Post-discharge adherence with venous thromboembolism prophylaxis after orthopedic trauma: Results from a randomized controlled trial of aspirin versus low molecular weight heparin

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BACKGROUND: Orthopedic trauma patients are often treated with venous thromboembolism (VTE) chemoprophylaxis with aspirin or low molecular weight heparin (LMWH) after discharge from their index admission, but adherence patterns are not known. We hypothesized that overall adherence would be moderate and greater with aspirin compared to LMWH.

METHODS: We conducted a randomized controlled trial of adult trauma patients with an operative extremity fracture or any pelvic/acetabular fracture requiring VTE prophylaxis. Patients were randomized to receive either LMWH 30 mg BID or aspirin 81 mg BID. Patients prescribed outpatient prophylaxis were contacted between 10 and 21 days after discharge to assess adherence measured by the validated Morisky Medication Adherence Scale (MMAS-8). Adherence scores were compared between the two treatment arms with similar results for intention-to-treat and as-treated analyses. As-treated multivariable logistic regression was performed to determine factors associated with low-medium adherence scores.

RESULTS: One hundred fifty patients (64 on LMWH, 86 on aspirin) on chemoprophylaxis at time of follow-up completed the questionnaire. As-treated analysis showed that adherence was high overall (mean MMAS 7.2 out of 8, SD 1.5) and similar for the two regimens (LMWH: 7.4 vs. aspirin: 7.0, $p = 0.13$). However, patients on LMWH were more likely to feel hassled by their regimen (23% vs. 9%, $p = 0.02$). In a multivariable model, low-medium adherence was associated with taking LMWH as the prophylaxis medication (aOR 2.34, CI 1.06–5.18, $p = 0.04$), having to self-administer the prophylaxis (aOR 4.44, CI 1.45–13.61, $p < 0.01$), being of male sex (aOR 2.46, CI 1.10–5.49, $p = 0.03$), and of younger age (aOR 0.72 per additional 10 years of age, CI 0.57–0.91, $p < 0.01$).

CONCLUSIONS: Overall post-discharge adherence with VTE prophylaxis was high. Several factors, including prophylaxis by LMWH, were associated with decreased adherence. These factors should be considered when managing patients and designing efficacy trials. (*J Trauma Acute Care Surg.* 2018;84: 564–574. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)

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KEY WORDS: Orthopedic trauma; venous thromboembolism; adherence; chemoprophylaxis.

Trauma patients are at high risk of venous thromboembolism (VTE) with pulmonary embolism (PE) being the third most common cause of death in patients who survive the first 24 hours.[1–4] Orthopedic trauma patients are at especially high risk because of several well-known risk factors inherent to their injuries including need for long operations, concomitant vascular injuries, and prolonged immobility.[2,5–9] To reduce this risk, many are treated with VTE chemoprophylaxis often extending after discharge from the index admission.

Low molecular weight heparin (LMWH) and aspirin are two of the most commonly prescribed medications for chemoprophylaxis in this population, but the optimal regimen remains unclear.[9–14] Both the Eastern Association for the Surgery of Trauma and the American College of Chest Physicians recommend LMWH for VTE prophylaxis in trauma patients.[14,15] Many orthopedic surgeons, however, prefer aspirin based on recent studies that suggest aspirin may be an equally effective alternative with reduced risk of wound and bleeding complications.[12,16–21] As a result, the American College of Chest Physicians guidelines now include aspirin as an option for chemoprophylaxis in high-risk orthopedic surgery patients.[14] However, only limited data is available specific to orthopedic trauma patients who may have even higher VTE and bleeding risk. As a result of poor scientific support for the various regimens, the Orthopedic Trauma Association Evidence Based Quality Value and Safety Committee has noted a wide variability in prescribed regimens and has emphasized the need for standardized guidelines to improve care.[22] Apart from aspirin, a variety of oral direct and indirect thrombin inhibitors have been used and recommended after high-risk orthopedic surgery. However, unlike aspirin, oral direct and indirect thrombin inhibitors are not commonly used for prophylaxis in the trauma population due to the frequency of non-orthopedic injuries and concern for bleeding.

Consideration of patient adherence patterns with prescribed regimens is critical when creating guidelines. An estimated 20–50% of patients taking medication are non-adherent, and poor medication adherence incurs billions of dollars per year in excess healthcare costs.[23,24] Non-adherence to VTE prophylaxis can result in particularly severe consequences including fatal PE. Patient medication refusal is a leading cause of non-administration of VTE prophylaxis in inpatients, and missed doses are highly associated with increased VTE incidence.[25–27] Studies on patient preferences for VTE prophylaxis regimens have found the majority of patients prefer oral administration over subcutaneous injection.[28–30]

Unfortunately, few studies have examined adherence with the most common VTE prophylaxis regimens after discharge from the index admission, when the majority of chemoprophylaxis doses are taken for many orthopedic trauma patients. Although it has been shown that patients can be taught to properly self-administer injections of LMWH, studies have found orthopedic patients have varying non-adherence rates to LMWH (up to 40%) in the outpatient setting with patients missing up to 50% of their doses.[31–35] Studies comparing adherence patterns with oral versus injected chemoprophylaxis regimens are even fewer with mixed results. Berggvist et al. found that injection was not a barrier to good compliance, whereas Peidro-Garcés et al. found patients on an oral regimen were more compliant.[34,35]

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To our knowledge, there has been no direct comparison of post-discharge adherence with aspirin to LMWH for VTE prophylaxis in orthopedic trauma patients. Such a comparison is needed to inform guidelines and future studies on efficacy. We sought to identify adherence patterns in orthopedic trauma patients discharged from the hospital on VTE prophylaxis as a secondary outcome in a pragmatic randomized controlled trial (A Different Approach to Preventing Thrombosis [ADAPT]) designed to evaluate the safety of aspirin versus LMWH as the primary outcome. Adherence was measured with the Morisky Medication Adherence Scale (MMAS-8).[36–38] We hypothesized that post-discharge adherence with these regimens is moderate, and adherence with an aspirin regimen is greater than with LMWH.

METHODS

This study was conducted as a secondary analysis of patients enrolled in the ADAPT randomized controlled trial as registered on ClinicalTrials.gov (identifier: NCT02774265, IRB: HP-00065750).[39] All adult (age ≥ 18 years) trauma patients presenting to the R Adams Cowley Shock Trauma Center with an operative extremity fracture proximal to the metatarsals/carpals or any pelvic or acetabular fracture requiring VTE prophylaxis were included in the trial. Prisoners, pregnant patients, non–English-speaking patients, and patients on pre-existing anticoagulation or a new oral anticoagulant (not including anti-platelet agents), with an indication for therapeutic anticoagulation or aspirin dose greater than 81 mg daily, or with a contraindication to either prophylaxis regimen were excluded. Patients on or requiring low-dose daily aspirin or other anti-platelets were included in the study because these patients would typically receive VTE chemoprophylaxis in addition to their antiplatelet agents. Eligible patients were approached before the third dose of prophylaxis, and informed consent was obtained for all enrolled patients.

Enrolled patients were randomized at the beginning of their index admission to receive either LMWH 30 mg BID (with allowance for dose adjustment according to BMI) or aspirin 81 mg BID for the remainder of their VTE prophylaxis course. Duration of prophylaxis was determined by the treating physician as indicated by the patient's injuries. Patients requiring post-discharge prophylaxis were to continue receiving the randomized medication unless a medical contraindication occurred. Patients who were discharged on VTE prophylaxis and remained on it at 2-week (10–21 days) study follow-up between April and November 2016 were included in this adherence study. These patients were approached at their scheduled follow-up appointment or called and asked to complete the MMAS-8 based on their experience with the chemoprophylaxis regimen prescribed.

The MMAS-8 is an eight-item patient questionnaire endorsed by the American Medical Association as a tool to identify and prevent medication non-adherence (Fig. 1). The scale is well validated and has been used globally to determine adherence with a wide array of medications for a variety of medical conditions. The tool has proven effective in monitoring adherence with oral medications, subcutaneous injection medications, and anticoagulants in previous studies. Completed MMAS-8 surveys are scored from 0 (lowest adherence) to 8 (highest adherence), and results are used to categorize patients into low, medium, and high adherence groups according to the scale's scoring algorithm. Low corresponds to scores of less than 6, medium to scores of 6 to less than 8, and high to a score of 8.

The sample size calculation was based on pilot data from our institution. We determined that enrollment of 126 patients will give the analysis 80% power to detect an effect size of 0.5 and at a two-sided alpha level of 0.05 on the assumption of mean MMAS-8 scores of 7.5 (SD 1.0) and 7.0 (SD 1.0) in the aspirin and LMWH groups, respectively.

Analyses for the study was performed using both intention-to-treat and as-treated to account for patient medication crossover. The results from both methods of analyses are included in the results. Patient demographics and clinical characteristics were compared by the as-treated regimen group using Student's t tests for normally distributed continuous variables, Wilcoxon rank-sum tests for non-parametric continuous variables, and χ^2 tests for nominal data. Adherence levels using the MMAS-8 survey were compared by regimen group using a χ^2 test, and median scores were compared using a Wilcoxon rank-sum test. Responses to each MMAS-8 question were compared by current medication using χ^2 tests. Possible determinants of low-medium adherence were assessed using a forward stepwise procedure with all available demographic and clinical variables. To enter and remove terms in the model, we used $p < 0.25$ and $p > 0.1$, respectively. Selected variables were then included in a multivariable logistic regression model, and presented as unadjusted and adjusted odds ratios with 95% confidence intervals. Similar stepwise procedures were also used to assess factors associated with medication crossover, stratifying the sample by prophylaxis medication. A p value <0.05 was considered significant. All statistical analyses were performed using JMP Pro version 13 (SAS Institute, Cary, NC).

One hundred fifty patients of 217 patients (70%) enrolled in the ADAPT trial who were prescribed outpatient chemoprophylaxis at the time of study follow-up completed the survey (Fig. 2). Two patients declined participation in the survey at time of contact, and eight were unable to complete the survey because of altered mental status. The remaining 57 patients who were excluded from analysis could not be reached during the study follow-up time period.

This study was approved by the University of Maryland Institutional Review Board.

RESULTS

Eighty patients were randomized to aspirin and 70 patients to LMWH. With a crossover rate of 10% at the 2-week follow-up (6% in aspirin vs. 14% in LMWH, $p = 0.10$), 64 were included in the LMWH regimen and 86 in the aspirin group for as-treated analyses (Fig. 2). The majority of patients were men (65%) with a mean age of 44 years (SD 17.5). The mean Injury Severity Score was 9.9 (SD 5.6) with 97% of patients having lower extremity or pelvis/acetabular injuries and only 19% having upper extremity injuries. One-quarter of patients had multi-limb trauma. Nine percent were uninsured. There were no differences in demographic variables between regimens in as-treated analysis, except more patients on LMWH had their medication administered by a nurse and there was a higher proportion of non–weight-bearing lower extremity patients

©Morisky Medication Adherence Scale (MMAS-8-Item).

You indicated that you are taking medication(s) for your **(name of health condition)**. Individuals have identified several issues regarding their medication-taking behavior, and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your atrial **(name of health condition) medication(s).**

(Please mark your response below)

	No	Yes
1. Do you sometimes forget to take your **(name of health condition)-**related medication(s)?		
2. People sometimes miss taking their medication(s) for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your **(name of health condition)-**related medication(s)?		
3. Have you ever cut back or stopped taking your medication(s) without telling your doctor, because you felt worse when you took it?		
4. When you travel or leave home, do you sometimes forget to bring along your **(name of health condition)-**related medication(s)?		
5. Did you take your **(name of health condition)-**related medication(s) yesterday?		
6. When you feel like your **(name of health condition)-**related condition is under control, do you sometimes stop taking your medication(s)?		
7. Taking medication(s) every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your **(name of health condition)-**related condition treatment plan?		

8. How often do you have difficulty remembering to take all your medication(s)?

(Please circle your answer below)

Never/Rarely

Once in a while

Sometimes

Usually

All the time

Figure 1. Morisky Medication Adherence Scale (MMAS-8). A copy of the MMAS-8 survey administered to patients.

at discharge in the aspirin group (Table 1). In intention-to-treat analysis, there was no significant difference between regimens for these same demographic variables.

Adherence was high overall (mean MMAS 7.2, SD 1.5). Ninety-eight patients (65%) had high, 32 (21%) had medium, and 20 (13%) had low adherence. Adherence for the two regimens was similar (Table 2). However, patients on LMWH were more likely to report feeling hassled by their regimen (23% vs. 9%, $p = 0.02$) (Table 3) in both intention-to-treat and as-treated analyses.

Although there was no difference in adherence between medication regimens in our bivariable unadjusted analysis, a significant difference was observed when adjusting for baseline factors associated with adherence in our as-treated multivariable analysis (Table 4). Patients taking LMWH prophylaxis were two times more likely to have low-medium adherence than patients on aspirin (aOR 2.34, CI 1.06–5.18, $p = 0.04$). In addition, worse adherence was associated with self-administering the prophylaxis (aOR 4.54, CI 1.45–13.61, $p < 0.01$), being of male sex (aOR 2.46, CI 1.10–5.49, $p = 0.03$), and younger age (aOR 0.72 for every 10-year increase, CI 0.57–0.91, $p < 0.01$). We also observed a marginal association with low-medium adherence and being uninsured (aOR 3.03, CI 0.87–13.61, $p = 0.08$).

With respect to crossover, 10 patients randomized to LMWH were on an aspirin regimen at time of study follow-up, and 4 patients randomized to aspirin were on a LMWH regimen (Fig. 2). None of the observed variables from our study were associated with medication crossover in patients taking LMWH. In patients randomized to the aspirin group, each additional day as an inpatient was associated with a 21% increase in the likelihood of medication crossover (OR 1.22, 95% CI 1.04–1.42, $p = 0.01$).

Although patient location at time of survey was not collected, 25% (n = 37; intention-to-treat: 21 in the aspirin arm, 16 in the LMWH arm; as-treated: 22 on aspirin, 15 on LMWH) of patients in the study were discharged to a rehabilitation or outpatient residential center (i.e., skilled nursing facility) based on our hospital trauma registry data for study patients. Twenty patients were discharged to an inpatient acute rehabilitation facility, 13 to a subacute rehab facility, and 4 to a residential facility.

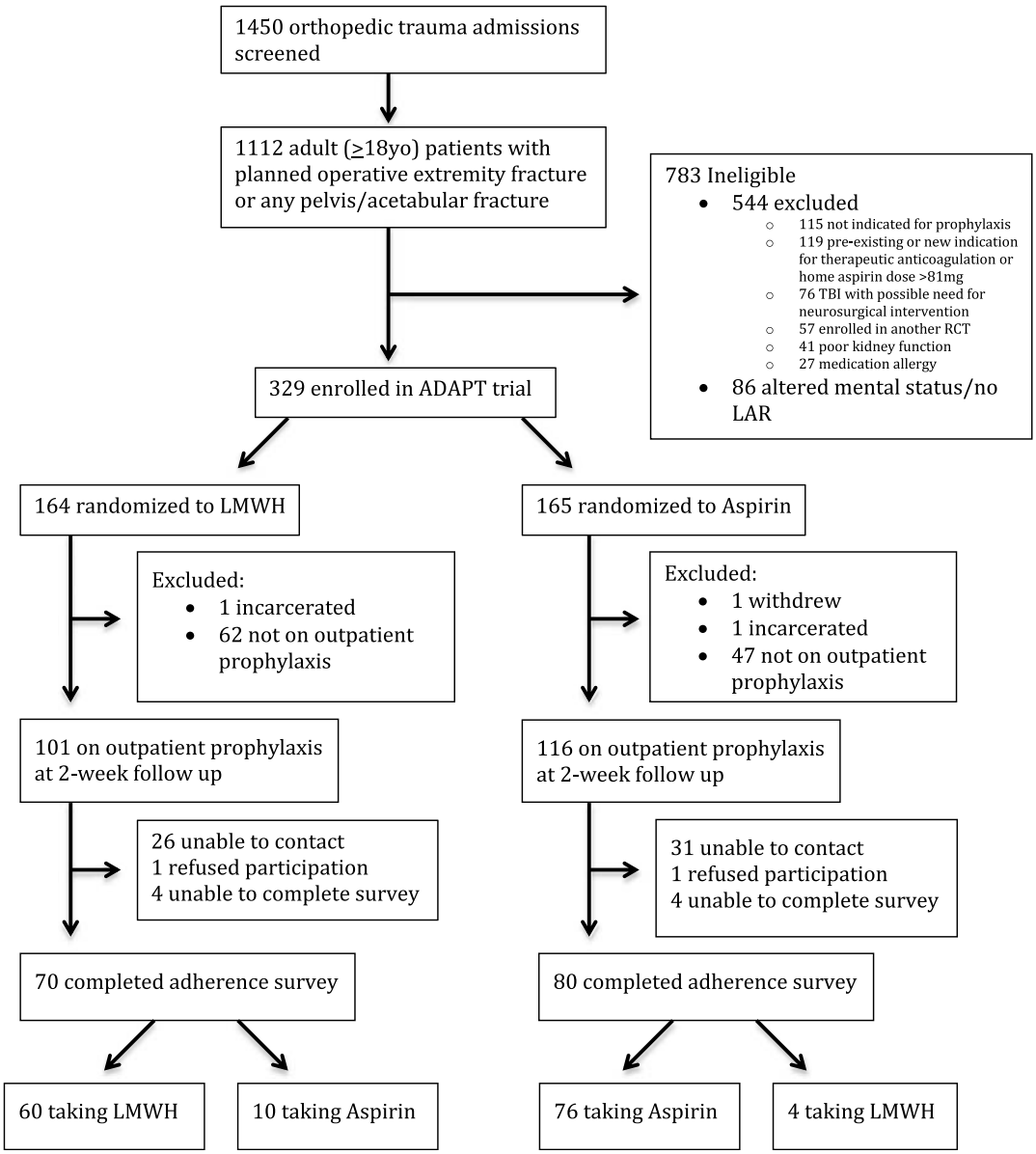

Figure 2. CONSORT diagram. Screening, eligibility, and enrollment statistics for the study. Of note, 12 of the patients not discharged on prophylaxis were excluded from the study because of a new indication for therapeutic anticoagulation before or on discharge. Patients excluded because they were unable to complete the survey did not have the cognitive capacity to answer the questions because of diseases like dementia or sequelae of traumatic brain injury.

There was no difference in disposition by randomization arm (p = 0.2). In a sub-analysis that excluded patients discharged to a rehabilitation center or outpatient residential facility, study results remain nearly identical. The baseline demographics of the two populations were similar and only differed with respect to variables that were already investigated in our analysis. In addition, discharge to a facility was not significantly associated with adherence (p = 0.77) when examined as a covariate for our adherence multivariable model. In our multivariable model of factors associated with low-medium adherence when excluding patients discharged to a facility, the point estimate for the odds ratio associated with treatment regimen increases to 2.32 (95% CI 0.95–5.69, p = 0.06) but is no longer statistically significant likely because of sample size.

DISCUSSION

Orthopedic trauma patients have high VTE risk. Controversy exists as to the optimal chemoprophylaxis regimen in this population. As a result, there is wide variability in prescribed regimens and a need for guidelines to improve patient care.[22] Commonly prescribed regimens include medications given by subcutaneous injection including heparin and LMWH and oral anticoagulants including aspirin and other oral direct and

TABLE 1. Patient Characteristics by VTE Prophylaxis Regimen Received as an Outpatient in As-treated Analysis

	Aspirin (n = 86)	LMWH (n = 64)	*p*
Age (years), mean (SD)	44.7 (18.0)	43.9 (16.8)	0.78
Sex, n (%)			
Male	54 (63)	43 (67)	0.58
Female	32 (37)	21 (33)	
Race, n (%)			
White	56 (65)	40 (63)	0.62
Black	19 (22)	19 (30)	
Hispanic	3 (3)	1 (2)	
Mixed	4 (5)	2 (3)	
Other	4 (5)	1 (2)	
Current smoker, n (%)	33 (38)	24 (38)	0.97
History of VTE, n (%)	6 (7)	3 (5)	0.56
Comorbidities, n (%)			
Peptic ulcer	6 (7)	2 (3)	0.31
Diabetes	5 (6)	6 (10)	0.41
Active cancer	1 (1)	2 (3)	0.41
Immunosuppressed	3 (3)	5 (8)	0.23
Additional medications, n (%)			
Aspirin, daily pre-injury	9 (10)	7 (11)	0.93
Plavix, pre-injury	0 (0)	1 (2)	0.25
OCP/estrogen	2 (2)	1 (2)	0.75
BMI, n (%)			
Underweight (BMI < 18.5)	2 (2)	0 (0)	0.12
Normal weight (18.5–24.9)	27 (32)	19 (30)	
Overweight (25.0–29.9)	30 (35)	15 (23)	
Obese (≥30.0)	26 (61)	30 (47)	
ISS, mean (SD)	9.6 (5.4)	10.2 (5.8)	0.51
Open fracture, n (%)	18 (21)	15 (23)	0.71
Fracture location, n (%)			
Upper extremity	16 (19)	12 (19)	0.98
Lower extremity and pelvis/acetabular	83 (97)	62 (97)	0.90
Multi-limb	19 (22)	19 (30)	0.29
Non-orthopedic injury, n (%)			
Abdomen	4 (5)	3 (5)	0.99
Head†	15 (17)	14 (22)	0.50
Chest	16 (19)	14 (22)	0.62
Vascular	4 (5)	1 (2)	0.30
Hospital length of stay, mean (SD)	5.1 (3.8)	5.8 (4.4)	0.31
Uninsured, n (%)	9 (10)	5 (8)	0.58
Non-weight-bearing lower extremity at discharge*, n (%)	40 (47)	20 (31)	0.04
Prophylaxis administered by health provider, n (%)	13 (15)	24 (38)	<0.01

*Only 7 patients were non-weight-bearing on bilateral lower extremities at discharge.

†Although TBI was not an exclusion criteria for the ADAPT trial, only 4 patients had a brain AIS of 3, which was the highest score in the study.

VTE, venous thromboembolism; LMWH, low molecular weight heparin; BMI, body mass index; ISS, Injury Severity Score.

indirect thrombin inhibitors that are less commonly used in the multitrauma patient population. Given adherence is thought to have a significant impact on efficacy of these regimens and there is a documented patient preference for oral prophylaxis, it is important to understand adherence patterns when creating these guidelines. Our study is the first to our knowledge to evaluate post-discharge adherence with the two most commonly prescribed prophylaxis regimens in this population: aspirin and LMWH.

Our results indicate that orthopedic trauma patients are in general moderate to highly adherent with outpatient VTE prophylaxis. We hypothesized that patients on an aspirin regimen would be more adherent based on studies that have shown a strong preference for oral administration over subcutaneous injection if all other factors were equal.[28–30] Although adherence was similar between regimens in our bivariable analysis, our hypothesis that LMWH is independently associated with lower adherence was confirmed in a multivariable model when adjusting for patient age, sex, health insurance status, and whether the medication is administered by a health provider. In this adjusted model, patients who were on an aspirin regimen where two times more likely to have high adherence than patients on LMWH.

In a discrete choice experiment of patient preferences for VTE chemoprophylaxis conducted in orthopedic trauma patients, patients were willing to change their preference from an oral regimen to a subcutaneous injection regimen with less than a 1% absolute reduction in risk of fatal PE.[30] To participate in the ADAPT trial, study patients were given education on their risk of VTE including potential fatal PE and the need for chemoprophylaxis as part of informed consent. The informed consent process may have created a Hawthorne effect, leading to improved adherence in both groups. More patients on the LMWH regimen responded that they felt hassled about sticking to their treatment plan in the survey, and this finding was supported with our multivariable assessment of the determinants of high adherence. This finding is consistent with the known patient preference for the oral route. Although it is unlikely that adherence with either regimen is completely hassle-free, our results suggest that patient satisfaction may be higher with an oral aspirin regimen if the regimens are equivalent in safety and efficacy, although these points await the results of further research.

In addition to the association with an aspirin regimen and high adherence scores, several other patient factors were associated with having high adherence. Patients with high adherence were on average older. Although reasons for non-adherence were not solicited, younger patients may not take the risk of VTE as seriously or may not be as used to taking regular medications.

Female patients were more likely to have high adherence scores. Other studies have also shown that reasons for non-adherence can vary based on gender, and specific patient beliefs explain a significant portion of variance in adherence patterns.[40–42] Specifically, men have been found to be more likely to report forgetting to take medications and thinking that they had recovered as reasons for non-adherence. These factors may contribute to lower adherence in male patients in our patient population.

Patients with insurance showed a trend toward better rates of high adherence, potentially a result of easier access to medications. Not surprisingly, patients who had a health provider administer their chemoprophylaxis also had better rates of adherence likely caused by greater familiarity with the medications and administration instructions. Most of these patients are in rehabilitation or nursing facilities where prophylaxis administration is part of the protocol. It could be argued that patients discharged

TABLE 2. Bivariate Analysis of Adherence by Regimen Based on MMAS-8 Scores

	Intention-to-Treat			As-Treated		
Adherence	**Aspirin (n = 80)**	**LMWH (n = 70)**	***p***	**Aspirin (n = 86)**	**LMWH (n = 64)**	***p***
Low (n, %)	8 (10.0%)	12 (17.1%)	0.24	9 (10.5%)	11 (17.2%)	0.35
Medium (n, %)	15 (18.8%)	17 (24.3%)		17 (19.8%)	15 (23.4%)	
High (n, %)	57 (71.3%)	41 (58.6%)		60 (69.8%)	38 (59.4%)	
Total MMAS-8 (median, IQR)	8 (7–8)	8 (6.8–8)	0.13	8 (7–8)	8 (6.7–8)	0.20

LMWH, low molecular weight heparin; MMAS, Morisky Medication Adherence Scale.

to a facility where medically trained personnel administer medications are a different population of patients and should be evaluated separately when assessing adherence. However, the goal of this study was to assess whether patients were receiving their medications after discharge from their index trauma admission and these are common discharge destinations for orthopedic trauma patients. Additionally, in our sub-analysis of patients who were not discharged to a rehabilitation or outpatient residential facility, we found nearly identical adherence patterns to our original analysis and discharge to a facility was not a significant covariate when examined as part of our multivariable adherence model. In fact, the point estimate for the odds ratio increased for the association of medication regimen with adherence in patients not discharged to a facility despite no longer being statistically significant. This suggests that the regimen is still an important determinate of adherence in patients who are not at these centers, but that the sub-analysis sample size was too small to reach statistical significance.

Strengths of this study include the randomized prospective design, the pragmatic nature of the study, and the standardized assessment of outcomes. In addition, the large sample size in this complex patient population allows for adequate evaluation of our specific study question.

The study is limited in its generalizability to other health care systems or patient populations because it was only conducted at one center. First, we had a low rate of uninsured patients. With implementation of the Affordable Care Act, many patients who previously were uninsured now have access to free or affordable insurance. As a result, we have seen an increase in the number of insured patients in our center. The uninsured rate in our study is on par with the Center for Disease Control reported rates in Medicaid expansion states at the time of our study.[43] In addition, if a patient is uninsured on presentation for their index trauma admission, our hospital social workers will work to obtain insurance for them during their admission. These factors are likely the reason for our low percentage of uninsured patients and may limit generalizability to other urban trauma centers in places where insurance is not as accessible or where there are not inpatient resources to help uninsured patients obtain insurance. Second, one-quarter of our patients were discharged to a health care facility where medical staff administer the prophylaxis, and rates of discharge to rehabilitation centers may not be the same at other hospitals.

Having insurance and having medical staff administer prophylaxis after discharge were both associated with higher adherence in our study and may partially account for the surprisingly high adherence we found in our study population. As a result, in a purely outpatient population, adherence is likely lower. For these reasons, we controlled for both of these factors in our multivariable analysis.

In addition, 30% of eligible patients did not complete the survey. These patients may have had higher or lower rates of adherence that might affect results. Despite randomization, there

TABLE 3. Bivariate Analysis of Percent of Patients Answering Yes to MMAS-8 Questions by Regimen

	Intention-to-Treat			As-Treated		
MMAS Question	**Aspirin (n, %)**	**LMWH (n, %)**	***p***	**Aspirin (n, %)**	**LMWH (n, %)**	***p***
1	12 (15.0%)	10 (14.3%)	0.90	13 (14.9%)	9 (14.6%)	0.88
2	10 (12.5%)	15 (21.4%)	0.14	12 (13.8%)	13 (20.3%)	0.29
3	0 (0%)	2 (2.9%	0.13	1 (1.2%)	1 (1.56%)	0.83
4	3 (6.1%)	3 (8.1%)	0.72	3 (5.77%)	3 (8.8%)	0.59
5	75 (93.8%)	61 (87.1%)	0.17	80 (93.0%)	56 (41.2%)	0.25
6	3 (5.6%)	1 (2.3%)	0.43	3 (5.4%)	1 (2.44%)	0.48
7	6 (7.5%)	17 (24.3%)	<0.01	8 (9.3%)	15 (23.4%)	0.02
8	Aspirin	LMWH	0.12	Aspirin	LMWH	0.35
Never/rarely	70 (87.5%)	64 (91.4%)		76 (87.4%)	59 (92.2%)	
Once in a while	7 (8.8%)	1 (1.4%)		7 (8.1%)	1 (1.6%)	
Sometimes	2 (2.5%)	3 (4.3%)		2 (2.3%)	3 (4.7%)	
Usually	1 (1.3%)	0 (0%)		1 (1.2%)	0 (0%)	
All the time	0 (0%)	2 (2.9%)		1 (1.2%)	1 (1.6%)	

LMWH, low molecular weight heparin; MMAS, Morisky Medication Adherence Scale.

TABLE 4. Multivariable Regression Analysis of Factors Associated With Low-Medium Adherence in As-treated Analysis (AUCROC = 0.77)

Variable	Level	Low-Medium Adherence (n = 52)	High Adherence (n = 98)	Unadjusted			Adjusted		
				OR	95% CI	*p*	OR	95% CI	*p*
Medication	Aspirin	26 (50%)	26 (50%)		Reference (1.00)			Reference (1.00)	
	LMWH	60 (61%)	38 (39%)	1.51	0.77–2.97	0.23	2.34	1.06–5.18	0.04
Administration, by	Health provider	5 (10%)	32 (33%)		Reference (1.00)			Reference (1.00)	
	Self/family	47 (90%)	66 (67%)	4.56	1.65–12.56	<0.01	4.44	1.45–13.61	<0.01
Sex	Female	22 (42%)	32 (33%)	Reference (1.00)	Reference (1.00)				
	Male	30 (58%)	66 (67%)	1.51	0.76–3.03	0.24	2.46	1.10–5.49	0.03
Age (for every 10-year increase over 18 years)	Mean: 38 (SD 15)	Mean: 48 (SD 18)	0.69	0.55–0.86	<0.01	0.72	0.57–0.91	<0.01	
Insurance status	Private/public	43 (83%)	93 (95%)	Reference (1.00)	Reference (1.00)				
	Uninsured	9 (17%)	5 (5%)	3.89	1.23–12.31	0.02	3.03	0.87–13.61	0.08

LMWH, low molecular weight heparin; OR, odds ratio; CI, confidence interval.

were also some differences between groups that might affect outcomes. Finally, the study was underpowered for some results. For example, differences in crossover may have been significant with a larger sample size.

As expected, there was some crossover between groups because of the pragmatic nature of the study, and this may have affected our results to some degree. However, crossover was examined as a possible covariate in our determinants of high adherence model, but was not found to be independently associated with high adherence. In addition, results from intention-to-treat analysis were similar to the as-treated analysis.

We evaluated outpatient adherence based on the regimen the patient was on at the time of the survey. There was no difference in baseline demographics between the groups except for in who administered the medication and in weight-bearing status. More patients in the LMWH group had their medication administered by a nurse. This may have artificially increased adherence in this group, reducing the difference in adherence seen between regimens, although we attempted to account for this with multivariable modeling. Also, patients on LMWH are typically given teaching on medication administration before discharge whereas patients on aspirin are not. This practice could also potentially lead to higher adherence in the LMWH group. More patients in the aspirin group were non-weight-bearing in a lower extremity on discharge. Given studies have reported the feeling that a patient has recovered as a reason for non-adherence, patients who are non-weight-bearing may have higher adherence as they are less likely to think they have recovered. As a result, the difference in weight-bearing status may improve adherence in the aspirin group over the LMWH group.

Patient medications are often changed from those prescribed at discharge in rehabilitation centers or at outpatient follow-up appointments.[44] This problem is likely exacerbated by the lack of evidence and clear guidelines for the best regimen in this population. Interestingly, more patients randomized to the LMWH regimen had their VTE prophylaxis regimen changed to the non-allocated medication at 2-week follow-up. Reason for crossover was not assessed at this timepoint, but this finding may represent a bias in favor of prophylaxis with aspirin by orthopedic surgeons because our patient population is more likely to have outpatient follow-up with orthopedic surgeons than trauma surgeons during this timeframe. Alternatively, patients may have preferred to switch given the previously documented patient preference for oral medications. On the other hand, increased hospital length of stay was a risk factor for crossover in patients randomized to the aspirin regimen. This may represent a bias in favor of LMWH prophylaxis by trauma surgeons because patients with longer hospital length of stays likely have multiple and more severe injuries including non-orthopedic injuries that require admission to and follow-up with the general surgery trauma service at our hospital. Alternatively, it may be that these patients are more likely to be discharged to rehabilitation where LMWH is standard of care consistent with our finding that patients on LMWH prophylaxis at time of analysis were more likely to have their prophylaxis administered by a nurse.

We think the findings of this study provide important insight into adherence patterns with the regimens that patients actually receive after discharge. The results of our study highlight an overall high adherence but have identified clinically important patient demographic factors when assessing adherence and developing guidelines in this population.

In addition to assessing adherence, it is important to assess efficacy. As a pragmatic trial, the ADAPT trial did not screen for VTE. Patients were only tested for VTE if symptomatic. Patients who were diagnosed with a VTE would require therapeutic anticoagulation and would therefore not be eligible to participate in this adherence sub-study so we are unable to comment on efficacy. It is important recognize that these two medications have differing mechanisms of action: aspirin working as a platelet inhibitor and LMWH working on the thrombin pathway. Quality data comparing efficacy of these two medications with different mechanisms of actions is still needed and will require a large randomized controlled trial. Such a trial could consider using thromboelastography to assess pharmacologic efficacy of aspirin prophylaxis. Our results may be useful when designing trials like those to explore efficacy of these regimens as well as for clinicians who are managing these patients.

AUTHORSHIP

Contributions for each author are listed by name.
B.H.: design, data acquisition, analysis and interpretation of data
R.V.B.: design, data acquisition
N.O.: design, analysis and interpretation of data

G.S.: design, analysis and interpretation of data
T.M.: design, analysis and interpretation of data
R.O.: design, analysis and interpretation of data
H.J.: design, analysis and interpretation of data
P.B.: design, data acquisition
G.R.: data acquisition
D.M.: data acquisition
Y.D.: design, data acquisition
D.M.: data acquisition
D.C.: data acquisition
T.S.: design, analysis and interpretation of data
D.S.: design, analysis and interpretation of data

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DISCLOSURE

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DISCUSSION

Dr. M. Margaret Knudson (San Francisco, California): Good morning, everyone. It is obvious that no medication is likely to be effective in preventing VTE if it's not taken. Thus, I would like to congratulate the authors on addressing a very timely topic.

In a similar study on adherence performed on in-patients at our hospital, we noted that sequential pneumatic compression devices seemed to be effective only in the neurosurgical patients. Apparently, it is hard to get out of those leg squeezing boots if you are in a coma.

While I enjoyed reading this manuscript, I noticed one major flaw in the design. Because Questions 1 through 5 and also Question 8 of the MMAS-8 scale focused on forgetting or altering the prescribed medication or failure to pack it if you leave home, is it really fair to lump the patients who were discharged to home with those who were discharged to a nursing home where, presumably, medical personnel were giving their medication on a regular basis?

I would suggest that the authors repeat the analysis within these two groups and do them individually.

Secondly, although you found that insurance status did not really favor either drug, knowing how expensive enoxaparin is compared with aspirin, what happens when the patient has to renew their prescription as an outpatient? Was this perhaps a reason for the crossover that you described?

And, third, you gave us no information on outcomes, including bleeding complications, with either drug. And we really want to know was there a difference in the DVT and PE rate in the ADAPT trial comparing low-molecular weight heparin to aspirin?

Thank you for the opportunity to discuss this paper and congratulations again to the authors for focusing on the outpatient care of our trauma patients.

Dr. Carl. J. Hauser (Boston, Massachusetts): Carl Hauser, Boston. Two brief questions.

Number 1. I noticed you refer to the drug as "Lovenox" rather than enoxaparin. Does that reflect funding status?

Number 2. You used low-dose 'baby' aspirin at 81 milligrams TWICE a day. The rationale for giving aspirin at a low-dose and a longer interval is that way it's a better inhibitor of thromboxane synthase and less effective at inhibiting prostaglandin synthase. So you're making low-dose aspirin less effective by giving it twice a day. Why not just give regular-dose aspirin once a day or low-dose aspirin once every-other-day? That's the right way to do it.

Dr. Walter L. Biffl (Honolulu, HI): You did not present efficacy data. Are those results being presented somewhere else or do you have them?

In many cases, the drug was administered by a health care provider. Are these patients in skilled nursing facilities? How does that affect the results?

The background of this study was ostensibly based on orthopaedic concerns about bleeding in arthroplasty. Are the patient populations comparable? Arthroplasty patients are ambulatory after surgery but you've got a lot of patients in this study who are non-weight bearing. Are there data suggesting that aspirin is efficacious in trauma patients?

Dr. Elliott R. Haut (Baltimore, Maryland): Hi, Elliott Haut, Baltimore, MD. We have looked at a lot of patient education and clearly for patients who don't realize how important these medications are they've been less compliant.

And I'm curious if you've given any standardized education to the patients to tell them how important this is because of these medications? And is that different between the injectable medications versus the oral meds?

Dr. Kevin M. Schuster (New Haven, Connecticut): Nicely presented. I'm curious about the bias introduced by the enrollment process and having a patient who is going to consent to stabbing themselves in the leg twice a day with enoxaparin. Is that group self-selecting and different from the overall population? Do you have any data on the group that refused to participate? And what are the differences?

Dr. Bryce E. Haac (Baltimore, Maryland): Thank you, Dr. Knudson, for reviewing our work and for providing your questions in advance. These are all very good questions.

First with respect to including patients in SNF, rehab centers and the timing that we chose for our study: this is a small study, and we wanted to maximize our power.

We felt that at the two-week time point we would get the maximum number of patients who were still on prophylaxis and that this would be descriptive of overall what patients are getting after they leave the hospital for the index admission, which was the goal of our study. However, I do agree that this is an important thing to look at and we will look at that.

With regards to insurance status, I'm not sure that we were adequately powered necessarily to detect a difference in insurance status with respect to adherence. There was a trend toward it so I agree, this could be a barrier to adherence in the outpatient setting. However, I don't think it was a reason for crossover in our study because patients are usually discharged with up to three weeks of prophylaxis from our center which would extend beyond the study timeframe. We can get the prescription approved

prior to discharge from the hospital, so within the study timeframe patients should not have had to renew their prescription.

Finally, with respect to efficacy, which a few people asked about, and bleeding and wound complication results, we are also anxiously awaiting these results. The ADAPT trial follow-up was a three-month period and so we are currently conducting analysis of those results and hope to be able to present it soon. It is not scheduled to be presented anywhere yet.

For health care providers administering medications, yes, these patients, we assume, are mostly in skilled nursing centers or in rehab centers.

And with respect to the arthroplasty population, we agree that this is a different patient population. These patients are ambulatory after their surgery. And they are actually informed ahead of time that they are going to need aggressive physical therapy; whereas, the trauma patients are presenting in an emergency setting and they are uneducated about these things beforehand and may not want to be as cooperative.

In terms of patient education, I do think that the informed consent process is one of the reasons that we may have had such high adherence in our study compared to what you might expect in this population. As part of that process they were told about the purpose of both of the medications and the results of what can happen if you are not given these medications, including risk of fatal PE. And in previous studies that we have conducted at our center we have found that patients find preventing fatal PE to be an important thing.

And, finally, talking about bias with enrollment, why were patients refusing, some patients did refuse because they just didn't want to be part of a research study.

In general, part of our center's protocol is to give patients low-molecular weight heparin as the standard prophylaxis.

So patients who were inclined to want to take aspirin, in general, were more likely to want to consent to the study because they would have a 50 percent chance of taking a pill instead of an injection.

However, that doesn't hold true for all patients. As we know, with this patient population sometimes people just don't want to be in a research study.

And sorry, I forgot to address funding status– this was an unfunded trial. We used the generic enoxaparin in our study. Regarding the chosen dosing of medications, the enoxaparin dosing is standard, but there are a variety of dosing regimens used for aspirin. We chose BID dosing to have the same frequency of dosing in both arms. We chose 81mg BID because this is most similar to the 160mg daily dose used in the Pulmonary Embolism Prevention (PEP) trial which was conducted in patients with hip fractures and is one of the few available studies examining the use of Aspirin after orthopedic trauma.