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. The Centers for Disease Control and Prevention define TBI as an injury to the head that results in disrupted brain functioning. The prevalence of TBI has increased during the past decade by almost 8.4% worldwide, 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.

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. This high prevalence of falls in elderly individuals has many causes. 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. Second, musculoskeletal weakness due to aging (i.e., sarcopenia) leads to deteriorated balance control and a propensity to fall. 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. In addition, elderly patients exhibit a high predisposition to thromboembolic complications, for which they are commonly prescribed antithrombotic and/or anticoagulant drugs 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
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. 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. 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. Moreover, the brief half-life of DOACs may help prevent unwanted interactions with other medications used by elderly patients. 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 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, while others found a longer intensive care unit stay in patients receiving DOACs. Similarly, some studies reported higher risks of intracranial hemorrhage progression in patients with TBI receiving VK-antagonists, and others reported lower risks in the same patients as compared to the risks of patients with TBI on DOACs.

To the best of our knowledge, only one systematic review and meta-analysis 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 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 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. 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 to conduct a with-
in-group meta-analysis based on the random-effects model. 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 ($\geq 75\%$). We evaluated the publication bias following the Duval and Tweedy’s 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. We used tables to annotate the relevant data from the studies. Table I summarizes these data.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study type</th>
<th>Sample description</th>
<th>Age (M ± SD years)</th>
<th>Drugs</th>
<th>ICH progression (%)</th>
<th>Mortality (%)</th>
<th>Surgery intervention (%)</th>
<th>Hospital stay (days)</th>
<th>Intensive care unit stay (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hecht et al27</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>VK-antagonists: 669 (314F, 355M) DOACs: 188 (99F, 89M)</td>
<td>VK-antagonists: 81.1 ± 7.8 DOACs: 81.2 ± 7.7</td>
<td>VK-antagonists: Warfarin DOACs: -</td>
<td>-</td>
<td>-</td>
<td>VK-antagonists: 21.6 DOACs: 18.1</td>
<td>VK-antagonists: 6.7 ± 4.8 DOACs: 5.2 ± 4.6</td>
<td>VK-antagonists: 4.4 ± 4.8 DOACs: 3.5 ± 4.4</td>
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<td>Shin et al34</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>VK-antagonists: 97 (46F, 51M) DOACs: 39 (12F, 27M)</td>
<td>VK-antagonists: 78.5 ± 13.8 DOACs: 79.2 ± 11.7</td>
<td>VK-antagonists: Warfarin DOACs: Dabigatran, rivaroxaban or apixaban</td>
<td>VK-antagonists: 13 DOACs: 4</td>
<td>8.2</td>
<td>VK-antagonists: 13.4 DOACs: 5.2</td>
<td>VK-antagonists: 6.1 ± 6.1 DOACs: 5.4 ± 6.9</td>
<td>-</td>
</tr>
<tr>
<td>Eibinger et al26</td>
<td>Switzerland</td>
<td>Retrospective cohort study</td>
<td>VK-antagonists: 1613 DOACs: 1178</td>
<td>VK-ANT: 80.4 ± 6.8 DOACs: 81.2 ± 7</td>
<td>VK-antagonists: Warfarin DOACs: -</td>
<td>-</td>
<td>-</td>
<td>VK-antagonists: 32.7 DOACs: 30.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Savioli et al28</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>VK-antagonists: 156 (114F, 42M) DOACs: 78 (39F, 39M)</td>
<td>VK-ANT: 82 ± 10 DOACs: 80 ± 10</td>
<td>VK-antagonists: Warfarin, acenocumarol DOACs: apixaban, dabigatran, edoxaban, rivaroxaban</td>
<td>VK-antagonists: 31.9 DOACs: 18.2</td>
<td>22.8</td>
<td>VK-antagonists: 15.3 DOACs: 9.1</td>
<td>VK-antagonists: 27.8 DOACs: 168</td>
<td>VK-antagonists: 70 DOACs: 49</td>
</tr>
<tr>
<td>Scotti et al29</td>
<td>Canada</td>
<td>Retrospective cohort study</td>
<td>VK-antagonists: 151 DOACs: 59</td>
<td>VK-ANT: 80.9 ± 7.9</td>
<td>VK-antagonists: Warfarin DOACs: Dabigatran, rivaroxaban or apixaban</td>
<td>VK-antagonists: 31.9 DOACs: 18.2</td>
<td>22.8</td>
<td>VK-antagonists: 15.3 DOACs: 9.1</td>
<td>VK-antagonists: 27.8 DOACs: 168</td>
<td>VK-antagonists: 70 DOACs: 49</td>
</tr>
<tr>
<td>Prexl et al31</td>
<td>Austria</td>
<td>Retrospective cohort study</td>
<td>VK-antagonists: 32 (17F, 15M) DOACs: 33 (19F, 14M)</td>
<td>VK-ANT: 81 DOACs: 82</td>
<td>VK-antagonists: phenprocoumon, acenocumarol DOACs: Dabigatran, rivaroxaban, edoxaban, rivaroxaban</td>
<td>VK-antagonists: 59.4 DOACs: 24.2</td>
<td>21.8</td>
<td>VK-antagonists: 3 DOACs: 3</td>
<td>VK-antagonists: 27.5 DOACs: 168</td>
<td>VK-antagonists: 70 DOACs: 49</td>
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<tr>
<td>Zeeshan et al33</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>VK-antagonists: 230 (60F, 170M) DOACs: 98 (36F, 62M)</td>
<td>VK-ANT: 62 ± 13.9 DOACs: 57 ± 16.8</td>
<td>VK-antagonists: Warfarin, acenocumarol DOACs: apixaban, dabigatran, edoxaban, rivaroxaban</td>
<td>VK-antagonists: 13 DOACs: 26</td>
<td>9</td>
<td>VK-antagonists: 4 DOACs: 5</td>
<td>VK-antagonists: 4 DOACs: 5</td>
<td>VK-antagonists: 1 DOACs: 3</td>
</tr>
<tr>
<td>Batey et al30</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>VK-antagonists: 141 (74F, 67M) DOACs: 36 (19F, 17M)</td>
<td>VK-ANT: 81 ± 8 DOACs: 81 ± 8</td>
<td>VK-antagonists: Warfarin, acenocumarol DOACs: apixaban, dabigatran, edoxaban, rivaroxaban</td>
<td>VK-antagonists: 13 DOACs: 26</td>
<td>9</td>
<td>VK-antagonists: 4 DOACs: 5</td>
<td>VK-antagonists: 4 DOACs: 5</td>
<td>VK-antagonists: 1 DOACs: 3</td>
</tr>
<tr>
<td>Feeney et al32</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>VK-antagonists: 101 (60F, 61M) DOACs: 61 (27F, 34M)</td>
<td>VK-ANT: 75.6 ± 13 DOACs: 77.2 ± 11.2</td>
<td>VK-antagonists: Warfarin DOACs: Rivaroxaban</td>
<td>VK-antagonists: 20 DOACs: 50</td>
<td>0</td>
<td>VK-antagonists: 60 DOACs: 33</td>
<td>VK-antagonists: 6.6 ± 2.6 DOACs: 4.2 ± 1.6</td>
<td>-</td>
</tr>
<tr>
<td>Beynon et al35</td>
<td>Germany</td>
<td>Retrospective cohort study</td>
<td>VK-antagonists: 5 (3F, 2M) DOACs: 6 (2F, 4M)</td>
<td>VK-ANT: 74 ± 17 DOACs: 71 ± 25</td>
<td>VK-antagonists: Warfarin, acenocumarol DOACs: Rivaroxaban</td>
<td>VK-antagonists: 20 DOACs: 50</td>
<td>0</td>
<td>VK-antagonists: 60 DOACs: 33</td>
<td>VK-antagonists: 6.6 ± 2.6 DOACs: 4.2 ± 1.6</td>
<td>-</td>
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<tr>
<td>Parra et al33</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>VK-antagonists: 15 (5F, 10M) DOACs: 5 (2F, 3M)</td>
<td>VK-ANT: 83.9 DOACs: 81.6</td>
<td>VK-antagonists: Warfarin, acenocumarol DOACs: apixaban, dabigatran, edoxaban, rivaroxaban</td>
<td>VK-antagonists: 20 DOACs: 80</td>
<td>0</td>
<td>VK-antagonists: 0 DOACs: 40</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

M, mean; SD, standard deviation; VK-antagonists, vitamin-K antagonist; DOACs, direct oral anticoagulants.
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 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.
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 compared the intensive care unit stay between the two groups of patients. 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 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% CI, -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 VK-antagonists than for those who had received DOACs (Figure 6) (odds ratio, 1.22; 95% CI, 0.41 to 3.37; p<0.01). 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 to 3.37; p=0.6).
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 VK-antagonists (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...
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. Elderly patients also frequently present thromboembolic disorder risks for which they are regularly prescribed antithrombotic prophylaxis. VK-antagonist use has been associated with intracranial hemorrhagic complications in elderly patients due to polypharmacy drug interactions,

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
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<tr>
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<td>0.810</td>
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<td>0.492</td>
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<td>0.219</td>
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<td>0.634</td>
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<td>2.346</td>
<td>1.131</td>
<td>4.866</td>
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<td>60.325</td>
<td>1.001</td>
<td>0.317</td>
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<td>Parra et al. (2013)</td>
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<td>2.664</td>
<td>294.285</td>
<td>2.776</td>
<td>0.005</td>
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<td></td>
<td>1.222</td>
<td>0.418</td>
<td>3.576</td>
<td>0.366</td>
<td>0.714</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
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</thead>
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<td>Hecht et al. (2020)</td>
<td>1.210</td>
<td>0.799</td>
<td>1.832</td>
<td>0.898</td>
<td>0.369</td>
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<td>Shin et al. (2020)</td>
<td>2.863</td>
<td>0.615</td>
<td>13.330</td>
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<td>0.061</td>
<td>37.606</td>
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<td>0.800</td>
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<td>0.899</td>
<td>3.323</td>
<td>1.640</td>
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</table>

Figure 7. Odds of undergoing surgical intervention 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\textsuperscript{47,48}. DOACs have been used as a safer alternative\textsuperscript{49,50}, but this is largely based on their efficacy and low anticoagulative risks and not on direct comparisons. Santusiano et al\textsuperscript{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\textsuperscript{33}, in a three-year retrospective observational study, compared the outcomes of patients with perioperative consumption of DOACs with those consuming VK-antagonists with those having 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, Parra et al\textsuperscript{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\textsuperscript{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\textsuperscript{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 ($g=0.13$).

<table>
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<th>Study name</th>
<th>Odds ratio</th>
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<th>p-Value</th>
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<td>Parra et al. (2013)</td>
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**Figure 8.** Odds of overall mortality in patients with traumatic brain injury who had received either vitamin-K antagonist or direct oral anticoagulants.
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. We know that this could raise 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. 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


