not available, the first platelet count within 24 hours of heparin exposure was the baseline count.

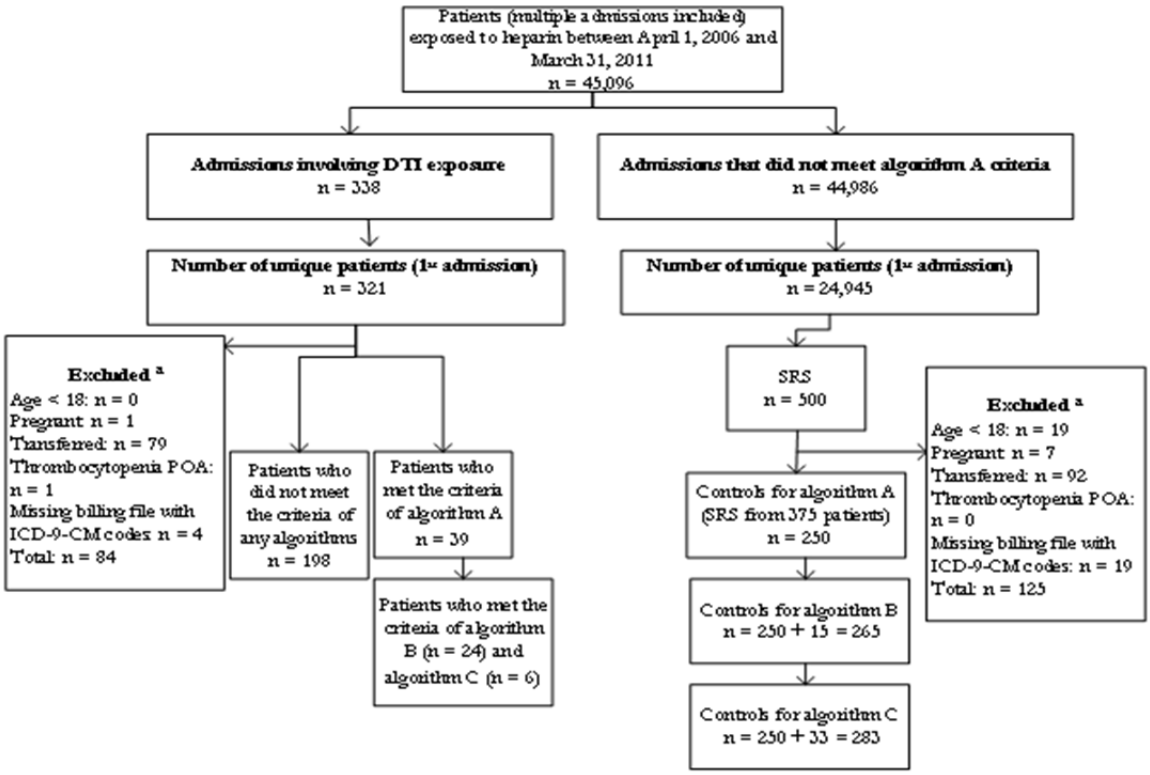

Figure 2. Sampling scheme for the algorithms.
SRS=simple random sample, POA=present on admission
[a] Not mutually exclusive

2.4.6 Ascertainment of clinically suspected and confirmed HIT in patients identified by algorithm A

Patients with clinically suspected HIT were defined as those who were tested for the presence of HIT antibodies and were administered a DTI with the *intent* to treat HIT. Of the patients identified by algorithm A, patients initiated on DTIs without the intention to treat HIT (eg, percutaneous coronary intervention) would be considered to not have suspected HIT, regardless of whether they underwent diagnostic testing. Determination of suspected and confirmed HIT by clinicians was used as the gold standard. The clinical experts used the following criteria to establish the presence of confirmed HIT: results of the serotonin release assay (SRA) (gold standard diagnostic test) when available, results of an ELISA test when the SRA was not available, timing of the drop in platelet count in relation to exposure to heparin, the presence of newly formed venous thromboembolism and arterial thrombosis, and the absence of other factors that can explain the drop in platelet count. An attending faculty (W.G.) and a clinical pharmacist (E.N.) experienced in the management of anticoagulation therapies ascertained suspected and confirmed HIT for all thirty-nine patients identified to be HIT positive by algorithm A. Disagreements between the two clinicians were resolved via adjudication by a third clinical pharmacy expert (Y.L.).

Ascertainment of clinically suspected and confirmed HIT in patients not identified by algorithm A

Given limited resources, we developed flowcharts to ascertain HIT in a random sample of patients not identified by algorithm A. In order to ensure that the ascertainment of HIT status by these criteria was correct, the experts reviewed the medical records of 10% of the random sample and all (n=2) patients identified as HIT positive. Given that ELISA/SRA/HIPA are used to diagnose HIT, we developed separate flowcharts for patients with (Figure 3) and without (Figure 4) a diagnostic testing record.

In patients with diagnostic testing (Figure 3), positive ELISA and negative heparin-induced platelet activation (HIPA) results were considered HIT positive only if the platelet count drop (>50% drop from baseline or $< 150 \times 10^9$/L) occurred on or after the 5th day of heparin treatment,[6,25] HIT was explicitly mentioned in the EMR, and DTI was continued after the test results were available. If these criteria were not satisfied, patients were classified as HIT positive only if at least one of the following symptoms associated with HIT was present: acute systemic reaction within 30 minutes of heparin administration,[37] skin necrosis at the site of heparin injection,[6,25,38] and thrombosis.[39] These criteria were developed due to the high false positive and false negative rates associated with ELISA and HIPA tests, respectively.[40,41]

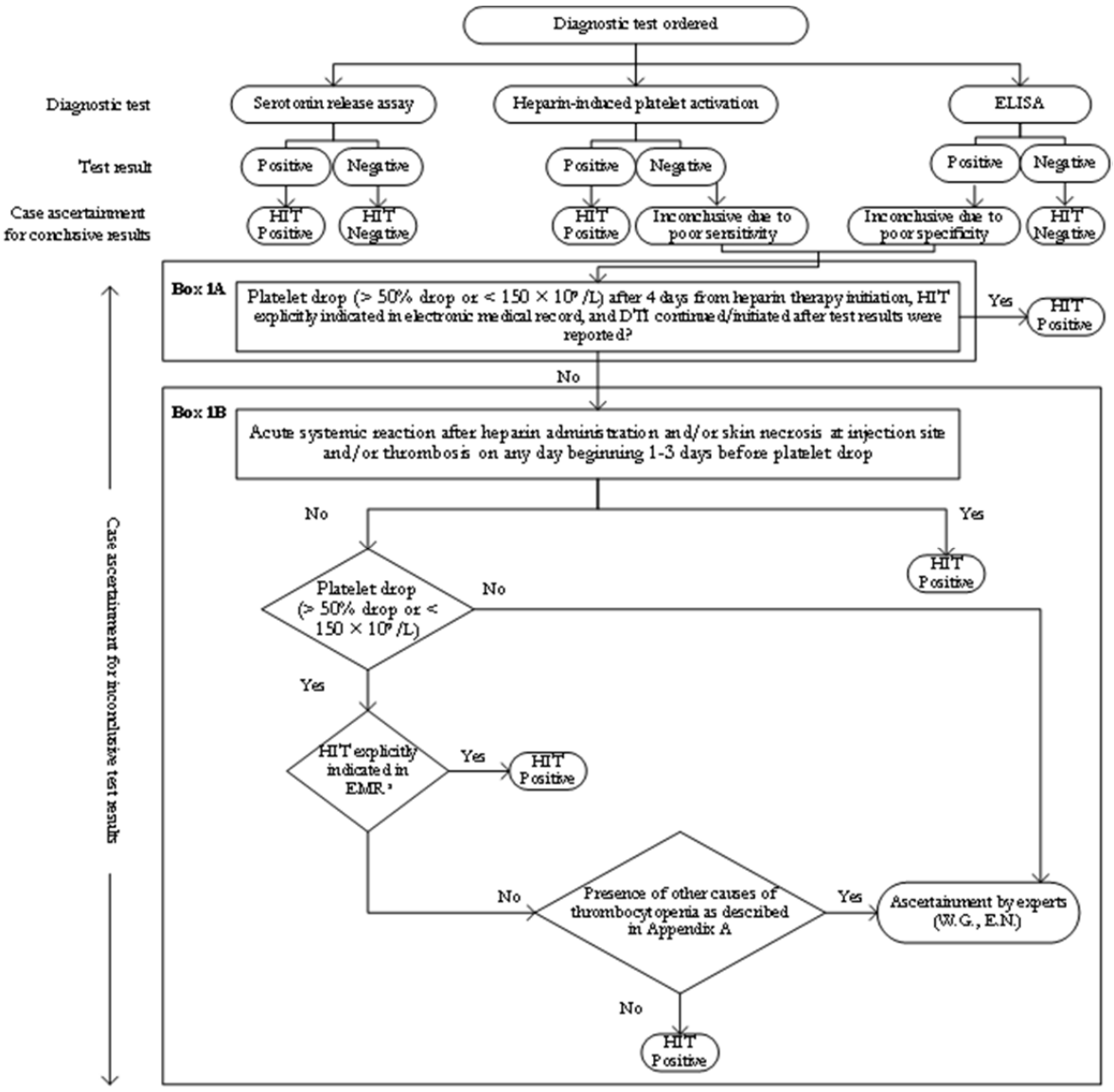

Figure 3. Flow chart for ascertaining heparin-induced thrombocytopenia among patients who had diagnostic testing.

ELISA=enzyme-linked immunosorbent assay, HIT=heparin-induced thrombocytopenia, DTI=direct thrombin inhibitor, EMR=electronic medical record

[a] HIT should be explicitly indicated in the electronic medical record after test results are obtained

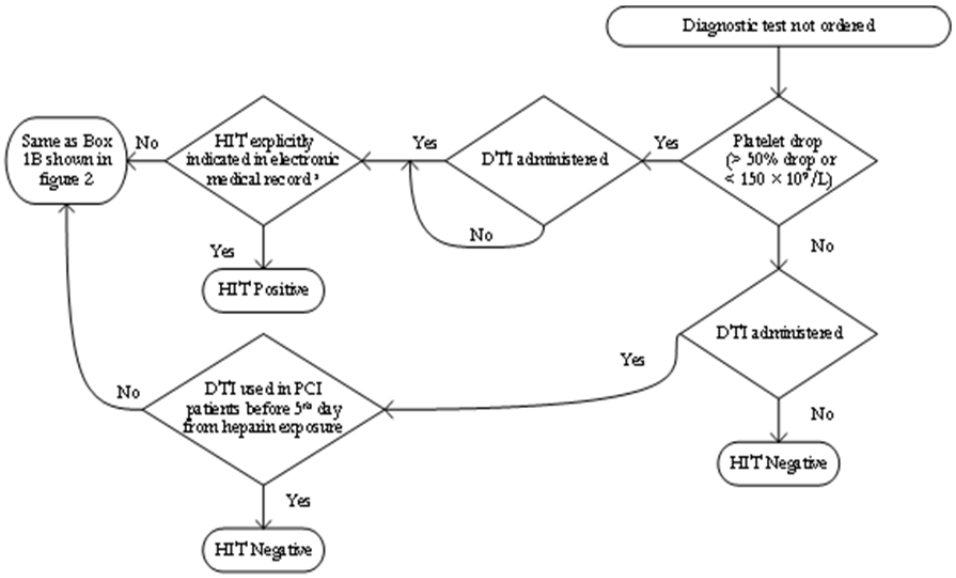

Figure 4. Flow chart for ascertaining heparin-induced thrombocytopenia among patients who did not have diagnostic testing.
DTI=direct thrombin inhibitor, HIT=heparin-induced thrombocytopenia, PCI=percutaneous coronary intervention
[a] HIT should be explicitly indicated in the electronic medical record after test results are obtained

2.4.7 Statistical Analysis

The differences in characteristics between patients with and without confirmed/suspected HIT were tested using Fisher's exact test for categorical variables, as some cell counts were less than five. Mann-Whitney-Wilcoxon rank sum test was used for age and length-of-stay (LOS) due to non-normal distributions. Medians (interquartile range) and frequencies (proportions) were reported for continuous and categorical variables, respectively.

Clopper-Pearson exact 95% confidence intervals were constructed for sensitivity, specificity, PPV and NPV of the algorithms. The omnibus Fisher's exact test was used to test if the differences in performance between the three algorithms were statistically significant. In addition, bootstrapping was used to test significance in PPV taking into account the dependency of the groups as algorithms B and C were subsets of algorithm A. First, logistic regression was used to obtain the beta coefficient (β) for each pairwise comparison in the original sample. Second, a thousand replicates were randomly sampled with replacement. Specifically, patients in the algorithm C were first randomly sampled with replacement (n_1), then patients in algorithm B but not C (n_2), and finally patients in algorithm A but not B (n_3). Third, logistic regression based beta coefficients (β') were obtained for each replicate. Fourth, the sampling distribution was centered at the null (i.e. 0) by taking the difference between the beta coefficient for each replicate and original sample ($\beta^* = \beta - \beta'$). Last, a p-value was calculated as the proportion of replicates with a β^* more extreme than the observed β, and a Bonferroni corrected alpha (adjusted alpha for three comparisons = 0.016) was used for the pairwise comparisons. Similarly, bootstrap hypothesis tests were used to test significance in NPV, sensitivity and specificity. In addition, we have presented the performance of algorithms B and C after excluding from the controls the patients identified by algorithm A that did not meet the definition of algorithms B and C. Further, subgroup analyses were conducted for

cardiac surgery,[6,8,19,42] cancer,[6] intensive care stay,[6] UFH dose (prophylaxis and treatment dose), insurance status, gender[43] and heart failure[44] to identify groups for which algorithm performance may change due to differences in incidence of HIT. Frequency weights were used and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used to conduct all analyses. Frequency weights for patients who did not meet the definition of algorithm A were calculated as the ratio of total number of such at-risk patients who met the inclusion criteria to the number of randomly sampled patients. Institutional review board approval, waiver of informed consent and waiver of authorization (protocol #2012-1068) were obtained from the University of Illinois at Chicago.

2.5 Results

2.5.1 Patient characteristics

Of the 45,096 hospital inpatient admissions involving heparin/LMWH exposure during the study period, 338 (0.7%) had a record of DTI use (Figure 1). Based on the first admission, we identified 321 unique at-risk patients exposed to DTI during their hospital stay. Of the 237 patients who met the inclusion criteria, 39 (16.5%), 24 (10.1%) and 6 (2.5%) of these patients were identified by algorithms A, B and C respectively. The ICD-9-CM codes 289.84, 287.4 and 287.5 were present in the records of 11 (4.6%), 27 (11.4%) and 19 (8.0%) patients, respectively. Of the 500 randomly sampled patients from a pool of 24,945 at-risk patients who did not meet the definition of algorithm A, 375 (75%) met the inclusion criteria. Therefore, the total number of patients who did not meet the definition of algorithm A but had satisfied the inclusion criteria was estimated to be 18,709 (75% of 24,945).

The number of patients with clinically confirmed and suspected HIT among at-risk patients was 0.06% and 0.21%, respectively (Table II). There were six disagreements (kappa = 0.73; 95% CI, 0.52-0.94) between expert clinicians in the ascertainment of confirmed HIT and those were resolved via adjudication by the 3rd expert. There was perfect agreement between the experts in the

ascertainment of clinically suspected HIT. Distributions of age, sex, race/ethnicity, insurance status, hepatic impairment, heart failure, autoimmune disease and cardiovascular surgery were similar between patients with and without HIT. Patients with confirmed HIT had a longer median length-of-stay (LOS) (25 days vs. 4 days; P<0.001), were more likely to receive treatment dose UFH (58.3% vs. 8.5%; P<0.001), receive platelet transfusion (16.7% vs. 0.0%; P<0.001) and have an ICU stay (66.7% vs. 13.7%; P<0.001) than patients without confirmed HIT. The proportion of patients with platelet count drop greater than 50% from baseline or less than 150×10^9/L count after 4 days from heparin exposure was higher among those with confirmed HIT compared to patients without HIT (66. 7% vs. 1.3%; P<0.001). Similar differences were observed between patients with and without clinically suspected HIT for treatment dose UFH, platelet transfusion, ICU stay, LOS and drop in platelet count.

TABLE II. CHARACTERISTICS OF WEIGHTED COHORT BY CONFIRMED OR SUSPECTED HIT

Characteristic	Confirmed HIT		Suspected HIT	
	No HIT (N = 18,736)	HIT (N = 12)	No HIT (N = 18,709)	HIT (N = 39)
Age in years, median (IQR)	54 (39-66)	56.50 (51-62.5)	54 (39-66)	57 (50-68)
Male, n (%)	8318 (44.39)	5 (41.67)	8,307 (44.40)	16 (41.03)
Race/ethnicity, n (%)				
Asian	524 (2.80)	1 (8.33)	524 (2.80)	1 (2.56)
Non-Hispanic Black	10,567 (56.40)	6 (50)	10,552 (56.40)	21 (53.85)
Hispanic	2,927 (15.62)	2 (16.67)	2,918 (15.60)	10 (25.64)
Non-Hispanic White	4,719 (25.19)	3 (25)	4,715 (25.20)	7 (17.95)
Insured, n (%)	17,612 (94)	12 (100)	17,586 (94)	38 (97.44)
Length of stay in days, median (IQR) [c d]	4 (2-6)	25 (22-35)	4 (2-6)	28 (18-38)
Type of heparin exposure, n (%) [c d]				
UFH flush	150 (0.80)	0 (0)	150 (0.80)	0 (0)
Prophylaxis dose				
Only UFH	14,893 (79.49)	4 (33.33)	14,892 (79.60)	5 (12.82)
Only LMWH	1,198 (6.40)	0 (0)	1,197 (6.40)	1 (2.56)
Both UFH and LMWH	76 (0.40)	0 (0)	75 (0.40)	1 (2.56)
Treatment dose				
Only UFH	1,589 (8.48)	7 (58.33)	1,572 (8.40)	24 (61.54)
Only LMWH	374 (2)	0 (0)	374 (2)	0 (0)
Both UFH and LMWH	456 (2.43)	1 (8.33)	449 (2.40)	8 (20.51)
DTI, n (%) [c d]	102 (0.54)	12 (100)	75 (0.40)	39 (100)
Cancer, n (%) [c d]	2,855 (15.24)	6 (50)	2,844 (15.20)	17 (43.59)
Heart failure, n (%)	2,477 (13.22)	2 (16.67)	2,470 (13.20)	9 (23.08)
Intensive care unit, n (%) [c d]	2,564 (13.69)	8 (66.67)	2,544 (13.60)	28 (71.79)
Surgery, n (%) [b]				
Cardiovascular	976 (5.21)	1 (8.33)	973 (5.20)	4 (10.26)
Orthopedic	1,572 (8.39)	0 (0)	1,572 (8.40)	0 (0)
Drop in platelet count below threshold, n (%) [a c d]	241 (1.28)	8 (66.67)	225 (1.20)	24 (61.54)

HIT=heparin-induced thrombocytopenia, IQR=interquartile range, UFH=unfractionated heparin, LMWH=low-molecular-weight heparin, DTI=direct thrombin inhibitor

[a] Threshold is defined as drop in platelet count below 150×10^9 /L or > 50% drop in platelet count from baseline after 4 days from heparin exposure

[b] Categories are not mutually exclusive

[c] Difference between patients with and without confirmed HIT was statistically significant (P<0.05)

[d] Difference between patients with and without suspected HIT was statistically significant (P<0.05)

2.5.2 Algorithm performance for confirmed HIT

Table III shows the performance of the algorithms for patients with confirmed HIT by subgroups. The NPV and specificity of the algorithms was high (>99%) across the patient subgroups. Some of the differences in specificity and NPV between the algorithms were statistically significant but small (<1%). The omnibus test for difference in sensitivity between the three algorithms for the overall sample was statistically significant (P=0.024). Based on the bootstrapped hypothesis testing, algorithm A had a significantly higher sensitivity compared to algorithm B (P=0.012) and C (P=0.005). The sensitivity ranged from 33.3% to 100% in the overall sample and subgroups. Algorithm B had lower sensitivity compared to algorithm A as three of the twelve patients with confirmed HIT had missing ICD-9-CM codes for thrombocytopenia. The PPV of the algorithms, except for algorithm C in the cancer subgroup, were found to be low (<50%). Even though the difference in PPV between the three algorithms was not statistically significant, the trend indicates that the more restrictive algorithms (B and C) had higher PPV compared to algorithm A. When patients identified by algorithm A that did not meet the definitions of the other two algorithms were excluded from the controls for algorithms B and C, the sensitivity and NPV of the two algorithms were 100% while the specificity remained high (> 99%).

In comparing the performance metrics of algorithms A and B calculated before and after October 1, 2008, the average PPV increased for algorithms A (25% vs. 40%; P=0.32) and B (28.57% vs. 50%; P=0.40). Similarly, the average sensitivity of algorithm B increased after October 1, 2008 (66.67% vs. 83.33%; P=1.00). However, these changes were not statistically significant. Both specificity and NPV for the two algorithms were similar for the two periods.

The performance of the algorithms can be improved by the use of diagnostic test results. All 39 patients who met the criteria of algorithm A were initiated on argatroban after being suspected of HIT. Twenty-seven (69.2%) of these patients did not have HIT. Ten (37%) patients without HIT

had false positive ELISA test results. The ELISA test results were negative for 63% of the patients without HIT. This suggests that the PPV can be increased by the inclusion of diagnostic test results in the algorithms' definition.

TABLE III. SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF THE ALGORITHMS FOR CONFIRMED HIT

	Algorithm	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Overall [a b c d e f g]	A	12	27	0	18,709	100 (73.54-100)	99.86 (99.79-99.91)	30.77 (17.02-47.57)	100 (99.98-100)
	B	9	15	3	18,721	75 (42.81-94.51)	99.92 (99.87-99.96)	37.50 (18.80-59.41)	99.98 (99.95-100)
	C	3	3	3	8,687	50 (11.81-88.19)	99.97 (99.90-99.99)	50 (11.81-88.19)	99.97 (99.90-99.99)
Cancer	A	6	11	0	2,844	100 (54.07-100)	99.61 (99.31-99.81)	35.29 (14.21-61.67)	100 (99.87-100)
	B	5	6	1	2,849	83.33 (35.88-99.58)	99.79 (99.54-99.92)	45.45 (16.75-76.62)	99.96 (99.80-100)
	C	2	0	1	824	66.67 (9.43-99.16)	100 (99.55-100)	100 (15.81-100)	99.88 (99.55-100)
Male	A	5	11	0	8,307	100 (47.82-100)	99.87 (99.76-99.93)	31.25 (11.02-58.66)	100 (99.96-100)
	B	3	5	2	8,313	60 (14.66-94.73)	99.94 (99.86-99.98)	37.50 (8.52-75.51)	99.98 (99.91-100)
	C	0	0	2	3,519	NA	100 (99.90-100)	NA	99.94 (99.79-99.99)
Female	A	7	16	0	10,402	100 (59.04-100)	99.85 (99.75-99.91)	30.43 (13.21-52.92)	100 (99.96-100)
	B	6	10	1	10,408	85.71 (42.13-99.64)	99.90 (99.82-99.95)	37.50 (15.20-64.57)	99.99 (99.95-100)
	C	3	3	1	5,168	75 (19.41-99.37)	99.94 (99.83-99.99)	50 (11.81-88.19)	99.98 (99.89-100)
UFH prophylaxis dose	A	4	1	0	14,892	100 (39.76-100)	99.99 (99.96-100)	80 (28.36-99.49)	100 (99.98-100)
	B	3	1	1	14,892	75 (19.41-99.37)	99.99 (99.96-100)	75 (19.41-99.37)	99.99 (99.96-100)
	C	1	1	2	7,259	33.33 (0.84-90.57)	99.99 (99.92-100)	50 (1.26-98.74)	99.97 (99.90-100)

TABLE III. SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF THE ALGORITHMS FOR CONFIRMED HIT

	Algorithm	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
UFH treatment dose	A	7	17	0	1,572	100 (59.04-100)	98.93 (98.29-99.38)	29.17 (12.62-51.09)	100 (99.77-100)
	B	5	10	2	1,579	71.43 (29.04-96.33)	99.37 (98.85-99.70)	33.33 (11.82-61.62)	99.87 (99.54-99.98)
	C	1	1	1	528	50 (1.26-98.74)	99.81 (98.95-100)	50 (1.26-98.74)	99.81 (98.95-100)
Cardiac	A	1	3	0	973	100 (2.50-100)	99.69 (99.10-99.94)	25 (0.63-80.59)	100 (99.62-100)
Surgery	B	1	1	0	975	100 (2.50-100)	99.90 (99.43-100)	50 (1.26-98.74)	100 (99.62-100)
	C	0	0	0	376	NA	100 (99.02-100)	NA	100 (99.02-100)
Insured [a b c d e f g]	A	12	26	0	17,586	100 (73.54-100)	99.85 (99.78-99.90)	31.58 (17.50-48.65)	100 (99.98-100)
	B	9	14	3	17,598	75 (42.81-94.51)	99.92 (99.87-99.96)	39.13 (19.71-61.46)	99.98 (99.95-100)
	C	3	3	3	8,088	50 (11.81-88.19)	99.96 (99.89-99.99)	50 (11.81-88.19)	99.96 (99.89-99.99)
ICU	A	8	20	0	2,544	100 (63.06-100)	99.22 (98.80-99.52)	28.57 (13.22-48.67)	100 (99.86-100)
	B	7	11	1	2,553	87.50 (47.35-99.68)	99.57 (99.23-99.79)	38.89 (17.30-64.25)	99.96 (99.78-100)
	C	2	2	2	1,126	50 (6.76-93.24)	99.82 (99.36-99.98)	50 (6.76-93.24)	99.82 (99.36-99.98)
Heart	A	2	7	0	2,470	100 (15.81-100)	99.72 (99.42-99.89)	22.22 (2.81-60.01)	100 (99.85-100)
Failure	B	2	4	0	2,473	100 (15.81-100)	99.84 (99.59-99.96)	33.33 (4.33-77.72)	100 (99.85-100)
	C	0	1	0	825	NA	99.88 (99.33-100)	0 (0-97.50)	100 (99.55-100)

HIT=heparin-induced thrombocytopenia, TP=true positive, FP=false positive, FN=false negative, TN=true negative, NPV=negative predictive value, UFH=unfractionated heparin, ICU=intensive care unit, PPV=positive predictive value, NA=not applicable, algorithm A= the initiation of DTI therapy and an order for an HIT diagnostic test at more than 4 days after heparin initiation, algorithm B= algorithm A plus presence of ICD-9-CM code 287.4, 287.5, or 289.84, algorithm C= algorithm A plus presence of ICD-9-CM code 289.84 after October 1, 2008.

Data are presented as percentage (95% confidence interval) for test characteristics, respectively

[a] Significant differences ($p < 0.05$) in sensitivity detected between the algorithms by omnibus fisher's exact test

[b] Significant differences ($p < 0.016$) in sensitivity detected between algorithms A and B

[c] Significant differences ($p < 0.016$) in sensitivity detected between algorithms A and C

[d] Significant differences ($p < 0.05$) in specificity detected between the algorithms by omnibus fisher's exact test

[e] Significant difference ($p < 0.016$) in specificity detected between algorithms A and B

[f] Significant differences ($p < 0.05$) in NPV detected between the algorithms by omnibus fisher's exact test

[g] Significant difference ($p < 0.016$) in NPV detected between algorithms A and C

2.5.3 Algorithm performance for suspected HIT

Table IV shows the performance of the algorithms for suspected HIT by subgroups. Given that all patients who met the criteria of the algorithms were treated with DTI due to the suspicion of HIT, the PPV and specificity for the algorithms were 100% across all subgroups. Some of the differences in NPV between the algorithms were statistically significant but small (< 1%). The omnibus test for differences in sensitivity between the three algorithms were found to be statistically significant ($P<0.05$) for all subgroups except for patients who were administered a prophylaxis dose of UFH ($P=0.231$) and had undergone cardiac surgery ($P=0.063$). Algorithm A had higher sensitivity (100%) compared to algorithm B (≤ 80%) across most of the subgroups ($P<0.016$). Similarly, algorithm C had lower sensitivity (< 55%) than algorithm A for most of the subgroups ($P<0.016$). Pairwise differences in sensitivity between algorithms B and C across the subgroups were not found to be statistically significant except for males ($P<0.001$). When patients identified by algorithm A that did not meet the definitions of the other two algorithms were excluded from the controls for algorithms B and C, the sensitivity, specificity and NPV of the two algorithms were identical (100%).

In comparing the performance metrics of algorithms A and B calculated before and after October 1, 2008, the average sensitivity increased for algorithm B (58.33% vs. 66.67%; $P=0.74$). However, this change was not statistically significant. The other performance metrics did not change for algorithm B. The performance of algorithm A for suspected HIT did not change over time.

TABLE IV. SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF THE ALGORITHMS FOR SUSPECTED HIT

	Algorithm	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Overall [a b c e f]	A	39	0	0	18,709	100 (90.97-100)	100 (99.98-100)	100 (90.97-100)	100 (99.98-100)
	B	24	0	15	18,709	61.54 (44.62-76.64)	100 (99.98-100)	100 (85.75-100)	99.92 (99.87-99.96)
	C	6	0	9	8,681	40 (16.34-67.71)	100 (99.96-100)	100 (54.07-100)	99.90 (99.80-99.95)
Cancer [a b e f]	A	17	0	0	2,844	100 (80.49-100)	100 (99.87-100)	100 (80.49-100)	100 (99.87-100)
	B	11	0	6	2,844	64.71 (38.33-85.79)	100 (99.87-100)	100 (71.51-100)	99.79 (99.54-99.92)
	C	2	0	2	823	50 (6.76-93.24)	100 (99.55-100)	100 (15.81-100)	99.76 (99.13-99.97)
Male [a b c d e f]	A	16	0	0	8,307	100 (79.41-100)	100 (99.96-100)	100 (79.41-100)	100 (99.96-100)
	B	8	0	8	8,307	50 (24.65-75.35)	100 (99.96-100)	100 (63.06-100)	99.90 (99.81-99.96)
	C	0	0	4	3,517	0 (0-60.23)	100 (99.90-100)	NA	99.89 (99.71-99.97)
Female [a b c e f]	A	23	0	0	10,402	100 (85.18-100)	100 (99.96-100)	100 (85.18-100)	100 (99.96-100)
	B	16	0	7	10,402	69.57 (47.08-86.79)	100 (99.96-100)	100 (79.41-100)	99.93 (99.86-99.97)
	C	6	0	5	5,164	54.55 (23.38-83.25)	100 (99.93-100)	100 (54.07-100)	99.90 (99.77-99.97)
UFH prophylaxis dose	A	5	0	0	14,892	100 (47.82-100)	100 (99.98-100)	100 (47.82-100)	100 (99.98-100)
	B	4	0	1	14,892	80 (28.36-99.49)	100 (99.98-100)	100 (39.76-100)	99.99 (99.96-100)
	C	2	0	2	7,259	50 (6.76-93.24)	100 (99.95-100)	100 (15.81-100)	99.97 (99.90-100)

TABLE IV. SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF THE ALGORITHMS FOR SUSPECTED HIT

	Algorithm	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
UFH treatment dose [a b c e f]	A	24	0	0	1,572	100 (85.75-100)	100 (99.77-100)	100 (85.75-100)	100 (99.77-100)
	B	15	0	9	1,572	62.50 (40.59-81.20)	100 (99.77-100)	100 (78.20-100)	99.43 (98.92-99.74)
	C	2	0	5	524	28.57 (3.67-70.96)	100 (99.30-100)	100 (15.81-100)	99.05 (97.81-99.69)
Cardiac	A	4	0	0	973	100 (39.76-100)	100 (99.62-100)	100 (39.76-100)	100 (99.62-100)
Surgery	B	2	0	2	973	50 (6.76-93.24)	100 (99.62-100)	100 (15.81-100)	99.79 (99.26-99.98)
	C	0	0	2	374	0 (0-84.19)	100 (99.02-100)	NA	99.47 (98.09-99.94)
Insured [a b c e f]	A	38	0	0	17,586	100 (90.75-100)	100 (99.98-100)	100 (90.75-100)	100 (99.98-100)
	B	23	0	15	17,586	60.53 (43.39-75.96)	100 (99.98-100)	100 (85.18-100)	99.91 (99.86-99.95)
	C	6	0	9	8,082	40 (16.34-67.71)	100 (99.95-100)	100 (54.07-100)	99.89 (99.79-99.95)
ICU [a b c e f]	A	28	0	0	2,544	100 (87.66-100)	100 (99.86-100)	100 (87.66-100)	100 (99.86-100)
	B	18	0	10	2,544	64.29 (44.07-81.36)	100 (99.86-100)	100 (81.47-100)	99.61 (99.28-99.81)
	C	4	0	5	1,123	44.44 (13.70-78.80)	100 (99.67-100)	100 (39.76-100)	99.56 (98.97-99.86)
Heart	A	9	0	0	2,470	100 (66.37-100)	100 (99.85-100)	100 (66.37-100)	100 (99.85-100)
Failure [a b c]	B	6	0	3	2,470	66.67 (29.93-92.51)	100 (99.85-100)	100 (54.07-100)	99.88 (99.65-99.97)
	C	1	0	2	823	33.33 (0.84-90.57)	100 (99.55-100)	100 (2.50-100)	99.76 (99.13-99.97)

HIT=heparin-induced thrombocytopenia, TP=true positive, FP=false positive, FN=false negative, TN=true negative, NPV=negative predictive value, UFH=unfractionated heparin, ICU=intensive care unit, PPV=positive predictive value, NA=not applicable, algorithm A= the initiation of DTI therapy and an order for an HIT diagnostic test at more than 4 days after heparin initiation, algorithm B= algorithm A plus presence of ICD-9-CM code 287.4, 287.5, or 289.84, algorithm C= algorithm A plus presence of ICD-9-CM code 289.84 after October 1, 2008.

Data are presented as percentage (95% confidence interval) for test characteristics, respectively

[a] Significant differences ($p < 0.05$) in sensitivity detected between the algorithms by omnibus fisher's exact test

[b] Significant difference ($p < 0.016$) in sensitivity detected between algorithms A and B

[c] Significant difference ($p < 0.016$) in sensitivity detected between algorithms A and C

[d] Significant difference ($p < 0.016$) in sensitivity detected between algorithms B and C

[e] Significant differences ($p < 0.05$) in NPV detected between the algorithms by omnibus fisher's exact test

[f] Significant difference ($p < 0.016$) in NPV detected between algorithms A and B, A and C, and B and C

2.6 Discussion

The primary goal of this study was to determine whether algorithms, based on electronic medical record and billing data (medication data, diagnostic test orders and diagnostic codes), can be used to accurately identify individuals with clinically suspected or confirmed HIT. Our findings suggest that all three algorithms accurately identify suspected HIT but are not ideal for the identification of confirmed HIT because of the high false positives rates (>50%). The observed difference in the PPV of the algorithms between confirmed and suspected HIT was due to the initiation of DTIs when clinicians suspected HIT. Only some of the suspected cases turned out to have HIT. For example, 43.6% of the patients identified by algorithm A were diagnosed with thrombocytopenia unrelated to heparin based on negative ELISA test results. DTI treatment was continued for some (25.6%) of the patients with false positive ELISA results. The sensitivity of the two algorithms that depended on the presence of ICD-9-CM codes for the identification of patients was poor for both confirmed and suspected HIT. Given the imperfect sensitivity, at least 25% and 39% of confirmed and suspected HIT patients, respectively, will fail to be identified by these two algorithms due to the absence of ICD-9-CM codes. In general, there appears to be a trade-off between sensitivity and PPV. Both the specificity and NPV of the three algorithms were high (>99%) for confirmed and suspected HIT patients. The chance of patients not identified by the algorithms but having confirmed or suspected HIT is very small (<1%) which is reflected by the high NPVs. Results of this study suggests that algorithm A is the most appropriate criteria to identify patients with high clinical suspicion of HIT due to its ability to capture all cases and its having 100% PPV. Performance of the algorithms did not improve in the subgroup analysis.

We are not aware of other studies that have proposed and evaluated the performance of algorithms for the identification of confirmed and clinically suspected HIT. Previous studies that have evaluated the PPV of algorithms for identifying patients with other types of thrombocytopenia,

such as immune thrombocytopenic purpura, reported low PPVs (45.5%-74%) similar to the performance of our algorithms for confirmed HIT.[32,45-47] The algorithms reported in previous studies were based on ICD-9-CM codes. Low PPVs reported by these studies were due to the use of incorrect ICD-9-CM codes (25.7%-34.2%)[32,47] for patients who had experienced a drop in platelet count from other causes of thrombocytopenia such as sepsis,[32] chemotherapy, or human immunodeficiency virus (HIV).[47] Similarly, a multitude of risk factors for thrombocytopenia makes it challenging to diagnose HIT. Only eight (33.3%) of the 24 patients who met the definition of our algorithm A and had experienced a significant drop in platelet count had HIT. The sensitivity of algorithm A, 100%, in this study is consistent with that of a previously validated algorithm (defined by ICD-9-CM codes 287.3, 287.4 and 287.5) by Segal et al. for the identification of patients with immune thrombocytopenic purpura.[32] However, the sensitivity of algorithms B and C were lower due to the absence of ICD-9-CM codes in the patients' health records.

There are several limitations related to this study. First, the results are from a single institution and potentially have limited generalizability due to differences in patient mix, diagnostic testing, and coding procedures compared to other institutions. However, the choice of algorithm A for suspected HIT is unlikely to change due to the differences in patient mix given that it outperformed the other two algorithms across all subgroups. By definition, algorithm A identifies patients with suspected HIT regardless of ICD-9-CM codes, and therefore, is immune to differences in ICD-9-CM coding procedure. ELISA, the most widely used test, has a high false positive rate (15%-18%) that may lead to over-diagnosis and incorrect ICD-9-CM coding.[6] Serotonin release assay (SRA) is the gold standard test for the diagnosis of HIT, and can be used to confirm positive ELISA test results.[6] However, only three (7.69%) patients suspected to have HIT were tested by the SRA at UI Health. Therefore, the performance of the algorithms B and C may improve for hospitals with a higher use of SRA. To the best of our knowledge, no previous study has examined the

differences in patient mix, diagnostic testing, and coding procedures between institutions for HIT. A multicenter study would help in confirming the findings of our study.

Second, the algorithms were defined such that patients suspected to have HIT less than four days after the initiation of heparin treatment were excluded. HIT can develop during this period if the patient had been exposed to heparin within the previous 100 days.[6] However, including such patients will lead to a higher false positive rate because a drop in platelet count experienced during this period could be from other causes. Third, although the PPVs of the algorithms based on ICD-9-CM codes were higher than algorithm A for confirmed HIT, the study was not powered to detect statistically significant difference in the PPVs. However, the algorithms will not be useful for the identification of confirmed HIT in future research studies even if this study was sufficiently powered, as the PPVs were found to be less than optimal. Of note, the number of patients identified by algorithm C was very small (n = 6). Due to the small number of patients in this group, the presence of a few false positives can significantly degrade the performance of algorithm C. Therefore, the PPV of algorithm C for confirmed HIT may improve with an increase in the number of patients identified by algorithm C. The 100% PPV of algorithm A for suspected HIT could be due to the small sample size at our hospital, as patients switched from heparin to DTI without the intention to treat HIT (eg, bivalirudin for anticoagulation during percutaneous coronary intervention) may be rare. Last, the omnibus Fisher's exact test did not account for the dependency between the three groups. However, we were able to account for this dependency in bootstrapped pairwise tests.

In conclusion, this is the first study to demonstrate the feasibility of identifying suspected HIT by algorithms designed using pharmacy medication data, diagnostic test orders and diagnostic codes. The same cannot be said for confirmed HIT due to the high proportion of false positives. All three algorithms will greatly overestimate the incidence of confirmed HIT and underestimate the

incidence of thrombosis. The findings of this study demonstrate the difficulty in identifying a rare immune-mediated disorder by algorithms as the diagnosis and subsequent ICD-9-CM coding is complicated by the presence of other risk factors for thrombocytopenia. Future studies may be able to improve the performance of the algorithms for confirmed HIT by including diagnostic test results. We recommend the use of algorithm A over B and C for the identification of suspected HIT in future observational studies because of its 100% PPV and ability to capture all patients with suspected HIT. Moreover, both algorithm B and C fail to capture patients without ICD-9-CM codes. Restricting patients to subgroups with higher incidence of HIT is not likely to be beneficial because the performance of algorithm A, in terms of PPV, was optimal for patients with suspected HIT across all subgroups.

3 COMPARATIVE EFFECTIVENESS AND SAFETY OF ARGATROBAN AND BIVALIRUDIN IN PATIENTS WITH SUSPECTED HEPARIN-INDUCED THROMBOCYTOPENIA

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3.1 Abstract

Heparin-induced thrombocytopenia (HIT) is a prothrombotic condition that requires immediate treatment, usually with direct thrombin inhibitors (DTIs). However, the treatment may cause major bleeding. Data comparing the effectiveness and safety of DTIs in the treatment of HIT is limited. Therefore, we compared the effectiveness and safety of two DTIs, argatroban and bivalirudin, in patients with suspected HIT in a real-world setting. The Clinical Database/Resource Manager data from the UHC were used to identify hospitalized patients with suspected HIT discharged between 2009 to 2012. Using propensity scores, up to three argatroban-treated patients were matched to each bivalirudin-treated patient. The rates of thrombosis, major bleeding, amputation and mortality were compared using hazard ratios (HRs) from Cox proportional hazard regression models. Of the 2,408 matched patients, 709 (29.4%) received bivalirudin and 1,699 (70.6%) received argatroban. Compared to bivalirudin, argatroban exhibited a less harmful effect for major bleeding (6.1% vs. 11.4%; P<0.05). The risk of thrombosis (7.7% vs. 9.5%; P=0.14), amputation (2.1% vs. 2.00%; P=0.82) and mortality (24.2% vs. 25.5%; P=0.49) were similar in argatroban-and bivalirudin-treated patients. The results were robust to alternative definitions of the outcomes. Compared with bivalirudin-treated patients, argatroban-treated patients were less likely to experience major bleeding.

3.2 Introduction

Patients who undergo surgery or have medical conditions such as pneumonia, stroke, acute spinal cord injury, congestive heart failure and myocardial infarction are at risk of developing thrombosis.[1] Heparin is administered for thromboprophylaxis to an estimated 12 million hospitalized patients in the United States each year.[2-4] Exposure to heparin can lead to heparin-induced thrombocytopenia (HIT) in 0.5-5% of patients.[5-8] Twenty-four percent of patients with HIT experience potentially fatal thrombosis and mortality and amputation due to thrombosis occur in 5% and 3% of patients with HIT, respectively.[10]

Direct thrombin inhibitors (DTIs) are the preferred treatment option for HIT. Argatroban is the only DTI approved by the US Food and Drug Administration (FDA) available in the US for the treatment of HIT.[2,48] Although treatment with argatroban can reduce the absolute risk for thrombosis by 18%, it also causes major bleeding in an estimated 6% of patients with HIT.[10] Of note, it is recommended to initiate DTI treatment at the time of clinical suspicion of HIT and not necessarily after the confirmation of HIT by a diagnostic test. The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines recommend treatment in patients strongly suspected to have HIT (on clinical grounds) for two reasons.[19] First, the diagnosis of HIT is complicated by other risk factors for thrombocytopenia such as surgery, infection, and medications.[6,25] Second, the widely used enzyme-linked immunosorbent assay (ELISA) test can be inaccurate for the diagnosis of HIT. Up to two-thirds of patients are falsely diagnosed with HIT by ELISA.[19] In addition, a delay in the treatment of HIT can increase the risk of thrombosis.[49] Therefore, the evaluation of outcomes in patients with suspected HIT, our target patient population, is of critical importance to clinicians and drug policy makers.

The off-label use of another DTI, bivalirudin, has also been reported in the treatment of suspected HIT.[2,5,16] At this time, bivalirudin is only approved by the FDA for anticoagulation in

patients undergoing percutaneous coronary intervention (PCI).[2,5] Three single-center retrospective cohort studies have compared the effectiveness and safety of argatroban and bivalirudin in patients with suspected HIT.[2,5,16] However, these studies were underpowered to detect differences in outcomes, and did not provide necessary evidence to understand the comparative effectiveness and safety of DTIs in suspected HIT. These results have limited generalizability. Therefore, little is known about outcome differences between these two DTI's in a real-world setting.

We conducted a large observational study to address these limitations. The objective of this study was to determine the comparative effectiveness and safety of argatroban and. bivalirudin, in terms of clinical outcomes such as thrombosis, major bleeding, amputation and mortality, in patients with suspected HIT.

3.3 Methods

3.3.1 Study Design and Data Source

In this retrospective cohort study, the Clinical Database/Resource Manager (CDB/RM) data from January 1, 2009 through December 31, 2012 were obtained from UHC (previously known as the University HealthSystem Consortium). UHC is a non-profit alliance of 120 academic medical centers in the US.[50] The CDB/RM includes data on patient demographics, diagnoses, procedures, costs, laboratory test orders, pharmacy orders, and discharge status.

3.3.2 Study Population

Patients with suspected HIT were identified by a validated algorithm that was defined as: initiation of DTI treatment and an order for an HIT diagnostic test more than 4 days after exposure to heparin. The positive predictive value associated with this algorithm was 100% (95% CI: 90.97-100).[27] The dates of service reported in the pharmacy claims were used to identify the dates of DTI exposure. Admissions with a record of continous or intermittent DTI administration were included in this study.

Children (age <18 years) or pregnant women were excluded as guidelines on the therapeutic activated partial thromboplastin time (aPTT) have not been established in these groups, and DTI use within these populations is rare.[6] Admissions with a same date of service for both argatroban and bivalirudin and hospitals that exclusively used one of the DTIs (argatroban or bivalirudin) for the treatment of suspected HIT were also excluded from the analysis. For patients with more than one admission, only the first admission for suspected HIT was included.

3.3.3 Outcomes

The outcomes measured in this study were major bleeding, thrombosis, amputation and mortality. Patients were followed from the index date (first date of DTI treatment) to the first event within 30 days of DTI initiation. For the bleeding outcome, patients without an event were censored at the end of DTI treatment or 30th day, whichever was earlier. For other outcomes, patients without an event were censored at the discharge date or 30th day, whichever was earlier.

Two previously used definitions of major bleeding were modified to identify the date of an event: (1) transfusion of a blood product (ICD-9-CM 99.00-99.05 and 99.07)[51,52] or decompressive craniectomy/ ventriculostomy (ICD-9-CM 01.21, 01.24, 02.2) during the DTI treatment; and (2) transfusion of a blood product plus the presence of an ICD-9-CM code for bleeding as listed by Wise et al.[52] or decompressive craniectomy/ventriculostomy plus the presence of an ICD-9-CM code for intracranial hemorrhage (ICD-9-CM 430.xx-432.xx, 852.xx) during the DTI treatment.

Thrombosis was identified by the ICD-9-CM codes. Thrombosis included deep vein thrombosis (DVT), pulmonary embolism, cerebral venous thrombosis, arterial thrombosis, ischemic stroke, and myocardial infarction (MI).[2,9,53] The CDB/RM does not have date stamps for the diagnostic ICD-9-CM codes, and therefore, imaging procedures were used to identify the dates of thrombosis. In current clinical practice, a patient with symptoms of thrombosis is likely to undergo repeated imaging until the thrombosis is confirmed. Therefore, the last date of an imaging procedure

was used to identify the date of incidence for all thromboses except MI. The date of a MI event was identified by assuming a gap of one day between an event and the date of a percutaneous coronary intervention (PCI), as CDB/RM data is granular only down to one day. Current guidelines recommend that a primary PCI procedure may be performed within 12-24 hours of the onset of symptoms.[54] No patient in the cohort underwent a coronary artery bypass-graft for a MI event after the initiation of DTI treatment.

Amputation of the extremity was identified by the presence of procedure codes (ICD-9-CM 84.0x, 84.1x). The date of discharge and patient status at discharge were used to identify the date of death.

3.3.4 Covariates

Using ICD-9-CM codes, potential confounders included the list of diagnoses that were present-on-admission and procedures (e.g., surgery) performed before the initiation of DTI treatment as follows: anemia,[55-57] blood disorders,[57-59] cardiovascular diseases,[57,60-64] cancer,[55,57,58,63] cerebrovascular disease,[57,61,64,65] drug and alcohol abuse,[55,57,58] diabetes,[55,57,60,62] extremity paresis,[26,57] fluid and electrolyte imbalance,[55,57] hypercholesterolemia,[60,66] hypertension,[57,60] hypothyroidism,[55,57] inflammatory bowel disease,[67] infections,[57,62] liver and renal impairment,[26,57,64,68] neurological disorders,[55,57,61,64] obesity,[55,57] peptic ulcer,[57,69] peripheral vascular disease,[57,70] pulmonary disease,[55,57,64,71] rheumatologic disease,[57,67] smoker,[60] thrombophilia,[59] bleeding before the initiation of DTI,[58,68] varicose veins,[67] weight loss,[57] patient demographics,[26,55,64,68,70,72] primary payer,[55,68] and surgeries.[64,71,73-75]

In addition, we included the year of admission and type of physician (primary care, specialty, surgery, unknown/other) in the analysis. The year of admission was a proxy for the change in clinical practice and preference for a DTI in hospitals over time, and the knowledge on diagnoses and management of thrombosis can vary by the type of physician.[76]

3.3.5 Statistical analysis

Propensity scores were used to reduce the effects of confounding.[77] A logistic regression model (c-statistic = 0.71) was used to predict the probability of receiving argatroban conditional on the patient characteristics that were not balanced ($P<0.05$) between the two groups (Table V).[78] Up to three argatroban-treated patients were matched to each bivalirudin-treated patient without replacement. Greedy matching with a caliper equal to 0.2 of the "standard deviation of the logit of the propensity score"[79] was used to form matched groups.[79,80] After matching, a standardized difference of < 0.10 indicated sufficient balance.[77]

Time-to-event curves were constructed by the Kaplan-Meier method. For the Cox regression analyses, log-log survival curves were used to assess the proportional hazard (PH) assumption. Hazard ratios (HRs) for thrombosis and mortality were calculated for separate periods by a piecewise Cox proportional hazard regression stratified by matched pairs, as the log-log survival curves were not parallel. In order to account for the clustering effect within hospitals and high-risk groups, robust standard errors were calculated using sandwich estimators.[51,81] High-risk groups were patients who experienced thrombosis and bleeding before the initiation of DTI treatment. The HRs were adjusted for residual confounders. These variables changed the HR by more than 10% and had a standardized difference of ≥ 0.10 or p-value < 0.05 after matching. SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used to conduct all statistical analyses. University of Illinois at Chicago's institutional review board reviewed and approved this study.

3.3.6 Sensitivity analyses

Several sensitivity analyses were conducted to assess the robustness of the findings. First, because the events experienced on the first day of treatment may have occurred before the initiation of DTI treatment, HRs were calculated dropping the first day of treatment. Second, the date for MI was determined by the date of a PCI. In the primary analysis, it was assumed that a PCI was

performed a day after the onset of symptoms. This gap was varied from 0 to 4 days for patients with a MI event in the sensitivity analyses. Third, thrombosis at other sites was determined by the dates of imaging procedures. Some of the charge descriptions for imaging procedures were not sufficiently granular to rule out their use for other diagnoses. Therefore, only imaging procedure descriptions specific to thrombosis were used in the sensitivity analyses. Fourth, the rates of thrombosis were evaluated in the low-risk subgroup i.e. HIT not complicated with a thrombosis at the time of treatment initiation. We were unable to perform the analysis in the high-risk subgroup due to the small sample size (post-matched n=130). Last, major bleeding during the DTI treatment could be due to warfarin cotherapy, surgery or thrombolytic infusion. Therefore, we compared the bleeding rate between the DTIs by ignoring events experienced on the day of warfarin cotherapy, surgery or thrombolytic infusion.

3.4 Results

From 1 January 2009 through 31 December 2012, there were 3,586 admissions of suspected HIT that met the inclusion criteria (Figure 5). In the unmatched cohort, patients receiving bivalirudin were more likely to have a cardiovascular condition, cardiovascular surgery, diabetes, peripheral vascular disease, and bleeding prior to the initiation of DTI treatment. The use of bivalirudin increased from 13.7% to 24.1% of patients during the observation period. A total of 709 bivalirudin-treated patients were matched to 1,699 argatroban-treated patients (Table V). In the matched cohort, the majority of the patients were male (60.8%) and white (64.2%). The mean (standard deviation) age of the patients was 62.7 years (14.6). Patients were treated with a DTI for an average of 5 days in both groups. Both bivalirudin and argatroban-treated patients had a similar average length of stay after the initiation of DTI treatment (15.8 days vs. 15.2 days; P=0.14).

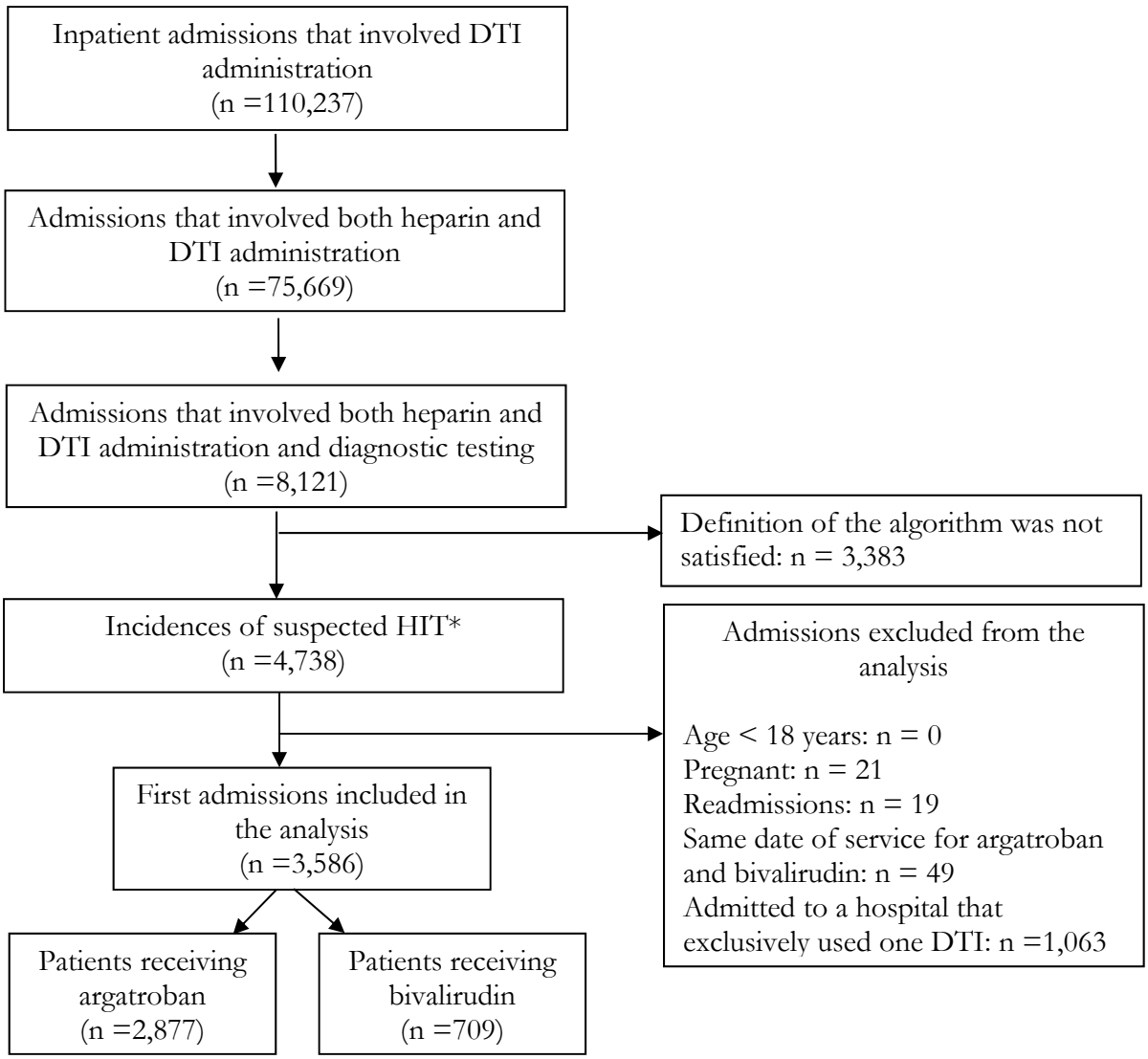


Figure 5. Patient selection process for the study cohort
HIT=heparin-induced thrombocytopenia; DTIs=direct thrombin inhibitors argatroban or bivalirudin.
* Patients with suspected heparin-induced thrombocytopenia were identified by an algorithm. The validated algorithm was defined as: initiation of DTI treatment and an order for an HIT diagnostic test more than 4 days after exposure to heparin.

TABLE V. COVARIATE BALANCE BEFORE AND AFTER PROPENSITY SCORE MATCHING

Characteristics	Before Matching				After Matching			
	Bivalirudin (n = 709)	Argatroban (n = 2,877)	P Value	Standardized Difference	Bivalirudin (n = 709)	Argatroban (n = 1,699)	P Value	Standardized Difference
Age in years, mean (std)	62.10 (14.2)	62.32 (15.2)	0.71	0.02	62.10 (14.2)	63.00 (14.8)	0.03	0.06
Year of admission, n (%)								
2009	50 (7.1)	363 (12.6)	<0.01	0.19	50 (7.1)	143 (8.5)	0.71	0.05
2010	174 (24.5)	835 (29.0)		0.10	174 (24.5)	454 (26.7)		0.05
2011	229 (32.3)	872 (30.3)		0.04	229 (32.3)	551 (32.4)		0.00
2012	256 (36.1)	807 (28.1)		0.17	256 (36.1)	551 (32.4)		0.08
Male, n (%)	438 (61.8)	1,579 (54.9)	<0.01	0.14	438 (61.8)	1,026 (60.4)	0.75	0.03
Race, n (%)								
Unknown	8 (1.1)	84 (2.9)	<0.01	0.13	8 (1.1)	19 (1.1)	1.00	0.00
White	440 (62.1)	1,944 (67.6)		0.12	440 (62.1)	1,107 (65.2)		0.06
Black	169 (23.8)	559 (19.4)		0.11	169 (23.8)	375 (22.0)		0.04
Native American/Eskimo	0 (0)	9 (0.3)		-	0 (0)	1 (0.1)		-
Asian	27 (3.8)	51 (1.8)		0.12	27 (3.8)	42 (2.4)		0.08
Other	65 (9.2)	223 (7.8)		0.05	65 (9.2)	153 (9.0)		0.01
Hawaiian/Pacific Islander	0 (0)	6 (0.2)		-	0 (0)	1 (0.1)		-
Multiracial	0 (0)	1 (0.0)		-	0 (0)	1 (0.1)		-
Primary payer, n (%)			0.13				0.25	
Private	199 (28.1)	708 (24.6)		0.08	199 (28.1)	444 (26.1)		0.04
Medicaid	79 (11.1)	388 (13.5)		0.07	79 (11.1)	216 (12.7)		0.05
Medicare	371 (52.3)	1,575 (54.7)		0.05	371 (52.3)	922 (54.3)		0.04
Other/unknown	36 (5.1)	121 (4.2)		0.04	36 (5.1)	68 (4.0)		0.05
Uninsured	24 (3.4)	85 (3.0)		0.03	24 (3.4)	49 (2.9)		0.03

TABLE V. COVARIATE BALANCE BEFORE AND AFTER PROPENSITY SCORE MATCHING

Characteristics	Before Matching				After Matching			
	Bivalirudin (n = 709)	Argatroban (n = 2,877)	P Value	Standardized Difference	Bivalirudin (n = 709)	Argatroban (n = 1,699)	P Value	Standardized Difference
Type of physician, n (%)			<0.01				0.83	
Primary care	79 (11.1)	783 (27.2)		0.42	79 (11.1)	215 (12.7)		0.05
Specialty	301 (42.5)	1,064 (37.0)		0.11	301 (42.5)	727 (42.8)		0.01
Surgery	300 (42.3)	977 (34.0)		0.17	300 (42.3)	709 (41.7)		0.01
Unknown/other	29 (4.1)	53 (1.8)		0.13	29 (4.1)	48 (2.8)		0.01
Medical conditions at admission, n (%)								
AIDS	7 (1.0)	22 (0.8)	0.55	0.02	7 (1.0)	11 (0.7)	0.34	0.04
Alcohol abuse	32 (4.5)	175 (6.1)	0.11	0.07	32 (4.5)	108 (6.4)	0.11	0.08
Anemia	215 (30.3)	1,100 (38.2)	<0.01	0.17	215 (30.3)	531 (31.3)	0.57	0.02
Bleeding*	425 (59.9)	1,573 (54.7)	0.01	0.11	425 (59.9)	954 (56.2)	0.42	0.08
Cancer	99 (14.0)	643 (22.4)	<0.01	0.22	99 (14.0)	270 (15.9)	0.94	0.05
Cardiac arrest	16 (2.3)	35 (1.2)	0.04	0.08	16 (2.3)	30 (1.8)	1.00	0.04
Cardiac arrhythmias	251 (35.4)	992 (34.5)	0.64	0.02	251 (35.4)	652 (38.4)	0.04	0.06
Cerebrovascular disease (excluding intracranial hemorrhage)	35 (4.9)	151 (5.3)	0.74	0.01	35 (4.9)	98 (5.8)	0.34	0.04
Chronic pulmonary disease	156 (22.0)	703 (24.4)	0.17	0.06	156 (22.0)	397 (23.4)	0.51	0.03
Platelet or coagulation defect	119 (16.8)	495 (17.2)	0.79	0.01	119 (16.8)	255 (15.0)	0.14	0.05
Coronary artery disease	386 (54.4)	1,027 (35.7)	<0.01	0.38	386 (54.4)	794 (46.7)	0.64	0.16
Congestive heart failure	357 (50.4)	1,096 (38.1)	<0.01	0.25	357 (50.4)	777 (45.7)	0.81	0.09
Dementia	0 (0.0)	10 (0.4)	0.23	-	0 (0.0)	5 (0.3)	0.97	-
Depression	92 (13.0)	372 (12.9)	0.97	0.00	92 (13.0)	192 (11.3)	0.11	0.05
Diabetes	260 (36.7)	916 (31.8)	0.01	0.10	260 (36.7)	585 (34.4)	0.76	0.05
Drug abuse	32 (4.5)	91 (3.2)	0.08	0.07	32 (4.5)	50 (2.9)	0.04	0.08
Extremity paresis	13 (1.8)	80 (2.8)	0.16	0.06	13 (1.8)	32 (1.9)	0.98	0.00
Fluid and electrolyte imbalance	180 (25.4)	959 (33.3)	<0.01	0.18	180 (25.4)	456 (26.8)	0.77	0.03

TABLE V. COVARIATE BALANCE BEFORE AND AFTER PROPENSITY SCORE MATCHING

	Bivalirudin (n = 709)	Argatroban (n = 2,877)	P Value	Standardized Difference	Bivalirudin (n = 709)	Argatroban (n = 1,699)	P Value	Standardized Difference
Hepatic impairment	127 (17.9)	454 (15.8)	0.17	0.06	127 (17.9)	248 (14.6)	0.02	0.09
History of coagulation disorder	0 (0.0)	1 (0.0)	1.00	-	0 (0.0)	0 (0.0)	-	-
Hypercholesterolemia	0 (0.0)	0 (0.0)	-		0 (0.0)	0 (0.0)	-	-
Hypertension	473 (66.7)	1,883 (65.5)	0.53	0.03	473 (66.7)	1,157 (68.1)	0.14	0.03
Hypothyroidism	75 (10.6)	382 (13.3)	0.05	0.08	75 (10.6)	227 (13.4)	0.05	0.09
Inflammatory bowel disease	6 (0.9)	38 (1.3)	0.30	0.05	6 (0.9)	21 (1.2)	0.59	0.04
Neurologic disorder	67 (9.5)	253 (8.8)	0.58	0.02	67 (9.5)	132 (7.8)	0.11	0.06
Old myocardial infarction	0 (0.0)	1 (0.0)	1.00	-	0 (0.0)	1 (0.1)	0.97	-
Obesity	110 (15.5)	507 (17.6)	0.18	0.06	110 (15.5)	288 (17.0)	0.29	0.04
Peptic ulcer	11 (1.6)	45 (1.6)	0.98	0.00	11 (1.6)	20 (1.2)	0.33	0.03
Peripheral vascular disease	156 (22.0)	505 (17.6)	0.01	0.11	156 (22.0)	354 (20.8)	0.96	0.03
Pneumonia	57 (8.0)	389 (13.5)	<0.01	0.18	57 (8.0)	154 (9.1)	0.89	0.04
Psychoses	6 (0.9)	45 (1.6)	0.15	0.07	6 (0.9)	25 (1.5)	0.29	0.06
Pulmonary circulation disorder	6 (0.9)	14 (0.5)	0.25	0.04	6 (0.9)	10 (0.6)	0.33	0.03
Pulmonary insufficiency	11 (1.6)	64 (2.2)	0.26	0.05	11 (1.6)	36 (2.1)	0.58	0.04
Renal impairment	338 (47.7)	1,461 (50.8)	0.14	0.06	338 (47.7)	857 (50.4)	0.13	0.06
Rheumatologic disease	32 (4.5)	147 (5.1)	0.51	0.03	32 (4.5)	64 (3.8)	0.32	0.04
Skin infection	12 (1.7)	85 (3.0)	0.06	0.08	12 (1.7)	50 (2.9)	0.10	0.08
Thrombophilia	18 (2.5)	61 (2.1)	0.50	0.03	18 (2.5)	35 (2.1)	0.40	0.03
Urinary tract infection	47 (6.6)	320 (11.1)	<0.01	0.16	47 (6.6)	130 (7.7)	0.93	0.04
Valvular disease	228 (32.2)	644 (22.4)	<0.01	0.22	228 (32.2)	483 (28.4)	0.73	0.08
Varicose veins	20 (2.8)	62 (2.2)	0.29	0.04	20 (2.8)	39 (2.3)	0.37	0.03
Weight loss	82 (11.6)	402 (14.0)	0.09	0.07	82 (11.6)	191 (11.2)	0.51	0.01

TABLE V. COVARIATE BALANCE BEFORE AND AFTER PROPENSITY SCORE MATCHING

Characteristics	Before Matching				After Matching			
	Bivalirudin (n = 709)	Argatroban (n = 2,877)	P Value	Standardized Difference	Bivalirudin (n = 709)	Argatroban (n = 1,699)	P Value	Standardized Difference
Procedures before the suspicion of HIT, n (%)								
Amputation	5 (0.7)	31 (1.1)	0.37	0.04	5 (0.7)	18 (1.1)	0.51	0.04
Abdomen surgery	143 (20.2)	669 (23.3)	0.08	0.08	143 (20.2)	361 (21.3)	0.66	0.03
Cardiovascular surgery	362 (51.1)	841 (29.2)	<0.01	0.46	362 (51.1)	733 (43.1)	0.87	0.16
Orthopedic surgery	52 (7.3)	266 (9.3)	0.11	0.07	52 (7.3)	159 (9.4)	0.24	0.07

* Presence of any ICD-9-CM code for bleeding at admission or blood transfusion before the initiation of direct thrombin inhibitor (DTI) treatment or an intracranial hemorrhage with decompressive craniectomy/ventriculostomy before the initiation of DTI treatment

3.4.1 Major bleeding based on blood transfusion and decompressive craniectomy/ventriculostomy

Among patients with major bleeding, the median (interquartile range [IQR]) time to bleeding was 2 days (1-3 days). Major bleeding occurred in 81 (11.4%) bivalirudin-treated patients and 103 (6.1%) argatroban-treated patients ($P<0.05$). The Kaplan-Meier curves show that the majority (84.6%) of the events were experienced during the first 7 days of argatroban treatment (Figure 6). Similarly, the majority (79.0%) of events were experienced during the first week of bivalirudin treatment.

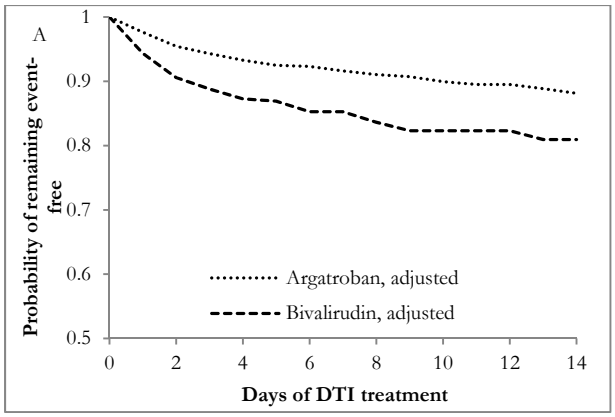
No major bleeding event was observed after the 14th day of treatment. Argatroban, compared with bivalirudin treatment, significantly reduced the incidence of major bleeding at 14 days (hazard ratio [HR] 0.47; 95% confidence interval [CI], 0.34-0.62) (Table VI). Argatroban exhibited a less harmful effect even when the first day of treatment was excluded from the analysis (HR 0.59; 95% CI, 0.40-0.87). When events experienced on the day of warfarin cotherapy, surgery or thrombolytic infusion were excluded, argatroban-treated patients were also less likely to experience major bleeding at 14 days (HR 0.57; 95% CI, 0.41-0.80).

3.4.2 Major bleeding based on blood transfusion, decompressive craniectomy/ventriculostomy and diagnostic codes

Major bleeding occurred in 25 (3.5 %) bivalirudin-treated patients and 27 (1.6%) argatroban-treated patients ($P<0.05$) for this cohort. No intracranial hemorrhages were observed in the cohort. Bleeding sites included gastrointestinal tract (46.2%), hemoptysis (5.8%), epistaxis (3.8 %), and other locations (44.2 %).

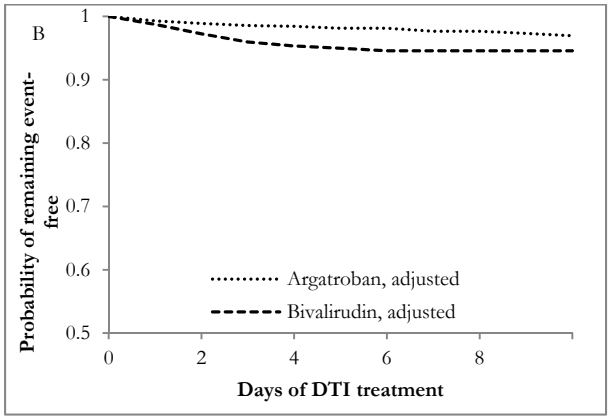
No major bleeding event was observed after the 10th day of treatment. Compared to bivalirudin treatment, argatroban treatment produced less bleeding at 10 days (HR 0.39; 95% CI, 0.24-0.63) (Table VI). The lower risk of harm associated with the use of argatroban relative to

bivalirudin remained statistically significant when the first day of treatment was excluded from the analysis (HR 0.28; 95% CI, 0.13-0.60). When events experienced on the day of warfarin cotherapy, surgery or thrombolytic infusion were excluded, the incidence of major bleeding in the argatroban group (1.4%) was lower than the bivalirudin group (2.4%) (HR 0.52; 95% CI, 0.29-0.93).



Patients at risk, n

Matched cohort								
Argatroban	1,699	1,201	735	498	329	239	162	121
Bivalirudin	709	448	289	213	154	110	74	51



Patients at risk, n

Matched cohort						
Argatroban	1,699	1,220	765	521	350	255
Bivalirudin	709	469	306	229	164	119

Figure 6. Kaplan Meier survival curves for major bleeding.
Panel A shows data for bleeding events defined as transfusion of a blood product (ICD-9-CM 99.00-99.05 and 99.07) or decompressive craniectomy/ ventriculostomy (ICD-9-CM 01.21, 01.24, 02.2) during the DTI treatment
Panel B shows data for bleeding events defined as transfusion of a blood product plus the presence of an ICD-9-CM code for bleeding or decompressive craniectomy/ventriculostomy plus the presence of an ICD-9-CM code for intracranial hemorrhage (ICD-9-CM 430.xx-432.xx, 852.xx) during the DTI treatment.
DTI=direct thrombin inhibitor

TABLE VI. OUTCOMES BY THE TYPE OF DIRECT THROMBIN INHIBITOR

Outcomes	Time (days)	Unadjusted Analysis			Adjusted Analysis		
		Bivalirudin (n = 709)	Argatroban (n = 2,877)	HR (95% CI)	Bivalirudin (n = 709)	Argatroban (n = 1,699)	HR (95% CI)
Primary analysis							
Thrombosis, n (%)	≤ 10	55 (7.8)	179 (6.2)	0.80 (0.59-1.08)	55 (7.8)	93 (5.5)	0.74 (0.50-1.10)
	> 10 to ≤ 30	12 (1.7)	58 (2.0)	1.34 (0.72-2.49)	12 (1.7)	37 (2.2)	1.43 (0.66-3.14)
Bleeding (procedures), n (%)	≤ 14	81 (11.4)	208 (7.2)	0.63 (0.49-0.81)	81 (11.4)	103 (6.1)	0.47 (0.35-0.62)
Bleeding (procedures with ICD-9 codes), n (%)	≤ 10	25 (3.5)	56 (1.9)	0.55 (0.34-0.88)	25 (3.5)	27 (1.6)	0.39 (0.24-0.63)
Amputation, n (%)	≤ 30	14 (2.0)	48 (1.7)	0.87 (0.48-1.58)	14 (2.0)	36 (2.1)	1.10 (0.49-2.47)
Mortality, n (%)	≤ 12	113 (15.9)	491 (17.1)	1.08 (0.88-1.32)	113 (15.9)	287 (16.9)	1.11 (0.91-1.35)
	> 12 to ≤ 30	68 (9.6)	178 (6.2)	0.73 (0.55-0.97)	68 (9.6)	124 (7.3)	0.75 (0.53-1.07)
	At discharge [a]	215 (30.3)	763 (26.5)	0.87 (0.77-0.99)	215 (30.3)	471 (27.7)	0.93 (0.78-1.10)
Sensitivity analysis [b]							
Thrombosis, n (%)	First day	26 (3.7)	77 (2.7)	0.92 (0.64-1.32)	26 (3.7)	43 (2.5)	0.73 (0.43-1.25)
	> 1 to ≤ 10	29 (4.1)	102 (3.6)	0.86 (0.57-1.29)	29 (4.1)	50 (2.9)	0.89 (0.62-1.27)
Bleeding (procedures), n (%)	First day	40 (5.6)	92 (3.2)	0.57 (0.39-0.82)	40 (5.6)	40 (2.4)	0.38 (0.28-0.53)
	> 1 to ≤ 14	41 (5.8)	116 (4.0)	0.69 (0.48-0.98)	41 (5.8)	63 (3.7)	0.59 (0.40-0.87)
Bleeding (procedures with ICD-9 codes), n (%)	First day	9 (1.3)	27 (0.9)	0.74 (0.35-1.57)	9 (1.3)	12 (0.7)	0.53 (0.29-0.99)
	> 1 to ≤ 10	16 (2.3)	29 (1.0)	0.44 (0.24-0.82)	16 (2.3)	15 (0.9)	0.28 (0.13-0.60)
Amputation, n (%)	First day	2 (0.3)	5 (0.2)	0.62 (0.12-3.17)	2 (0.3)	3 (0.2)	0.54 (0.11-2.59)
	> 1 to ≤ 30	12 (1.7)	43 (1.5)	0.91 (0.48-1.73)	12 (1.7)	33 (1.9)	1.21 (0.56-2.64)

HR=hazard ratio, CI = confidence interval, DTI=direct thrombin inhibitor, ICH=intracranial hemorrhage

a Relative risk (95% CI)

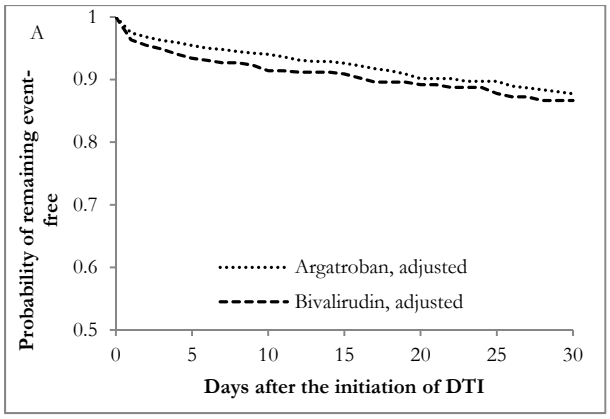
b Hazard ratios for the first day and subsequent time point have been reported to examine the extent of falsely captured events (i.e.

3.4.3 Thrombosis and Amputation

Among patients with thrombosis, the median (IQR) time to thrombosis was 3 days (1-10 days). Thrombosis occurred in 67 (9.4 %) bivalirudin-treated patients and 130 (7.6 %) argatroban-treated patients (P=0.14). Sites included DVT (36.6%), pulmonary embolism (19.3%), cerebral venous thrombosis (0.5%), arterial thrombosis (11.2%), stroke (31.5%), and myocardial infarction (1.0 %). The events experienced during the first week of DTI treatment constituted a large proportion (46.2%) of thrombosis (Figure 7). Of the patients with thrombosis, the recommended duration of warfarin cotherapy (≥5 days) was achieved in only 12 (17.9 %) and 18 (13.8 %) patients treated with bivalirudin and argatroban, respectively (P=0.45). Compared with bivalirudin group, argatroban-treated patients had a similar risk for experiencing thrombosis at 10 days (HR 0.74; 95% CI, 0.50-1.10) (Table VI). The finding did not change when the first day of treatment was excluded from the analysis (HR 0.89; 95% CI, 0.62-1.27). The direction of HR was reversed for the subsequent time point (HR 1.43; 95% CI, 0.66-3.14).

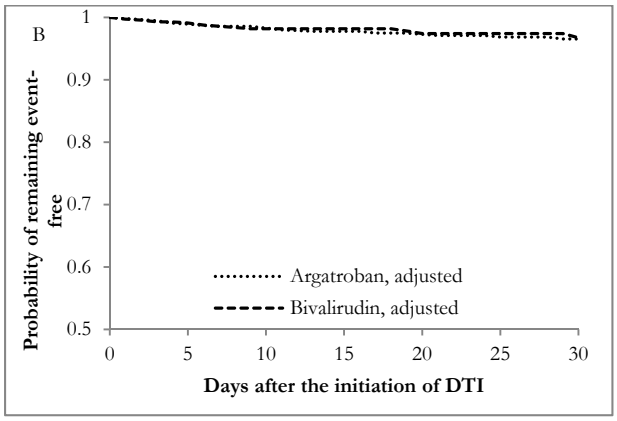
The hazard ratio and statistical significance were not affected when the gap between the onset of MI symptoms and PCI was varied from 0 days to 4 days. A MI event occurred on the 3rd and 11th day of follow-up in the bivalirudin group. When only imaging procedure descriptions specific to thrombosis were used, the risk of thrombosis was similar between argatroban and bivalirudin at 10 days (HR 0.64; 95% CI, 0.31-1.29). The hazard ratio for the subsequent time point is not reported, as seven patients experienced thrombosis in the argatroban group compared to zero in the bivalirudin group. Within the low-risk subgroup, the risk of thrombosis was not different between the DTIs at 10 days (HR 0.77; 95% CI, 0.53-1.12) and 30 days (HR 2.05; 95% CI, 0.80-5.30).

Amputation was performed in 14 (2.0%) bivalirudin-treated patients and 36 (2.1%) argatroban-treated patients (P=0.82). The difference in the risk of amputation was not statistically significant at 30 days (HR 1.10; 95% CI, 0.49-2.47) (Table VI).



Patients at risk, n

Matched cohort							
Argatroban	1,699	1,412	1,023	697	490	367	266
Bivalirudin	709	561	426	312	226	179	132



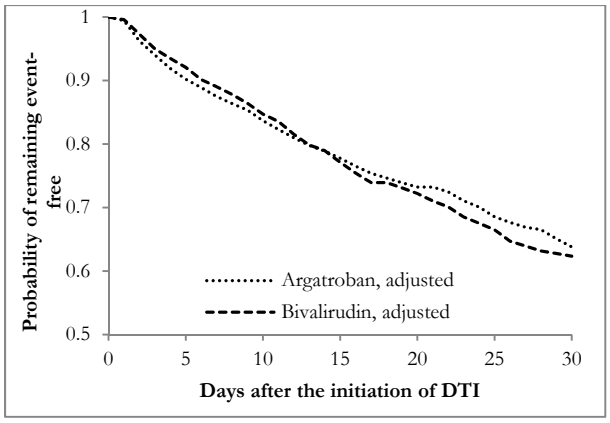
Patients at risk, n

Matched cohort							
Argatroban	1,699	1,454	1,072	739	532	398	291
Bivalirudin	709	595	454	336	245	191	144

Figure 7. Kaplan Meier survival curves for thrombosis and amputation.
Panel A shows data for thrombosis
Panel B shows data for amputation
DTI=direct thrombin inhibitor

3.4.4 Mortality

Death occurred in 181 (25.5%) bivalirudin-treated patients and 411 (24.2%) argatroban-treated patients (P=0.49). There was no clear difference in the risk of mortality between the DTIs (Figure 8). When patients were followed until discharge, the risk for mortality was similar between argatroban and bivalirudin (relative risk 0.93; 95% CI, 0.78-1.10) (Table VI).



Patients at risk, n							
Matched cohort							
Argatroban	1,699	1,468	1,087	756	544	412	301
Bivalirudin	709	599	464	342	250	196	147

Figure 8. Kaplan Meier survival curves for mortality.
DTI=direct thrombin inhibitor

3.5 Discussion

The objective of this study was to compare the outcomes between argatroban and bivalirudin-treated patients with suspected HIT. Patients treated with argatroban were less likely to experience major bleeding compared to bivalirudin-treated patients, regardless of the definition used for major bleeding. A large proportion of the major bleeding events occurred on the first day of DTI treatment. This may be due to the dose adjustments needed to achieve and maintain therapeutic aPTT on the first day of treatment. An overdose during these adjustments may result in bleeding. Dang et al. have reported an average time to first therapeutic aPTT of 14 hours and 8.5 hours for argatroban and bivalirudin, respectively (P=0.12).[5] However, the results did not change when events on the first day were excluded from the analysis. The effectiveness of both DTIs, in terms of thrombosis, was similar. This may explain the non-difference in the risk for amputation. The reduced risk for bleeding associated with argatroban may not have been sufficient to produce a benefit in terms of mortality. This may be due to the absence of bleeding at potentially fatal sites such as an intracranial hemorrhage.

The findings of this study are important given the increase in the utilization of heparin for thromboprophylaxis. The utilization of heparin during an inpatient stay increased from 34% to 41% of all US hospitalizations from 2006 to 2010.[82] This may in turn lead to a higher incidence of HIT that requires treatment with a DTI. However, the choice of one DTI over another is not clear. Current ACCP guidelines recommend argatroban over other nonheparin anticoagulants such as bivalirudin for the treatment of HIT.[6] This recommendation is due to the absence of evidence on comparative effectiveness and safety of DTIs.[6] The evidence supporting the use of bivalirudin in patients with HIT is limited to case-series.[83] This study provides evidence to help healthcare providers make treatment decisions. Compared with previous studies,[2,5,16] the strengths of our study include the use of a large number of hospitalizations (from 105 of academic medical centers), the use

of propensity scores to adjust for confounding and time-to-event analysis that accounts for the differences in the length of follow-up between patients. Previous studies were underpowered to detect differences in outcomes, as the number of patients per each arm was low (range: 13 to 102).[2,5,16] The incidence of thrombosis and major bleeding ranged from 4.3% to 23% and 11% to 62% of argatroban-treated patients, respectively.[2,5,16] The incidence of thrombosis and major bleeding was similar in the bivalirudin group.[2,5,16] The wide variation in the rates of thrombosis and major bleeding reported by these studies may be due to the small sample sizes and differences in the definitions of the outcomes. In addition, two studies did not adjust for potential confounders,[5,16] while the third study was a subgroup analysis in patients receiving renal replacement therapy.[2]

The results of our study are consistent with a previous clinical trial that compared the outcomes between historical controls and argatroban-treated patients.[10] It was the largest study of patients with isolated HIT (n = 321).[10] The definition of therapeutic aPTT (1.5-3 times patient baseline) in the clinical trial was the same as the current ACCP guidelines used by hospitals to treat suspected HIT. Major bleeding was defined as hemorrhage requiring a transfusion of ≥ 2 Units of blood due to a hemoglobin decrease ≥ 2 gram/deciliter, or bleeding was intracranial, retroperitoneal, or into a prosthetic joint.[10] In that study, 8% of argatroban-treated patients with isolated HIT experienced thrombosis while 6% experienced major bleeding.[10] When the cohort in our study was restricted to patients with isolated HIT (low-risk subgroup), the rates for thrombosis and major bleeding were 7.5% and 6.7%, respectively, for argatroban-treated patients. The consistency in the rates for bleeding and thrombosis helps validate the use of imaging procedures and blood transfusions in our study. In addition, amputation was performed in 2% of patients in the clinical trial compared with 1.9% of patients in our study.[10] The average length of treatment (5 days) for both DTI groups was equal in our study, and consistent with the clinical trial in patients with actual

HIT.[20] Given these observations, it appears that the proportion of unknown non-HIT cases in both groups did not influence the findings of our study.

As with other observational studies, there are limitations with the methods in this study. First, the date of thrombosis was identified via imaging procedures. Some of the descriptions for imaging procedures were not sufficiently granular to rule out their use for other diagnoses. However, the percentage of thrombosis identified by such descriptions were similar between bivalirudin-and argatroban-treated patients (84% vs. 80%; P=0.54). In addition, the findings did not change when events were identified by imaging procedure descriptions specific to thrombosis. Thrombosis diagnosed without the use of imaging were not captured in the analysis. However, only 14% and 17% of patients were diagnosed with a DVT without the use of an imaging procedure in the two groups (P=0.09). Similarly, no difference was observed in the percentage of arterial thrombosis diagnosed without an imaging procedure (2% vs. 2%). Thus, the use of imaging procedures to identify the timing of thrombosis is unlikely to bias the results.

Second, major bleeding was identified by procedures such as blood transfusion and decompressive craniectomy/ventriculostomy. This definition is likely to capture only severe cases of intracranial hemorrhage (ICH), as not all events require a decompressive craniectomy/ventriculostomy. Only 10% and 27% of ICH events required a craniectomy/ventriculostomy during the hospitalization for bivalirudin and argatroban groups, respectively (P=0.13). Therefore, the harmful effect of bivalirudin (vs. argatroban) may be biased downwards. The conclusions of this study will not change even if ICH without a craniectomy/ventriculostomy were captured. In addition, intracranial hemorrhage is rare in the HIT population. A previous clinical trial for argatroban observed no ICH event in 418 patients treated with argatroban.[20]

Third, the algorithm did not capture patients without diagnostic testing for HIT. Relaxing the algorithm's criteria to include such patients can potentially bias the rate of thrombosis in favor of bivalirudin. Bivalirudin is indicated for anticoagulation in patients undergoing PCI while argatroban is indicated for the treatment of HIT. Thus, non-HIT cases that are less likely to experience thrombosis will be included in the bivalirudin group. Fourth, the CDB/RM does not include data from non-academic medical centers. Results may not be generalizable to non-academic medical centers. A previous study has shown that the adherence to core quality-of-care measures for heart failure, as identified by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), differs between academic and non-academic hospitals.[84] We are not aware of any such studies for suspected HIT. Although the rates for events may be higher in the non-academic centers for both DTIs, there is no reason to believe that the observed difference in events between the DTIs will change.

Last, propensity score matching was used to balance the treatment groups on diagnoses present-on-admission. However, a diagnosis of hepatic impairment after an admission may influence the choice of argatroban. Of the patients with hepatic impairment, 43% and 44% were diagnosed post-admission for bivalirudin and argatroban, respectively (P=0.82). Therefore, both treatment groups will have a similar proportion of patients with hepatic impairment even if the post-admission diagnosis was before the initiation of DTI treatment. In addition, only observed confounders were used to estimate the propensity score. Residual confounding from unobserved or unknown variables may exist.

To the best of our knowledge, this is the largest study to compare the effectiveness and safety of DTIs for the treatment of suspected HIT in a real-world setting. Argatroban-treated patients were at a lower risk of experiencing major bleeding events compared with bivalirudin-treated patients. Although the lower acquisition cost of bivalirudin may be one of the reasons for its

use in patients with suspected HIT,[5] the rate of major bleeding is higher than with argatroban. These bleeding events may in turn drive up costs. Hence, it is important that providers consider both costs and harms associated with DTIs when making treatment decisions. Future research on the cost-effectiveness of DTIs for the treatment of suspected HIT is needed to provide guidance to healthcare providers. We did not find differences in the risk of thrombosis, amputation and mortality between the two DTIs. These findings need to be confirmed in a sufficiently powered randomized clinical trial. The findings of this study are not applicable to patients with severe hepatic impairment as bivalirudin may be the only treatment option for these patients.

4 The Off-Label Use of Bivalirudin for Anticoagulation in Hospitalized Patients: An Administrative Claims Database Analysis

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4.1 Preface

This chapter of the dissertation will be submitted for publication as an article in the journal *Thrombosis Research*. This paper is the last of the three studies that comprise the dissertation research.

4.2 Abstract

Introduction: Bivalirudin has a labeled indication of percutaneous coronary intervention (PCI), yet off-label use has been observed for the treatment of suspected heparin-induced thrombocytopenia (HIT).Data on the extent and nature of off-label use is limited. We estimated the utilization of off-label bivalirudin use in these patients, and identified the factors associated with off-label bivalirudin use specifically in patients with suspected HIT.

Material and Methods: In this cross-sectional study, the Clinical Database and Resource Manager data from UHC were used to identify patients treated with direct thrombin inhibitors (DTIs) from 2010 to 2012. Off-label use was defined as the initiation of bivalirudin for indications other than a PCI. A hierarchical logistic regression model was used identify the hospital, visit, physician and patient characteristics associated with the off-label use of bivalirudin.

Results: The utilization of off-label bivalirudin use varied from 0.2% to 12.6% by the type of blood vessel surgery. Off-label use in patients with suspected HIT increased from 39% in 2010 to 55% in 2012 (OR 1.42; 95% CI, 1.14-1.76). Patients with coronary artery disease (OR 1.45; 95% CI, 1.02-2.06) and hepatic impairment (OR 2.10; 95% CI, 1.34-3.29) were at increased odds of receiving

bivalirudin for the treatment of HIT. Compared with primary care-treated patients with suspected HIT, surgeon-treated patients were more likely to receive bivalirudin (OR 2.94; 95% CI, 1.73-5.00).

Conclusions: Off-label bivalirudin use in patients without hepatic impairment should be scrutinized. The safety and efficacy of off-label bivalirudin use requires further investigation.

4.3 Introduction

The United States Food and Drug Administration (FDA) approves specific indications for medications based on the safety and efficacy evidence generated from clinical trials.[85] However, clinicians are allowed to prescribe medications for indications not approved (off-label) by the US FDA.[86,87] Off-label prescribing is a trade-off between a physician's freedom to decide in the best interest of the patient (benefit via innovation) and the risk of potential harm.[85] Off-label use of medications may not have the same degree of evidence on safety and effectiveness compared to approved indications by the FDA.[86] A 2001 study using the IMS National Disease and Therapeutic Index found that 21% of all prescriptions in the US were for off-label uses and that the majority of off-label prescriptions (73%) had insufficient scientific evidence such as controlled trials to support off-label use.[88]

Direct thrombin inhibitors (DTIs) are a class of medications sometimes used off-label. DTIs such as bivalirudin and argatroban are used for thromboprophylaxis due to their thrombin inhibiting property.[89] While argatroban is indicated for the treatment of heparin-induced thrombocytopenia (HIT), bivalirudin is only approved for anticoagulation in patients undergoing percutaneous coronary intervention (PCI), regardless of HIT status.[12-14] However, bivalirudin is used for off-label indications such as the treatment of suspected HIT,[2,5,15,16] percutaneous peripheral intervention (PPI),[90,91] and coronary artery bypass graft (CABG),[90,92,93] among others. Reasons for the off-label use of bivalirudin include disease and drug similarities ("drug class effect"),[17] and lower medication cost

compared to argatroban.[18] Other reasons include clinician's experience with bivalirudin, proteolytic elimination, and minimal interference with the International Normalized Ratio (INR).[15]

Although these injectable DTIs were approved in the year 2000,[2] the frequency of patients administered DTIs for off-label uses in the US is not yet known. Of concern, a recent multi-center study showed that bivalirudin-treated patients (off-label) were more likely to experience major bleeding than argatroban-treated patients (on-label) with suspected HIT (11.4% vs. 6.1%; $P<0.05$). Further, the lower per day cost of bivalirudin ($891 in 2014) relative to argatroban ($1,100 in 2014)[5,18] may be offset by the increased costs due to more major bleeding events ($12,713 in 2014).[94,95] In order to judge the appropriateness of off-label bivalirudin use in patients with suspected HIT, it is important to understand its relationship with the hospital, visit, physician and patient characteristics. To the best of our knowledge, no previous study has estimated the extent of off-label bivalirudin use in the above-mentioned patient populations and examined the factors associated with the off-label bivalirudin use in patients with suspected HIT.

There are two primary objectives of this study: (1) estimate the frequency of off-label use of bivalirudin for the treatment of suspected HIT, blood vessel surgeries such as CABG and PPI, and noninvasive management of myocardial infarction (MI)/unstable angina (UA); and (2) identify the hospital, visit, physician and patient characteristics associated with the off-label use of bivalirudin (not initiated for PCI) in patients with suspected HIT.

4.4 Methods

4.4.1 Study design and data source

In this cross-sectional study, patient-level Clinical Database/Resource Manager (CDB/RM) data for patients who received a DTI during hospitalizations were obtained from UHC (previously known as the University HealthSystem Consortium). The CDB/RM is an administrative claims database from academic medical centers in the US that includes information on diagnoses,

procedures, prescriptions, laboratory tests, imaging procedures, discharge costs, type of physician, and visit characteristics. Hospitalizations in 2012 were included for objective 1 while hospitalizations from January 2010 to December 2012 were included for objective 2 to examine the change in off-label bivalirudin use over time.

4.4.2 Inclusion and exclusion criteria

4.4.2.1 Objective 1 frequency of off-label use of bivalirudin

A previously validated algorithm was used to identify patients with suspected HIT.[27] Patients initiated on a DTI and tested for HIT by a diagnostic test more than 4 days after exposure to heparin were suspected to have HIT. The positive predictive value of the algorithm was 100% (95% CI: 90.97-100).[27] The temporal relationship between drug administration and diagnostic testing were determined by the dates of service reported in the claims. Patients who underwent CABG (36.1x), PPI (39.90, 39.50, 00.55) and other blood vessel surgery (00.61-00.65, 36.2x-36.9x, 38.x, 39.x) were identified by ICD-9-CM procedure codes. The management of MI/UA (ICD-9-CM diagnostic codes 410.x, 411.1 during a hospitalization) was considered noninvasive in the absence of PCI and CABG surgery. Patients were excluded if a DTI was ordered before admission as we were unable to link procedures with the date of DTI initiation. First and subsequent admissions of patients were included for this objective.

4.4.2.2 Objective 2 hospital, visit, physician and patient characteristics associated with the off-label use of bivalirudin

All patients with suspected HIT identified by the above described algorithm but not initiated on a DTI for a PCI procedure (ICD-9-CM codes 00.66, 36.0x) were included, regardless of continuous or intermittent DTI treatment. Pregnant women and children (age < 18 years) were excluded, as these patients were rare. Admissions were excluded if dates of service for both argatroban and bivalirudin were the same, as these may be coding errors. Given that we were

interested in examining factors associated with the use of bivalirudin (vs. argatroban), hospitals that exclusively used one DTI during any year in the observation period or did not have DTI prescriptions during the preceding year were excluded. The preference for one DTI over another in these hospitals may be due to hospital-level factors (eg, formulary) and unrelated to patient characteristics. Only the first admission was included for patients with readmissions.

4.4.3 Variables

Off-label use of bivalirudin was the primary outcome variable. The FDA approved bivalirudin for anticoagulation in patients undergoing percutaneous coronary intervention (PCI) or percutaneous transluminal coronary angioplasty (PTCA).[12,14] In addition, the use of bivalirudin in patients with HIT or at-risk of HIT and undergoing PCI is approved.[12,14] However, the FDA has not approved bivalirudin for the treatment of HIT. For objective 1, the utilization of off-label use of bivalirudin was calculated as the proportion of patients initiated on bivalirudin without a coinciding PCI procedure.

The outcome for objective 2 was the proportion of DTI-treated patients with suspected HIT initiated on bivalirudin without a coinciding PCI procedure. DTI treatments for objective 2 included both argatroban (on-label) and bivalirudin (off-label).

Variables that could potentially explain the off-label use of bivalirudin in patients with suspected HIT included patient comorbidities present on admission (POA) (eg, anemia, cancer, cardiovascular conditions, diabetes, infections, organ impairment); patient demographics (i.e., age, gender, race, primary payer); and visit characteristics (i.e., year of admission, admission source, admit type). Comorbidities were identified by ICD-9-CM diagnosis codes. Year of admission was included to examine evidence of changes in preference for bivalirudin over time. In addition, hospital characteristics such as geographic location (northeast, midwest/west, south), ownership type (public, non-for-profit), and experience in the use of bivalirudin relative to argatroban were examined.

Experience in the use of bivalirudin relative to argatroban was categorized based on the median of the percentage of DTI-treated patients administered bivalirudin within hospitals during the preceding year (< 90%, ≥ 90%).DTI-treated patients included those administered argatroban and bivalirudin for any indication in the hospital. The overall use of argatroban was lower than bivalirudin. Type of physician (i.e., primary care, specialty, surgery, unknown/other) was also included in the analysis as there may be differences in knowledge related to the diagnosis and management of thrombosis.[76] In addition, specialists such as cardiologists may prefer bivalirudin to argatroban due to experience gained from its common use in PCI.[15,21] Of note, the type of physician was based on the physician who signed the discharge papers.

4.4.4 Statistical analyses

Descriptive statistics were used for objective 1 while multivariate regression model was used for objective 2. Given that patients are nested within hospitals (i.e., clustered), ignoring between-hospital differences may lead to false conclusions about the association between factors and off-label bivalirudin use. There may also be differences in the patient mix and treatment practice/protocol (unobserved) between hospitals. Therefore, a hierarchical (mixed-effects) logistic regression model was used to examine the relationship between the off-label use of bivalirudin and potential explanatory factors (hospital, visit, patient, physician characteristics).[96] Further, we used a random-intercept model to account for the between-hospital variations. A fixed-effects only regression model was not used, as it assumes that measurements of patients are independent or not clustered within hospitals.

A two-step procedure was used to select variables for the regression model. First, a hierarchical logistic regression model was used in the bivariate analyses. Second, all fixed-effect variables found to be associated ($P<0.05$) with the off-label use of bivalirudin in the bivariate analyses were included in the model. A Chi-square test based on the difference in -2log-likelihood

values was used to determine the statistical significance of random effects such as hospital and year of admission .[97] The autocorrelation due to measurements within hospitals over time was not statistically significant (P=0.31), and therefore, only between-hospital variation in the off-label bivalirudin use was modeled using a random-intercept (P<0.01). An intraclass correlation coefficient (ICC) was estimated to determine the magnitude of between-hospital variation in the off-label use of bivalirudin. Interactions between year of admission and other covariates were tested and found to not be statistically significant. All statistical analyses were conducted in SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). The University of Illinois at Chicago's institutional review board reviewed and approved the study protocol.

4.5 Results

Of the 30,827 bivalirudin-treated patients in 2012, a total of 6,595 (21.4%) patients received the medication for non-approved indications. Bivalirudin was used to treat a large proportion (27.1%) of the 1,488 patients with suspected HIT. The off-label use of bivalirudin in 21,958 patients who underwent CABG was rare (0.2%). An estimated 4.4% of 16,942 patients who underwent PPI received off-label bivalirudin. The utilization of off-label use of bivalirudin for other blood vessel surgeries and noninvasive management of MI/UA was 12.6% and 4.1%, respectively. Of note, 2,383 (36.1%) of the 6,595 patients were switched from heparin to bivalirudin. The off-label indication for 2,277 (34.5%) patients was not identifiable in the data. Patient characteristics for these 2,277 patients are shown in Table VII. The majority of patients for whom the off-label indication was not identifiable had coronary artery disease (75.6%) and hypertension (73.8%).

TABLE VII. CHARACTERISTICS OF PATIENTS FOR WHOM BIVALIRUDIN WAS USED FOR AN UNKNOWN OFF-LABEL INDICATION

Characteristics	**Off-label bivalirudin (n = 2,277)**
Age in years, mean (std)	62.9 (13.9)
Male, n (%)	1,459 (64.1)
Race, n (%)	
Unknown	31 (1.4)
White	1,563 (68.6)
Black	326 (14.3)
Native American/Eskimo	11 (0.5)
Asian	39 (1.7)
Other	306 (13.4)
Multiracial	1 (0.0)
Primary payer, n (%)	
Private	709 (31.1)
Medicaid	232 (10.2)
Medicare	1,157 (50.8)
Other/unknown	78 (3.4)
Uninsured	101 (4.4)
Medical conditions at admission, n (%)	
AIDS	4 (0.2)
Alcohol abuse	78 (3.4)
Anemia	430 (18.9)
Bleeding*	94 (4.1)
Cancer	167 (7.3)
Cardiac arrest	21 (0.9)
Cardiac arrhythmias	644 (28.3)
Cerebrovascular disease (excluding intracranial hemorrhage)	105 (4.6)
Chronic pulmonary disease	456 (20.0)
Platelet or coagulation defect	186 (8.2)
Coronary artery disease	1,721 (75.6)
Congestive heart failure	709 (31.1)
Dementia	1 (0.04)
Depression	259 (11.4)
Diabetes	811 (35.6)
Drug abuse	65 (2.9)
Extremity paresis	16 (0.7)

TABLE VII. CHARACTERISTICS OF PATIENTS FOR WHOM BIVALIRUDIN WAS USED FOR AN UNKNOWN OFF-LABEL INDICATION

Characteristics	**Off-label bivalirudin (n = 2,277)**
Fluid and electrolyte imbalance	260 (11.4)
Hepatic impairment	159 (7.0)
Hypertension	1,680 (73.8)
Hypothyroidism	259 (11.4)
Inflammatory bowel disease	16 (0.7)
Neurologic disorder	84 (3.7)
Obesity	392 (17.2)
Peptic ulcer	21 (0.9)
Peripheral vascular disease	369 (16.2)
Pneumonia	69 (3.0)
Psychoses	11 (0.5)
Pulmonary circulation disorder	5 (0.2)
Pulmonary insufficiency	6 (0.3)
Renal impairment	572 (25.1)
Rheumatologic disease	74 (3.3)
Skin infection	40 (1.8)
Thrombophilia	22 (1.0)
Urinary tract infection	100 (4.4)
Valvular disease	351 (15.4)
Varicose veins	41 (1.8)
Weight loss	56 (2.5)

* Presence of any ICD-9-CM code for bleeding at admission or blood transfusion before the initiation of direct thrombin inhibitor (DTI) treatment or an intracranial hemorrhage with decompressive craniectomy/ventriculostomy before the initiation of DTI treatment

Ninety hospitals used DTIs for the treatment of suspected HIT from 2010 to 2012. A total of 4,042 patients with suspected HIT were admitted to these 90 hospitals. Only 14 hospitals with 1,031 admissions of suspected HIT used both argatroban and bivalirudin from 2010 to 2012. The off-label use of bivalirudin ranged from 3.9% to 80.1% of patients with suspected HIT across these 14 hospitals. The remaining 77 hospitals with 3,011 admissions of suspected HIT exclusively used one DTI for at least one year during the observation period.

The characteristics of the 1,031 patients with suspected HIT admitted to hospitals that used both DTIs from 2010 to 2012 are shown in Table VIII. The majority of the patients were male (59.3%). The study cohort was also predominantly white (68.1%) with an average age of 62.5 years. Medicare was the primary payer for 55.7% of patients. A large proportion of patients had cardiovascular conditions such as coronary artery disease (41.2%), congestive heart failure (44.2%) and valvular disease (28.2%). In addition, liver and kidney impairments were observed in 17% and 51.3% of patients, respectively.

TABLE VIII. CHARACTERISTICS OF PATIENTS WITH SUSPECTED HEPARIN-INDUCED THROMBOCYTOPENIA

Characteristics	**Off-label Bivalirudin (n = 482)**	**On-label Argatroban (n = 549)**	**P Value**
Hospital			
Region, n (%)			0.15
Northeast	102 (21.2)	155 (28.2)	
Midwest/West	27 (5.6)	151 (27.5)	
South	353 (73.2)	243 (44.3)	
Owner, n (%)			0.82
Public	181 (37.6)	164 (29.9)	
Not-for-profit	301 (62.5)	385 (70.1)	
Percent of DTI-treated patients administered bivalirudin during a preceding year, median (IQR)			0.66
< 90%	200 (41.5)	258 (47.0)	
≥90%	282 (58.5)	291 (53.0)	
Visit			
Year of admission, n (%)			<0.01
2010	132 (27.4)	203 (37.0)	
2011	165 (34.2)	192 (35.0)	
2012	185 (38.4)	154 (28.1)	
Admission Source, n (%)			0.01
Non-facility	192 (39.8)	250 (45.5)	
Clinic referral	82 (17.0)	71 (12.9)	
Transfer from a hospital	180 (37.3)	164 (29.9)	
Transfer from another healthcare facility	8 (1.7)	26 (4.7)	
Emergency room	16 (3.3)	34 (6.2)	
Other/Unknown	4 (0.8)	4 (0.7)	
Admission Type, n (%)			<0.01
Emergency department	164 (34.0)	259 (47.2)	
Urgent	212 (44.0)	189 (34.4)	
Elective	96 (19.9)	93 (16.9)	
Trauma center	10 (2.1)	8 (1.5)	
Type of physician, n (%)			<0.01
Primary care	39 (8.1)	149 (27.1)	
Specialty	199 (41.3)	207 (37.7)	
Surgery	233 (48.3)	180 (32.79)	
Unknown/other	11 (2.3)	13 (2.37)	

TABLE VIII. CHARACTERISTICS OF PATIENTS WITH SUSPECTED HEPARIN-INDUCED THROMBOCYTOPENIA

Characteristics	**Off-label Bivalirudin (n = 482)**	**On-label Argatroban (n = 549)**	**P Value**
Patient characteristics			
Age in years, mean (std)	61.26 (14.3)	63.62 (15.4)	0.48
Male, n (%)	300 (62.2)	311 (56.7)	1.00
Race, n (%)			0.02
Unknown	4 (0.8)	2 (0.4)	
White	289 (60.0)	413 (75.2)	
Black	129 (26.8)	92 (16.8)	
Native American/Eskimo	0 (0.0)	2 (0.4)	
Asian	17 (3.5)	6 (1.1)	
Other	43 (8.9)	34 (6.2)	
Primary payer, n (%)			0.51
Private	136 (28.2)	156 (28.4)	
Medicaid	53 (11.0)	42 (7.7)	
Medicare	255 (52.9)	319 (58.1)	
Other/unknown	24 (5.0)	15 (2.7)	
Uninsured	14 (2.9)	17 (3.1)	
Medical conditions at admission, n (%)			
AIDS	5 (1.0)	3 (0.6)	0.37
Alcohol abuse	24 (5.0)	24 (4.4)	0.75
Anemia	132 (27.4)	221 (40.3)	<0.01
Major bleeding*	311 (64.5)	328 (59.74)	0.04
Cancer	67 (13.9)	119 (21.7)	0.01
Cardiac arrest	5 (1.0)	6 (1.1)	0.35
Cardiac arrhythmias	184 (38.2)	202 (36.8)	0.81
Cerebrovascular disease (excluding intracranial hemorrhage)	18 (3.7)	26 (4.7)	0.58
Chronic pulmonary disease	102 (21.2)	144 (26.2)	0.18
Platelet or coagulation defect	76 (15.8)	98 (17.9)	0.30
Coronary artery disease	226 (46.9)	199 (36.3)	<0.01
Congestive heart failure	234 (48.6)	222 (40.4)	0.04
Dementia	0 (0.0)	1 (0.2)	0.73
Depression	55 (11.4)	77 (14.0)	0.40
Diabetes	169 (35.1)	187 (34.1)	0.75
Drug abuse	22 (4.6)	15 (2.7)	0.08

TABLE VIII. CHARACTERISTICS OF PATIENTS WITH SUSPECTED HEPARIN-INDUCED THROMBOCYTOPENIA

Characteristics	**Off-label Bivalirudin (n = 482)**	**On-label Argatroban (n = 549)**	**P Value**
Extremity paresis	9 (1.9)	22 (4.0)	0.05
Fluid and electrolyte imbalance	115 (23.9)	200 (36.4)	<0.01
Hepatic impairment	94 (19.5)	81 (14.8)	0.02
Hypertension	310 (64.3)	382 (69.6)	0.05
Hypothyroidism	44 (9.1)	72 (13.1)	0.38
Inflammatory bowel disease	4 (0.8)	8 (1.5)	0.11
Neurologic disorder	47 (9.8)	39 (7.1)	0.14
Obesity	85 (17.6)	117 (21.3)	0.05
Peptic ulcer	7 (1.5)	9 (1.6)	0.71
Peripheral vascular disease	104 (21.6)	96 (17.5)	0.05
Pneumonia	38 (7.9)	58 (10.6)	0.19
Psychoses	6 (1.2)	6 (1.1)	0.92
Pulmonary circulation disorder	5 (1.0)	4 (0.7)	0.31
Pulmonary insufficiency	7 (1.5)	8 (1.5)	0.82
Renal impairment	237 (49.2)	292 (53.2)	0.21
Rheumatologic disease	20 (4.2)	26 (4.7)	0.78
Skin infection	4 (0.8)	20 (3.6)	<0.01
Thrombophilia	13 (2.7)	10 (1.8)	0.51
Urinary tract infection	38 (7.9)	60 (10.9)	0.27
Valvular disease	154 (32.0)	137 (25.0)	0.04
Varicose veins	15 (3.1)	9 (1.6)	0.21
Weight loss	65 (13.5)	94 (17.1)	0.70

* Presence of any ICD-9-CM code for bleeding at admission or blood transfusion before the initiation of direct thrombin inhibitor (DTI) treatment or an intracranial hemorrhage with decompressive craniectomy/ventriculostomy before the initiation of DTI treatment

A total of 482 (46.8%) patients with suspected HIT were administered a DTI for an off-label use (Figure 9). However, this proportion changed over time. The off-label use increased from 39% to 55% of patients with suspected HIT from 2010 to 2012 (P<0.01) (Table VIII). Bivalirudin-treated patients had a longer treatment duration compared to argatroban-treated patients (5.8 vs. 4.5 days; P<0.01). However, the difference in length of stay after the initiation of treatment was not statistically significant (16.3 vs. 14.5 days; P=0.25). Hospital location (P=0.15), ownership (P=0.82) and experience with bivalirudin relative to argatroban (P=0.66) were not found to be related to the off-label use of DTIs. Most of the off-label and on-label DTI recipients were admitted for urgent (44%) and emergency care (34.4%), respectively (P<0.01). Differences were observed in the prescribing behavior between types of physicians (P<0.01). A large proportion of off-label bivalirudin recipients were treated by surgeons (48.3%). Medicare was predominantly the primary payer in both the off-label and on-label groups (52.9% vs. 58.1%; P=0.51). In addition, the proportion of patients with cardiovascular diseases and hepatic impairment was higher in the off-label group than the on-label group.

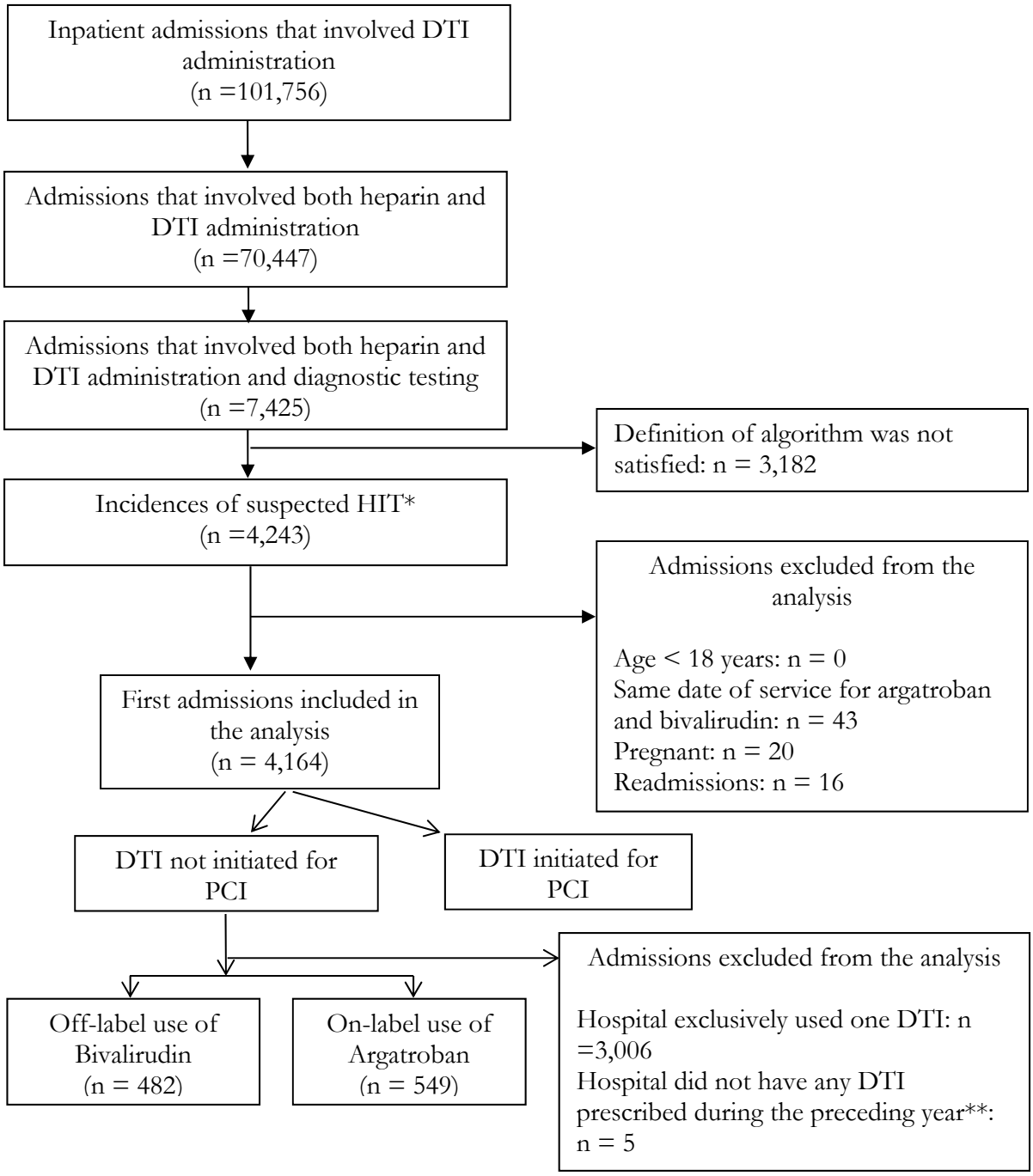

Figure 9. Patient selection process for the study cohort
HIT=heparin-induced thrombocytopenia; DTIs=direct thrombin inhibitors; PCI=percutaneous coronary intervention
* Patients with suspected heparin-induced thrombocytopenia were identified by the algorithm
** Percentage of DTI-treated patients administered bivalirudin during a preceding year was used to capture a hospital's experience of using bivalirudin relative to argatroban.

In the multivariate mixed-effects regression, model, between-hospital variance accounted for a significant proportion of the total variance in the off-label use of bivalirudin (ICC 0.67) (Table IX) and the between-hospital variance in the off-label use of bivalirudin was statistically significant ($P<0.01$). Several factors were found to be associated with the off-label use of bivalirudin in the multivariate analysis (Table IX). The odds of off-label bivalirudin use were found to increase over time (OR 1.42; 95% CI, 1.14-1.76). Patients treated by specialists (OR 2.18; 95% CI, 1.31-3.63) and surgeons (OR 2.94; 95% CI, 1.73-5.00) were more likely to be prescribed off-label bivalirudin than those treated by primary care doctors. Of all comorbidities, hepatic impairment was most strongly associated with the off-label use of bivalirudin (OR 2.10; 95% CI, 1.34-3.29). Patients with coronary artery disease (OR 1.45; 95% CI, 1.02-2.06) were also at increased odds of receiving off-label bivalirudin. The opposite was true for patients with fluid and electrolyte imbalance (OR 0.54; 95% CI, 0.37-0.78), and skin infection (OR 0.19; 95% CI, 0.05-0.68).

TABLE IX. MULTIVARIABLE REGRESSION ANALYSIS TO IDENTIFY THE CHARACTERISTICS ASSOCIATED WITH OFF-LABEL USE OF BIVALIRUDIN

Characteristics	**OR (95% CI)**	**Estimated Beta (Standard Error)**	**P-Value**
Fixed-effects			
Visit			
Year of admission	1.42 (1.14-1.76)	0.35 (0.11)	<0.01
Admission Source			
Non-facility	Reference	Reference	-
Clinic referral	1.28 (0.70-2.36)	0.25 (0.31)	0.41
Transfer from a hospital	1.21 (0.74-1.97)	0.19 (0.25)	0.45
Transfer from another healthcare facility	0.74 (0.26-2.07)	-0.31 (0.53)	0.55
Emergency room	0.88 (0.39-2.00)	-0.13 (0.42)	0.76
Other/Unknown	1.38 (0.25-7.73)	0.32 (0.88)	0.72
Admission Type			
Emergency department	Reference	Reference	-
Urgent	1.11 (0.66-1.84)	0.10 (0.26)	0.71
Elective	1.57 (0.92-2.66)	0.45 (0.27)	0.10
Trauma center	1.43 (0.39-5.23)	0.36 (0.66)	0.58
Type of physician			
Primary care	Reference	Reference	-
Specialty	2.18 (1.31-3.63)	0.78 (0.26)	<0.01
Surgery	2.94 (1.73-5.00)	1.08 (0.27)	<0.01
Unknown/other	5.10 (1.54-16.87)	1.63 (0.61)	<0.01

TABLE IX. MULTIVARIABLE REGRESSION ANALYSES TO IDENTIFY THE CHARACTERISTICS ASSOCIATED WITH THE OFF-LABEL USE OF BIVALIRUDIN

Characteristics	**OR (95% CI)**	**Estimated Beta (Standard Error)**	**P-Value**
Patient characteristics			
Race			
Unknown	5.21 (0.57-47.69)	1.65 (1.13)	0.14
White	Reference	Reference	-
Black	0.84 (0.55-1.30)	-0.17 (0.22)	0.43
Native American/Eskimo	0.00 (0.00- >1)	-6.13 (24.64)	0.80
Asian	3.25 (1.06-9.95)	1.18 (0.57)	0.04
Other	1.32 (0.71-2.48)	0.28 (0.32)	0.39
Medical conditions at admission			
Anemia	0.72 (0.51-1.02)	-0.33 (0.18)	0.07
Major bleeding†	1.31 (0.92-1.86)	0.27 (0.18)	0.12
Cancer	0.64 (0.40-1.02)	-0.45 (0.24)	0.06
Coronary artery disease	1.45 (1.02-2.06)	0.37 (0.18)	0.04
Congestive heart failure	1.32 (0.93-1.88)	0.28 (0.18)	0.13
Fluid and electrolyte imbalance	0.54 (0.37-0.78)	-0.62 (0.19)	<0.01
Hepatic impairment	2.10 (1.34-3.29)	0.74 (0.23)	<0.01
Skin infection	0.19 (0.05-0.68)	-1.68 (0.66)	0.01
Valvular disease	0.88 (0.60-1.31)	-0.12 (0.20)	0.55
Random-effects			
Individual hospital effect (intercept variance)	-	2.08 (0.86)	<0.01

4.6 Discussion

One of the objectives of this study was to estimate the frequency of off-label use of bivalirudin for the treatment of suspected HIT, blood vessel surgeries such as CABG and PPI, and noninvasive management of MI/UA. One in four patients with suspected HIT was administered off-label bivalirudin. Up to one in ten patients received bivalirudin for other indications such as blood vessel surgeries and noninvasive management of MI/UA. There are two potential explanations for the off-label use of bivalirudin in patients without suspected HIT. First, physicians may prescribe bivalirudin for patients with a history of HIT (unobserved variable), as heparin may be considered too risky. Exposure to heparin within the first 100 days of HIT may lead to recurrent rapid-onset HIT.[98] Second, the use of bivalirudin for the management of MI/UA without an invasive strategy may be just a function of change in the decision to proceed with a planned PCI (approved indication).

Evidence on the safety and efficacy of bivalirudin is inadequate to determine if the use of bivalirudin over other non-heparin anticoagulants will be beneficial to patients. Two randomized clinical trials (RCTs) have compared bivalirudin with heparin in patients undergoing CABG.[99,100] The risk of stroke was lower in the bivalirudin group compared to the heparin group in one the RCTs (0% vs. 5.5%; $P<0.05$).[100] However, difference was not observed in the extent of blood loss in both groups (median 717 ml vs 783 ml).[100] No study has compared bivalirudin with non-heparin anticoagulants in patients who require CABG and the benefit associated with the off-label use of bivalirudin in CABG remains unclear. The 2014 American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend bivalirudin only in patients undergoing an invasive strategy such as PCI (Class I; level of evidence B).[101] However, noninvasive management of MI/UA by bivalirudin is not among the recommendations in the 2014 AHA/ACC guidelines.[101] Fondaparinux, a non-heparin anticoagulant, is currently available and recommended for noninvasive

management of MI/UA.[101] No RCT has examined bivalirudin in patients who undergo PPI or other blood surgeries. The Angiomax Peripheral Procedure Registry of Vascular Events Trial (APPROVE) is a multi-center registry of bivalirudin-treated patients who underwent PPIs. The proportion of patients who experienced ischemia (1.4%) and major bleeding (2.2%) was low in this registry.[91] However, the registry did not include patients treated with other non-heparin anticoagulants.

The second objective of this study was to identify factors associated with the off-label use of bivalirudin in patients with suspected HIT. Bivalirudin is eliminated by both enzymic (80%) and renal (20%) metabolism.[19] It may be possible that physicians prefer argatroban to bivalirudin when patients suffer from fluid and electrolyte imbalance, a symptom of renal failure, as argatroban is mainly eliminated by the liver.[19] Further, excessive build-up of bivalirudin may lead to bleeding events although treatment with a reduced dose of bivalirudin is an option.[102] The 2012 American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines for the treatment of HIT recommended argatroban to bivalirudin for patients who require renal replacement therapy (Grade 2C).[6] However, there is no head-to-head trial comparing the DTIs in patients with renal impairment. The guidelines assigned Grade 2C to their recommendation as evidence on the use of argatroban in patients with renal impairment was from a single-center retrospective chart review study (n = 47).[103] The rate of major bleeding (6%) and thrombosis (4%) reported in this study was considered low by the guidelines.[6,103] Similarly, bivalirudin could be preferred over argatroban for patients with hepatic impairment. The relationship between coronary artery disease and off-label use of bivalirudin is not surprising. Treatment of coronary artery disease may require CABG or PCI. The 2012 ACCP guidelines for the treatment of HIT recommend bivalirudin to argatroban for patients who require urgent CABG (Grade 2C) or PCI (Grade 2B).[6] Physicians may prefer bivalirudin to argatroban if they expect the use an invasive strategy to treat patients admitted with a

cardiovascular disease. The reason for the association between off-label use and skin infection is not clear. To the best of our knowledge, no previous study has reported drug interactions between bivalirudin and antibiotics. However, hepatotoxicity due to antibiotics for the treatment of skin infections may be one of the potential reasons for using bivalirudin over argatroban.[104]

We find the extensive off-label use of bivalirudin for the treatment of suspected HIT worrisome due to the risk of bleeding, except in patients with hepatic impairment. A recent observational study found bivalirudin-treated patients were more likely to experience major bleeding than argatroban-treated patients with suspected HIT (11.4% vs. 6.1%; $P<0.05$). Hospitals may prefer bivalirudin to argatroban due to the lower medication cost per day ($891 vs. $1,100 in 2014).[5,18] However, with the cost per major bleeding event at $12,713 in 2014 (inflated from 2004 using the Consumer Price Index),[94,95] the cost per bivalirudin-treated patient may no longer be lower than argatroban-treatment patients.

The findings of this study are timely due to the increase in the use of heparin among hospitalized patients from 34% in 2006 to 41% in 2010.[82] Increases in heparin use may lead to a higher incidence of HIT that in turn may increase the use of off-label bivalirudin. Although the off-label use of bivalirudin for the treatment of HIT was observed at hospitals,[2,5,16] the factors associated with its use were unknown. The use of DTIs may lead to major bleeding events in patients with suspected HIT. Therefore, it is important to question the off-label use of bivalirudin in patients without hepatic impairment. In addition, our findings indicate the widespread off-label bivalirudin use in patients who undergo blood vessel surgeries, and therefore, there is a need to investigate the efficacy and safety of bivalirudin in these patients.

To the best of our knowledge, no previous study has examined the association between off-label use of bivalirudin and hospital, visit, physician and patient characteristics using multivariable regression technique. However, the results of our study are consistent with a previous single-center

observational study that provided data on the characteristics of their study cohort. Skrupky et al. examined the differences in thrombosis and major bleeding between the bivalirudin (n=92) and argatroban (n=46) at a 1250-bed tertiary care academic medical center.[16] In their study, patients with liver dysfunction and medical history of cardiac disease were more likely to be administered bivalirudin than argatroban (45% vs. 17%; P=0.02, and 71% vs. 37%; P<0.01, respectively) and the majority of bivalirudin-treated patients had undergone cardiac surgery (64% vs. 0%; P<0.01).[16] This is consistent with our finding that patients with cardiovascular conditions and hepatic impairment are likely to receive bivalirudin over argatroban. However, Skrupky et al. did not provide data on the hospital and physician characteristics.

There were several limitations to our study. First, we were not able to identify patients with a history of HIT, the extent of organ dysfunction, and concomitant drug use. Patient's history of HIT may explain the large proportion (34.5%) of off-label uses that we were not able to determine. Although exposure to heparin within 100 days of a previous HIT can trigger a rapid-onset HIT,[98] our experience suggests that physicians prefer bivalirudin to heparin in patients with a history of HIT, regardless of the timing of previous HIT. The overuse of bivalirudin in this scenario requires further examination. The decrease in elimination of argatroban due to hepatic impairment may be a function of its severity. The CDB/RM data obtained for this study did not include laboratory data needed to categorize hepatic impairment by the level of severity. Although this does not affect the finding of our study, it may be useful to identify the comorbidities associated with off-label use with more granularity. Both DTIs interact with a large number of drugs (eg, aspirin, streptokinase) that may potentially increase in the risk of bleeding.[105] However, most of the concomitant drugs interact with both argatroban and bivalirudin,[105] and there is no reason to believe that drug interaction influences the choice of off-label bivalirudin for the treatment of HIT.

Second, patient comorbidities were identified by ICD-9-CM codes present-on-admission. It is possible for diagnosis to occur during the course of hospitalization but before the initiation of DTI. Differences in post-admission diagnosis between the comparison groups may lead to false conclusions about the association of factors with the off-label use of bivalirudin. Of the patients with hepatic impairment, similar proportions (43.0% vs. 40.9%; P=0.71) of patients were diagnosed with this comorbidity after admission in the bivalirudin and argatroban groups, respectively. Similarly, there was no statistically significant difference in the proportion of diagnosis made after admission for coronary artery disease (3.4% vs. 2.0%; P=0.36). However, the same did not hold true for fluid and electrolyte imbalance (66.9% vs. 51.8%; P<0.01). Although patients with fluid and electrolyte imbalance were at decreased odds of receiving off-label bivalirudin, inclusion of post-admission diagnosis diluted this relationship. Fluid and electrolyte imbalance was no longer associated with the off-label use of bivalirudin when post-admission diagnosis, regardless of the timing, was included in the analysis (OR 0.71; 95% CI, 0.50-1.03). Therefore, the relationship between off-label bivalirudin use and fluid and electrolyte imbalance may be sensitive to this limitation.

Third, data from only academic medical centers were included in the CDB/RM. The knowledge on treatment guidelines and clinical practice may be different from non-academic medical centers. A recent study has shown that the conformity with the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) quality-of-care measures for heart failure was different between academic and non-academic medical centers.[84] We are not aware of any such studies in patients with HIT.

Fourth, we were unable to examine any change in the off-label use of bivalirudin due to the update in the 2012 ACCP guidelines for the treatment of HIT. Data beyond 2012 was not available at the time of this study. The 2012 ACCP guidelines recommend the use of argatroban over

bivalirudin in patients with HIT not undergoing PCI or CABG (Grade 2C), as evidence on the efficacy of bivalirudin is limited to case series.[6] Although the previous 2008 ACCP guidelines recommend both bivalirudin and argatroban for the treatment of HIT, the grade of evidence was higher for argatroban (Grade 1C) than bivalirudin (Grade 2C).[19] Both guidelines acknowledged that the evidence for bivalirudin was weak.[6,19] However, clinicians may not comply with changes in the guidelines. For example, the rate of compliance with the 2008 ACCP guidelines on platelet count monitoring was between 23.0% and 41.5%.[6,106] Therefore, it is unlikely that results of this study will not be applicable in the current clinical practice.

Fifth, the use of only two DTIs was examined in this study. Other treatment alternatives for HIT include lepirudin, danaparoid and desirudin though lepirudin and danaparoid are no longer available in the US. We were unable to include desirudin in the analysis as it was not mapped in the CDB/RM data. However, no previous study has shown widespread use of desirudin. In addition, the 2012 ACCP guidelines for the treatment of HIT do not recommend desirudin as a treatment alternative for HIT due to the absence of sufficient evidence on efficacy.[6]

Sixth, the classification for type of physician was based on the physician who signed the discharge papers. It may be possible that more than one physician was involved in the treatment of a patient during the hospitalization. Therefore, it is difficult to attribute prescriptions to the type of physician. However, the type of physician may be correlated with the nature of care (e.g., cardiovascular surgery) received by the patient. Our findings on the association between the type of physician and off-label bivalirudin use may reflect the likelihood of receiving bivalirudin by the nature of care (e.g., surgical vs. medical patient) in addition to the type of physician.

Last, the algorithm did not identify patients with suspected HIT not tested for antibodies. Inclusion of such patients could potentially increase false-positives in the bivalirudin group, as bivalirudin is widely used for PCI. This may increase the frequency of patients with cardiovascular

conditions in the bivalirudin group, and thus lead to false associations between more cardiovascular conditions (other than coronary artery disease) and off-label use of bivalirudin.

To the best of our knowledge, this is the first study to examine the association between off-label use of bivalirudin and hospital, visit, physician and patient characteristics in patients with suspected HIT. The off-label use of bivalirudin increased from nearly one-third to half of DTI-treated patients with suspected HIT over a period of 3 years (2010-2012). In addition, off-label use in patients with suspected HIT varied by the type of physician and by patient comorbidity. Measures to increase awareness among physicians regarding the recent evidence on the increased risk of major bleeding with bivalirudin relative to argatroban may help in decreasing the off-label use of bivalirudin in patients without hepatic impairment. In addition, investigation is needed to examine the relative effectiveness and safety of DTIs in patients who require anticoagulation for blood vessel surgeries and the treatment of suspected HIT.

5. OVERALL CONCLUSIONS

The primary goal of this dissertation was to examine the off-label use and clinical consequences of DTIs in patients with suspected HIT. Data on the relative effectievness and safety of DTIs is limited and insufficient to help strengthen current treatment guidelines. Given that it was not feasible to use secondary databases as the data source for addressing this gap in evidence, first an additional analysis was conducted to develop and validate algorithms for the identification of patients with suspected HIT.

This dissertation demonstrated the feasibility of identifying patients with suspected HIT using algorithms developed by claims data such as prescription orders, diagnostic test orders and ICD-9-CM codes. The algorithms will enable the use of observational data in future studies, thereby reducing the cost and time of data collection compared to the use of electronic medical records. However, the identification of patients with actual HIT was found to not be feasible. Use of algorithms to identify actual HIT may lead to a higher rate of false-positives and lower incidence of thrombosis in future studies. Reasons include the initiation of DTI treatment at the time of clinical suspicion without confirmation of HIT coupled with the multitude of risk factors for thrombocytopenia. Of note, the performance of algorithms to identify actual HIT may be improved by incorporating diagnostic test results as a criteria in future studies.

Using an algorithm to identify patients with suspected HIT in an observtional database, we found that argatroban-treated patients were at a lower risk of experiencing major bleeding than bivaliruin-treated patients. The current 2012 ACCP guidelines do not include bivalirudin as one of the recommended DTIs for the treatment of HIT (without PCI) due to the lack of comparative evidence. Thus, the preference of one DTI over another is not clear for the treatment of HIT. However, the use of bivalirudin to treat suspected HIT as an off-label use is common. This dissertation provides evidence to address the current gap in guidelines so that clinicians do not

expose patients to an unnecessary bleeding risk by prescribing bivalirudin. An exception would be patients with severe hepatic impairement and skin infections as argatroban is not an option due its hepatic route of elimination. One of the reasons for the off-label use of bivalirudin is its lower acquisition cost compared to argatroban. However, drug cost savings from the use of bivalirudin may be offset by an increase in the frequency of bleeding events compared to argatroban. Thus, clinicians need to consider both safety and costs when making treatment decisions. The off-label use of bivalirudin increased from one-third to half of DTI-treated patients with suspected HIT over a period of three years. This shows the urgent need to scrutinize prescriptions and strengthen hospital protocols for anticoagulation. The findings of this dissertation may help in the scrutiny of prescriptions through the identification of physicians more likely to order bivalirudin.

Future research is needed to examine the relative effectiveness and safety of argatroban and bivalirudin for anticoagulation during blood vessel surgeries. Additional research is needed to validate the methods of outcome measurements and findings of this dissertation, as proxy variables were used to quantify both effectiveness and safety.

CITED LITERATURE

1. Arnold DM, Kahn SR, Shrier I. Missed opportunities for prevention of venous thromboembolism: an evaluation of the use of thromboprophylaxis guidelines. Chest 2001;120:1964-71.

2. Abel EE, Kane-Gill SL, Seybert AL, Kellum JA. Direct thrombin inhibitors for management of heparin-induced thrombocytopenia in patients receiving renal replacement therapy: comparison of clinical outcomes. American journal of health-system pharmacy: AJHP: official journal of the American Society of Health-System Pharmacists 2012;69:1559-67.

3. Chong BH. Heparin-induced thrombocytopenia. Journal of thrombosis and haemostasis : JTH 2003;1:1471-8.

4. Rice L. Heparin-induced thrombocytopenia: myths and misconceptions (that will cause trouble for you and your patient). Archives of internal medicine 2004;164:1961-4.

5. Dang CH, Durkalski VL, Nappi JM. Evaluation of treatment with direct thrombin inhibitors in patients with heparin-induced thrombocytopenia. Pharmacotherapy 2006;26:461-8.

6. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e495S-530S.

7. Warkentin TE, Roberts RS, Hirsh J, Kelton JG. An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. Archives of internal medicine 2003;163:2518-24.

8. Warkentin TE, Sheppard JA, Horsewood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk for heparin-induced thrombocytopenia. Blood 2000;96:1703-8.

9. Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis and management. British journal of haematology 2003;121:535-55.

10. Lewis BE, Wallis DE, Hursting MJ, Levine RL, Leya F. Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. Chest 2006;129:1407-16.

11. Smythe MA, Koerber JM, Fitzgerald M, Mattson JC. The financial impact of heparin-induced thrombocytopenia. Chest 2008;134:568-73.

12. Angiomax (bivalirudin) package insert. In. Parsippany, NJ: The Medicines Company; 2013.

13. Argatroban package insert. In. Research Triangle Park, NC: GlaxoSmithKline; 2014.

14. FDA Online Label Repository. U.S. Department of Health & Human Services. (Accessed January 27, 2015, at http://labels.fda.gov/.)

15. Joseph L, Casanegra AI, Dhariwal M, et al. Bivalirudin for the treatment of patients with confirmed or suspected heparin-induced thrombocytopenia. Journal of thrombosis and haemostasis: JTH 2014;12:1044-53.

16. Skrupky LP, Smith JR, Deal EN, et al. Comparison of bivalirudin and argatroban for the management of heparin-induced thrombocytopenia. Pharmacotherapy 2010;30:1229-38.

17. Stafford RS. Regulating off-label drug use--rethinking the role of the FDA. The New England journal of medicine 2008;358:1427-9.

18. REDBOOK Online. In. Greenwood Village, CO: Truven Health Analytics; 2014.

19. Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:340S-80S.

20. Lewis BE, Wallis DE, Leya F, Hursting MJ, Kelton JG. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Archives of internal medicine 2003;163:1849-56.

21. Bivalirudin called safe and effective in HIT. Frontline Medical Communications Inc., 2014. (Accessed February 2, 2015, at http://www.acssurgerynews.com/single-view/bivalirudin-called-safe-and-effective-in-hit/43bbceb1bff1a5515102a7f2feb71e57.html.)

22. Schumock GT, Pickard AS. Comparative effectiveness research: Relevance and applications to pharmacy. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 2009;66:1278-86.

23. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Medical care 2005;43:480-5.

24. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. The New England journal of medicine 2001;344:1286-92.

25. Cuker A, Arepally G, Crowther MA, et al. The HIT Expert Probability (HEP) Score: a novel pre-test probability model for heparin-induced thrombocytopenia based on broad expert opinion. Journal of thrombosis and haemostasis: JTH 2010;8:2642-50.

26. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Archives of internal medicine 2000;160:761-8.

27. Abstracts of the 60th annual meeting of the scientific and standardization committee of the international society on thrombosis and haemostasis june 23-26, 2014. Journal of thrombosis and haemostasis: JTH 2014;12 Suppl 1:1-106.

28. O'Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: ICD code accuracy. Health services research 2005;40:1620-39.

29. ICD-9-CM Coordination and Maintenance Committee Meeting. CDC/National Center for Health Statistics, 2007. (Accessed 8 August, 2013, at http://www.cdc.gov/nchs/data/icd/agendaSep07.pdf.)

30. Degli Esposti L, Didoni G, Simon T, Buda S, Sangiorgi D, Degli Esposti E. Analysis of disease patterns and cost of treatments for prevention of deep venous thrombosis after total knee or hip replacement: results from the Practice Analysis of THromboprophylaxis after Orthopaedic Surgery (PATHOS) study. ClinicoEconomics and outcomes research : CEOR 2013;5:1-7.

31. Happe LE, Farrelly EM, Stanford RH, Sarnes MW. Cost and occurrence of thrombocytopenia in patients receiving venous thromboembolism prophylaxis following major orthopaedic surgeries. Journal of thrombosis and thrombolysis 2008;26:125-31.

32. Segal JB, Powe NR. Accuracy of identification of patients with immune thrombocytopenic purpura through administrative records: a data validation study. American journal of hematology 2004;75:12-7.

33. Lubenow N, Kempf R, Eichner A, Eichler P, Carlsson LE, Greinacher A. Heparin-induced thrombocytopenia: temporal pattern of thrombocytopenia in relation to initial use or reexposure to heparin. Chest 2002;122:37-42.

34. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. The New England journal of medicine 1995;332:1330-5.

35. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.

36. Reese JA, Li X, Hauben M, et al. Identifying drugs that cause acute thrombocytopenia: an analysis using 3 distinct methods. Blood 2010;116:2127-33.

37. Warkentin TE, Roberts RS, Hirsh J, Kelton JG. Heparin-induced skin lesions and other unusual sequelae of the heparin-induced thrombocytopenia syndrome: a nested cohort study. Chest 2005;127:1857-61.

38. Warkentin TE, Linkins LA. Non-necrotizing heparin-induced skin lesions and the 4T's score. Journal of thrombosis and haemostasis: JTH 2010;8:1483-5.

39. Selleng K, Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia in intensive care patients. Critical care medicine 2007;35:1165-76.

40. Chong BH, Burgess J, Ismail F. The clinical usefulness of the platelet aggregation test for the diagnosis of heparin-induced thrombocytopenia. Thrombosis and haemostasis 1993;69:344-50.

41. Napolitano LM, Warkentin TE, Almahameed A, Nasraway SA. Heparin-induced thrombocytopenia in the critical care setting: diagnosis and management. Critical care medicine 2006;34:2898-911.

42. Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, Eichler P. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. Thrombosis and haemostasis 2005;94:132-5.

43. Warkentin TE, Sheppard JA, Sigouin CS, Kohlmann T, Eichler P, Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. Blood 2006;108:2937-41.

44. Kato S, Takahashi K, Ayabe K, et al. Heparin-induced thrombocytopenia: analysis of risk factors in medical inpatients. British journal of haematology 2011;154:373-7.

45. Wahl PM, Terrell DR, George JN, et al. Validation of claims-based diagnostic codes for idiopathic thrombotic thrombocytopenic purpura in a commercially-insured population. Thrombosis and haemostasis 2010;103:1203-9.

46. Schech SD, Brinker A, Shatin D, Burgess M. New-onset and idiopathic thrombotic thrombocytopenic purpura: incidence, diagnostic validity, and potential risk factors. American journal of hematology 2006;81:657-63.

47. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. Determining a definite diagnosis of primary immune thrombocytopenia by medical record review. American journal of hematology 2012;87:843-7.

48. Drugs to be Discontinued. U.S. Department of Health and Human Services, U.S. Food and Drug Administration, 2013. (Accessed 4 December, 2013, at http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050794.htm.)

49. Arnold RJ, Kim R, Tang B. The cost-effectiveness of argatroban treatment in heparin-induced thrombocytopenia: the effect of early versus delayed treatment. Cardiology in review 2006;14:7-13.

50. About UHC. University HealthSystem Consortium, 2013. (Accessed 8 September, 2014, at https://www.uhc.edu/membership/our-members.)

51. Rassen JA, Mittleman MA, Glynn RJ, Alan Brookhart M, Schneeweiss S. Safety and effectiveness of bivalirudin in routine care of patients undergoing percutaneous coronary intervention. European heart journal 2010;31:561-72.

52. Wise GR, Schwartz BP, Dittoe N, et al. Comparative effectiveness analysis of anticoagulant strategies in a large observational database of percutaneous coronary interventions. Journal of interventional cardiology 2012;25:278-88.

53. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. The American journal of medicine 1996;101:502-7.

54. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:e574-651.

55. Henry AJ, Hevelone ND, Belkin M, Nguyen LL. Socioeconomic and hospital-related predictors of amputation for critical limb ischemia. Journal of vascular surgery 2011;53:330-9 e1.

56. Manzano-Fernandez S, Cambronero F, Caro-Martinez C, et al. Mild kidney disease as a risk factor for major bleeding in patients with atrial fibrillation undergoing percutaneous coronary stenting. Thrombosis and haemostasis 2012;107:51-8.

57. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical care 2005;43:1130-9.

58. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. European heart journal 2012;33:1500-10.

59. Spyropoulos AC, Anderson FA, Jr., Fitzgerald G, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest 2011;140:706-14.

60. Alberts MJ, Bhatt DL, Smith SC, Jr., et al. Risk factors and outcomes for patients with vascular disease and serious bleeding events. Heart (British Cardiac Society) 2011;97:1507-12.

61. Jones WS, Patel MR, Dai D, et al. Temporal trends and geographic variation of lower-extremity amputation in patients with peripheral artery disease: results from U.S. Medicare 2000-2008. Journal of the American College of Cardiology 2012;60:2230-6.

62. Gangireddy C, Rectenwald JR, Upchurch GR, et al. Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. Journal of vascular surgery 2007;45:335-41; discussion 41-2.

63. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer 2013;119:648-55.

64. Memtsoudis SG, Besculides MC, Gaber L, Liu S, Gonzalez Della Valle A. Risk factors for pulmonary embolism after hip and knee arthroplasty: a population-based study. International orthopaedics 2009;33:1739-45.

65. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. Journal of clinical epidemiology 1992;45:613-9.

66. Lehto S, Ronnemaa T, Pyorala K, Laakso M. Risk factors predicting lower extremity amputations in patients with NIDDM. Diabetes care 1996;19:607-12.

67. Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithm (QThrombosis) to estimate future risk of venous thromboembolism: prospective cohort study. BMJ (Clinical research ed) 2011;343:d4656.

68. Landefeld CS, Cook EF, Flatley M, Weisberg M, Goldman L. Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. The American journal of medicine 1987;82:703-13.

69. Mahan CE, Spyropoulos AC, Fisher MD, et al. Antithrombotic medication use and bleeding risk in medically ill patients after hospitalization. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 2013;19:504-12.

70. Hochholzer W, Wiviott SD, Antman EM, et al. Predictors of bleeding and time dependence of association of bleeding with mortality: insights from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel--Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). Circulation 2011;123:2681-9.

71. Kelton JG, Hursting MJ, Heddle N, Lewis BE. Predictors of clinical outcome in patients with heparin-induced thrombocytopenia treated with direct thrombin inhibition. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis 2008;19:471-5.

72. Lenderink T, Boersma E, Ruzyllo W, et al. Bleeding events with abciximab in acute coronary syndromes without early revascularization: An analysis of GUSTO IV-ACS. American heart journal 2004;147:865-73.

73. Spyropoulos AC, Hussein M, Lin J, Battleman D. Rates of symptomatic venous thromboembolism in US surgical patients: a retrospective administrative database study. Journal of thrombosis and thrombolysis 2009;28:458-64.

74. Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. Thrombosis and haemostasis 2001;86:452-63.

75. Rothberg MB, Lindenauer PK, Lahti M, Pekow PS, Selker HP. Risk factor model to predict venous thromboembolism in hospitalized medical patients. Journal of hospital medicine : an official publication of the Society of Hospital Medicine 2011;6:202-9.

76. Zierler BK, Meissner MH, Cain K, Strandness DE, Jr. A survey of physicians' knowledge and management of venous thromboembolism. Vascular and endovascular surgery 2002;36:367-75.

77. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate behavioral research 2011;46:399-424.

78. Suarez D, Faries DE. Propensity score stratification and regression. In: Faries DE, Leon AC, Haro JM, Obenchain RL, eds. Analysis of observational health care data using SAS®. Cary, NC: SAS Institute Inc; 2010.

79. Austin PC, Chiu M, Ko DT, Goeree R, Tu JV. Propensity score matching for estimating treatment effects. In: Faries DE, Leon AC, Haro JM, Obenchain RL, eds. Analysis of observational health care data using SAS®. Cary, NC: SAS Institute Inc; 2010.

80. %gmatch. Mayo Clinic, 2004. (Accessed 10 August, 2014, at http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros.)

81. Huber PJ. The behavior of maximum likelihood estimates under nonstandard conditions. In: Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability. Berkeley, CA: University of California Press; 1967:221-33.

82. Grosse SD, Presley RJ, Yusuf H, Richardson LC, Amin AN. Trends in thromboprophylaxis use in US Hospitals, 2006–2010. Blood 2013;122:1707.

83. Kiser TH, Burch JC, Klem PM, Hassell KL. Safety, efficacy, and dosing requirements of bivalirudin in patients with heparin-induced thrombocytopenia. Pharmacotherapy 2008;28:1115-24.

84. Fonarow GC, Yancy CW, Heywood JT. Adherence to heart failure quality-of-care indicators in US hospitals: analysis of the ADHERE Registry. Archives of internal medicine 2005;165:1469-77.

85. Morris J. The use of observational health-care data to identify and report on off-label use of biopharmaceutical products. Clinical pharmacology and therapeutics 2012;91:937-42.

86. Walton SM, Schumock GT. Should off-label drugs be included as comparators in pharmacoeconomic studies? PharmacoEconomics 2014;32:1035-7.

87. Stafford RS. Off-label use of drugs and medical devices: a review of policy implications. Clinical pharmacology and therapeutics 2012;91:920-5.

88. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Archives of internal medicine 2006;166:1021-6.

89. Warkentin TE, Greinacher A, Koster A. Bivalirudin. Thrombosis and haemostasis 2008;99:830-9.

90. Shammas NW. Bivalirudin: pharmacology and clinical applications. Cardiovascular drug reviews 2005;23:345-60.

91. Allie DE, Hall P, Shammas NW, et al. The Angiomax Peripheral Procedure Registry of Vascular Events Trial (APPROVE): in-hospital and 30-day results. The Journal of invasive cardiology 2004;16:651-6.

92. Koster A, Spiess B, Chew DP, et al. Effectiveness of bivalirudin as a replacement for heparin during cardiopulmonary bypass in patients undergoing coronary artery bypass grafting. The American journal of cardiology 2004;93:356-9.

93. Dyke CM, Koster A, Veale JJ, Maier GW, McNiff T, Levy JH. Preemptive use of bivalirudin for urgent on-pump coronary artery bypass grafting in patients with potential heparin-induced thrombocytopenia. The Annals of thoracic surgery 2005;80:299-303.

94. Patrick AR, Winkelmayer WC, Avorn J, Fischer MA. Strategies for the management of suspected heparin-induced thrombocytopenia: a cost-effectiveness analysis. PharmacoEconomics 2007;25:949-61.

95. Consumer Price Index. 2014. (Accessed February 25, 2015, at http://data.bls.gov/cgi-bin/dsrv?cu.)

96. Hedeker D, Gibbons RD. Mixed-effects regression models for binary outcomes. In: Balding DJ, Cressie NAC, Fisher NI, et al., eds. Longitudinal data analysis. Hoboken, NJ: John Wiley & Sons, Inc.; 2006:149-86.

97. Hedeker D. Generalized linear mixed models. In: Everitt BS, Howell DC, eds. Encyclopedia of statistics in behavioral science. Hoboken, NJ John Wiley & Sons Inc.; 2005.

98. Warkentin TE. Clinical picture of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. Heparin-induced thrombocytopenia. Boca Raton, FL: CRC Press; 2007:21-66.

99. Dyke CM, Smedira NG, Koster A, et al. A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: the EVOLUTION-ON study. The Journal of thoracic and cardiovascular surgery 2006;131:533-9.

100. Smedira NG, Dyke CM, Koster A, et al. Anticoagulation with bivalirudin for off-pump coronary artery bypass grafting: the results of the EVOLUTION-OFF study. The Journal of thoracic and cardiovascular surgery 2006;131:686-92.

101. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2014;64:e139-228.

102. Tsu LV, Dager WE. Bivalirudin dosing adjustments for reduced renal function with or without hemodialysis in the management of heparin-induced thrombocytopenia. The Annals of pharmacotherapy 2011;45:1185-92.

103. Reddy BV, Grossman EJ, Trevino SA, Hursting MJ, Murray PT. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia requiring renal replacement therapy. The Annals of pharmacotherapy 2005;39:1601-5.

104. Polson JE. Hepatotoxicity due to antibiotics. Clinics in liver disease 2007;11:549-61, vi.

105. DRUGDEX System [database on the Internet]. Truven Health Analytics Inc., 2015. (Accessed 5 February 2015, at www.micromedexsolutions.com.)

106. ten Berg MJ, van den Bemt PM, Huisman A, Schobben AF, Egberts TC, van Solinge WW. Compliance with platelet count monitoring recommendations and management of possible heparin-induced thrombocytopenia in hospitalized patients receiving low-molecular-weight heparin. The Annals of pharmacotherapy 2009;43:1405-12.

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EDUCATION

In progress	**Doctoral Candidate**, Pharmacy Systems, Outcomes and Policy University of Illinois at Chicago (UIC), IL, USA Major: Pharmacoeconomics, Minor: Pharmacoepidemiology
January 2008	**Master of Science**, Pharmacy Administration University of the Sciences in Philadelphia (USP), PA, USA Major: Pharmacoeconomics
April 2006	**Bachelor of Pharmacy** University of Pune, Pune, India

WORK EXPERIENCE

March 2015-current	**Manager, Global Health Technology Assessment,** Eisai Inc., Woodcliff Lake, NJ
May 2009-December 2014	**Graduate Hourly Position/Graduate Research Assistant,** University of Illinois at Chicago, Chicago, IL
August 2008-May 2013	**Teaching Assistant,** University of Illinois at Chicago, Chicago, IL
May 2012-August 2012	**HEOR Intern,** Pharmerit North America LLC, Bethesda, MD
November 2004	**Intern,** Alembic Limited, Vadodara, India

PUBLICATIONS

- **Patel V,** Lin FJ, Ojo O, Rao S, Yu S, Zhan L, Touchette DR. Cost-utility analysis of genotype-guided antiplatelet therapy in patients with moderate-to-high risk acute coronary syndrome and planned percutaneous coronary intervention. Pharmacy Practice 2014 Jul-Sep; 12(3): 438.
- Saavedra JM, Boguniewicz M, Chamlin S, Lake A, Nedorost S, Czerkies LA, **Patel V**, Botteman MF, Horodniceanu EG. Patterns of clinical management of atopic dermatitis in infants and toddlers: A survey of three physician specialties in the United States. The Journal of Pediatrics 2013; 163(6): 1747-1753.

MANUSCRIPTS IN PREPARATION

- **Patel V**, Walton S, Galanter W, Lee T, Schumock G, Nutescu E. The validity of algorithms for identifying suspected and confirmed heparin-induced thrombocytopenia.
- **Patel V**, Lee T, Galanter W, Schumock G, Nutescu E, Walton S. Comparative effectiveness and safety of argatroban and bivalirudin in patients with suspected heparin-induced thrombocytopenia.
- **Patel V**, Lee T, Schumock G, Galanter W, Nutescu E, Walton S. Prevalence and factors associated with the off-label use of bivalirudin in hospitalized patients.

CONFERENCE POSTERS

- **Patel V**, Walton S, Galanter W, Lee T, Schumock G, Nutescu E. The validity of algorithms for identifying suspected and confirmed heparin-induced thrombocytopenia. 60th Annual Meeting of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, Milwaukee, Wisconsin, USA. June 2014
- Czerkies L, Horodniceanu E, **Patel V**, Botteman M, Saavedra J. Differences in dietary management of infant atopic dermatitis among pediatricians, allergists, and dermatologists in the United States. 2013 American Academy of Allergy Asthma and Immunology Annual Meeting, San Antonio, Texas, USA. February 2013
- Rao S, Lin FJ, Ojo O, **Patel V**, Yu S, Zhan L, Touchette DR. A decision modeling approach to evaluate the cost-effectiveness of prasugrel versus clopidogrel in patients with planned percutaneous coronary intervention. ISPOR 16th Annual International Meeting, Baltimore, MD, USA. May 2011
- **Patel V**, Touchette DR, Yang Y, Nutescu E, Kim K, Vidanovic V, Galanter W. Cost-effectiveness of strategies for diagnosing heparin-induced thrombocytopenia. ISPOR 15th Annual International Meeting, Atlanta, GA, USA. May 2010
- **Patel V**, Shaw JW, Leischow SJ, Ranger-Moore J, Muramoto M. Effect of nicotine gum price on medication acquisition and smoking cessation in an over-the-counter setting. ISPOR 15th Annual International Meeting, Atlanta, GA, USA. May 2010
- **Patel V**, McGhan WF. Cost-effectiveness of noninvasive magnetic resonance direct thrombus imaging and ultrasonography for diagnosing distal deep vein thrombosis. ISPOR 15th Annual International Meeting, Atlanta, GA, USA. May 2010
- **Patel V,** McGhan WF. Cost-effectiveness of Different Strategies for Diagnosis of Deep Vein Thrombosis. ISPOR 13th Annual International Meeting, Toronto, Ontario, Canada. May 2008

COMPUTER SKILLS

- SAS & STATA — Data management, descriptive statistics, and regression analysis
- Microsoft Excel & TreeAge Pro — Cost-effectiveness decision modeling
- Microsoft Access — Running queries and analyzing datasets

SCHOLARSHIPS AND AWARDS

- ISPOR Distinguished Service Award, ISPOR 17th Annual International Meeting, Washington, DC, 2012
  For service to the society as a member of the survey committee

- Lloyd Yale Scholarship, UIC College of Pharmacy, 2008-2009
  For teaching assistantship excellence

- Sir Ratan Tata Trust Scholarship, India, 2004-2005
  For scoring distinction (72%) in first year Bachelor of Pharmacy exam

LEADERSHIP EXPERIENCE

- **President**, International Society for Pharmacoeconomics and Outcomes Research Student Chapter at UIC, 2011-2012

- **Alternate Representative**, Graduate Student Council, Department of Pharmacy Administration, University of Illinois at Chicago, 2008-2009

- **Secretary**, International Society for Pharmacoeconomics and Outcomes Research Student Chapter at USP, 2006-2007