CHEST Online Supplement

# Comparative Effectiveness of Enoxaparin vs Dalteparin for Thromboprophylaxis After Traumatic Injury

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**e-Appendix 1.**

**Data Analysis methods supplement**

Checking the assumptions of the difference-in-differences models

The aggregation of enoxaparin time periods (01/04-12/09 and 02/13-03/14) assumes a constant baseline rate of venous thromboembolism across those two time periods. We verified this assumption by constructing a Poisson regression model that included a term for time period (Enoxaparin period 1: 01/04-12/09 vs. enoxaparin period 2: 02/13-03/14), which showed a constant rate for period 2 vs. period 1: (IRR 0.96, 0.65-1.41). In addition, the difference-in-differences model assumes parallel trends in the outcome between treatment and control groups in the enoxaparin time period. This assumption was verified by introducing an interaction term between calendar year and group (LMWH vs. UFH control) in enoxaparin time periods (IRR 1.07, 0.94 - 1.23), which showed no significant deviation from parallel trends of VTE rate in the LMWH vs. UFH control. Lastly, all models were examined for overdispersion, with no evidence for significant overdispersion found.

Methods to tabulate missed doses

The cumulative percentage of scheduled doses missed was defined as 1 - (cumulative doses received during follow-up / cumulative number of expected doses during follow-up). The expected number of doses was based on the standard dosing regimens used during the study period: the enoxaparin regimen was 30 mg every 12 hours (2 expected doses per day), the dalteparin regimen was 5000 IU every 24 hours (1 expected dose per day) and the heparin regimen was 5000 IU every 8 hours (3 expected doses per day). The counting of missed doses began at the time of the first dose, so that missed doses due to delay of initiation were not included. Expected dose values for the last day of follow-up were adjusted to account for the time of exit from the cohort. For the purposes of analysis, missed doses were categorized as above or below 80%. There are no previous studies in the trauma population that that have examined the optimal threshold for missed doses. The 80% threshold was thus chosen because this is a standard cutoff used in other studies and quality improvement initiatives.[1,2]

**Multivariable Poisson regression model specifications**

Secondary outcome models

1. VTE + mortality
   – Adjusted for age, injury severity score, mechanical prophylaxis, coronary artery disease, hypertension, stroke, malignancy, mechanical ventilation, vasopressor use, femur fracture, race, intensive care unit admission, vein injury

2. Pulmonary embolism
   – Adjusted for injury severity score, mechanical prophylaxis, mechanical ventilation, femur fracture, race, vasopressor use, vein injury

3. All deep vein thrombosis
   – Adjusted for baseline hemoglobin concentration, hypertension, mechanical ventilation, femur fracture, vein injury, intensive care unit admission, vasopressor use

4. Proximal deep vein thrombosis
   – Adjusted for mechanical ventilation, femur fracture, vein injury, intensive care unit admission, surgery, vasopressor use

Sensitivity analysis models

1. Negative binomial regression model
   – Adjusted for injury severity score, mechanical prophylaxis, hypertension, mechanical ventilation, femur fracture, vein injury, intensive care unit admission

2. At least one US
   – Adjusted for injury severity score, baseline platelet count, diabetes mellitus, hypertension, stroke, spinal cord injury, vasopressor use, mechanical ventilation, femur fracture, pelvis fracture, intensive care unit admission, history of prior thrombosis

3. Censor follow-up at last dose
   – Adjusted for injury severity score, mechanical prophylaxis, mechanical ventilation, femur fracture, vein injury, intensive care unit admission, hypertension, vasopressor use

4. Admission after 2007
   – Adjusted for injury severity score, baseline hemoglobin concentration, baseline platelet concentration, hypertension, spinal cord injury, blood product transfusion in the emergency department, mechanical ventilation, vasopressor use

5. Initiation within 24 hours of admission
   – Adjusted femur fracture, baseline vasopressor use

6. Missed < 20% of scheduled doses
   – Adjusted for mechanical ventilation, vein injury, vasopressor use

7. Initiation within 24 hours and missed < 20% of scheduled doses
   – Adjusted for vasopressor use

**e-Table 1** Venous thromboembolism diagnosis codes and case definitions

| Code | Description |
|---|---|
| **PE** | |
| 415.11 | Iatrogenic pulmonary embolism and infarction |
| 415.13 | Saddle embolus of pulmonary artery |
| 415.19 | Other pulmonary embolism and infarction |
| | |
| **LE DVT** | |
| 451.11 | Thrombophlebitis, deep vessels of lower extremities femoral vein |
| 451.19 | Thrombophlebitis of deep vessel of lower extremities, other (Femoropopliteal vein, popliteal vein, tibial vein) |
| 451.2 | Phlebitis and thrombophlebitis of lower extremities, unspecified |
| 451.81 | Thrombophlebitis of other sites iliac vein |
| 453.40 | Venous embolism and thrombosis of unspecified deep vessels of lower |
| 453.41 | extremity |
| 453.42 | Venous embolism and thrombosis of deep vessels of proximal lower extremity |
| 453.6 | Venous embolism and thrombosis of deep vessels of distal lower extremity |
| 453.8 | Venous embolism and thrombosis of superficial vessels of lower extremity |
| | Acute venous embolism and thrombosis of other specified veins (Pre-2009) |
| **Other DVT** | |
| 451.9 | Phlebitis and thrombophlebitis of unspecified site |
| 453.2 | Other venous embolism and thrombosis of inferior vena cava |
| 453.89 | Acute venous embolism and thrombosis of other specified vein |
| 453.9 | Other venous embolism and thrombosis of unspecified site |
| | |
| **UE DVT** | |
| 451.82 | Phlebitis and thrombophlebitis of superficial veins of upper extremities (Antecubital vein, basilic vein, cephalic vein) |
| 451.83 | Phlebitis and thrombophlebitis of deep veins of upper extremities (brachial vein, radial vein, ulnar vein) |
| 451.84 | Phlebitis and thrombophlebitis of deep veins of upper extremities, unspecified |
| 451.89 | Phlebitis and thrombophlebitis of other veins (Axillary vein, Jugular vein, Subclavian vein, thrombophlebitis of breast) |
| 453.81 | Acute venous embolism and thrombosis of superficial veins of upper extremity |
| 453.82 | Acute venous embolism and thrombosis of deep veins of upper extremity |
| 453.83 | Acute venous embolism and thrombosis of upper extremity, unspecified |
| 453.84 | Acute venous embolism and thrombosis of axillary veins |
| 453.85 | Acute venous embolism and thrombosis of subclavian veins |
| 453.86 | Acute venous embolism and thrombosis of internal jugular veins |
| 453.87 | Acute venous embolism and thrombosis of other thoracic veins |

**Deep Vein Thrombosis**
Radiographic confirmation of DVT required explicit documentation of thrombosis in a report from a compression ultrasound exam or a contrast enhanced computed tomography of the lower extremities. In the absence of radiographic evidence for DVT in the EMR, autopsy reports were reviewed if available. Proximal lower extremity DVT was defined as thrombosis in the iliac, common femoral, superficial femoral, deep femoral, or popliteal veins. Distal lower extremity thrombosis was defined as thrombosis in the peroneal, anterior, posterior tibial, gastrocnemius, soleal, or saphenous veins.

**Pulmonary Embolism**
Radiographic confirmation of PE required a positive computed tomography angiogram (CTA) of the lungs or ventilation-perfusion scan. In the absence of radiographic evidence for PE in

the EMR, autopsy reports were reviewed if available. CTA confirmation required explicit documentation of a filling defect in one or more pulmonary arteries AND an explicit mention by the radiologist of pulmonary embolism being present. VQ scan confirmation required explicit documentation of "high probability for pulmonary embolism". Autopsy confirmation required explicit documentation of thrombosis in one or more pulmonary arteries and documentation of the diagnosis of "pulmonary embolism" .

**e-Table 2** Frequency of missed doses

| **Percent Scheduled Doses Missed** | **Enoxaparin, n=2371** | **Dalteparin, n=1046** | **Heparin, n=2463** |
|---|---|---|---|
| < 5 % | 1431 (60.3) | 750 (71.7) | 1013 (41.1) |
| 5% - 19.99 % | 568 (23.9) | 131 (12.5) | 732 (29.7) |
| 20% - 49.99 % | 281 (11.9) | 158 (15.1) | 609 (24.7) |
| ≥ 50% | 91 (3.8) | 7 (0.7) | 109 (4.4) |

**e-Table 3.** VTE surveillance: Percentage of patients with at least one duplex ultrasound

| **Period** | **LMWH group** | **UFH control** | **p** |
|---|---|---|---|
| Enoxaparin time period | 1205/2371 (50.8) | 807/1539 (52.4) | 0.32 |
| Dalteparin time period | 628/1046 (60.0) | 544/924 (58.9) | 0.60 |

## Multiple imputation analysis

Imputation Methods

Multiple imputation of missing baseline covariates was completed using the multiple imputation program in Stata/SE, version 14.2 for Mac. Imputed values were obtained using data augmentation, an iterative Markov chain Monte Carlo method.[3-5] Imputed values were generated assuming an underlying multivariate normal model and the Jeffreys noninformative prior distribution.[5] Fifty imputation data sets were produced, using an initial burn-in run of 500 iterations and a 500-iteration burn-in between each replication. The imputation model included all covariates included in the primary analysis (see Table 1), exposure variables, the difference-in-differences interaction term, and additional auxiliary variables plausibly associated with the missing values.[6,7] These included the outcome variable (venous thromboembolism), hospital length of stay, and 30-day in-hospital mortality.

Continuous variables were assessed for normality and transformed accordingly for the imputation step, followed by reverse transformation for analysis in the multiply imputed data set. Binomial variables were treated as normally distributed in the imputation procedures and the imputed values rounded to zero or one using a cut- off value of 0.5.[5] Multilevel categorical variables were rounded to the nearest integer value according to the underlying coding scheme.[5]

Estimation of the differences-in-differences parameter in the multiply imputed data set was conducted using the mi estimate command, which adjusts coefficients and standard errors for the variability between imputations according to the combination rules of Rubin.[4] Model specification began with the primary analysis Poisson regression model, with additional models that adjusted for covariates not included in the primary analysis. These included patient weight, body mass index, body surface area, and glomerular filtration rate. The latter 3 variables were derived using the multiply imputed values for height, weight, and creatinine.

**e-Table 4** Missing data prevalence

| Variable | Missing | Non-missing |
|---|---|---|
| **Covariates in primary analysis** | | |
| Age | 1 | 6203 |
| ISS | 260 | 5944 |
| Creatinine | 42 | 6162 |
| Hemoglobin | 46 | 6158 |
| Platelet count | 30 | 6174 |
| Injury Type | 1 | 6203 |
| Race | 8 | 6196 |
| Sex | 3 | 6201 |
| **Additional covariates included in sensitivity analysis*** | | |
| Height | 940 | 5264 |
| Weight | 746 | 5458 |

*These variables were used to derive additional covariates, including body surface area and glomerular filtration rate

**e-Table 5** Baseline characteristics of patients with missing data

| | **Missing Data n=324** | **Complete Data n=5880** | **SDF** |
|---|---|---|---|
| **Demographics** | | | |
| Age, years, med. (IQR) | 54 (43-71) | 48 (31-64) | 0.328 |
| Length of stay, days, med (IQR) | 5 (3-9) | 6 (4-11) | |
| Venous thromboembolism, n (%) | 1 (0.3) | 190 (3.2) | -0.223 |
| 30-day mortality, n (%) | 12 (3.7) | 128 (2.2) | 0.090 |
| **Injury characteristics** | | | |
| TBI, n (%) | 5 (1.5) | 825 (14.0) | -0.479 |
| Femur fracture, n (%) | 4 (1.2) | 749 (12.7) | -0.463 |
| Pelvis fracture, n (%) | 11 (3.4) | 630 (10.7) | -0.289 |
| Spine cord injury, n (%) | 0 (0.0) | 215 (3.7) | -0.275 |
| Pulmonary contusion, n (%) | 7 (2.2) | 510 (8.7) | -0.291 |
| Vein injury, n (%) | 1 (0.3) | 85 (1.5) | -0.122 |
| **Treatment characteristics** | | | |
| ICU admission, n (%) | | | |
| Mechanical ventilation, n (%) | 39 (12.0) | 1424 (24.2) | -0.320 |
| Surgery, n (%) | 19 (5.9) | 1254 (21.3) | -0.463 |
| ED transfusion, n (%) | | | |
| None | 319 (98.5) | 5530 (94.1) | 0.234 |
| 1-unit | 3 (0.9) | 130 (2.21) | -0.104 |
| >=2 units | 2 (0.6) | 220 (3.74) | -0.215 |
| Mechanical prophylaxis, n (%) | 150 (46.3) | 3910 (66.5) | -0.416 |
| **Comorbidities** | | | |
| Heart failure, n (%) | 17 (5.3) | 174 (2.9) | 0.115 |
| Myocardial infarction, n (%) | 13 (4.0) | 176 (2.9) | 0.055 |
| Atrial fibrillation, n (%) | 20 (6.2) | 337 (5.7) | 0.019 |
| Hypertension, n (%) | 129 (39.8) | 1965 (33.4) | 0.133 |
| Stroke, n (%) | 27 (8.3) | 250 (4.3) | 0.169 |
| COPD, n (%) | 19 (5.9) | 247 (4.2) | 0.076 |
| Liver disease, n (%) | 0 (0.0) | 56 (0.9) | -0.139 |
| Malignancy, n (%) | 23 (7.1) | 313 (5.3) | 0.074 |
| Prior thrombosis, n (%) | 8 (2.5) | 92 (1.56) | 0.064 |
| Thrombophilia, n (%) | 0 (0.0) | 72 (1.2) | -0.157 |
| ESRD, n (%) | 11 (3.4) | 87 (1.5) | 0.124 |
| **Baseline medications** | | | |
| Antiplatelets, n (%) | 77 (23.77) | 931 (15.8) | 0.200 |
| RASS, n (%) | 30 (9.3) | 415 (7.1) | 0.080 |
| Vasopressors, n (%) | 13(4.0) | 245 (4.2) | 0.008 |
| Statins, n (% | 52 (16.1) | 576 (9.8) | 0.187 |

The distribution of baseline characteristics of patients with missing covariate is notable for an older age, lower prevalence of injuries, greater burden of comorbid illness, and a shorter hospital length of stay. These data suggest that patients with missing data were overall at a lower risk of venous thromboembolism, which accords with the lower observed rate of thrombosis in this group.

**e-Table 6** Observed vs. Imputed values for covariates with ≥ 0.5% of values missing

| Variable | Imputed Values | Observed Values |
|---|---|---|
| **Covariates in primary analysis** | | |
| ISS, med (IQR) | 4.7 (2.7-8.1) | 10 (5-17) |
| Creatinine, med (IQR) | 0.9 (0.7-1.2) | 0.9 (0.7-1.1) |
| Hemoglobin, med (IQR) | 12.3 (10.7-13.9) | 12.1 (10.5-13.5) |
| Platelet count, med (IQR) | 242 (187-293) | 203 (161-251) |
| **Additional covariates included in sensitivity analysis** | | |
| Height, med (IQR) | 172.6 (164.6-179.7) | 172.7 (165.1-180.3) |
| Weight, med (IQR) | 75.8 (63.3-90.6) | 78.2 (68.0-90.7) |

Most imputed values are similar to observed values, with the exception of ISS (imputed values lower) and platelet count (imputed values higher). These differences are consistent with the lower burden of injury and severity of illness in the missing-data group as detailed in Table S.2

**e-Table 7** Multiple Imputation Estimation of Differences-in-Differences

| Analysis | Difference-in-differences (95% CI) |
|---|---|
| 1) Primary analysis model | 0.99 (0.53-1.87) |
| 2) Primary model + weight | 0.99 (0.53-1.88) |
| 3) Primary model + BMI | 0.99 (0.53-1.87) |
| 4) Primary model + BSA | 1.00 (0.54-1.88) |
| 5) Primary model + BSA + GFR | 0.99 (0.53-1.86) |

BMI- body mass index; BSA- body surface area; GFR- glomerular filtration rate

**References**


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