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REVIEW

Mild Traumatic Brain Injury in Elderly Patients Receiving Direct Oral Anticoagulants: A Systematic Review and Meta-Analysis

Juliette A.L. Santing,[1] Ying Xing Lee,[1] Joukje van der Naalt,[2] Crispijn L. van den Brand,[3] and Korné Jellema[1]

Abstract

The aim of this work was to conduct a systematic review and meta-analysis of studies reporting on the risk of traumatic intracerebral hemorrhage (tICH), the course of tICH, and its treatment and mortality rates in elderly mild traumatic brain injury (mTBI) patients using direct oral anticoagulants (DOACs). We consulted PubMed and Embase for relevant cohort and case-control studies with a control group. Two authors independently selected studies, assessed methodological quality, and extracted outcome data. Estimates were pooled with the Mantel-Haenszel random-effects method. We identified 16 articles comprising 3671 elderly mTBI patients using DOACs. Use of DOACs was associated with a reduced risk of tICH compared to the use of vitamin K antagonists (VKAs; odds ratio [OR], 0.44; 95% confidence interval [CI], 0.29–0.65; $I^2 = 22\%$) and a similar risk compared to the use of antiplatelet therapy (APT; OR, 0.98; 95% CI, 0.39–2.44; $I^2 = 0\%$). Reversal agent use and neurosurgical intervention rate were lower in patients using DOACs compared to patients using VKAs (OR, 0.10; 95% CI, 0.06–0.16; $I^2 = 0\%$ and OR, 0.37; 95% CI, 0.21–0.67; $I^2 = 0\%$, respectively). There was no significant difference in neurosurgical intervention rate between patients who used DOACs versus patients who used APT (OR, 0.58; 95% CI, 0.15–2.21; $I^2 = 41\%$) or no antithrombotic therapy (OR, 0.76; 95% CI, 0.20–2.86; $I^2 = 23\%$). ICH progression, risk of delayed ICH, and TBI-related in-hospital mortality were comparable among treatment groups. The present study indicates that elderly patients using DOACs have a lower risk of adverse outcome compared to patients using VKAs and a similar risk compared to patients using APT after mTBI.

Keywords: DOAC; elderly; intracerebral hemorrhage; mild traumatic brain injury; minor head injury reversal agent; VKA

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Introduction

TRAUMATIC BRAIN INJURY (TBI) IS A COMMON AND A major cause of death and disability worldwide.[1–4] Although TBI occurs at all ages, the highest combined incidence of TBI-related emergency department (ED) visits, hospitalizations, and deaths occurs in elderly patients (>60 years).[3,5,6] Compared to younger patients with TBI, elderly patients experience higher morbidity and mortality and slower recovery trajectories, even after mild traumatic brain injury (mTBI).[6] This is, in part, linked to pre-existing neurological or systemic comorbidities.[7]

Pre-injury cardiovascular conditions are common in older age, and therefore antithrombotic therapy (ATT) is often prescribed in the geriatric population. Patients

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using antiplatelet therapy (APT) or vitamin K antagonists (VKAs) have an increased risk for traumatic intracerebral hemorrhage (tICH) formation and secondary progression of hematomas after TBI.[8–11] In recent years, direct oral anticoagulants (DOACs; such as apixaban, edoxaban, rivaroxaban, and dabigatran) are increasingly used as an alternative to VKAs for the prevention of systemic embolism or stroke in patients with non-valvular atrial fibrillation and treatment of venous thromboembolism.[12] Consequently, physicians must deal with a growing number of geriatric patients who have sustained a TBI with concomitant intake of DOACs. Current guidelines and management strategies are, however, still based on experience with patients using APT or VKAs.[13–15]

In the current systematic review and meta-analysis, we aim to assess the available data from previous studies regarding the relationship between pre-injury DOAC use and the risk of traumatic hemorrhagic complications, the course of the tICH, and its treatment and mortality rates in elderly mTBI patients.

Methods

We performed this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[16,17] The methodology was registered with the PROSPERO online database of systematic reviews.[18]

Information sources and search strategy

We searched PubMed and Embase using a search strategy including two main terms: ''traumatic brain injury'' and ''direct oral anticoagulants.'' The full search strategy is presented in the Supplementary Materials.

Eligibility criteria

We included retrospective as well as prospective, observational cohort studies and case-control studies that evaluated the relationship between (any type of) DOAC and tICH after mTBI (Glasgow Coma Scale [GCS] score, 13–15) in elderly patients, that is, mean age (median age if mean was not available) of all patients included was at least 60 years. If data on mTBI could not be separated from moderate TBI (GCS, 9–12), but the latter encompassed <5% of the study population, the study was included. We excluded studies if studies: 1) had no control group (i.e., studies reporting only on patients using DOACs); 2) involved both TBI and non-TBI patients but no separately reported data on TBI patients were available; or 3) reported only composite outcomes but no specific data on the individual study outcomes.

The main outcome measure was tICH (defined as epidural hemorrhage, traumatic subdural hemorrhage, traumatic subarachnoid hemorrhage, or traumatic intraparenchymal hemorrhage) on a head computerized tomography (CT) scan; other outcome measures of interest were the use of reversal agents and/or a neurosurgical intervention, the course of tICH with hematoma progression or occurrence of delayed ICH (dICH) on a repeated head CT scan, and in-hospital mortality related to TBI. For studies to be eligible, we had to be able to extract data on at least one of these outcomes. No limits were placed on characteristics of participants, date of publication, or language of publication.

Selection and data collection process

Two authors (J.S., Y.X.L.) selected articles and extracted data; each step in the selection and data extraction was performed independently by these authors. Any disagreements were resolved after discussion and consensus. We extracted data regarding study design, study location, sample sizes, characteristics of participants (including age and GCS score), intervention (type of DOAC), control group (such as no ATT, [dual] APT, VKA), treatment modalities (reversal agents, neurosurgical interventions performed), ICH progression (increased ICH volume on a repeated CT scan, obtained per routine or if neurological deterioration occurred, as compared with the volume on the primary CT scan), TBI-related in-hospital mortality, and dICH (new ICH on a repeated CT scan after an initial negative CT scan). After data synthesis, clinical heterogeneity in the selected studies was assessed based on the collected variables.

Statistical analysis

Results are reported as pooled odds ratios (ORs) with accompanying 95% confidence intervals (CIs), with a two-sided $p < 0.05$ considered statistically significant. We reviewed the data for statistical heterogeneity using the I^2 statistic. The meta-analysis was performed using the random-effects model. Pre-specified subgroup analyses were performed for type of DOAC (apixaban, edoxaban, rivaroxaban, and dabigatran; other) and type of control group (no ATT, [dual] APT, and VKA). All analyses were made with RevMan (version 5.4 from The Cochrane Collaboration [2020]).

Risk of bias assessment

Methodological quality of the studies was assessed independently by two authors (J.S., Y.X.L.) with the Newcastle-Ottawa Scale (NOS) for assessment.[19] Any disagreements were resolved by discussion and consensus. The NOS consists of three components assessing the studies on selection (four items), comparability (one item), and exposure (three items). Each item is scored with a maximum of one star, except the item comparability, that could be scored two stars; therefore, a maximum

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of nine stars can be scored. Studies were rated as low risk of bias if they received nine stars, moderate risk of bias if they received seven or eight stars, and high risk of bias if they received less than seven stars.

Results

Study selection

The literature search was performed in March 2021 and yielded 297 articles after removal of duplicates. We screened citations on title and abstract and excluded 239. We obtained 58 citations in full text. After this assessment, another 41 articles were excluded, leaving 17 articles. Of these 17 articles, two were based on the same study results,[20,35] and two were partly based on the same study results.[25,26] Duplicate results were only used once for the meta-analysis (Fig. 1).

Study characteristics

We included 16 studies (17 publications) with a total of 3671 elderly mTBI patients (Table 1). Two studies are prospective cohort studies; the other 14 studies are retrospective cohort studies. All manuscripts were written in English and published between 2015 and 2021. Eight studies were carried out in the United States, two in Austria, one in Germany, and six in Italy. Two studies investigated specifically the use of dabigatran and two studies of rivaroxaban. The remaining 12 studies included mixed groups of patients taking dabigatran, apixaban, edoxaban, and rivaroxaban. The control groups consisted of patients with TBI using no ATT, (dual) APT, or VKAs. Each study focused on several variables as outcomes of interest, and no single variable was evaluated in every study. Incidence of tICH on head CT after mTBI was assessed in eight studies. Frequency of a neurosurgical intervention was recorded in 13 studies, frequency of ICH progression in seven studies, occurrence of dICH in six studies, use of reversal agents in seven studies, and TBI-related in-hospital mortality in 13 studies (Table 2).

Risk of bias within studies

Using the NOS, four studies were rated as low risk and 12 were rated as moderate risk of bias. For each study, the NOS ratings are presented in Table 3.

Outcomes

Risk of traumatic intracerebral hemorrhage. Eight studies including 2574 patients assessed the risk of tICH in elderly patients after mTBI.[23,24,28,29,31,33,35,36] Patients using DOACs had a lower risk of tICH compared to patients using VKAs (eight studies; OR, 0.44; 95% CI, 0.29–0.65), with evidence of low grade of heterogeneity ($I^2 = 22\%$, random effect; Fig. 2A). Patients using DOACs and those on APT had similar odds of tICH (two studies[28,29]; OR, 0.98; 95% CI, 0.39–2.44), with no evidence of heterogeneity ($I^2 = 0\%$, random effect; Fig. 2B). One study[28] compared patients using DOACs to patients using dual APT, so this study was not included in the main analysis. This study found no difference in tICH between treatment groups.

Neurosurgical intervention. Thirteen studies including 3143 patients assessed the rate of a neurosurgical intervention in elderly patients with tICH after mTBI.[21–23,25,27–35] Patients using DOACs received less often a neurosurgical intervention compared to patients using VKAs (13 studies; OR, 0.37; 95% CI, 0.21–0.67), with no evidence of heterogeneity ($I^2 = 0\%$, random effect; Fig. 3A). There was no difference between patients using DOACs compared to patients using APT (four studies[21,28,29,32]; OR, 0.58; 95% CI, 0.15–2.21), with moderate heterogeneity ($I^2 = 41\%$ random effect), or patients using no ATT (four studies[21,28,30,32]; OR, 0.76; 95% CI, 0.20–2.86), with evidence of low grade of heterogeneity ($I^2 = 23\%$, random effect; Fig. 3B,C). One study[28] compared patients using DOACs to patients using dual APT, so was not included in the main analysis. The data of this study found no difference in neurosurgical interventions between treatment groups.

Hematoma progression. Seven studies including 913 patients assessed hematoma progression in elderly patients with tICH after mTBI.[21,22,26,29,30,32,34] There was no significant difference in the rate of ICH progression between patients using DOACs compared to patients using VKAs (seven studies; OR, 0.63; 95% CI, 0.37–1.08; $I^2 = 50\%$, random effect) or patients using APT (three studies[21,29,32]; OR, 0.68; 95% CI, 0.30–1.53), with evidence of substantial heterogeneity ($I^2 = 50\%$ and $I^2 = 58\%$, respectively, random effect; Fig. 4A,B). Patients using DOACs had a higher, but not significant, rate of ICH progression compared to patients using no ATT (three studies[21,30,32]; OR, 3.39; 95% CI, 0.39–39.60), with evidence of substantial heterogeneity ($I^2 = 82\%$, random effect; Fig. 4C).

Risk of delayed intracerebral hemorrhage. Six studies including 2279 patients assessed dICH in elderly patients after mTBI.[23–25,28,33,36] There was no difference in the rate of dICH between patients using DOACs compared

FIG. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of included studies. DOAC, direct oral anticoagulants; mTBI, mild traumatic brain injury; PICO, Patient Problem (or Population); Intervention; Comparison or Control; and Outcome.

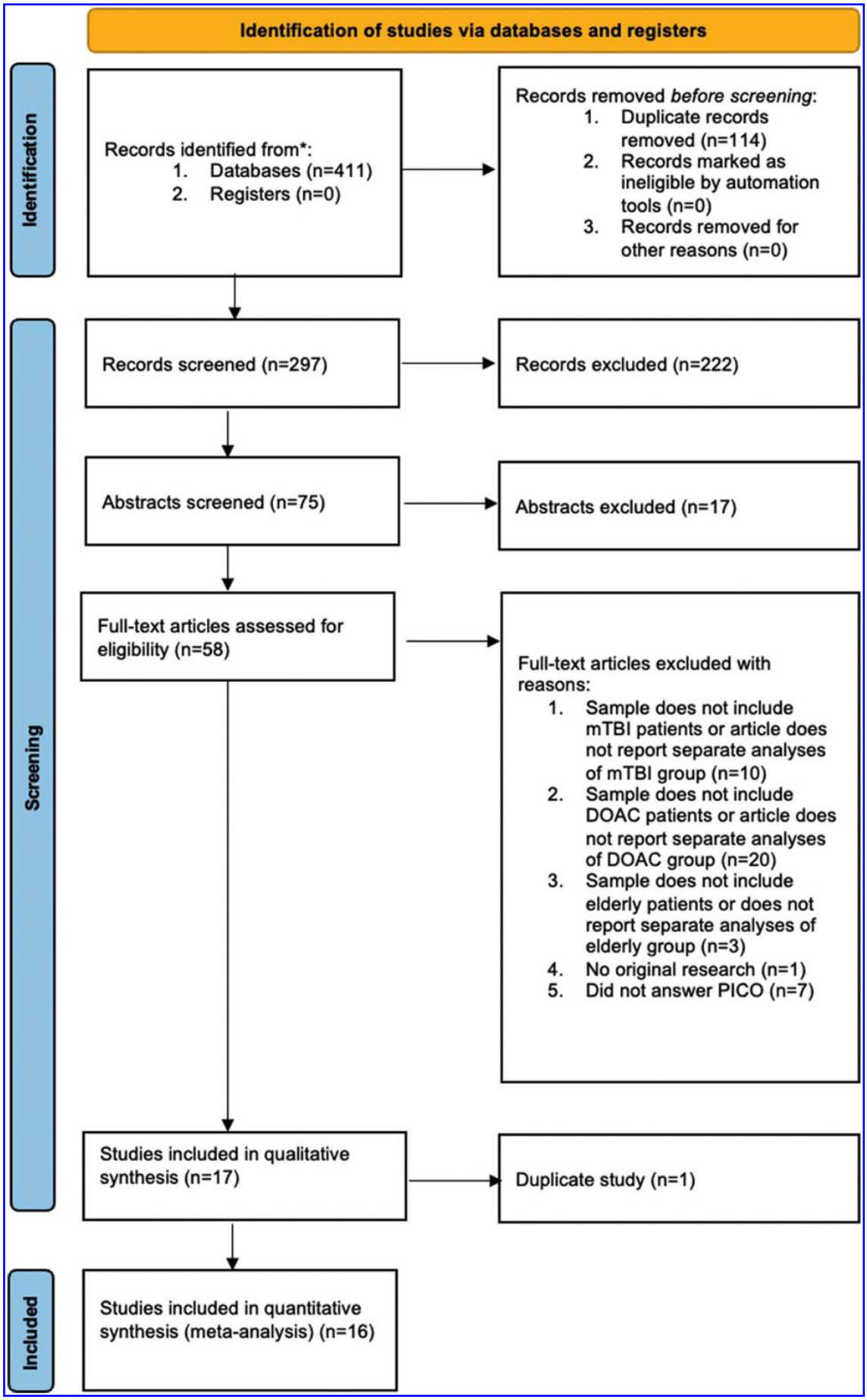

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Table 1. Characteristics of Studies

Source	Design	Inclusion criteria	Single-/multi-center, setting	Country	No. of patients	DOAC type	Control	Age, mean (SD)	GCS score, mean (SD)	LOS (days), mean (SD)
Beynon (2015)[21]	Retrospective cohort	Age: all, mTBI (GCS 13–15), tICH on initial CT	Single center, HW, level 1	Germany	DOAC: 6 VKA: 5 APT: 22 No ATT: 37	Rivaroxaban	VKA, APT, no ATT	DOAC: 71 ± 25 VKA: 74 ± 17 APT: 78 ± 9 No ATT: 60 ± 20 $p < 0.05$ (no ATT vs. APT/VKA)	DOAC: 14.60 ± 0.79 VKA: 14.60 ± 0.55 APT: 14.30 ± 0.77 No ATT: 14.60 ± 0.69 p = NS	DOAC: 4.2 ± 1.6 VKA: 6.6 ± 2.6 APT: 4.1 ± 3.0 No ATT: 6.5 ± 5.9 p = NS
Billings (2020)[22]	Retrospective cohort	Age: all, tICH on initial CT	Single center, HW, level 1	USA	DOAC: 25 VKA: 50	NR	VKA	DOAC: 78[a] VKA: 78[a] p = NS	DOAC: 15[a] VKA: 15[a] p = NR	DOAC: 4[a] VKA: 4[a] p = NS
Cipriano (2021)[23]	Prospective cohort	Age: 18+, mTBI (GCS 13–15)	Single center, ED, level 2	Italy	DOAC: 266 VKA: 207	Apixaban, dabigatran, edoxaban, rivaroxaban	VKA	DOAC: 81.8 ± 8.9 VKA: 81.8 ± 8.6 p = NR	DOAC: 14.90 ± 0.23 VKA: 14.90 ± 0.17 p = NR	NR
Cocca (2019)[24]	Retrospective cohort	Age: 64+, FS	Single center, ED, level 1	USA	DOAC: 44 VKA: 33	NR	VKA	DOAC: 79.0 ± 7.6 VKA: 81.5 ± 7.7 p = 0.160	DOAC: 14.7 ± 0.9 VKA: 14.4 ± 2.3 p = 0.342	DOAC: 2 [1–6][a] VKA: 4 [1–9][a] p = 0.057
Cohan I (2020)[25]	Retrospective cohort	Age: all, negative initial CT	Multi-center, ED, level 1	USA	DOAC: 177 VKA: 246	Apixaban, dabigatran, rivaroxaban	VKA	DOAC: 79 ± 13 VKA: 77 ± 14 p = 0.22	DOAC: 14.6 ± 1.1 VKA: 14.6 ± 1.2 p = 0.96	NR
Cohan II (2020)[26]	Retrospective cohort	Age: all, negative initial CT	Single center, ED, level 1	USA	DOAC: 141 VKA: 191	Apixaban, dabigatran, rivaroxaban	VKA	DOAC: 77.0 ± 1.1 VKA: 78.0 ± 1.0 p = 0.7	DOAC: 14.70 ± 0.05 VKA: 14.70 ± 0.10 p = 0.32	NR
Feeney (2016)[27]	Retrospective cohort	Age: all, tICH on initial CT	Single center, HW/ICU, level 2	USA	DOAC: 61 VKA: 101	NR	VKA	DOAC: 77.2 ± 11.2 VKA: 79.5 ± 13.0 p = 0.25	DOAC: 14[a] VKA: 13[a] p = 0.12	DOAC: 4 [3–5][a] VKA: 4 [3.0–6.5][a] p = 1.0
Galliazzo (2019)[28]	Retrospective cohort	Age: 18+, mTBI (GCS 13–15)	Single center, ED, level 1	Italy	DOAC: 51 VKA: 120 APT: 407 Dual ATT: 43	Apixaban, dabigatran, edoxaban, rivaroxaban	VKA, APT, dual ATT, no ATT[c]	DOAC: 90.2%[b] VKA: 92.4%[b] APT: 95.8%[b] Dual ATT: 91.3%[b] p = NR	DOAC: 14.90 ± 0.14 VKA: 15.0 ± 0.0 APT: 14.90 ± 0.14 Dual ATT: 14.9 ± 0.1 p = 0.34	NR
Jentzsch (2018)[29]	Retrospective cohort	Age: all	Single center, ED, level 1	Austria	DOAC: 23 VKA: 23 APT: 23	Rivaroxaban	VKA, APT	DOAC: 76 [66–87][a] VKA: 80 [66–88][a] APT: 79 [66–88][a] p = 0.97	DOAC: 15 [14–15][a] VKA: 15 [14–15][a] APT: 15 [14–15][a] p = 0.95	DOAC: 5 [2–5][a] VKA: 5 [2–5][a] APT: [2–4][a] p = 0.94
Parra (2013)[30]	Retrospective cohort	Age: 18+, FS, tICH on initial CT	Single center, ED, level 1	USA	DOAC: 5 VKA: 15 No ATT: 25	Dabigatran	VKA, no ATT	DOAC: 81.6 VKA: 83.9 No ATT: 75.0 p = 0.46 (DOAC vs. VKA)	DOAC: 14.6 VKA: 14.6 No ATT: 14.2 p = 1.00	NR
Pozzessere (2015)[31]	Retrospective cohort	Age: 65+, LOC or external signs of TBI	Single center, ED, level 2	USA	DOAC: 49 VKA: 198	Dabigatran	VKA	DOAC: 84.2 ± 6.1 VKA: 84.7 ± 6.8 p = 0.59	DOAC: 14.8 ± 0.5 VKA: 14.5 ± 1.5 p = 0.165	DOAC: 2.7 ± 1.7 VKA: 2.9 ± 2.5

(*continued*)

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Table 1. (Continued)

Source	Design	Inclusion criteria	Single-/multi-center, setting	Country	No. of patients	DOAC type	Control	Age, mean (SD)	GCS score, mean (SD)	LOS (days), mean (SD)
Prexl (2018)[32]	Retrospective	Age: 60+, tICH on initial CT or at risk of dICH, admitted to the ICU	Single center, ICU, level 1	Austria	DOAC: 33 VKA: 32 APT: 41 No ATT: 80	Apixaban, dabigatran, edoxaban, rivaroxaban	VKA, APT, no ATT	DOAC: 82 [75.5–84.5][a] VKA: 81 [74–85][a] APT: 80 [72–86][a] No ATT: 74 [64.5–81.0][a] $p < 0.0001$	DOAC: 14 [14–15][a] VKA: 14 [13–15][a] APT: 14.5 [12.75–15.00][a] No ATT: 14 [12–15][a] p = NS	DOAC: 168 [76.0–345.5][a] VKA: 278.5 [109.5–368.0][a] APT: 217 [121–413][a] No ATT: 242 [123.0–407.5][a] p = NS
Savioli (2020)[33]	Retrospective cohort	Age: 18+, mTBI (GCS 13–15)	Single center, ED, level 2	Italy	DOAC: 156 VKA: 78	Apixaban, dabigatran, edoxaban, rivaroxaban	VKA, no ATT[c]	DOAC: 80 ± 10 VKA: 82 ± 10 p = NR	DOAC: NR VKA: NR	NR
Shin (2020)[34]	Retrospective cohort	Age: 18+, tICH on initial CT	Single center, HW, level 1	USA	DOAC: 39 VKA: 97	Apixaban, dabigatran, rivaroxaban	VKA	DOAC: 79.2 ± 11.7 VKA: 78.5 ± 13.8 $p = 0.77$	DOAC: 15 [14–15][a] VKA: 15 [14–15][a] $p = 0.14$	DOAC: 5.4 ± 6.9 VKA: 6.1 ± 6.1 $p = 0.77$
Spinola (2019)[35]	Prospective cohort	Age: all, mTBI (GCS 14–15), no neurological deficit or sign of skull fracture	Single center, ED, level 2	Italy	DOAC: 226 VKA: 176	Apixaban, dabigatran, edoxaban, rivaroxaban	VKA	DOAC: 81.5 VKA: 83.1 p = NR	DOAC: NR VKA: NR	NR
Turcato (2019)[36]	Retrospective cohort	Age: all, mTBI (GCS 13–15) regardless LOC	Single center, ED, level 2	Italy	DOAC: 183 VKA: 268	NR	VKA	DOAC: 82 [78–87][a] VKA: 83 [78–88][a] $p = 0.815$	DOAC: NR VKA: NR	NR

[a]Median.
[b]Percentage >65 years.
[c]Excluded from analysis because of age <60 years.

APT, antiplatelet therapy; ATT, antithrombotic therapy; DOAC, direct oral anticoagulant; dICH, delayed intracerebral hemorrhage; CT, computed tomography; ED, emergency department; FS, fall from standing height; GCS, Glasgow Coma Scale; HW, hospital ward; ICH, intracerebral hemorrhage; ICU, intensive care unit; LOC, loss of consciousness; LOS, length of stay; mTBI, mild traumatic brain injury; NR, not reported; NS, not significant; TBI, traumatic brain injury; tICH, traumatic intracerebral hemorrhage; VKA, vitamin K antagonist.

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Table 2. Study Outcomes

Source	tICH, n (%)	Neurosurgical intervention, n (%)	Hematoma progression, n (%)	dICH, n (%)	Reversal agent use, n (%)	TBI-related in-hospital mortality, n (%)
Beynon (2015)[21]	—	DOAC: 2/6 (33.3) VKA: 3/5 (60.0) APT: 7/22 (31.8) No ATT: 6/37 (16.2) p=NS	DOAC: 3/6 (50.0) VKA: 1/5 (20.0) APT: 4/22 (18.2) No ATT: 4/37 (10.8) p<0.05 (DOAC vs. no ATT)	—	—	DOAC: 2/6 (33.3) VKA: 0/5 (0.0) APT: 0/22 (0.0) No ATT: 0/37 (0.0) p<0.05 (DOAC vs. VKA, APT, and no ATT)
Billings (2020)[22]	—	DOAC: 1/25 (4.0) VKA: 8/50 (16.0) p=0.257	DOAC: 7/25 (28.0) VKA: 21/50 (42.0) p=0.342	—	DOAC: 10/25 (40.0) VKA: 39/50 (78.0) p=0.32	DOAC: 1/25 (4.0) VKA: 9/50 (18.0) p=0.150
Cipriano (2021)[23]	DOAC: 17/266 (6.4) VKA: 33/207 (15.9) p<0.05	DOAC: 1/20 (5.0) VKA: 1/34 (2.9) p=NR	—	DOAC: 3/245 (1.2)[b] VKA: 1/169 (0.59)[b] p=NR	DOAC: 9/17 (52.9) VKA: 28/33 (84.8) p=NR	DOAC: 1/20 (5.0) VKA: 3/34 (8.8) p=NR
Cocca (2019)[24]	DOAC: 6/44 (13.6) VKA: 10/33 (30) p=0.074	—	—	DOAC: 6/44 (13.6) VKA: 0/33 (0.0) p=NR	—	—
Cohan I (2020)[25]	—	DOAC: 0/4 (0.0) VKA: 2/10 (20.0) p=NR		DOAC: 4/177 (2.3) VKA: 10/246 (4.1) p=0.131	—	DOAC: 0/4 (0.0) VKA: 3/10 (30.0) p=0.26
Cohan II (2020)[26]	—	[a]	DOAC: 0/3 (0.0) VKA: 1/5 (20.0) p=NR	[a]	DOAC: 0/3 (0.0) VKA: 4/5 (80.0) p=NR	[a]
Feeney (2016)[27]	—	DOAC: 5/61 (8.2) VKA: 27/101 (26.7) p=0.02	—	—	—	DOAC: 3/61 (4.9) VKA: 21/101 (20.8) p<0.008
Galliazzo (2019)[28]	DOAC: 2/51 (3.9) VKA: 5/120 (4.2) APT: 22/407 (5.4) Dual ATT: 3/46 (6.5) p=0.86	DOAC: 0/2 (0.0) VKA: 0/5 (0.0) APT: 0/22 (0.0) Dual ATT: 0/3 (0.0) p=NR	—	DOAC: 0/29 (0.0)[b]VKA: 0/86 (0.0)[b] APT: 2/131 (1.5)[b] Dual ATT: 0/28 (0.0)[b] p=NR	—	DOAC: 1/2 (50.0) VKA: 0/5 (0.0) APT: 0/22 (0.0) Dual ATT: 0/3 (0.0) p=NR
Jentzsch (2018)[29]	DOAC: 11/23 (47.8) VKA: 8/23 (34.8) APT: 10/23 (43.5) p=0.72	DOAC: 4/11 (36.3) VKA: 2/8 (25.0) APT: 3/10 (30.0) p=0.90	DOAC: 1/11 (9.0) VKA: 1/8 (12.5) APT: 3/10 (30.0) p=0.42	—	—	DOAC: 1/11 (9.0) VKA: 0/8 (0.0) APT: 0/10 (0.0) p=1.0
Parra (2013)[30]	—	DOAC: 0/5 (0.0) VKA: 3/15 (20.0) No ATT: 4/25 (16.0) p=NR	DOAC: 4/5 (80.0) VKA: 3/15 (20.0) No ATT: 4/25 (16.0) p=0.03	—	DOAC: 4/5 (80.0) VKA: 15/15 (100.0) No ATT: NR p=NR	DOAC: 2/5 (40.0) VKA: 0/15 (0.0) No ATT: 0/25 (0.0) p=0.05
Pozzessere (2015)[31]	DOAC: 4/49 (8.2) VKA: 27/198 (13.6) p=0.279	DOAC: 0/4 (0.0) VKA: 2/27 (7.4) p=0.346	—	—	—	NSR
Prexl (2018)[32]	—	DOAC: 2/33 (6.1) VKA: 9/32 (28.1) APT: 11/41 (26.8) No ATT: 12/80 (15) p=NS	DOAC: 8/33 (24.2) VKA: 19/32 (59.4) APT: 16/41 (39.0) No ATT: 27/80 (33.8) p=0.023	—	DOAC: 8/33 (24.2) VKA: 27/32 (84.4) APT: 8/41 (19.5) No ATT: 3/80 (3.8) p=< 0.0001	DOAC: 1/33 (3.0) VKA: 7/32 (21.9) APT: 3/41 (7.3) No ATT: 6/80 (7.5) p<0.05

(*continued*)

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Table 2. (Continued)

Source	tICH, n (%)	Neurosurgical intervention, n (%)	Hematoma progression, n (%)	dICH, n (%)	Reversal agent use, n (%)	TBI-related in-hospital mortality, n (%)
Savioli (2020)[33]	DOAC: 3/78 (3.8) VKA: 22/156 (14.1) $p > 0.05$	DOAC: 0/4 (0.0) VKA: 1/27 (3.7) $p > 0.05$	—	DOAC: 1/78 (1.3) VKA: 5/156 (3.2) $p =$ NR	—	DOAC: 0/4 (0.0) VKA: 0/27 (0.0) $p =$ NR
Shin (2020)[34]	—	DOAC: 2/39 (5.1) VKA: 13/97 (13.4) $p = 0.23$	DOAC: 4/36 (11.1)[b] VKA: 13/89 (14.6)[b] $p = 0.77$	—	DOAC: 13/39 (33.3) VKA: 84/97 (86.6) $p < 0.001$	DOAC: 5/39 (12.8) VKA: 8/97 (8.2) $p =$ NR
Spinola (2019)[35]	DOAC: 6/226 (2.7) VKA: 18/176 (10.2) $p < 0.01$	DOAC: 0/6 (0.0) VKA: 1/18 (5.6) $p = 0.44$	—	—	DOAC: 1/6 (16.7) VKA: 18/18 (100.0) $p =$ NR	DOAC: 0/6 (0.0) VKA: 2/18 (11.1) $p = 0.19$
Turcato (2019)[36]	DOAC: 10/183 (5.5) VKA: 31/268 (11.6) $p = 0.03$	NSR	—	DOAC: 4/183 (2.2) VKA: 9/268 (3.4) $p = 0.570$	—	NSR

[a]Duplicate results,
[b]Total patients with a repeat head CT.
APT, antiplatelet therapy; ATT, antithrombotic therapy; DOAC, direct oral anticoagulant; dICH, delayed intracerebral hemorrhage; ICH, intracerebral hemorrhage; NR, not reported; NSR, not separately reported; tICH, traumatic intracerebral hemorrhage; VKA, vitamin K antagonist.

Table 3. Risk of Bias with the Newcastle-Ottawa Assessment Scale

Source	Selection	Comparability	Outcome	Risk of bias
Beynon (2015)[21]	****	*	**	Moderate risk
Billings (2020)[22]	****	**	**	Moderate risk
Cipriano (2021)[23]	****	**	**	Moderate risk
Cocca(2019)[24]	****	**	**	Moderate risk
Cohan I (2020)[25]	****	**	***	Low risk
Cohan II (2020)[26]	****	**	***	Low risk
Feeney (2016)[27]	****	**	**	Moderate risk
Galliazzo (2019)[28]	****	**	**	Moderate risk
Jentzsch (2018)[29]	****	**	**	Moderate risk
Parra (2013)[30]	****	**	**	Moderate risk
Pozzessere (2015)[31]	****	*	**	Moderate risk
Prexl (2018)[32]	****	*	**	Moderate risk
Savioli (2020)[33]	****	**	***	Low risk
Shin (2020)[34]	****	**	**	Moderate risk
Spinola (2019)[35]	****	**	**	Moderate risk
Turcato (2019)[36]	****	**	***	Low risk

to patients using VKAs (six studies; OR, 0.82; 95% CI, 0.35–1.91), with evidence of low grade of heterogeneity ($I^2 = 20\%$, random effect; Fig. 5). One study[28] compared patients using DOACs to patients using APT and dual APT, so this study was not included in the main analysis. The data of this study found no difference in dICH between treatment groups.

Use of reversal agents. Seven studies including 1649 patients assessed use of reversal agents in elderly patients with tICH after mTBI.[22,23,26,30,32,34,35] Patients using DOACs received less often reversal agents than patients using VKAs (seven studies; OR, 0.10; 95% CI, 0.06–0.16), with no evidence of heterogeneity ($I^2 = 0\%$, random effect; Fig. 6). One study[32] compared patients using DOACs to patients using APT and no ATT, so was not included in the main analysis. The data of this study found no difference in the use of reversal agents between treatment groups.

Traumatic brain injury–related in-hospital mortality. Twelve studies including 2896 patients assessed TBI-related in-hospital mortality in elderly patients with tICH after mTBI.[21–23,25,27–30,32–35] There was no difference in mortality between patients using DOACs compared to patients using VKAs (12 studies; OR, 0.75; 95% CI, 0.28–2.00), with evidence of moderate heterogeneity ($I^2 = 48\%$, random effect; Fig. 7A), patients using DOACs compared to patients using APT (four studies[21,28,29,32]; OR, 4.78; 95% CI, 0.47–48.40), with evidence of substantial heterogeneity ($I^2 = 56\%$, random effect; Fig. 7B), and patients using DOACs compared to patients using no ATT (three studies[21,30,32]; OR, 3.35; 95% CI, 1.26–8.92), with evidence of substantial heterogeneity ($I^2 = 76\%$, random effect; Fig. 7C). One study[32] compared patients using DOACs to patients using dual APT, so was not included in the main analysis.

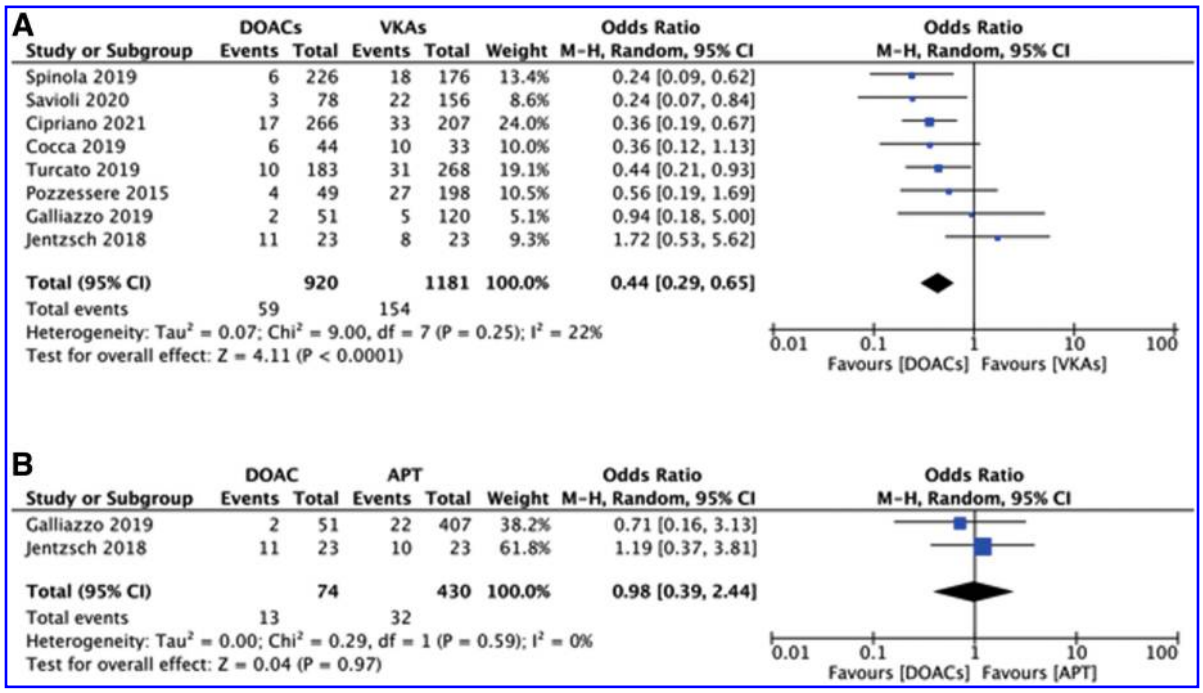

FIG. 2. Forest plot of pre-injury (**A**) DOAC versus VKA use and (**B**) DOAC versus APT use in elderly mTBI patients with tICH as the dependent outcome. APT, antiplatelet therapy; CI, confidence interval; DOAC, direct oral anticoagulants; mTBI, mild traumatic brain injury; tICH, traumatic intracerebral hemorrhage; VKA, vitamin K antagonist.

The data of this study found no difference in in-hospital mortality between patients treated with either DOACs or dual APT.

Discussion

This meta-analysis demonstrated a significant lower risk of tICH and rate of neurosurgical interventions after mTBI in elderly patients using DOACs compared to patients using VKAs. Elderly patients using DOACs with tICH received less often reversal agents compared to elderly patients with tICH using VKAs. We found no significant difference between elderly patients using DOACs compared to other treatment groups for the incidence of ICH progression, dICH, and in-hospital mortality.

Regarding treatment options, we found, in agreement with other authors, that patients using DOACs received less often reversal agents compared to patients using VKAs.[57] There was a paucity of studies comparing the use of reversal agents in patients using DOACs to patients using APT. This is likely attributable to insufficient evidence to support routine administration of platelets in patients using APT with tICH.[38] In studies, reversal of the anticoagulant effect of DOACs was performed in 0–80% compared to 78–100% of the anticoagulant effect of VKAs.[22,23,26,30,32,34,35] This could have several causes. First, most of the included studies were executed before the approval of specific reversal agents, and evidence-based guidelines/recommendation for DOAC reversal were lacking. This may have constrained the use of reversal agents in clinical practice. Second, reversal methods have not been well documented to improve outcomes in patients with tICH receiving DOACs to date. Although studies reported much higher rates of reversal for patients using VKAs, ICH progression and mortality rates were comparable, and neurosurgical procedures were even significantly less in mTBI patients with tICH using DOACs.

It is possible that observed favorable outcomes of DOAC-associated bleeding made physicians reluctant to attempt reversal and expose patients to devastating thromboembolic complications. Third, measurement of the anticoagulant activity of DOACs is more complex than the anticoagulant activity of VKAs. When considering a reversal agent, it is important to assess the degree of anticoagulation and the likelihood that the DOAC contributes to an ongoing and progressive bleeding. Laboratory parameters, such as international normalized ratio, prothrombin time, and activated partial thromboplastin time, are used to measure the effect of VKAs; however, these standard coagulation tests are unreliable to assed the degree of DOAC anticoagulation. Specific tests, which allow the quantification of dabigatran or

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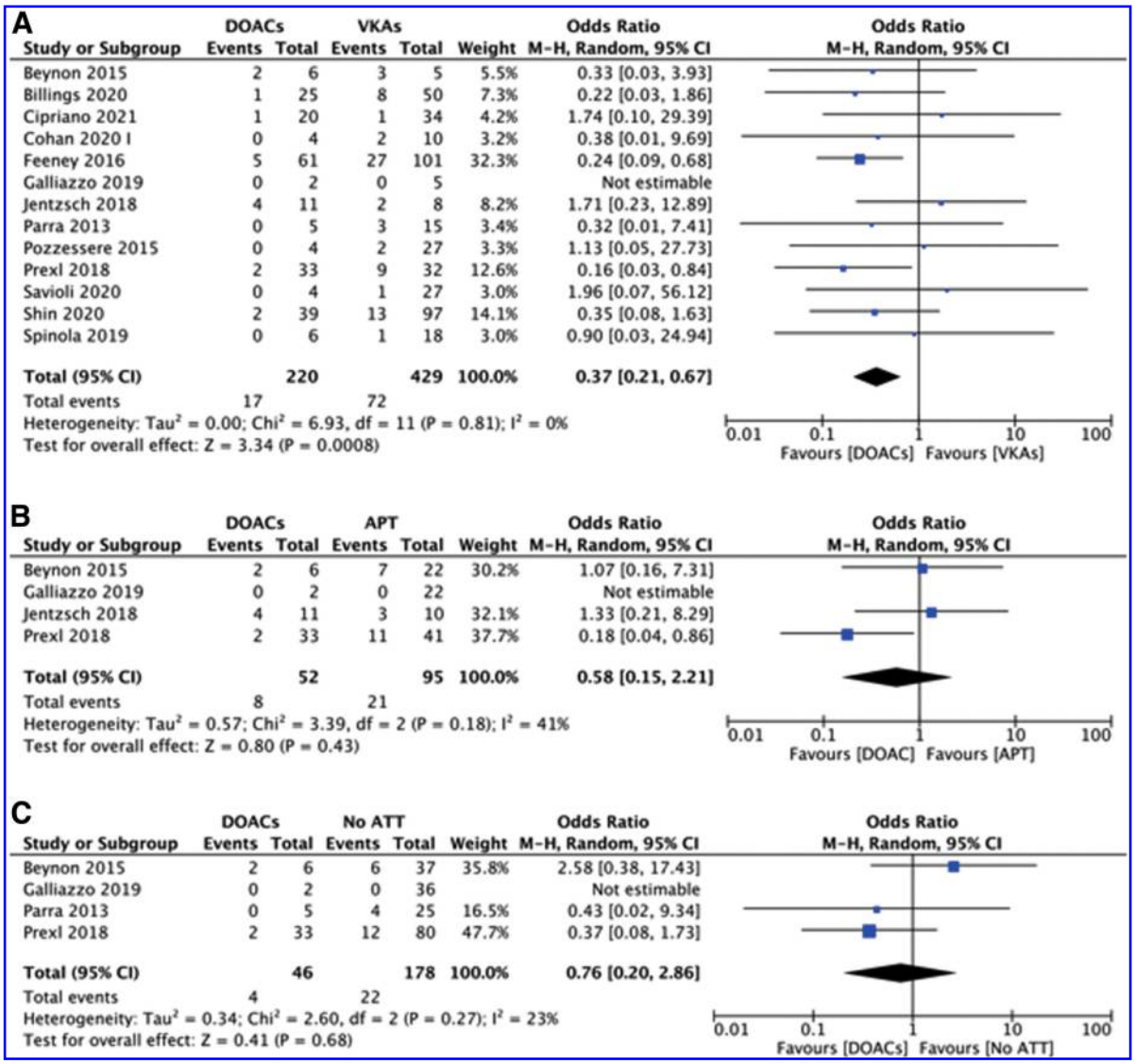

FIG. 3. Forest plot of pre-injury (**A**) DOAC versus VKA use, (**B**) DOAC versus APT use, and (**C**) no ATT use in elderly mTBI patients with neurosurgical intervention as the dependent outcome. APT, antiplatelet therapy; ATT, antithrombotic therapy; DOAC, direct oral anticoagulants; mTBI, mild traumatic brain injury; VKA, vitamin K antagonist.

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Xa inhibitors, are not universally available in all hospitals. Therefore, clinicians in most centers estimate the degree of anticoagulation based on the specific agent, dose, interval since last dose, and renal and hepatic function before deciding to treat with a reversal agent.[39]

None of the included studies in the current meta-analysis reported the measurement of anticoagulant activity. Nevertheless, it might be that patients were not treated with a reversal agent because of physicians' inability to evaluate the anticoagulant activity of the DOACs or that patients did not have relevant plasma DOAC levels. Last, DOAC reversal agents are associated with significant financial cost, with specific antidotes generally being more expensive than non-specific factor concentrates. This may have slowed down the adoption of reversal agents in many hospitals.

The observation that elderly patients using DOACs have a lower risk of tICH after mTBI compared to elderly patients using VKAs is in line with other studies, which showed that the risk of life-threatening and fatal bleeding is generally lower in patients on DOACs than on VKAs, including a significantly lower risk of spontaneous ICH.[37,40–44] A recent retrospective study observed that among elderly, anticoagulated patients who had

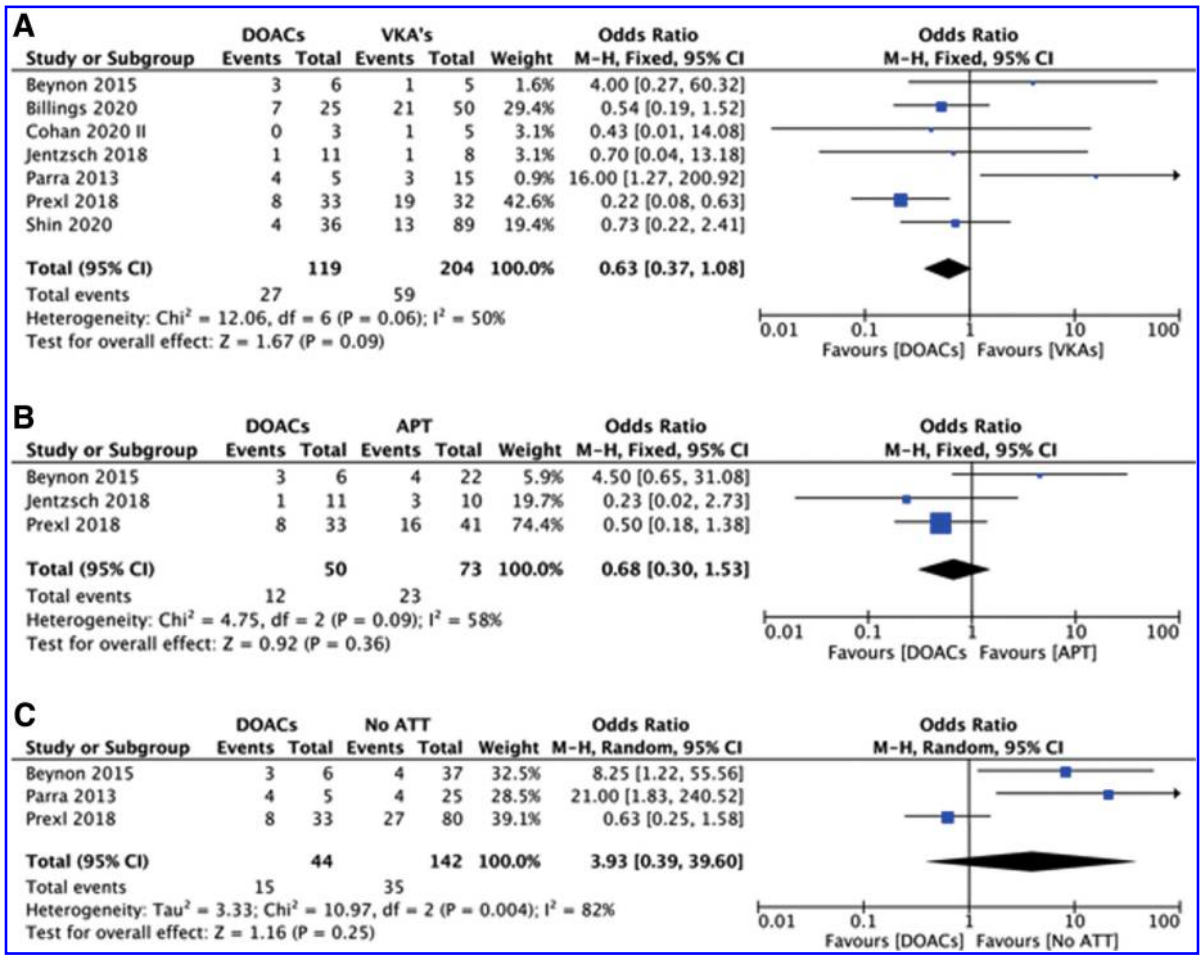

FIG. 4. Forest plot of pre-injury (**A**) DOAC versus VKA use, (**B**) DOAC versus APT use, and (**C**) no ATT use in elderly mTBI patients with hematoma progression as the dependent outcome. APT, antiplatelet therapy; ATT, antithrombotic therapy; DOAC, direct oral anticoagulant; mTBI, mild traumatic brain injury; VKA, vitamin K antagonist.

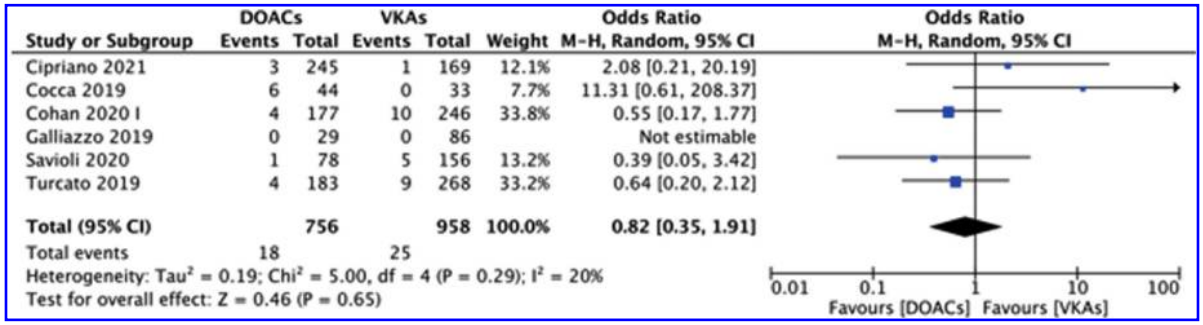

FIG. 5. Forest plot of pre-injury DOAC versus VKA use in elderly mTBI patients with dICH as the dependent outcome. dICH, delayed intracerebral hemorrhage; DOAC, direct oral anticoagulants; mTBI, mild traumatic brain injury; VKA, vitamin K antagonist.

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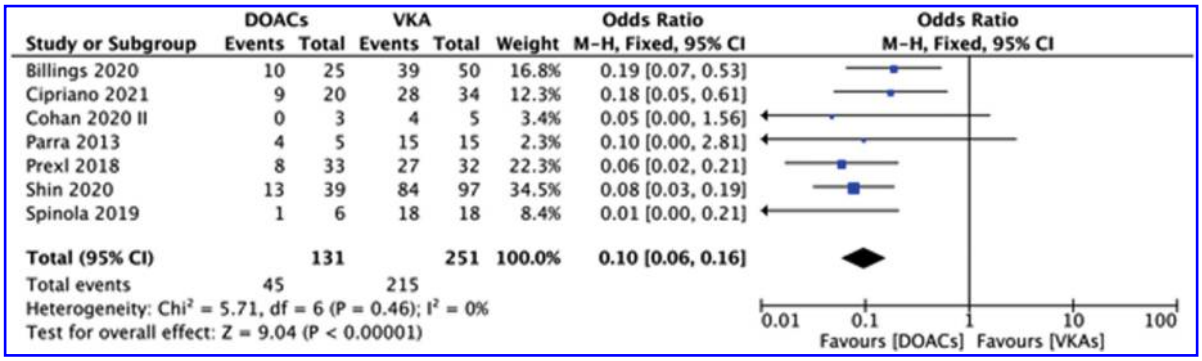

FIG. 6. Forest plot of pre-injury DOAC versus VKA use in elderly mTBI patients with reversal agent use as the dependent outcome. DOAC, direct oral anticoagulants; mTBI, mild traumatic brain injury; VKA, vitamin K antagonist.

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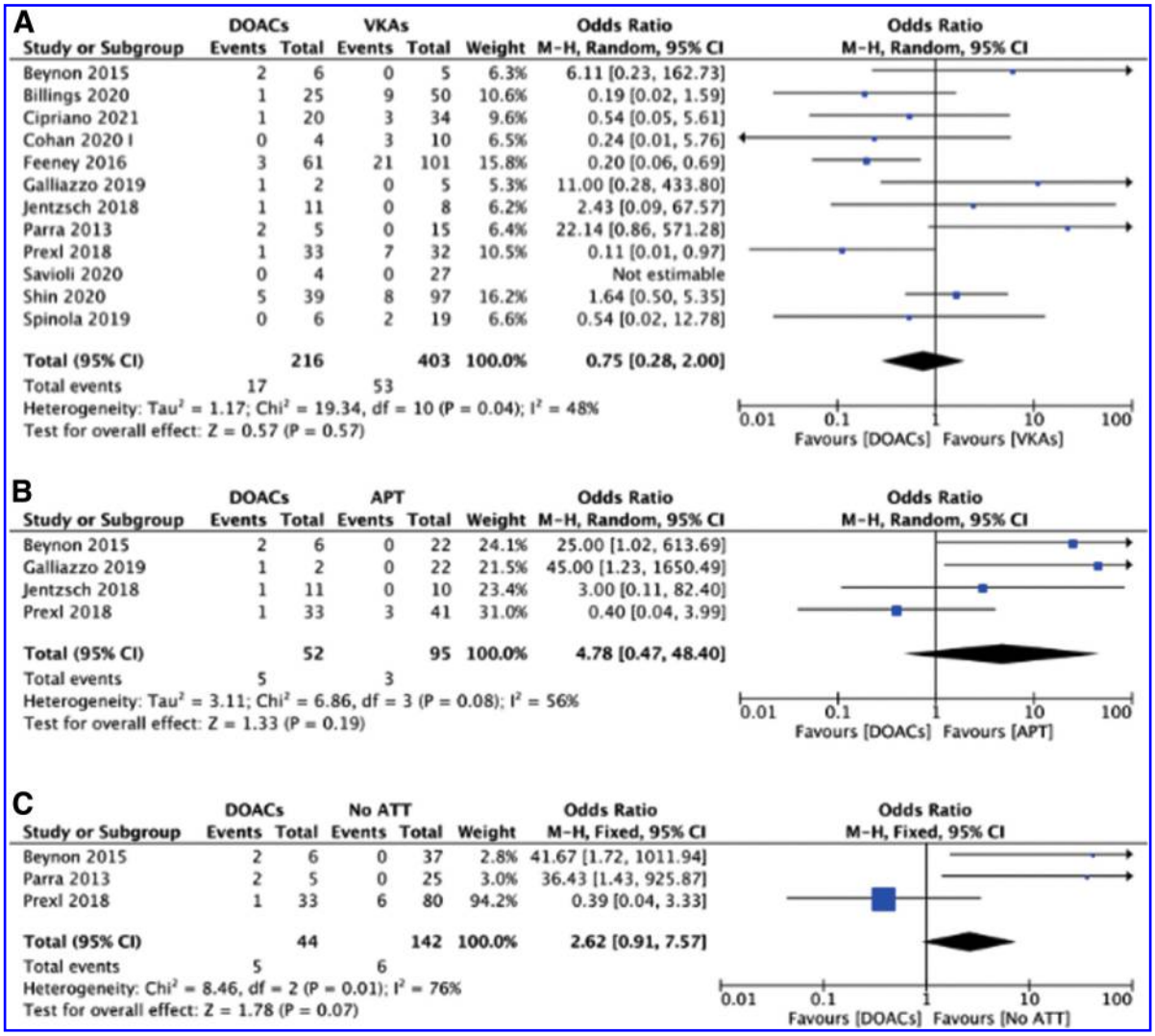

FIG. 7. Forest plot of pre-injury (**A**) DOAC versus VKA use, (**B**) DOAC versus APT use, and (**C**) no ATT use in elderly mTBI patients with mortality as the dependent outcome. APT, antiplatelet therapy; ATT, antithrombotic therapy; DOAC, direct oral anticoagulants; mTBI, mild traumatic brain injury; VKA, vitamin K antagonist.

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fallen from standing, those under DOACs had a lower proportional incidence of bleeding complications in general and an even lower incidence of tICH than in patients under VKAs.[59] Two other meta-analyses also found a favorable safety profile of DOACs in elderly mTBI patients.[45,46.] The reported risk of adverse outcome (any death, ICH, or neurosurgical intervention) in patients using DOACs after mTBI in these studies was low and not increased compared to patients using VKAs.

Studies comparing DOACs and APT are limited; one study found a similar tICH rate in elderly patients using DOACs compared to elderly patients using APT.[28] Two meta-analyses revealed that pre-injury use of APT was associated with an increased incidence of tICH after mTBI. No difference was found in the composite outcome of mortality and neurosurgery[11,47] These findings, however, should be interpreted with caution given the wide variability in the incidence of ICH among studies and methodological flaws of several included studies.

The risk of adverse advents that physicians are willing to accept depends on the clinical scenario and the consequences of these adverse events.[48–51] There is a low threshold to perform a head CT in mTBI patients using DOACs. A more restrictive scanning policy in these patients to reduce the risk of radiation, costs, and the use of time and resources does not outweigh the risk of missing a potential lethal intracranial injury for most doctors. A prospective study found no adverse outcomes in asymptomatic neurologically intact patients using DOACs after a ground-level fall, which could support a selective imaging approach in subgroups.[52] At this moment, there is a paucity on data regarding subgroups of elderly patients on DOACs who are at lower risk of adverse outcomes. The current meta-analysis did not find a higher rate of neurosurgical procedures in elderly patients using DOACs compared to patients using APT, VKAs, or patients without ATT. This likely reflects the favorable safety profile of DOACs. It is, however, possible that elderly mTBI patients with tICH received less often a neurosurgical intervention, because of the reluctance of neurosurgeons to perform surgery in the elderly population, given that age is an independent factor for increased morbidity with additional comorbid medical conditions.

If immediate tICH has been ruled out, clinicians are still worried about the risk of dICH among elderly mTBI patients using anticoagulants. Because of this feared complication, some guidelines recommend admission for 24-h clinical observation and repeat imaging in these patients.[53,54] There is, however, an ongoing debate regarding management of mTBI patients using anticoagulants with a negative initial head CT. A large meta-analysis found that the incidence of dICH was 0.6% and the risk of death or neurosurgical intervention was 0.13% in mTBI patients using VKAs.[55] Another meta-analysis showed a risk of dICH in mTBI patients using APT of 0.18%.[56] Therefore, the authors of these two studies concluded that, for most patients, discharge after an initial negative head CT is defendable. There is a lack of data on the need for observation or repeat CT head in elderly mTBI patients specifically using DOACs in case of a negative CT. We found no difference in the rate of dICH between elderly mTBI patients using DOACs compared to patients using APT or VKAs.

A recent meta-analysis reported that the risk of developing a new dICH in blunt TBI patients using DOACs on a second CT head imaging within 24 h after an initial negative CT head imaging is extremely low. Even when present, this rarely requires a neurosurgical intervention.[57] One should also keep in mind that hospitalization of elderly patients may result in functional decline despite cure or repair of the condition for which they were admitted.[58,59] These findings suggest that routine hospitalization and use of repeat CT head imaging after a negative initial CT in elderly mTBI patients does not result in significant clinical benefits and will result in unnecessary costs and overutilization of healthcare resources.

Strengths and limitations

The large number of patients, assessment of many outcomes, and comparison of DOACs to VKAs, (double) APT, or no ATT as well constitute a significant strength of our study.

The major limitation of this meta-analysis is the methodological quality of the studies that were available for analysis. All included studies were observational studies, and most of the included studies were single-center retrospective studies. The risk of reporting and publication bias was inherent in all included studies. Another limitation is that all DOACs were pooled in one group. It is possible that different DOACs have different outcomes. There were insufficient studies on different DOACs to perform pre-specified subgroup analyses for type of DOAC. Further, we were unable to evaluate clinical, laboratory, and neuroimaging characteristics for predicting adverse outcome. We were also unable to assess which patients were receiving treatment for reversal, when this therapy was administered, and whether patients responded appropriately in a timely manner. At last, follow-up was limited in most of the included studies, and it is possible that delayed deterioration occurred.

Conclusion

Elderly mTBI patients using DOACs seem to have a lower risk of adverse outcome compared to patients using VKAs and a similar risk compared to patients using APT. Future prospective studies are warranted to guide management of elderly mTBI patients using DOACs to inform future revisions of mTBI guidelines.

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Authors' Contributions

The authors have made the following declarations about their contributions: Conceived and designed the review: J.S. Literature search: J.S. Identification of articles, data collection, and quality assesment: J.S., Y.X.L. Analysis of the data: J.S. Wrote the manuscript: J.S., with input from Y.X.L., J.N., C.B., and K.J. All authors revised the manuscript critically and approved the final version.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Materials

Literature Search Strategy

References

1. Langlois, J.A., Rutland-Brown, W., and Wald, M.M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. J. Head Trauma Rehabil. 21, 375–378.
2. Styrke, J., Stålnacke, B.M., Sojka, P., and Björnstig, U. (2007). Traumatic brain injuries in a well-defined population: epidemiological aspects and severity. J. Neurotrauma 24, 1425–1436.
3. Taylor, C.A., Bell, J.M., Breiding, M.J., and Xu, L. (2017). Traumatic brain injury-related emergency department visits, hospitalizations, and deaths—United States, 2007 and 2013. Morbid. Mortal. Wkly. Rep. 66, 1–16.
4. Centers for Disease Control and Prevention. (2014). Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. National Center for Injury Prevention and Control, Division of Unintentional Injury Prevention: Atlanta, GA. www.cdc.gov/traumaticbraininjury/pubs/congress_epi_rehab.html (Last accessed: June 6, 2021).
5. Faul, M., Xu, L., Wald, M.M., Coronado, V., and Dellinger, A.M. (2010). Traumatic brain injury in the United States: national estimates of prevalence and incidence, 2002–2006. Inj. Prev. 16, A268.
6. Ramanathan, D.M., McWilliams, N., Schatz, P., and Hillary, F.G. (2012). Epidemiological shifts in elderly traumatic brain injury: 18-year trends in Pennsylvania. J. Neurotrauma 29, 1371–1378.
7. Dams-O'Connor, K., Gibbons, L.E., Landau, A., Larson, E.B., and Crane, P.K. (2016). Health problems precede traumatic brain injury in older adults. J. Am. Geriatr. Soc. 64, 844–848.
8. Cohen, D.B., Rinker, C., and Wilberger, J.E. (2006). Traumatic brain injury in anticoagulated patients. J. Trauma 60, 553–557.
9. Li, J., Brown, J., and Levine, M. (2001). Mild head injury, anticoagulants, and risk of intracranial injury. Lancet 357, 771–772.
10. Minhas, H., Welsher, A., Turcotte, M., Eventov, M., Mason, S., Nishijima, D.K., Versmée, G., Li, M., and de Wit, K. (2018). Incidence of intracranial bleeding in anticoagulated patients with minor head injury: a systematic review and meta-analysis of prospective studies. Br. J. Haematol. 183, 119–126.
11. van den Brand, C.L., Tolido, T., Rambach, A.H., Hunink, M.G., Patka, P., & Jellema, K. (2017). Systematic review and meta-analysis: is pre-injury antiplatelet therapy associated with traumatic intracranial hemorrhage? J. Neurotrauma 34, 1–7.
12. Barnes, G.D., Lucas, E., Alexander, G.C., and Goldberger, Z.D. (2015). National trends in ambulatory oral anticoagulant use. Am. J. Med. 128, 1300–1305.e2.
13. Centers for Disease Control and Prevention's (CDC) and American College of Emergency Physicians (ACEP). (2016). Mild TBI Clinical Policy for adults. www.cdc.gov/traumaticbraininjury/ pdf/TBI_Clinicians_Factsheet-a.pdf (Last accessed June 6, 2021).
14. Federation of Medical Specialists (2010). Mild traumatic head/brain injury (MHI/mTBI). richtlijnendatabase.nl/richtlijn/licht_traumatisch_hoofd_hersenletsel_lth/licht_traumatisch_hoofd_hersenletsel_-_startpagina.html#algemeen (Last accessed June 6, 2021).
15. UK NCGC. (2014). Head Injury: Triage, Assessment, Investigation and Early Management of Head Injury in Children, Young People and Adults. www.nice.org.uk/guidance/CG176 (Last accessed June 6, 2021).
16. Moher, D., Liberati, A., Tetzlaff, J., and Altman, D.G.; PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097.
17. Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., and Thacker, S.B. (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283, 2008–2012.
18. Santing, J.A.L., Lee Y.X., van der Naalt J., van den Brand C.L., and Jellema, K. (2021). Mild traumatic brain injury in elderly patients receiving direct oral anticoagulants: a systematic review and meta-analysis. PROSPERO 2021 CRD42021261933. www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021261933 (Last accessed February 1, 2022).
19. Wells, G.A., Wells, G., Shea, B., Shea, B., O'Connell, D., Peterson, J., Welch, Losos, M., Tugwell, P., Ga, S.W., Zello, G.A., and Petersen, J.A. (2014). The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses.www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Last accessed June 6, 2021).
20. Riccardi, A., Spinola, B., Minuto, P., Ghinatti, M., Guiddo, G., Malerba, M., and Lerza, R. (2017). Intracranial complications after minor head injury (MHI) in patients taking vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs). Am. J. Emerg. Med. 35, 1317–1319.
21. Beynon, C., Sakowitz, O.W., Störzinger, D., Orakcioglu, B., Radbruch, A., Potzy, A., and Unterberg, A.W. (2015). Intracranial haemorrhage in patients treated with direct oral anticoagulants. Thromb. Res. 136, 560–565.
22. Billings, J.D., Khan, A.D., McVicker, J.H., and Schroeppel, T.J. (2020). Newer and better? Comparing direct oral anticoagulants to warfarin in patients with traumatic intracranial hemorrhage. Am. Surg. 86, 1062–1066.
23. Cipriano, A., Park, N., Pecori, A., Bionda, A., Bardini, M., Frassi, F., Lami, V., Leoli, F., Manca, M.L., Del Prato, S., Santini, M., and Ghiadoni, L. (2021). Predictors of post-traumatic complication of mild brain injury in anticoagulated patients: DOACs are safer than VKAs. Intern. Emerg. Med. 16, 1061–1070.
24. Cocca, A.T., Privette, A., Leon, S.M., Crookes, B.A., Hall, G., Lena, J., and Eriksson, E.A. (2019). Delayed intracranial hemorrhage in anticoagulated geriatric patients after ground level falls. J. Emerg. Med. 57, 812–816.
25. Cohan, C.M., Beattie, G., Bowman, J.A., Galante, J.M., Kwok, A.M., Dirks, R.C., Kornblith, L.Z., Plevin, R., Browder, T.D., and Victorino, G.P. (2020). Repeat computed tomography head scan is not indicated in trauma patients taking novel anticoagulation: a multicenter study. J. Trauma Acute Care Surg. 89, 301–310.
26. Cohan, C.M., Beattie, G., Dominguez, D.A., Glass, M., Palmer, B., and Victorino, G.P. (2020). Routine repeat head CT does not change management in trauma patients on novel anticoagulants. J. Surg. Res. 249, 114–120.
27. Feeney, J.M., Santone, E., DiFiori, M., Kis, L., Jayaraman, V., and Montgomery, S.C. (2016). 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. 81, 843–848.
28. Galliazzo, S., Bianchi, M.D., Virano, A., Trucchi, A., Donadini, M.P., Dentali, F., Bertù, L., Grandi, A.M., and Ageno, W. (2019). Intracranial bleeding risk after minor traumatic brain injury in patients on antithrombotic drugs. Thromb. Res. 174, 113–120.
29. Jentzsch, T., Moos, R.M., Neuhaus, V., Hussein, K., Farei-Campagna, J., Seifert, B., Simmen, H.P., Werner, C., and Osterhoff, G. (2018). Is rivaroxaban associated with higher morbidity and mortality in patients with traumatic head injuries? A retrospective cohort study comparing rivaroxaban, no anticoagulation, and phenprocoumon. Clin. Neurol. Neurosurg. 169, 116–120.
30. Parra, M.W., Zucker, L., Johnson, E.S., Gullett, D., Avila, C., Wichner, Z.A., and Kokaram, C.R. (2013). Dabigatran bleed risk with closed head injuries: are we prepared?. J. Neurosurg. 119, 760–765.

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31. Pozzessere, A., Grotts, J., and Kaminski, S. (2015). Dabigatran use does not increase intracranial hemorrhage in traumatic geriatric falls when compared with warfarin. Am. Surg. 81, 1039–1042.
32. Prexl, O., Bruckbauer, M., Voelckel, W., Grottke, O., Ponschab, M., Maegele, M., & Schöchl, H. (2018). The impact of direct oral anticoagulants in traumatic brain injury patients greater than 60-years-old. Scand. J. Trauma Resusc. Emerg. Med. 26, 20.
33. Savioli, G., Ceresa, I.F., Luzzi, S., Gragnaniello, C., Giotta Lucifero, A., Del Maestro, M., Marasco, S., Manzoni, F., Ciceri, L., Gelfi, E., Ricevuti, G., and Bressan, M.A. (2020). 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. Medicina (Kaunas) 56, 308.
34. Shin, S.S., Marsh, E.B., Ali, H., Nyquist, P.A., Hanley, D.F., and Ziai, W.C. (2020). Comparison of traumatic intracranial hemorrhage expansion and outcomes among patients on direct oral anticoagulants versus vitamin K antagonists. Neurocrit. Care 32, 407–418.
35. Spinola, M.B., Riccardi, A., Minuto, P., Campodonico, P., Motta, G., Malerba, M., Guiddo, G., and Lerza, R. (2019). Hemorrhagic risk and intracranial complications in patients with minor head injury (MHI) taking different oral anticoagulants. Am. J. Emerg. Med. 37, 1677–1680.
36. Turcato, G., Zannoni, M., Zaboli, A., Zorzi, E., Ricci, G., Pfeifer, N., Maccagnani, A., Tenci, A., and Bonora, A. (2019). Direct oral anticoagulant treatment and mild traumatic brain injury: risk of early and delayed bleeding and the severity of injuries compared with vitamin K antagonists. J. Emerg. Med. 57, 817–824.
37. Kobayashi, L., Barmparas, G., Bosarge, P., Brown, C.V., Bukur, M., Carrick, M.M., Catalano, R.D., Holly-Nicolas, J., Inaba, K., Kaminski, S., Klein, A.L., Kopelman, T., Ley, E.J., Martinez, E.M., Moore, F.O., Murry, J., Nirula, R., Paul, D., Quick, J., Rivera, O., Schreiber, M., and Coimbra, R.; AAST Multicenter Prospective Observational Study of Trauma Patients on Novel Oral Anticoagulants Study Group. (2017). Novel oral anticoagulants and trauma: the results of a prospective American Association for the Surgery of Trauma Multi-Institutional Trial. J. Trauma Acute Care Surg. 82, 827–835.
38. Nishijima, D.K., Zehtabchi, S., Berrong, J., and Legome, E. (2012). Utility of platelet transfusion in adult patients with traumatic intracranial hemorrhage and preinjury antiplatelet use: a systematic review. J. Trauma Acute Care Surg. 72, 1658–1663.
39. Tomaselli, G.F., Mahaffey, K.W., Cuker, A., Dobesh, P.P., Doherty, J.U., Eikelboom, J.W., Florido, R., Gluckman, T.J., Hucker, W.J., Mehran, R., Messé, S.R., Perino, A.C., Rodriguez, F., Sarode, R., Siegal, D.M., and Wiggins, B.S. (2020). 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. J. Am. Coll. Cardiol. 76, 594–622.
40. Rao, M.P., Vinereanu, D., Wojdyla, D.M., Alexander, J.H., Atar, D., Hylek, E.M., Hanna, M., Wallentin, L., Lopes, R.D., Gersh, B.J., and Granger, C.B.; Apixaban for Reduction in Stroke Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Investigators. (2018). Clinical outcomes and history of fall in patients with atrial fibrillation treated with oral anticoagulation: insights from the ARISTOTLE Trial. Am. J. Med. 131, 269–275.e2.
41. Müller, M., Chanias, I., Nagler, M., Exadaktylos, A.K., and Sauter, T.C. (2021). Falls in ED patients: do elderly patients on direct oral anticoagulants bleed less than those on vitamin K antagonists?. Scand. J. Trauma Resusc. Emerg. Med. 29, 56.
42. Sardar, P., Chatterjee, S., Wu, W.C., Lichstein, E., Ghosh, J., Aikat, S., and Mukherjee, D. (2013). New oral anticoagulants are not superior to warfarin in secondary prevention of stroke or transient ischemic attacks, but lower the risk of intracranial bleeding: insights from a meta-analysis and indirect treatment comparisons. PLoS One 8, e77694.
43. Chatterjee, S., Sardar, P., Biondi-Zoccai, G., and Kumbhani, D.J. (2013). New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation. JAMA Neurol. 70, 1486–1490.
44. Huang, W.Y., Singer, D.E., Wu, Y.L., Chiang, C.E., Weng, H.H., Lee, M., and Ovbiagele, B. (2018). Association of intracranial hemorrhage risk with non-vitamin K antagonist oral anticoagulant use vs aspirin use: a systematic review and meta-analysis. JAMA Neurol. 75, 1511–1518.
45. Nederpelt, C.J., van der Aalst, S., Rosenthal, M.G., Krijnen, P., Huisman, M.V., Peul, W.C., and Schipper, I.B. (2020). 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. 88, 186–194.
46. Fuller, G.W., Evans, R., Preston, L., Woods, H.B., and Mason, S. (2019). Should adults with mild head injury who are receiving direct oral anticoagulants undergo computed tomography scanning? A systematic review. Ann. Emerg. Med. 73, 66–75.
47. Fiorelli, E.M., Bozzano, V., Bonzi, M., Rossi, S.V., Colombo, G., Radici, G., Canini, T., Kurihara, H., Casazza, G., Solbiati, M., and Costantino, G. (2020). Incremental risk of intracranial hemorrhage after mild traumatic brain injury in patients on antiplatelet therapy: systematic review and meta-analysis. J. Emerg. Med. 59, 843–855.
48. Than, M., Herbert, M., Flaws, D., Cullen, L., Hess, E., Hollander, J.E., Diercks, D., Ardagh, M.W., Kline, J.A., Munro, Z., and Jaffe, A. (2013). What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department? A clinical survey. Int. J. Cardiol. 166, 752–754.
49. Andruchow, J.E., Raja, A.S., Prevedello, L.M., Zane, R.D., and Khorasani, R. (2012). Variation in head computed tomography use for emergency department trauma patients and physician risk tolerance. Arch. Intern. Med. 172, 660–661.
50. Kanzaria, H.K., Hoffman, J.R., Probst, M.A., Caloyeras, J.P., Berry, S.H., and Brook, R.H. (2015). Emergency physician perceptions of medically unnecessary advanced diagnostic imaging. Acad. Emerg. Med. 22, 390–398.
51. Wong, A.C., Kowalenko, T., Roahen-Harrison, S., Smith, B., Maio, R.F., and Stanley, R.M. (2011). A survey of emergency physicians' fear of malpractice and its association with the decision to order computed tomography scans for children with minor head trauma. Pediatr. Emerg. Care 27, 182–185.
52. Batey, M., Hecht, J., Callahan, C., and Wahl, W. (2018). Direct oral anticoagulants do not worsen traumatic brain injury after low-level falls in the elderly. Surgery 164, 814–819.
53. Vos, P.E., Alekseenko, Y., Battistin, L., Ehler, E., Gerstenbrand, F., Muresanu, D.F., Potapov, A., Stepan, C.A., Traubner, P., Vecsei, L., and von Wild, K.; European Federation of Neurological Societies. (2012). Mild traumatic brain injury. Eur. J. Neurol. 19, 191–198.
54. Menditto, V.G., Lucci, M., Polonara, S., Pomponio, G., and Gabrielli, A. (2012). Management of minor head injury in patients receiving oral anticoagulant therapy: a prospective study of a 24-hour observation protocol. Ann. Emerg. Med. 59, 451–455.
55. Chauny, J.M., Marquis, M., Bernard, F., Williamson, D., Albert, M., Laroche, M., and Daoust, R. (2016). Risk of delayed intracranial hemorrhage in anticoagulated patients with mild traumatic brain injury: systematic review and meta-analysis. J. Emerg. Med. 51, 519–528.
56. Colombo, G., Bonzi, M., Fiorelli, E., Jachetti, A., Bozzano, V., Casazza, G., Solbiati, M., and Costantino, G. (2021). Incidence of delayed bleeding in patients on antiplatelet therapy after mild traumatic brain injury: a systematic review and meta-analysis. Scand. J. Trauma Resusc. Emerg. Med., 29(1), 123.
57. Hickey, S., Hickman, Z.L., Conway, J., and Giwa, A. (2021). The effect of direct oral anti-coagulants on delayed traumatic intracranial hemorrhage after mild traumatic brain injury: a systematic review. J. Emerg. Med. 60, 321–330.
58. Hoogerduijn, J.G., Schuurmans, M.J., Duijnstee, M.S., de Rooij, S.E., and Grypdonck, M.F. (2007). A systematic review of predictors and screening instruments to identify older hospitalized patients at risk for functional decline. J. Clin. Nurs. 16, 46–57.
59. Boyd, C.M., Landefeld, C.S., Counsell, S.R., Palmer, R.M., Fortinsky, R.H., Kresevic, D., Burant, C., and Covinsky, K.E. (2008). Recovery of activities of daily living in older adults after hospitalization for acute medical illness. J. Am. Geriatr. Soc. 56, 2171–2179.