

Orthopaedics-2021: DIRECT ORAL ANTI-COAGULANTS IN THE PREVENTION OF VENOUS THROMBOEMBOLISM FOLLOWING SURGERY FOR HIP FRACTURE IN THE ELDERLY

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Venous thromboembolism (VTE), which comprises pulmonary embolism (PE) and deep vein thrombosis (DVT), is a significant cause of morbidity and mortality following hip fracture.¹ The elderly hip fracture population in particular is at the highest risk of developing VTE.² In the absence of prophylactic measures, the postoperative incidence of VTE following hip fracture is estimated to range between 40% and 60%.³ This is reduced to 1.4% to 3.5% with the use of effective anticoagulation strategies, which typically utilize anticoagulants such as low-molecular-weight heparin (LMWH), fondaparinux, or warfarin.⁴⁻⁶ In recent years, the role of direct oral anticoagulants (DOACs) in major orthopedic surgery has grown extensively.^{7,8} The DOACs are advantageous as they are administered orally, have a predictable pharmacological profile, and do not require monitoring.⁹ Furthermore, several studies have demonstrated that DOACs are associated with lower rates of VTE without increased risk of hemorrhage compared to conventional anticoagulants for lower limb orthopedic surgery.¹⁰⁻¹⁵ However, there is limited evidence regarding the use of DOACs as VTE prophylaxis following surgery for hip fracture, with LMWH the preferred form of anticoagulation.¹⁶ This study aims to evaluate the efficacy and safety of DOACs in older adults undergoing surgery for hip fracture.

Methods

Population This is a single-center, retrospective, population-based cohort study of patients receiving either a DOAC (apixaban, rivaroxaban, and dabigatran) or LMWH (dalteparin) for VTE prophylaxis following surgery for hip fracture from January 1, 2017, to December 31, 2018. Patients with any of the following were excluded: missing data, age <65 years, previous PE or DVT, previous major hemorrhage, underlying malignancy, or inherited disorder of coagulation. All patients were followed up for 30 days postoperatively.

Clinical Parameters The following data were obtained: patient demographics, comorbidities, fracture classification, American Society of Anesthesiologists (ASA) classification, time to surgery, procedure performed, and length of stay. The outcomes assessed were incidence of PE and DVT, incidence of major hemorrhage, blood transfusion, and death within 30 days of surgery. Both PE and DVT were diagnosed using computed tomography pulmonary angiography and duplex ultrasound scanning, respectively. Major hemorrhage was defined in accordance with the International Association of Thrombosis and Hemostasis Scientific Committee and included hemorrhage from the gastrointestinal, urinary,

and cerebrovascular systems.¹⁷ In the event of death, the coroner's report, hospital, and general practice records were reviewed to establish the cause of death.

Administration Regime The administration regime for all medications were based on guidelines from the British National Formulary. Apixaban was administered 2.5 mg twice daily to be started 12 to 24 hours after surgery. Rivaroxaban was administered 10 mg once daily to be started 6 to 10 hours after surgery. Dabigatran was administered at 75 mg, to be taken 1 to 4 hours after surgery, followed by 150 mg once daily for 10 days, to be taken on the first day after surgery. Dalteparin was administered initially at 5000 units for 1 dose, to be given on the evening before surgery, followed by 5000 units after 24 hours, and then 5000 units every 24 hours. The duration for treatment across both groups was standardized at 6 weeks (42 days).

Statistical Analysis Multivariate analysis was performed using IBM SPSS Statistics (Armonk, New York). Summary statistics are presented as percentages, means, and standard deviations. The Student *t* test was used to analyze parametric data, while the *w*² test was used to analyze categorical data. Relative risk (RR) is presented with 95% confidence interval (CI) and *P* value and calculated using the method described by Altman.¹⁸

Ethics Approval This was a retrospective study and only anonymized data previously acquired as part of the patient workup or for service evaluation purposes were used. Ethical approval was waived following review of the study proposal by the local ethics committee.

Results There were 379 patients who underwent surgery for hip fracture during the 2-year study period. Of these, 321 patients were included in this study, with 54 patients in the DOAC group and 267 patients in the LMWH group. In the DOAC group, 79.6% of patients received apixaban, 16.7% received rivaroxaban, and 3.7% received dabigatran. All patients included in the final analysis were followed up for a duration of 30 days. The mean age of the study cohort was 85.5 ± 11.0 years, and the male–female ratio was 104:217 (Tables 1 and 2). The right hip was involved in 43.0% of cases and the left in the remaining 57.0%. The cohort comprised intracapsular fractures in 59.2%, intertrochanteric fractures in 38.0%, and subtrochanteric fractures in the remaining 2.8%. Hemiarthroplasty was performed in 40.2% of cases, followed by dynamic hip screw in 44.9%, total hip arthroplasty in 11.2%, and intramedullary nailing in 3.7%. The mean time to surgery was 0.9 ± 0.6 days and length of hospital stay was 17.9 ± 13.3 days. Pre- and postoperative hemoglobin levels were 122.6 ± 15.3 g/L and 102.8 ± 16.3 g/L, respectively. The DOAC group had a VTE incidence of 0% compared to the LMWH group, which was 3.4% (RR: 0.26, 95% CI: 0.02–

4.34, P<0.05; Table 3). Pulmonary embolism occurred in 0% of patients in the DOAC group and in 3.0% in the LMWH group (RR: 0.29, 95%CI: 0.02-4.89, P<0.05), while DVT occurred in 0% of patients in the DOAC group and 0.3% of patients in the LMWH group (RR: 1.62, 95%CI: 0.07-39.35, P<0.05). Hemorrhage occurred in 7.4% of patients in the DOAC group and 3.0% of patients in the LMWH group (RR: 2.47, 95%CI: 0.77-7.91, P<0.05). The incidence of blood transfusion was 20.4% in the DOAC group and 23.6% in the LMWH group (RR: 0.86, 95%CI: 0.48-1.53, P<0.05). Wound hematoma occurred in 1.9% of patients treated with a DOAC and 1.1% of patients treated with LMWH (RR: 1.65, 95%CI: 0.17-15.55, P<0.05). All-cause mortality in the DOAC group was 7.4%. Comparatively, all-cause mortality in the LMWH group was 3.4% (RR: 2.20, 95%CI: 0.70-6.88, P<0.05). Mortality from VTE was 0% in the DOAC group and 0.7% in the LMWH group (RR: 0.97, 95%CI: 0.05-20.02, P<0.05). Mortality from hemorrhage was 1.9% in the DOAC group and 0.7% in the LMWH group (RR: 2.47, 95%CI: 0.23-26.78, P<0.05). Hemorrhage leading to death in the DOAC and LMWH groups was due to gastrointestinal and intracranial hemorrhage sources, respectively.

Discussion In the present study, the use of DOACs for VTE prophylaxis following surgery in older adults with hip fracture was associated with a similar rate of VTE compared to LMWH. These findings are comparable to previous studies evaluating the efficacy of DOAC therapy for prevention of VTE in lower limb orthopedic surgery.^{10-15,19,20} Although nonsignificant, there was a trend toward an elevated risk of hemorrhage, which was not reported in earlier studies of elective orthopedic surgery.^{10-15,19,20} The elderly hip fracture population are frail, have multiple comorbidities, and are at high risk of falls, which predispose them to life-threatening hemorrhage.² As such, this finding warrants further investigation. The rates of VTE in the DOAC and LMWH groups were 0% and 3.4%, respectively, which are comparable to the literature.^{21,22} In a randomized controlled trial (RCT) by Tang and colleagues, the rate of VTE was significantly lower with DOAC use at 5.2% compared to LMWH use at 14.7%.¹⁹ The

lower rates of VTE reported in both the DOAC and LMWH groups in the present study can be attributed to difference in study design. Patients enrolled in RCTs undergo routine investigation for VTE leading to detection of asymptomatic PE and DVT, although there remains considerable debate regarding the clinical significance of these.²³ In contrast, patients in our study only underwent further testing in the presence of clinical features, so only symptomatic VTE were

identified. Both the DOAC and LMWH cohorts in this study are very similar in terms of age, gender, fracture pattern, and classification. However, a larger proportion of patients in the DOAC group had an ASA classification grade of 3 or more, which may suggest a poorer prognosis for these patients. Furthermore, total hip replacements were performed more frequently in the LMWH group. This may be indicative of a higher baseline level of function and mobility in the LMWH group compared to the DOAC group. It must be noted that the DOAC group had a lower incidence of stage 4 and stage 5 chronic kidney disease, which may have influenced the decision to prescribe a DOAC over LMWH. The timing of DOAC administration remains unclear and varies with the DOAC type. The current consensus is that the DOAC should be resumed postoperatively once hemostasis has been achieved and after at least 24 hours (typically 2-3 days) following major surgery.^{24,25} There are several limitations that must be considered in the present study. The retrospective design of the study results in inherent biases and confounding factors that could potentially influence our findings. To minimize the effects of these, multi-variate analysis was used. The decision to prescribe a DOAC was made at the discretion of a senior clinician based on the presence of clinical risk factors for thromboembolic events such as atrial fibrillation or previous cerebrovascular accident, which was balanced against the risk of hemorrhage. Thus, the DOAC cohort is likely to represent a carefully selected population of patients who are most likely to benefit from therapy. The sample size of our study was restricted to 321 patients, and there was no a priori estimate of sample size. It is likely that a larger sample size would be required to detect a clinically significant difference between the 2 groups. This is reflective of prescribing practice in the United Kingdom where LMWH remains the first-line treatment for VTE prophylaxis, so only a small proportion of patients receive DOACs.

In the present study of a carefully selected cohort of patients, the effect of DOACs in reducing the risk of VTE following surgery for hip fracture in older adults was comparable to LMWH. However, a trend toward an increased risk of hemorrhage was noted, which necessitates further investigation. The elderly hip fracture population present an important clinical conundrum given that they are at increased risk of developing VTE as well as life-threatening hemorrhage. These risks can be mitigated through careful selection of patients. Future studies with larger patient populations will be required to identify patients who stand to benefit the most from treatment.