Clinical Outcomes After Conversion from Low-Molecular-Weight Heparin to Unfractionated Heparin for Venous Thromboembolism Prophylaxis

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ABSTRACT

• **Objective:** To measure clinical outcomes associated with heparin-induced thrombocytopenia (HIT) and acquisition costs of heparin after implementing a new order set promoting unfractionated heparin (UFH) use instead of low-molecular-weight heparin (LMWH) for venous thromboembolism (VTE) prophylaxis.

• **Methods:** This was single-center, retrospective, pre-post intervention analysis utilizing pharmacy, laboratory, and clinical data sources. Subjects were patients receiving VTE thromboprophylaxis with heparin at an acute care hospital. Usage rates for UFH and LMWH, acquisition costs for heparins, number of HIT assays, best practice advisories for HIT, and confirmed cases of HIT and HIT with thrombosis were assessed.

• **Results:** After order set intervention, UFH use increased from 43% of all prophylaxis orders to 86%. Net annual savings in acquisition costs for VTE prophylaxis was $131,000. After the intervention, HIT best practice advisories and number of monthly HIT assays fell 35% and 15%, respectively. In the 9-month pre-intervention period, HIT and HITT occurred in zero of 6717 patients receiving VTE prophylaxis. In the 25 months of post-intervention follow-up, HIT occurred in 3 of 44,240 patients ($P = 0.86$) receiving VTE prophylaxis, 2 of whom had HITT, all after receiving UFH. The median duration of UFH and LMWH use was 3.0 and 3.5 days, respectively.

• **Conclusion:** UFH use in hospitals can be safely maintained or increased among patient subpopulations that are not at high risk for HIT. A more nuanced approach to prophylaxis, taking into account individual patient risk and expected duration of therapy, may provide desired cost savings without provoking HIT.

Key words: heparin; heparin-induced thrombocytopenia; venous thromboembolism prophylaxis; cost-effectiveness.

Heparin-induced thrombocytopenia (HIT) and its more severe clinical complication, HIT with thrombosis (HITT), complicate the use of heparin products for venous thromboembolic (VTE) prophylaxis. The clinical characteristics and time course of thrombocytopenia in relation to heparin are well characterized (typically 30%–50% drop in platelet count 5–10 days after exposure), if not absolute. Risk calculation tools help to judge the clinical probability and guide ordering of appropriate confirmatory tests [1]. The incidence of HIT is higher with unfractionated heparin (UFH) than with low-molecular-weight heparin (LMWH). A meta-analysis of 5 randomized or prospective nonrandomized trials indicated a risk of 2.6% (95% CI, 1.5%–3.8%) for UFH and 0.2% (95% CI, 0.1%–0.4%) for LMWH [2], though the analyzed studies were heavily weighted by studies of orthopedic surgery patients, a high-risk group. However, not all patients are at equal risk for HIT, suggesting that LMWH may not be necessary for all patients [3]. Unfortunately, LMWH is considerably more expensive for hospitals to purchase than UFH, raising costs for a prophylactic treatment that is widely utilized. However, the higher incidence of HIT and HITT associated with UFH can erode any cost savings because of the additional cost of diagnosing HIT and need for temporary or long-term treatment with even more expensive alternative anticoagulants. Indeed,
a recent retrospective study suggested that the excess costs of evaluating and treating HIT were approximately $267,000 per year in Canadian dollars [4]. But contrary data has also been reported. A retrospective study of the consequences of increased prophylactic UFH use found no increase in ordered HIT assays or in the results of HIT testing or of inferred positive cases despite a growth of 71% in the number of patients receiving UFH prophylaxis [5].

In 2013, the pharmacy and therapeutics committee made a decision to encourage the use of UFH over LMWH for VTE prophylaxis by making changes to order sets to favor UFH over LMWH (enoxaparin). Given the uncertainty about excess risk of HIT, a monitoring work group was created to assess for any increase of either HIT or HITT that might follow, including any patient readmitted with thrombosis within 30 days of a discharge. In this paper, we report the impact of a hospital-wide conversion to UFH for VTE prophylaxis on the incidence of VTE, HIT, and HITT and acquisition costs of UFH and LMWH and use of alternative prophylactic anticoagulant medications.

**METHODS**

**Setting**

Anne Arundel Medical Center is a 383-bed acute care hospital with about 30,000 adult admissions and 10,000 inpatient surgeries annually. The average length of stay is approximately 3.6 days with a patient median age of 59 years. Caucasians comprise 75.3% of the admitted populations and African Americans 21.4%. Most patients are on Medicare (59%), while 29.5% have private insurance, 6.6% are on Medicaid, and 4.7% self-pay. The 9 most common medical principal diagnoses are sepsis, heart failure, chronic obstructive pulmonary disease, pneumonia, myocardial infarction, ischemic stroke, urinary tract infection, cardiac arrhythmia, and other infection. The 6 most common procedures include newborn delivery (with and without caesarean section), joint replacement surgery, bariatric procedures, cardiac catheterizations, other abdominal surgeries, and thoracotomy. The predominant medical care model is internal medicine and physician assistant acute care hospitalists attending both medicine and surgical patients. Obstetrical hospitalists care for admitted obstetric patients. Patients admitted to the intensive care units had only critical care trained physician specialists as attending physicians. No trainees cared for the patients described in this study.

**P&T Committee**

The P&T committee is a multidisciplinary group of health care professionals selected for appointment by the chairs of the committee (chair of medicine and director of pharmacy) and approved by the president of the medical staff. The committee has oversight responsibility for all medication policies, order sets involving medications, as well as the monitoring of clinical outcomes as they regard medications.

**Electronic Medical Record and Best Practice Advisory**

Throughout this study period both pre-and post-intervention, the EMR in use was Epic (Verona WI), used for all ordering and lab results. A best practice advisory was in place in the EMR that alerted providers to all cases of thrombocytopenia < 100,000/mm³ when there was concurrent order for any heparin. The best practice advisory highlighted the thrombocytopenia, advised the providers to consider HIT as a diagnosis and to order confirmation tests if clinically appropriate, providing a direct link to the HIT assay order screen. The best practice advisory did not access information from prior admissions where heparin might have been used nor determine the percentage drop from the baseline platelet count.

**HIT Case Definition and Assays**

The 2 laboratory tests for HIT on which this study is based are the heparin-induced platelet antibody test (also known as anti-PF4) and the serotonin release assay. The heparin-induced platelet antibody test is an enzyme-linked immunosorbent assay (ELISA) that detects IgG, IgM, and IgA antibodies against the platelet factor 4 (PF4/heparin complex). This test was reported as positive if the optical density was 0.4 or higher and generated an automatic request for a serotonin release assay (SRA), which is a functional assay that measures heparin-dependent platelet activation. The decision to order the SRA was therefore a “reflex” test and not made with any knowledge of clinical characteristics of the case. The HIT assays were performed by a reference lab, Quest Diagnostics, in the Chantilly, VA facility. HIT was said to be present when both a characteristic pattern of thrombocytopenia occurring after heparin use was seen [1] and when the confirmatory SRA was positive at a level of > 20% release.

**Order Set Modifications**

After the P&T committee decision to emphasize UFH for VTE prophylaxis in October 2013, the relevant elec-
tronic order sets were altered to highlight the fact that UFH was the first choice for VTE prophylaxis. The order sets still allowed LMWH (enoxaparin) or alternative anticoagulants at the prescribers’ discretion but indicated they were a second choice. Doses of UFH and LMWH in the order sets were standard based upon weight and estimates of creatinine clearance and, in the case of dosing frequency for UFH, based upon the risk of VTE. Order sets for the therapeutic treatment of VTE were not changed.

Data Collection and Analysis
The clinical research committee, the local oversight board for research and performance improvement analyses, reviewed this project and determined that it qualified as a performance improvement analysis based upon the standards of the U.S. Office of Human Research Protections. Some data were extracted from patient medical records and stored in a customized and password-protected database. Access to the database was limited to members of the analysis team and stripped of all patient identifiers under the HIPAA privacy rule standard for de-identification from 45 CFR 164.514(b) immediately following the collection of all data elements from the medical record.

An internal pharmacy database was used to determine the volume and actual acquisition cost of prophylactic anticoagulant doses administered during both pre- and post-intervention time periods. To determine if clinical suspicion for HIT increased after the intervention, a definitive listing of all ordered HIT assays was obtained from the HIPAA privacy rule standard for de-identification from 45 CFR 164.514(b) immediately following the collection of all data elements from the medical record.

HIT assays results returned to the chart within a median of 4 days for anti-platelet factor 4 and 5 days for SRA. Data on the number of HIT assays ordered was missing for 1 month in 2013 and 1 month in 2014 due to missing laboratory billing data. On average, the best practice advisory for HIT fired 35% less frequently after the intervention (Figure 2). The number of ordered serum ELISA HIT assays decreased slightly after the intervention from a mean of 18.2 per month to 15.4 per month despite the increase in UFH use. The distribution of the retrospectively measured 4T scores for patients with HIT testing is shown in the Table. There were no differences in the retrospectively calculated scores between the pre- and post-intervention time periods. Most patients had a moderate risk 4T score prior to having HIT assay ordered.

RESULTS
Heparin Use and Acquisition Costs
Annual hospital admissions and patient-days both increased 3% during the study time period to 29,975 annual adult admissions and 96,426 hospital days. However, the number of patients receiving any prophylactic anticoagulant increased 15% over the time period as a result of a simultaneous anti-VTE education campaign. After the modification in order sets there was a rapid increase in orders for prophylactic UFH and a corresponding decrease in the use of LMWH (Figure 1). A few patients received both at different times during their hospitalization. Prophylactic UFH orders increased from 43% of all prophylactic use pre-intervention to 86% by the second year of the intervention. There was a corresponding reduction in use of LMWH from 53% of all prophylaxis orders to 11% after the intervention. Other anticoagulants, fondaparinux and bivalrudin, together composed 5% and 4% of all prophylactic heparin in the pre- and post-intervention time periods, respectively. Pharmacy acquisition costs averaged $3.50 for daily doses of heparin and $24 for LMWH. With the shift in ordering pattern, acquisition costs of prophylactic LMWH fell by $165,000 annually with a concurrent offsetting increase in acquisition costs of UFH of $34,000 for a net savings of $131,000. The median duration of use was 3.5 days and 3.0 days for UFH and LMWH, respectively. Only 25% of treated patients had heparin exposure of > 5 days. Bleeding complications from any prophylaxis regimen were < 0.5% in both pre- and post-intervention time periods.

HIT Assays and Incidence of HIT and HITT
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In the 9 months pre-intervention, HIT and HITT occurred in zero of 6717 patients receiving at least 1 dose of VTE prophylaxis. In the 25 months of post-intervention
UNFRACTIONATED HEPARIN FOR VTE PROPHYLAXIS

Figure 1. Use of heparins for prophylaxis of venous thromboembolism (VTE) over time. LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

DISCUSSION

Because the efficacy of UFH and LMWH for VTE prophylaxis are equivalent [6], choosing between them involves many factors including patient-level risk factors such as renal function, risk of bleeding, as well as other considerations such as nursing time, patient preference, risk of HIT, and acquisition cost. Indeed, the most recent version of the American College of Chest Physicians guidelines for prophylaxis against VTE note that both drugs are recommended with an evidence grade of IB [7]. Cost is among the considerations considered appropriate in choosing among agents. The difference in acquisition costs of > $20 per patient per day can have a major financial impact on hospital’s pharmacy budget and may be decisive. But a focus only on acquisition cost is short sighted as the 2 medications have different complication rates with regard to HIT. Thus the need to track HIT incidence after protocol changes are made is paramount.

In our study, we did not measure thrombocytopenia as an endpoint because acquired thrombocytopenia is too common and multifactorial to be a meaningful. Rather, we used the clinical suspicion for HIT as measured by the number of times the BPA fired warnings of low platelets in the setting of recent heparin use and the number of times clinicians suspected HIT enough to order a HIT assay. We also used actual outcomes (clinically adjudicated cases of HIT and HITT). Our data shows substantial compliance among clinicians with the voluntary conversion to UFH with an immediate and sustained shift to UFH so that UFH was used in 86% of patients. Corresponding cost savings were achieved in heparin acquisition. Unlike some prior reports, there was a minimal burden of HIT as measured by the unchanged number of BPAs, monthly HIT assays and the unchanged clinical risk 4T scores among those patients in whom the test was ordered pre and post.

follow-up, 44,240 patients received prophylaxis with either heparin. HIT (clinical suspicion with positive antibody and confirmatory SRA) occurred in 3 patients, 2 of whom had HITT, all after UFH. This incidence was not statistically significant using chi square analysis (P = 0.86).
intervention. HIT rates were not statistically different after the order set conversion took effect.

Our results and study design are similar but not identical to that of Zhou et al, who found that a campaign to increase VTE prophylaxis resulted in 71% increase of UFH use over 5 years but no increase in number of HIT assays ordered or in the distribution of HIT assay results—both surrogate endpoints [5]. But not all analyses of heparin order interventions show similar results. A recent study of a heparin avoidance program in a Canadian tertiary care hospital showed a reduction of 79% and 91% in adjudicated cases of HIT and HITT respectively [4]. Moreover, hospital-related expenditures for HIT decreased by nearly $267,000 (Canadian dollars) per year though the additional acquisition costs of LMWH were not stated. A small retrospective heparin avoidance protocol among orthopedic surgery patients showed a reduction of HIT incidence from 5.2% with UFH to 0% with LMWH after universal substitution of LMWH for UFH [8]. A recent systematic review identified only 3 prospective studies involving over 1398 postoperative surgical patients that measured HIT and HITT as outcomes [9]. The review authors, in pooled analysis, found a lower incidence of HIT and HITT with LMWH postoperatively but downgraded the evidence to “low quality” due to methodologic issues and concerns over bias. A nested case-control study of adult medical patients found that HIT was 6 times more common with UFH than with LMWH and the cost of admissions associated with HIT was 3.5 times higher than for those without HIT, though this increase in costs are not necessarily due to the HIT diagnosis itself but may be markers of patients with more severe illness [10]. The duration of heparin therapy was not stated.

Figure 2. Number of best practice advisories (BPAs) for heparin-induced thrombocytopenia (HIT), HIT assays, confirmed cases of HIT, and confirmed cases of HIT with thrombosis (HITT).
There are several potential reasons that our data differs from some of the previous reports described above. We used a strict definition of HIT, requiring the serotonin release assay to be positive in the appropriate clinical setting and did not rely solely upon antibody tests to make the diagnosis, a less rigorous standard found in some studies. Furthermore, our results may differ from previously reports because of differences in patient risk and duration of therapy. Our institution does not perform cardiac surgery and the very large orthopedic surgery programs do not generally use heparin. Another potentially important difference in our study from prior studies is that many of the patients treated at this institution did not receive heparin long enough to be considered at risk; only a quarter were treated for longer than 5 days, generally considered a minumum [11]. This is less than half of the duration of the patients in the studies included in the meta-analysis of HIT incidence [2].

We do not contend that UFH is as safe as LMWH with regard to HIT for all populations, but rather that the increased risk is not manifest in all patient populations and settings and so the increased cost may not be justified in low-risk patients. Indeed while variability in HIT risk among patients is well documented [3,12], the guidelines for prophylaxis do not generally take this into account when recommending particular VTE prophylaxis strategies. Clinical practice guidelines do recommend different degrees of monitoring the platelet count based on risk of HIT however.

Our study had limitations, chief of which is the retrospective nature of the analysis; however, the methodology we used was similar to those of previous publications [4,5,8]. We may have missed some cases of HIT if a clinician did not order the assay in all appropriate patients but there is no reason to think that likelihood was any different pre- and post-intervention. In addition, though we reviewed every case of hospital-acquired thrombosis, it is possible that the clinical reviewers may have missed cases of HIT, especially if the thrombosis occurred before a substantial drop in the platelet count, which is rare but possible. Here too the chance of missing actual cases did not change between the pre- and post-intervention. Our study examined prophylaxis with heparin use and not therapeutic uses. Finally, while noting the acquisition cost reduction achieved with conversion to UFH, we were not able to calculate any excess expense attributed to the rare case of HIT and HIT that occurred. We believe our results are generalizable to hospitals with similar patient profiles.

The idea that patients with different risk factors might do well with different prophylaxis strategies needs to be better appreciated. Such information could be used as a guide to more individualized prophylaxis strategy aided by clinical decision support embedded within the EMR. In this way the benefit of LMWH in avoiding HIT could be reserved for those patients at greatest risk of HIT while simultaneously allowing hospitals not to overspend for prophylaxis in patients who will not benefit from LMWH. Such a strategy would need to be tested prospectively before widespread adoption.

As a result of our internal analysis we have altered our EMR-based best practice alert to conform to the 2013 American Society of Hematology guidelines [15], which is more informative than our original BPA. Specifically, the old guideline only warned if the platelet count was < 100,000/mm$^3$ in association with heparin. The revision notified if there is a > 30% fall regardless of the absolute count and informed prescribers of the 4T score to encourage more optimum use of the HIT assay, avoiding its use for low risk scores and encouraging its use for moderate to high risk scores. We are also strengthening the emphasis that moderate to high risk 4T patients receive alternative anticoagulation until results of the HIT assay are available as we found this not to be a be a universal practice. We recommend similar self-inspection to other institutions.

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Table. 4T Scores Among Patients with HIT Assays

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<tr>
<th>4T Score</th>
<th>HIT Assays 2013–2015 n = 197</th>
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<tbody>
<tr>
<td>0–3</td>
<td>25%</td>
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<tr>
<td>4 and 5</td>
<td>66%</td>
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<td>6–8</td>
<td>9%</td>
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HIT = heparin-induced thrombocytopenia.
References


