TRAUMA/SYSTEMATIC REVIEW/META-ANALYSIS

Should Adults With Mild Head Injury Who Are Receiving Direct Oral Anticoagulants Undergo Computed Tomography Scanning? A Systematic Review

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Study objective: Patients receiving direct oral anticoagulant medications commonly undergo computed tomography head scanning after mild traumatic brain injury, regardless of symptoms or signs. International guidelines have noted a lack of evidence to support management decisions for such patients. This systematic review aims to identify, appraise, and synthesize the current evidence for the risk of adverse outcome in patients receiving direct oral anticoagulants after mild head injury.

Methods: A protocol was registered with PROSPERO and review methodology followed Cochrane Collaboration recommendations. Studies of adult patients with mild head injury (Glasgow Coma Scale score 13 to 15) and who were receiving direct oral anticoagulants that reported the risk of adverse outcome after the head injury were eligible for inclusion. A comprehensive range of bibliographic databases and gray literature was examined with a sensitive search strategy. Selection of eligible studies, data extraction, and risk of bias were evaluated independently by separate reviewers. A random-effects meta-analysis was used to provide a pooled estimate of the risk of adverse outcome. The overall quality of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation Working Group approach.

Results: A total of 4,886 articles were screened for inclusion, of which 7 cohort studies including 346 patients met inclusion criteria. All studies were at high or unclear risk of bias as a result of selection and information bias. Estimates of adverse outcome (any death, intracranial hematoma, or neurosurgery) ranged from 0.0% to 8.3%. A random-effects meta-analysis showed a weighted composite outcome risk of 3.7% (95% confidence interval 1.7% to 5.8%; I^2=3.3%). The overall quality of the body of evidence was low as a result of imprecision, indirectness, and risk of bias.

Conclusion: There are limited data available to characterize the risk of adverse outcome in patients receiving direct oral anticoagulants after mild traumatic brain injury. A sufficiently powered prospective cohort study is required to validly define this risk, identify clinical features predictive of adverse outcome, and inform future head injury guidelines. [Ann Emerg Med. 2018;■:1-10.]

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INTRODUCTION

Head injury is a common presentation that may result in traumatic brain injury. It is responsible for 1.4 million emergency department (ED) attendances annually in the United Kingdom.[1,2] Mild traumatic brain injury, classified as Glasgow Coma Scale (GCS) scores 13 to 15, is usually self-limiting, with less than 1% of patients having life-threatening sequelae.[3,4] However, up to 7% of patients may have intracranial injuries identified by computed tomography (CT) head imaging.[4] Risk stratification using clinical decision rules, followed by early CT head scanning to detect intracranial pathology, is the current standard of care for these patients.[5]

Up to 2.4% of the adult population of England are receiving anticoagulation therapy, with a concomitant increased risk of sustaining intracranial bleeding after head injury.[6] Patients receiving anticoagulants tend to be elderly and have comorbidities increasing their risk of falls and subsequent head injury.[7] The management of anticoagulated patients after head injury therefore presents a clinical challenge in an expanding and important group of patients. Traditionally, warfarin has been the most widely prescribed anticoagulant. However, in recent years, direct oral anticoagulants have been introduced.[6]

Recent guidance from the UK National Institute for Health and Care Excellence, published in 2014,

Editor's Capsule Summary

What is already known on this topic
Patients who sustain minor head trauma and are receiving warfarin anticoagulation have a 6% to 7% risk of abnormality on computed tomography (CT) scan of the head, supporting liberal CT scanning for these patients.

What question this study addressed
What is the risk of serious CT scan findings or complications in minor head injury patients receiving direct oral anticoagulants?

What this study adds to our knowledge
In this systematic review, 7 studies with high risk of bias included 346 patients. The pooled risk estimate for direct oral anticoagulant–treated patients who had intracranial hemorrhage, neurosurgery, or death was 4% (95% confidence interval 2% to 6%), and there were insufficient data to identify subgroups of patients with lower risk.

How this is relevant to clinical practice
Liberal CT scanning is reasonable for direct oral anticoagulant–treated patients with minor head injuries.

mild head injury as the top priority for stemming imaging overuse in the ED.[12] Moreover, the 2016 Academic Emergency Medicine consensus conference Shared Decision Making in the Emergency Department emphasized that the "patient and clinician must know and understand the best available evidence concerning the risks and benefits" of any diagnostic test to facilitate shared decisionmaking.[13] The Preventing Over-diagnosis consensus conference stated that obtaining meaningful decision thresholds through systematic reviews was a top 5 research priority.[14]

Direct oral anticoagulant manufacturers claim drug efficacy similar to that of warfarin, with greater ease of administration and lower bleeding risk.[15] However, there are few data on direct oral anticoagulant use in actual populations with mild traumatic brain injury. If the bleeding risk is lower than that for warfarin, or if a suitable clinical decision rule could be developed for patients receiving direct oral anticoagulants, there is the potential to reduce the number of CT head scans currently performed without increasing the risk of adverse outcome. This systematic review aimed to guide decisions on whether patients receiving direct oral anticoagulants and with mild traumatic brain injury or head injury require CT head scanning. Specific objectives were to determine the risk of adverse outcome in this patient group after mild traumatic brain injury and to characterize any demographic and clinical risk factors for significant injury.

MATERIALS AND METHODS
Study Design
A systematic review was conducted, following guidelines from the Cochrane Collaboration.[16] A review protocol was registered with an international prospective register of systematic reviews. The review question was, What is the risk of adverse outcome in patients sustaining a mild traumatic brain injury while receiving anticoagulation with a direct oral anticoagulant?

A comprehensive range of electronic information sources was examined, including major bibliographic databases, conference proceedings, and gray literature (Figure 1). Search strategies for bibliographic databases were developed iteratively in conjunction with an information specialist and were adapted for use in other data sources (Figure 2). Reference list checking, citation searching, and contact with subject experts were additionally performed. Searches were not restricted by date, language, study design, or publication status. An update search was conducted in MEDLINE and EMBASE immediately before article

recommends that a CT scan be performed within 8 hours for adults and children receiving warfarin and presenting with head injury in the absence of other indications, even if patients are initially asymptomatic.[2] No specific guidance was provided for direct oral anticoagulants despite their increasing use; but CT scanning is recommended within 8 hours for adults with some loss of consciousness or amnesia since the injury and any history of bleeding or clotting disorders, regardless of other symptoms or GCS score. Current practice in UK EDs may be more conservative, reflecting international guidelines,[8,9] with mandatory CT head scanning of any patient receiving a direct oral anticoagulant and with visible external signs of head trauma, such as abrasions, regardless of symptoms.

CT scanning incurs financial costs, longer ED stays, and cancer risks from radiation exposure. Consequently, there has been much interest, exemplified by the Choosing Wisely and Right Care Alliance campaigns, in ensuring that imaging decisions are supported by evidence and are truly necessary.[10,11] The American College of Emergency Physicians (ACEP) identified avoiding CT use in low-risk

Electronic Information Sources
1. Cochrane Database of Systematic Reviews (through the Cochrane Library)
2. Cochrane Injuries Group Specialized Register (through the Cochrane Library)
3. Database of Abstracts of Reviews of Effectiveness (DARE, through the Cochrane Library)
4. Cochrane Central Register of Controlled Trials (CENTRAL, through the Cochrane Library)
5. metaRegister of Controlled Trials (mRCT)
6. ClinicalTrials.gov
7. MEDLINE (through the OVID and PubMed platforms)
8. EMBASE (through the OVID platform)
9. CINAHL (through the OVID platform)
10. Science Citation Index (SCI, through the Web of Science)
11. ZETOC
12. Conference Proceedings Citation Index–Science (through the Web of Science)
13. EThOS: UK E-Theses Online Service
14. ProQuest Dissertation & Theses Database
15. National Clinical Guidelines Clearing House Web site
16. World Wide Web

Nonelectronic Data Sources
1. Checking reference lists of included articles
2. Checking reference lists of existing literature and systematic reviews
3. Corresponding with experts in the field and relevant study authors

Figure 1. Information sources. *CINAHL,* Cumulative Index to Nursing and Allied Health Literature.

1. Craniocerebral Trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2. ((head or brain) adj3 (injur* or trauma)).ti,ab.
3. (skull adj3 fracture*).ti,ab.
4. or/1-4
5. exp Anticoagulants/
6. (anticoagulant* ti,ab.
7. (Factor Xa inhibitor or Direct Xa inhibitor* or xabans or Apixaban or Betrixaban or Edoxaban or Otamixaban or Rivaroxaban or Direct thrombin inhibitor* or Bivalirudin or Lepirudin or Desirudin or Argatroban or Dabigatran or Melagatran or Ximelagatran).mp.
8. (NOAC* or DOAC* or Novel oral anticoag* or Direct oral anticoag* or Target-specific oral anticoag* or TSOAC or Oral direct inhibitor or ODI or Specific oral direct anticoag* or SODA).mp
9. or/5-8
10. 4 and 9

Figure 2. Search strategy.

from an established Cochrane Collaboration form, was piloted and used.[16] Study authors were contacted when additional information was necessary to assess study eligibility or risk of bias, or obtain relevant results.

We used a methodological component approach, based on recommendations of the Grading of Recommendations Assessment, Development and Evaluation Working Group,[17] to assess risk of bias in studies comprising the domains of selection bias, information bias, reporting bias, and other sources of bias. Risk of bias in each domain was classified as low, moderate, or high relative to the criterion standard of a perfectly performed, unbiased study directly addressing the systematic review question. A single unblinded reviewer (G.W.F.) judged the risk of bias in identified studies, explicitly recording the aspects of study design on which judgments were based. A second reviewer checked the risk of bias assessments independently (R.E.).

submission. References were managed in EndNote (version X6.0.1; Thomson Reuters, Ontario, Canada).

Data Collection and Processing

Systematic review inclusion criteria are detailed in Figure 3. Two reviewers (R.E. and L.P.) screened all citations to establish eligibility and decide whether to acquire the full articles. They then independently examined all retrieved full-text articles against the inclusion criteria to identify eligible studies. A third reviewer (G.W.F.) arbitrated in cases of disagreement. A single reviewer (R.E.) extracted data on study characteristics, participants, interventions, and outcomes, with accuracy checked by a second reviewer (G.W.F.). A standardized data extraction form, customized

Primary Data Analysis

We examined the incidence proportion ("risk") of adverse outcome (ie, numerator of the number of adverse outcomes during the specified follow-up interval and

Population:
    Adults patients >16 y
    Sustaining a clinically relevant head injury (judged
        by attending clinician)
    Mild traumatic brain injury: GCS scores 13–15
    Presenting to the hospital

Exposure:
    DOACs, comprising direct thrombin inhibitors
        (dabigatran), or direct factor Xa inhibitors
        (rivaroxaban, apixaban, edoxaban)

Outcomes:
    TBI-related adverse outcome within 3 mo of
        initial hospital attendance, either alone or in
        combination, including:
- Death
- Disability
- Neurosurgery after initial injury
- Clinically significant intracranial hemorrhage (eg, Abbreviated Injury Score ≥2)
- Reattendance
- Other significant deleterious sequelae

DOAC, Direct oral anticoagulant; *TBI*, traumatic brain injury.

Figure 3. Systematic review inclusion criteria.

denominator of the studied cohort enrolled and followed up). We compared study-specific estimates of risk, which could include any combination of adverse outcome type, using forest plots and heterogeneity assessed subjectively by visual inspection, Cochrane Q test, and the I^2 statistic.[18,19] A quantitative synthesis was performed after confirmation that studies had relatively homogenous participants and results ($I^2 <25\%$). A random-effects meta-analysis was subsequently performed with the binomial distribution to model the within-study variability and exact binomial 95% confidence intervals (CIs) calculated. Cohen's κ statistics were calculated to assess interrater agreement for study selection, data extraction, and risk-of-bias assessments. Altman's scale was used for assessing the strength of agreement demonstrated by κ statistics: <0.20 poor, 0.21 to 0.39 fair, 0.40 to 0.59 moderate, 0.60 to 0.79 good, and 0.80 to 1.0 very good.[20] Statistical analyses were carried out in Stata (version 13.1; StataCorp, College Station, TX), using the metaprop command.[21] An a priori subgroup analysis of patients with asymptomatic mild traumatic brain injury, GCS score 15, and normal neurology was prespecified if possible. Examination of the association of individual demographic variables (eg, age) and clinical features (eg, headache) with adverse outcome after head injury in patients receiving direct oral anticoagulants was also planned.

The overall quality of evidence for the risk estimate was assessed with the Grading of Recommendations Assessment, Development and Evaluation approach for prognosis research.[17] This specifies 4 levels of quality (high, moderate, low, and very low), with perfectly performed studies providing high-quality evidence. The body of evidence is downgraded in the presence of within-study risk of bias, indirectness of evidence, heterogeneity, imprecision of effect estimates, and risk of publication bias. Publication bias was evaluated by inspection of funnel plots (logit event rate against standard error), Egger's test, and scrutiny of study registration databases for missing studies.[22]

RESULTS

We screened 4,886 citations for eligibility and retrieved the full text of 114 articles for detailed evaluation. During full-text examination, 7 eligible observational studies were identified for inclusion in the review, including a total of 346 patients.[23-29] Two potentially eligible studies were retrieved that included patients with head injury who were receiving direct oral anticoagulants[30,31]; however, details defining whether the study population met inclusion criteria or data allowing estimation of risk of adverse outcome were not presented. We contacted the authors, but the research teams were unable to provide this information. Interrater agreement for study selection was good (κ=0.7; 95% CI 0.6 to 0.8). Figure 4 summarizes the selection of included studies.

The characteristics of included studies are summarized in Table 1. Study designs comprised retrospective and prospective cohort studies performed in the United States, Italy, and Switzerland. Mild head injury was variably defined as GCS scores 13 to 15,[23,25] GCS score 15 with symptoms,[29] or GCS scores 14 to 15 (all other studies). Unselected patients presenting to EDs were enrolled by 5 studies, with patients aged 54 years or older and transported by emergency medical services (EMS) to the hospital included in the remaining 2 studies. The studied direct oral anticoagulants comprised dabigatran, rivaroxaban, edoxaban, and apixaban. Length of follow-up varied from an initial postpresentation CT head scan to 1 month after head injury. Outcomes included CT-detected intracranial hematoma, neurosurgery, readmission, and mortality. Disability was not assessed in any study. Interrater agreement for data extraction was very good (κ=0.8; 95% CI 0.7-0.9).
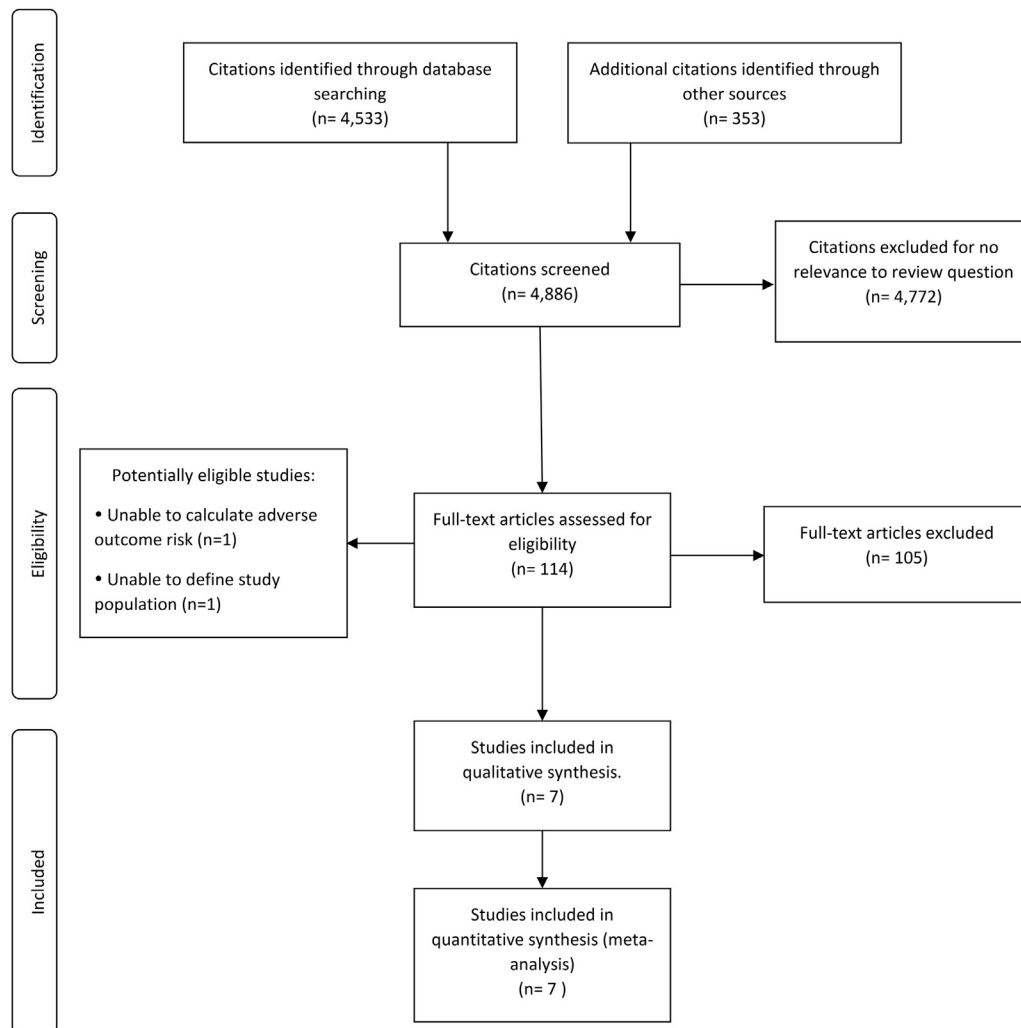
Figure 4. Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart describing systematic review study selection.

The risk of bias for included studies is summarized in Table 2, with a detailed rationale presented in Table E1, available online at http://www.annemergmed. com. The overall risk of bias relative to a perfectly performed unbiased study directly addressing the review question was high or unclear for all studies. The main limitations were possible selection bias from incomplete enrollment of eligible patients in retrospective chart review studies, and incomplete outcome ascertainment as a result of nonassessment of postdischarge adverse outcomes. Interrater agreement for risk-of-bias assessment was very good (no disagreements; κ=1.0; 95% CI 1.0 to 1.0).

Estimates of adverse outcome ranged from 0.0% to 8.3% across included studies, as presented in a forest plot in Figure 5. Although point estimates for adverse outcome risk varied, 95% CIs for each study overlapped, suggesting relatively homogenous results. The I^2 statistic was 3.3%, with a nonsignificant Q statistic (P=0.40). A random-effects meta-analysis showed a weighted adverse outcome risk of 3.7% (95% CI 1.7% to 5.8%). There were insufficient data to examine asymptomatic patients with GCS score 15, or to characterize individual clinical and demographic risk factors for adverse outcome. The Grading of Recommendations Assessment, Development and Evaluation quality of evidence was downgraded to low quality according to methodology (high or unclear risk of bias), precision (relatively wide 95% CI for pooled adverse event estimate), and indirectness of evidence (study populations' not reflecting undifferentiated ED patients). The quality rating was not affected by heterogeneity or publication bias (no funnel plot asymmetry, nonsignificant Egger's test result (P=.8), and no registered but unpublished studies).

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Table 1. Characteristics of included studies.

Study	Study Design	Date, Country	No. of Patients*	Setting	Inclusion Criteria	Exclusion Criteria	DOACs	Outcomes	Notes
McCammack,[23] 2015	RCS	2012–2013, US	2	ED	GCS score 13–15	Not reported	Dabigatran	Within 6 h: ICH	All patients: Received admission CT head scan CT head scan 6 h postinjury
Cipriano,[25] 2018	PCS	2016, Italy	85	ED	GCS score 13–15	Delayed presentation >48 h Not receiving DOAC for >24 h	Dabigatran, rivaroxaban, apixaban, edoxaban	1-mo FU: ICH Neurosurgery Readmission Death	All patients: Received admission CT head scan Observed for minimum 24 h
Chenoweth,[24] 2017	RCS	2010–2015, US	33	ED	GCS score 14–15 Received CT head scan	Interfacility transfers Pregnant patients	Dabigatran	Inpatient: ICH Neurosurgery Death	
Nishijima,[26] 2017	RCS	2012, US	12	EMS	>55 y Transported by EMS GCS score 14–15	Interfacility transfers Transported to a nonparticipating hospital Prisoners Unable to link hospital and EMS data	Dabigatran, rivaroxaban, apixaban, edoxaban	Inpatient: ICH Neurosurgery Death	
Nishijima,[27] 2017	PCS	2015–2016, US	41	EMS	>55 y Transported by EMS GCS score 14–15	Interfacility transfers Transported to a nonparticipating hospital Unable to link hospital and EMS data	Dabigatran, rivaroxaban, apixaban, edoxaban	Inpatient: ICH Neurosurgery Death	
Riccardi,[28] 2017	PCS	2016, Italy	107	ED	Ground-level fall GCS score 14–15	Mechanical heart valve replacement Concomitant antiplatelets	Dabigatran, rivaroxaban, apixaban	1-mo FU: ICH Neurosurgery Readmission Death	All patients: Received admission CT head scan Observed for minimum 24 h
Uccella,[29] 2018	RCS	2014–2016, Switzerland	60	ED	GCS score 15 Witnessed LOC, amnesia, or disorientation	Not reported	Dabigatran, rivaroxaban, apixaban, edoxaban	Inpatient: ICH	All patients received admission CT head scan

RCS, retrospective cohort study; *US*, United States; *ICH*, intracranial hematoma; *FU*, follow-up; *PCS*, prospective cohort study; *LOC*, loss of consciousness.
*All studies included adults receiving DOACs after blunt mild head injury.

Table 2. Summary of risk of bias assessment.

| | Risk-of-Bias Domain | | | | |
| | Selection | | Information | Reporting | |
Study	Representative Sample: Risk of Outcome Does Not Influence Selection Into Study/Accurate Measurement of Exposure: Patients Correctly Identified as Receiving DOACs	Complete Follow-up: Risk of Outcome Does Not Influence Attrition	Accurate Measurement of Outcome: Patients Correctly Classified as Having Adverse Outcome	Nonselective Reporting of Outcomes	Other
McCammack, 2015	Moderate	Low	High	Low	Low
Chenoweth, 2017	Moderate	Low	High	Low	Low
Cipriano, 2018	Moderate	Unclear	Low	Low	Low
Nishijima,[26] 2017	Moderate	Low	High	Low	Low
Nishijima,[27] 2017	High	Low	High	Low	Low
Riccardi, 2017	Unclear	Low	Low	Low	Low
Uccella, 2018	Unclear	Unclear	High	Low	Low

LIMITATIONS

To maximize internal validity, Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were followed to ensure that all relevant evidence was included, accurately and precisely coded, validly assessed for risk of bias, and impartially analyzed and interpreted (Table E2, available online at http://www.annemergmed.com).[16,32] However, there are a number of potential methodological weaknesses. We did not perform hand searching (ie, manual page-by-page examination of the entire contents) of journals or conference proceedings, and did not include regional bibliographic databases, although the yield of such searches is generally low.[16] Inadequate reporting of
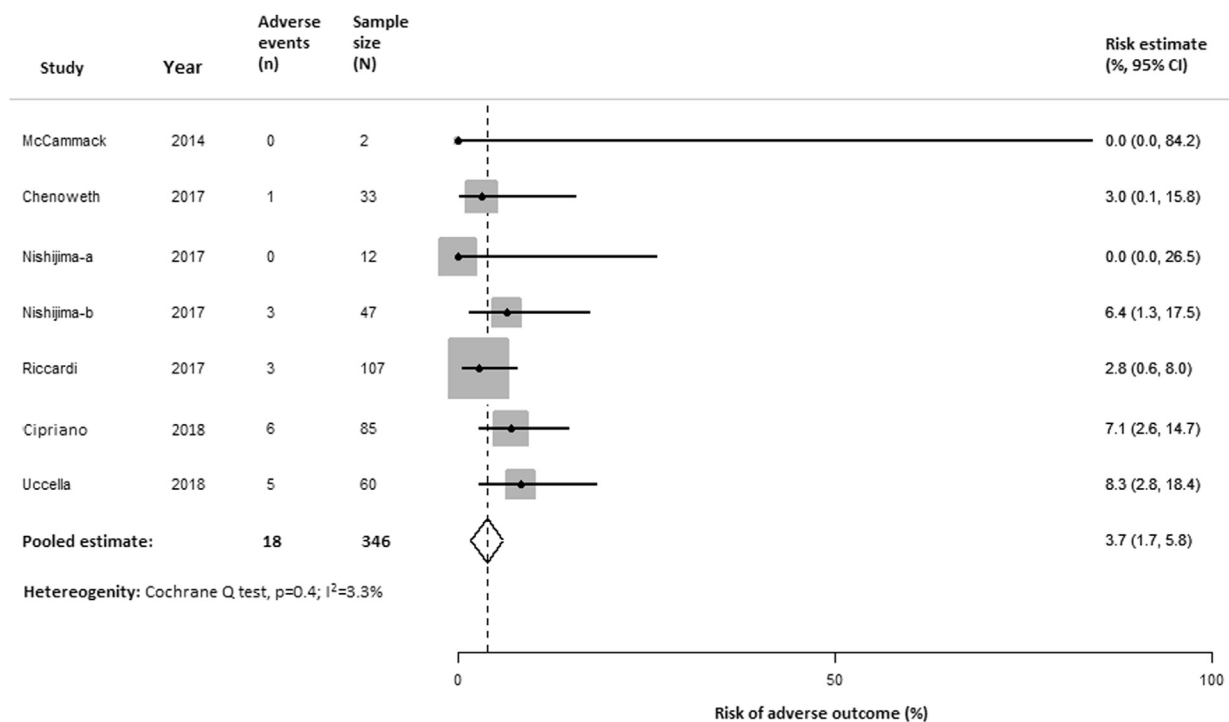

Figure 5. Forest plot presenting individual and pooled risk of adverse outcome after mild head injury while the patient is receiving DOACs. Dots represent point estimates, shaded boxes indicate study weights, and whiskers represent 95% CIs.

nonrandomized studies and poor indexing in databases may have impaired the detection of published information. Given the low number of included studies, we had limited power to assess the presence of publication bias. Furthermore, we were unable to obtain usable data on 2 potentially eligible studies from the research teams. Decisions on study relevance, information gathering, and validity were unblinded and could have been influenced by preformed opinions. However, masking is resource intensive with uncertain benefits.[16] Included studies used different definitions for adverse outcome, and often did not report constituents of composite outcomes separately, challenging interpretation of a pooled risk estimate. Finally, quantitative synthesis of homogenous studies at high or unclear risk of systematic error may have provided precise but "spurious" results because of underlying biases.[33]

DISCUSSION

To our knowledge, this is the first systematic review to evaluate outcomes after mild head injury of patients receiving direct oral anticoagulants. Limited data were available, giving a relatively imprecise pooled adverse outcome risk of 4% (95% CI 2% to 6%). Included studies were at high or unclear risk of bias. The overall quality of available evidence was low, indicating little confidence in the reported pooled risk estimate.

International guidelines recommend CT head imaging for patients receiving direct oral anticoagulants after mild head injury regardless of symptoms, but recognize a paucity of evidence to support this recommendation.[2,8,9] The reported pooled adverse outcome risk of 4% outwardly supports this guidance. However, a number of issues require consideration when this finding is interpreted. First, the internal validity of individual study results is uncertain and firm conclusions therefore cannot be drawn. Inaccurate identification of cases in retrospective chart review studies or incomplete prospective enrollment may have introduced selection bias of uncertain magnitude and direction. Inadequate follow-up, restricted to initial CT head scan or inpatient stay, was conducted in 5 studies, which may have underestimated adverse outcomes from postdischarge deaths, readmissions, or deterioration.

Second, study inclusion criteria did not always reflect undifferentiated patients presenting to EDs after mild head injury, which could limit the generalizability of findings. One study included only ground-level falls, 2 enrolled only patients older than 55 years and transported by EMS, and one study included only symptomatic patients with GCS score 15. Unfortunately, there were insufficient numbers of

studied patients to provide a precise risk estimate or assess differential risk across isolated head injury or polytrauma, alternative direct oral anticoagulants, or different anticoagulant indications.

Third, although a composite endpoint is conventionally used in studies of mild traumatic brain injury, individual outcome components vary in severity. A recent systematic review reported that 90% of intracranial hematoma detected in mild traumatic brain injury does not result in clinical deterioration or require neurosurgery.[34] The clinical significance and importance to patients of such incidental intracranial hematomas are uncertain. Death, disability, neurosurgery, or readmission may represent more relevant patient-orientated endpoints. Precise estimates for each of these outcomes were unavailable but would allow more nuanced imaging decisions.

Fourth, we were not able to report a valid risk estimate for the subgroup of asymptomatic patients with mild traumatic brain injury and GCS score 15 who might be expected to have a lower probability of adverse outcome and who might be otherwise discharged without investigation if not receiving direct oral anticoagulants. Mild traumatic brain injury is conventionally defined as GCS scores 13 to 15, with poorer prognosis and increased incidence of intracranial abnormalities as GCS score decreases.[8] Patients with GCS scores less than 15 and concomitant use of anticoagulant medication will generally undergo routine CT head scanning.[2,8,9] Uccella et al[29] found a relatively high incidence (8%) of intracranial hematoma in patients with GCS score 15 who were receiving direct oral anticoagulants and had witnessed loss of consciousness, amnesia, or disorientation. Ideally, a direct oral anticoagulant–specific clinical decision tool could be developed, incorporating the predictive value of clinical and patient characteristics.

Fifth, the acceptable risk threshold for patients after mild head injury to allow omission of routine CT scanning is unknown and may vary across patients, clinicians, and health systems, depending on personal, cultural, medicolegal, and economic factors. It could be quantified in future clinical practice by shared decisionmaking or defined on a population level by investigation of the stated preferences of clinicians or patients, benchmarking, other currently tolerated clinical risks; calculated through economic evaluation; or determined by decision analytic techniques (eg, the Pauker method).[35-38] However, in developed health systems it is likely that a very low risk threshold exists, and barriers to reducing CT use may include the ready availability of imaging, the ubiquity of the practice, the relatively low radiation risk (particularly among older patients, who tend to sustain head injuries

while receiving direct oral anticoagulants), and the perceived medicolegal repercussions of forgoing imaging.

To our knowledge, there are no previous systematic reviews examining the risk of adverse outcome after mild head injury for patients receiving direct oral anticoagulants, but a larger literature is available examining the effects of warfarin. The AHEAD study is the most recent and comprehensive investigation, including 3,416 adults who had experienced mild blunt traumatic brain injury and were currently receiving warfarin.[39] The overall adverse outcome estimate was slightly higher, at 5.9% (95% CI 5.2% to 6.7%), than the reported pooled result for direct oral anticoagulants. For patients with GCS score 15 and no associated symptoms, the risk of adverse outcome was lower, at 2.7% (95% CI 2.1% to 3.6%). Given the paucity of available data, it is not possible to say conclusively whether the adverse outcome risk differs compared with that for direct oral anticoagulants.

In summary, there are limited data available to characterize the risk of adverse outcome in patients receiving direct oral anticoagulants after mild head injury. A sufficiently powered prospective cohort study is required to validly define this risk, identify clinical features predictive of adverse outcome, and inform future revisions of head injury guidelines (eg, ACEP's 2008 policy).[9] However, because to our knowledge there are currently no prospective studies registered in international research databases (eg, ClinicalTrials.gov), it is likely that the reported information is the best evidence that will be available for the foreseeable future.[40]

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