Direct oral anticoagulants are a potential alternative to low-molecular-weight heparin for thromboprophylaxis in trauma patients sustaining lower extremity fractures

Nederpelt, C.J.; Breen, K.A.; Hechi, M.W. el; Krijnen, P.; Huisman, M.V.; Schipper, I.B.; ... ; Rosenthal, M.G.

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.JournalofSurgicalResearch.com

Check for updates

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

Charlie J. Nederpelt, BSc,[a,b,] Kerry A. Breen, BS,[a] Majed W. el Hechi, MD,[a] Pieta Krijnen, PhD,[b] Menno V. Huisman, MD, PhD,[c] Inger B. Schipper, MD, PhD,[b] Haytham M.A. Kaafarani, MD, MPH,[a,d] and Martin G. Rosenthal, MD[a]*

[a] *Division of Trauma, Emergency Surgery and Surgical Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts*
[b] *Department of Trauma Surgery, Leiden University Medical Center, Leiden University, Leiden, the Netherlands*
[c] *Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden University, Leiden, the Netherlands*
[d] *Center for Outcomes & Patient Safety in Surgery (COMPASS), Massachusetts General Hospital, Boston, Massachusetts*

ARTICLE INFO

Article history:
Received 28 April 2020
Received in revised form
31 August 2020
Accepted 13 October 2020
Available online 11 November 2020

Keywords:
Trauma
Lower extremity
Thromboprophylaxis
Direct oral anticoagulant
Low molecular weight heparin

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 anticoagusants (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 with low-molecular-weight heparin (LMWH) in trauma patients sustaining LEF.

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

Results: Of 1,009,922 patients in trauma quality improvement program, 167,640 met inclusion criteria (165,009 received LMWH and 2631 received DOACs). After propensity score matching, 2280 predominantly elderly (median age: 67 y) isolated femur fracture patients (median ISS: 10) were included in each group (4560 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% *versus* 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 LEF. Further

The authors report no potential conflicts of interest pertaining to the topic of this submission.

* *Corresponding author*. Massachusetts General Hospital, 165 Cambridge Street, Boston, MA 02114. Tel.: + 1-617-726-9591.
E-mail address: charlie.nederpelt@live.nl (C.J. Nederpelt).

https://doi.org/10.1016/j.jss.2020.10.009

prospective research is warranted to consolidate the safety of DOAC thromboprophylaxis in trauma patients with LEF. Favorable oral administration and likely increased adherence could benefit this high-risk population.

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, that is dabigatran (DTI), 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 DTI, inferior for rivaroxaban, and superior for apixaban when compared with 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 with 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 contraindications 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 with LMWH in trauma patients sustaining LEF.

Methods

We used the ACS-TQIP database from 2013 to 2016, the years for which data on thromboprophylaxis were available. TQIP contains exclusively deidentified data, and 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 on request.

We included all adult (≥16 y 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, ninth and 10th Revisions, Clinical Modifications were used (Appendix A). Patients with known bleeding disorders (e.g., vitamin K deficiency, hemophilia, and 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, and race); injury parameters (injury severity score [ISS], abbreviated injury scale [AIS], mechanism of injury, emergency department [ED] Glasgow Coma Scale, and vital signs (systolic blood pressure and pulse), International Classification of Diseases 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 h; intensive care unit length of stay; in-hospital complications; and in-hospital mortality. Traumatic brain injury, spinal cord injury, and various internal organ injuries (cardiac, genitourinary, hollow viscus, major vascular, and intra-abdominal) were included as covariates to identify possible contraindications 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 computed tomography 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 postthromboprophylaxis 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 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 before treatment allocation in a clinical setting: age [continuous], sex, race, all comorbidities (e.g., cirrhosis, chronic obstructive pulmonary disease, 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, contraindications to starting thromboprophylaxis (i.e.,

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 AIS—extremity	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.

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 before 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 prematching and postmatching. All normally distributed continuous variables are displayed as a mean with standard deviation. Median and

Table 2 – 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	–
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.

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-squared 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 preinjury anticoagulation use. The final study population consisted of 167,640 patients; 165,009 received LMWH as thromboprophylaxis and 2631 received DOACs, of which 137 received DTI and 2494 received factor Xa inhibitors (not further specified to apixaban, betrixaban, edoxaban, or rivaroxaban). Baseline characteristics, ED presentation, and injury patterns prematching 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.

Because of the difference in group size, 86.7% of DOAC patients, but only 1.4% of LMWH patients were matched. After propensity score matching, the study groups were best described as older (median age: 68 *versus* 65 y, $P < 0.047$) patients, predominantly suffering from isolated, moderately severe (median AIS extremity = 3 and median ISS = 10) femur fractures (87.1% *versus* 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 *versus* 33 h postadmission, $P < 0.0001$). 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% *versus* 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 LEF using DOACs as thromboprophylaxis compared with those using LMWH. The odds of major bleeding events, measured using a proxy variable, were comparable in both treatment groups. Real world data on the use of both medications in trauma patients

Table 3 – 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.

indicate that DOACs and LMWH were generally prescribed to different population, but when a population of predominantly femur fracture patients was 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

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.

recent randomized controlled trial compared rivaroxaban with enoxaparin in a population of both elective and traumatic nonmajor 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 nonoperatively managed pelvic fracture patients and reported improved effectiveness of DOACs, without increasing the risk of bleeding complications.[28] The use of DOACs for prevention of VTE in nonoperatively managed pelvic fractures, or in any trauma patient, is not an officially approved indication in the United States 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 postsurgical thromboprophylaxis.[29-32]

Rivaroxaban has also been compared with LMWH for VTE prophylaxis in a population of acutely ill medical patients in the MAGELLAN trial.[33] In this trial, DOACs were noninferior for prevention of VTE at 10 d and superior at 35 d, but led to significantly more bleeding events. The results of MAGELLAN have led to the Food and Drug Administration 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 DTI and apixaban for the prevention of VTE in elective hip and knee replacement surgery.[3] Because the trauma population is markedly different from the elective arthroplasty population and the medically ill, and our population only included 137 patients receiving DTI, further research comparing the effectiveness of different DOACs in the trauma population is warranted.

Besides the inherent limitations associated with retrospective studies using routinely collected health care 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 with the DOAC group and the resultant statistical power. We have controlled for potential confounding by indication by PSM on an extensive list of relevant baseline and injury characteristics, as well as potential contraindications to type and timing of thromboprophylaxis. We cannot, however, rule out the presence of unmeasured confounding in this cohort. Second, 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 use a randomized design or include the timing of VTE occurrence in their outcome reporting. Third, the doses of the medications were not reported in TQIP. It is possible that higher doses of DOACs were prescribed, as the use of DOACs is considered "off-label," and dosing guidelines were therefore not in place. Third, 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] are the approved and indicated reversal agents for life-threatening hemorrhage associated with DTI 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 nonrandomized 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 LEF 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.

Acknowledgment

Author's contributions: C.J.N., P.K., I.B.S., M.V.H., and M.G.R. were involved in study conception and design. C.J.N., K.A.B., and M.W.H. performed data preparation and analysis. All authors were involved in result interpretation. C.J.N. wrote the manuscript. All authors were involved in manuscript revision.

Disclosure

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

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jss.2020.10.009.

REFERENCES

1. Lassen MR, Gent M, Kakkar AK, et al. The effects of rivaroxaban on the complications of surgery after total hip or knee replacement: results from the RECORD programme. *J Bone Joint Surg Br*. 2012;94:1573–1578.
2. Eriksson BI, Kakkar AK, Turpie AG, et al. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. *J Bone Joint Surg Br*. 2009;91:636–644.
3. Mayer A, Schuster P, Fink B. A comparison of apixaban and dabigatran etexilate for thromboprophylaxis following hip and knee replacement surgery. *Arch Orthop Trauma Surg*. 2017;137:797–803.
4. Bonarelli S, Bacchin MR, Frugiuele I, Feoli MA, Facchini F, Altimari V. Dabigatran etexilate and LMWH for the prevention of venous thromboembolism in 532 patients undergoing hip surgery. *Eur Rev Med Pharmacol Sci*. 2015;19:897–903.
5. Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ*. 2012;344:e3675.
6. Kendoff D, Perka C, Fritsche HM, Gehrke T, Hube R. Oral thromboprophylaxis following total hip or knee replacement: review and multicentre experience with dabigatran etexilate. *Open Orthop J*. 2011;5:395–399.
7. Rachidi S, Aldin ES, Greenberg C, Sachs B, Streiff M, Zeidan AM. The use of novel oral anticoagulants for thromboprophylaxis after elective major orthopedic surgery. *Expert Rev Hematol*. 2013;6:677–695.
8. Rogers FB. Venous thromboembolism in trauma patients: a review. *Surgery*. 2001;130:1–12.
9. Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol*. 2007;44:62–69.
10. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. *N Engl J Med*. 1994;331:1601–1606.
11. Meizoso JP, Karcutskie CAt, Ray JJ, et al. A simplified stratification system for venous thromboembolism risk in severely injured trauma patients. *J Surg Res*. 2017;207:138–144.
12. Karcutskie CA, Meizoso JP, Ray JJ, et al. Association of mechanism of injury with risk for venous thromboembolism after trauma. *JAMA Surg*. 2017;152:35–40.
13. Chana-Rodriguez F, Mananes RP, Rojo-Manaute J, Haro JA, Vaquero-Martin J. Methods and guidelines for venous thromboembolism prevention in polytrauma patients with pelvic and acetabular fractures. *Open Orthop J*. 2015;9:313–320.
14. Barrera LM, Perel P, Ker K, Cirocchi R, Farinella E, Morales Uribe CH. Thromboprophylaxis for trauma patients. *Cochrane Database Syst Rev*. 2013;3:CD008303.
15. Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med*. 1996;335:701–707.
16. Byrne JP, Geerts W, Mason SA, et al. Effectiveness of low-molecular-weight heparin versus unfractionated heparin to prevent pulmonary embolism following major trauma: a propensity-matched analysis. *J Trauma Acute Care Surg*. 2017;82:252–262.
17. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of chest physicians Evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl l). e419S-e96S.

18. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med*. 2015;12:e1001885.
19. Schulman S, Angeras U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8:202–204.
20. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694.
21. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate versus enoxaparin for venous thromboembolism prevention after total hip arthroplasty: pooled analysis of two phase 3 randomized trials. *Thromb J*. 2015;13:36.
22. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost*. 2007;5:2178–2185.
23. Forster R, Stewart M. Anticoagulants (extended duration) for prevention of venous thromboembolism following total hip or knee replacement or hip fracture repair. *Cochrane Database Syst Rev*. 2016;3:CD004179.
24. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med*. 2008;358:2765–2775.
25. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med*. 2009;361:594–604.
26. Lassen MR, Gallus A, Raskob GE, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med*. 2010;363:2487–2498.
27. Samama CM, Laporte S, Rosencher N, et al. Rivaroxaban or enoxaparin in nonmajor orthopedic surgery. *N Engl J Med*. 2020;382:1916–1925.
28. Hamidi M, Zeeshan M, Sakran JV, et al. Direct oral anticoagulants vs low-molecular-weight heparin for thromboprophylaxis in nonoperative pelvic fractures. *J Am Coll Surg*. 2019;228:89–97.
29. Torrejon Torres R, Saunders R, Ho KM. A comparative cost-effectiveness analysis of mechanical and pharmacological VTE prophylaxis after lower limb arthroplasty in Australia. *J Orthop Surg Res*. 2019;14:93.
30. Diamantopoulos A, Lees M, Wells PS, Forster F, Ananthapavan J, McDonald H. Cost-effectiveness of rivaroxaban versus enoxaparin for the prevention of postsurgical venous thromboembolism in Canada. *Thromb Haemost*. 2010;104:760–770.
31. Ryttberg L, Diamantopoulos A, Forster F, Lees M, Fraschke A, Bjorholt I. Cost-effectiveness of rivaroxaban versus heparins for prevention of venous thromboembolism after total hip or knee surgery in Sweden. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11:601–615.
32. Monreal M, Folkerts K, Diamantopoulos A, Imberti D, Brosa M. Cost-effectiveness impact of rivaroxaban versus new and existing prophylaxis for the prevention of venous thromboembolism after total hip or knee replacement surgery in France, Italy and Spain. *Thromb Haemost*. 2013;110:987–994.
33. Cohen AT, Spiro TE, Buller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368:513–523.
34. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380:1326–1335.
35. Pollack Jr CV, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377:431–441.
36. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–1100.