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# Real-world analysis of thromboprophylaxis use during autologous hematopoietic stem cell transplantation for multiple myeloma

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Multiple myeloma (MM) patients are at risk of venous thromboembolism (VTE) during autologous hematopoietic transplant (autoHSCT). Only 14% of transplant centers have a hematopoietic stem cell transplant (HSCT)-specific thromboprophylaxis protocol.[1] Concerns with thromboprophylaxis include (1) bleeding risk, (2) perspective that thrombocytopenia protects against clotting, and (3) lack of literature for thromboprophylaxis in HSCT.

We conducted a retrospective, single-center study. Data was obtained from the registry of Cedars Sinai Medical Center (CSMC). Eligible patients were adults 18 years or older with MM admitted for autoHSCT at CSMC between July 2016 and July 2024. Patients' age, sex, race, Body Mass Index (BMI), estimated glomerular filtration rate (eGFR), smoking history, antiplatelet and prothrombotic medications (immunomodulators, etc) within 6 months prior until 30-days after HSCT, VTE and bleeding history, Karnofsky Performance Scale (KPS), and Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) were collected. A double-lumen peripherally inserted central catheter (PICC) was placed in all patients 1-day prior to conditioning with melphalan 140 or 200mg/m$^2$. Patients receiving therapeutic anticoagulation were excluded.

The primary outcomes are a composite of bleeding events (BE) within 30 days of autoHSCT. Secondary outcomes are a composite of thrombotic events (TE) within 30 days of autoHSCT. Exploratory outcomes were platelet levels at BE and TE, length of stay (LOS), and overall survival (OS). BE and TE were defined per the International Society of Thrombosis and Hemostasis criteria.[2]

VTE prophylaxis (VTE ppx) was started on admission at the discretion of the attending physician. Unfractionated heparin (UFH) 5000 unit subcutaneous (SC) twice daily or low-molecular weight heparin (LMWH) 40 mg SC daily were administered until platelet count dropped below 50,000/mcL. Duration of VTE ppx did not include therapeutic doses if TE occurred.

Patients' baseline characteristics were compared using chi-squared test for categorical variables, and the Mann-Whitney U test for continuous variables. Univariate logistic regression was used to identify risk factors of bleeding or VTE. Patients' age, sex, race, BMI, eGFR, smoking history, VTE and bleeding history, KPS, HCT-CI, and receipt, type, and duration of anticoagulant were included in the analysis. Overall survival was calculated using the Kaplan–Meier method and the two groups were compared using the log-rank test. All *p*-values were two-sided, and less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS software for Windows, version 9.4 (SAS Institute, Cary, NC).

A total of 407 MM patients were included. VTE ppx was received in 296 (72.7%) patients **(Table 1).** LMWH was administered in 263 patients and UFH in 33 patients for a median of 8 days (range 1–17 days). Only race, KPS, prior VTE, and LOS differed.

Immunomodulators were exposed in 77.0% of VTE ppx group and 74.8% of none group. Among 33 patients with prior bleeding, 21 were clinically relevant nonmajor bleeding (CRNMB), and 12 were minor. Non-Hispanic Caucasian patients received more VTE ppx (44.6% vs 30.6%, *p=0.011*). Patients with KPS greater than 80 received more VTE ppx (95.3% vs 85.6%, *p=0.001*). Patients with prior VTE received more VTE ppx (10.8% vs 3.6%, *p=0.023*).

The primary outcome of composite BE occurred in 16 of 407 patients (3.9%). Among those 16, 81.3% were patients with VTE ppx and 18.3% were those without VTE ppx *(p=0.44).* The 30-day cumulative incidence of BE between VTE ppx (4.1%, 95% CI: 2.2-6.8) and no ppx (2.7 %, 95% CI: 0.7-7.1) groups did not show statistical difference (p=0.5133). Only 2 major bleedings occurred while 9 were CRNMB and 5 were minor. Most common bleeding sites were gastrointestinal and nasal. The median time to BE was 11.5 days (range 2–21 days) (**Figure 1**). Only 1 out of 16 BE occurred on VTE ppx while 15 out of 16 BEs occurred a median 6.2 days after VTE ppx. Thirteen of 16 BE occurred in patients who received VTE ppx. No baseline characteristics were associated with BE (**Table 2**). Among 296 patients who received VTE ppx, 13 patients (4.4%) experienced BE. Among 111 patients who did not receive VTE ppx, 3 patients (2.7%) had BE.

Only patients who received anticoagulants were included in the subgroup analysis (**Supplemental Table 1**). The duration and type of anticoagulants were not associated with BE.

The secondary outcome of composite TE occurred in 24 of 407 patients (5.9%). Among those 24, 58.3% were patients with VTE ppx and 41.7% were those without (*p=0.11).* The 30-day cumulative incidence of TE between VTE ppx (4.4%, 95% CI: 2.5-7.2) and no ppx (7.2 %, 95% CI: 3.4-13) groups did not show statistical difference (p=0.2522). Twenty patients had a PICC-associated VTE. Other TE were splenic artery thrombosis, non-PICC arm vein thrombosis, cardiac allograft thrombosis, and atrial thrombosis. The median time to a TE was 10.5 days (range 0–26 days). Among 24 patients with TE, 10 patients (41.7%) did not receive VTE ppx. No one developed heparin-induced thrombocytopenia (HIT).

Thirty six of 407 patients had a prior VTE and 32 of them (89%) received VTE ppx. Three patients (9.4%) still developed TE. Of 371 patients without prior VTE, 264 (71.1%) received VTE ppx and 11 (4.2%) still developed TE. Of 107 without prior VTE nor received VTE ppx, 10 patients (9.3%) developed TE.

No baseline characteristics were associated with TE (**Table 2**). In the subgroup analysis of patients on VTE ppx (**Supplemental Table 1**), each additional day of anticoagulant showed a trend of decreased TE (OR: 0.82, CI: 0.68-1.0, *p*=0.055). Receiving LMWH over UFH showed a statistically significant reduction in TE (OR:0.20, CI: 0.06-0.63, *p*=0.006). Receiving LMWH over none showed a statistically significant reduced TE

(OR: 0.36, CI: 0.14-0.91, *p*=0.03). Receiving UFH over none was not statistically significant in reducing TE (OR: 1.80, CI: 0.57-5.71, *p*=0.31).

The exploratory outcomes of median platelet count at BE was 19,000/mcL (range 2,000–219,000/mcL) and at TE was 42,500/mcL (range 6,000–237,000/mcL). The median platelet count at VTE ppx initiation was 178,000/mcL (range 49,000–489,000/mcL) and at the last VTE ppx dose was 85,000/mcL (range 34–478,000/mcl).

Although median LOS was 15 days for both groups, the distribution of longer stay was heavier in patients who did not receive VTE ppx, resulting in a statistically significant difference (*p*=0.0035).

Three of 407 patients (0.7%) died within 30 days post-HSCT. All three patients developed a TE. One patient received VTE ppx and had a BE 9 days after discontinuation. Two deaths were related to TE. Overall survival at 30-days was 99.7% for VTE ppx group and 98.2% for none (*p*=0.1247).

In our center, most MM patients received VTE ppx during autoHSCT. Patients were more likely to receive VTE ppx when prior VTE, non-Hispanic Caucasian ethnicity, and higher KPS. VTE ppx was not associated with a statistically significant increase in BE and showed a trend of halving the rate of TE without statistical significance, which may be from our study being underpowered. A stronger trend in decreased TE with longer duration of VTE ppx use was seen without increasing the risk of BE. This data is meaningful in a retrospective study where start and end of VTE ppx were not controlled, and we predict a different effect in single versus multiple doses of VTE ppx during a 15-day hospitalization. Most TE were PICC-associated DVT. Safe and effective thromboprophylaxis effect for central-line thrombosis has been reported in malignancies in a meta-analysis. [3]

We observed both thrombosis and bleeding during thrombocytopenia. Thrombocytopenia likely reduces thrombosis but is not protective as activated platelets during inflammation increase the risk of thrombosis. [4] Our concern for direct bleeding from VTE ppx was lessened as only one patient experienced a minor BE while on VTE ppx. BE occurred a week after the last dose of VTE ppx, suggesting bleeding was from severe thrombocytopenia than from anticoagulation.

LMWH was associated with a statistically significant lower TE than UFH or no VTE ppx. Cardiac literature has shown superiority of LMWH over UFH in reducing mortality and bleeding. [5] LMWH has advantages including predictable anticoagulant response, less binding to platelets and endothelial cells, and increased inhibition of thrombin generation. [6] LMWH may also have beneficial, non-anticoagulant properties in glycocalyx shedding prevention, antiinflammation, angiogenesis and cell adhesion inhibition, and endothelial function improvement. [7]

Due to the retrospective nature of the study, variables such as bleeding or thrombotic history, and over-the counter medications may be inaccurately captured. PICC-associated VTE may be underreported as PICCs were removed after new swelling or pain without radiographic evaluation. The choice of VTE ppx likely represents residual confounding and selection bias of the attending physicians. Multivariate analysis could not be performed due to limited cases of TE and BE.

Preventing thrombosis is preferred over managing a TE during HSCT. PICC-associated VTEs are not often hazardous, but lead to line removal, limb pain, or quandaries over methods of anticoagulation while increasing hospital costs and patient concerns. As a result of our study, our division protocolized the use of VTE ppx for MM patients during autoHSCT.

This research was reviewed and approved by the institutional review board of Cedars Sinai Medical Center.

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**Table 1.** Baseline Characteristics. References of each variable are anticoagulant usage (No), race (Non-Hispanic Caucasian), history of smoking (Never), Sex (male), KPS (≥80), HCT-CI (0-2), and type of anticoagulant (Heparin).

| **Table 1. Baseline patient characteristics (N=407)** | | | |
|---|---|---|---|
| | **VTE ppx (n=296)** | **No ppx (n=111)** | **P-value** |
| **Patient age : Median (Min-Max)** | 63 (29-79) | 62 (34-77) | 0.561 |
| **Sex, n (%)** | | | 0.075 |
| Male | 163 (55.1) | 72 (64.9) | |
| Female | 133 (44.9) | 39 (35.1) | |
| **Race, n (%)** | | | 0.011 |
| Non-Hispanic/Caucasian | 132 (44.6) | 34 (30.6) | |
| Others | 164 (55.4) | 77 (69.4) | |
| **Disease, n (%)** | | | 0.815 |
| Multiple Myeloma | 281 (94.9) | 106 (95.5) | |
| Amyloidosis | 15 (5.1) | 5 (4.5) | |
| **eGFR : Median (Min-Max)** | 90.8 (4.6-126.1) | 89.5 (7.3-132.1) | 0.802 |
| **BMI : Mean (Min-Max)** | 26.8 (16.8-44.2) | 26.5 (16.2-41.6) | 0.753 |
| **KPS, n (%)** | | | 0.001 |
| 100-80 | 282 (95.3) | 95 (85.6) | |
| < 80 | 14 (4.7) | 16 (14.4) | |
| **HCT-CI, n (%)** | | | 0.919 |
| 0-2 | 151 (51.0) | 56 (50.5) | |
| ≥3 | 145 (49.0) | 55 (49.6) | |
| **Smoking status, n (%)** | | | 0.327 |
| Never | 207 (69.9) | 72 (64.9) | |
| Active/former | 89 (30.1) | 39 (35.1) | |
| **Medications causing clotting risk, n (%) **** | 248 (83.8) | 99 (89.2) | 0.171 |
| **Antiplatelet, n (%) *** | 181 (61.2) | 68 (61.3) | 0.983 |
| **Prior VTE, n (%)** | 32 (10.8) | 4 (3.6) | 0.023 |
| **Prior bleeding, n (%)** | 21 (7.1) | 12 (10.8) | 0.221 |

- VTE: Venous Thromboembolism Event, ppx: prophylaxis,
eGFR: estimated glomerular filtration rate, BMI : Body Mass Index,
KPS: Karnofsky Performance Scale,
HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index
* during auto-HSCT admission

** within 30-days prior or 30-days after HSCT

‘**Table 2.** Clinical risk factors associated with bleeding or thrombotic events.

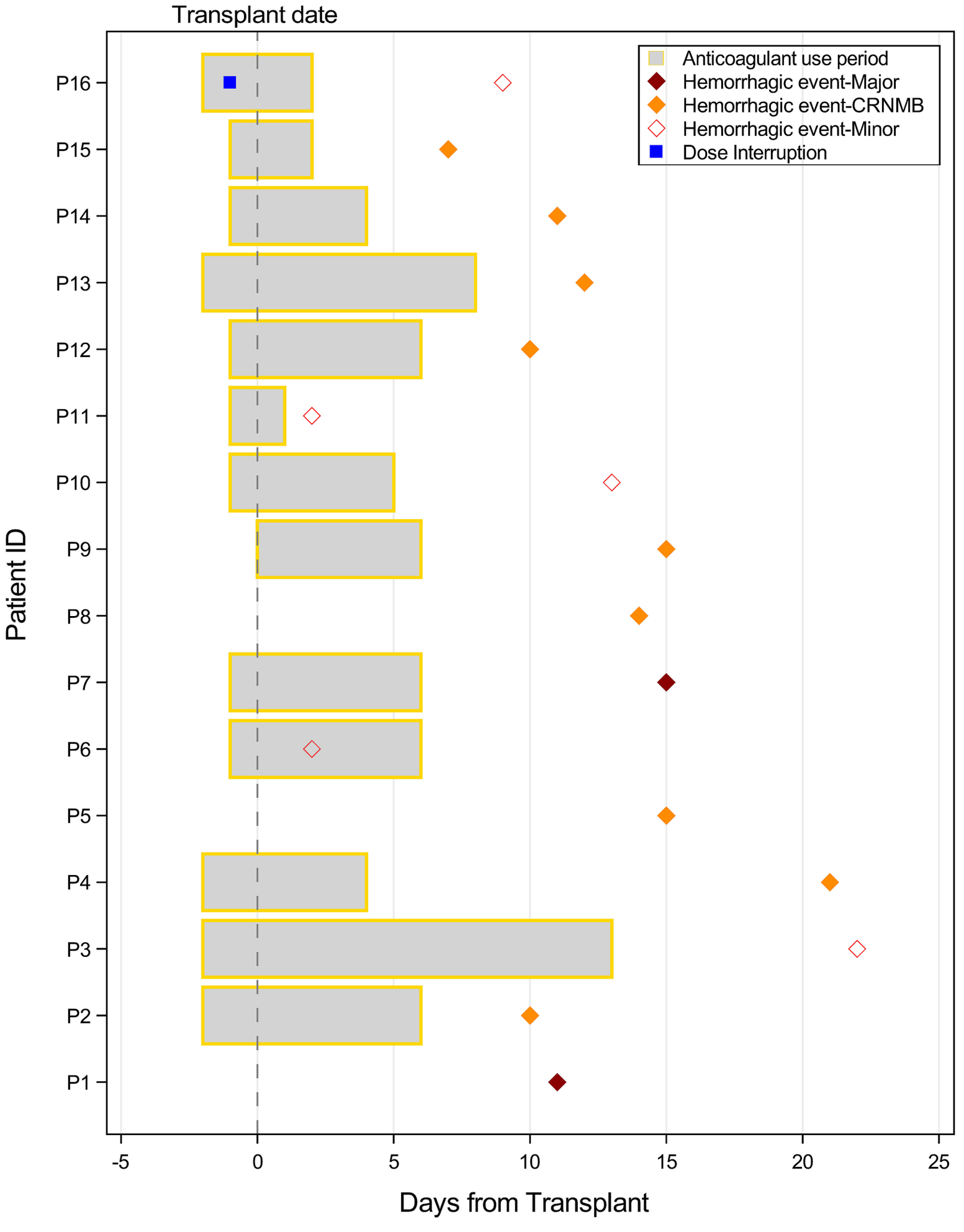
| **Table 2. Clinical risk factors associated with a bleeding event or thrombotic event in univariate logistic analysis (n=407).** | | | | |
|---|---|---|---|---|
| | Bleeding event (n=16) | | Thrombotic event (n=24) | |
| | Odds ratio (95% CI) | *p*-value | Odds ratio (95% CI) | *p*-value |
| Age for each 1 year increase | 1.01 (0.96-1.07) | 0.727 | 1.00 (0.96-1.04) | 0.999 |
| Sex (Female vs Male) | 1.80 (0.66-4.93) | 0.254 | 1.99 (0.86-4.60) | 0.106 |
| Race (Others vs Caucasian/White) | 1.54 (0.53-4.52) | 0.432 | 0.56 (0.25-1.29) | 0.174 |
| BMI for each 1 unit increase | 0.97 (0.87-1.08) | 0.519 | 1.04 (0.96-1.13) | 0.325 |
| eGFR for 1 unit increase | 0.99 (0.97-1.01) | 0.218 | 0.99 (0.97-1.00) | 0.073 |
| KPS (<80 vs ≥80) | 0.83 (0.11-6.53) | 0.861 | 1.89 (0.53-6.72) | 0.329 |
| HCT-CI (≥3 vs 0-2) | 0.80 (0.29-2.19) | 0.661 | 1.24 (0.54-2.83) | 0.612 |
| History of smoking (Yes vs Never) | 0.49 (0.14-1.75) | 0.274 | 0.89 (0.36-2.21) | 0.804 |
| Medications causing clotting risk (IMiD vs No) | 1.16 (0.25-5.34) | 0.845 | 0.64 (0.23-1.80) | 0.638 |
| Anticoagulant (Yes vs No) | 1.65 (0.46-5.92) | 0.439 | 0.50 (0.22-1.17) | 0.108 |
| Antiplatelet (Yes vs No) | 1.06 (0.38-2.97) | 0.912 | 0.62 (0.27-1.41) | 0.251 |
| Prior VTE (Yes vs No) | 0.68 (0.09-5.29) | 0.711 | 1.52 (0.43-5.35) | 0.519 |

- VTE: Venous thromboembolism, eGFR: estimated Glomerular Filteration Rate, BMI : Body Mass Index, IMiD : Immunomodulatory dug, Prior VTE: Prior venous thromboembolism event, KPS: Karnofsky Performance Scale, HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index, CI: Confidence Interval

**Figure 1.** Swimmer plot of bleeding episodes in all patients.

Each row represents a patient who experienced bleeding. The shaded area represents the period during which patients received thromboprophylaxis. A bleeding event was defined based on ISTH bleeding definition where major event is defined as (1) fatal bleeding, (2) symptomatic bleeding in a critical area or organ, (3) bleeding with a 2 g/dL or more fall of hemoglobin level, or more than two units of red cell transfusion. Minor bleeding is defined as all reported bleedings not classified as major. All but one bleeding event occurred after an average of 6.2 days from thromboprophylaxis discontinuation. One minor hemorrhagic event occurred during thromboprophylaxis.

Figure 1. Swimmer Plot: Anticoagulant Use and Hemorrhagic Events (n=16)



Supplementary

| Supplementary Table 1. Clinical risk factors associated with a bleeding event or thrombotic event among patients with VTE ppx in univariate logistic analysis (n=296) | | | | |
|---|---|---|---|---|
| | Bleeding event (n=13) | | Thrombotic event (n=14) | |
| | Odds ratio (95% CI) | *p* -value | Odds ratio (95% CI) | *p* -value |
| Duration of Anticoagulant use for 1 day increase | 1.04 (0.83-1.32) | 0.719 | 0.82 (0.68-1.00) | 0.055 |
| Type of anticoagulant (Enoxaparin vs Heparin) | 0.68 (0.14-3.20) | 0.622 | 0.20 (0.06-0.63) | 0.006 |

- VTE: Venous thromboembolism