ABSTRACT

Study hypothesis

Patients taking direct oral anticoagulant medications (DOACs) commonly undergo computed tomography (CT) head scanning following mild traumatic brain injury, regardless of symptoms or signs. International guidelines have noted a lack of evidence to support management decisions in such patients. This systematic review aimed to identify, appraise and synthesize the current evidence for the risk of adverse outcome in patients taking DOACs following mild head injury.

Methods

A protocol was registered with PROSPERO (CRD42017071411) and review methodology followed Cochrane Collaboration recommendations. Studies of adult patients with mild head injury (Glasgow Coma Scale (GCS) 13-15) taking DOACs, which reported the risk of adverse outcome following the head injury, were eligible for inclusion. A comprehensive range of bibliographic databases and grey literature were examined using a sensitive search strategy. Selection of eligible studies, data extraction, and risk of bias was 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 using the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) approach.

Results

4,185 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 secondary to selection and information bias. Estimates of adverse outcome (any death, intracranial hematoma (ICH), or neurosurgery) ranged from 0.0% to 8.3%. A random effects meta-analysis showed a weighted composite outcome risk of 3.7% (95% CI 1.7-5.8%), I^2=3.3%). The overall quality of the body of evidence was low secondary to imprecision, indirectness and risk of bias.

Conclusions

There is limited data available to characterize the risk of adverse outcome in patients taking DOACs following 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.

INTRODUCTION

Head injury is a common presentation that may result in traumatic brain injury (TBI). It is responsible for 1.4 million emergency department (ED) attendances annually in the United Kingdom.[1 2] Mild TBI, classified as Glasgow Coma Scale (GCS) 13 to 15 is usually self-limiting, with less than 1% of patients having life-threatening sequelae.[3 4] However, up to 7% 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 taking anticoagulation therapy, with a concomitant increased risk of sustaining intracranial bleeding following head injury.[6] Patients taking anticoagulants tend to be elderly and have comorbidities increasing their risk of falls and subsequent head injury.[7] The management of anticoagulated patients following 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 (DOACs) have been introduced.[6]

Recent guidance from the UK National Institute for Health and Care Excellence (NICE) published in 2014 recommends a CT scan should be performed within 8 hours for adults and children on warfarin presenting with head injury in the absence of other indications, even if initially asymptomatic.[2] No specific guidance was provided for DOACs 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. Current practice in UK EDs may be more conservative, reflecting international guidelines,[8 9] with mandatory CT head scanning of any patient taking a DOAC with visible external signs of head trauma, such as abrasions, regardless of symptoms.

CT scanning incurs financial costs, longer emergency department 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 imaging decisions are supported by evidence and are truly necessary.[10 11] The American College of Emergency Physicians identified avoiding CT use in low-risk 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 decision making.[13] The Preventing Over-diagnosis Consensus Conference recommended that obtaining meaningful decision thresholds via systematic reviews was a top five research priority.[14]

DOAC manufacturers claim similar efficacy to warfarin with greater ease of administration and lower bleeding risk.[15] However, there is little data on DOAC use in real-world populations with mild TBI. If the bleeding risk is lower than warfarin, or if a suitable clinical decision rule could be developed for patients taking DOACs, 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 taking DOACs with mild TBI/head injury require CT head scanning. Specific objectives were to determine the risk of adverse outcome in this patient group following mild TBI and to characterize any demographic and clinical risk factors for significant injury.

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 (PROSPERO Number CRD42017071411). The review question was: What is the risk of adverse outcome in patients sustaining a mild TBI while anticoagulated with a DOAC?

Information Sources and search strategy

A comprehensive range of electronic information sources were examined, including major bibliographic databases, conference proceedings, and grey literature (Table 1). Search strategies for bibliographic databases were developed iteratively in conjunction with an information specialist and were adapted for use in other data sources (Table 2). Reference list checking, citation searching and contact with subject experts was additionally performed. Searches were not restricted by date, language, study design, or publication status. An update search was conducted in MEDLINE and EMBASE immediately prior to submission (10th May 2018). References were managed in EndNote (Thomson Reuters, CA, USA).

Selection of studies and data collection

Systematic review inclusion criteria are detailed in table 3. Two reviewers (RE and LP) screened all citations to establish eligibility, and to decide whether or not to acquire the full articles. Two reviewers (RE and LP) then independently examined all retrieved full text articles against the inclusion criteria to identify eligible studies. A third reviewer (GF) arbitrated in cases of disagreement. A single reviewer (RE) extracted data on study characteristics, participants, interventions and outcomes; with accuracy checked by a second reviewer (GF). A standardized data extraction form, customized from an established Cochrane Collaboration form was piloted and used.[16] Study authors were contacted where additional information was necessary to assess study eligibility or risk of bias, or obtain relevant results.

Assessment of risk of bias of included studies

We used a methodological component approach, based on recommendations of the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) prognosis 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 gold standard of a perfectly performed, unbiased study directly addressing the systematic review question. A single un-blinded reviewer (GF) 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 (RE).

Data synthesis and analysis

We examined the incidence proportion ('risk') of adverse outcome (i.e. numerator of the number of adverse outcomes during the specified follow up interval; and 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 confirming that studies had relatively homogenous participants and results (I^2 <25%). A random effects meta-analysis was subsequently performed using the binomial distribution to model the within-study variability and exact binomial 95% confidence intervals calculated. Cohen's Kappa statistics were calculated to assess inter-rater agreement for study selection, data extraction, and risk of bias assessments. Altman's scale was used for assessing the strength of agreement demonstrated by kappa statistics: <0.20 Poor, 0.21-0.39 Fair, 0.40-0.59 Moderate, 0.60-0.79 Good, 0.80-1.0 Very Good.[20] Statistical analyses were carried out in Stata version 13.1 (StataCorp, College Station, USA) using the *metaprop* command.[21] An *a priori* subgroup analyses of asymptomatic mild TBI patients with GCS 15 and normal neurology was pre-specified if possible. Examination of the association of individual demographic variables (e.g. age) and clinical features (e.g. headache) with adverse outcome following head injury in patients taking DOACs was also planned.

Assessment of overall quality of evidence

The overall quality of evidence for the risk estimate was assessed using the GRADE approach for prognosis research.[17] This specifies four 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

Study selection

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: McCammack 2014;[23] Chenoweth 2017;[24] Cipriani 2017;[25] Nishijima 2017a;[26] Nishijima 2017b;[27] Riccardi 2017;[28] Uccella 2018;[29] including a total of 346 patients. Two potentially eligible studies were retrieved which included patients with head injury taking DOACs (Bauman 2017,[30] Jentzsch 2018);[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. Inter-rater agreement for study selection was good (Kappa=0.7, 95% CI 0.6-0.8). Figure 1 summarizes the selection of included studies.

Study characteristics

The characteristics of included studies are summarized in table 4. Study designs comprised retrospective and prospective cohort studies performed in the United States, Italy, and Switzerland. Mild head injury was variably defined as GCS 13-15 (McCammack 2014 and Cipriani 2017), GCS 15 with symptoms (Uccella 2018), or GCS 14-15 (all other studies). Unselected patients presenting to emergency departments were enrolled by five studies; with patients aged >54 years and transported by emergency medical services to hospital included in the remaining two studies. The studied DOACs comprised dabigatran, rivaroxaban, edoxaban and apixaban. Length of follow-up varied from an initial post-presentation CT head to 1 month post head injury. Outcomes included CT-detected ICH, neurosurgery, readmission and mortality. Disability was not assessed in any study. Inter-rater agreement for data extraction was very good (Kappa=0.8, 95% CI 0.6-0.8).

Risk of bias

The risk of bias for included studies is summarized in table 5, with a detailed rationale presented in the web appendix. 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 enrolment of eligible patients in retrospective chart review studies; and incomplete outcome ascertainment secondary to non-assessment of post discharge adverse outcomes.

Inter-rater agreement for risk of bias assessment was very good (no disagreements, kappa statistic=1.0, 95% CI 1.0-1.0).

Reported results and overall quality of evidence

Estimates of adverse outcome ranged from 0.0% to 8.3% across included studies, as presented in a Forest plot in Figure 2. Although point estimates for adverse outcome risk varied, 95% confidence intervals for each study overlapped suggesting relatively homogenous results. The I^2 statistic was 3.3% with a non-significant Q statistic (p=0.4). A random effects meta-analysis showed a weighted adverse outcome risk of 3.7% (95% CI 1.7-5.8%). There was insufficient data to examine asymptomatic patients with GCS 15, or to characterize individual clinical and demographic risk factors for adverse outcome. The GRADE quality of evidence was downgraded to low quality based on: methodology (high or unclear risk of bias); precision (relatively wide 95% confidence interval for pooled adverse event estimate); and indirectness of evidence (study populations' not reflecting undifferentiated emergency department patients). The quality rating was not affected by heterogeneity or publication bias (no Funnel plot asymmetry, non-significant Egger's test (p=0.8) and no registered, but unpublished studies).

LIMITATIONS

To maximize internal validity Cochrane Collaboration and PRISMA 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 (see web appendix).[16 32] However, there are a number of potential methodological weaknesses. We did not perform hand searching (i.e. 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 non-randomized studies and poor indexing in databases may impair 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 useable data on two potentially eligible studies from the research teams. Decisions on study relevance, information gathering, and validity were un-blinded and could potentially have been influenced by pre-formed 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 provide precise, but 'spurious' results secondary to underlying biases.[33]

DISCUSSION

This is the first systematic review to evaluate outcomes after mild head injury in patients taking DOACs. Limited data were available giving a relatively imprecise pooled adverse outcome risk of 4% (95% CI 2-6%). 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 taking DOACs following 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 interpreting this finding. Firstly, 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 five studies which may underestimate adverse outcomes from post-discharge deaths, readmissions or deterioration.

Secondly, study inclusion criteria did not always reflect undifferentiated patients presenting to emergency departments following mild head injury, which could limit the generalizability of findings. One study included only ground level falls, two studies only enrolled patients aged over 55 years and transported by emergency medical services, whilst one study included only symptomatic GCS 15 patients. Unfortunately, there were insufficient numbers of studied patients to provide a precise risk estimate or assess differential risk across isolated head injury/polytrauma, alternative DOACs, or different anticoagulant indications.

Thirdly, although a composite endpoint is conventionally used in studies of mild TBI, individual outcome components vary in severity. A recent systematic review reported that 90% of ICH detected in mild TBI does not result in clinical deterioration or require neurosurgery.[34] The clinical significance, and importance to patients, of such incidental ICH is 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.

Fourthly, we were not able to report a valid risk estimate for the subgroup of asymptomatic patients with mild TBI and GCS 15 that might be expected to have a lower probability of adverse outcome and

who might be otherwise discharged without investigation if not taking DOACs. Mild TBI is conventionally defined as GCS 13-15, with poorer prognosis and increased incidence of intracranial abnormalities as GCS falls.[8] Patients with GCS<15 and concomitant use of anticoagulant medication will generally undergo routine CT head scanning.[2 8 9] Of interest, Ucculla and colleagues found a relatively high 8% incidence of ICH in GCS 15 patients taking DOACs with witnessed loss of consciousness, amnesia or disorientation.[29] Ideally a DOAC specific clinical decision tool could be developed, incorporating the predictive value of clinical and patient characteristics.

Finally, the acceptable risk threshold for patients following 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 decision making, or defined on a population level by investigating the stated preferences of clinicians or patients, benchmarking other currently tolerated clinical risks, calculated through economic evaluation, or determined by decision analytic techniques (e.g. 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 on DOACs), and the perceived medicolegal repercussions of forgoing imaging.

There are no previous systematic reviews examining the risk of adverse outcome after mild head injury on DOACs, 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 suffered mild blunt TBI and were currently taking 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 DOACs. For patients with GCS 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 DOACs.

In summary, there is limited data available to characterize the risk of adverse outcome in patients taking DOACs following 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 (e.g. American College of Emergency Physician's 2008 policy).[9] However, as there are currently no prospective studies registered in international research databases (e.g.

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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