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Association of sex and aspirin use with postoperative bleeding in patients with lower extremity long bone fractures

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ABSTRACT

Objective The perioperative management of patients on antiplatelet drugs is a rising challenge in orthopedic trauma because antiplatelet drugs are frequently encountered and carry an increased risk of hemorrhagic consequences. The study objective was to examine the effect of aspirin on bleeding outcomes for patients with lower extremity fractures.

Methods This retrospective study included patients requiring surgical fixation of traumatic hip, femur, and tibia fractures from January 1, 2018, to March 1, 2020. Patients were excluded if they had a significant head injury, were on chronic anticoagulant therapy, or they did not receive venous thromboembolism chemoprophylaxis. Comparisons between aspirin users (patients on aspirin therapy preinjury) and non-aspirin users were examined using χ^2 tests, Cochran-Mantel-Haenszel tests, and multivariate logistic regression. The primary outcome was an overt, actionable bleed (eg, blood transfusion for surgical site hemorrhage) within 24 hours postoperative.

Results There were 864 patients with lower extremity long bone fractures and 24% were aspirin users. The incidence of postoperative bleeding was 8.8% and significantly differed for patients taking aspirin versus not (13.6% vs 7.3%, p=0.01). However, biological sex at birth (M/F) was a significant effect modifier (interaction p=0.04). Among women, there were significantly more postoperative bleeds for aspirin users (17.8% aspirin vs 7.4% no aspirin, adjusted OR (AOR): 2.48 (1.28–4.81), p=0.01). Among men, there were similar postoperative bleeding events by aspirin use (5.6% aspirin vs 7.2% no aspirin, AOR: 0.50 (0.14–1.82), p=0.30). Postoperative hemoglobin values <8 g/dL were more frequent among female aspirin users (21.5% aspirin vs 12.5% no aspirin, p=0.01), but this association was not observed in men (p=0.43).

Conclusion Women taking aspirin who suffer lower extremity fractures have greater than twofold greater odds of a postoperative bleeding event. These findings suggest adequate perioperative planning to ensure blood availability, and increased awareness to monitor closely for hemorrhage in the 24-hour postoperative window for women taking aspirin preinjury.

Level of evidence IV

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The risk of postoperative bleeding differs for aspirin as compared with clopidogrel and other antiplatelet and anticoagulant agents.

WHAT THIS STUDY ADDS

⇒ This study of 864 patients with femur, tibia, or hip fractures identified significantly more postoperative bleeding events for patients taking aspirin preinjury. However, sex was a significant effect modifier, and aspirin use increased odds of a postoperative bleed in women only, by greater than twofold, whereas there was no association among men.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ There is a significant knowledge gap regarding sex differences in platelet biology and response to therapeutics, especially in the setting of traumatic injury. These findings suggest adequate perioperative planning to ensure blood availability, and increased awareness to monitor closely for hemorrhage in the 24-hour postoperative window, for women taking aspirin preinjury.

BACKGROUND

With an aging population, it is increasingly common for the trauma and orthopedic surgeon to encounter patients on antithrombotic therapy who necessitate an urgent surgical intervention of lower extremity injuries.[1 2] Among patients sustaining a hip fracture, 30–40% are taking an anticoagulant or antiplatelet medication.[3] In the USA, as many as 29 million adults >40 years old and nearly half of adults >70 years old use aspirin for primary prevention of cardiovascular disease (CVD).[4]

The most significant side effect of antiplatelet therapy, which includes antiplatelet agents' aspirin and clopidogrel, is an increased risk of bleeding. Even very low doses of aspirin have been shown to increase bleeding risk.[5] However, there are differences in bleeding risk for aspirin and clopidogrel, and these differences are reflected in guidelines on perioperative administration of antiplatelets: aspirin continuation is suggested, whereas clopidogrel should be stopped 5 days before surgery.[6]

Among surgically managed hip or femur fractures, clopidogrel has been shown to result in an increase in blood transfusions and blood loss,[7 8] whereas aspirin use has not consistently shown an association with bleeding outcomes. Compared with patients not taking aspirin, aspirin users had a greater likelihood of receiving a blood transfusion postoperatively in one study,[9] no difference

in blood loss or transfusion requirements in one study,[10] and greater blood loss and need for transfusion before, but not after, propensity matching.[11]

Lower extremity fractures are also in the highest-risk group for developing a venous thromboembolism (VTE) and current clinical practice is to administer thromboprophylactic agents within 24 hours of injury.[12] Anticoagulants (low molecular weight heparin (LMWH), unfractionated heparin, coumadin) and antiplatelet agents are used as VTE chemoprophylaxis; there is debate regarding the superiority of LMWH to antiplatelet agents for VTE chemoprophylaxis.[12–14] Trauma patients on routine antiplatelet therapy are therefore frequently exposed to additional antithrombotic agents, leading to debate regarding whether there is an increased risk for bleeding complications.

In a prior study conducted by our group which identified no association between timing of VTE chemoprophylaxis and development of clinically significant bleeding events, we also reported a higher incidence of preinjury antiplatelet therapy for patients who developed a postoperative bleed compared with patients that did not have a clinically significant bleeding event (37.5% vs 25.1% respectively, p=0.03).[15] However, all antiplatelet agents were examined together, and the risk of bleeding differs for aspirin, the most commonly prescribed antiplatelet agent, and clopidogrel and other antiplatelet agents.[6]

The objective of this study was to examine the association between preinjury aspirin therapy and development of a clinically significant postoperative bleed for patients requiring surgical fixation of lower extremity long bone fractures.

METHODS

Design and aims

This study was performed as a secondary analysis of a previously published multicenter observational retrospective cohort study.[15] Institutional Review Board approval was obtained from each participating facility with a waiver of informed consent.

The primary study aim was to analyze whether the incidence of clinically significant postoperative bleeding differs by aspirin use. We hypothesized that aspirin users would have a greater incidence of bleeding events than non-aspirin users.

Secondary aims were as follows: (1) Identify whether there are certain populations or subgroups who are at increased risk of clinically significant postoperative bleeding by aspirin use. (2) Examine whether the timing of VTE chemoprophylaxis influences the association between clinically significant postoperative bleeding and aspirin use. (3) Examine whether secondary clinical outcomes differ by aspirin use.

Setting, population

There were five participating Level I trauma centers in the USA. Patients were identified from the trauma registries at each participating facility using the following criteria: index admission between January 1, 2018, and March 1, 2020; femur, hip, or tibia fracture; surgical repair of the femur, hip, or tibia; age ≥18 years; receipt of VTE chemoprophylaxis; no moderate or severe head or spinal injury as identified by Abbreviated Injury Scale score >1 to the head or spine regions; no chronic anticoagulation prior to admission (n=877). Patients were manually excluded during chart review or analysis if they were taking an antiplatelet agent other than aspirin, or their antiplatelet status was unknown (n=13).

Variables

Variables were collected from the trauma registries and electronic health records (EHR) at each participating site by dedicated trauma registrars and clinical study coordinators. The primary independent variable was preinjury aspirin use (yes vs no). Aspirin therapy was ascertained from the EHR from admission history and physical or physicians' notes. Clinical study coordinators were not blinded to aspirin status when collecting bleeding events; however, antiplatelet use was originally collected as a study covariate only.

The primary outcome of interest was the incidence (%) of a clinically significant postoperative bleeding event, which was abstracted from the EHR and defined a priori as an overt hemorrhage (eg, palpable hematomas at the surgical site or extensive hemorrhage on the bandage) that were actionable (ie, blood transfusion associated with a decrease in hemoglobin level of at least 2 g/dL; blood transfusion for intraoperative bleeding based on hemodynamic changes and communication with the surgeon regarding ongoing blood loss; wound dehiscence or compartment syndrome; return to the operating room for bleeding control or hematoma evacuation or wound management secondary to bleeding). The postoperative period was defined from surgery initiation to 24 hours after surgery completion and captured bleeding events related to the long bone repair surgery.

Secondary outcomes included clinically significant bleeding events within 48 hours postoperative, total intraoperative blood loss (mL, estimated visually), initial and postoperative hemoglobin values, in-hospital mortality, and symptomatic VTE during the acute hospitalization period. Mortality was collected from the trauma registries and all other secondary outcomes were abstracted from the EHR.

Covariates that were collected from the trauma registries included patient demographics (age, sex, race, comorbidities), cause of injury, injury severity score (ISS), emergency department (ED) systolic blood pressure, ED Glasgow Coma Scale score (GCS), open fracture status and grade. Comorbidities with ≥10% incidence were analyzed. Covariates that were abstracted from the EHR included timing of VTE chemoprophylaxis in relation to the long bone surgery, time to surgery, time in surgery, and non-orthopedic surgical procedures. For timing of VTE chemoprophylaxis, patients were categorized into three groups: (1) initiated preoperatively; (2) initiated within 12 hours postoperatively; (3) initiated>12 hours postoperatively.

Statistical analysis

Analyses were performed with SAS (SAS institute, Cary, North Carolina, USA). A significance level of p=0.05 was used. There was no imputation. This secondary analysis was not powered a priori; our primary aim was 80% powered a posteriori with 738 patients. The initial study's primary aim examining the association between VTE chemoprophylaxis timing and postoperative bleeding events was 80% powered a priori with 612 patients.

Univariate comparisons between aspirin status, postoperative bleeding, and study covariates were made using χ^2 tests and Wilcoxon rank-sum tests. Cochran-Mantel-Henzael and Breslow day tests were used to identify any significant interaction between study covariates, aspirin status, and postoperative bleeding events.

Wilcoxon rank-sum tests were used to evaluate secondary continuous outcomes of median (IQR) intraoperative blood loss and median (IQR) change in hemoglobin (postoperative – initial values). X^2 tests were used to evaluate secondary categorical outcomes (%) of postoperative bleeding within 48 hours,

Table 1 Differences in covariates by use of preinjury aspirin therapy

Covariate	Aspirin	No aspirin	P value
(%) or median (IQR)	N=206	n=658	
Demographics			
Age ≥70 years	160 (77.7)	295 (44.8)	**<0.001**
Male sex	71 (34.5)	292 (44.4)	**0.01**
White race	194 (94.2)	557 (84.7)	**<0.001**
Comorbidities			
Hypertension	137 (66.5)	230 (35.0)	**<0.001**
Smoker	13 (6.3)	118 (17.9)	**<0.001**
Dementia	44 (21.4)	72 (10.9)	**<0.001**
Functionally dependent	62 (30.1)	102 (15.5)	**<0.001**
Diabetes	47 (22.8)	80 (12.2)	**<0.001**
Advance directive	50 (24.3)	81 (12.3)	**<0.001**
Injury characteristics			
Fall cause of injury	190 (92.2)	442 (67.2)	**<0.001**
ISS >10	2 (1.0)	64 (9.7)	**<0.001**
ED Glasgow coma score 15	163 (84.5)	573 (88.8)	0.10
ED SBP <90 mm Hg	0.0	11 (1.7)	0.08
ED SBP >160 mm Hg	77 (37.4)	161 (24.5)	**<0.001**
Open fracture	8 (3.9)	62 (9.4)	**0.01**
Procedure information			
Long bone orthopedic procedure			**0.007**
Tibia	39 (18.9)	193 (29.3)	
Femur	61 (29.6)	204 (31.0)	
Hip	106 (51.5)	267 (40.6)	
Arrival to long bone surgery, h	19 (13–24)	18 (10–23)	**0.01**
Total time in surgery, h	0.8 (0.5–1.3)	1.1 (0.6–1.8)	**<0.001**
Non-orthopedic procedure	4 (1.9)	13 (2.0)	1.0
VTE chemoprophylaxis timing			0.60
Initiated preoperative	67 (32.5)	194 (29.5)	
Initiated within 12 hours postoperative	32 (15.5)	118 (17.9)	
Initiated >12 hours postoperative	107 (51.9)	346 (52.6)	0.40
Arrival to VTE prophylaxis, h	27 (9–41)	25 (10–39)	

Bolding denotes statistical significance.
ED, emergency department; h, hours; ISS, injury severity score; SBP, systolic blood pressure; VTE, venous thromboembolism.

mortality, symptomatic VTE, initial and postoperative hemoglobin values <12 g/dL (women) or <13.5 g/dL (men), low postoperative hemoglobin <8 g/dL, and intraoperative blood loss >250 mL.

Multivariate logistic regression was used to identify variables that were independently associated with the primary outcome of developing a postoperative bleeding event within 24 hours. Covariates that were significantly associated with either the exposure (aspirin use) or outcome (postoperative bleeding) in univariate analyses at the p<0.05 level were adjusted for in the regression model. Collinearity between model covariates was assessed with Spearman rank correlation and defined as Rs >0.40. Age and fall cause of injury were collinear and fall was not adjusted for, as 96% of patients ≥70 years old were injured by a fall (Rs=0.55). ED GCS (15 or <15) was collinear with dementia status and ED GCS was not adjusted in the model, as nearly all patients (95%) without dementia had an ED GCS 15 (Rs=0.53). The multivariate logistic regression models included adjustment for age, sex, race, fracture diagnosis (femur, hip, tibia), open fracture status, ISS, time from arrival to surgery (hours), total time in surgery (hours), ED hypertension, and all examined comorbidities.

RESULTS

There were 864 patients with surgically managed lower extremity long bone fractures. Long bone fractures included tibia (26.3%), femur (30.7%) and hip (43.1%). The median (IQR) ISS was 9 (9–10) and the median age of patients was 71 (52–84).

Aspirin therapy was prevalent at 23.8% (n=206). Compared with patients not taking aspirin, aspirin users were more likely to be older (≥70 years: 77.7% vs 44.8%, p<0.001), white (94.2% vs 84.7%, p<0.001), women (65.5% vs 55.6%, p=0.01), with more comorbidities (p<0.05 for all examined comorbidities), to be injured in a fall (92.2% vs 67.2%, p<0.001), to have a hip fracture (51.5% vs 40.6%, p=0.007), and to be hypertensive in the ED (systolic blood pressure (SBP) >160 mm Hg, 37.4% vs 24.5%, p<0.001); they were less likely to have an ISS >10 (1.0% vs 9.7%, p<0.001) and less likely to have an open fracture (3.9% vs 9.4%, p=0.01), table 1. Aspirin users were also

Table 2 Differences in covariates by clinically significant postoperative bleed

Covariate	Bleed	No bleed	P value
(%) or median (IQR)	N=76	n=788	
Demographics			
Age ≥70	56 (73.7)	399 (50.6)	**<0.001**
Male sex	25 (32.9)	338 (42.9)	0.09
White race	67 (88.2)	684 (86.8)	0.74
Preinjury aspirin use	28 (36.8)	178 (22.6)	**0.005**
Comorbidities			
Hypertension	46 (60.5)	321 (40.7)	**<0.001**
Smoker	6 (7.9)	125 (15.9)	0.06
Dementia	14 (18.4)	102 (12.9)	0.18
Functionally dependent	25 (32.9)	139 (17.6)	**0.001**
Diabetes	12 (15.8)	115 (14.6)	0.78
Advance directive	21 (27.6)	110 (14.0)	**0.002**
Injury characteristics			
Fall cause of injury	64 (84.2)	568 (72.1)	**0.02**
ISS >10	13 (17.1)	53 (6.7)	**0.001**
ED Glasgow coma score 15	52 (70.3)	684 (89.5)	**<0.001**
ED SBP <90 mm Hg	2 (2.7)	9 (1.2)	0.25
ED SBP >160 mm Hg	24 (31.6)	214 (27.2)	0.41
Open fracture	5 (6.8)	65 (8.3)	0.61
Procedure information			
Long bone orthopedic procedure			**<0.001**
Tibia	8 (10.5)	224 (28.4)	
Femur	38 (50.0)	227 (28.8)	
Hip	30 (39.5)	343 (43.5)	
Arrival to long bone surgery, h	17.9 (13-24)	17.9 (11-24)	0.39
Total time in surgery, h	1.3 (0.7–2.2)	0.9 (0.6–1.7)	**0.05**
Non-orthopedic procedure	2 (2.6)	15 (1.9)	0.66
VTE chemoprophylaxis timing			0.11
Initiated preoperative	28 (36.8)	233 (29.6)	0.49
Initiated within 12 hours postoperative	7 (9.2)	143 (18.2)	
Initiated >12 hours postoperative	41 (54.0)	412 (52.3)	
Arrival to VTE prophylaxis, h	27.8 (8-41)	25.8 (11-39)	

Bolding denotes statistical significance.
ED, emergency department; h, hours; ISS, injury severity score; SBP, systolic blood pressure; VTE, venous thromboembolism.

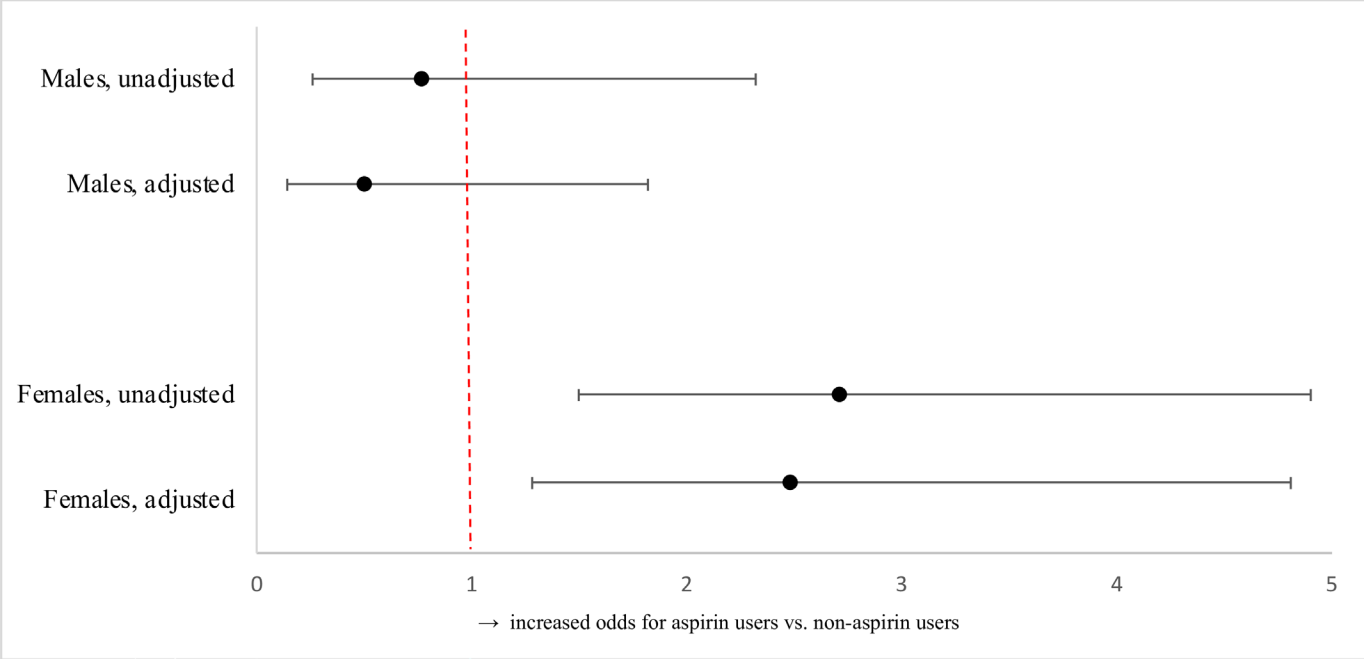

Figure 1 Odds of postoperative bleeding event within 24 hours of surgery for aspirin users versus non-aspirin users, controlling for sex. Test for interaction between sex and aspirin use on the risk of postoperative bleed: p=0.043 (unadjusted), p=0.039 (adjusted).

more likely to have a longer median time from arrival to surgery (19.1 hours vs 17.6 hours, p=0.02) and a shorter median total time in surgery (0.8 hours vs 1.1 hours, p<0.001) than non-aspirin users. Aspirin use was not associated with timing of VTE chemoprophylaxis (p=0.60), with the majority of aspirin users and non-users initiating prophylaxis more than 12 hours postoperatively (51.9% vs 52.6%). The median time to initiate VTE chemoprophylaxis from arrival was similar by aspirin use (27.3 hours aspirin vs 25.4 hours no aspirin, p=0.40).

Postoperative bleeding

The incidence of a postoperative bleed within 24 hours was 8.8% (n=76). The majority (81.3%) of postoperative bleeds were surgical site hemorrhage requiring a blood transfusion, followed by oozing hemorrhage requiring blood transfusion (11.4%), intraoperative hemorrhage requiring blood transfusion (6.5%), and extremity compartment syndrome (n=1, 0.8%).

Compared with patients who did not develop a postoperative bleed, patients with postoperative bleeding were more likely to be aspirin users (36.8% vs 22.6%, p=0.005), more likely to be older (age ≥70, 73.7% vs 50.6%, p=0.001), to be injured in a fall (84.2% vs 72.1%, p-0.02), to have comorbidities of hypertension, functional dependence and an advance directive, to have an ISS >10 (17.1% vs 6.7%, p=0.001), and to have a femur fracture (50.0% vs 28.8%, p<0.001), but they were less likely have a GCS 15 (70.3% vs 89.5%), table 2. There were no differences by postoperative bleed status in sex, race, ED SBP, open fracture status, and non-orthopedic surgical procedure status. There were also no differences in bleeding incidence by timing of VTE chemoprophylaxis, supporting our prior findings that the timing of VTE chemoprophylaxis was not associated with development of a postoperative bleed. There was no interaction between timing of VTE chemoprophylaxis, aspirin use and postoperative bleeding (Breslow day test, p=0.27).

The incidence of a postoperative bleed was significantly greater for aspirin users than those who were not taking aspirin (13.6% vs 7.3%), with 2-fold increased odds for aspirin users vs non-users (OR: 2.0 (1.2–3.3), p=0.005. However, we identified a statistically significant interaction between patient sex (biological sex at birth), aspirin use, and postoperative bleeding (Breslow day test, p=0.04), figure 1.

Postoperative bleeding by sex

For women who were taking aspirin, 17.8% developed postoperative bleeding, compared with 7.4% of women who were non-aspirin users (figure 2). This difference was greater than twofold increased odds of a postoperative bleed for female aspirin users than female non-aspirin users, before adjustment (OR: 2.7 (1.5–4.9), p<0.001). The population attributable risk, or the incidence of postoperative bleeds in women that can be attributed to aspirin use, was 27.5%; In other words, 14 of 51 postoperative bleeds can be attributed to aspirin use.[16]

On the contrary, for men there was no observed association between postoperative bleeds and aspirin use (figures 1 and 2). The incidence of a postoperative bleed was 5.6% for male aspirin users and 7.2% for male non-aspirin users (OR=0.77, p=0.64).

In the adjusted model, the interaction term between aspirin use and sex remained significant, p=0.039. The final regression models for postoperative bleed were stratified by sex (table 3).

For women, aspirin use was associated with 2.5-fold increased odds of postoperative bleed, after adjustment (AOR: 2.5 (1.3–4.8), p=0.01). Additionally for women, a femur fracture diagnosis was associated with an increased odds of postoperative bleed as compared with a hip fracture (adjusted OR (AOR): 2.8 (1.4–5.7) p<0.001). No other covariate was independently associated with an increased odds of postoperative bleed in women (table 3).

Among men, aspirin use was not associated with the odds of postoperative bleed, after adjustment (AOR: 0.5 (0.1–1.8), p=0.30). Independent associations with a postoperative bleed for men were age ≥70 years (AOR: 3.5 (1.0–11.8, p=0.05), ISS >10 vs ≤10 (AOR: 11.6 (2.7–49.5), p=0.001), comorbidity of functional dependence (AOR: 8.8 (2.7–29.2), p<0.001), and longer time from arrival to surgery (AOR: 1.18 (1.0–1.3),

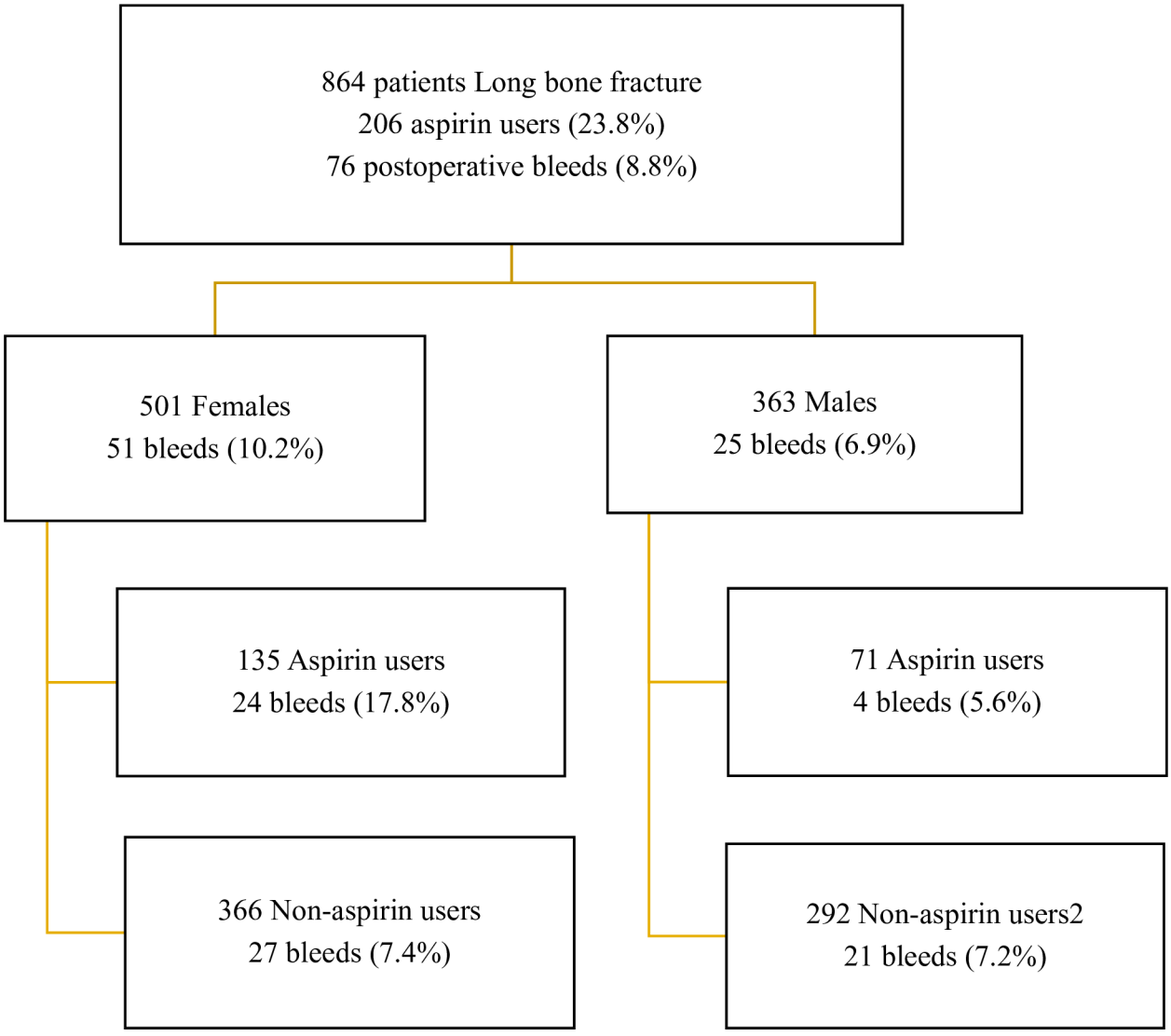

Figure 2 Incidence of postoperative bleeding events within 24 hours of surgery, by sex and preinjury aspirin use.

p=0.02) equating to 18% increased odds for each 6-hour delay to surgery (table 3).

Secondary outcomes

Secondary outcomes are shown in table 4, stratified by sex. For women, aspirin use was associated with a greater likelihood of a low hemoglobin <12.0 g/dL, initially (36.1% aspirin vs 24.3% no aspirin, p=0.01) and postoperatively (87.7% aspirin vs 79.9% no aspirin, p=0.05), and a postoperative hemoglobin <8 g/dL (21.5% aspirin vs 12.5% no aspirin, p=0.01). Bleeding events within 48 hours postoperative were also greater for female aspirin users than females not taking aspirin (32.6% vs 13.7%, p<0.001). Other clinical outcomes did not differ by aspirin use in women. For men, preinjury aspirin use was associated with a greater likelihood of a low initial hemoglobin <13.5 g/dL (47.9% aspirin vs 32.2% no aspirin, p=0.01), but there were no other differences in secondary outcomes, including postoperative bleeding within 48 hours.

Finally, we examined the timing of VTE chemoprophylaxis on the incidence of a postoperative bleed by sex, to analyze whether there is a favored time to initiate prophylaxis (online supplemental table S1). The overall rate of postoperative bleeding among aspirin users was 13.6% and did not differ by timing of VTE chemoprophylaxis, overall or for men or women. The overall rate of postoperative bleed among non-aspirin users was 7.3%, and did not differ by timing of VTE chemoprophylaxis, overall or for men or women.

DISCUSSION

We sought to analyze whether preinjury aspirin use was associated with a greater incidence of postoperative bleeding events in patients with lower extremity long bone fractures. Prior to adjustment, aspirin therapy was associated with a significant increase in postoperative bleeding events. However, a major finding of this study was that biological sex significantly modified the relationship between aspirin use and development of a postoperative bleed. Female aspirin users had 2.5-fold increased odds of a postoperative bleed compared with female non-aspirin users. Whereas for men, there was no association between aspirin use and postoperative bleeding.

These findings suggest the presence of sex-specific platelet biology and response to antithrombotic therapies after traumatic injury. Others have described some of the factors contributing to sex-related differences in platelet function, such as platelet aggregation and reactivity, platelet activation and the inflammatory response, and aspirin metabolism and aspirin

Table 3 Multivariate logistic regression model of hemorrhage within 24 hours postoperative

Effect	Women (n=501): OR (95% CI) c-statistic: 0.77	Men (n=363): OR (95% CI) c-statistic: 0.88
Aspirin vs no aspirin	**2.48 (1.28 to 4.81)**	0.50 (0.14 to 1.82)
Femur vs hip fracture	**2.84 (1.43 to 5.65)**	0.90 (0.30 to 2.73)
Tibia vs hip fracture	0.63 (0.21 to 1.91)	0.13 (0.01 to 1.29)
Open fracture (vs closed)	1.38 (0.31 to 6.27)	2.18 (0.32 to 14.77)
Injury severity score >10 vs ≤10	2.62 (0.71 to 9.77)	**11.65 (2.74 to 49.48)**
Age ≥70 vs < 70	2.25 (0.84 to 6.01)	**3.48 (1.02 to 11.82)**
White race vs other	0.86 (0.28 to 2.67)	1.26 (0.35 to 4.54)
Hypertension comorbidity vs not	1.42 (0.72 to 2.79)	2.42 (0.83 to 7.03)
Functionally dependent vs independent	0.98 (0.48 to 2.00)	**8.80 (2.66 to 29.18)**
Smoker vs non-smoker	0.99 (0.25 to 3.88)	0.88 (0.22 to 3.57)
Dementia vs not	0.97 (0.42 to 2.23)	0.40 (0.08 to 2.11)
Diabetes vs not	1.30 (0.55 to 3.10)	0.56 (0.13 to 2.38)
ADLC present vs absent	2.00 (0.95 to 4.21)	0.93 (0.20 to 4.28)
Time from arrival to surgery (per 6 hours)	1.00 (0.90 to 1.10)	**1.18 (1.03 to 1.34)**
Total time in surgery (per 30 min)	1.10 (0.98 to 1.23)	1.05 (0.96 to 1.16)
ED hypertension >160 mm Hg	0.75 (0.38 to 1.51)	1.81 (0.57 to 5.73)

Bolding denotes statistical significance.
ADLC, advance directive limiting care; ED, emergency department.

"resistance".[17–19] Hormones also play a role in platelet biology and inflammation, potentially influencing the risk of thrombosis. However, the effects of hormones on homeostasis are complex and sometimes conflicting. Estrogen can affect the anticoagulant system by decreasing the levels of natural anticoagulants such as protein S and antithrombin III,[20] and estrogen has also been shown to increase the production of certain clotting factors, such as von Willebrand factor and fibrinogen.[21] Testosterone has been found to inhibit platelet aggregation by reducing the expression of platelet surface receptors involved in platelet activation, such as P-selectin and glycoprotein IIb/IIIa,[22] whereas estrogen can enhance platelet aggregation.[20] It is unclear how hormones might relate to platelet function and bleeding risk in our population, where the median age was 70. Further research is needed to fully understand the relationship between hormones and platelet function, including mechanism and clinical implications.

Current antiplatelet guidelines are based on data derived primarily from men, as women are generally under-represented in trials[23]; for instance, in the ARRIVE trial fewer than 30% of enrolled patients were women.[24] It is imperative to understand the sex-specific implications that delve into the biology of platelet function and response to therapies to optimize antithrombotic strategies. It may also be beneficial to evaluate sex-specific risk-benefit ratios of antiplatelet agents in settings where there is an increased risk of bleeding, such as in acute care surgery and traumatic injury.

In the orthopedic trauma setting there have been few studies directly examining postoperative bleeding by aspirin use, and even fewer studies evaluated sex-specific differences. Kragh *et al* examined perioperative use of aspirin during hip fracture surgery and reported greater intraoperative blood loss and higher 1-year mortality for patients receiving aspirin perioperatively.[25] The investigators also examined sex-specific differences in mortality, reporting a higher 1-year mortality for patients taking aspirin versus not on aspirin, for women (32% vs 9%) and marginally higher 1-year mortality for men (25% vs 14%), although the interaction term was not significant (p=0.25). Akaoka *et al*, examined risk factors for perioperative decreases in hemoglobin for patients with proximal femoral fractures, and identified anticoagulant and antiplatelet agents were significantly associated

Table 4 Secondary outcomes by biological sex

	Women (n=501)			Men (n=363)		
Outcome	Aspirin (n=135)	No aspirin (n=366)	P value	Aspirin (n=71)	No Aspirin (n=292)	P value
In-hospital mortality (%)	0 (0)	3 (0.8)	0.57	2 (2.8)	2 (0.7)	0.17
Symptomatic VTE (%)	1 (0.7)	1 (0.3)	0.47	1 (1.4)	5 (1.7)	1.0
Bleed within 48 hours postop (%)	44 (32.6)	50 (13.7)	**<0.001**	10 (14.1)	30 (10.3)	0.36
Hemoglobin (Hgb), g/dL						
Low initial Hgb (%)*	48 (36.1)	88 (24.3)	**0.01**	33 (47.9)	94 (32.2)	**0.01**
Low postop Hgb (%)*	114 (87.7)	275 (79.9)	**0.05**	63 (92.7)	224 (83.3)	0.05
Postop Hgb <8 (%)	28 (21.5)	43 (12.5)	**0.01**	6 (8.8)	17 (6.3)	0.43
Median change in Hgb†	−2.9 (−4.1 to −1.9)	−2.8 (−3.8 to −1.6)	0.47	−2.4 (−3.8 to −1.5)	−2.5 (−3.7 to −1.4)	0.86
Median intraop blood loss (mL)	50 (25–100)	50 (25–100)	0.59	50 (25–100)	55 (25–150)	0.24
Intraop blood loss >250 mL (%)	11 (8.2)	23 (6.3)	0.46	7 (9.9)	41 (14.0)	0.19

Bolding denotes statistical significance.
*<12.0, women; <13.5, men.
†Change: postoperative - initial.

with decreases in hemoglobin, as were fracture type, platelet count, and operative time. Women were found to have a 0.55 g/dL greater decrease in hemoglobin than men that was borderline significant, p=0.07.[26] Hang *et al*, studied the effect of perioperative administration of aspirin for patients undergoing total knee arthroplasty and reported that continued aspirin therapy did not affect blood loss, and female sex was also not a risk factor for blood loss in their population.[27]

In the setting of CVD, there have been numerous studies examining sex-specific differences in bleeding outcomes with aspirin and other antiplatelet agents. A meta-analysis of CVD primary prevention trials demonstrated that aspirin treatment was associated with increased odds of bleeding for both women and men.[28] In a study of over 13,000 patients treated with percutaneous coronary intervention for acute coronary syndrome, dual antiplatelet therapy with aspirin and glycoprotein IIb/IIIa inhibitors was an independent risk factor for bleeding in women but not in men.[29] The CRUSADE bleeding score was developed in over 70,000 patients with non-ST elevation myocardial infarction, and female sex was found to be an independent predictor of in-hospital major bleeding.[30] Conversely, the US preventative task force examined bleeding risks with aspirin for primary prevention of CVD and reported that men had a twofold greater risk of major bleeding than women, and the risk of hospitalization for major bleeding was greater for men and for patients taking aspirin.[5] Although not directly applicable to postoperative bleeding events after traumatic injury, these large studies performed in the CVD setting suggest potential sex disparities in the response to antithrombotic therapies that affects the risks of bleeding.

There are several limitations to this study. Primarily, this was a secondary analysis of a retrospective cohort study that was powered a posteriori. We are initiating an adequately powered confirmatory prospective cohort study to evaluate the association between aspirin use and bleeding outcomes by sex. Antiplatelet use was documented in the original study as a covariate and therefore additional characteristics about aspirin use are unknown, including the dosage of aspirin and continuation or interruption of aspirin during the perioperative period. Aspirin dosage, duration and continuation are being collected as part of the prospective study, as well as relevant laboratory markers that are indicative of aspirin metabolism or blood loss. Likewise, we did not collect data on hormone replacement therapy (HRT) or oral contraceptive use because biological sex was originally a covariate; whereas our female population's median age of 77 years was beyond menopause, non-elevated estrogen-related platelet effects may still be a factor in the relationship we observed and we will be collecting HRT and contraceptive status in the upcoming study. Next, there were institutional preferences in whether to order and when to initiate VTE chemoprophylaxis. Most facilities prefer 30 mg Lovenox two times per day and between 40% and 80% of patients begin initiation postoperatively, whereas one facility prefers 40 mg Lovenox one time per day and 71% of patients are initiated preoperatively. There was no interaction between timing of VTE chemoprophylaxis, postoperative bleeding events, and hospital, and all facilities were modeled together. Still, patients who never received VTE chemoprophylaxis were excluded from the analysis. Next, only one institution had a transfusion management guideline that outlined a transfusion threshold, and this center considered hemoglobin <7 g/dL as a restrictive transfusion threshold. Finally, hemoglobin values are higher for patients living at higher altitudes and most (68%) study participants were treated at hospitals in Colorado (~5,000–6,000 feet elevation). Also, hemoglobin values were documented at prescribed intervals only, so it cannot be addressed whether patients on aspirin were more likely to have a postoperative decline in hemoglobin.

CONCLUSIONS

There is a significant knowledge gap regarding sex differences in platelet biology and response to therapeutics, especially in the setting of traumatic injury. For patients with major orthopedic surgery for long bone fractures, the incidence of a clinically significant postoperative bleed was over twofold greater for women who were on preinjury aspirin therapy than women not taking aspirin or other antiplatelet agents, with nearly 28% of postoperative bleeding events attributable to aspirin use in the female population. Female aspirin users also had an increased likelihood of low hemoglobin values preoperatively and postoperatively compared with females not taking aspirin.

We did not find that preinjury aspirin use was associated with the timing of VTE chemoprophylaxis initiation nor was VTE chemoprophylaxis timing associated with the incidence of postoperative bleeding, regardless of sex or aspirin use, suggesting there is no optimal time to initiate VTE chemoprophylaxis. Although not studied here, we are not advocating delaying surgery for female patients taking aspirin preinjury to decrease the incidence of postoperative bleed, as early surgical management of traumatic lower extremity fractures has been shown to improve clinical outcomes and is standard care.

These findings may illicit more questions than answers, as the main finding of a sex disparity in the association between aspirin use and bleeding outcomes is novel in the setting of trauma. Additional prospectively powered studies are needed to confirm our findings. In the meantime, these findings may have some utility for patient discussion and prognostication, suggesting that adequate perioperative planning is needed to ensure blood availability for females taking aspirin preinjury and an increased awareness to monitor closely for hemorrhage in the immediate postoperative window.

Correction notice Published version has incorrect affiliation for author David Bar-Or. The correct affiliation is Trauma Research Department, Swedish Medical Center, Englewood, CO, USA.

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