WEB APPENDIX

Table A1. Systematic review inclusion criteria

Review question:
'What is the risk of adverse outcome in patients sustaining a mild TBI while anticoagulated with a DOAC?'

Inclusion criteria:
Population:
•Adults patients >16 years
•Sustaining a clinically relevant head injury (judged by attending clinician)
•Mild traumatic brain injury: GCS 14-15
•Presenting to hospital

Exposure:
•Direct Oral Anticoagulants, comprising: direct thrombin inhibitors (dabigatran); or direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban).

Outcomes:
TBI related adverse outcome within 3 months of initial hospital attendance, either alone or in combination, including:
•Death
•Disability
•Neurosurgery following initial injury
•Clinically significant intracranial haemorrhage e.g. Abbreviated Injury Score ≥2
•Re-attendance
•Other significant deleterious sequelae.

Table A2. Systematic review information sources

Electronic information sources
1. Cochrane Database of Systematic Reviews (via Cochrane Library)
2. Cochrane Injuries Group Specialised Register (via Cochrane Library)
3. Database of Abstracts of Reviews of Effectiveness (DARE, via Cochrane Library)
4. Cochrane Central Register of Controlled Trials (CENTRAL, via Cochrane Library)
5. metaRegister of Controlled Trials (mRCT)
6. ClinicalTrials.gov
7. MEDLINE (via OVID and PubMed platforms)
8. EMBASE (via OVID platform)
9. CINAHL (via OVID platform)
10. Science Citation Index (SCI, via Web of Science)
11. ZETOC
12. Conference Proceedings Citation Index – Science (via Web of Science)
13. EThOS: UK E-Theses Online Service
14. ProQuest Dissertation & Theses Database
15. National Clinical Guidelines Clearing House website
16. World wide web
Non-electronic data sources
1. Checking reference lists of included articles
2. Checking reference lists of existing literature and systematic reviews
3. Correspondence with experts in the field, and relevant study authors

Table A3. Systematic review search strategy

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

Table A4. Characteristics of studies included in the updated meta-analysis

Study	Study design	Date, country	N patients*	Setting	Inclusion criteria	Exclusion criteria	DOACs	Outcomes	Notes
Chenoweth 2017	RCS	2010-2015 US	33	ED	•GCS 14-15 •Received CT head scan	•Interfacility transfers •Pregnant patients.	Dabigatran	Inpatient: •ICH •Neurosurgery •Length of stay	
Nishijima 2017a	RCS	2012 US	12	EMS	•>55 years •Transported by EMS •GCS 14-15	•Interfacility transfers •Transported to a non-participating hospital •Prisoners •Unable to link hospital & EMS data.	Dabigatran, rivaroxaban, apixaban, edoxaban	Inpatient: •ICH •Neurosurgery •Death	
Nishijima; 2017b	PCS	2015-2016 US	41	EMS	•>55 years •Transported by EMS •GCS 14-15	•Interfacility transfers •Transported to a non-participating hospital, •Unable to link hospital & EMS data.	Dabigatran, rivaroxaban, apixaban, edoxaban	Inpatient: •ICH •Neurosurgery •Death	
Riccardi 2017	PCS	2016 Italy	107	ED	•Ground level fall •GCS 14-15	•Mechanical heart valve replacement •Concomitant anti-platelets	Dabigatran, rivaroxaban, apixaban	1 month FU: •ICH •Neurosurgery •Readmission •Death	All patients: •Received admission CT head •Observed for minimum 24 hours

Study	Study design	Date, country	N patients*	Setting	Inclusion criteria	Exclusion criteria	DOACs	Outcomes	Notes
Spinola 2019	PCS	2016-2018 Italy	226	ED	•GCS 14,15	•Mechanical heart valve replacement •Antiplatelet therapies	Not reported	1 month FU: •ICH •Neurosurgery •Readmission •Death	
Turcato 2019	RCS	2017-2018, Italy	163	ED	•GCS 13-15†	•'Inadequate anticoagulant treatment'	Not reported	•Early ICH •Delayed ICH to 30 days •Neurosurgery •Intensive care •TBI related inpatient death	All patients underwent an immediate CT brain a second CT scan after 24 h (T1), with a clinical observation period between prior to discharge from the ED.

*All studies included adults taking DOACs following blunt mild head injury; US: United States of America; GCS: Glasgow Coma Scale; RCS: Retrospective cohort study; PCS: Prospective cohort study; EMS: Emergency medical services; ED: Emergency department; ICH: intracranial haematoma; CT: Computed tomography. †Data for GCS 14-15 patients requested from authors.

Table A5. Risk of bias in studies included in updated meta-analysis

Study		Risk of Bias Domain				
	EQUATOR reporting guidelines used	**Selection bias-a**	**Selection bias-b**	**Information bias**	**Reporting bias**	**Other bias**
		Representative sample - risk of outcome doesn't influence selection into study. Accurate measurement of exposure – patients correctly classified as taking DOACs.	*Complete follow up - risk of outcome doesn't influence attrition.*	*Accurate measurement of outcome – patients correctly classified as having adverse outcome*	*Non-selective reporting of outcomes*	*Any other systematic errors*
Chenoweth 2017	No	MODERATE‡ •Patients identified by CT head records only. •Some patients on DOACs may not have received a CT head scan. •Limited ability to obtain clinical information from electronic records.	LOW •Full inpatient follow up	HIGH† •Post discharge outcomes not collected.	LOW •No plausible other outcomes omitted	LOW •No other biases identified
Nishijima 2017a	No	MODERATE‡ • ICD-9 codes used that may not accurately identify all patients with blunt head injury. •Exclusion of 174 (7.6%; 173 for unmatched hospital data •Anticoagulant and antiplatelet use was determined according to ED and hospital documentation. It is possible that a variety of factors such as limited access to medication lists, language barriers, altered mental status, or dementia limited the ability of EMS providers to accurately ascertain medication use. •No information on DOACs in patients taking combination antiplatelets/anticoagulants	LOW •Full inpatient follow up	HIGH† •Post discharge outcomes not collected.	LOW •No plausible other outcomes omitted	LOW •No other biases identified

Nishijima; 2017b	No	HIGH‡ •49% of eligible patients were not enrolled. •Unmatched data exclusion n=52 •Prospective data collection with dedicated form •No information on DOACs in patients taking combination antiplatelets/anticoagulants	LOW •Full inpatient follow up	HIGH† •Post discharge outcomes not collected.	LOW •No plausible other outcomes omitted	LOW •No other biases identified
Riccardi 2017	No	UNCLEAR* •No details given on case identification •No details given on data collection	LOW •Complete follow up to 1 month	LOW •All patients received CT scan. •Post discharge outcomes collected	LOW •No plausible other outcomes omitted	LOW •No other biases identified
Spinola 2019	No	UNCLEAR* •No details given on case identification •Limited details given on data collection	UNCLEAR* •Limited details of telephone follow up provided.	LOW •Post discharge outcomes reported	LOW •No plausible other outcomes omitted	LOW •No other biases identified
Turcato 2019	No	HIGH‡ •No details given on case identification •Limited details given on data collection •Patients with no initial ED CT brain excluded •Patients with 'inadequate clinical details' excluded	UNCLEAR* •Limited details of follow up •7 patients lost at follow-up.	LOW •All patients received CT scan. •Post discharge outcomes collected	LOW •No plausible other outcomes omitted	LOW •No other biases identified

*Unknown direction of bias; †Bias likely to underestimate risk of adverse outcome; ‡ Bias likely to overestimate risk of adverse outcome