Effectiveness of a clinical decision support system to identify heparin induced thrombocytopenia

Article *in* Journal of Thrombosis and Thrombolysis · November 2008

DOI: 10.1007/s11239-008-0279-x · Source: PubMed

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Effectiveness of a Clinical Decision Support System to Identify Heparin Induced Thrombocytopenia

Running Title: HIT CDSS

Authors:
Jeffrey M. Riggio, MD, MSc
Assistant Professor of Medicine, Thomas Jefferson University
Jefferson Internal Medicine Associates
833 Chestnut Street Suite 701
Philadelphia, PA 19107

Mandelin K. Cooper, PharmD
Department of Pharmacy
Clinical Pharmacist Specialist, Wesley Medical Center
550 N Hillside
Wichita, KS 67214

Benjamin E. Leiby, PhD
Assistant Professor, Division of Biostatistics
Department of Pharmacology and Experimental Therapeutics
Thomas Jefferson University
1015 Chestnut St., Suite M100
Philadelphia, PA 19107

Jeanine M. Walenga, PhD
Professor
Thoracic & Cardiovascular Surgery and Pathology
Cardiovascular Institute
Loyola University Medical Center
2160 S. First Avenue
Maywood, Illinois 60153

Geno J. Merli, MD
Professor of Medicine, Thomas Jefferson University
Sr. Vice President and Chief Medical Officer
Director, Jefferson Center for Vascular Diseases
111 S. 11th Street
Suite 2210 Gibbon Building
Philadelphia, PA 19107

Jonathan E. Gottlieb, MD
Professor of Medicine, Washington University School of Medicine

Vice President and Chief Medical Officer
Barnes-Jewish Hospital
Mailstop 90-91-313
One Barnes-Jewish Hospital Plaza
St. Louis, MO 63110

Funding: No funding has been received in regards to this manuscript.

Conflict of Interest: No author has a conflict of interest in regards to this manuscript.

Corresponding Author:

Jeffrey M. Riggio, MD, MSc
Assistant Professor of Medicine
Jefferson Internal Medicine Associates
833 Chestnut Street Suite 701
Philadelphia, PA 19107

Email : jeff.riggio@jefferson.edu
Phone : 215 955 0734
Fax : 215 503 9239

Keywords: heparin induced thrombocytopenia, clinical decision support system, computer alert, computerized provider order entry

Abstract

BACKGROUND: Subtle decreases in platelet count may impede timely recognition of heparin-induced thrombocytopenia (HIT), placing the patient at increased risk of thrombotic events. OBJECTIVE: A clinical decision support system (CDSS) was developed to alert physicians using computerized provider order entry when a patient with an active order for heparin experienced platelet count decreases consistent with heparin induced thrombocytopenia (HIT). METHODS: Comparisons for timeliness of HIT identification and treatment were evaluated for the year preceding and year following implementation of the CDSS in patients with laboratory confirmation of HIT. RESULTS: During the intervention time period, the CDSS alert occurred 41,922 times identifying 2,036 patients who had 2,338 inpatient admissions. The CDSS had no significant impact on time from fall in platelet count to HIT laboratory testing(control 2.3 days vs intervention 3.0 days p=0.30) and therapy(control 19.3 days vs intervention 15.0 days p=0.45), and appeared to delay discontinuation of heparin products(control 1.3 days vs. intervention 2.9 days p=0.04). However, discontinuation of heparin following shorter exposure duration and after smaller decrease in platelet count occurred during the intervention period. The HIT CDSS sensitivity and specificity were each 87% with a negative predictive value of 99.9% and positive predictive value of 2.3%. CONCLUSIONS: Implementation of a CDSS did not appear to improve the ability to detect and respond to potential HIT, but resulted in increased laboratory testing and changes in clinician reactions to decreasing platelet counts that deserve further study.

Introduction

Heparin induced thrombocytopenia (HIT) is a clinicopathological syndrome associated with significant morbidity and mortality [1]. The incidence of HIT ranges from 1-3% depending on the type of heparin product and patient population [2, 3]. Criteria for the diagnosis of HIT in patients treated with heparin products include either a significant proportional platelet count decrease (for example, a 50% decrease from maximum value), or a decrease below a specified threshold (for example, 150,000 platelets/mm^3) [4-5]. The highest risk of developing HIT occurs between 5 and 10 days of initial exposure to unfractionated (UFH) or low molecular weight heparin (LMWH) [6-8]. Paradoxically, HIT is a disorder of thrombosis rather than bleeding [9-11]. The risk of developing a clinically significant thrombotic event within 30 days of diagnosis of HIT has been estimated at 52.8% [12].

The prompt recognition of a proportional decrease in platelet count remains one of the challenges of managing HIT. As Bates and Gawande observed, "monitoring is inherently boring and is not performed well by humans" [13]. It is important to diagnose and initiate HIT treatment quickly to prevent thrombotic complications. The lower the platelet nadir the more likely the patient will develop a thrombosis [14, 15]. Various algorithms and recommendations have been developed to help physicians in diagnosis of HIT; however, the challenge remains detecting a subtle fall in platelet count that remains within 'normal' range [16, 17].

Computerized prescriber order entry (CPOE) systems provide opportunities to screen clinical data based on predefined criteria to identify conditions and apply decision support [18-20]. While most CPOE systems provide basic safety features such as maximum dose checking and

drug interaction screening, additional programming was performed to implement this clinical decision support system (CDSS) to identify potential HIT. We hypothesized that incorporating decision support algorithms into CPOE to alert clinicians of potential HIT would facilitate more rapid diagnosis of HIT and initiation of treatment. We describe a novel CDSS to alert physicians of the possibility of HIT. The objectives of this study were to assess the effectiveness of the CDSS to identify potential HIT, improve timeliness of diagnosis and treatment of HIT, and prevent clinical thrombotic events.

Methods

Study Design

This retrospective study was performed at Thomas Jefferson University Hospital (TJUH) a 728 bed tertiary care teaching hospital in Philadelphia. CPOE was initiated in 2001 and implementation was completed throughout the hospital by 2003. At the time of this study, the LastWord (Version 4.2.9 by GE Healthcare) CPOE system provided a self-documenting system that recorded dates and times of medication, laboratory, radiology orders and procedures and admission and discharge information as clinicians interacted with the system. The CDSS program, written by developers at the hospital, screened a parallel data repository that mirrored active orders and results once every 4 hours. When conditions specified by the CDSS were met, the program generated an alert that appeared in the transactional CPOE application to any clinician who accessed the identified patient record. The rule looked for the condition such that in patients with an active order for heparin products the platelet count dropped during a three week time period by 50%, or 30% if the absolute platelet count was less than 150,000 platelets/mm^3. Although a trigger of 30% reduction in the absolute platelet count to below

150,000 platelets/mm3 has not been extensively validated, we included this trigger to help capture those with an absolute drop below 150,000 platelets/mm3. The recent 8th edition ACCP guidelines concur that "there is no single definition of thrombocytopenia that meets all clinical situations" (21). If either of these conditions occurred with an active order for a heparin product a "pop-up" alert appeared suggesting the provider evaluate the patient for HIT. The alert included the patient's name, medical record number, baseline platelet count and date and most recent platelet count and date (Figure 1). No patients were excluded on the basis of age, sex, admitting diagnosis, service, type or dose of heparin product.

Patients were confirmed to have HIT if they had a positive ^{14}C-serotonin release assay with either a decrease in platelets by 50% or a decrease by 30% if the absolute platelet count was less than 150,000 platelets/mm^3 while on heparin (UFH or enoxaparin). Enoxaparin was the only available LMWH at TJUH during the study period. The HIT antibodies by ELISA testing was used to determine the time for HIT laboratory testing and not to confirm the diagnosis of HIT. The control group was defined by identifying all patients described above during a 12-month period preceding the implementation of the CDSS (March 2004 and March 2005). The intervention period included patients admitted during a 12-month period following implementation of the CDSS (September 2005 to September 2006) following a two-month period to allow for clinician familiarity with the alert. This study was approved by the Thomas Jefferson University Institutional Review Board. The requirement for informed consent was waived.

Follow-up for Thrombosis

The records of patients with confirmed HIT were assessed for presence or absence of thrombotic complications as documented by objective imaging reports during the 30 days following HIT diagnosis; only thrombotic events occurring after the initiation of heparin products were included. Duplex ultrasounds were required for diagnosis of extremity thromboses, thoracic computed tomography (CT) or ventilation-perfusion scans for diagnosis of pulmonary embolism, and head CT or magnetic resonance imaging (MRI) or angiography (MRA) defined stroke diagnosis. Troponin levels and a documented clinical diagnosis in the medical record were used to identify myocardial infarction.

Study End Points

Three primary parameters were evaluated before and after the implementation of the CDSS: time from platelet count criterion to heparin product discontinuation, time from platelet count criterion to HIT treatment initiation, and time from platelet count criterion to the first HIT laboratory testing. The 14C-serotonin release assay was performed weekly at Jefferson Hospital with the following specifications: low dose unfractionated heparin dilution 0.5 unit/mL, high dose unfractionated heparin dilution 50 unit/mL, using single donor for fresh platelets.
HIT antibodies by ELISA testing (antibodies directed to the platelet factor 4-heparin complex) were assessed by ASSERACHROM HPIA from Diagnostica Stago, Parsippany, NJ. Both ELISA and ^{14}C-serotonin release assay were ordered at the discretion of the clinician; there was no reflex testing done by our laboratory for these conditions or results.

Each parameter was assessed from the CDSS thresholds of platelet count decrease. We also evaluated secondary outcomes of incidence of thrombotic events and the proportion of HIT laboratory tests ordered. The time from heparin initiation to the alert was done to help us evaluate the alert rules and determine if the time frame it was looking at was too long or short. For example, if a patient was on heparin 2 days and had the alert, it may not be HIT. It was more of an internal control to detect if the alert was actually finding HIT. The sensitivity, specificity, positive and negative predictive values of the CDSS were calculated.

Statistical Analysis

Three time-to-event outcomes were compared before and after implementation of the CDSS using the log-rank test. Proportional hazards regression was used to adjust these comparisons for differences between groups in baseline covariates and assess potential effect modification and confounding. The proportional hazards assumption was tested by including a log-time by intervention group interaction term in the model. A variable was considered to be an effect-modifier if the p-value for the intervention group by variable interaction term was less than 0.15. A variable was considered a confounder if the adjusted log hazard ratio differed from the unadjusted log hazard ratio by +/- 15%. Hazard ratios were estimated from the proportional hazards model with ratios greater than 1 indicating that the intervention group was more likely to have an event. Differences in the rates of thrombotic events and HIT assay tests were evaluated using logistic regression. P-values were calculated for the test of the hypothesis that the odds ratio = 1 (i.e., no difference). Due to the low incidence of thrombotic events, exact methods were used to produce 95% confidence intervals and compute p-values. Sensitivity and specificity were calculated requiring ^{14}C-serotonin release assay criteria to define positivity for

HIT. All analyses were performed using SAS version 9.1 (Copyright 2005, SAS Institute, Cary, NC) and LogXact Version 7.0 (Copyright 2005, Cytel Software Corporation).

Results

During the intervention time period, the CDSS alert occurred 41,922 times identifying 2,036 patients who had 2,338 inpatient admissions. The HIT CDSS was found to have a sensitivity of 87% and a specificity of 87%. The positive predictive value of the alert was 2.3% and the negative predictive value was 99.9%. Of all patients receiving heparin during this time period, 13% developed platelet count decreases that triggered an alert for possible HIT. The ^{14}C-serotonin release assay was positive in 81 patients during the control and 76 patients during the intervention period (Table 1). Of those identified as positive, 47 of 81 in the control and 53 of 76 in the intervention periods also met the CDSS criteria of an active heparin order and proportional platelet count decrease. Fifty-seven patients did not meet the CDSS criteria in the combined control and intervention periods. Thirty-three of these patients were not on heparin and either had a history of HIT or had been transferred from another institution. The remaining 24 patients did not have a platelet count decrease meeting the CDSS thresholds.

The analysis of the 24 patients that had exposure to heparin, but did not have a platelet count decrease meeting the CDSS thresholds, revealed the following. One intervention patient had a platelet count decrease meeting the CDSS thresholds, but was only on heparin drip for 2 hours and the alert was never generated because it was within the 4 hour window. Of the remaining 23 patients, the platelet nadir percent decrease while on heparin compared with the previous highest platelet count from the preceding 21 days, showed the following: 11 had less 20% decrease, 9

had 20-30% decrease, 1 had 30-40% decrease and 2 had 40-50% decrease. The platelet percent decrease off heparin when the HIT laboratory test was ordered compared with the previous highest platelet count from the preceding 21 days, showed the following: 9 had less 20% decrease, 2 had 20-30% decrease, 3 had 30-40% decrease, 2 had 40-50% decrease and 7 had >50% decrease. Furthermore, 3 of these patients had a higher baseline platelet count beyond 21days but less than 90 days that would have cause a platelet count decrease meeting the CDSS thresholds *while* on heparin.

Control and intervention patients with confirmed HIT were similar with regard to age, gender and type of heparin product (Table 2). In the control period, the majority of diagnostic interventions occurred due to a 50% platelet count decrease while in the intervention period more alerts occurred following a 30% platelet count decrease (p=0.0002). The median interval between the point of heparin discontinuation and the preceding alert threshold platelet count criterion occurrence (Table 3) was 1.3 days in the control and 2.9 days in the intervention period (p=0.04). The median interval between HIT laboratory test order and preceding platelet count criterion was 2.3 days in the control and 3.0 days during the intervention period (p=0. 30). Median direct thrombin inhibitor initiation occurred 19.3 days following platelet count criterion in the control and 15.0 days in the intervention periods (p=0.45). Fifty-five percent of patients in the control and 45% in the intervention period were discharged before a DTI was started.

We calculated hazard ratios comparing the intervention period to the control period overall and by category of potential effect modifiers for each of the primary endpoints (Table 4). During the intervention period, the time from platelet count criterion to heparin product discontinuation was

significantly longer in the intervention period with a hazard ratio of 0.66 (95% CI 0.44-0.99), but duration of heparin exposure and magnitude of platelet count decrease were found to be confounders of this association. After adjustment for these factors, the hazard ratio was no longer significant (0.79; 95% CI 0.50-1.24). The effect of the intervention on the time to first HIT laboratory test drawn differed by service type (p=0.10).

Assessment of secondary endpoints revealed that ^{14}C-serotonin release assay was ordered in 1.9% of admissions in the control (610 assays) and 2.5% in the intervention period (826 assays; p<0.0001 The ELISA test was not available during the control period and an additional 330 ELISA tests were done in the intervention period. A total of 1156 HIT laboratory tests were done in the interventional period on 674 unique hospitalizations. Of the 2338 inpatient admissions that the CDSS alert occurred, 445 (19%) had at least one HIT lab test performed (64% ^{14}C-serotonin release assay only, 1 % ELISA only, 35% both tests). The absolute number of clinically documented thrombotic events among the confirmed HIT patients was small and similar in control and intervention periods, except for an increase in superficial thrombosis during the intervention period (p= 0.02, Table 5).

Discussion

We hypothesized that among clinicians caring for patients receiving heparin, the suspicion and treatment of HIT should occur earlier following a defined fall in platelet count with the CDSS in place than without. We found no clear alteration in promptness of ordering appropriate measures (HIT laboratory test and DTI initiation), and an apparent delay in discontinuation of heparin products. In addition, the secondary endpoints suggested an increased frequency of superficial

thrombosis in the intervention group, although the numbers were small. Implementation of the CDSS resulted in better ability to detect more subtle changes in platelet count (i.e. more ^{14}C-serotonin release assays were ordered for a 30% decrease, and fewer for a 50% decrease, during the intervention period. Despite this apparent increased sensitivity, there was no improvement in time to therapeutic intervention. When an alert accompanied first occurrence of platelet count criterion, clinicians appeared to delay discontinuation of heparin by an additional 1.6 days compared to time to discontinuation without the alert. What accounts for this seemingly paradoxical result? With a positive predictive value of only 2.3% and 41,922 alerts, physicians may have become desensitized to alerted patients due to alert fatigue [22]. Modifications of the CDSS are planned to decrease the number of alerts and improve the specificity of the program.

Review of those patients that had exposure to heparin, but did not have a platelet count decrease meeting the CDSS thresholds, reveals that the baseline platelet count should be considered 90 days in past, not just 21 days used in our study. Also, after exposure to heparin was stopped the platelet decrease continued in 52% of the patients to the CDSS thresholds when the HIT laboratory test was ordered(7/23 by less 50% drop; 5/23 30% decrease with absolute platelet count was less than 150,000 platelets/mm^3). These findings will be used to determine modifications to the CDSS.

Treatment of HIT should not be delayed awaiting laboratory confirmation but should be initiated on clinical suspicion [11, 23]. The highest risk of thrombosis occurs between the time of diagnosis of HIT and initiation of therapy [24]. In many institutions where the results of HIT assays are not available daily, ^{14}C-serotonin release assay and HIT antibodies by ELISA testing

(platelet factor 4) tests may be only performed weekly. We measured only the time to ordering of diagnostic testing and not time to receipt of results, but waiting for laboratory confirmation of HIT could have delayed therapy by days. Nevertheless, a delay in laboratory results cannot explain all of the findings. Physicians discontinued heparin as the first step of treating HIT but failed reliably to start therapy immediately after stopping the offending agent. During both the control and intervention periods the median time for initiation of HIT treatment in those patients who received therapy was longer than 15 days, and more than 45% of patients were never started on a DTI during their admission. It is clear that more education on HIT management is needed. If an option were added to the CDSS that prompted the prescriber to order a DTI perhaps this treatment delay would be prevented.

Analysis of effect modification and confounding provided some insight to the results. The effect of the alert on time until laboratory test draw was dependent on specialty service, with surgeons ordering appropriate laboratory tests earlier during the alert period. Perhaps surgeons were more aware of platelet count trends. While there may be other effect modifiers, the confidence intervals and p-values were too large to draw any firm conclusions. For example, time until heparin discontinuation was dependent on alert type and duration of heparin exposure. If a patient had been exposed to heparin for fewer than 5 days or had not had a dramatic platelet decrease, then HIT may not have been high in a clinician's differential, possibly resulting in a delay in heparin discontinuation. Average duration of heparin therapy prior to the alert was shorter during the intervention period, perhaps accounting for some of the longer time to discontinuation. Furthermore, the criterion of a positive ^{14}C-serotonin release assay to establish a HIT positive patient identifies the most obvious HIT patients. Because HIT is often not an easy

diagnosis, less obvious HIT patients may have been missed in this 'first approach' of the CDSS but future iterations of the program will try to capture these 'difficult' patients.

Clinical decision support systems are used for a variety of conditions including preventative medicine, medication dosing, and diagnosing medical conditions [18-20, 25-32]. Tools designed to help with diagnosis have had variable impact on improvement of practitioner performance [19, 20, 25]. A CDSS related to HIT has been utilized at Mayo Clinic as part of a nurse driven heparin nomogram system (HNS) [33]. The HNS incorporates patient specific information to make dosage recommendations and order laboratory levels. In addition, this system has a method of alerting nurses and physicians if the platelet count drops below 100,000 platelets/mm^3, with a resulting notification rate of 6% for all patients monitored by the HNS system. Our HIT CDSS had a notification rate of 13%; the difference may reflect our more sensitive definition of HIT [4]. Evans and colleagues described a CDSS to help with the appropriate selection of antibiotics. While this tool improved antibiotic decision-making, one important finding was that the recommendations were not followed automatically [34].

Our goal was not to promulgate "cookbook medicine" but to give clinicians information to help with diagnosis and choose appropriate therapy. The HIT CDSS did not lead to every patient with thrombocytopenia undergoing evaluation for HIT with a laboratory test. Clinicians apparently incorporated the alerts into their decision making to help with diagnosis, and did not regard it as providing a definitive diagnosis.

Although computerized reminders, alerts and other programs have been implemented with the intention of improving physician compliance and patient care, the utility of this approach may be highly dependent upon the specific details of implementation [35]. For example, if our alert had incorporated educational components that gave the clinician options to discontinue heparin, order a HIT laboratory test and start a DTI from the same screen as the platelet information, the results may have been different. Kucher and colleagues describe an alert that gave information and treatment options on the same screen for venous thromboembolism prophylaxis. This addition of treatment options increased prophylaxis in comparison to a previous alert that only suggested prophylaxis for patients [36]. For the HIT CDSS there must be methods to either exclude or allow the clinician to "turn off" the alert for patients who do not have the condition and eliminate extra alerts that contribute to alert desensitization and/or fatigue.

The conclusions of this study are limited by its retrospective design and by our decision to include only the heparin antibody positive patients in the analysis. During the control period, it would have been advantageous to attempt to identify platelet count criteria that went unnoticed, as defined by failure to discontinue heparin, order HIT laboratory confirmation or substitute a direct thrombin inhibitor, and compare these results with those during the intervention period. Unfortunately, the data were not available in a format that permitted this type of query. Moreover, had the alerts been followed concurrently it may have been possible to identify in greater detail how clinicians used or disregarded the alerts and determine which patients should have been evaluated for HIT. It is possible that prescribing practices may have changed between the control and intervention periods, but we think this is unlikely. Because Thomas Jefferson University Hospital had already in place an anti-thrombotic service, physicians may have had a

high level of awareness of HIT making it difficult to improve upon this responsiveness. Furthermore, both periods had a computer system that displayed labs in a trended fashion thus making the intervention potentially redundant. In conclusion, our HIT CDSS was able to identify potential HIT with good sensitivity and specificity, but the relatively low prevalence resulted in many false positive alerts, perhaps desensitizing the clinicians to the alert. Although more confirmatory laboratory testing was ordered during the intervention period, the time to treatment or testing was not shortened by the alert. The CDSS was able to trigger an alert that resulted in clinician response for more subtle changes in platelet count and following shorter durations of heparin treatment, but we observed no decrease in thrombotic events. We plan modifications to reduce the number of alerts and potentially improve patient outcomes. As clinical information technology adoption gains more momentum, it becomes increasingly crucial to improve our ability to design and implement truly effective decision support tools if we are to realize the benefit that these technologies promise [37].

Acknowledgement:
Special thanks to TJUH Information Systems (Arlene Peters, Renee Brandell-Marino, Mary McNichol, Michael Ekshtut, et al)

Figure 1. Pop Up Alert

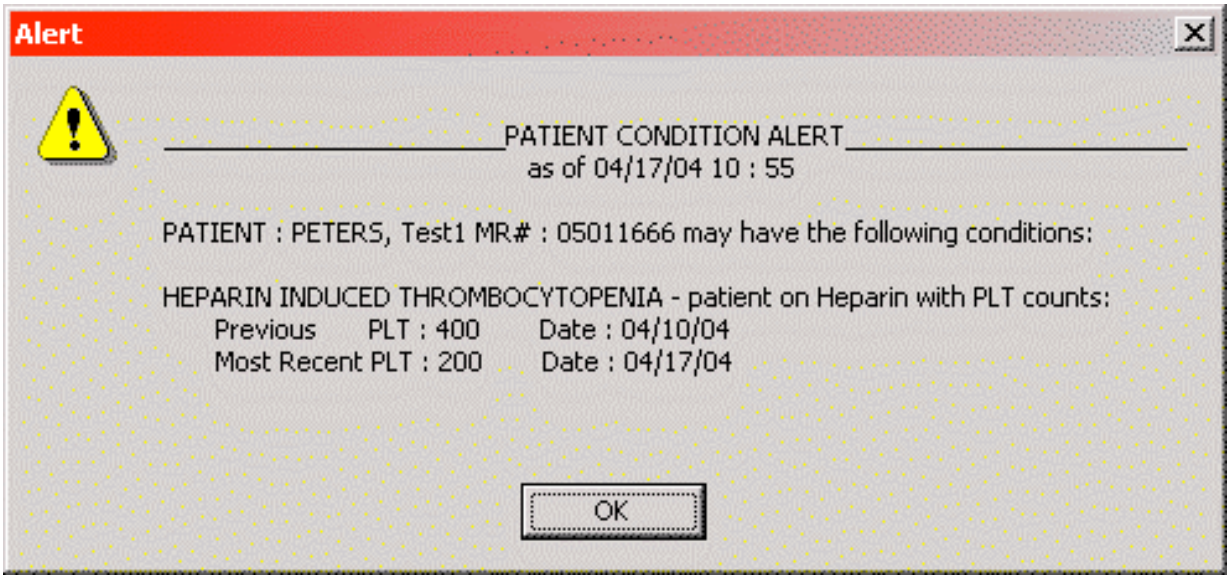

Table 1. Demographics

	Control	Intervention
Total Admissions	32,152	33,452
Admissions on UFH	11,111	11,154
Admissions on LMWH	4,806	4,952
Admissions on both UFH & LMWH*	1,370	1,561
Total HIT Assays (^{14}C-serotonin release assay)	610	826
HIT ELISA Test	N/A	330
Assay Positive	81	76
Assay Positive and Meet platelet count criterion	47	53
Assay Positive and NOT Meet platelet count criterion	34	23
- Not on Heparin	18	15
- Platelet count above Platelet count criterion	16	8

*Note: No patient was on UFH and LMWH at the same time but some were exposed to both products during a single admission. Assay Positive refers to a positive ^{14}C-serotonin release assay.

Table 2. Patients with HIT and Met Alert Criteria

		Control (n=47)	Intervention (n=53)	p-value
Age*		63.4 (14.5)	59.5 (12.7)	0.12
Sex	Male	25 (53.2)	32 (60.4)	0.47
	Female	22 (46.8)	21 (39.6)	
Platelet count criterion Type	50% drop	35 (74.5)	20 (37.7)	0.0002
	30% drop with platelet less than 150	12 (25.5)	33 (62.3)	
Treatment	LMWH	7 (14.9)	6 (11.3)	0.73
	UFH	35 (74.5)	39 (73.6)	
	Both	5 (10.6)	8 (15.1)	
Time on Heparin/ Enoxaparin	<=5 days	23 (48.9)	32 (60.4)	0.25
	>5 days	24 (51.1)	21 (39.6)	
Service	MED	25 (53.2)	37 (69.8)	0.09
	SUR	22 (46.8)	16 (30.2)	

* Age: Mean (standard deviation). All others: Frequency (percent)

Table 3. Evaluation of HIT CDSS

Outcome (Times in days)	Control		Intervention		Log rank test p-value
	N	Median (95% CI)*	N	Median (95% CI)*	
Time from platelet count criterion until heparin/enoxaparin d/c	47	1.3 (0.9-2.3)	53	2.9 (1.8-3.2)	0.04
Time from platelet count criterion until 1st HIT laboratory test drawn†	46	2.3 (1.6-3.6)	51	3.0 (2.0-4.0)	0.30
Time from platelet count criterion until direct thrombin inhibitor started	47	19.3 (11.1-35.8)	53	15.0 (7.3-27.3)	0.45
Time from platelet high until alert platelet	47	5.3 (4.7-6.8)	53	4.3 (2.6-6.4)	0.56

*CI denotes confidence interval.

†For the outcome of the time until the first HIT assay was ordered one patient in the control and two patients in the intervention group were excluded due to the HIT assay being ordered prior to the platelet count decreasing to CDSS thresholds.

Table 4. Assessment of Effect Modification

		Time from platelet count criterion until heparin discontinued		Time from platelet count criterion until 1st HIT laboratory test drawn		Time from platelet count criterion until direct thrombin inhibitor started	
Clinically Important Factor		Hazard Ratio (95% CI)*	Interaction p-value†	Hazard Ratio (95% CI)*	Interaction p-value†	Hazard Ratio (95% CI)*	Interaction p-value†
Unadjusted		0.66 (0.44-0.99)		0.81 (0.54-1.21)		1.13 (0.76-1.68)	
Age	<55	0.71 (0.33-1.54)	0.85	0.77 (0.36-1.68)	0.93	2.51 (0.66-9.57)	0.24
	≥55	0.65 (0.41-1.03)		0.80 (0.50-1.29)		1.03 (0.55-1.95)	
Sex	Male	0.67 (0.39-1.13)	0.96	0.83 (0.49-1.42)	0.89	1.29 (0.61-2.70)	0.88
	Female	0.68 (0.37-1.25)		0.79 (0.42-1.46)		1.18 (0.49-2.85)	
Platelet count criterion type	50% drop	0.87 (0.50-1.51)	0.44	1.03 (0.59-1.80)	0.30	1.33 (0.61-2.92)	0.92
	30% drop with platelet less than 150	0.62 (0.31-1.21)		0.65 (0.33-1.28)		1.42 (0.48-4.24)	
Treatment	LMWH	0.76 (0.25-2.26)	0.56	1.30 (0.43-3.90)	0.43	2.31 (0.51-10.49)	0.56
	UFH	0.59 (0.37-0.95)		0.68 (0.43-1.10)		1.22 (0.62-2.39)	
	Both	1.14 (0.37-3.52)		1.23 (0.40-3.81)		0.69 (0.14-3.42)	
Time on Heparin	≤ 5 days	0.89 (0.50-1.60)	0.27	0.79 (0.44-1.43)	0.87	1.68 (0.69-4.05)	0.40
	> 5 days	0.56 (0.32-0.98)		0.84 (0.49-1.47)		1.02 (0.49-2.15)	
Service	MED	0.59 (0.31-1.14)	0.66	1.07 (0.63-1.79)	0.10	1.22 (0.59-2.54)	0.94
	SUR	0.71 (0.43-1.19)		0.52 (0.26-1.03)		1.28 (0.52-3.19)	

*CI denotes confidence interval.

†The null hypothesis is that there are no significant differences between subgroups.

Table 5. Thrombotic Events

	Control (n=47)	Intervention (n=53)	Adjusted Odds ratio (95% CI)*	P value
Deep Vein Thrombosis	8 (17.0%)	13 (24.5%)	1.6 (0.54-4.9)	0.50
Superficial Thrombosis	1 (2.1%)	7 (13.2%)	11.7 (1.3-581)	0.02
Pulmonary Embolism	2 (4.3%)	2 (3.8%)	0.88 (0.06-12.7)	1.0
Myocardial Infarction	2 (4.3%)	4 (7.6%)	1.8 (0.25-21.1)	0.80
Stroke	1 (2.1%)	4 (7.6%)	4.8 (0.47-49)	0.35

*CI denotes confidence interval.

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