Trauma and thrombosis in the DOAC era: promise and peril of direct oral anticoagulant use in injured patients

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Part 1: Thromboprophylaxis in lower extremity trauma

Chapter 2

Direct Oral Anticoagulants Are a Potential Alternative to Low-Molecular-Weight Heparin for Thromboprophylaxis in Trauma Patients Sustaining Lower Extremity Fractures

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Abstract

Background: Trauma patients are at a significant risk of venous thromboembolism (VTE), with lower extremity fractures (LEF) being independent risk factors. Use of direct oral anticoagulants (DOACs) for VTE prophylaxis is effective in elective orthopedic surgery, but currently not approved for trauma patients. The primary objective of this study was to compare the effectiveness and safety of thromboprophylaxis of DOACs to LMWH in trauma patients sustaining LEF.

Materials and Methods: We included adult trauma patients admitted to trauma quality improvement program (TQIP) participating trauma centers (between 2013 - 2016), who sustained LEF and were started on DOACs or low molecular weight heparin (LMWH) for thromboprophylaxis after admission. Propensity score matching (PSM) was performed to compare symptomatic VTE and bleeding control interventions between the groups.

Results: Of 1,009,922 patients in TQIP, 167,640 met inclusion criteria (165,009 received LMWH, 2,631 received DOACs). After PSM, 2,280 predominantly elderly (median age: 67) isolated femur fracture patients (median ISS: 10) were included in each group (4,560 patients in total). Symptomatic VTE occurred in 1.4% of patients in both matched groups (p=0.992). Bleeding control interventions occurred less often in the DOAC group, albeit statistically insignificant (5.8% vs. 6.0%, p=0.772).

Conclusions: This study found similar rates of VTE and bleeding control measures for thromboprophylaxis with DOACs or LMWH in matched trauma patients with lower extremity fractures. Further prospective research is warranted to consolidate the safety of DOAC thromboprophylaxis in trauma patients with LEF. Favorable per os administration and likely increased adherence could benefit this high-risk population.

Keywords: trauma; lower extremity; thromboprophylaxis; direct oral anticoagulant; low molecular weight heparin

Background

Several randomized controlled trials have studied the effectiveness and safety of Direct Oral Anticoagulants (DOACs) for thromboprophylaxis in elective total hip arthroplasty (THA) and total knee arthroplasty (TKA) (1-4). A meta-analysis of 16 randomized trials found DOACs, i.e. dabigatran, rivaroxaban and apixaban, to be equivalent or superior to low molecular weight heparin (LMWH) in terms of venous thromboembolism (VTE) prevention (5). Safety, measured through the incidence of major bleeding, was equivalent for dabigatran, inferior for rivaroxaban, and superior for apixaban when compared to enoxaparin for THA and TKA. Following these positive results on the effectiveness and safety of DOACs, their use for thromboprophylaxis was approved for patients undergoing elective THA and/or TKA in over 100 countries (6, 7).

While the use of DOACs for thromboprophylaxis in elective patients has been studied, VTE pharmacologic prophylaxis (PTP) in trauma patients is currently not an approved indication. The incidence of symptomatic VTE in trauma patients is significantly increased, with an in-hospital incidence of 2-12%, compared to a yearly incidence of circa 0.1% in the general population (8, 9). Lower extremity fractures (LEF), specifically pelvic, tibial and femoral fractures, are independent risk factors for developing VTE (10-13). A meta-analysis of randomized trials indicated that thromboprophylaxis halves the incidence of VTE after trauma (relative risk [RR] of 0.52) (14). PTP alone was demonstrated to be over twice as effective as mechanical prophylaxis alone (RR 0.48), and a combination is currently recommended (14). When prescribing PTP, the choice of prophylactic medication is still subject to discourse, with LMWH being the current standard (15-17).

In the American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP) database, DOACs have been prescribed to trauma patients. The indications or rationale behind prescribing DOACs are not provided in TQIP. Reasons to prescribe DOACs ‘off label’ may include contra-indications to LMWH (e.g. heparin allergy) or the preference of

the treating physician. The primary objective of this study was to compare the effectiveness and safety of thromboprophylaxis of DOACs to LMWH in trauma patients sustaining LEF.

Methods

We used the American College of Surgeons Trauma Quality Improvement Program (TQIP) database from 2013 to 2016, the years for which data on thromboprophylaxis were available. TQIP contains exclusively de-identified data, therefore approval of the Institutional Review Board was not required for this study. We adhered to the STROBE – RECORD statement in reporting on this study (18). All code and algorithms used for this study will be made available upon request.

We included all adult (≥16 years old) trauma patients admitted to trauma centers participating in TQIP between 2013 and 2016, who sustained LEF (including pelvic and acetabular fractures) and were started on DOACs or LMWH for thromboprophylaxis after admission. To identify all patients with LEF, the International Classification of Diseases (ICD), 9th and 10th Revisions, Clinical Modifications were used (Appendix A). Patients with known bleeding disorders (e.g., vitamin K deficiency, hemophilia, thrombocytopenia) or chronic anticoagulation therapy with warfarin, DOACs, clopidogrel, or similar medications, (but not aspirin therapy) were excluded.

The following variables were extracted: demography (age, sex, race); injury parameters (injury severity score [ISS], abbreviated injury scale [AIS], mechanism of injury, emergency department [ED] Glasgow Coma Scale [GCS] and vital signs (systolic blood pressure [SBP], pulse), International Classification of Diseases (ICD) injury codes; comorbidities; timing and type of the first thromboprophylactic medication started; operative or conservative LEF management; pre-PTP bleeding control surgery requirement, transfusion volume in the first 24 hours; intensive care unit (ICU) length of stay (LOS); in-hospital complications; and in-hospital mortality. Traumatic brain injury (TBI), spinal cord

injury (SCI), and various internal organ injuries (cardiac, genito-urinary, hollow viscus, major vascular, intra-abdominal) were included as covariates to identify possible contra-indications for initiating thromboprophylaxis early.

The primary outcome is a composite outcome of in-hospital symptomatic DVT and PE, as confirmed by lower extremity ultrasound or CT angiography. Safety is assessed using a proxy variable of all major bleeding events requiring intervention, which is a composite of transfusion requirement, bleeding control surgery, or angioembolization post-thromboprophylaxis initiation. The ideal safety outcome of bleeding complications as defined by the International Society for Thrombosis and Hemostasis could not be assessed using the information present in TQIP (19, 20).

Propensity score matching (PSM) was performed to create comparable groups of patients who received either DOAC or LMWH thromboprophylaxis. The propensity scores were calculated using linear logistic regression based on the following variables, which were potentially known prior to treatment allocation in a clinical setting: age [continuous], sex, race, all comorbidities (e.g. cirrhosis, COPD, history of cardiovascular disease, malignancy and current chemotherapy, smoking status, drug abuse etc.), emergency department pulse and systolic blood pressure [continuous], positive alcohol test on admission, injury mechanism and severity (ISS and AIS-lower extremity [both continuous]), femur fractures, tibial fractures, pelvic fractures, contra-indications to starting thromboprophylaxis (i.e. spine fractures, spinal cord injuries, traumatic intracranial hemorrhage, organ injuries, concomitant upper and lower extremity fractures, surgical versus conservative management of fractures and acute hemorrhage, and transfusion requirement prior to thromboprophylaxis start. DOAC and LMWH patients were matched one-to-one in a nearest-neighbor fashion on ascending observations.

Baseline variables, as well as the outcomes of interest, were compared between the groups pre- and post-matching. All normally distributed continuous variables are displayed as a mean with standard deviation. Median and interquartile range notation is used for

variables with a skewed distribution. Continuous variables were compared using Mann-Whitney test or Student's *t*-test. Categorical variables are summarized as proportions and compared using Chi^2-analysis.

Results

1,009,922 patients were identified in TQIP between 2013 and 2016, of which 335,597 sustained LEF. Of these, 179,257 received thromboprophylaxis with DOACs or LMWH. Of these, 11,617 patients were excluded due to a history of a bleeding disorder or pre-injury anticoagulation use. The final study population consisted of 167,640 patients; 165,009 received LMWH as thromboprophylaxis and 2,631 received DOACs, of which 137 received dabigatran (DTI) and 2,494 received FXa inhibitors (not further specified to apixaban, betrixaban, edoxaban or rivaroxaban). Baseline characteristics, ED presentation and injury patterns pre-matching are shown in **Table 1**. Univariate analysis indicates important differences in the studied demographics, comorbidities, and injury characteristics. The LMWH group comprises younger, less comorbid patients with higher rates of substance abuse who were more severely injured. LWMH patients received blood transfusion more often and at higher volumes. Surprisingly, thromboprophylaxis was started earlier in the LMWH group. Processes of care measures and study outcomes for unmatched patients are presented in **Table 2**.

Due the difference in group size, 86.7% of DOAC patients, but only 1.4% of LMWH patients were matched. After PSM, the study groups were best described as older (median age: 68 vs 65, $p<0.047$) patients, predominantly suffering from isolated, moderately severe (median AIS extremity = 3, median ISS = 10) femur fractures (87.1% vs 87.5% of patients). The matched groups were comparable at baseline with the exception of a statistically, but not clinically significant higher mean age in the LMWH group. Baseline characteristics, ED presentation and injury patterns of the matched groups are shown in **Table 3**. Notably,

LWMH patients were started on thromboprophylaxis significantly earlier than patients receiving DOACs (median of 40 vs 33 hours post-admission, p<0.0001). No other differences in processes of care measures were reported (**Table 4**).

The primary outcome of in-hospital symptomatic VTE occurred in 1.4% of patients in both matched groups (p=0.992). The safety outcome of bleeding control interventions occurred less often in the DOAC matched group, but this was not statistically significant (5.8% vs. 6.0%, p=0.772). No significant differences were found for any of the secondary outcome measures (**Table 4**).

Discussion

Our results from a propensity matched, nationwide cohort study indicate that the odds of developing in-hospital VTE were similar for trauma patients with lower extremity fractures using DOACs as thromboprophylaxis compared to those using LMWH. The odds of major bleeding events, measured using a proxy variable, was comparable in both treatment groups. Real world data on the use of both medications in trauma patients indicates that DOACs and LMWH were generally prescribed to different population, but when a population of predominantly femur fracture patients were analyzed, no significant differences in the rates of VTE and bleeding control measures were reported.

The results found in this study are in line with the results from randomized trials comparing DOACs and LMWH for elective THA and TKA, such as the RE-NOVATE, RE-MODEL, RECORD and ADVANCE trials (2, 21-26). Experience with DOACs in trauma patients is extremely rare, as it is an off-label use. A recent randomized controlled trial compared rivaroxaban to enoxaparin in a population of both elective and traumatic non-major orthopedic surgery patients, and found a significant reduction in symptomatic VTE, but no difference in bleeding (27). Moreover, a retrospective cohort study, also using TQIP, compared DOACs and LMWH for non-operatively managed pelvic fractures patients and

reported improved effectiveness of DOACs, without increasing the risk of bleeding complications (28). The use of DOACs for prevention of VTE in non-operatively managed pelvic fractures, or in any trauma patient, is not an officially approved indication in the US or in the European Union. It is therefore of interest to identify the patterns and rationale behind prescribing DOACs for thromboprophylaxis in trauma patients. Furthermore, cost-effectiveness of thromboprophylaxis with DOACs should be studied in trauma patients, as apixaban and rivaroxaban have proven to be cost-effective over LMWH for post-surgical thromboprophylaxis (29-32).

Rivaroxaban has also been compared to LMWH for VTE prophylaxis in a population of acutely ill medical patients in the MAGELLAN trial (33). In this trial, DOACs were non-inferior for prevention of VTE at 10 days and superior at 35 days, but led to significantly more bleeding events. The results of MAGELLAN have led to the Food and Drug Administration (FDA) approval of rivaroxaban for in-hospital VTE prophylaxis in acutely ill medical patients. This approval further expands the list of indications of DOACs beyond elective surgical patients.

Another point of interest is a potential difference in effectiveness and safety between various factor Xa inhibitors and direct thrombin inhibitors. A previous study found no significant differences between dabigatran and apixaban for the prevention of VTE in elective hip and knee replacement surgery (3). Since the trauma population is markedly different from the elective arthroplasty population and the medically ill, and our population only included 137 patients receiving dabigatran, further research comparing the effectiveness of different DOACs in the trauma population is warranted.

Beside the inherent limitations associated with retrospective studies using routinely collected healthcare data, we report several limitations that may have influenced the result of this study. First of all, the DOAC group differed significantly from the LMWH group in various studied comorbidities, vital signs, ISS, surgeries and processes of care. This is, in part, due to the large sample size of the LMWH group, in comparison to the DOAC group and the

resultant statistical power. We have controlled for potential confounding by indication by propensity score matching on an extensive list of relevant baseline and injury characteristics, as well as potential contra-indications to type and timing of thromboprophylaxis. We cannot, however, rule out the presence of unmeasured confounding in this cohort. Secondly, the timing of VTE occurrence was not available through TQIP, and as such it is not appropriate to allude to possible causality between the choice of anticoagulant medication and the incidence of VTE. Future research into this topic should employ a randomized design, or include the timing of VTE occurrence in their outcome reporting. Thirdly, the doses of the medications were not reported in TQIP. It is possible that higher doses of DOAC were prescribed, as the use of DOACS is considered 'off-label' and dosing guidelines were therefore not in place. Thirdly, safety was assessed by deduction of a proxy variable for interventions to treat bleeding after thromboprophylaxis was started, as bleeding complications, the ideal safety outcome, are not available through the TQIP database. By use of this proxy outcome, we assessed the most severe bleeding complications, as opposed to any clinically relevant bleeding. Bleeding complications may also warrant discontinuation of anticoagulant medication and use of (drug-specific) reversal agents, which is similarly not available in TQIP. It is important to note that idarucizumab [Praxbind, Boehringer Ingelheim, Ingelheim am Rhein, Germany] and andexanet alfa [Ondexxya, Portola Pharmaceuticals, South San Francisco, USA] are the approved and indicated reversal agents for life-threatening hemorrhage associated to dabigatran and apixaban/rivaroxaban respectively (34, 35). Moreover, as our safety outcome is a therapeutic intervention, our study is limited by the fact that institutional practice patters may vary, between and within treatment groups. Furthermore, it is not certain that these bleeding complications were directly attributable to initiation of thromboprophylaxis with DOACs or LMWH. Other factors, such as surgical management, initial bleeding, and comorbidities may have influenced the rate of bleeding complications (36). Using non-randomized data also does not allow inferring a causal relationship.

Conclusion

The association found in our study suggests similar rates of VTE and bleeding control measures in trauma patients with lower extremity fractures treated with DOACs or LMWH for thromboprophylaxis. Further prospective, and ideally randomized research is warranted to consolidate the safety of DOAC use for prevention of VTE in trauma patients with LEF, and in the general trauma population. A favorable per os administration and likely increased adherence could benefit this high-risk population.

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Figures and Tables

Table 1 ⊖ Baseline characteristics, emergency department presentation, and injury pattern of unmatched cohorts.

Variable	DOAC (n = 2.631)	LMWH (n = 165.009)	P-value
Median age (IQR)	69 (51-80)	51 (28-69)	<0.0001
Female	61.6%	45.5%	<0.0001
Diabetes	17.0%	12.2%	<0.0001
Smoker	12.9%	22.5%	<0.0001
History cerebrovascular accident	3.0%	2.0%	<0.0001
Hypertension	48.6%	34.1%	<0.0001
History myocardial infarction	1.1%	0.9%	0.149
History peripheral vascular disease	0.7%	0.6%	0.312
Congestive heart failure	5.1%	2.9%	<0.0001
Cirrhosis	0.6%	0.7%	0.624
Chemotherapy	0.8%	0.3%	<0.0001
Disseminated cancer	0.9%	0.6%	0.143
Chronic renal failure	1.4%	1.0%	0.032
Drug abuse	2.9%	7.3%	<0.0001
Alcoholism	4.1%	6.6%	<0.0001
Chronic obstructive pulmonary disease	10.6%	7.9%	<0.0001
Dementia	10.5%	6.1%	<0.0001
Psychiatric illness	12.4%	10.5%	0.003
Emergency department presentation			
Median ISS [IQR]	10 [9-10]	10 [9-17]	<0.0001
Blut mechanism of injury	98.86%	95.10%	<0.0001
Mean SBP in the ED (SD)	146 (28)	137 (27)	0.353
Mean pulse (SD)	83 (17)	90 (20)	<0.0001
Median GCS (IQR)	15 [15-15]	15 [15-15]	<0.0001
Positive ETOH test	8.3%	5.1%	<0.0001
Injury pattern			
Median AISdextremity	3 (3-3)	3 (2-3)	<0.0001
Upper and lower extremity injured	17.07%	30.21%	<0.0001
Femur fracture	88.4%	61.1%	<0.0001
Tibial fracture	7.0%	18.6%	<0.0001
Traumatic brain injury	4.7%	12.9%	<0.0001
Rib fracture	5.5%	19.7%	<0.0001
Pelvic fracture	6.1%	22.6%	<0.0001
Spinal fracture	0.1%	17.1%	<0.0001
Spinal cord injury	0.2%	0.7%	0.001
Organ and soft tissue injuries			
Thoracic organ injury	2.6%	11.7%	<0.0001
Hollow viscus injury	0.3%	2.4%	<0.0001
Other intra-abdominal organ	1.6%	9.3%	<0.0001
Major vascular injury	0.2%	1.0%	<0.0001
Genitourinary injury	0.3%	1.7%	<0.0001

ISS = Injury Severity Score; SBP = systolic blood pressure; ED = emergency department; GCS = Glasgow Coma Score; ETOH = ethanol/alcohol; AIS = abbreviated injury score; DOAC = direct oral anticoagulant; LMWH = low-molecular-weight heparin; IQR = interquartile range; SD = standard deviation.

Table 2 e Processes of care and outcome measures of unmatched cohorts.

Variable	DOAC (n = 2631)	LMWH (n = 165,009)	P-value
Acute bleeding control surgery pre-PTP	0.5%	3.5%	<0.0001
Hours to prophylaxis started	46.3 (38.6)	41.9 (43.8)	<0.0001
Min-Max	0-492	0-488	e
Patients requiring RBC transfusion pre-PTP	1.3%	5.5%	<0.0001
RBC transfusion in 24 h (mL) (SD)	1117 (198)	1767 (24.6)	0.393
ICU LOS days (SD)	5.2 (5.7)	7.2 (8.1)	<0.0001
Nonoperatively managed LEF	7.8%	19.4%	<0.0001
Outcomes measures			
Symptomatic venous thromboembolism	1.4%	2.5%	<0.0001
Pulmonary embolism	0.6%	0.9%	0.048
Deep venous thrombosis	0.9%	1.8%	0.001
Bleeding control intervention	5.8%	5.7%	0.761
Bleeding control surgery	0.0%	0.1%	0.204
Angioembolization	0.0%	0.0%	0.489
Blood component transfusion post-PTP	5.8%	5.6%	0.649
Myocardial infarction	0.3%	0.3%	0.745
Unplanned ICU readmission	1.4%	1.7%	0.311
Unplanned intubation	0.5%	1.3%	0.001
In-hospital mortality	0.6%	1.0%	0.051

DOAC = Direct oral anticoagulant; LMWH = low-molecular-weight heparin; PTP = pharmacologic thromboprophylaxis; RBC = red blood cells; IQR = interquartile range; ICU = Intensive Care Unit; LOS = Length of Stay; LEF = lower extremity fracture; ICU = intensive care unit.

Table 3 e Baseline characteristics, emergency department presentation, and injury pattern of propensity score matched cohorts.

Variable	DOAC (n = 2.280)	LMWH (n = 2.280)	P-value
Median age (IQR)	68 (48-79)	65 (41-80)	0.047
Female	58.7%	58.7%	0.974
Diabetes	16.8%	16.1%	0.497
Smoker	13.9%	14.9%	0.329
History cerebrovascular accident	3.0%	2.9%	0.918
Hypertension	47.2%	48.4%	0.783
History myocardial infarction	1.1%	0.9%	0.369
History peripheral vascular disease	0.8%	0.7%	0.595
Congestive heart failure	4.5%	3.7%	0.172
Cirrhosis	0.6%	0.6%	0.842
Chemotherapy	0.2%	0.3%	0.529
Disseminated cancer	0.9%	0.6%	0.232
Chronic renal failure	1.2%	1.2%	0.900
Drug abuse	3.3%	3.9%	0.308
Alcoholism	4.3%	4.3%	0.927
Chronic obstructive pulmonary disease	10.0%	10.1%	0.747
Dementia	10.0%	10.5%	0.647
Psychiatric illness	11.3%	11.2%	0.937
Emergency department presentation			
Median ISS [IQR]	10 [9-10]	10 [9-10]	0.483
Mechanism of injury	98.6%	98.7%	0.791
Median SBP in the ED (IQR)	142 (124-160)	141 (124-158)	0.515
Median pulse (IQR)	81 (71-94)	82 (82-93)	0.469
Median GCS (IQR)	15 (15-15)	15 (15-15)	0.505
Positive ETOH test	5.0%	5.1%	0.909
Injury pattern			
Median AIS-extremity	3 (3-3)	3 (3-3)	0.501
Upper and lower extremity injured	17.6%	19..0%	0.208
Femur fracture	87.1%	87.5%	0.632
Tibial fracture	7.6%	7.1%	0.481
Traumatic brain injury	5.4%	4.3%	0.093
Rib fracture	6.0%	6.7%	0.314
Pelvic fracture	6.9%	6.4%	0.795
Spinal fracture	5.9%	5.7%	0.794
Spinal cord injury	0.2%	0.4%	0.405
Organ and soft tissue injuries			
Thoracic organ injury	2.9%	3.0%	0.943
Hollow viscus injury	0.4%	0.4%	0.996
Other intra-abdominal organ	1.8%	2.0%	0.672
Major vascular injury	0.2%	0.1%	0.477
Genitourinary injury	0.3%	0.2%	0.560

ISS = Injury Severity Score; SBP = systolic blood pressure; ED = emergency department; GCS = Glasgow Coma Score; ETOH = ethanol/alcohol; AIS = abbreviated injury score; DOAC = direct oral anticoagulant; LMWH = low-molecular-weight heparin; IQR = interquartile range; SD = standard deviation.

Table 4 ⊖ Processes of care and outcome measures of propensity score matched cohorts.

Variable	DOAC (n = 2.280)	LMWH (n = 2.280)	P-value
Acute bleeding control surgery pre-PTP	0.5%	0.6%	0.846
Median hours to prophylaxis (IQR)	40 (28-53)	33 (19-45)	<0.0001
Min-max	0-755	0-411	⊖
Patients requiring RBC transfusion pre-PTP	1.7%	2.0%	0.517
RBC transfusion in 24 h (mL) (SD)	930 (320-1500)	1200 (600-1960)	0.499
ICU LOS days (SD)	5.4 (5.7)	5.7 (5.6)	0.604
Nonoperatively managed LEF	8.5%	8.6%	0.895
Outcomes measures			
Symptomatic venous thromboembolism	1.4%	0.4%	0.992
Pulmonary embolism	0.5%	0.6%	0.687
Deep venous thrombosis	1.0%	0.9%	0.871
Bleeding control intervention	5.8%	6.0%	0.772
Bleeding control surgery	0.0%	0.1%	0.158
Angioembolization	0	0	⊖
Blood component transfusion post-PTP	5.8%	6.0%	0.722
Myocardial infarction	0.4%	0.3%	0.435
Unplanned ICU readmission	1.3%	1.3%	0.888
Unplanned intubation	0.6%	0.4%	0.271
In-hospital mortality	0.7%	0.8%	0.736

DOAC = direct oral anticoagulant; LMWH = low-molecular-weight heparin; PTP = pharmacologic thromboprophylaxis; RBC = red blood cells; IQR = interquartile range; ICU = intensive care unit; LOS = length of stay; LEF = lower extremity fracture.