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Effect of preinjury use of direct oral anticoagulants *vs.* Vitamin K antagonists on outcomes of hip fracture: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Elderly patients with hip fractures are frequently under anticoagulant therapy. We aimed to assess if outcomes of hip fracture patients undergoing surgical intervention differ with prior use of direct oral anticoagulants (DOAC) or Vitamin K antagonists (VKA).

MATERIALS AND METHODS: PubMed, Embase, and Google Scholar were searched for comparative studies published up to June 20, 2021. Dichotomous variables were summarized using odds ratio (OR) and continuous variables using mean difference (MD).

RESULTS: Fourteen studies were included. There was no difference in the time to surgery between patients on DOAC or VKA (MD: 2.50 95% CI -2.10, 7.10 I^2=76% p=0.29). Number of undergoing surgeries within 48 hours was not significantly different between the two groups (OR: 0.77 95% CI 0.56, 1.06 I^2=10% p=0.10). Mortality rates (OR: 0.84 95% CI 0.62, 1.14 I^2=12% p=0.27), blood transfusion requirement (OR: 1.08 95% CI 0.80, 1.47 I^2=30% p=0.62) and length of hospital stay (MD: 0.26 95% CI -0.70, 1.21 I^2=0% p=0.60) was also not significantly different between patients on DOAC or VKA.

CONCLUSIONS: There is no difference in surgical delay, early mortality, blood transfusion rates and length of hospital stay between DOAC uses and VKA users undergoing hip fracture surgery.

Key Words:
Antithrombotic, Anticoagulants, Injury, Hip fracture, Surgery.

Introduction

Hip fracture is a debilitating condition that has a high prevalence worldwide. Global estimates suggest that around 4.5 million adults are diagnosed with hip fractures every year resulting in annual healthcare expenditure of about $9.8million in the USA alone[1]. Owing to the high fragility of bone and increased tendency of falls, the elderly constitute a significant proportion of patients sustaining hip fractures[2]. Elderly patients frequently have multiple comorbidities and are usually under the prescription of several medications[3]. Given that oral anticoagulants are increasingly prescribed for a variety of indications, the number of hip fracture patients under oral anticoagulants is expected to rise in the near future[4,5].

Perioperative management of hip fracture patients under anticoagulant therapy involves balancing the risk associated with delayed surgical intervention and intra-operative hemostasis. Early surgery for hip fractures seems logical as the condition leads to prolonged immobilization, risk of venous thromboembolism, and pressure sores[6]. Indeed, delayed surgery is associated with a 36% increased risk of mortality in hip fracture patients[7]. While the guidelines of the National Institute for Health and Care Excellence (NICE)[8], the British Orthopaedic and Geriatric Associations[9] and the American Academy of Orthopaedic Surgeons[10] recommend early surgical intervention within 48 hours of injury to optimize outcomes, the use of anticoagulants is frequently associated with surgical delay in patients with hip fractures[1,11]. In a recent systematic review and meta-analysis, You et al[12] have analyzed evidence on the effects of anticoagulant therapy on outcomes of hip fracture patients. Pooling data from 21 studies, the authors concluded that the use of pre-injury anticoagulant drugs results

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in a statistically significant 13.7-hour delay in surgery for hip fracture as compared to patients, not under any anticoagulant therapy. The use of anticoagulants was also associated with 1.4 times higher odds of mortality as compared to non-anticoagulated patients.

In the past, Vitamin K antagonists (VKA) like warfarin, acenocoumarol, phenprocoumon have been the first choice of drugs in patients in need of anticoagulation for any indication[13]. However, in recent times direct-acting oral anticoagulants (DOAC) like apixaban, rivaroxaban, and dabigatran have achieved widespread adoption for preventing thromboembolism[14,15]. One reason for this change is that DOAC is thought to have a better safety profile with a more predictable anticoagulant action as compared to VKA[14,15]. Considering the baseline differences in these two classes of drugs, it would be interesting to know if outcomes of hip fracture patients differ with pre-injury use of DOAC *vs.* VKA.

You et al[12] in their review have also compared outcomes of hip fracture patients under these two classes of drugs. However, owing to scarce literature during the conduct of their study, they could include only a maximum of seven studies in their comparative analysis. With publications of new studies[16-18] in the past few years, there is a need for a comprehensive and updated comparison of outcomes of hip fracture between patients on DOAC and VKA. In this context, the current study was designed to analyze if the time to surgery (TTS), mortality rates, blood transfusion rates, and length of hospital stay (LOS) differ with pre-injury use of DOAC or VKA in patients with hip fracture undergoing surgical intervention.

Materials and Methods

The specifications of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement were followed during this review[19]. We registered the protocol on PROSPERO (CRD42021260508) before beginning with the study.

Literature Search

The search of relevant studies for the review was carried out electronically on the databases of PubMed, Embase, and Google Scholar. This was done by two reviewers working independently of each other. The time limits defined for the search were from the establishment of these databases to June 20, 2021. Search was limited to English language studies only. We selected the following terms to explore for pertinent articles: "hip fracture", "Subtrochanteric fracture", " intertrochanteric fracture", "femoral neck fracture", "direct oral anticoagulants", "apixaban", "rivaroxaban", "dabigatran", "edoxaban", "betrixaban", "vitamin K antagonists", "warfarin", and "antithrombotic". Several search queries in different combinations were conducted using Boolean operators "AND" and "OR". Details of the search strategy common to all databases are presented in **Supplementary Table I**. After the initial search, the results were deduplicated and the remaining articles were assessed by their titles and abstracts. Full texts of suitable articles were then sourced which were then assessed based on the inclusion criteria and any differences were resolved by consensus. Finally, a hand-search was performed on the reference list of included studies to find any unidentified studies.

Eligibility Criteria

We framed the inclusion criteria on PICOS (Population, Intervention, Comparison, Outcome, Study type). Details are as follows:

1. Patients aged more than 18 years of age with hip fractures undergoing surgical intervention and under anticoagulant therapy (Population).
2. Use of DOAC (Intervention)
3. Use of VKA (Comparison)
4. At least one of the following- TTS, mortality rate, blood transfusion rate, or LOS (Outcome).
5. All cohort studies, cross-sectional studies, case-control studies, randomized controlled trials were eligible (Study type).

Exclusion criteria were: (1) Studies with DOAC/VKA and control groups and not reporting separate data for DOAC and VKA (2) Studies not reporting any of the relevant outcomes (3) Studies with less than 10 patients in each arm (4) Studies published only as abstracts.

For studies with overlapping data, the article with the largest sample size was included.

Data Extraction and Quality Assessment

The following data were sourced from the studies: name of first author, year, study type, study location, the population included, joint studied, sample size, demographic details, Charlson comorbidity index, International normalization ratio (INR) at the time of admission, surgery

type, use of reversal agent, and outcomes. This was also carried out by two authors independent of each other.

The risk of bias in studies was judged using the Newcastle-Ottawa scale (NOS)[20]. Two reviewers examined each study for selection of study population, comparability, and outcomes. Points were awarded for each domain with a maximum score of nine. Any disagreements were solved by consensus.

Statistical Analysis

The software "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) was used for the analysis. Ordinal data were summarized with odds ratios (OR) with 95% confidence intervals (CI) and continuous data using mean difference and 95% CI; all in a random effects model. In case studies reported continuous variables as median and interquartile range, the data were converted to mean and standard deviation[21]. Since data were reported only graphically, the software Engauge Digitizer was used to extract numerical data.

We also judged the influence of each study on the pooled effect with a sensitivity analysis. Subgroup analysis was conducted for mortality outcomes based on the follow-up period. We assessed interstudy heterogeneity with the I^2 statistic. The values were defined as 25-50% (low heterogeneity), 50-75% (medium heterogeneity), and >75% (substantial heterogeneity). Publication bias was assessed by visual inspection of funnel plots.

Results

Search and Study Details

Details of the literature search are presented in Figure 1. We found 2252 unique articles after initial screening. After that, 2212 articles were excluded as they were non-relevant. Total of 40 studies were evaluated by their full texts. Twenty-six studies were excluded as they did not meet the inclusion criteria. In the end, 14 studies[16-18,22-32] were included.

Table I presents the baseline details of the studies. Two were case-control studies while the remaining were retrospective cohort studies. Most of them were carried out in Europe with just three studies from North America and two from Asia. A total of 1982 patients on DOAC were compared with 5277 on VKA in the included studies. The sample size, however, varied widely ranging from 13 to 1063 patients in the DOAC arm and 15 to 4162 individuals in the VKA arm. The mean age of patients was >60 years in all studies. Data on CCI were reported only by six studies and INR values only by five studies. The NOS score of the studies was high with five studies achieving a score of 7 and nine achieving a score of 8.

Meta-Analysis

A total of 11 studies reported TTS in their study participants. Comparing data of 807 patients on DOAC with 975 patients on VKA, we note no statistically significant difference in the TTS in hours (MD: 2.50 95% CI -2.10, 7.10 I^2=76% p=0.29) (Figure 2). There was no evidence of publication bias on visual inspection of the funnel plot (**Supplementary Figure 1**). On sensitivity analysis, the results did not change on the exclusion of any of the included studies. Five studies also reported data on the number of patients undergoing surgery within 48 hours

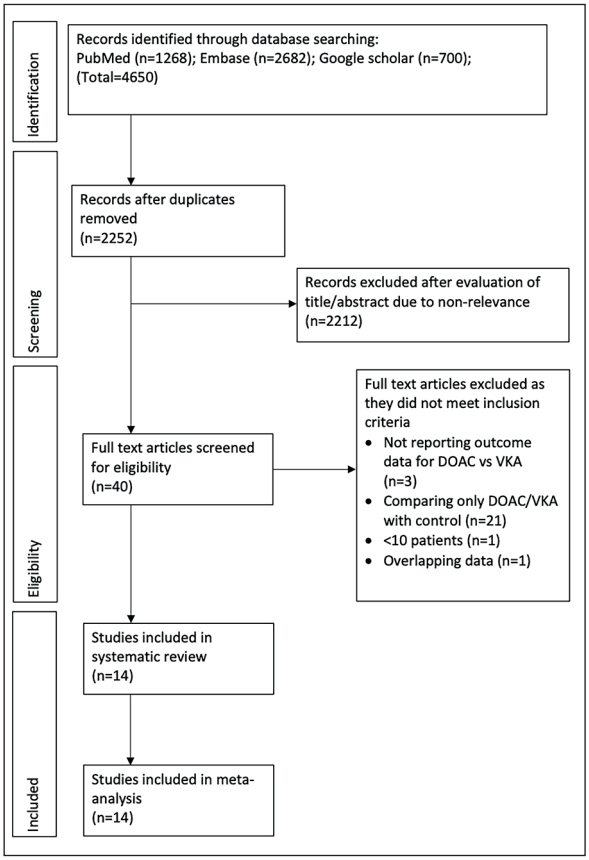

Figure 1. Study flow-chart.

Table I. Details of included studies.

Study	Location	Type	Population	Sample size		Mean age (years)		Male gender (%)		CCI		INR at admission		Surgery type		Reversal used (%)		NOS
				DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	
Tran 2015[26]	Canada	CC	Acute hip fracture	27	233	86	86	37	37	NR	NR	NR	NR	HA (40.7) STR (59.3) Both (0)	HA (45.5) STR (53.6) Both (0.9)	NR	NR	8
Rutenberg 2018[28]	Israel	RC	Operative fragility hip fracture (≥ 65 years)	47	103	82.9	82.2	35.6	30.7	7.3±1.8	6.5±2.3	1.3±0.3	2.4± 0.9	NR	NR	0	All with INR > 1.5	8
Lott 2018[27]	USA	RC	Isolated hip fracture (≥ 60 years)	28	37	NR	NR	NR	NR	NR	NR	NR	2.3± 0.7	NR	NR	NR	70.2	8
Bruckbauer 2019[30]	Austria	RC	Isolated hip fracture (≥ 65 years)	54	59	87	82.7	35.2	45.8	6[5-7]^	6[4-8]^	1.38^ [1.15-1.65]	2.28 [1.83 -2.88]^	NR	NR	3.7	84.7	7
Daugaard 2019[29]	Denmark	RC	First time hip fracture (≥ 65 years)	1063	4162	NR	NR	34.6	39.6	1-2 (47.8%) ≥ 3 (31.4%)	1-2 (45.3%) ≥3 (30.7%)	NR	NR	NR	NR	NR	NR	8
Hourston 2019[22]	UK	RC	Femoral neck fracture	32	83	87	34	19	31	NR	NR	NR	NR	NR	NR	NR	NR	8
Schuetze 2019[32]	Germany	RC	Femoral neck fractures operated within 24 hours	52	25	NR	NR	NR	NR	NR	NR	NR	NR	Nail (100)	Nail (100)	NR*	NR*	7
Cafaro 2020[31]	Canada	RC	Acute hip fracture	31	28	86	90	33.6	46.4	NR	NR	NR	>1.5 in 96.4% patients	HA (32.2) ORIF (67.7)	HA (25) ORIF (64.3) CPP (10.7)	NR	48	8

Continued

Table I *(Continued)*. Details of included studies.

Study	Location	Type	Population	Sample size		Mean age (years)		Male gender (%)		CCI		INR at admission		Surgery type		Reversal used (%)		NOS
				DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	
Caternicchia 2020[24]	Italy	RC	Acute hip fracture	43	48	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7
Creeper 2020[25]	Australia	RC	Acute hip fracture	82	63	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7
Shani 2020[16]	Israel	RC	First operative hip fracture (≥ 65 years)	415	311	83.9	82.6	31.6	39.9	5.1± 3.1	4.8± 3.3	NR (72) ORIF (38)	NR (66.6) ORIF (33.4)	HA	HA	NR	NR	8
Suciu 2020[23]	Romania	RC	Acute hip fracture (> 55 years)	13	18	79	79.1	30.8	44.4	5[4-5]^	5[4-5]^	NR	NR	NR	NR	NR	NR	7
Gosch 2021[17]	Germany	CC	Fragility hip fracture (>70 years)	26	15	86	85.9	43.9	46.7	2±1.8	1.9±2.1	1.8±0.9	2.4±1.2	NR	NR	NR	NR	8
Mahmood 202[18]	UK	RC	Acute hip fracture	69	92	84.3	83.8	30	46	NR	NR	NR	NR	HA (39) ORIF (61)	HA (37) ORIF (63)	NR*	100*	8

^Median [Interquartile range]. *Bridging with heparin for all patients. CC, case control; CCI, Charlson comorbidity index CPP, Cephalomedullary Percutaneous Pinning; DOAC, Directly acting oral anticoagulants; ORIF, Open Reduction Internal Fixation; HA, Hip arthroplasty; NR, not reported; RC, retrospective cohort; VKA, vitamin K antagonist; NOS, Newcastle Ottawa Scale; STR, Subtrochanteric repair.

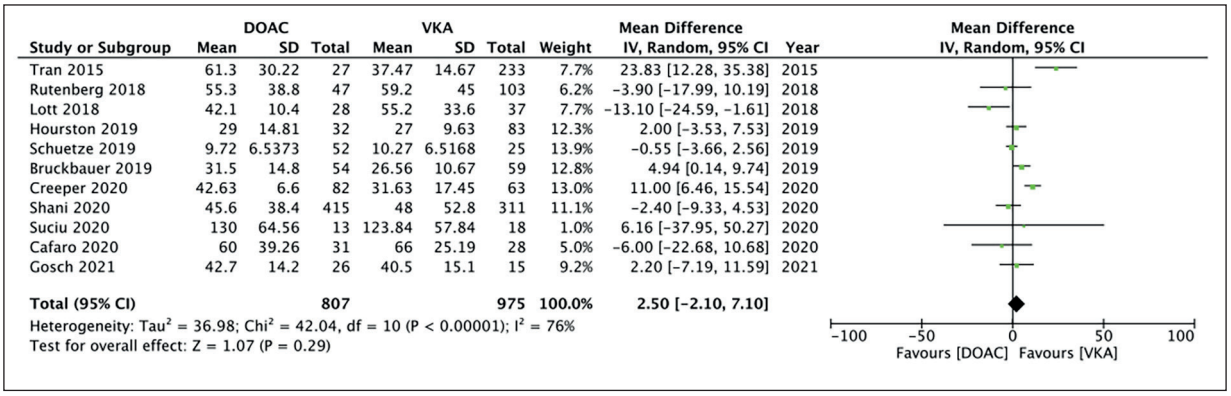

Figure 2. Meta-analysis of time to surgery (TTS) between hip fracture patients on DOAC and VKA.

of admission. On pooled analysis, there was no difference in the number of patients undergoing surgery <48 hours after admission between DOAC and VKA groups (OR: 0.77 95% CI 0.56, 1.06 I^2=10% p=0.10) (Figure 3).

Mortality data were reported by nine studies. Overall, we found no statistically significant difference in early mortality between DOAC and VKA groups (OR: 0.84 95% CI 0.62, 1.14 I^2=12% p=0.27) (Figure 4). On subgroup analysis, the difference remained non-significant for in-hospital mortality (OR: 0.52 95% CI 0.21, 1.28 I^2=0% p=0.15) and 30-day mortality (OR: 0.86 95% CI 0.57, 1.30 I^2=40% p=0.48). The results were stable on sensitivity analysis.

Eight studies[17,18,23,25,29-32] reported data on the incidence of blood transfusion in the perioperative period. Meta-analysis comparing 1390 patients in the DOAC group with 4462 patients in the VKA group revealed no statistically significant difference in the odds of transfusion between the two groups (OR: 1.08 95% CI 0.80, 1.47 I^2=30% p=0.62) (Figure 5). On sensitivity analysis, the results did not change on the exclusion of any of the included studies.

Data for LOS in days was reported by six studies. On pooled analysis of 560 participants in the DOAC group and 512 participants in the VKA group, we noted no statistically significant difference in LOS between the two groups (MD: 0.26 95% CI -0.70, 1.21 I^2=0% p=0.60) (Figure 6). There was no change in the significance of results on the exclusion of any study.

Discussion

Our meta-analysis including 14 recent studies with 5279 participants indicates that there is no difference in TTS in hip fracture patients on DOAC or VKA. The proportion of patients undergoing surgery within the recommended 48-hours' time frame was also not different between the two classes of drugs. Preinjury use

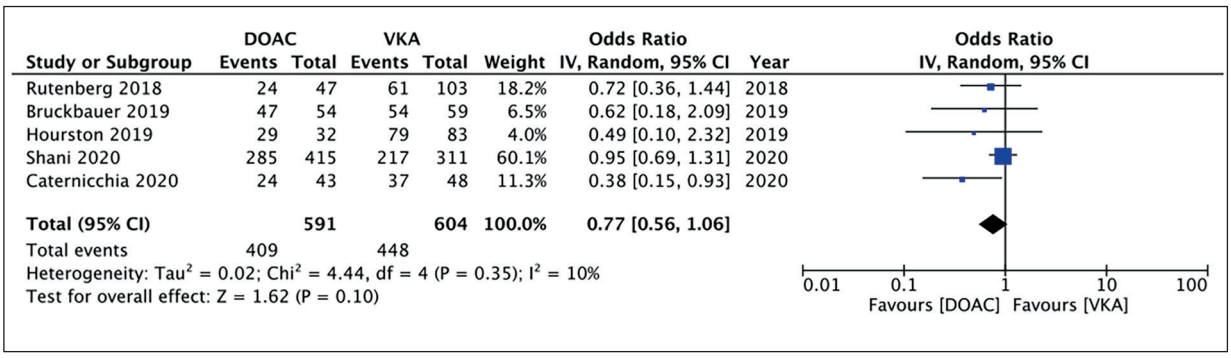

Figure 3. Meta-analysis of number of patients receiving surgical intervention <48 hours between hip fracture patients on DOAC and VKA.

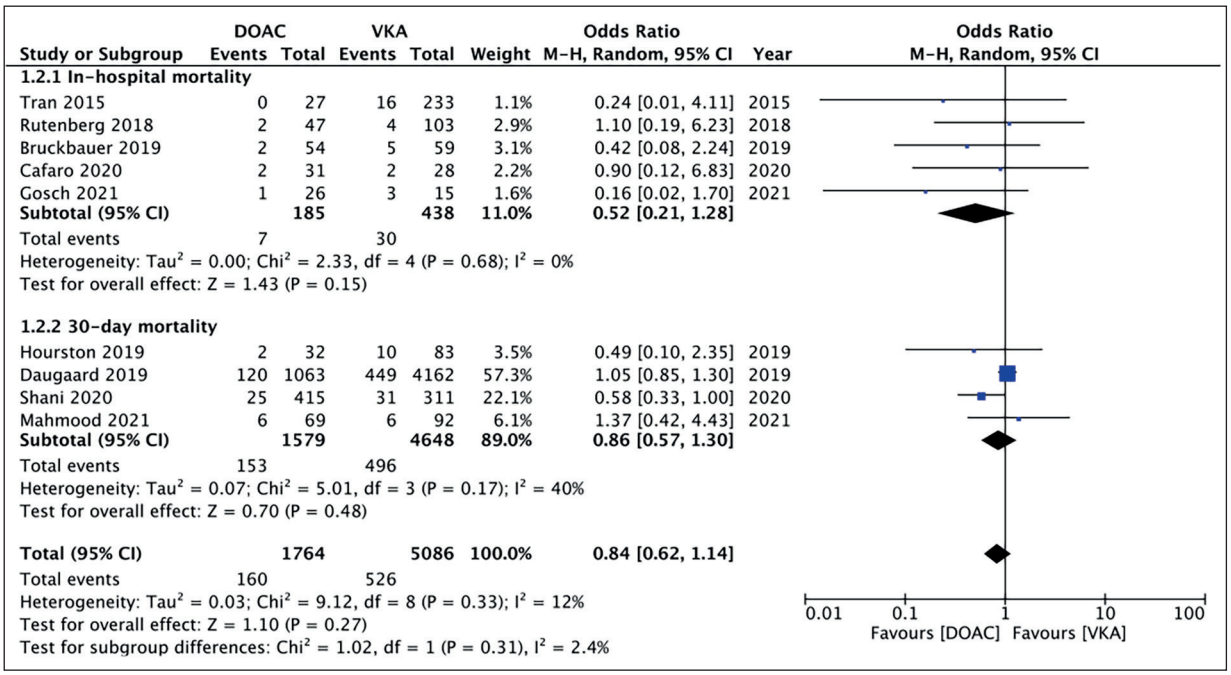

Figure 4. Meta-analysis of mortality rates between hip fracture patients on DOAC and VKA with subgroup analysis based on the timing of mortality.

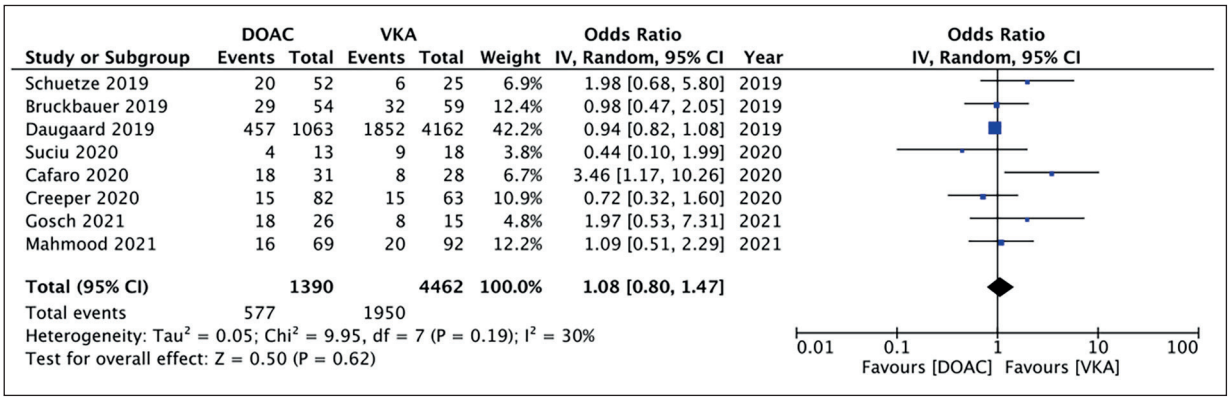

Figure 5. Meta-analysis of blood transfusion rates between hip fracture patients on DOAC and VKA.

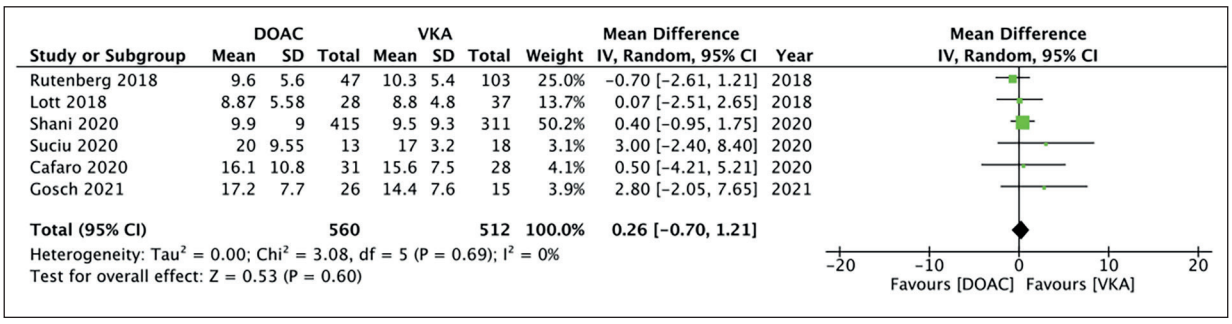

Figure 6. Meta-analysis of length of hospital stay (LOS) between hip fracture patients on DOAC and VKA.

of either DOAC or VKA had no impact on mortality rates, the incidence of blood transfusion as well as LOS.

According to data from the Danish registry, around 40% of individuals who sustain hip fractures are under antithrombotic therapy[29]. Indeed, with such high numbers, clinicians must formulate perioperative strategies taking into account the effects of these drugs on patient outcomes. A common dilemma faced by orthopedic surgeons while managing anticoagulated hip fracture patients is balancing the timing of surgical intervention, as delayed intervention can increase mortality while early surgery can be associated with intraoperative hemostasis problems[1,11]. Given the importance of this subject, several reviews have assessed the impact of antiplatelet and anticoagulants on outcomes of hip fracture patients undergoing surgical intervention[12,33-35]. However, an important limitation of these reviews is their inability to comprehensively differentiate between the different classes of anticoagulant drugs owing to the availability of a limited number of studies.

Since their introduction in 2008, DOAC are increasingly replaced VKA for prophylaxis against thromboembolism[14,15]. Recent studies[36,37] have provided recommendations for perioperative management of DOAC patients undergoing elective surgery but have excluded patients in need of urgent or emergency surgical intervention. To date, there are no clear guidelines on the management of hip fracture patients on DOAC[38]. However, few recent trials have assessed the safety of early surgery in hip fracture patients on VKA as well as DOAC. Mattisson et al[39] have evaluated outcomes of early surgical intervention (<24 hours) in 99 hip fracture patients on warfarin wherein all patients were reversed to INR≤1.5 before surgery. They reported no significant increase in blood loss, perioperative transfusion rates, or mortality in patients on warfarin as compared to controls. In another study, Franklin et al[40] have demonstrated that early surgical intervention (<48 hours) in hip fracture patients on DOAC does not lead to worse clinical outcomes. While the effect of VKA can be reversed by vitamin K or prothrombin complex concentrate, agents for reversal of DOAC are still under development or quite expensive for routine use[41]. However, an important advantage of DOAC vis-à-vis VKA is that they offer intermittent anticoagulation due to their shorter half-life of 7-17 hours, and the peak drug concentration is reached at 1-4 hours[42]. After 24 hours from the last dose of DOAC, 80% of the drug is eliminated in patients with normal renal function and urgent surgery may be performed with minimal anticoagulant effect[43]apixaban, edoxaban tosylate, and rivaroxaban. A good understanding of these agents' pharmacologic properties is important for surgeons given their marked differences compared with warfarin sodium. This review highlights key practical issues surrounding the use of NOACs in the perioperative setting. OBSERVATIONS The PubMed and Cochrane Library databases were searched for English-language studies from May 1, 2009, until May 1, 2017, for randomized clinical trials, meta-analyses, systematic reviews, observational studies, and clinical guidelines. From a systematic review of the published literature that included 70 articles and 166 404 patients, this study identified 5 key practical issues surrounding the use of NOACs in the perioperative setting. These include patient populations for which NOAC use is indicated and contraindicated, the timing of NOAC treatment cessation before invasive interventions, management of NOAC-treated patients requiring urgent interventions, the need for "bridging," and the timing of NOAC treatment's reinitiation after invasive interventions. Important findings are as follows: NOAC agents are not recommended for patients with mechanical heart valves or advanced kidney disease (creatinine clearance, <15 mL/min. Considering these factors and the results of the above-mentioned studies[39,40], it is not surprising to note the lack of statistically significant difference in outcomes between DOAC and VKA in our meta-analysis.

Analyzing TTS, we noted no statistically significant difference between DOAC and VKA groups. The number of patients undergoing surgery within the recommended duration of <48hours was also not significantly different. Our results concur with that of You et al[12] but the significantly higher statistical power achieved in our analysis increases the credibility of our results.

In our analysis, early mortality rates in DOAC and VKA groups were 9% and 10.3% respectively with no statistically significant difference between the two cohorts. These figures are only marginally higher than the 6.1% 30-day mortality rate reported in the recent National Hip Fracture database[44]. It is important to note that several factors like age, gender, comorbidity status, hemoglobin levels, and presence of malignancy can influence mortality rates in hip fracture patients[2]; and crude death rates only provide an approximate comparison between the two groups.

A major concern in managing anticoagulated hip fracture patients is the risk of major bleeding and the resultant requirement of blood transfusion. While data on major bleeding was scarcely reported, most studies did report rates of perioperative transfusion in DOAC and VKA groups. Overall, 41.5% of patients on DOAC and 43.7% patients on VKA needed blood transfusion with no significant difference between the two cohorts. Our analysis presents the first pooled comparison of transfusion rates in hip fracture patients which has not been reported by earlier meta-analysis studies[12,34]. Our comparison of crude transfusion rates is similar to the multi-variable adjusted outcomes reported by Daugaard et al[29]. Analyzing a large sample from the Danish registry, the reported the risk of perioperative transfusion with DOAC and VKA to be similar with only a marginal non-significant increase with DOAC[DOAC- risk ratio (RR): 1.07 95% CI: 1.00, 1.14 and VKA- RR 0.99 95% 0.95, 1.04]. Similar results have been reported by Little et al[45] in a retrospective study comparing outcomes amongst DOAC and VKA users undergoing major cardiac surgery. The authors reported no statistically significant difference in blood product usage or bleeding episodes between DOAC and VKA users. An important factor that can potentially influence transfusion and bleeding rates is the degree of reversal of anticoagulation. However, recent studies have suggested that anticoagulant reversal may have no impact on bleeding, transfusion rates, and 30-day mortality in hip fracture patients, and delay in surgery due to reversal may be unnecessary[46,47]. Owing to a lack of data on reversal in the included studies, we were unable to gauge the impact of this variable on our study outcomes.

Our study should be interpreted with the following limitations. Firstly, all the data analyzed were from retrospective studies which have inherent selection bias. We could pool only crude data from the included studies which may have been influenced by several known and unknown confounding factors. Pooled analysis of multivariable-adjusted data would have strengthened the conclusion of our review. Secondly, several details like comorbidity status, type of fracture, type of surgery, INR levels, etc. were not provided by the included studies and the baseline status of the study cohorts was not very clear. Furthermore, information on the exact surgical protocol, the perioperative anticoagulant management protocol, and the use of reversal agents was not explicitly mentioned in most studies. The role of these factors in influencing the study results cannot be understated. Lastly, many important variables like rate of perioperative thromboembolism, total blood loss, and anesthetic complications like delirium could not be assessed due to lack of adequate data.

The strength of the study lies in the large number of studies included for the pooled analysis as compared to prior reviews. The stability of the results on sensitivity analysis also lends credibility to our results.

Conclusions

To conclude, data from retrospective studies indicate that there is no difference in surgical delay with pre-injury use of DOAC or VKA in hip fracture patients. Early mortality, need for blood transfusion and LOS are also not different between DOAC uses and VKA users.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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