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Outcomes of elderly patients with traumatic brain injury associated with the pre-injury antithrombotic prophylaxis type – A systematic review and meta-analysis

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Abstract. – OBJECTIVE: Our review aims at comparing the morbidity and mortality-related risks associated with the pre-injury administration of VK-antagonists or DOACs in elderly patients with TBI.

MATERIALS AND METHODS: We performed a systematic search of the academic literature across five databases (Web of Science, EMBASE, CENTRAL, Scopus, and MEDLINE), following PRISMA guidelines. We conducted a random-effect meta-analysis to compare the influence of pre-injury VK-antagonists or DOACs administration on the overall intensive care unit and hospital stays of patients with TBI. We also evaluated the overall risks associated with VK-antagonists and with DOACs for intracranial hemorrhage progression, surgical intervention, and overall mortality in patients with TBI.

RESULTS: From 973 studies, we found 11 eligible with 4,991 patients with traumatic brain injury (mean age, 77.82 ± 6.76 years). Our meta-analysis revealed insignificantly higher odds of surgical intervention (OR=1.72) and mortality (OR=1.07) associated with VK-antagonists administration than with DOACs administration. Similarly, we found that the intensive care unit (Hedge's *g*, 0.13) and hospital (*g*, 0.26) stays were insignificantly longer for individuals on VK-antagonists than for those on DOAC. Moreover, we observed insignificantly higher intracranial hemorrhage progression risks (OR=1.22) for individuals receiving DOACs than for those receiving VK-antagonists.

CONCLUSIONS: This study provides evidence on the morbidity and mortality-related outcomes associated with the pre-injury administration of VK-antagonists or DOACs in patients with TBI. We found no significant differences between VK-antagonists and DOACs on the overall morbidity (hospital and intensive care unit stays, intracranial hemorrhage, and surgical intervention frequency) and mortality outcomes in elderly patients with TBI.

Key Words:
Vitamin-K antagonist, Traumatic brain injury, Direct oral anticoagulant drugs, Morbidity, Mortality.

Introduction

Traumatic brain injury (TBI) is a common cause of morbidity and mortality worldwide[1,2]. The Centers for Disease Control and Prevention define TBI as an injury to the head that results in disrupted brain functioning[3]. The prevalence of TBI has increased during the past decade by almost 8.4% worldwide[4,5], and a global burden of disease report calculated that almost 69 million (95% CI 64 to 74 million) individuals worldwide are estimated to sustain a TBI each year almost[6,7].

TBI is common in elderly populations. The mean rate of fall-related TBIs in the elderly is almost twice as frequent as that in younger populations[8-10]. This high prevalence of falls in elderly individuals has many causes[11]. First, age-related brain structure degeneration and subarachnoid thickening both increase the risk of subdural hematomas due to the rupture of bridging veins during TBIs[12,13]risk factors, clinical presentation, management and outcome in elderly patients with CSDH by retrospective study of the period 1996-1999 in the three district hospitals of North Wales. 40 cases of CSDH were identified in patients >65 years, the incidence in this population being 8.2/100,000. Falls (57%. Second, musculoskeletal weakness due to aging (i.e., sarcopenia) leads to deteriorated balance control and a propensity to fall[14-16]. In addition, elderly patients exhibit a high predisposition to thromboembolic complications, for which they are commonly prescribed antithrombotic and/or anticoagulant drugs[17-19]and the risk of thromboembolism increases with age. Anticoagulants are recommended for indications including the prevention of venous thromboembolism in surgical and medical patients, treatment of venous thromboembolism and stroke prevention in patients with atrial fibrillation. Traditional anticoagulants that have been used include unfractionated heparin, low

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molecular weight heparin, fondaparinux and vitamin K antagonists. However, these agents are all associated with drawbacks (i.e. parenteral administration or frequent coagulation monitoring/dose titration. The long-term administration of these drugs is considered a major risk factor for intracranial hemorrhagic complications during TBIs[20,21]. Patients on conventional vitamin-K antagonists (VK-antagonists – warfarin, acenocoumarol), who experience TBIs, have an increased risk of intracranial hemorrhage and higher rates of mortality compared to other patients[20,22]. Thus, the newer class of anticoagulant direct oral anticoagulants (DOACs, such as dabigatran and rivaroxaban) have been proposed to improve outcomes. DOACs are thought to provide comparable or even higher effectiveness than conventional VK-antagonists[23]. Moreover, the brief half-life of DOACs may help prevent unwanted interactions with other medications used by elderly patients[24,25]. Despite these apparent benefits of DOACs used as prophylaxis for reducing intracranial hemorrhage in elderly patients, no study has yet synthesized the evidence regarding the morbidity and mortality-related outcomes of these two classes of anticoagulant agents in elderly patients with TBI.

Individual retrospective cohort studies[26-29] have compared morbidity and mortality-related outcomes of pre-injury administration of DOAC and VK-antagonists in patients with TBI. However, a lack of consensus exists regarding the intensive care unit stay lengths and intracranial hemorrhage progressions between patients with TBI who had received DOACs and those who had received VK-antagonists. Some studies reported an increase in the intensive care unit stay in patients receiving VK-antagonists[27,30,31], while others found a longer intensive care unit stay in patients receiving DOACs[32,33]. Similarly, some studies reported higher risks of intracranial hemorrhage progression in patients with TBI receiving VK-antagonists[29,31,34], and others reported lower risks in the same patients as compared to the risks of patients with TBI on DOACs[33,35].

To the best of our knowledge, only one systematic review and meta-analysis[36] have evaluated the morbidity and mortality-related risks associated with pre-TBI administration of DOACs or VK-antagonists.

The findings of this article are limited because the review did not assess the total intensive care unit and hospital stays and because many relevant high-quality cohort studies[26-29,34] have been published since then.

Therefore, in this systematic review and meta-analysis, we assess the morbidity and mortality-related outcomes associated with the pre-injury administration of VK-antagonists or DOACs in elderly patients with TBI. Our findings should help clinicians worldwide weigh the impact of pre-injury administration of DOACs *vs.* VK-antagonists on patients with high TBI risks.

Materials and Methods

We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[37] while conducting this meta-analysis.

Data Search Strategy

We searched on five scientific databases (Web of Science, MEDLINE, CENTRAL, EMBASE, and Scopus) from inception till December 2020, using a combination of MeSH keywords, including "Vitamin-K Antagonists", "Direct oral anticoagulants", "warfarin", "heparin", "anticoagulants", "traumatic brain injury", "TBI", "intracranial hemorrhage", "morbidity", and "mortality". In addition, we manually searched the bibliography sections of the included studies to identify further relevant studies. Our inclusion criteria were the following:

a. Studies comparing the overall incidence of intracranial hemorrhage progression, surgical intervention, and mortality outcomes in patients with TBI who had been using either VK-antagonists or DOACs.

b. Studies evaluating the overall intensive care unit and hospital stays in patients with TBI who had been using either VK-antagonists or DOACs.

c. Studies on humans.

d. Case-control studies, prospective or retrospective cohort studies.

e. Studies published in peer-reviewed scientific journals.

f. Studies published in English.

Two reviewers independently screened the studies. Disagreements were resolved by discussion with a third independent reviewer.

Quality Assessment

Two reviewers independently assessed the risk of bias in the included studies using Cochrane's risk of a bias assessment tool for non-randomized controlled trials[38]. This tool evaluates selective reporting, confounding bias, outcome measurements, and incomplete data availability outcomes as bias threats. Disagreements between the two reviewers were resolved by discussions with a third reviewer.

Statistical Analysis

We used the Comprehensive Meta-analysis (CMA) version 2.0 software[39] to conduct a with-

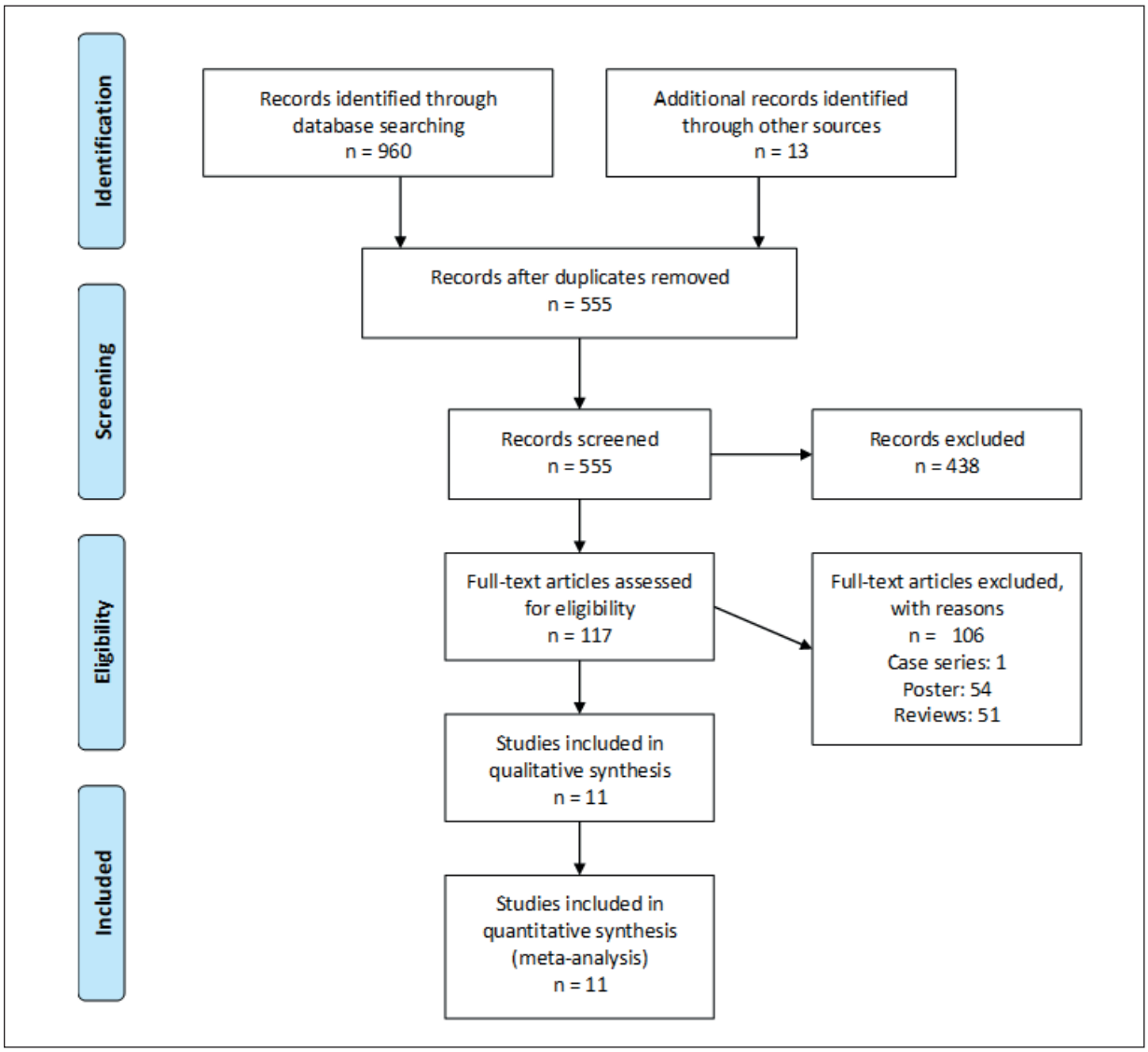

Figure 1. PRISMA flowchart.

in-group meta-analysis based on the random-effects model[40]. We calculated Hedge's *g* as a weighted effect size to compare the overall hospital and intensive care unit stays of the patients with TBI who had received either VK-antagonists or DOACs. We also calculated odds ratios to compare intracranial hemorrhage progression, surgical intervention, and mortality outcomes of the two same groups of patients. We computed I^2 statistics to assess the heterogeneity among the studies included, and we classified the heterogeneity as negligible (between 0% and 25%), moderate (between 25% and 75%), or substantial (≥ 75%)[41]. We evaluated the publication bias following the Duval and Tweedy's[42] trim and fill procedure, which estimates the potential missed studies due to publication bias in a funnel plot. We set the significance level for this study at 5%.

Results

The search across the five academic databases provided 960 studies. We identified 13 more by screening the reference sections of the studies included. We were left with 11 studies fitting all our inclusion criteria (Figure 1). All of the included studies were retrospective in nature[26-35,43]. We used tables to annotate the relevant data from the studies. Table I summarizes these data.

Table I. Details of the studies included.

Study	Country	Study type	Sample description	Age (M ± SD years)	Drugs	ICH progression (%)	Mortality (%)	Surgery intervention (%)	Hospital stay (days)	Intensive care unit stay (days)
Hecht et al[27]	USA	Retrospective cohort study	VK-antagonists: 669 (314F, 355M) DOACs: 188 (99F, 89M)	VK-antagonists: 81.1 ± 7.8 DOACs: 81.2 ± 7.7	VK-antagonists: Warfarin DOACs: -	-	-	VK-antagonists: 21.6 DOACs: 18.1	VK-antagonists: 6.7 ± 7.4 DOACs: 5.2 ± 4.6	VK-antagonists: 4.4 ± 4.8 DOACs: 3.5 ± 3.4
Shin et al[34]	USA	Retrospective cohort study	VK-antagonists: 97 (46F, 51M) DOACs: 39 (12F, 27M)	VK-antagonists: 78.5 ± 13.8 DOACs: 79.2 ± 11.7	VK-antagonists: Warfarin DOACs: Dabigatran, rivaroxaban or apixaban	VK-antagonists: 13 DOACs: 4	VK-antagonists: 8.2 DOACs: 12.8	VK-antagonists: 13.4 DOACs: 5.2	VK-antagonists: 6.1 ± 6.1 DOACs: 5.4 ± 6.9	-
Eibinger et al[26]	Switzerland	Retrospective cohort study	VK-antagonists: 1613 DOACs: 1178	VK-ANT: 80.4 ± 6.8 DOACs: 81.2 ± 7	-	-	VK-antagonists: 32.7 DOACs: 30.1	-	-	-
Savioli et al[28]	USA	Retrospective cohort study	VK-antagonists: 156 (114F, 42M) DOACs: 78 (39F, 39M)	VK-ANT: 82 ± 10 DOACs: 80 ± 10	VK-antagonists: Warfarin, acenocumarol DOACs: apixaban, dabigatran, edoxaban, rivaroxaban	-	VK-antagonists: 0 DOACs: 0	VK-antagonists: 0.64 DOACs: 0	-	-
Scotti et al[29]	Canada	Retrospective cohort study	VK-antagonists: 151 DOACs: 59	80.9 ± 7.9	VK-antagonists: Warfarin DOACs: Dabigatran, rivaroxaban or apixaban	VK-antagonists: 31.9 DOACs: 18.2	VK-antagonists: 22.8 DOACs: 20.8	VK-antagonists: 15.3 DOACs: 9.1	-	-
Prexl et al[31]	Austria	Retrospective cohort study	VK-antagonists: 32 (17F, 15M) DOACs: 33 (19F, 14M)	VK-ANT: 81 DOACs: 82	VK-antagonists: phenprocoumon, acenocoumarol DOACs: Dabigatran, rivaroxaban, edoxaban, apixaban	VK-antagonists: 59.4 DOACs: 24.2	VK-antagonists: 21.8 DOACs: 3	-	VK-antagonists: 278.5 DOACs: 168	VK-antagonists: 70 DOACs: 49
Zeeshan et al[33]	USA	Retrospective cohort study	VK-antagonists: 230 (60F, 170M) DOACs: 98 (36F, 62M)	VK-ANT: 62 ± 13.9 DOACs: 57 ± 16.8	-	VK-antagonists: 13 DOACs: 26	VK-antagonists: 13 DOACs: 26	VK-antagonists: 9 DOACs: 20	VK-antagonists: 4 DOACs: 5	VK-antagonists: 1 DOACs: 3
Batey et al[30]	USA	Retrospective cohort study	VK-antagonists: 141 (74F, 67M) DOACs: 36 (19F, 17M)	VK-ANT: 81 ± 8 DOACs: 81 ± 8	-	-	VK-antagonists: 13 DOACs: 7	VK-antagonists: 18 DOACs: 1	VK-ANT: 5.4 ± 5.3 DOACs: 4 ± 2	VK-ANT: 3.2 ± 4.2 DOACs: 1.8 ± 3.1
Feeney et al[32]	USA	Retrospective cohort study	VK-antagonists: 101 (60F, 61M) DOACs: 61 (27F, 34M)	VK-ANT: 79.5 ± 13 DOACs: 77.2 ± 11.2	-	-	VK-antagonists: 20.8 DOACs: 4.9	VK-antagonists: 27 DOACs: 5	VK-antagonists: 4 DOACs: 4	VK-antagonists: 1.2 DOACs: 1.4
Beynon et al[35]	Germany	Retrospective cohort study	VK-antagonists: 5 (3F, 2M) DOACs: 6 (2F, 4M)	VK-ANT: 74 ± 17 DOACs: 71 ± 25	VK-antagonists: Warfarin, DOACs: Rivaroxaban	VK-antagonists: 20 DOACs: 50	VK-antagonists: 0 DOACs: 33.3	VK-antagonists: 60 DOACs: 33	VK-ANT: 6.6 ± 2.6 DOACs: 4.2 ± 1.6	-
Parra et al[43]	USA	Retrospective cohort study	VK-antagonists: 15 (5F, 10M) DOACs: 5 (2F, 3M)	VK-ANT: 83.9 DOACs: 81.6	VK-antagonists: Warfarin, acenocumarol DOACs: apixaban, dabigatran, edoxaban, rivaroxaban	VK-antagonists: w20 DOACs: 80	VK-antagonists: 0 DOACs: 40	-	-	-

M, mean; SD, standard deviation; VK-antagonists, vitamin-K antagonist; DOACs, direct oral anticoagulants.

Table II. Risk of bias according to ROBINS-I assessment tool.

Study	Confounding bias	Selection bias	Deviation from intended intervention	Missing data	Measurement in outcome	Selection of reported result	Classification of intervention
Hecht et al[27]	+	?	+	-	+	+	+
Shin et al[34]	+	+	+	+	+	?	+
Eibinger et al[26]	+	-	+	-	-	?	+
Savioli et al[28]	+	?	+	-	+	+	+
Scotti et al[29]	+	+	+	?	+	+	+
Prexl et al[31]	+	?	+	-	+	+	+
Zeeshan et al[33]	+	+	+	+	+	?	+
Batey et al[30]	+	?	+	-	+	+	+
Feeney et al[32]	+	?	+	-	+	+	+
Beynon et al[35]	+	?	+	-	+	+	+
Parra et al[43]	+	?	+	-	+	+	+

Participant Information

We obtained data from 4,991 patients with TBI (948 women, 1,062 men). Two studies[26,29] failed to provide gender distribution data. A total of 3,210 (693 women and 773 men) had received VK-antagonists, whereas 1,781 (255 women and 289 men) had received DOACs.

The mean age of the participants was as 77.82 ± 6.76 years. The mean age of the patients who had received VK-antagonists was 78.34 ± 6.30 years, and that of those who had received DOACs was 77.14 ± 7.79 years. One of the included studies[29] failed to discriminate the age distributions of their groups (mean, 80.9 ± 7.9 years for all the patients as a group).

Quality Assessment for Non-Randomized Controlled Trials

Table II shows the results of our ROBINS-I tool methodology risk of bias analysis for the non-randomized controlled trials. We found an overall low risk, where missing data, reported results selection, and selection accounted for most of the bias present. Figure 2 depicts the overall risk of bias according to Duval and Tweedy's trim and fill procedure.

Publication Bias

We used Duval and Tweedy's trim and fill method to estimate missing studies according to the random-effects model on either side of the mean effect of the funnel plot. We found three missing studies

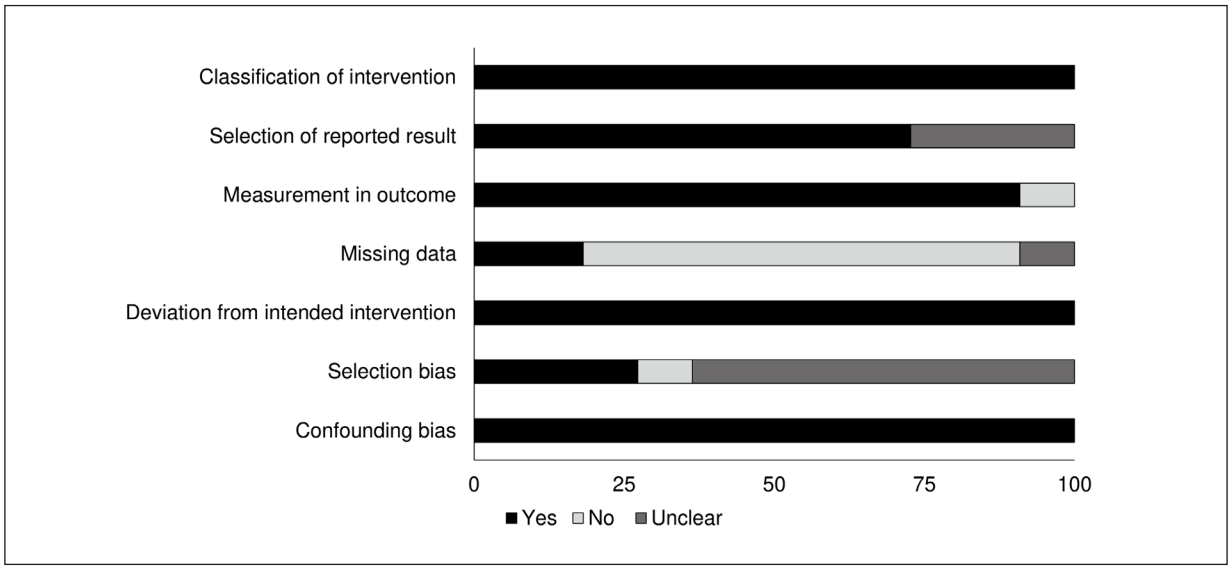

Figure 2. Risk of bias according to the Cochrane risk of bias assessment for the randomized controlled trials.

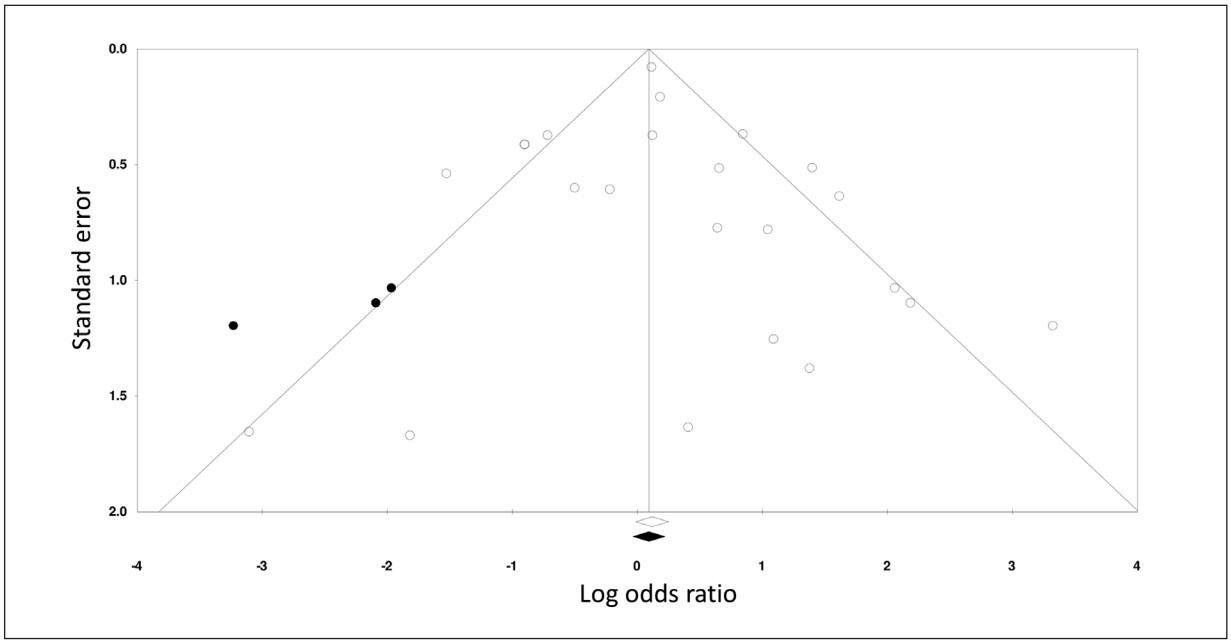

Figure 3. Publication bias by Duval & Tweedy's trim and fill method.

on the left side of the mean effect. The overall random-effects model determined the point estimate (1.23) and the 95% confidence interval (95% CI, 0.86 to 1.75) for the combined studies; the trim and fill method imputed point estimate were 1.06 with a 95% CI of 0.73 to 1.53 (Figure 3).

Meta-Analysis Report

Intensive care unit stay

The weighted effect sizes are presented as black boxes and 95% confidence intervals as whiskers. A negative effect size represents a longer intensive care unit stay for the patients receiving direct oral anticoagulants, and a positive effect size represents a longer intensive care unit stay for the patients receiving vitamin-K antagonists.

Five studies[27-29,33,43] compared the intensive care unit stay between the groups. We observed a positive insignificant 'small' effect suggesting a longer hospital stay for the patients who had received VK-antagonists than for those who had received DOACs (Figure 4) (Hedge's *g*, 0.13; 95% CI, -0.23 to 0.49; p=0.48) with negligible heterogeneity (I^2, 17.6%).

Hospital stay duration

The weighted effect sizes are presented as black boxes and the 95% confidence intervals as whiskers. A negative effect size represents a longer hospital stay for the patients who had received direct oral anticoagulants, and a positive effect size represents a longer hospital stay for the patients who had received vitamin-K antagonists.

Seven studies[27,30-35] compared the hospital stays between the two groups of patients. We observed a positive insignificant 'medium' effect suggesting a longer hospital stay for the group of patients who had received VK-antagonists than for those who had received DOACs (Figure 5) (Hedge's *g*, 0.26; 95% C.I, -0.01 to 0.05; p=0.06) with moderate heterogeneity (I^2, 38.8%).

Intracranial hemorrhage progression

The odds ratios are presented as black boxes and the 95% confidence intervals as whiskers. A negative odds ratio represents a higher risk of intracranial hemorrhage progression for the patients who had received direct oral anticoagulants, and a positive odds ratio represents a higher risk of intracranial hemorrhage progression for the patients who had received vitamin-K antagonists.

Six studies compared the incidence of intracranial hemorrhage progression between the two groups of patients[29,31,33-35,43]. We found an insignificant increase in odds of intracranial hemorrhage progression in the patients who had received DOACs compared to those who had received VK-antagonists (Figure 6) (odds ratio, 1.22; 95% CI, 0.41

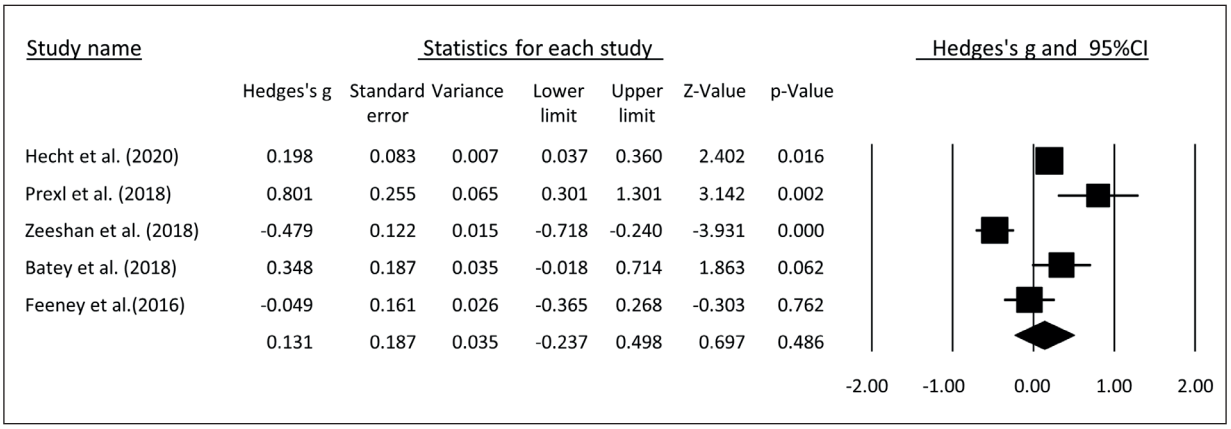

Figure 4. Overall intensive care unit stay for patients with traumatic brain injury who had received either vitamin-K antagonists or direct oral anticoagulants.

to 3.57; p=0.71), with moderate heterogeneity (I^2, 27.6%).

Surgical-Intervention

Eight studies[27-30,32-35] compared the odds of undergoing surgical interventions between the two groups of patients. We observed an insignificant increase in odds of surgical intervention in the patients who had received VK-antagonists compared to the patients who had received DOACs (Figure 7) (odds ratio, 1.72; 95% CI, 0.89 to 3.32; p=0.10), without heterogeneity (I^2, 0%).

Mortality

Nine studies[26,28-35,43] compared the odds of overall mortality between the two patient groups. We observed an insignificant increase in odds of mortality for patients who had received VK-antagonists compared to those who had received DOACs (Figure 8) (odds ratio, 1.07; 95% CI, 0.60 to 1.89; p=0.80) with moderate heterogeneity (I^2, 38.6%).

Discussion

In this systematic review and meta-analysis, we provide comprehensive evidence on morbidity- and mortality-related outcomes of patients with TBI who had received either VK-antagonists or DOACs before the TBI. We observed no significant differences in terms of morbidity outcomes including hospital and intensive care unit stay lengths in

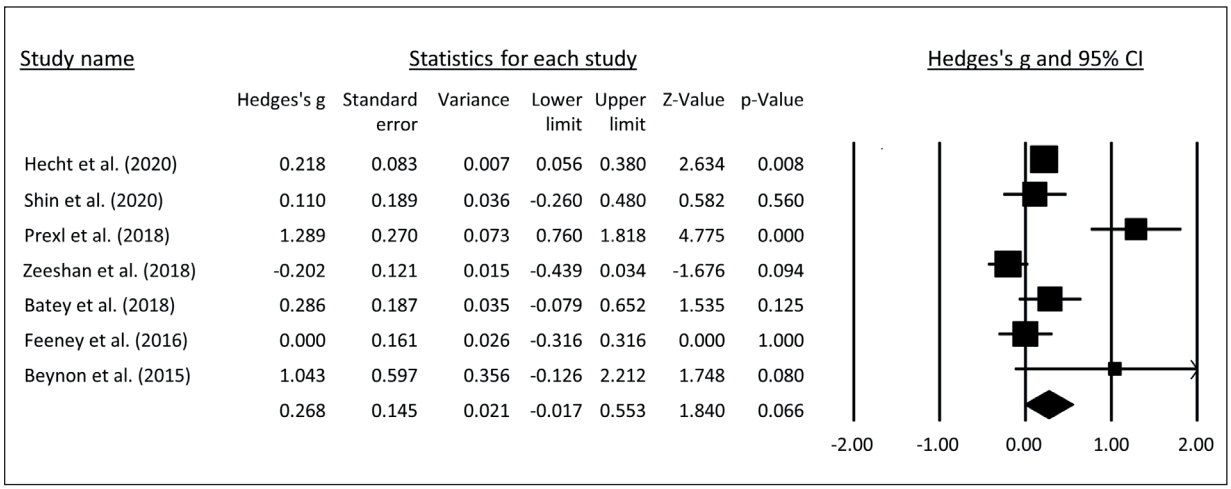

Figure 5. Overall hospital stay for patients with traumatic brain injury who had received either vitamin-K antagonist or direct oral anticoagulants.

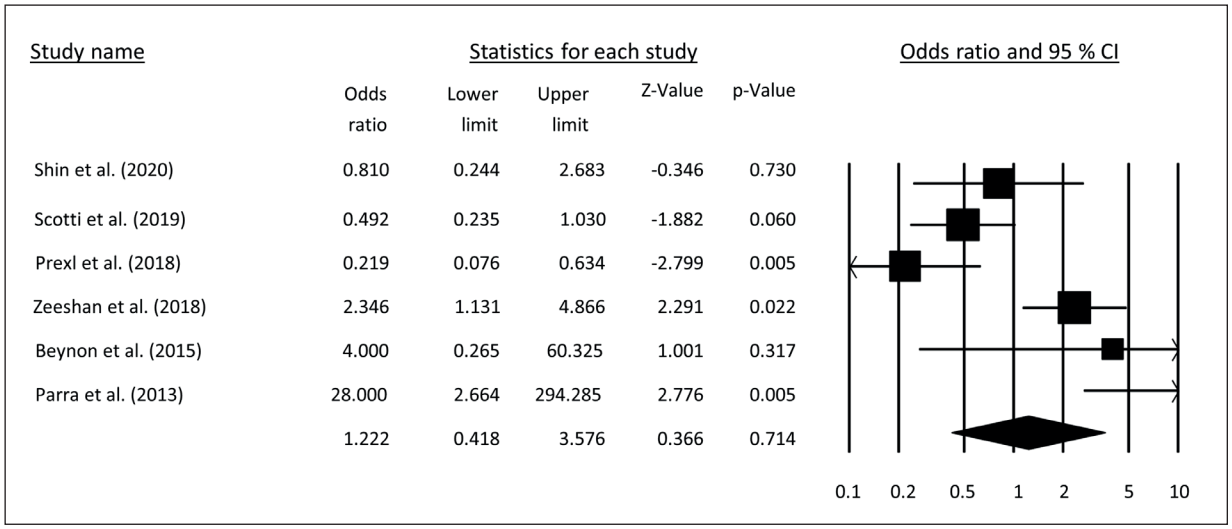

Figure 6. Odds of intracranial hemorrhage progression in patients with traumatic brain injury who had received either vitamin-K antagonist or direct oral anticoagulants.

patients who had received VK-antagonists than in those who had received DOACs. We also found no significant changes between the pre-injury administration of VK-antagonists and DOACs on the mortality of patients with TBI. The management of TBI in elderly population groups is challenging for neurologists due to the pathophysiological mechanisms, co-existing morbidities, and different manifestations of the condition[44-46]. Elderly patients also frequently present thromboembolic disorder risks for which they are regularly prescribed antithrombotic prophylaxis[17-19]. This practice reduces morbidity- and mortality-related outcomes associated with thromboembolism but increases the patients' risks of developing intracranial hemorrhages after TBIs[20]. VK-antagonist use has been associated with intracranial hemorrhagic complications in elderly patients due to polypharmacy drug interactions,

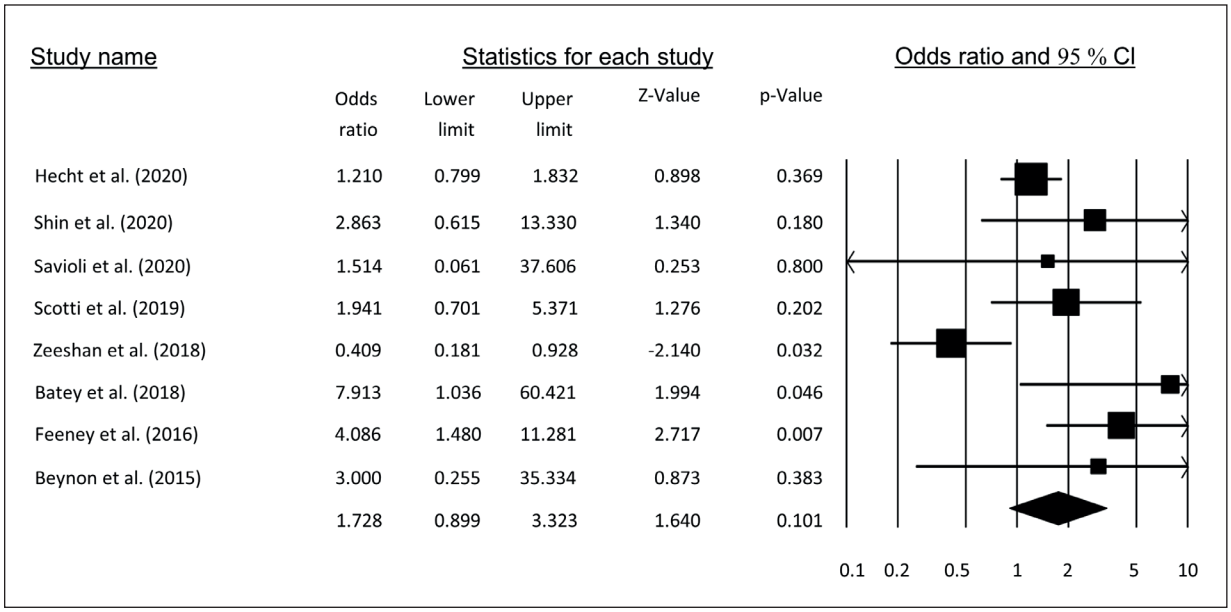

Figure 7. Odds of undergoing surgical intervention in patients with traumatic brain injury who had received either vitamin-K antagonist or direct oral anticoagulants.

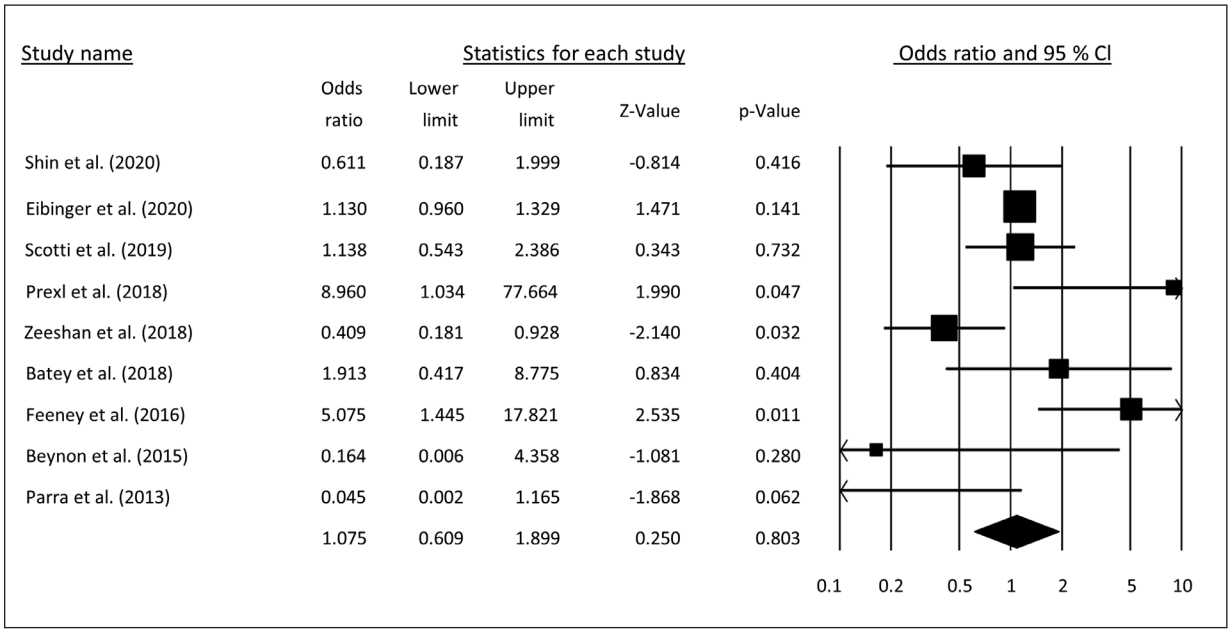

Figure 8. Odds of overall mortality in patients with traumatic brain injury who had received either vitamin-K antagonist or direct oral anticoagulants.

co-existing illnesses, and the common inability to fastly metabolize the drug[47,48]. DOACs have been used as a safer alternative[49,50], but this is largely based on their efficacy and low anticoagulative risks and not on direct comparisons. Santeusiano et al[51] reported that DOACs, such as dabigatran, do not need oxidative metabolization and that they are less likely to interact with co-prescribed drugs, such as cyclosporines than with VK-antagonists.

We observed that the outcomes (intracranial hemorrhage progression, neurosurgical intervention predisposition, and mortality) of patients with TBI differed between those who had taken DOACs and those who had taken VK-antagonists. Zeeshan et al[33], in a three-year retrospective observational study, compared the outcomes of patients with perioperative consumption of DOACs with those consuming VK-antagonists amongst a cohort of 210 patients with TBI. The authors reported a higher rate of intracranial hemorrhage progression and mortality for the group on DOACs compared to the group on VK-antagonists. Likewise, the rate of neurosurgical interventions (craniotomy and intracranial pressure evaluation) was higher for the DOACs group than for the VK-antagonists group. The authors attributed the morbidity and mortality outcomes of DOACs to the lack of effective reversal strategies for these agents[33]. Likewise, Parra et al[43] also reported that the pre-TBI use of DOACs was associated with an increased risk of intracranial hemorrhage progression and mortality. In this case, the authors also concluded that the DOAC outcomes were due to the lack of established reversal protocols and/or antidotes. In our meta-analysis, however, we observed no significant changes between the pre-TBI consumption of DOACs and the VK-antagonists on the risks of intracranial hemorrhage (OR=1.22), mortality (OR=1.07), and frequent neurosurgical interventions (OR=1.72) in patients with TBI.

We also assessed the impact of pre-injury DOACs or VK-antagonists on the overall hospital and intensive care unit stays in patients with TBI. Here again, we observed a lack of consensus in the literature: Zeeshan et al[33] reported an increase in the mean intensive care unit and hospital stays for the DOACs group (intensive care unit median, 3; IQR, 2 to 5 days, hospital stay mean, 5; IQR, 4 to 8 days), as compared to those in the VK-antagonists group (intensive care unit median, 1; IQR, 1 to 4 days, hospital stay mean, 4; IQR, 3 to 8 days). On the other hand, Prexl et al[31] reported an increase in the intensive care unit and hospital stays in the VK-antagonists group as compared to those in the DOACs group. These variable morbidity outcomes are confusing for neurologists deciding whether to continue antithrombotic medications or prescribe effective antithrombotic prophylaxis in elderly patients with TBI risks. In our meta-analysis' findings, we observed no significant differences between the patients consuming DOACs and VK-antagonists during the hospital stay (Hedge's g=0.26), and intensive care unit stay (g=0.13).

We are aware of the limitations in our systematic review and meta-analysis. First, we failed to pre-register the study in a systematic review repository such as those on the PROSPERO York or Joanna Briggs Institute[52]. We know that this could outraise concerns on the validity of our review. However, our attempts at registering the study failed due to the extended waiting times needed (more than a year) at those repositories, due to the COVID-19 crisis. Second, the paucity of data between the groups receiving VK-antagonists and DOACs could have biased our findings on the intensive care unit stay length. We only included five studies in the comparative analysis of intensive care unit stay, and we found a large difference in sample sizes (individuals on DOACs, n=416; individuals on VK-antagonists, n=1,173). Therefore, we cannot rule out a type II error for the evaluation of this outcome between these drugs[53]. Future studies should address this limitation with larger cohort studies that assess the intensive care unit stay in patients with TBI receiving DOAC or VK-antagonists. Clarifying the impact of these antithrombotic medications in patients with TBI is important to improve outcomes for elderly patients with TBI.

Conclusions

We summarized the evidence regarding the morbidity and mortality-related outcomes associated with the pre-injury administration of VK-antagonists or DOACs in patients with TBI. We provided statistical evidence suggesting no significant differences in terms of intensive care unit, intracranial hemorrhage progression, and hospital stays and mortality for patients with TBI using VK-antagonists or DOACs pre-injury. Our findings can help clinicians to develop best practice guidelines for reducing morbidity and mortality complications of anticoagulant drug therapy in patients with TBI.

Acknowledgements

None.

Conflict of Interest

All authors declare no conflict of interest.

Funding

None.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Clearance

Not applicable.

Authors' Contributions

YL, LY conceived and designed the study; HG and XZ, were involved in literature search and data collection; XH analyzed the data; YL, XH wrote the paper; and LY, HG, XZ reviewed and edited the manuscript. All authors read and approved the final manuscript.

References

1) Gardner RC, Dams-O'Connor K, Morrissey MR, Manley GT. Geriatric Traumatic Brain Injury: Epidemiology, Outcomes, Knowledge Gaps, and Future Directions. J Neurotrauma 2018; 35: 889-906.
2) Lasry O, Liu EY, Powell GA, Ruel-Laliberté J, Marcoux J, Buckeridge DL. Epidemiology of recurrent traumatic brain injury in the general population: A systematic review. Neurology 2017; 89: 2198-2209.
3) Peterson AB, Xu L, Daugherty J, Breiding MJ. Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths: 24. Available at: https://www.cdc.gov/traumaticbraininjury/pdf/TBI-Surveillance-Report-FINAL_508.pdf.
4) Corrigan JD, Yang J, Singichetti B, Manchester K, Bogner J. Lifetime prevalence of traumatic brain injury with loss of consciousness. Inj Prev J Int Soc Child Adolesc Inj Prev 2018; 24: 396-404.
5) Kisser J, Waldstein SR, Evans MK, Zonderman AB. Lifetime prevalence of traumatic brain injury in a demographically diverse community sample. Brain Inj 2017; 31: 620-623.
6) Badhiwala JH, Wilson JR, Fehlings MG. Global burden of traumatic brain and spinal cord injury. Lancet Neurol 2019; 18: 24-25.
7) GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019; 18: 56-87.
8) Gaetani P, Revay M, Sciacca S, Pessina F, Aimar E, Levi D, Morenghi E. Traumatic brain injury in the elderly: considerations in a series of 103 patients older than 70. J Neurosurg Sci 2012; 56: 231-237.
9) Haring RS, Narang K, Canner JK, Asemota AO, George BP, Selvarajah S, Haider AH, Schneider EB. Traumatic brain injury in the elderly: morbidity and mortality trends and risk factors. J Surg Res 2015; 195: 1-9.

10) Mak CHK, Wong SKH, Wong GK, Ng S, Wang KKW, Lam PK, Poon WS. Traumatic Brain Injury in the Elderly: Is it as Bad as we Think? Curr Transl Geriatr Exp Gerontol Rep 2012; 1: 171-178.
11) Sturnieks DL, St George R, Lord SR. Balance disorders in the elderly. Neurophysiol Clin Clin Neurophysiol 2008; 38: 467-478.
12) Asghar M, Adhiyaman V, Greenway MW, Bhowmick BK, Bates A. Chronic subdural haematoma in the elderly--a North Wales experience. J R Soc Med 2002; 95: 290-292.
13) Zhou Z, Li X, Kleiven S. Biomechanics of Acute Subdural Hematoma in the Elderly: A Fluid-Structure Interaction Study. J Neurotrauma 2019; 36: 2099-2108.
14) Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 2004; 52: 1121-1129.
15) Orr R. Contribution of muscle weakness to postural instability in the elderly. A systematic review. Eur J Phys Rehabil Med 2010; 46: 183-220.
16) Simpson JM. Elderly People at Risk of Fall The Role of Muscle Weakness. Physiotherapy 1993; 79: 831-835.
17) Bauersachs RM. Use of anticoagulants in elderly patients. Thromb Res 2012; 129: 107-115.
18) Robert-Ebadi H, Le Gal G, Righini M. Use of anticoagulants in elderly patients: practical recommendations. Clin Interv Aging 2009; 4: 165-177.
19) Robert-Ebadi H, Righini M. Anticoagulation in the Elderly. Pharmaceuticals 2010; 3: 3543-3569.
20) Franko J, Kish KJ, O'Connell BG, Subramanian S, Yuschak JV. Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. J Trauma 2006; 61: 107-110.
21) Pieracci FM, Eachempati SR, Shou J, Hydo LJ, Barie PS. Degree of anticoagulation, but not warfarin use itself, predicts adverse outcomes after traumatic brain injury in elderly trauma patients. J Trauma 2007; 63: 525-530.
22) Karni A, Holtzman R, Bass T, Zorman G, Carter L, Rodriguez L, Bennett-Shipman VJ, Lottenberg L. Traumatic head injury in the anticoagulated elderly patient: a lethal combination. Am Surg 2001; 67: 1098-1100.
23) Hellfritzsch M, Adelborg K, Damkier P, Paaske Johnsen S, Hallas J, Pottegård A, Grove EL. Effectiveness and safety of direct oral anticoagulants in atrial fibrillation patients switched from vitamin K antagonists: A systematic review and meta-analysis. Basic Clin Pharmacol Toxicol 2019; 126: 21-31.
24) Andreotti F, Rocca B, Husted S, Ajjan RA, ten Berg J, Cattaneo M, Collet JP, De Caterina R, Fox KA, Halvorsen S, Huber K, Hylek EM, Lip GY, Montalescot G, Morais J, Patrono C, Verheugt FW, Wallentin L, Weiss TW, Storey RF; ESC Thrombosis Working Group. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. Eur Heart J 2015; 36: 3238-3249.
25) Kurogi R, Nishimura K, Nakai M, Kada A, Kamitani S, Nakagawara J, Toyoda K, Ogasawara K, Ono J, Shiokawa Y, Aruga T, Miyachi S, Nagata I, Matsuda S, Yoshimura S, Okuchi K, Suzuki A, Nakamura F, Onozuka D, Ido K, Kurogi A, Mukae N, Nishimura A, Arimura K, Kitazono T, Hagihara A, Iihara K; J-ASPECT Study Collaborators. Comparing intracerebral hemorrhages associated with direct oral anticoagulants or warfarin. Neurology 2018; 90: e1143-e1149.
26) Eibinger N, Halvachizadeh S, Hallmann B, Seibert FJ, Puchwein P, Berk T, Lefering R, Sprengel K, Pape HC, Jensen KO, The TraumaRegister Dgu. Is the Regular Intake of Anticoagulative Agents an Independent Risk Factor for the Severity of Traumatic Brain Injuries in Geriatric Patients? A Retrospective Analysis of 10,559 Patients from the TraumaRegister DGU®. Brain Sci 2020; 10: 842
27) Hecht JP, LaDuke ZJ, Cain-Nielsen AH, Hemmila MR, Wahl WL. Effect of Preinjury Oral Anticoagulants on Outcomes Following Traumatic Brain Injury from Falls in Older Adults. Pharmacotherapy 2020; 40: 604-613.
28) Savioli G, Ceresa IF, Luzzi S, Gragnaniello C, Giotta Lucifero A, Del Maestro M, Marasco S, Manzoni F, Ciceri L, Gelfi E, Ricevuti G, Bressan MA. Rates of Intracranial Hemorrhage in Mild Head Trauma Patients Presenting to Emergency Department and Their Management: A Comparison of Direct Oral Anticoagulant Drugs with Vitamin K Antagonists. Med Kaunas Lith 2020; 56: 308.
29) Scotti P, Séguin C, Lo BWY, de Guise E, Troquet J-M, Marcoux J. Antithrombotic agents and traumatic brain injury in the elderly population: hemorrhage patterns and outcomes. J Neurosurg 2019; 1-10.
30) Batey M, Hecht J, Callahan C, Wahl W. Direct oral anticoagulants do not worsen traumatic brain injury after low-level falls in the elderly. Surgery 2018; 164: 814-819.
31) Prexl O, Bruckbauer M, Voelckel W, Grottke O, Ponschab M, Maegele M, Schöchl H. The impact of direct oral anticoagulants in traumatic brain injury patients greater than 60-years-old. Scand J Trauma Resusc Emerg Med 2018; 26: 20.
32) Feeney JM, Santone E, DiFiori M, Kis L, Jayaraman V, Montgomery SC. Compared to warfarin, direct oral anticoagulants are associated with lower mortality in patients with blunt traumatic intracranial hemorrhage: A TQIP study. J Trauma Acute Care Surg 2016; 81: 843-848.
33) Zeeshan M, Jehan F, O'Keeffe T, Khan M, Zakaria ER, Hamidi M, Gries L, Kulvatunyou N, Joseph B. The novel oral anticoagulants (NOACs) have worse outcomes compared with warfarin in patients with intracranial hemorrhage after TBI. J Trauma Acute Care Surg 2018; 85: 915-920.
34) Shin SS, Marsh EB, Ali H, Nyquist PA, Hanley DF, Ziai WC. Comparison of Traumatic Intracranial Hemorrhage Expansion and Outcomes Among Patients on Direct Oral Anticoagulants Versus Vitamin k Antagonists. Neurocrit Care 2020; 32: 407-418.

35) Beynon C, Potzy A, Sakowitz OW, Unterberg AW. Rivaroxaban and intracranial haemorrhage after mild traumatic brain injury: A dangerous combination? Clin Neurol Neurosurg 2015; 136: 73-78.

36) Nederpelt CJ, van der Aalst SJM, Rosenthal MG, Krijnen P, Huisman MV, Peul WC, Schipper IB. Consequences of pre-injury utilization of direct oral anticoagulants in patients with traumatic brain injury: A systematic review and meta-analysis. J Trauma Acute Care Surg 2020; 88: 186-194.

37) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.

38) Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016; 355: i4919.

39) Bax L, Yu L-M, Ikeda N, Moons KGM. A systematic comparison of software dedicated to meta-analysis of causal studies. BMC Med Res Methodol 2007; 7: 40.

40) Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc 2009; 172:137-159.

41) Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.

42) Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56: 455-463.

43) Parra MW, Zucker L, Johnson ES, Gullett D, Avila C, Wichner ZA, Kokaram CR. Dabigatran bleed risk with closed head injuries: are we prepared? J Neurosurg 2013; 119: 760-765.

44) Eshel I, Marion DW. Traumatic Brain Injury (TBI): Current Diagnostic and Therapeutic Challenges. In: Tsao JW, editor. Traumatic Brain Injury: A Clinician's Guide to Diagnosis, Management, and Rehabilitation [Internet]. Cham: Springer International Publishing; 2020 [cited 2021 Apr 22]. pp. 421-437. Available at: https://doi.org/10.1007/978-3-030-22436-3_21

45) Flanagan SR, Hibbard MR, Riordan B, Gordon WA. Traumatic brain injury in the elderly: diagnostic and treatment challenges. Clin Geriatr Med 2006; 22: 449-468.

46) Hu M, Zobina I, Lowman A, Marsh E. Challenges in predicting traumatic brain injury outcomes. J Neurol 2020; 267: 3785-3787.

47) Fihn SD, Callahan CM, Martin DC, McDonell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. Ann Intern Med 1996; 124: 970-979.

48) Shepherd AM, Hewick DS, Moreland TA, Stevenson IH. Age as a determinant of sensitivity to warfarin. Br J Clin Pharmacol 1977; 4: 315-320.

49) Ha FJ, Barra S, Brown AJ, Begley DA, Grace AA, Agarwal S. Continuous and minimally-interrupted direct oral anticoagulant are both safe compared with vitamin K antagonist for atrial fibrillation ablation: An updated meta-analysis. Int J Cardiol 2018; 262: 51-56.

50) van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014; 124: 1968-1975.

51) Santeusanio AD, Weinberg AD, Florman SS, Schiano TD. Safety of direct-acting oral anticoagulants relative to warfarin in a matched cohort of liver transplant recipients. Clin Transplant 2020; 34: e13756.

52) PLoS Medicine Editors. Best practice in systematic reviews: the importance of protocols and registration. PLoS Med 2011; 8: e1001009.

53) Harmon LJ, Losos JB. The effect of intraspecific sample size on type I and type II error rates in comparative studies. Evol Int J Org Evol 2005; 59: 2705-2710.