Trauma and thrombosis in the DOAC era: promise and peril of direct oral anticoagulant use in injured patients

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Chapter 5

Consequences of pre-injury utilization of direct oral anticoagulants (DOACs) in patients with traumatic brain injury (TBI): a systematic review and meta-analysis

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Abstract

Background: The rapid adoption and widespread use of direct oral anticoagulants (DOACs) has outpaced research efforts to establish their effects in bleeding trauma patients. In patients with complicated traumatic brain injury (TBI) caused by intracranial hemor- rhage, DOAC use may be associated with higher bleeding volume and potentially more disastrous sequelae than use of vita- min K antagonists (VKAs). In the current systematic review and meta-analysis we set out to evaluate the literature on the relationship between preinjury DOAC use and course of the intracranial hemorrhage. (ICH), its treatment and mortality rates in TBI patients, and to compare these outcomes to those of patients with preinjury VKA use.

Methods: PubMed, Embase, Web of Science, and the Cochrane Library were searched using a search strategy including three main terms: “traumatic brain injury,” “direct oral anticoagulants,” and “vitamin K antagonists.” There were 1,446 abstracts screened, and ultimately, six included articles. Random effects modeling meta-analysis was performed on in-hospital mortality, ICH progression and neurosurgical intervention rate.

Results: All cohorts had similar baseline and emergency department parameters. Within individual studies surgery rate, reversal agents used, ICH progression and in-hospital mortality differed significantly between DOAC and VKA cohorts. Meta-analysis showed no significant difference in in-hospital mortality (odds ratio [OR], 0.98; 95% confidence interval [CI], 0.23–4.06; I^2 = 76%; p = 0.97), neurosurgical interventions (OR, 0.48; 95% CI, 0.14–1.63; p = 0.24), or ICH progression rates (OR, 1.86; 95% CI, 0.32–10.66; p = 0.49) between patients that used preinjury DOACs versus patients that used VKAs.

Conclusion: Direct oral anticoagulant-using mild TBI patients do not appear to be at an increased risk of in-hospital mortality, nor of increased ICH progression or surgery rates, compared with those taking VKAs.

Introduction

Oral anticoagulants are often used by the frail and elderly with multiple comorbidities. In this population, impaired mobility, sight and stability often lead to head injuries due to falls and traffic accidents. After minor or moderate head injuries, and particularly after intracranial hemorrhage (ICH), pre-injury anticoagulation use is known to contribute to mortality and the incidence of complications. (1-3)

For over sixty years, vitamin K antagonists (VKAs), such as warfarin, phenprocoumon and acenocoumarol, have been the mainstay treatment modality for the prevention of ischemic stroke in patients with atrial fibrillation and the treatment of patients with acute venous thromboembolism. Direct oral anticoagulants (DOACs) are a new class of oral anticoagulants that comprise two different types, i.e. direct thrombin inhibitors (DTI) such as dabigatran, and factor Xa inhibitors such as apixaban, betrixaban, edoxaban and rivaroxaban. At present, the prescription rates of DOACs match those of warfarin in the United States and parts of Western Europe for first time prescriptions.(4-9)

Arguably improved effectiveness and comparable safety profile, along with their relative ease of use, render DOACs a good alternative to warfarin. Recent studies have indicated that DOACs are similarly effective, or even more effective than VKAs for the prevention of ischemic stroke and are associated with similar or fewer major bleeding events (MBE), including intracranial hemorrhage (ICH).(10-13)

In patients with non-traumatic intracranial hemorrhage, DOAC use appears to be associated with a similar distribution of ICH types, and equivalent to improved outcomes and mortality compared to the use of VKAs.(14-19) Two studies also report significantly lower ICH volumes in DOAC users compared to VKA users on emergency department (ED) presentation. This is attributed to favorable pharmacological qualities of DOACs, including shorter half-lives and more selective inhibition of the extrinsic coagulation pathway.(14, 19) It is unknown, however, how the risks of pre-injury DOAC use compare with those of pre-injury use of VKAs in patients with traumatic brain injuries (TBIs). This is of particular interest, since even a small volume hemorrhage can have disastrous sequelae within the confined space of

the cranium. With the increasing number of trauma patients on DOACs, emergency physicians, trauma surgeons and neurosurgeons need to be well versed in the data on the safety of different anticoagulants in TBI and other trauma patients.

In the current systematic review and meta-analysis we set out to evaluate the literature on the relationship between pre-injury DOAC use and course of the ICH, its treatment and mortality rates in TBI patients, and to compare these outcomes to those of patients with pre-injury VKA use.

Methods

The primary objective of this study, by methods of a systematic review, was to investigate the consequences of pre-injury DOAC use in TBI patients and to compare pre-injury DOAC use associated in-hospital mortality to mortality in TBI patients on pre-injury VKA use**.** The secondary objectives were to compare injury characteristics, treatment modalities and complication rates of TBI patients on pre-injury DOAC versus VKA therapy.

Search Strategy & Eligibility

The systematic review and meta-analysis were performed following the PRISMA Statement.(20) PubMed, Embase, Web of Science and the Cochrane Library were searched using a search strategy including three main terms: ‘traumatic brain injury’, ‘direct oral anticoagulants’ and ‘vitamin K antagonists’. The full search strategy is presented in Appendix A. Studies were selected if all of the following inclusion criteria were met: 1. Cohort study of adult trauma patients with traumatic ICHs with or without additional injury; 2. pre-injury use of oral anticoagulation (DOACs and VKA cohorts); 3. if involving both TBI and non-TBI patients: separately reporting data on the TBI patients; 4. reporting on pre-injury patient demography, comorbidity, and one or more of the following: mortality, in-hospital treatment, (bleeding) complications; 5. written in English or Dutch. Studies were excluded if meeting any of the

following criteria: 1. study design without comparative cohort; 2. involving patients with intracranial bleeding as adverse drug event instead of traumatic event.

Data Extraction

Data on study design, inclusion and exclusion criteria, age, sex, co-medication, comorbidity, Abbreviated Injury Scale (AIS) score/Injury Severity Scale (ISS) score, admission vital signs and laboratory values, ICH size and type, treatment modalities (reversal agents, neurosurgical interventions performed, transfusions), ICH progression (increased ICH volume on CT scan as compared to the volume on the primary CT scan), ICU and hospital length of stay, Glasgow Outcome Score (GOS), readmission rates and in-hospital mortality were collected from the included studies using a standardized data collection sheet. After data synthesis, clinical heterogeneity in the selected studies was assessed based on the collected variables.

Meta-analysis

Statistical heterogeneity was determined using the I^2 statistic and Chi-square test. A random effects meta-analysis was indicated if clinical heterogeneity or statistical heterogeneity was assumed to be present. The authors reasoned that statistical heterogeneity was present if I^2 >50%. The random effects method of DerSimonian & Laird was used, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. (21, 22) All statistical analyses were performed using Review Manager software (RevMan 5.3, The Cochrane Collaboration).

Risk of Bias Assessment

Risk of bias in the included studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS) score (range 0-24, where higher scores represent higher quality reporting and methodology). (23) A funnel plot was constructed to assess the risk of publication bias.

Results

Selection

The literature search was performed on May 7th, 2019 and yielded 1446 articles after removal of duplicates. After screening titles and abstracts, 63 full-text articles were read, 6 of which met all inclusion criteria and were included (Figure 1).(24-29). The characteristics of the 6 selected articles and the included populations are summarized in Table 1.

Study Characteristics

In total, 2622 TBI patients were included, 239 on DOACs (9.1%), 524 on VKAs (20.0%) and 1859 controls without pre-injury use of anticoagulants (70.9%). All selected studies were retrospective cohort studies. No regression analyses were performed, but all outcomes were reported as proportions and compared on univariate analysis. One study used 1:2 propensity score matching to match DOAC to VKA patients.(29) Four studies were carried out in the United States, one in Germany and one in Austria.

Patient Population

The included patient population is best described as geriatric, with mean ages between 71 and 82, except for one study which included a much younger patient population (mean age of 61), and also significantly more female patients in the DOAC group.(29) Co-medication with antiplatelets or anti-thrombotics did not differ significantly between the cohorts. Several studies reported statistical differences on comorbidities in the DOAC and VKA groups. One study reported GI-comorbidities to be present less often in the DOAC group than in the VKA group (6% vs 40%, $p<0.01$).(24) No significant differences were reported between the groups for AIS, vital signs on admission, admission laboratory values, prothrombin time (PTT)/activated PTT or international normalized ratio (INR) (data shown in Appendix B). In one study, ISS was higher in the DOAC group, but this difference no longer

existed after matching.(29) The median GCS in all studies was between 14 and 15, corresponding to mild TBI. ICH types did not significantly differ between the cohorts. ICH size was only described in one study, which reported no significant difference between DOAC or VKA in patients with epidural and subdural hematomas (EDH: 4.4±3.2 mm vs 4.0±4.1 mm, p=0.12, SDH: 5.1±3.4 mm vs 4.8±3.7 mm, p=0.10).(29)

Outcomes

Several differences between the DOAC and VKA groups were present in the selected studies with regards to patient treatment such as the use of reversal agents, neurosurgery and transfusion. The main variables of interest are summarized in Table 2. In two studies DOAC patients were significantly less likely to receive transfusion products, and in case they did receive transfusion product it concerned lower volumes.(24, 26) The use of reversal agents in DOAC patients was reported in only two studies, as a result of the fact that the reversal agents were not approved for use during the inclusion periods of the other studies.(27, 28) Use of vitamin K for VKA patients was reported in one study, despite the established position of vitamin K and PCC in the management of VKA-associated bleeding. This study found a significantly higher rate of reversal agent use for VKA patients (24.2% Idarucizumab or PCC for DOAC patients vs. 84.4% vitamin K and PCC for VKA patients, p<0.0001).(28) Hospital length of stay (LOS) did not differ significantly between the DOAC and VKA cohorts (data shown in Appendix B in tables). In contrast, intensive care unit (ICU) LOS was significantly increased for the DOAC cohort in one of the studies, and another study also reported that DOAC patients required significantly less ventilator assistance (0% vs 10.6%, p<0.05).(24, 29)

The available literature was not unanimous in terms of outcome measures. Parameters for treatment and outcomes are summarized in Table 2. The overall mortality calculated on all included patients was 11.8% (95% CI 7.7-17.0%) for DOAC patients and

12.8% (95% CI 9.8-16.3%) for VKA patients. Considerable variance exists in reported mortality rates (0% to 40%). The causes of mortality were not reported and could not be compared between the two groups. DOAC patients underwent neurosurgical interventions significantly more often in two, and less often in one study, with the other three studies reporting no significant difference. ICH progression rates were higher for DOAC patients in three studies, two of which found a statistically significant difference.(25, 27, 29) GCS and GOSE at discharge were similar for DOAC patients and VKA patients (data shown in Appendix B).(25, 27, 29) Discharge rates to a rehabilitation center or skilled nursing facility (SNF) were significantly lower for DOAC patients in one study, but significantly higher in another.(26, 29) Readmission rates were not described in the included studies. Three studies concluded in favor of pre-injury DOAC exposure, and three studies favored VKAs when related to outcome after TBI with ICH.

Meta-analysis

The random effects meta-analysis showed that TBI patients on pre-injury DOACs and those on pre-injury VKAs had similar adjusted odds of in-hospital mortality: OR 0.98, 95% CI 0.23–4.06, p = 0.97, based on 634 patients across 6 studies (Figure 2). (22-27) However, the statistical heterogeneity between these studies was considerable (I^2=76%, Chi-square test: p = 0.0007). A second random effects meta-analysis showed 56% lower odds of undergoing neurosurgical intervention for DOAC TBI patients, but this effect was not statistically significant (OR 0.44, 95% CI 0.13 – 1.51, p = 0.19) (Figure 3). ICH progression rates were reported in 4 studies, showing 86% higher odds in the VKA group, but not statistically significant (OR 1.86, 95% CI 0.32 – 10.66, p=0.49) (Figure 4).(23, 25-27)

Risk of Bias Assessment

The sum of the scores for the risk of bias assessment are presented in the concise overview of the included articles in Table 1. Risk of bias assessments according to the MINORS tool are presented in Appendix C. All studies are retrospective cohort studies, thus

blinding and sample size calculations were not performed. Major bias was introduced by exclusion of transferred patients and patients who died within the first 24 hours. The funnel plot (Appendix D) does not indicate publication bias in any direction.

Discussion

This meta-analysis demonstrated no significant difference between pre-injury use of DOACs versus VKA for in-hospital mortality, surgery rates and incidence of ICH progression. Although the cohorts did not differ significantly on important variables (ISS, GCS, ICH types, co-medication and relevant comorbidities), individual studies reported significant differences in mortality rates.

Our results for mortality in TBI patients with ICH are in accordance with recent trauma literature. In a study that included all trauma patients, patients using DOACs or VKA had similar mortality rates.(30) Additionally, transfusions with fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) were less common in the DOAC group, similar to the results found in our review.(24, 26) However, hospital stays were longer for VKA patients, which was attributed to higher ISS in that group - something that was not found in this review. Another recent study on the impact of pre-injury anticoagulation on the general trauma population reported shorter hospital stays, decreased overall mortality, and decreased trauma-related mortality for patients on DOACs, compared to VKAs.(31) Subgroup analysis of TBI patients with pre-injury DOAC use showed lower mortality, but this did not reach statistical significance. A third study, looking at blunt chest trauma, found decreased mortality and transfusion requirements for DOAC patients. (32)

Two studies were identified comparing pre-injury DOACs and VKAs in patients presenting to the ED after ‘minor head injuries’, ’closed head injuries’ and falls, but without ICH on admission being an inclusion criterium.(33, 34) In these studies, reversal agents were

not used in DOAC patients, but 79% of VKA patients received vitamin K. Still, mortality was lower in the DOAC cohorts.

Subset analysis on patients with ICH was performed in the RE-LY trial, a randomized trial comparing DOACs to warfarin in terms of effectiveness and safety profiles for the prevention of thrombo-embolic events in atrial fibrillation.(35) This study reported higher overall mortality for traumatic ICH for DOAC patients (27%) versus VKA patients (20%). However, no p-values were calculated, and this finding was not further elucidated in the article, potentially due to sample size and lack of power for this specific comparison (n=35, 11 DOAC, 24 VKA patients).

As INR and aPTT/PTT are unreliable laboratory parameters to assess the degree of DOAC anticoagulation, and anti-Xa assays are not routinely performed in most centers, clinicians rely on the best estimate of the time since the last dose of DOAC to assess anticoagulation. None of the included studies measured the degree of anticoagulation. It is possible that DOAC patients were less strongly anticoagulated, considering the short half-lives (between 7 and 17 hours for the different DOACs, versus approximately 40 hours for warfarin) and lower reported compliance compared to warfarin (60% adherence versus 80% for warfarin).(36, 37)

At the time of most of the included studies reversal agents were not yet approved. This in part explains the infrequent use of reversal agents in TBI patients using DOACs prior to trauma. An explanation for the observation that DOAC patients received significantly less transfusion products was not found in the evaluated literature, as hemorrhage volume was not significantly different, and ISS, GCS and vital signs were similar. Despite differences in reversal and transfusion strategies, there was no difference in mortality for DOAC patients compared to VKA patients.

Several studies were identified that included both non-traumatic and traumatic ICHs.(38-42) Although the origin and thus pathophysiology of the bleeding obviously differ,

the management of traumatic and non-traumatic ICH share similarities in terms of reversal agents and transfusion strategies. One study demonstrated that vitamin K and 4-factor prothrombin complex concentrate (4-FPCC) were administered more often in patients on pre-injury VKAs for non-traumatic ICHs.(39) Without the use of reversal agents, DOAC-associated major hemorrhage had a mortality rate of 21 to 27%.(40, 42) No difference was found between patients treated with 4-FPCC/FFP and those with just supportive care.(40) Another study compared patients that used DOAC or VKA and presented to the ED for any bleeding event. They found no difference in mortality for gastro-intestinal bleeding (7% vs 7%), but higher mortality for DOAC-associated all-cause ICH (18% vs 4%, OR 4.4; 95% confidence interval 1.4-13.3).(41)

Limitations

We were not able to account for confounding by indication. In the studies identified in this meta-analysis, the indications for oral anticoagulant use were described only in some cases, however the rationale behind prescribing a DOAC instead of a VKA, were not further elucidated. All 6 included studies were conducted retrospectively, thereby making it difficult, if not impossible, to identify their rationales and preferences.

Furthermore, it is important to note that across the 6 studies included in this review, the included patient population is best described as having sustained mild TBI, with a median GCS on ED presentation of 14-15 and a mean age between 71 and 85. Our results therefore apply to elderly patients with mild TBI due to falls or minor trauma, and cannot be extrapolated to more severely injured patients.

Statistical analyses of baseline characteristics were missing in half the studies and no regression analyses were performed, due to small sample sizes. In addition to this, most studies did not calculate risk ratios, ORs and confidence intervals for the effects reported. The strength of the conclusion is therefore mostly based on the larger studies.(24, 26, 29)

One study reported different ORs for mild, moderate and severe TBI substrata. We decided to use the overall OR for in-hospital mortality, as the patients were comparable in terms of GCS and ISS to those in other cohorts. Since all ORs for substrata were lower than the overall OR, substituting any other OR would influence the adjusted OR towards favoring DOACs. Running the meta-analysis with the OR for mild TBI resulted in a lower, but still statistically insignificant OR for mortality for DOACs versus VKAs.

Due to the small sample sizes of the selected studies, an additional post-hoc power analysis was performed to assess what true effect size could have been detected. Based on the combined studied samples we would be able to ascertain a 10.5%, 11.6% and 16.7% risk difference for in-hospital mortality, ICH-progression and surgical intervention respectively.

Conclusion

The results of this random effects meta-analysis show that DOAC-using mild TBI patients do not appear to be at an increased risk of in-hospital mortality, nor of increased ICH progression or surgery rates, compared to those taking VKAs. However, specific recommendations on treatment options cannot be substantiated by current studies as they lack the necessary power and methodological completeness. Further studies including randomized trials and larger sample sizes are necessary to direct the management of DOAC-anticoagulated TBI patients.

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Author Contribution

CN and SA performed the literature search. CN, PK and IS were involved in study design. CN and SA collected the data. CN and PK analysed the data. All authors were involved in data interpretation CN and SA wrote the article. PK, MR, MH, WP and IS were involved in critical revision of the article.

Level of Evidence: Systematic review, level III.

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Figures and Tables

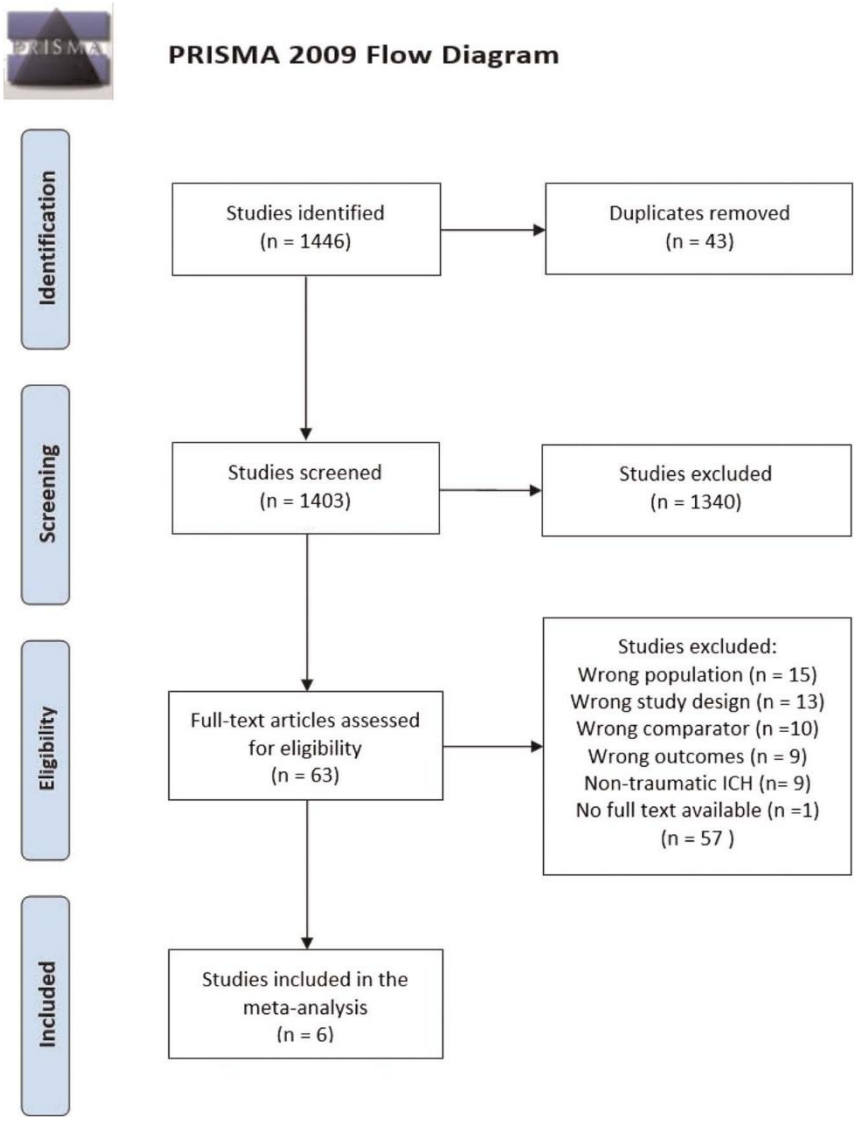

Figure 1. Study selection flow chart.

TABLE 1. Study Characteristics and Study Population

Reference	Risk of Bias (MINORS)	Inclusion Period	Inclusion Criteria	Exclusion Criteria	n (DOAC/ VKA/Control)*	Age (Mean ± SD) *	% Female *	ISS (Mean ± SD) *	GCS (Median (IQR)) *	ICH Types *
Batey 2018	16/24	May 2013– October 2015	Age: 65+ y, TBI	Transfers; multiple OAC or clopidogrel	36/141/523	81 ± 7 vs. 81 ± 8, p = NS	53 vs. 53 p = NS	–	15 ± 1 vs. 14 ± 2.4 vs. 13.8 ± 2.6 p = NS	–
Beynon 2015	15/24	October 2013– March 2014	Age: all, mild TBI (GCS13–15), tICH on CT	Dabigatran comedication	6/5/59	71 ± 25 vs. 74 ± 17	33 vs. 60 p = NS	–	Mean (SD) = 14.57 (0.79) vs. 14.6 (0.55), p = NR	SDH: 33% vs. 100%; ICH: 33% vs. 20%; SAH 33% vs. 20%, p = NR
Feeney 2016	18/24	June 2011– October 2015	Age: all Blunt tICH	–	61/101	77.2 ± 11.2 vs. 79.5 ± 13, p = 0.25	44.3 vs. 39.6, p = 0.74	(LQ,UQ) 16 (10, 25) vs. 17 (10, 25), p = 0.21	14 (14, 15) vs. 13 (13, 15) p = 0.12	SDH: 54.1% vs. 54.5%, p = 1.0 SAH: 41.0% vs. 27.7%, p = 0.09 IPH: 29.5% vs. 27.7%, p = 0.86 IVH: 13.1% vs. 12.9%, p = 1.0
Parra 2013	18/24	February 2011– May 2011	Age: 18+ y, CHI due to GLF	Suspected hypertensive ICH	5/15/25	81.6 vs. 83.9, p = 0.46	40 vs. 33, p = 1	20 vs. 16.47, p = 0.39	14.6 vs. 14.6, p = 1	SAH: 80% vs. 20%, p = NR SDH: 20% vs. 80%, p = NR IPH: 40% vs. 33%, p = NR
Prexl 2018	16/24	January 2014– May 2017	Age: 60+ y, TBI, ICH on initial CCT or at risk for delayed dICH, ICU/OR admission	no ICU admission, polytrauma	33/32/131	82 (75.5–84.5) vs. 81 (74–85), p = NR	57.6 vs. 53.1, p = NS	10 (9–16) vs. 14.5 (9–24), p = NR	14 (14–15) vs. 14 (13–15), p = NR	–
Zeeshan 2018	17/24	January 2014– December 2016)	Age: 18+ y, TBI, ICH on initial head CT	Known bleeding disorder; liver disease; penetrating injury; death <24 hours after injury	98/230/1131 Matched: 70 /140	59 ± 15.9 vs. 60 ± 14 .7, p = 0.21	36.8 vs. 26.3, p = 0.04	Unmatched: 17 (9–21) vs. 15 (10–19), p = 0.04; Matched: 15 (9–22) vs. 15 (9–21), p = 0.62	14 (8–15) vs. 14 (9–15), p = NR	EDH: 5.7% vs. 5.7%, p = 0.11 SDH: 48.6% vs. 49.2%, p = 0.19 SAH: 41.4% vs. 42.2%, p = 0.53 IPH: 7.1% vs. 6.4%, p = p0.76

* Results for DOAC group vs. VKA group.

All significant p values are printed in bold.

MINORS: Methodological Index for Non-randomized Studies, DOAC, direct oral anticoagulant; SD, standard deviation; (t)ICH: (traumatic) intracranial hemorrhage; LOC, loss of consciousness; GLF, ground level fall; MHI, minor head injury; OAC, oral anticoagulant; NS, nonsignificant; ASA, acetylsalicylic acid; AP, antiplatelet; IQR, interquartile range; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; EDH, epidural hemorrhage; IPH, intraparenchymal hemorrhage; NR, not reported.

TABLE 2. Treatment and Outcome Measures

Reference: (DOAC/VKA)	Patients Requiring Neurosurgery*	Reversal Agent Use *	Patients Requiring Transfusions*	Median ICU LOS (Days, IQR)*	In-Hospital Mortality *	ICH Progression *
Batey 2018 (36/141)	3% vs. 18%, $p < 0.05$	–	3% vs. 26%, $p < 0.01$ Mean Units: 4 vs. 6 ± 4, $p < 0.01$	Mean (SD): 1.6 ± 2.1 vs. 3.2 ± 4, $p = 0.02$	5% vs. 9%, p = NS	–
Beynon 2015 (6/5)	2/6 (33%) vs. 3/5 (60%), p = NS	–	–	–	33% vs. 0%, $p < 0.05$	50% vs. 20%, p = NR
Feeney 2016 (61/101)	8.2% vs. 26.7%, $p = 0.02$	–	14.8% vs. 21.8%, $p = 0.31$ Mean Units pRBC: 2 ± 0.88 vs. 4 ± 4.45, $p = 0.54$	1.4 (0.75, 2) vs. 1.2 (1, 3) $p = 0.87$	4.9% vs. 20.8%, $p = 0.01$	–
Parra 2013 (5/15)	0/0 (0%) vs. 3/15 (20%), p = NR	DOAC: 80% rFVIIa, 40% Dialysis VKA: NR	DOAC: 80% FFP, 60% PLTs, 40% FFP & PLT VKA: NR	4 (2–6) vs. 3.2 (1–10)	40% vs. 0%, $p = 0.05$	80% vs. 20%, $p = 0.03$
Prexl 2018 (33/32)	1/33 vs. 3/32, p = NS	24.2%, (4 Idarucizumab, 4 PCC) vs. 84.4% (27 Vit. K & PCC), $p < 0.0001$;	–	Mean Hours (±SD): 49 (22–92) vs. 70 (29.25–159.5), p = NS	3.33% vs. 21.88%, $p < 0.05$	24.2% vs. 59.4%, p = NR
Zeeshan 2018 (98/230)	Overall: 20% vs. 9.2%, $p = 0.04$ Mild: OR 1.93 (1.35–4.02) $p = 0.03$ Moderate: OR 1.59 (1.41–4.13) $p = 0.02$ Severe: OR, 1.12 (0.81–3.98) $p = 0.62$	–	–	3 (2–5) vs. 1 (1–4) $p = 0.04$	Overall: 20% vs. 9%, $p = 0.04$; Mild: OR, 2.01(1.71–4.43), $p = 0.01$ Moderate: OR, 1.91 (1.63–4.57), $p = 0.02$ Severe: OR, 1.57 (0.92–3.77), $p = 0.81$	Overall: 26% vs. 13%, $p = 0.03$; Mild: OR, 1.91 (1.58–3.71), $p = 0.02$ Moderate: OR, 1.97 (1.33–4.31), $p = 0.02$ Severe: OR, 1.42 (0.74–3.98), $p = 0.59$

* Results for DOAC group vs. VKA group.
All significant p values are printed in bold.
pRBC, packed red blood cells; rFVIIa, recombinant factor VIIa; PLT, platelets.

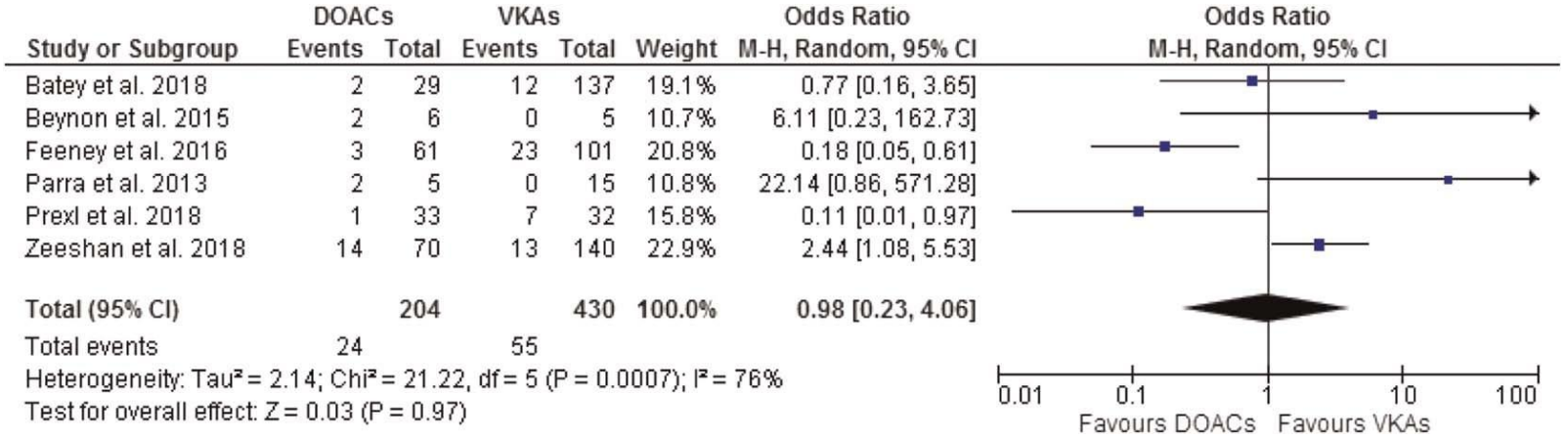

Figure 2. Forest plot of odds of in-hospital mortality for preinjury DOACs versus preinjury VKAs.

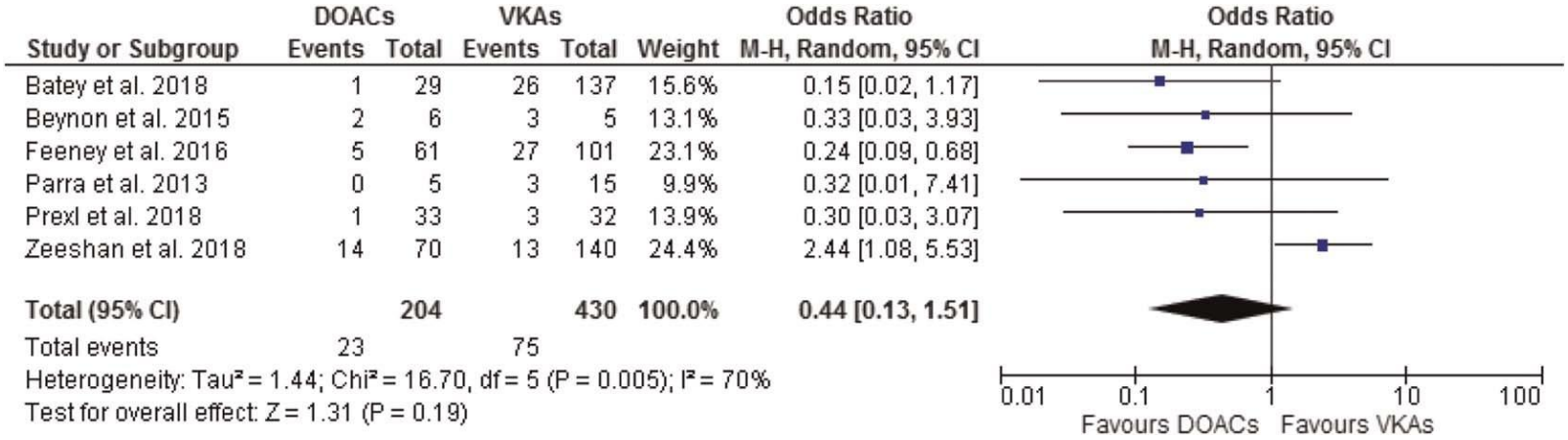

Figure 3. Forest plot of preinjury DOAC versus VKA use in TBI patients with neurosurgical intervention for TBI as the dependent outcome.

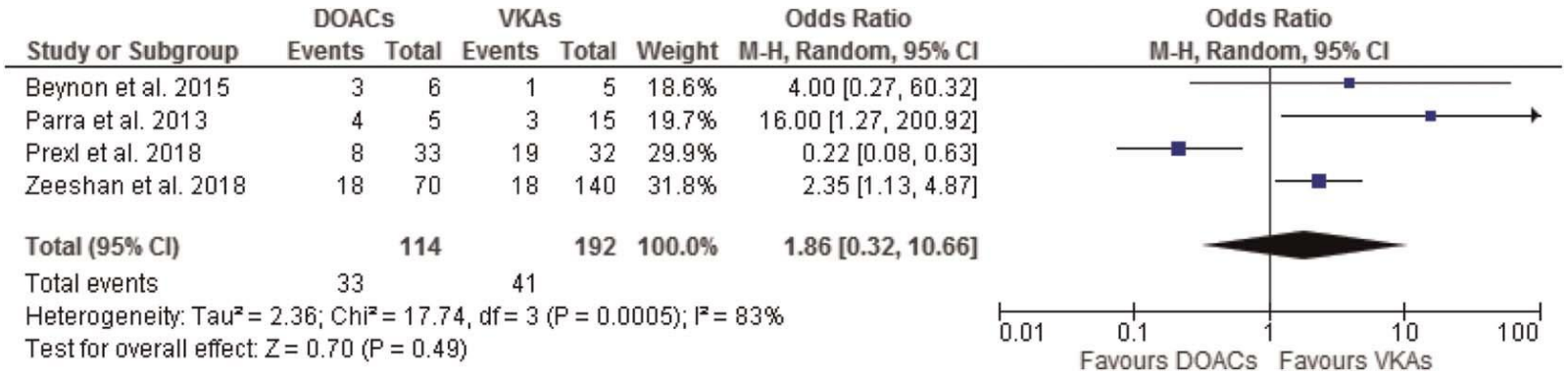

Figure 4. Forest plot of preinjury DOAC versus VKA use in TBI patients with ICH progression as the dependent outcome.