Equivalence of DOACS and LMWH for thromboprophylaxis after hip fracture surgery: Systematic review and meta-analysis

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Abstract

Background: Patients with hip fractures (HF) have an increased risk of venous thromboembolism (VTE). In elective orthopedic surgery direct oral anticoagulants (DOACs) have proven to be similarly or more effective compared to low molecular weight heparin (LMWH), but DOACs are not yet approved for thromboprophylaxis in trauma patients with HF. The aim of this study was to systematically review the literature comparing the effectiveness of DOACs and LMWH for thromboprophylaxis in trauma patients with surgically treated HF.

Materials and Methods: We searched PubMed, the Cochrane Library, Web of Science, and Embase. The primary outcome was the incidence of VTE (symptomatic and asymptomatic combined). Secondary outcomes were symptomatic VTE; a symptomatic VTE, symptomatic deep venous thrombosis (DVT); symptomatic pulmonary embolism (PE); major, clinically relevant non-major (CRNM), and minor bleeding.

Results: The search resulted in 738 titles. Five studies matched inclusion criteria. In total, 4748 hip fracture patients were analyzed (DOACs: 2276 patients, LMWH: 2472 patients). The pooled odds ratio for the risk of VTE for DOAC use was 0.52 (95% confidence interval 0.25–1.11, p = 0.09) compared to LMWH. No statistically significant differences between DOAC and LMWH were found for asymptomatic VTE, symptomatic DVT, PE, major or CRNM bleeding, and minor bleeding.

Conclusions: Meta-analysis of the literature suggests that DOACs are associated with equivalent effectiveness and safety compared to LMWH.

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Introduction

Venous thromboembolism (VTE), i.e. deep venous thrombosis (DVT) and pulmonary embolism (PE), is a potentially lethal, major public health concern. The reported incidence in the general population ranges from 83 to 184 per 100,000 patient years [1–6]. Major surgery, traumatic injury/fracture, hospitalization, and prior VTE are among the strongest predictors for developing VTE [7–9]. Patients with hip fractures are at a particularly high risk, due to prolonged non-weight bearing and extensive tissue damage [10–14]. While not indicated in all trauma patients, pharmacologic thromboprophylaxis lowers the risk of fatal PE in hip fracture patients [15–17].

Reports of high prevalence of fatal PE in hospitalized patients (5–30% on autopsy) have led to the identification of PE as the number one preventable cause of in-hospital mortality [18–21]. Moreover, DVTs result in a post-thrombotic syndrome in 20–60% of patients, which is associated with high morbidity, including edema and venous ulcers, and significantly decreased quality of life [22–25]. Pharmacologic and mechanical thromboprophylaxis are proven to be effective for the prevention of VTE, but guidelines are not consistently adhered to [17,26]. Considering the mortality and morbidity associated with VTE, especially in elderly hip fracture patients, it is imperative to continually evaluate and improve thromboprophylaxis guidelines.

Current guidelines recommend the subcutaneous administration of low molecular weight heparins (LMWH) as the first-choice treatment for patients with orthopedic trauma, in the absence of contra-indications and as soon as deemed safe [17,27]. In case of
elective total hip and knee arthroplasty, direct oral anticoagulants (DOACs) have proven to be similarly or even more effective compared to LMWH without increasing the risk of bleeding, as studied in numerous randomized trials and meta-analyses [28–33]. However, the role of DOACs in thromboprophylaxis guidelines after trauma is not yet established. Surprisingly, DOACs were prescribed off-label to trauma patients with lower extremity fractures in the United States, predominantly to those with surgically treated hip fractures [34]. Therefore, the primary aim of this study was to systematically review and summarize the current literature comparing the efficacy and safety of DOACs and LMWH for thromboprophylaxis in surgically treated hip fracture patients.

**Methods**

We adhered to the PRISMA statement in reporting this meta-analysis [35]. With the help of an experienced medical librarian, we searched PubMed, the Cochrane Library, Web of Science, and Embase using a combination of the search terms ‘direct oral anticoagulants’, ‘low molecular weight heparin’ and ‘lower extremity fractures’ (Appendix A). The inclusion criteria for study selection were the following: randomized controlled trials (RCT) or observational cohort studies; comparing post-operative thromboprophylaxis with DOACs to LMWH; in patients with traumatic hip fractures. Besides RCTs, non-randomized prospective and retrospective studies, as well as studies including both hip and other fractures were included considering the urgent demand for clinical evidence in the light of reported off-label prescription of DOACs to trauma patients, and considering the relative novelty of DOACs and an expected scarcity of literature on this topic. Studies were excluded if conservatively and operatively treated patients were not reported separately, if results for pathologic and traumatic fractures were not reported separately, if incidence of VTE (primary outcome of the meta-analysis) was not reported, or if medication type was switched (e.g. if in-hospital enoxaparin was switched to rivaroxaban at hospital discharge). Authors of studies on lower extremity trauma without hip fracture subset analysis were approached to provide outcome data of the surgically treated hip fracture patients in their study.

The primary outcome was VTE, both symptomatic and asymptomatic. Secondary outcomes were symptomatic VTE, symptomatic DVT, symptomatic PE, asymptomatic VTE, major bleeding, clinically relevant non-major (CRNM) bleeding, and minor bleeding.
Furthermore, we extracted the following data from included studies: country, study design, medication type and dose regimen, length of follow-up, and definition of outcome parameters.

Article selection and data extraction were performed independently by two authors (QB, CN) using the systematic review management tool Covidence (Covidence [Computer program]. Version accessed February 2020, Melbourne, Australia: Veritas Health Innovation). Disagreement was settled by a third reviewer (IS). Risk of Bias was assessed using the Cochrane risk-of-bias (RoB 2) tool for RCTs and the MINORS tool for cohort studies [36,37]. Data synthesis was performed using Review Manager (RevMan [Computer program]. Version 5.4.1, The Cochrane Collaboration, 2020). In case of statistical heterogeneity ($I^2 > 50\%$), a random effects model was used, otherwise a fixed effects model was used to calculate pooled odds ratios (OR) and 95% confidence intervals (CI). The within study OR were used for meta-analysis of the study outcomes. Two sub-analyses were performed to assess the pooled OR of the primary outcome in RCTs, and non-randomized studies separately. Furthermore, a funnel plot was constructed using the primary outcome to assess potential publication bias.

### Results

The final search strategy was performed on January 4, 2021 and resulted in 652 unique records. Two studies were identified that included surgically treated hip fracture patients but did not present subset analysis [34,38]. Subset data were obtained from one of these studies [34]. The process of article selection is presented in Fig. 1. Ultimately, five studies were included [34,39-42].

#### Risk of bias assessment

There was moderate to high risk of bias in the included studies, mostly due to retrospective study designs, industry involvement, incomplete outcome reporting, and inability to blind patients and study staff (Tables 1 and 2). The funnel plot for the primary outcome did not indicate potential publication bias towards effect or no-effect (Appendix Fig. 1).

### Study characteristics

The study characteristics and study population are described in Table 3. Among included studies were two RCTs, from Japan and China, and three retrospective cohort studies from the United Kingdom, China, and the United States. Treatment and follow-up duration were standardized in four studies, with one study reporting only in-hospital anticoagulant use and events. Treatment duration varied from 2 to 6 weeks, and follow-up varied from 2 to 5 weeks between studies.

#### Patient population

In total, 4767 patients were included in the studies. Nineteen patients were lost to follow-up in one RCT, leaving 4748 patients (DOAC: 2276, LMWH: 2472) for analysis of the primary outcome [39]. All studies predominantly included elderly patients (range of mean ages 65–85 years). One study only included patients with osteoporosis and traumatic hip fractures [42]. Two studies included only patients using rivaroxaban, one study included only patients using edoxaban, two studies included patients using various DOACs. The patients in LMWH cohorts used enoxaparin ($n = 2$), nadroparin ($n = 1$), dalteparin ($n = 1$), or various LMWH ($n = 1$). All patients received prophylactic doses. Four studies reported on baseline comparability of comorbidities; three found no differences while in the fourth study DOAC patients had significantly higher American Society of Anesthesiologists (ASA) scores (score 3/4: 94.4% in the DOAC group vs 71.5% LMWH group, $p = 0.01$) [40].

### Study outcomes

All study outcomes for the included studies are presented in Table 4. In one study, the primary study endpoint was not...
Table 3
Characteristics of the included studies.

| Author     | Country      | Design                        | Inclusion Period | Study Population | Prophylactic DOAC cohort | Prophylactic LMWH cohort | Treatment Duration | Follow-up Duration | % Female<sup>a</sup> | Mean Age (±SD)<sup>a</sup> | Comorbidity<sup>b</sup> |
|------------|--------------|-------------------------------|------------------|------------------|--------------------------|--------------------------|---------------------|---------------------|---------------------|------------------------|--------------------------|
| Fuji 2014  | Japan        | Multi-Center, Open Label, Industry Sponsored RCT | 10/2008 - 08/2009 | Femoral Neck Fractures | N = 61 Edoxaban 30 mg QD | N = 31 Enoxaparin 2000 IU BID | 11-14 Days | 25-35 Days | 81.4% vs 75.9% | 76.5 ± 11 vs 75.6 ± 12 | Not Reported |
| Goh 2020   | United Kingdom | Retrospective Cohort Study | 01/2017 - 12/2018 | Hip Fractures | N = 54 Apixaban 2.5 mg BID; Rivaroxaban 10 mg QD; Dalbigratran 150 mg QD | N = 267 Dalteparin 5000 IU QD | 42 Days | 30 Days | 35.2% vs 31.8% | 84.6 ± 8.3 vs 86.5 ± 13.7 | ASA 3/4: 94.4% vs 71.5% |
| Nederpelt 2020<sup>c</sup> | USA | Retrospective Registry Study | 01/2010-12/2016 | Hip Fractures | N = 1865 DOAC | N = 1880 LMWH | NR | In-hospital | 58.7% vs 58.7% | 68 vs 65 (p = 0.047) | 16 conditions: NS |
| Tang 2017  | China        | RCT                           | 09/2011 - 09/2016 | Femoral Neck Fractures | N = 96 Rivaroxaban 10 mg QD | N = 95 Enoxaparin 4000 IU QD | 28 Days | 30 Days | 64.6% vs 57.9% | 68 ± 7 p = 0.17 | History VTE: 3 (0.5%) vs 3 (0.4%) p = 0.58 |
| Zhang 2018 | China        | Multi-Center Retrospective Cohort Study | 06/2007 - 12/2015 | >60 yr, with Osteoporosis, THA for Femoral Neck Fractures | N = 200 Rivaroxaban 10 mg QD | N = 199 Nadroparin 0.3 mL | 14 Days | 14 Days | 43.5% vs 44.7% | 70.2 ± 9.2 vs 69.9 ± 8.9 | ASA status: NS |

DOAC: direct oral anticoagulant, LMWH: low molecular weight heparin, RCT: randomized controlled trial, THA: total hip arthroplasty, QD: quaque die (once daily), BID: bis in die (twice daily); NS: not statistically significant difference, ASA: American Society of Anesthesiologist.

<sup>a</sup> results for DOAC vs LMWH.

<sup>b</sup> The sample represents subgroup data of surgically treated hip fracture patients provided by the corresponding author.

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Table 4
Outcome parameters for surgically treated hip fracture patients using prophylactic LMWH or DOACs.

| Author     | S+ VTE | S+ DVT | S+ PE | S+ VTE | Total VTE | Major + CRNM bleeding | Major bleeding | CRNM bleeding | Minor bleeding |
|------------|--------|--------|-------|--------|-----------|----------------------|----------------|----------------|---------------|
| Fuji 2014  | 0 vs 0 | 0 vs 0 | 0 vs 0 | 3 (6.5%) vs 1 (3.7%) | 3 (6.5%) vs 1 (3.7%) | 2 (3.4%) vs 1 (1.7%) | 1 (1.7%) vs 1 (1.7%) | 13 (22%) vs 3 (10.3%) |
| Goh 2020   | 0 (0%) vs 9 (3.4%) | 0 (0%) vs 1 (0.5%) | 0 (0%) vs 8 (3.0%) | NR | 2 (3.4%) vs 1 (1.7%) | 1 (1.7%) vs 1 (1.7%) | 13 (22%) vs 3 (10.3%) |
| Nederpelt 2020<sup>c</sup> | 32 (1.4%) vs 11 (0.5%) | 22 (1.0%) vs 1 (0.5%) | 11 (0.5%) vs 2 (0.9%) | NR | 4 (7.4%) vs 4 (7.4%) | NR | NR | NR |
| Tang 2017  | 32 (1.4%) | 21 (0.9%) | 13 (0.6%) | 32 (1.4%) | 137 (6.0%) | NR | NR | NR |
| Zhang 2018 | 0 (0%) vs 2 (1.1%) | 0 vs 0 | 1 (1.0%) vs 2 (1.2%) | 5 (5.2%) vs 14 (14.7%) | 1 (1.7%) vs 1 (1.7%) | 13 (22%) vs 3 (10.3%) |

Results are presented as number of events (%) for DOAC vs LMWH.

DOAC: direct oral anticoagulant, LMWH: low molecular weight heparin, S+: symptomatic, S-: asymptomatic, VTE: venous thromboembolism, DVT: deep venous thrombosis, PE: pulmonary embolism, CRNM: clinically relevant non major, NS: not statistically significant difference, NR: not reported.

<sup>a</sup> No event rates are reported, instead the study reports "No significant differences were detected in major bleeding events."
specified as symptomatic or asymptomatic VTE [42]. Attempts to contact the authors were made but failed to clarify the matter. The events from this study were only included in the meta-analysis of total symptomatic and asymptomatic VTE. Thus, four studies reported symptomatic, clinically important DVT and PE, and two studies reported asymptomatic VTE, diagnosed through end-of-study ultrasound. All studies defined bleeding complications according to the International Society for Thrombosis and Hemostasis guidelines (ISTH) [43]. Uniform definition and reporting of VTE and bleeding complications, as well as comparability of the included patient populations allowed for meta-analysis of the results. Two studies reported rates of wound hematoma, another study reported the incidence of wound complications, including wound hematoma, margin necrosis and surgical site infection, among others. All included studies reported crude event rates, and did not report covariate-adjusted ORs. With the exception of one study that found a clinically important difference in comorbidity, the groups were comparable at baseline [40]. Therefore, meta-analysis of unadjusted outcome rates was performed.

DOAC patients had statistically non-significantly lower odds of VTE, including symptomatic and asymptomatic VTE (OR 0.52, 95% CI 0.25–1.11, p = 0.09, Fig. 2). The odds of symptomatic VTE, reported in 4 studies (n = 4349), did not differ significantly between the groups (OR 0.88, 95% CI 0.51–1.52, p = 0.67, Appendix, Fig. 2). Additionally, there were no differences in the odds of symptomatic PE (OR 0.81, 95% CI 0.39–1.70, p = 0.58, Appendix, Fig. 3) symptomatic DVT (OR 0.96, 95% CI 0.47–1.97, p = 0.92, Appendix, Figure 4) and asymptomatic VTE (OR 0.42, 95% CI 0.17–1.06, p = 0.07, Appendix Figure 5). Statistical heterogeneity, as assessed by I², was high for the primary outcome (I² = 63%), but absent for the secondary VTE outcomes (I² = 0% for symptomatic DVT and PE, and for asymptomatic VTE).

The rate of major and CRNM bleeding, reported in 4 studies (n = 4349), did not differ between DOAC and LMWH patients (OR 0.97, 95% CI 0.76–1.23, p = 0.27, Fig. 3). Similarly, there was no statistically significant difference in the odds of minor bleeding, studied in 2 studies with 293 patients, (OR 1.19, 95% CI 0.69–2.08, p = 0.53, Appendix Figure 6). Statistical heterogeneity was low for major and CRNM bleeding, as well as minor bleeding(I² = 23%, I² = 36% respectively).

Separate analysis of 2 RCTs and 3 non-randomized studies for the primary outcome of asymptomatic and symptomatic VTE demonstrated statistically non-significant lower odds of VTE for DOAC patients both in RCTs (OR 0.42, 95% CI 0.17–1.06, p = 0.07, Appendix Figure 7) and non-randomized studies (OR 0.46, 95% CI 0.14–1.54, p = 0.21, Appendix Figure 8). Statistical heterogeneity was low for the RCTs and high for the non-randomized studies, with I² = 33% and I² = 79% respectively.

Discussion

Meta-analysis of the included studies demonstrated comparable odds of developing VTE and bleeding complications with thromboprophylactic DOACs and LMWH in surgically treated hip fracture patients. Odds of VTE were consistently lower for DOAC patients, but these associations were not statistically significant, potentially due to lack of statistical power. This study supports equivalence, but future randomized studies with sufficient power are needed to confirm potential superiority of DOACs over LMWH for post-traumatic thromboprophylaxis.

Studies including non-hip fracture trauma patients reported equivalent or superior effectiveness and safety for DOACs. A previous RCT comparing thromboprophylactic rivaroxaban and enoxaparin in surgically treated non-major orthopedic patients found a trend towards reduced odds of symptomatic VTE for rivaroxaban in the sub-analysis of 863 trauma patients [44]. Moreover, non-randomized comparisons have reported superior effectiveness and safety of DOACs over LMWH in studies on multisystem trauma, nonoperatively treated pelvic trauma, and operatively treated spinal cord injuries [45–47]. Another cohort study including operated and conservatively treated patients with lower limb fractures demonstrated superior effectiveness of DOACs over LMWH, at equivalent safety [38].
If effectiveness and safety of thromboprophylaxis with DOACs are equivalent to those of LMWH, its role in thromboprophylaxis guidelines for trauma patients may depend on other factors that influence medication choice, such as patient tolerance and preference, route of drug administration, drug availability, and cost. Data supporting patient tolerance and preference of per oral and subcutaneous thromboprophylaxis, however, are scarce in the trauma population. One of the studies in the current meta-analysis reported significantly better compliance with DOACs than with LMWH [41]. A recent RCT comparing adherence with thromboprophylactic aspirin per os versus subcutaneous LMWH in patients with extremity or pelvic fractures found that LMWH was associated with significantly lower compliance and patient satisfaction, despite that both drugs were dosed once daily [48]. An RCT on non-major orthopedic surgery and a registry trial on hip fracture surgery and total hip and knee arthroplasty found similar compliance rates for per os versus subcutaneous anticoagulation [44,49].

Cost effectiveness analyses (CEA) of venous thromboprophylaxis in the trauma population have, to the best of our knowledge, not yet been published. CEs on DOAC versus LMWH thromboprophylaxis after elective major orthopedic surgery have shown that rivaroxaban and apixaban are cost-effective alternatives for LMWH, aspirin and dabigatran in the healthcare systems of Sweden, Australia and France [51–53]. In the absence of cost-effectiveness data in the trauma population, proxies for healthcare expenditure might be used, such as hospital length of stay. Three included studies reported length of stay, of which one RCT found a statistically significant lower length of stay in the DOAC arm, while two cohort studies found no significant difference [34,40,41]. An RCT comparing rivaroxaban to nadroparin in lower extremity fractures, operated and conservatively treated, found a significant reduction in LOS [38]. Future studies should include formal cost-effectiveness analysis of the studied medications.

Use of oral anticoagulation for thromboprophylaxis in trauma patients is met with inherent risks that should be mitigated. First, it is imperative to rule out active clinically relevant bleeding prior to initiation of any type of antithrombotic. Second, the decision to start anticoagulant drugs in patients with recent high-risk surgery, such as ocular, spinal or cerebral surgery, and those with known bleeding disorders, such as hemophilia or hepatogenic coagulopathy should be carefully considered, as benefits may be outweighed by the risk of eliciting bleeding. Drug-specific (relative) contra-indications must also be weighed. Patients with a history of heparin-induced thrombocytopenia should not receive heparinoids, including LMWH; whilst DOACs are not yet approved for patients with active malignancies or vascular malformations and pseudoaneurysms. In cases of uncertainty or unfamiliarity, a vascular medicine specialist may be consulted.

Limitations

This study has several limitations. First, the risk of bias assessment indicated several potential sources of bias in the included studies. Industry involvement and open label design in the RCTs could have posed significant risks, potentially introducing bias favoring the DOAC-group. However, the industry sponsored RCT clearly described reliable outcome assessment methods, and did not find a significant difference in either effectiveness or safety [39]. Notably, this RCT is the only study that found a higher odds of VTE for DOAC thromboprophylaxis, which may be due to the fact that it was the only study that prescribed edoxaban. Moreover, patient blinding was not possible in these studies due to differences in the route of administration. In the retrospective cohort studies, confounding by indication was the dominant cause of concern, as it was not reported why certain patients were prescribed (off-label) DOAC instead of LMWH, the standard treatment. A potential explanation is that DOAC patients used pre-injury DOACs for cardiovascular risk prevention and may have been ‘restared’ on DOACs. However, the included non-randomized studies reported no significant differences in baseline morbidity, with the exception of one study, where the DOAC cohort had a higher mean ASA score, biasing the results in favor of LMWH [40]. Despite reported baseline comparability of the cohorts, the presence of confounding by indication and unmeasured confounding cannot be ruled out in non-randomized cohort studies.

Second, there was variation in the medication used by the DOAC and LMWH groups. Previous studies in non-trauma populations have reported differences in efficacy and safety on head-to-head comparison of the different DOACs, with apixaban demonstrating superior VTE prevention with the lowest risk of hemorrhagic complications [28]. Direct comparison of nadroparin and enoxaparin has been performed in colorectal surgery, indicating no difference between the types of LMWH [54]. In this meta-analysis we were not able to perform similar head-to-head comparison, thus future research should determine which DOAC is optimal for thromboprophylaxis in surgically treated patients with hip fractures. Second, several factors are known to influence decision making concerning thromboprophylaxis but were not consistently reported in all included studies (e.g. injury severity score, and contra-indications to start thromboprophylaxis such as solid organ injuries, spinal cord injuries or intracranial hemorrhage). Beside clinical heterogeneity, statistical heterogeneity was also assessed, and identified for the meta-analysis of total VTE. This may be due to differing study medications and treatment durations.

Third, in previous publications it has been argued that PE, distal and proximal DVT are distinct entities, and that the influence of anticoagulant medication on their development may differ [55,56]. In our study, sub-analyses of symptomatic DVT, PE and of composite symptomatic VTE resulted in similar odds ratios as for the primary outcome, i.e. total VTE. The odds of symptomatic VTE in DOAC patients were consistently lower. However, none of the odds ratios were statistically significant, which may be due to a lack of statistical power. A pre-study power analysis was not performed.

Conclusion

Meta-analysis of the effectiveness and safety of thromboprophylaxis after surgically treated hip fractures suggests that DOACs are equally effective and safe compared to LMWH, the current standard. To determine the role of DOACs in thromboprophylaxis guidelines for trauma patients, future randomized studies with sufficient statistical power are needed. Such studies should ideally include cost-effectiveness analysis, as well as patient-related factors, such as adherence and preference.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2021.11.052.
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