National Institute for Health and Care Excellence

Draft

Head Injury: assessment and early management (update)

[E] Evidence reviews for selecting adults, children and infants with head injury for CT or MRI head scan in sub-groups

NICE guideline <number>

Evidence reviews underpinning recommendations x to y and research recommendations in the NICE guideline

September 2022

Draft for Consultation

This evidence review was developed by Guideline Development Team NGC

Contents

1 Selecting adults, children and infants with head injury for CT or MRI head scan in sub-groups

1.1 Review question

What are the indications for selecting adults, young people, children and infants with head injury for CT or MRI head scan in a sub-group including:

- people on anticoagulant or antiplatelet therapy, including those with no history of amnesia or loss of consciousness

- people with liver or coagulopathy disorders

- people with pre-injury cognitive impairment sustaining injury through low level falls

- people sustaining recurrent head injuries through sport

- people presenting more than 24 hours after injury?

1.1.1 Introduction

The committee identified specific sub-groups of people that frequently suffer head injuries. This protocol has been developed in order to assess the evidence of risk of intracranial injury within each subgroup, as there may be specific factors that affect these groups.

It is possible that people taking pre-injury anticoagulant or antiplatelet medication are at increased risk of significant intracranial injury. After an evidence review CG176 extended the recommendations for CT brain scan within 8 hours of head injury to people taking warfarin with no other high or medium risk factors for intracranial injury, considerably increasing imaging requirements. In 2019 NICE extended this recommendation to people taking pre-injury Direct Oral Anticoagulants (DOACs). The cost effectiveness of these recommendation has been questioned. CG176 made no similar specific recommendations with regard to people taking pre head injury antiplatelet agents, low molecular weight heparin, or with pre-injury liver or coagulation conditions (due to lack of evidence at that time).

People with cognitive impairment are prone to falls and sustaining head injury; the Canadian CT head rules (which have informed current recommendations for CT brain in adults) identified patients with head injury aged 65 and over - with of loss of consciousness or amnesia - as having increased risk of intracranial injury compared to younger adults. However, in people with pre-injury cognitive impairment it can be challenging to assess whether a head injury has been associated with loss of consciousness or new amnesia. This can lead to frequent, and possibly unnecessary, CT brain scans in people who fall often. This is also a concern for people who sustain recurrent head injury with associated loss of consciousness or amnesia in the context of sport, where younger people are at increased lifetime risk from radiation exposure. Finally, studies suggest that up to 10% of people attending Emergency Departments and primary care after head injury present more than 24 hours after the injury was sustained. Current recommendations for imaging were based on studies that excluded these patients, and there was a need to clarify the evidence in this cohort of people.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	i) Inclusion: Infants, children and adult with suspected or confirmed head injury Strata: - people on anticoagulant or antiplatelet therapy, including those with no history of amnesia or loss of consciousness - people with liver or coagulopathy disorders - people with pre-injury cognitive impairment sustaining injury through low energy impact/ low level falls - people sustaining recurrent head injuries - people presenting more than 24 hours after injury Strata: • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • Infants (aged <1 year) Mixed population studies will be included but downgraded for indirectness. Cut-off of 60% will be used for all age groups Exclusion: Adults, young people and children (including infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury.
Prognostic variables under consideration	Clinical variables applicable to both infants, children and adults Clinical variables: People on anticoagulant or antiplatelet therapy, • Age (below 65 years and over 65 years for adults). There is no age-cut off children • Glasgow Coma Scale (GCS) (13 to 15)** • neurological injury severity* • Patient's blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels, platelet count To analyse anti-coagulants and anti-platelets analysed separately People with liver or coagulopathy disorders • Age (below 65 years and over 65 years for adults). There is no age-cut off children • GCS (13 to 15)** • neurological injury severity* • Patient's blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels • other indicators of presence and severity of pre-injury disease such as American Society of Anaesthesiology scale (ASA-PS), Charlson comorbidity index (CCI) or single disease grades such as severity of liver/Chronic kidney disease

	People with pre-injury cognitive impairment sustaining injury through low energy impact/ low level falls • Age (below 65 years and over 65 years for adults). There is no age-cut off children • GCS (13 to 15)** • neurological injury severity* • Patient's blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels, platelet count • other indicators of presence and severity of pre-injury disease such as American Society of Anaesthesiology scale (ASA-PS), Charlson comorbidity index (CCI) or single disease grades such as severity of liver/ Chronic kidney disease • indicators of frailty if available such as Rockwood Clinical Frailty Scale or Electronic Frailty Index (for adults only – not applicable for children) People sustaining recurrent head injuries • Age (below 65 years and over 65 years for adults). There is no age-cut off children • GCS (13 to 15)** • neurological injury severity* • Patient's blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels • other indicators of presence and severity of pre-injury disease such as American Society of Anaesthesiology scale (ASA-PS), Charlson comorbidity index (CCI) or single disease grades such as severity of liver/ Chronic kidney disease, platelet count • indicators of frailty if available such as Rockwood Clinical Frailty Scale or Electronic Frailty Index People presenting more than 24 hours after injury • Age (below 65 years and over 65 years for adults). There is no age-cut off children • GCS (13 to 15)** • neurological injury severity* • Patient's blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels, platelet count *High risk Markers of neurological injury severity (pupillary responses (usually both, one or no pupils are reactive), and/or other focal neurological deficits, ** according to current guidance in people with GCS less than or equal to 12 CT head scan is done within 2 hours of injury. People with GCS =15 would be discharged Neurological severity as risk factors in NICE 2014 recommendations such as loss of consciousness (LOC), amnesia, focal neurological signs, or seizure.
Confounding factors	Key confounders: Age GCS Other confounders: Neurological injury severity

	Blood measures of coagulopathy
Outcomes	• Any traumatic intracranial abnormality detected by CT or MR imaging or autopsy • Any intracranial abnormality that causes death, neurosurgical intervention or neuro critical care.
Study design	Cohort studies (prospective and retrospective) Systematic reviews and meta-analyses of the above Case-control studies will be excluded.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in [Developing NICE guidelines: the manual](). Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to [NICE's conflicts of interest policy]().

1.1.4 Prognostic evidence

1.1.4.1 Included studies

A search was conducted for prospective and retrospective cohort studies in a sub-group (people on anticoagulant or antiplatelet therapy, including those with no history of amnesia or loss of consciousness; people with liver or coagulopathy disorders; people with pre-injury cognitive impairment sustaining injury through low energy impact/ low level falls; people sustaining recurrent head injuries; people presenting more than 24 hours after injury) for investigating the association of the following factors (age, GCS, neurological injury severity, patient's blood measures, other indicators of presence and severity of pre-injury disease) reporting outcomes of any traumatic intracranial abnormality detected by CT or MR imaging or autopsy; and/or any intracranial abnormality that causes death, neurosurgical intervention or neuro critical care.

The scope question had overall population and all the sub-groups (people on anti-coagulants/anti-platelets, people with liver or coagulopathy disorders; people with pre-injury cognitive impairment sustaining injury through low energy impact/ low level falls; people sustaining recurrent head injuries; people presenting more than 24 hours after injury) within the same question. Clinical decision rules (CDR) used to select people for imaging are for the overall population is covered in a separate evidence review (Evidence review D). For the sub-groups it will be elements of the CDRs that predicts intracranial injury such as age, GCS, neurological injury but are not necessarily configured as a CDR, hence a separate question was drafted for these sub-groups.

Thirteen cohort studies (5 prospective and 7 retrospective) were included in the review [1, 4, 6, 9, 12, 15, 16, 18, 24, 27, 28, 35, 36] these are summarised in below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

<u>Population</u>

Twelve studies were in adults and one study in infants (less than 24 months). There was no evidence for children.

Five studies were in adults on anti-coagulants only; 5 studies were in adults on anticoagulants and anti-platelets; 2 studies were in adults fall from a standing position; and one study was in infants with late presentation (> 24 hours post- injury).

In the strata anti-coagulants only, all 5 studies (Cipriano, 2018, Mason 2017, Turcato 2019, Turcato 2022, Brewer 2011) included only users (no non-users in the studies).

In the strata anti-coagulants and anti-platelets, only one study (Nishijima 2013) included people on anti-coagulants and anti-platelets only (no non-users in the studies). Other 4 studies in this stratum (Galliazzo, 2019, Hall, 2019, Nishijima, 2018, Dunham, 2014) were mixed population [people with (users) and without anti-coagulants/anti-platelets (non -users)]. The proportion of users in the studies varied from 30-70%. These studies included use of anticoagulants/anti-platelets as variables along with other variables such as age, GCS etc in the analysis. Data was not stratified separately for users and non-users in these studies. As other variables/risk factors in these studies will be applicable to the overall population rather than just the population on anticoagulants/anti-platelets, outcomes for these variables were downgraded for population indirectness.

Two studies (Ahmed 2015 and De Witt 2020) in the strata fall from standing position (low energy impact/ low level falls) were in older adults. Participants in both studies were on anti-coagulants/anti-platelets. It was not clear from the papers if the participants had pre-injury cognitive impairment hence, they were downgraded for population indirectness.

In the strata for infants with delayed presentation, the study included infants presenting <24 hours and > 24 hours post-injury. Results were not presented separately for these 2 populations; hence the outcomes for the variables were downgraded for population indirectness.

There was no evidence for people with liver or coagulopathy disorders and people sustaining recurrent head injuries in adults. There was no evidence for any strata in children. In infants there was evidence only for infants with delayed presentation.

<u>Clinical variables/ risk factors and confounders</u>

No studies were excluded based on the variables they had included in the multivariate analysis as any multivariate analysis was considered acceptable.

Most studies adjusted for confounders, but some did not for the key confounders of age and GCS. Studies were downgraded for risk for bias if they were not adjusted for key confounders.

<u>Outcomes</u>

All studies reported outcomes specified in the protocol.

<u>Analysis</u>

All studies included in the review had performed some form of multivariate analysis, though the variables included, and number of variables included varied across studies.

Studies reporting only univariate results were not included for any of the risk factors.

No studies reported comparable clinical variables, adjusting the same confounding variables, and different definitions of outcomes that could be meta-analysed. Therefore, all outcomes will be considered individually.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E**.**

<u>Evidence from NICE 2014 guideline (GC 176)</u>

Review question: What is the best clinical decision rule for selecting adults, infants and children with head injury for CT head scan who have no history of amnesia or loss of consciousness who are on anticoagulant or antiplatelet therapy? (2014)

Anti-coagulant therapy

No clinical decision rules studies were identified. The guideline reported validation studies assessing clinical decision rules, some of which provided data relating to patients with coagulopathy as a risk factor. This is presented in the GRADE tables section.

Anti-platelet therapy

One study was identified, but evidence in a GRADE table was not reported in the guideline.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix I.

1.1.5 Summary of studies included in the prognostic evidence

Table 2: Summary of studies included in the evidence review

Adults

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
Anti-coagulants only						
Cipriano, 2018[6] Italy	n=206 Inclusion criteria: Age above 18 years old; (2) MTBI, defined as blunt head injury associated with a GCS score of 13–15 regardless of the presence of loss of consciousness (LOC) immediately after the injury; (3) Patients on oral anti-coagulants (OAT); (4) single patient visit at the ED for trauma. Age mean (SD): 81.53 (8.44) years GCS n (%) 15: 99.0% (204) 14: 1.0% (2)	Prospective observational study Multivariate logistic regression performed with a penalized approach	VKA (vitamin K antagonists) treatment (yes/no) Age	MV (multivariate) analysis: Age, gender, VKA (vitamin K antagonists) agent treatment, high-energy impact, trauma above the clavicles, LOC (loss of consciousness), PTA (post-traumatic amnesia), presence of fractures, low platelet count (<150,000/mm3)	Intracranial haemorrhage	Not adjusted for key of GCS

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
Mason, 2017 [24] AHEAD study UK	N= 3566 (aged ≥16 years) who had suffered blunt head injury and were currently taking warfarin. Age n (%) <60: 251 (7.1) 60 to 69: 313 (8.9) 70 to 79: 925 (26.2) 80 to 89: 1674 (47.4) 90 plus: 371 (10.5) GCS n (%) 15: 2871 (81.2) 14: 275 (7.8) 13: 23 (0.7) <13: 60 (1.7) Not recorded at site: 305 (8.6)	Retrospective observational study Multivariable analysis	neurological symptoms - headache, vomiting, amnesia and loss of consciousness	MV analysis: neurological symptoms – (headache, vomiting, amnesia and loss of consciousness), age, gender	Predictors (neurological outcomes) of death or neurosurgery resulting from the initial injury	Not adjusted for key confounder of GCS
Turcato 2019[36] Italy	n=451(n= 268 were on vitamin K antagonists (VKAs) and n=183 on direct oral anticoagulants (DOACs) Inclusion criteria: patients treated with anticoagulants, GCS score of 13–15, regardless of the presence of loss of	Retrospective observational study Comparison study of people on VKA agents (vitamin K antagonists)vs people on DOAC (direct oral anti-coagulants) agents	VKA (vitamin K antagonists) treatment (yes/no) GCS < 15	MV analysis: Pre-trauma conditions (previous neurosurgery high-energy impact, alcohol abuse, post-trauma symptoms (amnesia, loss of consciousness, post-trauma seizures, vomiting, GCS < 15, worsening headache, trauma beyond clavicles, presence of cranial fracture)	Intracranial haemorrhage	Study drop-out not explored, no adjustment for key confounder of age

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
	consciousness or amnesia immediately after the injury. Age median (IQR): 83 (78–88) years GCS: not stated Includes symptomatic and asymptomatic patients (not reported proportion)	Multivariable analysis				
Turcato 2022 [35] Italy	N= 3054 on oral anti-coagulant therapy (OAT). – direct oral anticoagulants (DOACs)- 1212 (39.7%); Vitamin K antagonists (VKA) 1842 (60.3%) Inclusion criteria: All patients in OAT who required an evaluation in the ED for mild TBI Age in years, median (IQR): 83 (77-88) GCS: not stated	Multi-centre retrospective observational study binary logistic regression was used for the multivariate model using the stepwise regression method	GCS<15	MV analysis: GCS<15, Major trauma dynamic, Previous neurosurgery, LOC (loss of consciousness) , Post-traumatic amnesia, veadache, visible trauma above the clavicle, focal neurological signs, post-traumatic vomiting	Intracranial haemorrhage	No adjustment for key confounder of age
Anti-coagulants and anti-platelets						
Brewer, 2011[4] USA	n=141 Inclusion criteria: included all trauma registry patients with	Retrospective observation study	Aspirin (yes/no) Clopidogrel (yes/no) Warfarin (yes/no)	MV analysis: Age, gender, loss of consciousness (LOC), presence of fracture, mechanism of injury (fall or	Positive CT finding	Not adjusted for key confounder GCS

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
	minor head injury who presented with a GCS score of 15 while taking clopidogrel or warfarin and underwent head CT. Age mean (range): 79 (36-101) years GCS: 15	Forward and backward unconditioned logistic regression analysis	Age international normalized ratio (INR) Partial thromboplastin time (PTT),	motor vehicle collision, evidence of trauma above the clavicles on physical examination, presentation international normalized ratio (INR) and Partial thromboplastin time (PTT), presence of fracture		
Dunham 2014[12] USA	n=198 (36% were antithrombotic-negative and 64% antithrombotic-positive) Inclusion criteria: age ≥60 years, fall from standing height or motor vehicular crash, physical evidence for head trauma (facial fracture, skull fracture, scalp soft tissue injury, facial soft tissue injury, or cervical spine injury), and trauma centre admission Age mean (SD): 78.46 (10) years Admission GCS 3–12 n (%): 15 (7.6)	Retrospective, consecutive observational study Comparison of antithrombotic-negative and antithrombotic-positive individuals Multivariable analysis	Antithrombotic agent status (yes/no) Warfarin status (yes/no)	MV analysis: Brain atrophy occurrence, composite brain atrophy, admission major neurologic dysfunction	Intracranial haemorrhage	No description of excluded patients, no accounting for participant drop-out, no adjustment for key confounders of age and GCS Population indirectness: mixed population (participants with and without anti-thrombotics)

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
Galliazzo, 2019[15] Italy	n=1846 (n=459 CT not performed; n=1387 CT performed) Adults presenting to the ED with TBI 1222 (66.2%) patients in group 1 (no antithrombotic therapy prior to the index event), 407 (22.0%) in group 2 (one antiplatelet agent), 120 (6.5%) in group 3 (VKAs- vitamin K antagonists), 51 (2.8%) in group 4 (DOACs- direct-acting oral anticoagulants;) and 46 (2.5%) in group 5 (double antithrombotic therapy). Age median (IQR): 71 (46 to 83) years GCS score n (%) 15: 1811 (98.1) 14: 29 (1.6) 13: 6 (0.3)	Retrospective observation study Multivariate logistic regression	Antiplatelet yes/no VKA (vitamin K antagonists) (yes/no) DOACs (yes/no) Age older than 65 years GCS score < 15	MV analysis: Age older than 65 years, any ongoing antithrombotic treatment, history of epilepsy, history of Transient ischaemic attack (TIA)/stroke/neurosurgery, history of cerebral neoplasia and drug/alcohol intoxication as patient baseline risk factors; GCS score < 15, LOC (loss of consciousness), amnesia, vomiting, neurological signs, seizure, headache, clinical signs of skull fracture, complicated contused lacerated wound, other scalp lesions	Intracranial haemorrhage	Adjusted for key confounders age and GCS Population indirectness: mixed population (participants with and without anti-coagulants/anti-platelets)
Hall, 2019[18]	n=173	Retrospective observation study	Antiplatelet or anticoagulant (yes/no)	MV analysis: Presence of intracranial haemorrhage on the initial head CT scan,	Mortality for 30-day, 6-month,	Not adjusted for key founders of age and GCS

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
USA	Adults presenting to ED with blunt trauma OAP (oral anti-platelets)/OAC (oral anti-coagulants) (n = 115) No OAP/OAC (n= 58) In the OAP group, 75 patients took aspirin and 25 patients took clopidogrel. In the OAC group, 22 patients took warfarin, 2 took rivaroxaban, 1 took dabigatran, and 1 took apixaban. Age mean (SD): 86.9 (5.0) years on antiplatelets or anticoagulants, 87.1 (4.7) years not on antiplatelets or anticoagulants GCS: not stated	Comparison of antiplatelet / anticoagulation agents vs no antiplatelet / anticoagulation agents Multivariate analysis		disposition from the ED, and patient-specific comorbidities	and overall mortality	Population indirectness: mixed population (participants with and without anti-coagulants/anti-platelets)
Nishijima 2013[28] USA	n=982 Inclusion criteria: adult (≥ 18 years old) ED	Prospective observational study	Clopidogrel use (yes/no)	MV analysis: Age 65 years or older, non-ground level fall mechanism of injury,	Intracranial haemorrhage	Not adjusted for key confounder of GCS

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
	patients with pre-injury warfarin or clopidogrel use (within the prior seven days) and mild blunt head trauma (initial ED Glasgow Coma Scale (GCS) score 13 to 15). Age mean (SD): 75.4 years (12.6) years Admission GCS: 13 to 15	Multivariate analysis	Warfarin use (yes/no) Age 65 years or older	headache, vomiting, LOC (loss of consciousness) or amnesia, drug or alcohol intoxication, evidence of trauma above the clavicles, abnormal mental status		
Nishijima, 2018 [27] USA	n=1140 Inclusion criteria: patients 55 years and older with head trauma who were transported to a hospital by the participating EMS agencies Four hundred thirty-four (33%) patients had anticoagulant or antiplatelet use and 112 (10%) had traumatic ICH.	Prospective observational study Random-effects multivariate logistic regression model	Any anticoagulant agent or antiplatelet agent use (yes/no) Age 80 years or older abnormal initial GCS (< 15)	MV analysis: Age 80 years or older gender, an abnormal initial GCS (< 15), a mechanism of injury other than a fall from standing height or less, a history of loss of consciousness or amnesia, evidence of trauma above the clavicles, vomiting, headache, presence of physiological, anatomical, or mechanism of injury were defined a priori	Intracranial haemorrhage	Adjusted for key confounders age and GCS Population indirectness: mixed population (participants with and without anti-coagulants/anti-platelets)

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
	Age median (IQR): 73 (63 to 84) years GCS n(%) 15: 1003 (77) 14: 203 (16) 13: 32 (2) <13: 58 (4)					
Fall from standing position						
Ahmed, 2015[1] USA	n=163 Inclusion criteria: Adult patients (>18 years of age) were included in this study if they fell from a standing position (FFS) and had a computed tomography (CT) scan of the head to evaluate their injuries. n=91 CT bleeding, n=72 no CT bleeding Age mean (SD) No CT bleeding: 64.4 (22.7) years; CT bleeding: 71.5 (17.9) years GCS mean (SD) CT positive: 13.4 (2.9) CT negative 13.6 (3.1)	Prospective observational study Comparison CT bleeding vs no CT bleeding Multiple logistic regression	Age	MV analysis: Age, aspirin, gender	Mortality	Not adjusted for the key confounder of GCS

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
De Wit 2020[9] Canada	n=1753 Inclusion criteria: Patient's aged 65 or older who presented to the ED within 48 hours of the fall on ground level, a fall from one or two steps, or a fall off the bed, patients were not required to have hit their head Age > 60 years Age median (IQR): 82 (75-88) years GCS n (%) 15: 1437 (82) 14: 211 (12) < 14: 51 (3) Missing 60 (3)	Prospective observational study Multivariable analysis	Anticoagulant agent use (yes/no) Antiplatelet agent use (yes/no) GCS reduced from normal	MV analysis: New abnormality on neurologic examination, head laceration or bruise, chronic kidney disease (CKD), GCS reduced from normal, cancer treated in past two years, liver disease, history of major bleed in last two years, male, hypertension, dementia loss of consciousness, previous stroke or transient ischaemic attack (TIA), diabetes, age congestive heart failure, anticoagulant therapy, and antiplatelet use.	Intracranial haemorrhage	No adjustment for key confounder of age

Children

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
Gelernter, 2018[16] Israel	n=344 cases (n=68 with late presentation) The study group included children with late presentation, i.e. 24 hours post-injury	Retrospective cohort study Comparison of early vs late	Duration from injury (< 24 hours vs > 24 hours) Age GCS	MV analysis: Age, gender, GCS, hematoma, duration of injury	Significant TBI on CT	Adjusted for key confounders age and GCS Population indirectness: mixed population

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Limitations
	The control group included children with early presentation, who underwent CT within 24 hours of their injury. Age mean (SD) late vs early presentation: 11.4 (5.6) vs 10.5 (7.0) months GCS < 15 n (%) late vs early presentation: 10 (15) vs 48 (18)	presentation (> 24 hours) Logistic regression model				(infants presenting with < and > 24 hours after injury)

See Appendix D for full evidence tables

1 ## 1.1.6 Summary of the prognostic evidence

2 **Adults**

3 **Table 3: Clinical evidence summary: People on anticoagulants only**

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Independent predictors for intra cranial haemorrhage in people on anticoagulant therapy (all participants on Vitamin K antagonists (**VKA) and Direct oral anti-coagulants (DOACs)**			
Vitamin K antagonists (VKA) therapy (yes)	N=451 (1 study) Turcato 2019 [e,f]	HIGH	OR 2.33 (95% CI 1.117 to 4.847)
Vitamin K antagonists (VKAs) treatment (yes)	n=206 (1 study) Cipriano,2018[c,d] first CT scan (performed within 6 h of presentation)	LOW[a] Due to risk of bias cannot assess imprecision	OR 3.364 (no CI reported)
Amnesia (yes)	N=451 (1 study) Turcato 2019 [e,f]	HIGH	OR 2.81 (95% CI 1.102 to 6.556)
Post-traumatic amnesia (PTA) (yes)	206 (1 study) Cipriano,2018 [c,d] first CT scan (performed within 6 h of presentation)	LOW[a] Due to risk of bias cannot assess imprecision	OR 2.570 (no CI reported)
Loss of consciousness (yes)	N=451 (1 study) Turcato 2019 [e,f]	HIGH	OR 5.29 (95% CI 1.102 to 25.348)
GCS score < 15 (yes)	N=451 (1 study) Turcato 2019 [e,f]	HIGH	OR 4.72 (95% CI 1.938 to 11.492)
GCS <15 (yes)	N=3054 Turcato 2022 [g,h]	HIGH	OR 3.056 (95% CI 2.216 to 4.213)
Predictors (neurological symptoms) of death or neurosurgery resulting from the initial injury- Compared with no symptoms. - people taking warfarin (in people with GCS 15) (all **participants** on warfarin)			
Amnesia (yes)	N= 2871 (1 study) Mason, 2017[i]	LOW[a] Due to risk of bias	RR 3.48 (95% CI 2.13 to 5.70)
Vomiting (yes)	N= 2871 (1 study) Mason, 2017 [i]	VERY LOW[a,b] Due to risk of bias and imprecision	RR 1.80 (95% CI 0.97 to 3.36)
Loss of consciousness (LOC) (yes)	N= 2871 (1 study) Mason, 2017 [i]	LOW[a] Due to risk of bias	RR 1.75 (95% CI 1.03 to 2.99)
Headache(yes)	N= 2871 (1 study) Mason, 2017 [i]	VERY LOW[a,b]	RR 1.30 (95% CI 0.76 to 2.22)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
		Due to risk of bias and imprecision	

(a) Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of evidence was at very high risk of bias. Risk of bias was identified for incomplete results

(b) Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)

(c) Cipriano 2018: MV analysis- Age, gender, VKA (vitamin K antagonists) agent treatment, high-energy impact, trauma above the clavicles, LOC, PTA (post-traumatic amnesia), presence of fractures, low platelet count (<150,000/mm3)

(d) Cipriano 2018: Class of OAT: 58.7% (121) VKA (vitamin K antagonists), 41.3% (85) DOAC (direct oral anticoagulants), 23 out of 206 patients showed immediate ICH's signs at the first CT scan (prevalence rate 11.2%, 95% CI 6.5–15.5%). Only 1 (0.5%, 95% CI 0.0–1.4%) died because of ICH; no one required neurosurgical intervention. There was increased incidence of intracranial complications after mild TBI in patients treated with vitamin K antagonists compared with those receiving DOACs (15.7 vs. 4.7%, RR 3.34, 95% CI 1.18–9.46, P<0.05)

(e) Turcato 2019: MV analysis: Pre-trauma conditions (previous neurosurgery high-energy impact, alcohol abuse, post-trauma symptoms (amnesia, loss of consciousness, post-trauma seizures, vomiting, VKA therapy, GCS < 15, worsening headache, trauma beyond clavicles, presence of cranial fracture)

(f) Turcato 2019: n=451 (n= 268 were on VKAs and n=183 on DOACs). DOAC-treated patients had a lower overall ICH rate compared with the VKA-treated patients. In fact, only 7.7% (14/183) of DOAC-treated patients presented overall bleeding compared with the 14.9% (40/268) of VKA-treated patients (p = 0.026), whereas early bleeding was present in 5.5% (10/183) of DOAC-treated patients compared with the 11.6% (31/268) of VKA-treated patients (p = 0.030). No difference was found for delayed bleeding (3.8 vs. 2.3, p = 0.570). Globally, 1.6% of patients (7/451) required neurosurgical treatment; 0.7% of the patients (3/451) died as a result of ICH. There was no difference between the DOAC and VKA treatment groups

(g) Turcato 2022: MV analysis- GCS< 15, major trauma dynamic, Previous neurosurgery, Post-traumatic TLOC, Post-traumatic amnesia, Headache, Visible trauma above the clavicle, Focal neurological signs, Post-traumatic vomiting

(h) Turcato 2022: DOACs 1212 (39.7%); VKA 1842 (60.3%). post-traumatic ICH occurred in 9.5% of patients (290/3054) on OAT. 1.4% (43/3054) of patients underwent neurosurgery or died within 30 days as a result of ICH

(i) Mason 2017: MV analysis: neurological symptoms – (headache, vomiting, amnesia and loss of consciousness), age, gender

Table 4: Clinical evidence summary: anti-coagulants and anti-platelets

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Predictors of immediate traumatic intracranial haemorrhage- People on anticoagulant or antiplatelet (all participants on anticoagulant or antiplatelet therapy)			
Clopidogrel use (yes)	N=982 (1 study) Nishijima 2013[i,j]	VERY LOW[a,b] Due to risk of bias and imprecision	OR 1.68 (95% CI 0.19 to14.72)
Warfarin use (yes)	N=982 (1 study) Nishijima 2013[i,j]	VERY LOW[a,b] Due to risk of bias and imprecision	OR 0.62 (95% CI 0.070 to 5.49)
Vomiting (yes)	N=982 (1 study) Nishijima 2013[i,j]	LOW[a] Due to risk of bias	OR 3.68 (95% CI 1.55 to 8.76)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Abnormal mental status (yes)	N=982 (1 study) Nishijima 2013 [i,j]	LOW [a] Due to risk of bias	OR 3.08 (95% CI 1.60 to 5.94)
Headache (yes)	N=982 (1 study) Nishijima 2013 [i,j]	VERY LOW [a,b] Due to risk of bias and imprecision	OR 1.60; 95% CI 0.93 to 2.77)
Predictors of acute intra cranial bleeding complications (overall sample)-[anti-thrombotic therapy + people not on anti-thrombotic therapy in Galliazzo 2019 and anti-coagulant+antiplatelet in Nishijima 2018]			
Antithrombotic drug Antiplatelet (yes)	N=1846 (1 study) Galliazzo, 2019[d,e]	LOW[b] Due to imprecision	OR 1.93 (95% CI 0.98 to 3.80)
Antithrombotic drug Vitamin K antagonists (VKA) (yes)	N=1846 (1 study) Galliazzo, 2019 [d,e]	LOW[b] Due to, imprecision	OR 1.58 (95% CI 0.55 to 4.54)
Antithrombotic drug Direct oral anti-coagulants (DOACs) (yes)	N=1846 (1 study) Galliazzo, 2019 [d,e]	LOW[b] Due to imprecision	OR 1.54 (95% CI 0.33 to 7.16)
Antithrombotic drug Double therapy (yes)	N=1846 (1 study) Galliazzo, 2019	LOW[b] Due to imprecision	OR 2.11 (95% CI 0.51 to 8.67)
Any anticoagulant or antiplatelet use (yes)	N=1140 (1 study) Nishijima, 2018[k,l]	LOW[b] Due to imprecision	OR 1.53 (95% CI 0.99 to 2.38)
Age ≥65 years vs ≤65 years	N=1846 (1 study) Galliazzo, 2019 [d,e]	VERY LOW[b,c] Due to imprecision, indirectness	OR 1.89 (95% CI 0.92 to 3.87)
Age 80 years or older vs younger than 80	N=1140 (1 study) Nishijima, 2018 [k,l]	VERY LOW[b,c] Due to imprecision, indirectness	OR 1.53 (95% CI 0.96 to 2.43)
GCS <15 vs GCS >15	N=1846 (1 study) Galliazzo, 2019 [d,e]	VERY LOW[b,c] Due to imprecision, indirectness	OR 7.95 (95% CI 3.12 to 20.28)
Abnormal EMS GCS score, initial: [GCS score <15 vs GCS >15	N=1140 (1 study) Nishijima, 2018 [k,l]	LOW [c] Due to indirectness	OR 2.06 (95% CI 1.27 to 3.35)
Loss of consciousness (yes)	N=1846 (1 study) Galliazzo, 2019 [d,e]	VERY LOW[b,c] Due to imprecision, indirectness	OR 1.31 (95% CI 0.42 to 4.04)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Loss of consciousness or amnesia (yes)	N=1140 (1 study) Nishijima, 2018 [k,l]	LOW [c] Due to indirectness	OR 1.63 (95% CI 1.02 to 2.61)
Amnesia (yes)	N=1846 (1 study) Galliazzo, 2019 [d,e]	LOW[c] Due to indirectness	OR 6.49 (95% CI 3.57 to 11.82)
Neurological signs (yes)	N=1846 (1 study) Galliazzo, 2019	LOW[b,c] Due to imprecision, indirectness	OR 1.04 (95% CI 0.09 to 11.56)
Seizure (yes)	N=1846 (1 study) Galliazzo, 2019 [d,e]	LOW[c] Due to indirectness	not estimable
Headache (yes)	N=1846 (1 study) Galliazzo, 2019 [d,e]	LOW[c] Due to indirectness	OR 1.11 (95% CI 0.13 to 9.4)
History of headache (yes)	N=1140 (1 study) Nishijima, 2018 [k,l]	VERY LOW[b,c] Due to imprecision , indirectness	OR 1.11 (95% CI 0.44 to 2.76)
Vomiting (yes)	N=1846 (1 study) Galliazzo, 2019 [d,e]	LOW[c] Due to indirectness	OR 4.45 (95% CI 1.47 to 13.50)
History of vomiting (yes)	N=1140 (1 study) Nishijima, 2018 [k,l]	LOW [c] Due to indirectness	OR 6.65 (95% CI 2.61 to 16.96)
History of epilepsy (yes)	N=1846 (1 study) Galliazzo, 2019 [d,e]	VERY LOW[b,c] Due to imprecision, indirectness	OR 2.46 (95% CI 0.51 to 11.79)
Predictors for intracranial bleedings. only patients with CT performed. n=1387 CT performed - people on anti-thrombotic therapy + people not on anti-thrombotic therapy			
Antithrombotic drug Antiplatelet (yes)	n=1387 (1 study) Galliazzo, 2019 [d,e]	LOW[b] Due to imprecision	OR 1.70 (95% CI 0.87 to 3.33)
Antithrombotic drug Vitamin K antagonists (VKA) (yes)	n=1387 (1 study) Galliazzo, 2019 [d,e]	LOW[b] Due to imprecision	OR 1.33 (95% CI 0.47 to 3.77)
Antithrombotic drug Direct oral anti-coagulants (DOACs)	n=1387 (1 study)	LOW[b]	OR 1.28 (95% CI 0.28 to 5.88)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
(yes)	Galliazzo, 2019 [d,e]	Due to imprecision	
Antithrombotic drug Double therapy (yes)	n=1387 (1 study) Galliazzo, 2019 [d,e]	LOW[b] Due to imprecision	OR 1.84 (95% CI 0.46 to 7.44)
Age ≥65 vs ≤65	n=1387 (1 study) Galliazzo, 2019 [d,e]	VERY LOW[b,c] Due to imprecision, indirectness	OR 1.38 (95% CI 0.67 to 2.83)
GCS score <15 vs >15	n=1387 (1 study) Galliazzo, 2019 [d,e]	VERY LOW[b,c] Due to imprecision, indirectness	OR 6.69 (95% CI 2.67 to 16.77)
Loss of consciousness (yes)	n=1387 (1 study) Galliazzo, 2019 [d,e]	VERY LOW[b,c] Due to imprecision, indirectness	OR 1.10 (95% CI 0.36 to 3.37)
Amnesia (yes)	n=1387 (1 study) Galliazzo, 2019 [d,e]	VERY LOW[b,c] Due to imprecision, indirectness	OR 5.62 (95% CI 3.07 to 10.26)
Neurological signs (yes)	n=1387 (1 study) Galliazzo, 2019 [d,e]	VERY LOW[b,c] Due to imprecision, indirectness	OR 0.92 (95% CI 0.09 to 9.92)
Seizure (yes)	n=1387 (1 study) Galliazzo, 2019 [d,e]	LOW[,c] Due to indirectness	not estimable
Headache (yes)	n=1387 (1 study) Galliazzo, 2019 [d,e]	VERY LOW[b,c] Due to imprecision, indirectness	OR 0.91 (95% CI 0.10 to 8.02)
Vomiting (yes)	n=1387 (1 study) Galliazzo, 2019 [d,e]	LOW[,c] Due to indirectness	OR 4.33 (95% CI 1.43 to 13.11)
History of epilepsy (yes)	n=1387 (1 study) Galliazzo, 2019 [d,e]	VERY LOW[b,c] Due to imprecision, indirectness	OR 2.15 (95% CI 0.45 to 10.25)
Predictors of 30-day mortality - oral antiplatelet and oral anticoagulant + not on oral antiplatelet and oral anticoagulant			
Oral antiplatelet and oral anticoagulant (OAP/OAC) (yes)	N=173(1 study) Hall 2019 [f,g,h]	VERY LOW[a,b,c] Due to risk of bias, imprecision, indirectness	HR 1.5 (95% CI 0.5 to 5.3)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Predictors of 6-month mortality- oral antiplatelet and oral anticoagulant + not on oral antiplatelet and oral anticoagulant			
Higher Rockwood score (yes)	N=173(1 study) Hall 2019 [f,g,h]	VERY LOW[a,,c] Due to risk of bias, indirectness	HR 1.8 (95% CI 1.3 to 2.4)
oral antiplatelet and oral anticoagulant (OAP/OAC) (yes)	N=173(1 study) Hall 2019 [f,g,h]	VERY LOW[a,b,c] Due to risk of bias, imprecision, indirectness	HR 0.8 (95% CI 0.4 to 1.5)
Predictors of overall mortality- oral antiplatelet and oral anticoagulant + not on oral antiplatelet and oral anticoagulant			
Higher Rockwood score (yes)	N=173(1 study) Hall 2019 [f,g,h]	VERY LOW[a,c] Due to risk of bias, indirectness	HR 1.6 (95% CI 1.3 to 2.0)
Oral antiplatelet and oral anticoagulant (OAP/OAC) (yes)	N=173(1 study) Hall 2019[f,g,h]	VERY LOW [a,b,c] Due to risk of bias, imprecision, indirectness	HR 0.9 (95% CI 0.5 to 1.4)

(a) Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of evidence was at very high risk of bias. Risk of bias was identified for study confounding - not adjusted for key confounders (age, GCS)

(b) Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)

(c) Downgraded by 1 increment for population indirectness. Mixed population with and without anti-coagulants/anti-platelets.

(d) Galliazo 2019: MV analysis: Age older than 65 years, any ongoing antithrombotic treatment, history of epilepsy, history of TIA/stroke/neurosurgery, history of cerebral neoplasia and drug/alcohol intoxication as patient baseline risk factors; GCS score < 15, LOC, amnesia, vomiting, neurological signs, seizure, headache, clinical signs of skull fracture, complicated contused lacerated wound, other scalp lesions.

(e) Galliazo 2019: 1222 (66.2%) patients on no antithrombotic therapy prior to the index event), 407 (22.0%) on one antiplatelet agent), 120 (6.5%) on (VKAs), 51 (2.8%) on DOACs) and 46 (2.5%) on double antithrombotic therapy). Among patients who underwent brain CT, 68 (4.9% CI 95%: 3.9–6.2) had acute intracranial bleeding: 36 (4.6%; 95% CI: 3.2–6.3) in group no antithrombotic therapy prior to the index event, 22 (5.7%; 95% CI: 3.6–8.5) in group on one antiplatelet agent, 5 (4.2%; 95% CI: 1.4–9.5) in group on VKAs, 2 (3.9%; 95%: 0.5–13.5) in group on VKAs and DOACs and (7.0%; 95%CI: 1.5–19.1) in group on double antithrombotic therapy. Intracranial bleeding prevalence was similar among patient groups. None of the intracranial bleeding lesions required a neurosurgical treatment. Overall, only 1 patient died. He was on dabigatran (DOACs).

(f) Hall 2019: MV analysis: Presence of intracranial haemorrhage on the initial head CT scan, disposition from the ED, and patient-specific comorbidities

(g) Hall 2019: OAP/OAC (n = 115); no OAP/OAC (n= 58). In the OAP group, 75 patients took aspirin and 25 patients took clopidogrel. In the OAC group, 22 patients took warfarin, 2 took rivaroxaban, 1 took dabigatran, and 1 took apixaban.
Delayed intracranial haemorrhage did not occur in any patient discharged from the ED after the initial fall. However, 28 patients were readmitted to the hospital within 30 days of their sentinel fall, for an overall readmission rate of 17.5% (95% confidence interval [CI], 11.4–23.2). This group had a higher 6-month mortality (43%) than the group that did not get readmitted (16%, P=0.01).

(h) Hall 2019 (Rockwood score): Frailty was assessed retrospectively using the Rockwood Frailty Score, also known as the Canadian Study of Health and Aging Clinical Frailty Scale.15 All patients were assigned a frailty number (from 1, very fit, to 7, severely frail) based on functional data from the initial history and physical, progress notes, physical and occupational therapist notes, rehabilitation assessment, impact of comorbidities on independence, and ability to complete or perform activities of daily living. As an example, a score of 4, apparently vulnerable, is defined as those who are not frankly dependent but commonly complain of being slowed down or having disease symptoms, and a score of 7, moderately frail, describes those who require help with both instrumental and non-instrumental activities of daily living.

(i) Nishijima 2013: MV analysis: Age 65 years or older, non-ground level fall mechanism of injury, headache, vomiting, LOC or amnesia, drug or alcohol intoxication, evidence of trauma above the clavicles, abnormal mental status

(j) Nishijima 2013:
Warfarin use n (%): 714 (72.7)
Clopidogrel use n (%): 279 (28.4)
Concomitant aspirin use n (%): 45 (4.6)
There were 60 patients (6.1%; 95% CI = 4.7% to 7.8%) with the primary outcome of immediate traumatic ICH (t ICH) diagnosed on initial ED cranial CT. None of the 65 patients who did not receive initial ED cranial CT scans were later diagnosed with immediate tICH, although two patients were lost to follow-up. Of the 60 patients diagnosed with immediate tICH, there were 12 patients (20.0%; 95% CI = 10.8% to 32.3%) who received neurosurgical interventions

(k) Nishijima 2018: MV analysis: Age 80 years or older gender, an abnormal initial GCS (< 15), a mechanism of injury other than a fall from standing height or less, a history of loss of consciousness or amnesia, evidence of trauma above the clavicles, vomiting, headache, presence of physiological, anatomical, or mechanism of injury were defined a priori

(l) Nishijima 2018: Of the patients receiving a cranial CT scan, there were 112 (9.8%) with a traumatic ICH and 22(1.9%) with in-hospital neurosurgery or death due to trauma. Four hundred and thirty-four of 1304 patients (33.3%) had anticoagulant or antiplatelet use. There was no difference in the incidence of traumatic ICH in patients with (47/434; 10.8%, 95% CI 8.1%– 14.1%) and without (65/713; 9.1%, 95% CI 7.1%–11.5%) anticoagulant or antiplatelet use. There was also no difference in the incidence of in-hospital neurosurgery or death due to trauma in patients with (6/434; 1.4%, 95% CI 0.5%–3.0%) and without (16/713; 2.2%, 95% CI 1.3%–3.6%) anticoagulant or antiplatelet use. The incidence of traumatic ICH and in-hospital neurosurgery or death due to trauma also did not differ when compared across specific anticoagulant or antiplatelet medications.

Table 5: Clinical evidence summary: NICE guideline 2014 (CG 176)

Intracranial lesions in coagulopathy patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Coagulo-pathy	No coagulo-	Relative (95% CI)	Absolute		
Univariate analysis of coagulopathy versus non-coagulopathy in patients who would not have been scanned by NICE 2003 guideline, but were scanned according to NCWFNS proposal (follow-up 7 days)(g)[83]												
1[83]	Observational	Serious risk of bias(a,b,c)	No serious inconsistency	No serious indirectness	No serious imprecision	None	16/66 (24.2%)	24/435 (5.5%)	OR 5.48 (2.73 to 11.0)	-	Low	CRITICAL
Univariate analysis of coagulopathy versus non-coagulopathy in patients without loss of consciousness or amnesia (follow-up 7 days) (g)[81]												
1[81]	Observational	Serious risk of bias(a,b)	No serious inconsistency	No serious indirectness	No serious imprecision	None	25/83 (30.1%)	517/7872 (6.6%)	OR 6.1 (3.8 to 9.9)	-	Low	CRITICAL
Univariate analysis of coagulopathy versus non-coagulopathy. (follow-up 7 days) (g)[81]												
1[81]	Observational	Serious risk of bias(a,b)	No serious inconsistency	Serious indirectness(f)	No serious imprecision	None	67/265 (25.3%)	474/7690 (6.2%)	OR 5.1 (3.8 to 6.9)	-	Very low	CRITICAL
Multivariate analysis(d) of coagulopathy versus non-coagulopathy. (follow-up 7 days) (g)[81]												
1[81]	Observational	Serious risk of bias(a)	No serious inconsistency	Serious indirectness(f)	No serious imprecision	None	67/265 (25.3%)	474/7690 (6.2%)	Adjusted OR 8.4 (5.5 to	-	Very low	CRITICAL
Univariate analysis of coagulopathy versus non-coagulopathy in patients with loss of consciousness or amnesia. (follow-up 7 days) (g)[81]												
1[81]	Observational	Serious risk of bias(a,b)	No serious inconsistency	Serious indirectness(f)	No serious imprecision	None	42/182 (23.1%)	500/7773 (6.4%)	OR 4.4 (3.1 to 6.2)	-	Very low	CRITICAL
Multivariate analysis(e) of coagulopathy versus no coagulopathy in patients with loss of consciousness or amnesia. (follow-up 7 days) (g)[81]												

1[81]	Observational	Serious risk of bias[(a)]	No serious inconsistency	Serious indirectness[(f)]	No serious imprecision	None	42/182 (23.1%)	500/7773 (6.4%)	Adjuste d OR 4.8 (2.6 to	-	Very low	CRITICAL

(a) Post-hoc analysis of prospectively collected data relating to a cohort of 7955 mild head injury patients. Some patients were excluded from the eligible 9464 patients because of unclear history of trauma as the primary event (n=559), refusal of diagnostic and management procedures (n=235).Some of these patients may have been anticoagulated patients without loss of consciousness or amnesia.

(b) Univariate analysis.

(c) Also reports a further 1235/7955 patients excluded from the analysis for a variety of reasons (numbers not reported). Some of these patients may have been anticoagulated patients without loss of consciousness or amnesia.

(d) Multivariate stepwise logistic regression analysis. Variables included in analysis are risk factors used in the NCWFNS as indicators for a CT scan.

(e) Multivariate stepwise logistic regression analysis. Variables included in analysis are risk factors used in the NICE guideline (2003 version) as indicators for a CT scan.

(f) The population is not directly applicable. The effect size is reported to illustrate that all patients using warfarin have a large increased risk of developing intracranial lesions regardless of whether they have loss of consciousness or amnesia.

(g) Patients were followed for 7 days after trauma; later events were not considered in the paper’s analysis. The GDG agreed this was a suitable follow-up period for this question. All patients using warfarin were scanned according to the NCWFNS proposal.

Table 6: Clinical evidence summary: People with pre-injury cognitive impairment sustaining injury through low energy impact/ low level falls (fall from standing position)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Risk factors associated with the diagnosis of intracranial bleed (ICB) after a fall from a standing position			
Use of aspirin (gender was adjusted) Vs no aspirin use	N= 163 (1 study) Ahmed, 2015[d,e]	VERY LOW[a,c] Due to risk of bias, indirectness	OR 2.17, 95 % CI [1.06 to 4.60]
Anticoagulation therapy (yes)	N=1753 (1 study) De Wit 2020[f,g]	VERY LOW[a,b,c] Due to risk of bias and imprecision, indirectness	OR 0.87 (95% CI 0.48 to 1.59)
Antiplatelet therapy (yes)	N=1753 (1 study) De Wit 2020 [f,g]	VERY LOW[a,b,c] Due to risk of bias and imprecision, indirectness	OR 1.07 (95% CI 0.64 to 1.79)
Age ≥70 years (not adjusted for gender) vs age ≤70 years	N= 163 (1 study) Ahmed, 2015 [d,e]	VERY LOW[a,b,c] Due to risk of bias and imprecision, indirectness	OR 1.80, 95 % CI (0.85 to 3.90)
Age ≥70 years (gender was adjusted) vs age ≤70 years	N= 163 (1 study) Ahmed, 2015 [d,e]	VERY LOW[a,c] Due to risk of bias, indirectness	OR 2.67, 95 % CI (1.36 to 5.39)
Age, per year (All included patients above 65 years or older)	N=1753 (1 study) De Wit 2020 [f,g]	VERY LOW[a,b,c] Due to risk of bias and imprecision, indirectness	OR 0.98 (95% CI 0.96 to 1.01)
Reduced GCS compared to normal (yes)	N=1753 (1 study) De Wit 2020 [f,g]	VERY LOW[a,c] Due to risk of bias, indirectness	OR 1.9 (95% CI 1.0 to 3.4)
Loss of consciousness (yes)	N=1753 (1 study) De Wit 2020 [f,g]	VERY LOW[a,b,c] Due to risk of bias and imprecision, indirectness	OR 1.03 (95% CI 0.55 to 1.94)
Vomited after the fall (yes)	N=1753 (1 study) De Wit 2020 [f,g]	VERY LOW[a,b, c] Due to risk of bias and imprecision, indirectness	OR 1.46 (95% CI 0.57 to 3.71)

(a) Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of evidence was at very high risk of bias. Risk of bias was identified for study confounding - not adjusted for key confounders (age, GCS)

(b) Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)

(c) Downgraded by 1 increment for population indirectness Population were older fallers, it was not clear if they had pre-injury cognitive impairment

(d) Ahmed 2015: MV analysis: Age, aspirin, gender

(e) Ahmed 2015: Mortality: Twelve patients with ICB died (13.2 %, 95 % exact CI [7.0 %, 21.9 %]). This mortality rate was not significantly different from those patients who had no ICB (9.7 %, 95 % exact CI [4.0 %, 19.0 %])

(f) De wit 2020: MV analysis: New abnormality on neurologic examination, head laceration or bruise, CKD, GCS reduced from normal, cancer treated in past two years, liver disease, history of major bleed in last two years, male, hypertension, dementia loss of consciousness, previous stroke or TIA, diabetes, age congestive heart failure, anticoagulant therapy, and antiplatelet use.
(g) De wit 2020: 88 (5%) had ICH (76 at index ED visit and 12 during 42 day follow-up)

Infants

Table 7: Clinical evidence summary: Infants with late presentation (> 24 hours post-injury)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Variables associated with increased risk for significant TBI on CT in children with late presentation (> 24 hours + < 24 hours post-injury) [Significant TBI on CT includes any of the following descriptions: any intracranial bleeding, pneumocephalus, cerebral oedema, skull fracture depressed by at least the thickness of skull, or diastasis of the skull]			
Age, months Older age vs younger age (no cut-off specified) Mean age months: 11.4 (5.6)	N= 344(1 study) Gelernter, 2018d,e	LOW[c] Due to indirectness	OR 0.91 (95% CI 0.86 to 0.96)
GCS<15 vs GCS >15	N=344 (1 study) Gelernter, 2018 d,e	LOW[c] Due to indirectness	OR 5.88 (95% CI 2.69 to 13.02)
Duration from injury >24 hours vs duration <24 hours	N=68 (1 study) Gelernter, 2018 d,e	LOW[b] Due to imprecision	OR 1.63 (95% CI 0.79 to 3.44)
Variables associated with increased risk for any TBI on CT in children with late presentation (> 24 hours + < 24 hours post-injury) **[any TBI on CT as any finding on CT related to the injury (e.g. linear skull fracture)]**			
Age, months Older age vs younger age (no cut-off specified)	N=344 (1 study) Gelernter, 2018 d,e	LOW[c] Due to indirectness	OR 0.90 (95% CI 0.86 to 0.94)
GCS<15 vs GCS >15	N=344 (1 study) Gelernter, 2018 d,e	LOW[c] Due to indirectness	OR 2.44 (95% CI 1.17 to 5.26)
Duration from injury >24 hours vs duration <24 hours	N=344 (1 study) Gelernter, 2018 d,e	HIGH	OR 2.77 (95% CI 1.40 to 5.55)

(a) Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of evidence was at very high risk of bias. Risk of bias was identified for study confounding- not adjusted for key confounders (age, GCS)
(b) Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)
(c) Downgraded by 1 increment for population indirectness. Mixed population with infants < and > 24 hours after injury.
(d) Gelernter 2018: MV analysis: Age, gender, GCS, hematoma, duration of injury
(e) There were no significant differences between the groups in the incidence of significant TBI (22% vs 19%, p = 0.61), clinically important TBI and neurosurgery intervention. Any TBI on CT were found in 43 (63%) patients with late presentation compared with 116 (42%) patients with early presentation (p = 0.002, OR 2.37, 95% CI 1.37–4.1). There was no significant difference in hospitalisation duration between children with late and early presentation (mean 2.5 (SD 2.4) days vs 2.3 (SD 3.3) days, p = 0.84). There was borderline significant difference in intensive care unit admission between the groups (15% vs 26%, p = 0.057, OR 0.47 (CI 0.23–0.98)).

Narrative results: (Incomplete data reported in the papers)

Brewer, 2011 (very low-quality evidence) [anti-coagulants only]

Population: n=141

People with a GCS score of 15 while taking clopidogrel or warfarin and underwent head CT.

Outcome: Predictors of positive CT finding

Loss of consciousness (LOC) (Wald = 7.468, β= 1.179, p = 0.008) was the only predictor for a positive CT result. motor vehicle collision (MVC) as a mechanism of injury (Wald = 3.580, β= 1.404, p = 0.058) showed a trend toward significance.

Age, gender, presenting INR and PTT, external evidence of injury above the shoulders, and type of medication (warfarin, aspirin, or clopidogrel) did not reach statistical significance (data not reported)

Dunham 2014 (very low-quality evidence) [anti-coagulants and anti-platelets]

Population: n=198 (36% were antithrombotic (AT)-negative and 64% antithrombotic-positive) Patients with signs of external head trauma and age ≥60 years.

Outcome: Predictors of intercranial haemorrhage (ICH)

Multivariate analysis showed that intercranial haemorrhage (ICH) correlated with composite brain atrophy (p < 0.0001), but not antithrombotic agent status (p = 0.9293) (n = 192 antithrombotic positive or AT-negative patients).

ICH correlated with composite brain atrophy (p < 0.0001), but not platelet inhibitor agent status (p = 0.3205) (n = 143 antithrombotic -negative or platelet inhibitor-positive patients). ICH correlated with composite brain atrophy (p < 0.0001), but not warfarin status (p = 0.2733) (n = 114 antithrombotic negative or warfarin-positive patients). ICH had an independent association with composite brain atrophy (p < 0.001) and admission major neurologic dysfunction (p < 0.001), but not antithrombotic status (p = 0.9774) or age (p = 0.8566).

Multivariate logistic regression analysis indicated that ICH neurologic complications were independently associated with admission major neurologic dysfunction (p < 0.001) and ICH (p = 0.0218), but not antithrombotic status (p = 0.8953). ICH-neurologic complications were independently associated with admission major neurologic dysfunction (p > 0.001) and ICH (p = 0.0202), but not with platelet inhibitor-status (p = 0.7055). ICH-neurologic complications were independently associated with admission major neurologic dysfunction (p < 0.001) and ICH (p = 0.0209), but not with warfarin-status (p = 0.7219). In the 72 patients with ICH, the ICH-neurologic complication rate was similar for the antithrombotic -negative (17.4% [4/23]) and antithrombotic -positive (20.4% [10/49]; p = 1.0) groups.

Multivariate logistic regression analysis, ICH-neurologic complication was independently associated with admission major neurologic dysfunction (p < 0.001) and ICH (p = 0.0216), but not with antithrombotic -positive status (p = 0.9966) or coagulation intervention (p = 0.4160).

1.1.7 Economic evidence

1.1.7.1 Included studies

One health economic study with the relevant comparison was included in this review. [21] This is summarised in the health economic evidence profile below (Table 8) and the health economic evidence table in Appendix G.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix F.

1.1.8 Summary of included economic evidence

Table 8: Health economic evidence profile: CT scan vs no CT scan

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Kuczawski 2016[21] (UK)	Directly applicable [(a)]	Potentially serious limitations [(b)]	• Patient-level simulation model based on UK observational data • Cost-utility analysis (QALYs) • Population: People with head injury who were taking warfarin and presented to a hospital emergency department (ED) but with no amnesia or loss of consciousness • Comparators: 1. CT scan 2. No CT scan	Intervention 2 costs £250[(c)] more than intervention 1	Intervention 2 gives 0.0022 more QALYs than intervention 1	£111,600 per QALY gained	Threshold analysis: 58% of the inpatient attendances (<48 hours) would need to be avoided for intervention 2 to be cost effective (£30,000 threshold) Deterministic analyses increased GOS by 1 in those who survive and use different expert opinion for the treatment effects. Results remained robust in all analysis.

Abbreviations: CT = Computed tomography; GOS = Glasgow outcome scale; QALYs= quality-adjusted life years.
(a) UK NHS perspective.
(b) Relative treatment effects were estimated through expert opinion only and not through published trials or evidence arguably as there was no direct evidence available. The patient-level simulation model was based on a very small number of patients who did not receive CT and that would have benefited from CT: four who died and three that were re-admitted with a positive CT. Probabilistic analysis was not conducted. The population was people taking warfarin only so the results may not be transferable to people under other anticoagulative treatment. There were errors in the published calculations (personal communication Matthew Stevenson (14th July 2022)
(c) 2014 UK pounds [30]. Cost components incorporated: CT scan, neurosurgery, long-term care by GOS state. Admission was included but only in a threshold sensitivity analysis.

1.1.9 Economic model

1.1.9.1 Model specification

Population: Adults with mild head injury who were on warfarin and have no other indication for head CT scan (i.e. without amnesia or loss of consciousness).

Comparison: Head CT vs no Head CT

Outcomes: NHS cost, Quality-adjusted life-years (QALYs), Cost per QALY gained.

For model details see Appendix H.

1.1.9.3 Model results

The cost per QALY gained was greater than £20,000 in the base case analysis (Table 9) but was below £20,000 per QALY when alternative treatment effects were assumed. (Table 10).

Table 9: Health economic evidence profile: CT vs No CT for people on warfarin with minor head injury

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
NICE Methods and Economics Team 2022	Directly applicable	Minor limitations	• Patient simulation based on Kuczawski 2016 • Cost-utility analysis (QALYs) • Population: People on warfarin with minor head injury Time horizon: lifetime	£201[(a)]	0.0027 QALYs	£73,639 per QALY gained	The model was subject to various scenario analyses. The cost effectiveness varied from dominant (using an alternative treatment effect size) to £112,000 (using alternative unit costs and utilities).

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial
(a) 2021/22 UK pounds. Cost components incorporated: CT scan plus long-term care costs (primary and secondary care) by Glasgow Outcome Scale category.

1 **Table 10: Sensitivity analyses (deterministic)**

Analysis	Patients with an intracranial abnormality Immediate vs Delayed surgery			Skull fracture population CT vs No CT			Reduction in admissions required for CT to be cost effective	
	Incr Cost*	Incr QALYs*	Cost per QALY	Incr Cost	Incr QALYs	Cost per QALY	£20,000 per QALY	£30,000 per QALY
Base case (Probabilstic)	£23,156	0.59	£38,925	£201	0.0029	£68,966	54%	43%
Base case (Deterministic)	£23,177	0.59	£38,972	£202	0.0029	£69,010	54%	43%
Effect size (Base case=Kuczawski 2016[21])								
Effects from Pandor 2011	-£44,518	1.621	Dominant	-£131	0.0080	Dominant	N/A	N/A
Effects from Deverill 2007	£2,031	0.774	£2,625	£98	0.0038	£25,717	8%	N/A
Effects from Haselsberger 1988	-£11,607	3.301	Dominant	£31	0.0163	£1,895	N/A	N/A
Effects from Lecky 2016	-£4,731	1.010	Dominant	£65	0.0050	£12,997	N/A	N/A
Effects from Smits 2010	-£16,177	1.952	Dominant	£8	0.0096	£864	N/A	N/A
Effects from Kuczawski 2016 + additional improvement in GOS	£7,992	0.939	£8,511	£127	0.0046	£27,534	13%	N/A
Incidence of intracranial abnormality (Base case=0.49%)								
1%	£23,177	0.595	£38,972	£320	0.0059	£53,779	75%	53%
2%	£23,177	0.595	£38,972	£552	0.0119	£46,376	>100%	73%
5%	£23,177	0.595	£38,972	£1,247	0.0297	£41,934	>100%	>100%
Parameters from Kuczawski 2016[21]								
Kuczawski 2016 Costs	£33,839	0.595	£56,900	£259	0.0029	£88,281	63%	54%
Kuczawski 2016 Utilities	£23,177	0.500	£46,361	£202	0.0025	£82,094	57%	48%
Kuczawski 2016 Costs and utilities	£33,839	0.500	£67,688	£259	0.0025	£105,019	66%	59%

2 * For base case calculations see in Appendix H.

The first few columns of Table 10 show the change in outcomes as a result of earlier surgery for each patient that has an intracranial abnormality. These figures are then combined with the cost of a CT scan and the incidence of abnormalities to estimate the mean outcomes for CT vs No CT. In the base case analysis, the cost per QALY gained for CT was £69,000. When the incidence of an abnormality is increased the cost per QALY decreases but it does not drop below £20,000 per QALY. However, using four of the alternative measures of effect for immediate versus delayed surgery, the cost per QALY was below £20,000 and with the other two measures of treatment effect, a quite modest reduction in admission rate would be sufficient for the cost to be less than £20,000 per QALY gained.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Code	Description	Unit cost
RD01A	Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over	£146.75
RD01B	Magnetic Resonance Imaging Scan of One Area, without Contrast, between 6 and 18 years	£215.63
RD01C	Magnetic Resonance Imaging Scan of One Area, without Contrast, 5 years and under	£140.83
RD20A	Computerised Tomography Scan of One Area, without Contrast, 19 years and over	£88.06
RD20B	Computerised Tomography Scan of One Area, without Contrast, between 6 and 18 years	£159.25
RD20C	Computerised Tomography Scan of One Area, without Contrast, 5 years and under	£104.27
PF	Plain Film (including x-ray)	£28.62

Direct access costs from NHS Reference costs: 2019-2020 version 2

1.1.11 Evidence statements

Economic

- Two cost–utility analysis, including one original analysis, found that selecting a CT scan was not cost effective compared to no CT scan in a subgroup of people on warfarin with minor head injury but with no amnesia or loss of consciousness (ICERs: £111,600 and £69,000 per QALY gained respectively). However, they were very sensitive to assumptions about the effectiveness of immediate versus delayed surgery. These analyses were assessed as directly applicable with potentially serious limitations.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee considered all outcomes as equally important for decision making and therefore they have all been rated as critical: any traumatic intracranial abnormality detected by CT or MR imaging or autopsy and any intracranial abnormality that causes death, neurosurgical intervention or neuro critical care.

The majority of the studies reported predictors of intracranial abnormality; however, the outcome definition varied across studies. One study reported predictors of outcome death or neurosurgery and another study reported predictors of mortality at 30 days, 3 months and 6 months.

1.1.12.2 The quality of the evidence

There was evidence from thirteen studies- twelve studies were in adults and one study in infants (less than 24 months). There was no evidence for children.

Evidence was stratified as: adults on anti-coagulants only (5 studies); adults on anticoagulants and anti-platelets (5 studies); adults falling from a standing position (2 studies); and infants with late presentation (> 24 hours post- injury) (one study).

In the stratum with anti-coagulants only, all 5 studies included only users (no non-users in the studies). In the stratum with anti-coagulants and anti-platelets, only one study included people on anti-coagulants and anti-platelets only (no non-users in the studies). Other 4 studies in this stratum were mixed population [people with (users) and without anti-coagulants/anti-platelets (non -users)]. The proportion of users in the studies varied from 30-70%. These studies included use of anticoagulants/anti-platelets as variables along with other variables such as age, GCS etc in the analysis. Data was not stratified separately for users and non-users in these studies. As other variables/risk factors in these studies will be applicable to the overall population rather than just the population on anticoagulants/anti-platelets, outcomes for these variables were downgraded for population indirectness.

In the stratum for infants with delayed presentation, the study included infants presenting < and > 24 hours post-injury. Data was not stratified separately for these 2 populations; hence, the outcomes for the variables were downgraded for population indirectness.

Two studies in the stratum on fall from a standing position (low energy impact/ low level falls) were in older adults. It was not clear from the papers if the participants had pre-injury cognitive impairment; hence, they were downgraded for population indirectness.

There was no evidence for people with liver or coagulopathy disorders, people sustaining recurrent head injuries and delayed presentation in adults. There was no evidence for any strata in children. In infants there was evidence for infants <24 months with delayed presentation.

The quality of outcomes ranged between high to very low based on GRADE. Outcomes were commonly downgraded for risk of bias and indirectness, with some outcomes being downgraded for imprecision. Outcomes were commonly downgraded for risk of bias due to study confounding, some studies adjusted for key confounders age and GCS and a few adjusted for other confounder blood measures of coagulopathy. None of the studies adjusted for other confounder neurological injury severity. The majority of included studies were deemed to have indirect evidence. The reasons for this included population indirectness (mixed population including users and non-users for anti-coagulants/anti-platelets, no pre-injury cognitive impairment in low energy fallers and mixed population presenting <24 hours and > 24 hours post-injury). Studies were downgraded for imprecision if the confidence intervals crossed the null line.

The committee took into account the quality of the evidence, including the uncertainty in their interpretation of the evidence.

As studies were not comparable (including different clinical variables, not adjusting the same confounding variables, and different definitions of outcomes) no outcomes were meta-analysed and instead the outcomes from each study were reported separately.

1.1.12.3 Benefits and harms

<u>People on anticoagulant or antiplatelet therapy</u>

In adults only on anti-coagulants, limited evidence suggested that vitamin K antagonists, neurological symptoms (amnesia, loss of consciousness, headache, vomiting), GCS<15 were predictors of intracranial haemorrhage. Evidence from one study suggested that in people with GCS=15, neurological symptoms (amnesia, loss of consciousness, headache, vomiting) were predictors of death or neurosurgery. There was variation in the effect size for the risk factors. The committee acknowledged that some uncertainty existed across the effect sizes seen within the evidence.

In adults with head injury on anti-coagulants or anti-platelets (including users and non-users), the evidence suggested that clopidogrel, vitamin K antagonists, direct oral anticoagulant (DOACs), anti-platelet therapy, dual therapy (anti-coagulant and anti-platelet), GCS< 15, abnormal mental status, neurological signs and symptoms (vomiting, headaches, loss of consciousness, amnesia), older age (age > 65 years and age > 80 years from 2 studies), epilepsy/seizure, were predictors of intracranial haemorrhage. Warfarin was associated with low risk for predicting immediate intracranial haemorrhage. In adults with head injury on anti-coagulants or anti-platelets (including users and non-users) the evidence suggested that oral anti-platelet and anti-coagulant therapy were predictors of 30-day mortality; oral anti-platelet and anti-coagulant therapy and higher Rockwood score were predictors of 6-month mortality and higher Rockwood score was predictor of overall mortality. The committee acknowledged that some uncertainty existed across the effect sizes seen within the evidence.

There was no evidence for risk factors of neurological injury severity and blood measures of coagulopathy including INR.

The majority of the studies in this stratum were in a mixed population (users and non-users); hence, there is limited applicability of risk factors to people on anti-coagulants/anti-platelets. There was no evidence available for heparin (anti-coagulants) and aspirin (anti-platelets). There was no sufficient evidence according to drug class to make separate recommendations for these (anti-coagulants- warfarin, direct oral anticoagulant (DOACs), unfractionated heparin, low molecular weight heparin; antiplatelet-aspirin, platelet activation inhibitors e.g., clopidogrel/prasugrel).

In current practice, in accordance with the NICE 2014 recommendations CG 176, a CT scan is performed within 8 hours of injury in adults and children who have sustained a head injury with no other indications for a CT head scan and who are having anticoagulant treatment. The current strategy of scanning all people on anti-coagulants was not found to be cost-effective. The committee thought that the new evidence was not strong enough to warrant stopping scanning people with head injury who are on anticoagulants but have no other indication for imaging. However, they decided to weaken the recommendation from ‘offer’ to ‘consider’. They also agreed that antiplatelets should be included. Based on their experience and extrapolation of evidence in people presenting within 8 hours of injury the committee agreed that these recommendations could be applicable to people presenting after 8 hours injury, however imaging should be done within an hour of confirming that the person with head injury is anticoagulated.

NICE 2014 (CG 176) did not make specific recommendations for people on anti-platelets. In clinical practice there is variation with some services offering imaging to people on anti-platelets.

The majority of the studies in the review were in a mixed population (symptomatic and asymptomatic). Evidence suggested that asymptomatic people on anti-coagulants/anti-platelets are at lower risk of intracranial haemorrhage. Based on the evidence, CT scan could be limited to those with symptoms of traumatic brain injury such as loss of consciousness or amnesia. However, the committee thought that the new evidence was not strong enough to warrant stopping imaging in people with a head injury who are on anticoagulants but have no other indication for imaging. So, they decided CT scanning should be considered rather than automatically done in this group. Based on the evidence they also agreed that antiplatelets other than aspirin monotherapy should be included. The review findings suggested that people on anticoagulants (including warfarin and direct oral anticoagulants (DOACs)) or antiplatelets (excluding people on aspirin monotherapy) with low risk factors (no loss of consciousness, amnesia, GCS=15 and no other indications for CT brain scan) can be risk assessed (including other injuries, supervision at home, cause of incident and risk of further falls) and discharged safely without CT scan after shared decision making. The committee noted that the predominant purpose of scanning is in assisting with decisions on withholding anticoagulants/antiplatelets rather than a reason to consider neurosurgical intervention. This often generates a lot of anxiety for referrers and patients. The decision is often complex decisions and may need multidisciplinary discussion.

The committee highlighted that the clinician would either scan or admit someone for monitoring if any risks were identified - for example if a person (with pre-existing cognitive impairment) may be less likely to return to emergency department urgently if there were any signs of deterioration. The committee noted that if an intracranial haemorrhage was not detected at initial presentation this is more likely to result in delayed recovery rather than mortality. The committee also discussed that neurosurgical intervention for TBI is less likely to be offered in older adults (over 74 years) due to the risks outweighing the benefits.

The committee did not list specific antiplatelets in the recommendation as they did not want to be prescriptive and exclude any newer antiplatelets in development.

There was limited evidence on aspirin and from their knowledge and clinical experience the committee highlighted that the risk of intra cranial haemorrhage is low with this medication even in people with neurological symptoms such as loss of consciousness or amnesia. Hence, they agreed that people on aspirin monotherapy could be discharged without CT after shared decision making if there is no other indication for a CT brain scan or hospital admission.

There are certain cohorts who would benefit from CT scan, e.g., nursing home residents. The majority of these people would have conditions like dementia and may under-report symptoms. Hence it may be difficult to engage in shared decision making with this group of people.

Some people with low risk factors (no loss of consciousness, amnesia) may need admission irrespective of whether a CT scan is performed. These reasons may be due to other injuries (fractured ankle, wrist) or co-morbidities (e.g., atrial fibrillation).

There was no evidence for infants and children for anticoagulants or antiplatelets. In clinical practice use of anticoagulants/anti-platelets in children is much rarer. A very small subgroup have inborn errors of coagulation deficiency, which are genetic and will sometimes have other conditions such as low platelet counts. DOACs (anticoagulant) and aspirin (antiplatelet) are the most commonly used medications in children. However, due to the risk of Reye's Syndrome aspirin is avoided in children. Indications for aspirin use in children is mainly due to cardiac conditions or systemic inflammatory conditions.

There was no evidence in infants/children and no direct evidence for people on anticoagulants and antiplatelets, hence the committee drafted research recommendation to inform future guidance.

The committee discussed the importance of reversal of the effects of anticoagulants and antiplatelets. For advice on reversing warfarin and direct-acting oral anticoagulants (DOACs) for people with suspected traumatic intracranial haemorrhage, a recommendation was included to cross-refer to the NICE’s guideline on blood transfusion and NICE’s technology appraisal guidance on andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban. Anticoagulant or antiplatelet reversal would only be considered if there is intracranial haemorrhage on CT scan.

<u>People with liver or coagulopathy disorders</u>

There was no evidence for people with liver or coagulopathy disorders.

Current practice is variable, with some services offering imaging to people with liver disease who have no symptoms.

People with liver disease can sometimes have normal haemostasis as the pro- and anti-coagulant abnormalities balance out; however, sometimes these people are at high risk of bleeding especially with thrombocytopenia which can be quite severe and <50x10*9/l.

People with acquired coagulation defects can be a heterogenous and complex group and can include people with acquired haemophilia through to people with other abnormalities such as Disseminated intravascular coagulation (DIC). People with liver or coagulopathy disorders are at increased risk of bleeding, although some people will have thea tendency for increased clotting.

There was no evidence to make new recommendations.

The committee agreed to keep the existing recommendations in from the 2014 update of NICE's head injury guideline (CG 176) for people with bleeding and clotting disorders as there was no new evidence to change practice (rec 1.4.8 and 1.4.10). However, they changed the recommendation wording from 'history of bleeding or clotting disorders' to 'current bleeding or clotting disorders'. In children, some disorders are short-lived/resolve in a couple of months. In adults, a history of bleeding or clotting disorders is used to help screen people before surgery. However, this is a crude tool and may not be appropriate in this setting. Hence, the committee agreed to keep the changed wording for all age groups to help provide a consistent message.

Due to the lack of evidence, the committee agreed to draft a research recommendation to identify risk factors for people with liver and coagulopathy disorders.

People with pre-injury cognitive impairment sustaining injury through low energy impact/ low level falls

Limited evidence suggested that in adults falling from a standing position; age> 70 years, reduced GCS compared to normal, antiplatelet therapy, aspirin, neurological symptoms (loss of consciousness, vomiting after fall) were risk factors associated with the diagnosis of intracranial bleed. Anticoagulant therapy in this population was not associated with intracranial bleed. It was not clear if people in the studies had pre-injury cognitive impairment hence the applicability of this evidence is limited. The committee also acknowledged that some uncertainty existed across the effect sizes seen within the evidence.

Reasons for pre-injury cognitive impairment are different for adults and children. Examples of pre-injury cognitive impairment in children and adults include autism, Down syndrome, cerebral palsy, developmental delay, foetal alcohol syndrome, learning disability. Examples of pre-injury cognitive impairment seen only in adults include depression, dementia, medication side effects. There was no evidence available for any of these populations.

Frail older adults with cognitive impairment are at higher risk of head injury from low-energy falls.

The committee discussed the challenges in assessing risk in people with cognitive impairment. For example, people with dementia may under report or may be unaware of symptoms such as loss of consciousness or amnesia. It is also difficult to differentiate head injury symptoms from the pre-existing dementia in these people.

There was no evidence for infants and children.

The committee acknowledged the limited evidence for this group. They agreed to draft a research recommendation for people with pre-injury impairment with low energy falls where loss of consciousness or amnesia is difficult to assess or where pre-injury GCS is not 15.

People sustaining recurrent head injuries

There was no evidence for people sustaining recurrent head injuries in infants, children and adults. Recurrent head injuries could occur inpeople with epilepsy, people with mobility issues at high risk of falls and with some sports activities. Particularly in the context of sports injuries, these can be repeated and lead to cumulative risks to the individual.

Due to lack of evidence, the committee decided to make a research recommendation to identify risk factors for people with a history of recurrent head injuries including sports and falls and no other indications for CT scan according to existing NICE 2014 recommendations in CG 176.

<u>People presenting more than 24 hours after injury</u>

Evidence from one study in infants < 24 months suggested that younger age, GCS < 15, and duration of injury more than 24 hours were associated with increased risk of any TBI or significant TBI on CT.

There was no evidence for adults and children.

The committee discussed that adults presenting more than 24 hours after injury have increased risk factors such as vomiting, loss of consciousness etc, as they would be attending due to worsening of symptoms.

The committee noted that there would be concerns of non-accidental injury (NAI) particularly in children when presenting more than 24 hours after injury. In clinical practice, if there is any suspicion of NAI, a CT scan is performed regardless of GCS. Current NICE guidance for 'suspected child maltreatment' does not include guidance on imaging.

Currently, there is no guidance for people presenting more than 24 hours after injury. However, in practice those presenting more than 24 hours with symptoms like impaired conscious level, headache, or vomiting will get a CT scan.

Due to lack of evidence, the committee did not make any new recommendations for this group. NICE 2014 recommendations in CG 176 are for people presenting within 24 hours of injury. The committee agreed that these existing recommendations could be extrapolated to people presenting >24 hours after injury (recs 1.4.7 to 1.4.11). These recommendations are applicable to adults, children and infants.

The committee discussed that this was an important area, so a research recommendation was proposed, alongside extrapolation of the existing recommendations for people presenting more than 24 hours of injury.

1.1.12.4 Cost effectiveness and resource use

The committee were presented with the unit cost to the NHS of a short hospital stay for head injury to aid their deliberations.

<u>People on anticoagulant or antiplatelet therapy</u>

A single published economic model was found. This study estimated the impact of CT scanning for people with a head injury who are on warfarin therapy but have no other indication for imaging. Based on an incidence of adverse events of 0.5% and using expert opinion for health improvement, they estimated that CT scanning this population would cost £111,600 per QALY gained, although this was assuming that scanning did not reduce the number of admissions. The committee were concerned that the health improvement for people experiencing an adverse event was estimated by expert opinion retrospectively assessing a sample of just 7 adverse events. They also thought it likely that scanning would lead to a reduction in admissions.

The guideline health economist reconstructed this model and conducted further sensitivity analyses. Alternative unit costs and utilities were tried, and the prevalence of injury increased but the cost per QALY gained was still higher than £20,000. However, when the assumed improvement in patient outcomes for those experiencing an adverse event was increased in the model, the cost per QALY gained was below £20,000 per QALY gained, especially if there was a reduction in admissions.

The committee concluded that the cost effectiveness of CT scanning in this population is uncertain. They thought that the new clinical and economic evidence was not strong enough to cease all scanning of people with head injury who are on anticoagulants. However, they decided to weaken the guidance from offer to consider. They also made a research recommendation.

There was no clinical or economic evidence for people on antiplatelet therapy, but because the risk of having an adverse event was similar the committee included this population within the recommendations.

<u>People with liver or coagulopathy disorders</u>

There was no clinical or economic evidence for this question, so the committee made a research recommendation.

<u>People with pre-injury cognitive impairment sustaining injury through low energy impact/ low level falls</u>

No economic evaluations were found for this question. The clinical evidence was very limited, so the committee made a research recommendation.

<u>People sustaining recurrent head injuries</u>

There was no clinical or economic evidence for this question, so the committee made a research recommendation.

<u>People presenting more than 24 hours after injury</u>

No economic evaluations were found for this question. There was some clinical evidence that people presenting later than 24 hours have at least as high a risk of intracranial injury as those presenting within 24 hours.

The committee decided that the recommendations for imaging people within 24 hours should be extended to people arriving later. Although this has not been explicit in the guideline previously, it is thought that this does not represent a significant change in practice. This should be cost effective given that the evidence suggested a significant risk of intracranial injury.

Given the limitations of the clinical evidence, the committee also made a research recommendation for this population.

1.1.12.5 Other factors the committee took into account

None.

1.1.14 References

1. Ahmed N, Soroush A, Kuo YH, Davis JM. Risk associated with traumatic intracranial bleed and outcome in patients following a fall from a standing position. European Journal of Trauma and Emergency Surgery. 2015; 41(3):307-311

2. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in Health. 2010; 13(5):509-518

3. Beecham J, Perkins M, Snell T, Knapp M. Treatment paths and costs for young adults with acquired brain injury in the United Kingdom. Brain Injury. 2009; 23(1):30-38

4. Brewer ES, Reznikov B, Liberman RF, Baker RA, Rosenblatt MS, David CA et al. Incidence and predictors of intracranial hemorrhage after minor head trauma in patients taking anticoagulant and antiplatelet medication. Journal of Trauma-Injury Infection & Critical Care. 2011; 70(1):E1-5

5. Cheung PS, Lam JM, Yeung JH, Graham CA, Rainer TH. Outcome of traumatic extradural haematoma in Hong Kong. Injury. 2007; 38(1):76-80

6. Cipriano A, Pecori A, Bionda AE, Bardini M, Frassi F, Leoli F et al. Intracranial hemorrhage in anticoagulated patients with mild traumatic brain injury: significant differences between direct oral anticoagulants and vitamin K antagonists. Internal and Emergency Medicine. 2018; 13(7):1077-1087

7. Cook RJ, Dorsch NW, Fearnside MR, Chaseling R. Outcome prediction in extradural haematomas. Acta Neurochirurgica. 1988; 95(3-4):90-94

8. Cordobes F, Lobato RD, Rivas JJ, Munoz MJ, Chillon D, Portillo JM et al. Observations on 82 patients with extradural hematoma. Comparison of results before and after the advent of computerized tomography. Journal of Neurosurgery. 1981; 54(2):179-186

9. de Wit K, Parpia S, Varner C, Worster A, McLeod S, Clayton N et al. Clinical predictors of intracranial bleeding in older adults who have fallen: A cohort study. Journal of the American Geriatrics Society. 2020; 68(5):970-976

10. Department of Health and Social Care. NHS reference costs 2017/18. 2018. Available from: https://webarchive.nationalarchives.gov.uk/ukgwa/20200501111106/https://improvement.nhs.uk/resources/reference-costs/ Last accessed: 07/07/2022.

11. Deverill J, Aitken LM. Treatment of extradural haemorrhage in Queensland: interhospital transfer, preoperative delay and clinical outcome. Emergency Medicine Australasia. 2007; 19(4):325-332

12. Dunham CM, Hoffman DA, Huang GS, Omert LA, Gemmel DJ, Merrell R. Traumatic intracranial hemorrhage correlates with preinjury brain atrophy, but not with antithrombotic agent use: a retrospective study. PLoS ONE [Electronic Resource]. 2014; 9(10):e109473

13. Formby AP, Cookson R, Halliday S. Cost analysis of the legal declaratory relief requirement for withdrawing Clinically Assisted Nutrition and Hydration CANH) from patients in the Permanent Vegetative State (PVS) in England and Wales. 2015.

14. Fuller GW, Pattani H, Yeoman P. The nottingham head injury register: A survey of 1,276 adult cases of moderate and severe traumatic brain injury in a british neurosurgery centre. Journal of the Intensive Care Society. 2011; 12:29 - 36

15. Galliazzo S, Bianchi MD, Virano A, Trucchi A, Donadini MP, Dentali F et al. Intracranial bleeding risk after minor traumatic brain injury in patients on antithrombotic drugs. Thrombosis Research. 2019; 174:113-120

16. Gelernter R, Weiser G, Kozer E. Computed tomography findings in young children with minor head injury presenting to the emergency department greater than 24h post injury. Injury. 2018; 49(1):82-85

17. Gerlach R, Dittrich S, Schneider W, Ackermann H, Seifert V, Kieslich M. Traumatic epidural hematomas in children and adolescents: outcome analysis in 39 consecutive unselected cases. Pediatric Emergency Care. 2009; 25(3):164-169

18. Hall C, Essler S, Dandashi J, Corrigan M, Munoz-Maldonado Y, Juergens A et al. Impact of frailty and anticoagulation status on readmission and mortality rates following falls in patients over 80. Baylor University Medical Center Proceedings. 2019; 32(2):181-186

19. Haselsberger K, Pucher R, Auer LM. Prognosis after acute subdural or epidural haemorrhage. Acta Neurochirurgica. 1988; 90(3-4):111-116

20. Hernandez A, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. 2022. Available from: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d

21. Kuczawski M, Stevenson M, Goodacre S, Teare MD, Ramlakhan S, Morris F et al. Should all anticoagulated patients with head injury receive a CT scan? Decision-analysis modelling of an observational cohort. BMJ Open. 2016; 6(12):e013742

22. Lecky F, Russell W, Fuller G, McClelland G, Pennington E, Goodacre S et al. The Head Injury Transportation Straight to Neurosurgery (HITS-NS) randomised trial: a feasibility study. Health Technology Assessment. 2016; 20(1):1-198

23. Lee EJ, Hung YC, Wang LC, Chung KC, Chen HH. Factors influencing the functional outcome of patients with acute epidural hematomas: analysis of 200 patients undergoing surgery. Journal of Trauma. 1998; 45(5):946-952

24. Mason S, Kuczawski M, Teare MD, Stevenson M, Goodacre S, Ramlakhan S et al. AHEAD Study: an observational study of the management of anticoagulated patients who suffer head injury. BMJ Open. 2017; 7(1):e014324

25. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated January 2022]. London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction

26. NHS England and NHS Improvement. National Cost Collection Data Publication 2019-2020. London. 2020. Available from: https://www.england.nhs.uk/wp-content/uploads/2021/06/National-Cost-Collection-2019-20-Report-FINAL.pdf

27. Nishijima DK, Gaona SD, Waechter T, Maloney R, Blitz A, Elms AR et al. The incidence of traumatic intracranial hemorrhage in head-injured older adults transported by EMS with and without anticoagulant or antiplatelet use. Journal of Neurotrauma. 2018; 35(5):750-759

28. Nishijima DK, Offerman SR, Ballard DW, Vinson DR, Chettipally UK, Rauchwerger AS et al. Risk of traumatic intracranial hemorrhage in patients with head injury and

preinjury warfarin or clopidogrel use. Academic Emergency Medicine. 2013; 20(2):140-145

29. Office for National Statistics. National life tables – life expectancy in the UK: 2018 to 2020. 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/latest Last accessed: 07/07/2022.

30. Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP). 2012. Available from: http://www.oecd.org/std/ppp Last accessed: 7/7/2022.

31. Pandor A, Goodacre S, Harnan S, Holmes M, Pickering A, Fitgerald P et al. Diagnostic management strategies for adults and children with minor head injury: a systematic review and an economic evaluation. Health Technology Assessment. 2011; 15(27):1-283

32. Pandor A, Goodacre S, Harnan S, Holmes M, Pickering A, Fitzgerald P et al. Diagnostic management strategies for adults and children with minor head injury: a systematic review and an economic evaluation. Health Technology Assessment (Winchester, England). 2011; 15(27):1-202

33. Smits M, Dippel DW, Nederkoorn PJ, Dekker HM, Vos PE, Kool DR et al. Minor head injury: CT-based strategies for management - a cost-effectiveness analysis. Radiology. 2010; 254(2):532-540

34. Smits M, Hunink MG, van Rijssel DA, Dekker HM, Vos PE, Kool DR et al. Outcome after complicated minor head injury. AJNR: American Journal of Neuroradiology. 2008; 29(3):506-513

35. Turcato G, Cipriano A, Park N, Zaboli A, Ricci G, Riccardi A et al. "Decision tree analysis for assessing the risk of post-traumatic haemorrhage after mild traumatic brain injury in patients on oral anticoagulant therapy". BMC Emergency Medicine. 2022; 22(1)

36. Turcato G, Zannoni M, Zaboli A, Zorzi E, Ricci G, Pfeifer N et al. 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. The Journal of emergency medicine. 2019; 57(6):817-824

37. Ward Fuller G, Hernandez M, Pallot D, Lecky F, Stevenson M, Gabbe B. Health state preference weights for the Glasgow outcome scale following traumatic brain injury: A systematic review and mapping study. Value in Health. 2017; 20(1):141-151

38. Williams J, Roberts I, Shakur-Still H, Lecky FE, Chaudhri R, Miners A. Cost-effectiveness analysis of tranexamic acid for the treatment of traumatic brain injury, based on the results of the CRASH-3 randomised trial: a decision modelling approach. BMJ Global Health. 2020; 5(9)

1 # Appendices

2 ## Appendix A – Review protocols

3 **Review protocol for Indications for selecting adults, children and infants with head injury for CT or MRI head scan in a sub-group**

ID	Field	Content
0.	PROSPERO registration number	CRD42021283534
1.	Review title	2.1(b) What are the indications for selecting adults, children and infants with head injury for CT or MRI head scan in a sub-group including - people on anticoagulant or antiplatelet therapy, including those with no history of amnesia or loss of consciousness - people with liver or coagulopathy disorders - people with pre-injury cognitive impairment sustaining injury through low level falls - people sustaining recurrent head injuries through sport - people presenting more than 24 hours after injury?
2.	Review question	2.1 b What are the indications for selecting adults, children and infants with head injury for CT or MRI head scan, including: - people on anticoagulant or antiplatelet therapy, including those with no history of amnesia or loss of consciousness - people with liver or coagulopathy disorders

		- people with pre-injury cognitive impairment sustaining injury through low energy impact/ low level falls - people sustaining recurrent head injuries - people presenting more than 24 hours after injury?
3.	Objective	To determine which clinical variables (age, GCS, neurological injury severity, blood measures of coagulopathy) in a sub-group population are associated with any intracranial abnormality on CT/MRI or autopsy.
4.	Searches	The following databases (from inception) will be searched: [Amend if required] • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies • Letters and comments excluded Other searches: • Inclusion lists of systematic reviews

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Head Injury
6.	Population	i) Inclusion: Infants, children and adult with suspected or confirmed head injury Strata: - people on anticoagulant or antiplatelet therapy, including those with no history of amnesia or loss of consciousness - people with liver or coagulopathy disorders - people with pre-injury cognitive impairment sustaining injury through low energy impact/ low level falls - people sustaining recurrent head injuries - people presenting more than 24 hours after injury Strata: • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • Infants (aged <1 year) Mixed population studies will be included but downgraded for indirectness. Cut-off of 60% will be used for all age groups

		Exclusion: Adults, and children (including infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury. Evidence for people on anticoagulant and antiplatelet therapy should be reported separately (anticoagulant + antiplatelet as strata). Cognitive impairment not to include intoxication. Those whose GCS won't return to 15. Typically, older people but not excluding other populations with cognitive impairment. People sustaining recurrent head injuries to include recurrent sports-related head injury Delayed presentation to represent >24hr to 7 days (downgrade data >7days)
7.	Eligibility criteria – clinical variables/factors	Clinical variables applicable to both infants, children and adults Clinical variables: **People on anticoagulant or antiplatelet therapy** • Age (below 65 years and over 65 years for adults). There is no age-cut off children • GCS (13 to 15) • neurological injury severity* • Patient's blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels, platelet count To analyse anti-coagulants and anti-platelets analysed separately **People with liver or coagulopathy disorders** • Age (below 65 years and over 65 years for adults). There is no age-cut off children • GCS (13 to 15)

		• neurological injury severity* • Patient's blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels • other indicators of presence and severity of pre-injury disease such as American Society of Anaesthesiology scale (ASA-PS), Charlson comorbidity index (CCI) or single disease grades such as severity of liver/ Chronic kidney disease **People with pre-injury cognitive impairment sustaining injury through low energy impact/ low level falls** • Age (below 65 years and over 65 years for adults). There is no age-cut off children • GCS (13 to 15) • neurological injury severity* • Patient's blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels, platelet count • other indicators of presence and severity of pre-injury disease such as American Society of Anaesthesiology scale (ASA-PS), Charlson comorbidity index (CCI) or single disease grades such as severity of liver/ Chronic kidney disease • indicators of frailty if available such as Rockwood Clinical Frailty Scale or Electronic Frailty Index (for adults only – not applicable for children) **People sustaining recurrent head injuries** • Age (below 65 years and over 65 years for adults). There is no age-cut off children • GCS (13 to 15) • neurological injury severity* • Patient's blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels

		• other indicators of presence and severity of pre-injury disease such as American Society of Anaesthesiology scale (ASA-PS), Charlson comorbidity index (CCI) or single disease grades such as severity of liver/ Chronic kidney disease, platelet count • indicators of frailty if available such as Rockwood Clinical Frailty Scale or Electronic Frailty Index **People presenting more than 24 hours after injury** • Age (below 65 years and over 65 years for adults). There is no age-cut off children GCS (13 to 15) • neurological injury severity* • Patient's blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels, platelet count To make a note in the review: • if studies have included people with no history of amnesia or loss of consciousness. • duration of follow-up in the studies. • Whether they are anti-coagulated (include both prophylactic and fully anticoagulated and report in narrative what the studies included) The population with chronically depressed GCS – usually 14 – should be treated as having a low GCS if the GCS is lower than their usual presentation. *High risk Markers of neurological injury severity (pupillary responses (usually both, one or no pupils are reactive), and/or other focal neurological deficits, - Time from injury to recovering pre injury baseline GCS (usually 15 but can be lower if pre injury cognitive impairment) -presence of seizure post injury, -presence of vomiting post injury, -signs of possible skull fracture

		Moderate risk markers of neurological injury severity = duration of anyloss of consciousness and / or amnesia, Presence of High energy transfer mechanism of injury (defined in current recs). In people with GCS less than or equal to 12 CT head scan is done within 2 hours of injury. People with GCS =15 would be discharged
	confounding factors	Key confounders: Age GCS Other confounders: Neurological injury severity Blood measures of coagulopathy Include studies adjusted for age and GCS for all sub-groups. Do not exclude if other confounders not adjusted in the multivariate analysis. Include both comparative and non-comparative studies.
9.	Types of study to be included	Cohort studies (prospective and retrospective) Systematic reviews and meta-analyses of the above Case-control studies will be excluded.

10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. Studies not adjusted for key confounders
11.	Context	Clinical variables for selecting people for imaging in a sub-group of people with head injury.
12.	Primary outcomes (critical outcomes)	• Any traumatic intracranial abnormality detected by CT or MR imaging or autopsy -Any intracranial abnormality that causes death, neurosurgical intervention or neuro critical care. Note from studies severity of intra cranial abnormality needing neurocritical care. There are different ways of reporting- to report as in the papers. Association data: Adjusted RR or OR (adjusted for key confounders)
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately

		• a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
14.	Risk of bias (quality) assessment	The methodological quality of each study will be assessed using the QUIPS check list. The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
15.	Strategy for data synthesis	• meta-analyses will be performed if possible using Cochrane Review Manager (RevMan5) depending on the appropriateness of data. • If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.

16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present:
		
		For anticoagulant/antiplatelet strata:
		• Drug class
		  o Anti-coagulant
		    ▪ Warfarin
		    ▪ direct oral anticoagulant (DOACs)
		    ▪ unfractionated heparin
		    ▪ low molecular weight heparin
		  o Antiplatelet
		    ▪ Aspirin
		    ▪ Platelet activation inhibitors (e.g. clopidogrel/prasugrel

17.	Type and method of review	☐	Intervention	
		☒	Diagnostic association review	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]		
21.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☐
		Formal screening of search results	☐	☐

		against eligibility criteria		
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address] 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and [National Guideline Alliance / National Guideline Centre / NICE Guideline Updates Team / NICE Public Health Guideline Development Team] [Note it is essential to use the template text here and one of the centre options to enable PROSPERO to recognise this as a NICE protocol]		
24.	Review team members	[Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.] From the National Guideline Centre: [Guideline lead] [Senior systematic reviewer]		

		Systematic reviewer [Health economist] [Information specialist] [Others]
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
28.	Other registration details	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]
29.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts

		• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. [Add in any additional agree dissemination plans.]
31.	Keywords	Diagnosis, head injury, selection for CT/MRI
32.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]
33.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
34.	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]
35.	Details of final publication	www.nice.org.uk

1 **Health economic review protocol**

2 **Table 11: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. The search covered all years
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2006 or later that were included in the previous guidelines will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[25] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.

	• If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'.

	• Studies published before 2006 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[25]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 12: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 22 June 2022	Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 22 June 2022	Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2022 Issue 6 of 12	
Epistemonikos (The Epistemonikos Foundation)	Inception to 22 June 2022	Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2.	((skull or cranial) adj3 fracture*).ti,ab.
3.	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.
4.	(trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
5.	or/1-4

6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to English language
26.	tomography/ or exp tomography, emission-computed/ or exp tomography, x-ray/
27.	(compute* adj2 tomograph*).ti,ab.
28.	magnetic resonance imaging/
29.	MRI.ti,ab.
30.	((MR or magnetic resonance or NMR) adj2 (imag* or tomograph*)).ti,ab.
31.	(CT or CAT or PET or SPECT).ti,ab.
32.	or/26-31
33.	25 and 32
34.	Epidemiologic studies/
35.	Observational study/
36.	exp Cohort studies/
37.	(cohort adj (study or studies or analys* or data)).ti,ab.
38.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
39.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
40.	Controlled Before-After Studies/
41.	Historically Controlled Study/
42.	Interrupted Time Series Analysis/
43.	(before adj2 after adj2 (study or studies or data)).ti,ab.
44.	Cross-sectional studies/
45.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
46.	or/34-45
47.	Meta-Analysis/

48.	exp Meta-Analysis as Topic/
49.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
50.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
51.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
52.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
53.	(search* adj4 literature).ab.
54.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
55.	cochrane.jw.
56.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
57.	or/47-56
58.	46 or 57
59.	33 and 58

Embase (Ovid) search terms

1.	head injury/
2.	exp brain injury/
3.	skull injury/ or exp skull fracture/
4.	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.
5.	((skull or cranial) adj3 fracture*).ti,ab.
6.	(trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to english language
27.	*tomography/

28.	*brain tomography/
29.	exp *computer assisted tomography/
30.	exp *emission tomography/
31.	exp *x-ray tomography/
32.	(compute* adj2 tomograph*).ti,ab.
33.	*nuclear magnetic resonance imaging/
34.	MRI.ti,ab.
35.	((MR or magnetic resonance or NMR) adj2 (imag* or tomograph*)).ti,ab.
36.	(CT or CAT or PET or SPECT).ti,ab.
37.	or/27-36
38.	26 and 37
39.	Clinical study/
40.	Observational study/
41.	Family study/
42.	Longitudinal study/
43.	Retrospective study/
44.	Prospective study/
45.	Cohort analysis/
46.	Follow-up/
47.	cohort*.ti,ab.
48.	46 and 47
49.	(cohort adj (study or studies or analys* or data)).ti,ab.
50.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
51.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
52.	(before adj2 after adj2 (study or studies or data)).ti,ab.
53.	cross-sectional study/
54.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
55.	or/39-45,48-54
56.	systematic review/
57.	Meta-Analysis/
58.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
59.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
60.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
61.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
62.	(search* adj4 literature).ab.
63.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
64.	cochrane.jw.
65.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
66.	or/56-65
67.	55 or 66

68.	38 and 67

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Craniocerebral Trauma] this term only
#2.	MeSH descriptor: [Brain Injuries] explode all trees
#3.	MeSH descriptor: [Coma, Post-Head Injury] this term only
#4.	MeSH descriptor: [Head Injuries, Closed] explode all trees
#5.	MeSH descriptor: [Head Injuries, Penetrating] this term only
#6.	MeSH descriptor: [Intracranial Hemorrhage, Traumatic] explode all trees
#7.	MeSH descriptor: [Skull Fractures] explode all trees
#8.	((skull or cranial) near/3 fracture*):ti,ab
#9.	((head or brain or craniocerebral or cranial or skull) near/3 (injur* or trauma*)):ti,ab
#10.	(trauma* and ((subdural or intracranial) near/2 (h?ematoma* or h?emorrhage* or bleed*))):ti,ab
#11.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12.	MeSH descriptor: [Tomography] this term only
#13.	MeSH descriptor: [Tomography, Emission-Computed] explode all trees
#14.	MeSH descriptor: [Tomography, X-Ray] explode all trees
#15.	(compute* NEAR/2 tomograph*):ti,ab
#16.	MeSH descriptor: [Magnetic Resonance Imaging] this term only
#17.	MRI:ti,ab
#18.	((MR or magnetic resonance or NMR) NEAR/2 (imag* or tomograph*)):ti,ab
#19.	(CT or CAT or PET or SPECT):ti,ab
#20.	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21.	#11 AND #20

Epistemonikos search terms

1.	(advanced_title_en:(((skull OR cranial) AND fracture*)) OR advanced_abstract_en:(((skull OR cranial) AND fracture*))) OR (advanced_title_en:(((head OR brain OR craniocerebral OR cranial OR cerebral OR skull) AND (injur* OR trauma*))) OR advanced_abstract_en:(((head OR brain OR craniocerebral OR cranial OR cerebral OR skull) AND (injur* OR trauma*)))) AND (advanced_title_en:((tomograph* OR magnetic resonance OR neuroimag* OR MRI OR CT OR CAT OR PET OR SPECT)) OR advanced_abstract_en:((tomograph* OR magnetic resonance OR neuroimag* OR MRI OR CT OR CAT OR PET OR SPECT)))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Head Injury population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 13: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 22 June 2022 Quality of Life 1946 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Health Economics 1 January 2014 – 22 June 2022 Quality of Life 1974 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception – 22 June 2022	English language

Medline (Ovid) search terms

1.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2.	((skull or cranial) adj3 fracture*).ti,ab.
3.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
4.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/

12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to English language
26.	economics/
27.	value of life/
28.	exp "costs and cost analysis"/
29.	exp Economics, Hospital/
30.	exp Economics, medical/
31.	Economics, nursing/
32.	economics, pharmaceutical/
33.	exp "Fees and Charges"/
34.	exp budgets/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/26-41
43.	quality-adjusted life years/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.

51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/43-61
63.	25 and (42 or 62)

Embase (Ovid) search terms

1.	head injury/
2.	exp brain injury/
3.	skull injury/ or exp skull fracture/
4.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
5.	((skull or cranial) adj3 fracture*).ti,ab.
6.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24

26.	limit 25 to English language
27.	health economics/
28.	exp economic evaluation/
29.	exp health care cost/
30.	exp fee/
31.	budget/
32.	funding/
33.	budget*.ti,ab.
34.	cost*.ti.
35.	(economic* or pharmaco?economic*).ti.
36.	(price* or pricing*).ti,ab.
37.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38.	(financ* or fee or fees).ti,ab.
39.	(value adj2 (money or monetary)).ti,ab.
40.	or/27-39
41.	quality-adjusted life years/
42.	"quality of life index"/
43.	short form 12/ or short form 20/ or short form 36/ or short form 8/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/41-61
63.	26 and (40 or 62)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Brain Injuries EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Craniocerebral Trauma

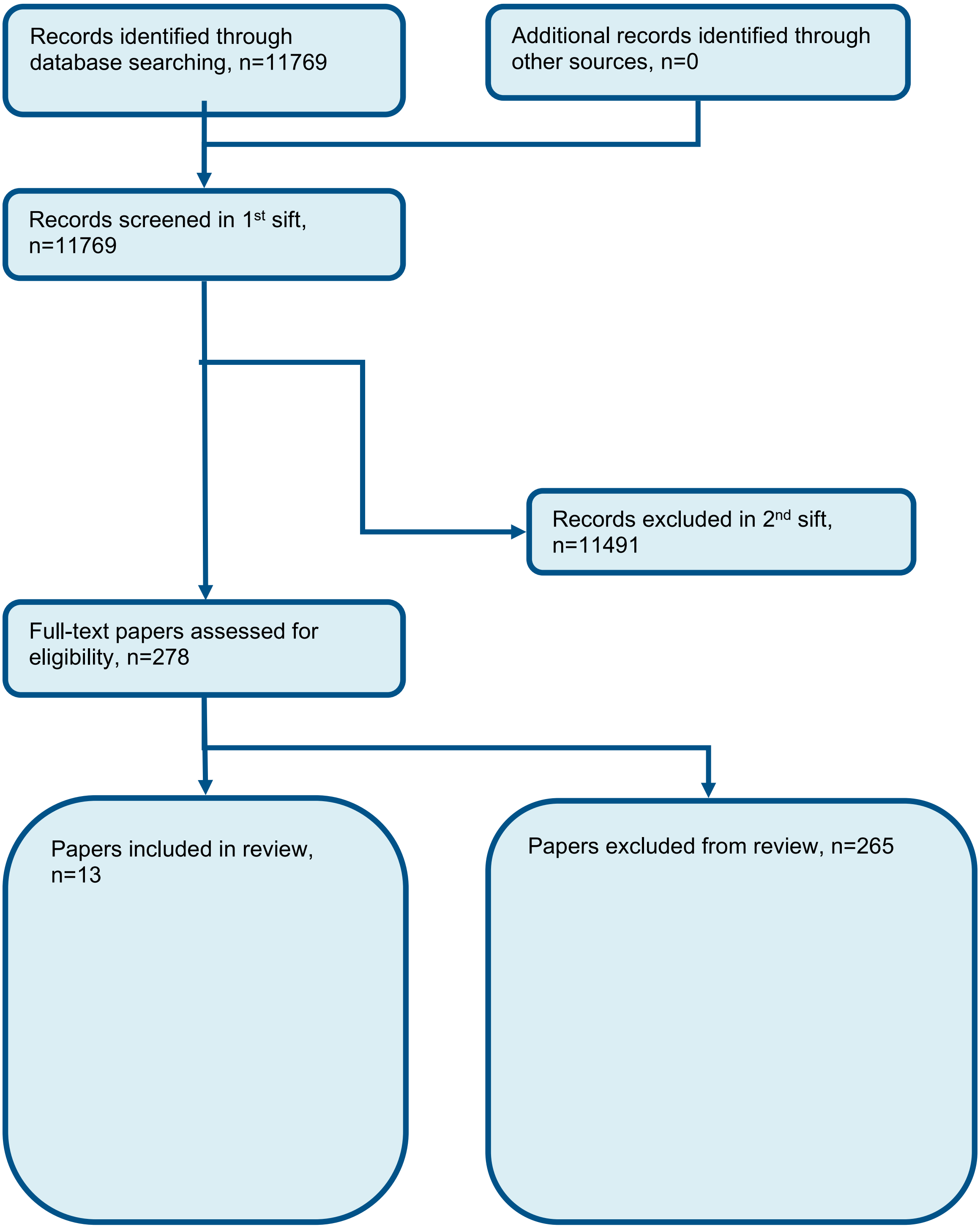
#3.	MeSH DESCRIPTOR Coma, Post-Head Injury
#4.	MeSH DESCRIPTOR Head Injuries, Closed EXPLODE ALL TREES
#5.	MeSH DESCRIPTOR Head Injuries, Penetrating
#6.	MeSH DESCRIPTOR Intracranial Hemorrhage, Traumatic EXPLODE ALL TREES
#7.	MeSH DESCRIPTOR Skull Fractures EXPLODE ALL TREES
#8.	(((skull or cranial) adj3 fracture*))
#9.	(((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)))
#10.	((trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))))
#11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

INAHTA search terms

1.	((((trauma* and ((subdural or intracranial or brain) and (haematoma* or hematoma* or haemorrhage* or hemorrhage* or bleed*))))[Title]) AND (((trauma* and ((subdural or intracranial or brain) and (haematoma* or hematoma* or haemorrhage* or hemorrhage* or bleed*))))[Title])) OR ((((skull or cranial) and fracture*))[Title] OR (((skull or cranial) and fracture*))[abs]) OR ((((head or brain or craniocerebral or intracranial or cranial or skull) and (injur* or trauma*)))[Title] OR (((head or brain or craniocerebral or intracranial or cranial or skull) and (injur* or trauma*)))[abs]) OR ("Skull Fractures"[mhe]) OR ("Intracranial Hemorrhage, Traumatic"[mhe]) OR ("Head Injuries, Penetrating"[mh]) OR ("Head Injuries, Closed"[mhe]) OR ("Coma, Post-Head Injury"[mh]) OR ("Brain Injuries"[mhe]) OR ("Craniocerebral Trauma"[mh])

Appendix C – Prognostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of the indications for selecting adults, children and infants with head injury for CT or MRI head scan in a sub-group



Appendix D – Prognostic evidence

Reference	Ahmed, 2015 [1]
Study type and analysis	Retrospective observational study Multiple logistic regression models were used to assess the association between the CT result and factors of interest while controlling for the potential confounding variables. USA
Number of participants and characteristics	N=163 (n=91 CT bleeding, n=72 no CT bleeding) **Inclusion criteria:** Adult patients (>18 years of age) were included in this study if they fell from a standing position (FFS) and had a computed tomography (CT) scan of the head to evaluate their injuries. **Exclusion criteria:** All patients who fell from any height above the ground were excluded. **Population characteristics:** • Age mean (SD) years: No CT bleeding -64.4 (22.7); CT bleeding: 71.5 (17.9) • Female: No CT bleeding -58.3 %; CT bleeding:52.7 % Use of: No CT bleeding / CT bleeding Aspirin 19.4 % / 34.1 % Plavix 12.5 % / 13.2 % Both aspirin and Plavix 8.3 % / 8.8 % Coumadin 9.7 % / 9.9 % Blood thinner 29.2 % / 41.8 % **Population source:** All patients at State designated Trauma Centre who had a fall from a standing position (FFS) were identified from the trauma registry
Clinical variables	Use of aspirin, Age >70 years Unclear if other variables were used in the analysis

Reference	Ahmed, 2015 [1]
Confounders	Multiple logistic regression models were used to assess the association between the CT result and factors of interest while controlling for the potential confounding variables. Age, aspirin, gender. Adjusted for gender. Not adjusted for the key confounder of GCS
Outcomes and effect sizes	Intracranial bleed (ICB) after a fall from a standing position. When evaluating the potential risk factors which may be associated with the diagnosis of ICB, use of aspirin showed a positive association when gender was adjusted (OR = 2.17, 95 % CI [1.06, 4.60], P = 0.04). However, when we further considered age of being equal to or older than 70 years, the association became not significant (OR = 1.80, 95 % CI [0.85, 3.90], P = 0.13). Patients >70 years of age were more likely to use aspirin (OR = 3.14, 95 % CI [1.37, 7.79], P = 0.004). However, when controlling for gender, it was found that only age >70 years was significantly associated with ICB (OR = 2.67, 95 % CI [1.36, 5.39], P = 0.005).
Limitations	Risk of bias (QUIPS): 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Indirectness: None
Comments	Mortality: Twelve patients with ICB died (13.2 %, 95 % exact CI [7.0 %, 21.9 %]). This mortality rate was not significantly different from those patients who had no ICB (9.7 %, 95 % exact CI [4.0 %, 19.0 %])

Reference	Brewer, 2011 [4]
Study type and analysis	Retrospective cohort study Forward and backward unconditioned logistic regression analysis was performed to assess the influence on a positive CT finding of age, gender, LOC, presence of fracture, mechanism of injury (fall or motor vehicle collision [MVC]), evidence of trauma above the clavicles on physical examination, type of anticoagulation, and presentation INR and PTT USA
Number of participants and characteristics	N= 141 **Inclusion criteria:** included all trauma registry patients with minor head injury from January 2004 through December 2006 who presented with a GCS score of 15 while taking clopidogrel or warfarin and underwent head CT. Inclusion criteria: an ICD9-CM diagnostic injury code between 800 and 959.9, excluding 905-909 (late effects of injuries), 910-924.9 (superficial injuries, including blisters, contusions, abrasions, and insect bites), and 930-939 (foreign bodies). Additional criteria include admission to the hospital, death in the emergency department because of traumatic injury, and all trauma transfers into or out of the institution. As a matter of institutional policy, all trauma registry patients taking warfarin and/or clopidogrel and presenting with history or signs of minor head trauma underwent head CT. **Exclusion criteria:** NR **Population characteristics:** Mean age 79 years (range, 36-101 years) Eighty-four patients were anticoagulated with warfarin, 21 patients had combined therapy (warfarin and aspirin, n = 18; warfarin and clopidogrel, n = 2; or warfarin, clopidogrel, and aspirin, n = 1), and 36 patients were only on antiplatelet therapy (clopidogrel, n = 15; clopidogrel and aspirin, n = 21). **Population source:** trauma registry
Clinical variables	age, gender, LOC, presence of fracture, mechanism of injury (fall or motor vehicle collision [MVC]), evidence of trauma above the clavicles on physical examination, type of anticoagulation, and presentation INR and PTT. Age and presentation INR and PTT were included as continuous variables. LOC, presence of fracture, mechanism of injury, evidence of trauma above the clavicles on physical examination, and type of anticoagulation were considered as categorical variables divided into two or three categories, respectively.
Confounders	Forward and backward unconditioned logistic regression analysis

Reference	Brewer, 2011 [4]
	Age, gender, LOC, presence of fracture, mechanism of injury (fall or motor vehicle collision, evidence of trauma above the clavicles on physical examination, presentation INR and PTT, presence of fracture, mechanism of injury, evidence of trauma above the clavicles on physical examination
Outcomes and effect sizes	Outcome: Predictors of positive CT finding Loss of consciousness (LOC) (Wald = 7.468, β= 1.179, p = 0.008) was the only predictor for a positive CT result. motor vehicle collision (MVC) as a mechanism of injury (Wald = 3.580, β= 1.404, p = 0.058) showed a trend toward significance. Age, gender, presenting INR and PTT, external evidence of injury above the shoulders, and type of medication (warfarin, aspirin, or clopidogrel) did not reach statistical significance (data not reported)
Limitations	Risk of bias (QUIPS): 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias HIGH OVERALL RISK OF BIAS HIGH Incomplete reporting of data Indirectness: none
Comments	Type of anticoagulant was defined as patients taking warfarin alone, patients taking warfarin and an antiplatelet agent, and patients taking only an antiplatelet agent. Aspirin use was also assessed and was included as an antiplatelet agent. None of the patients took aspirin alone, because the inclusion criteria required taking warfarin and/or clopidogrel. Forty-one (29%) patients were diagnosed with intracranial haemorrhage. Nineteen patients had subdural hematoma (SDH), 14 had subarachnoid haemorrhage, 5 had cerebral contusions, and 3 suffered multiple types of intracranial haemorrhage. Two patients suffered both subdural and sub-arachnoid haemorrhage, and one patient suffered haemorrhagic contusion and SDH. Thirty-nine (95%) of these 41 patients underwent reversal or discontinuation of clopidogrel and/or warfarin. Five patients required surgical evacuation of an intracranial haemorrhage: 4 via craniotomy and 1 via bur hole. Four of the 141 patients died. All patients who died had intracranial haemorrhage. Two patients who underwent craniotomy for evacuation of SDH died after 5 days and 8 days, respectively. In these two

Reference	Brewer, 2011 [4]
	patients, SDH and subsequent complications were the principle cause of death. The other two patients who died did not have documented reversal of warfarin or clopidogrel. These two patients had multiple other medical problems and injuries, and their intracranial haemorrhage was not the cause of death. One presented with an acute myocardial infarction that was the principal cause of death. The other had chronic lung disease and suffered multiple rib fractures, dying of respiratory failure. The frequency of a positive CT finding with regards to anticoagulation, antiplatelet, or combined therapy was 23 of 84 (27%), 15 of 36 (41%), or 3 of 21 (14%), respectively. The differences in frequency did not reach statistical significance. At the time of presentation, PTT and INR were obtained on 137 of 141 patients. One patient had INR only obtained, and neither was obtained on three patients. The mean presenting INR in patients with intracranial haemorrhage was 1.97 ± 0.92 when compared with 2.3 ± 1.2 for patients without intracranial haemorrhage (p = 0.0987). The presenting PTT of patients with and without intracranial haemorrhage was 32.8 ± 7.1 and 36.4 ± 14.9, respectively (p = 0.154). Fifteen of 35 (43%) patients with documented LOC had positive CT result. Seventeen of 93 (18%) patients with no LOC had positive CT result. In 13 patients, it remained unclear whether LOC had occurred or not, and these entries were treated as missing values for the statistical assessment. Nine of 13 (69%) of these patients had a positive CT result. Twenty-eight of 108 (26%) patients with external signs of injury above the clavicles had positive CT result.

Reference	Cipriano, 2018 [6]
Study type and analysis	Single-centre, prospective, observational study conducted at the ED of Pisa (Italy), a Level II Trauma Centre. Multivariate logistic regression was performed using a penalized approach; the penalized method produced the estimated odds ratios of selected predictors, but not their P values. Not adjusted for confounders. Italy
Number of participants and characteristics	N= 206 **Inclusion criteria:** Age above 18 years old; (2) MTBI, defined as blunt head injury associated with a GCS score of 13–15 regardless of the presence of loss of consciousness (LOC) immediately after the injury; (3) Patients on oral anti-coagulants (OAT); (4) single patient visit at the ED for trauma.

Reference	Cipriano, 2018 [6]
	Exclusion criteria: (1) Presentation to the ED more than 48 h from the trauma; (2) Ineffective OAT, defined as not adequate vitamin K antagonists (VKAs) intake for more than 1 week before the trauma, or last dose of direct oral anticoagulants (DOAC) longer than 24 h before the injury; (3) Inadequate anticoagulation effect in patients taking VKAs, defined as International Normalized Ratio (INR)<1.5. **Population characteristics:** • Age (SD): 81.53±8.44 years • Gender: 40.8% males Class of OAT: • 58.7% (121) VKA (vitamin K antagonists) • 41.3% (85) DOAC (direct oral anticoagulants) GCS score at ED presentation GCS 15: 99.0% (204) GCS 14: 1.0% (2) Platelet count (· 103/mm3): median (IQR)- 204 (74) **Population source:** From January 2016 to April 2017, 118,624 consecutive patients presented to the ED, among whom 6287 (5.3%) suffered a trauma; 4312 of these trauma patients (68.6%) had an MTBI. Among MTBI patients, 220 (5.1%) were on oral anti-coagulant therapy (OAT)
Clinical variables	Age Male sex High-energy impact Trauma above the clavicles LOC (loss of consciousness) PTA (Posttraumatic amnesia) Presence of fractures Concomitant antiplatelet treatment Low platelet count (<150,000/mm3)

Reference	Cipriano, 2018 [6]
Confounders	multivariate logistic regression Given the small number of events, multivariate logistic regression was performed using a penalized approach; the penalized method produced the estimated odds ratios of selected predictors, but not their P values. Age, gender, VKA agent treatment, high-energy impact, trauma above the clavicles, LOC, PTA, presence of fractures, low platelet count (<150,000/mm3) Not adjusted for key confounder of GCS
Outcomes and effect sizes	Immediate intra cranial haemorrhage (ICH) 23 out of 206 patients showed immediate ICH's signs at the first CT scan (prevalence rate 11.2%, 95% CI 6.5–15.5%) Only 1 (0.5%, 95% CI 0.0–1.4%) died because of ICH; no one required neurosurgical intervention. There was increased incidence of intracranial complications after mild TBI in patients treated with vitamin K antagonists compared with those receiving DOACs (15.7 vs. 4.7%, RR 3.34, 95% CI 1.18–9.46, P<0.05) <u>Comparison between clinical characteristics of patients with and without immediate intracranial haemorrhage: multivariate logistic regression—penalized approach</u> <u>(Odds ratio 95% CI)</u> Age, years: - Male sex: - vitamin K antagonists (VKAs) treatment: 3.364 (no CI reported) High-energy impact: 2.488 (no CI reported) Trauma above the clavicles: 3.175 (no CI reported) loss of consciousness (LOC): - post-traumatic amnesia (PTA): 2.570 (no CI reported) Presence of fractures: 2.569 (no CI reported) Concomitant antiplatelet treatment: - Low platelet count (<150,000/mm3): -

Reference	**Cipriano, 2018** [6]
	The multivariate logistic regression performed with a penalized approach five out of these parameters were selected as independent predictors of ICH: VKAs treatment (OR 3.364), high-energy impact (OR 2.488), trauma above the clavicles (OR 3.175), post-traumatic amnesia (PTA) (OR 2.570), and the presence of fractures (OR 2.569).
Limitations	Risk of bias (QUIPS): 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Indirectness: None
Comments	Immediate ICHs were, respectively: five parenchymal hematomas, seven subarachnoid haemorrhages, eight subdural hematomas, one epidural hematoma and two cases of concomitant subdural hematoma and subarachnoid haemorrhage; among them one patient died (prevalence rate in the study population: 0.5%, 95% CI 0.0–1.4%; 4.3% of the immediate ICH patients). None of other haemorrhagic patients required neurosurgical intervention. Intravenous administration of mannitol was necessary in only two patients. The prevalence rate of death or neurosurgical intervention due to immediate ICH was 0.5% (95% CI 0.0–1.4%). Regarding OAT treatment, 19 patients out of 23 (82.6%) were on warfarin, while only 4 out of 23 (17.4%) were on DOACs (1 on apixaban, 2 on rivaroxaban and 1 on edoxaban).

Reference	**De Wit 2020** [9]
Study type and analysis	A prospective observational study of conducted at 3 Canadian EDs between 14th December 2015 and 4th of January 2018 Adjusting data for new abnormality on neurologic examination, head laceration or bruise, CKD, GCS reduced from normal, cancer treated in past two years, liver disease, history of major bleed in last two years, male, hypertension, dementia loss of consciousness, previous stroke or TIA, diabetes, age congestive heart failure, anticoagulant therapy, and antiplatelet use.

Reference	De Wit 2020 [9]
	Canada

Number of participants and characteristics	N=1753
	
	Inclusion criteria: Patient’s aged 65 or older who presented to the ED within 48 hours of the fall on ground level, a fall from one or two steps, or a fall off the bed, patients were not required to have hit their head
	
	Exclusion criteria: transferred from another hospital, left the ED before completion of their assessment, all lived outside the geographic hospital catchment area.
	
	Population characteristics:
	• Age median (IQR): 82 (75-88) years
	• Male:Female = 676/1974
	• GCS n (%)
	  ○ 15: 1437 (82)
	  ○ 14: 211 (12)
	  ○ < 14: 51 (3)
	  ○ Missing 60 (3)
	Population source: Emergency Department of 3 Canadian hospitals

Clinical variables	Characteristic n (%) Antiplatelet use • Single antiplatelet: 576 (33) • Duel antiplatelet: 38 (2) Anticoagulant use • Warfarin 148 (8) • Apixaban 139 (8) • Rivaroxaban: 81 (5) Vomited: 69 (4) Retrospective amnesia: 109 (6) Bruise or laceration on head: 647 (37) Open/ depressed skull fracture: 4 (< 1) Signs of basal skull fracture: 9 (< 1)

Reference	De Wit 2020 [9]
Confounders	Multivariable analysis Adjusting data for new abnormality on neurologic examination, head laceration or bruise, CKD, GCS reduced from normal, cancer treated in past two years, liver disease, history of major bleed in last two years, male, hypertension, dementia loss of consciousness, previous stroke or TIA, diabetes, age congestive heart failure, anticoagulant therapy, and antiplatelet use. No adjustment for key confounder of age
Outcomes and effect sizes	Independent predictors for ICH in patients N=1075 (58%) had head CT; N=76 diagnosed with intracranial haemorrhage New abnormality on neurologic examination: OR 4.35 (95% CI 2.35-8.05) Head laceration or bruise: OR 4.33 (95% CI 2.70-6.96) CKD: OR 2.36 (95% CI 1.25-4.56) GCS reduced from normal: OR 1.87 (95% CI 1.04-3.36) Cancer treated in past 2 y: OR 1.82 (95% CI 0.91-3.66) Liver disease: OR 1.76 (95% CI 0.68-4.54) History of major bleed in past 2 years: OR 1.56 (95% CI 0.82-2.98) Vomited after the fall: OR 1.46 (95% CI 0.57-3.71) Male: OR 1.35 (95% CI 0.85-2.14) Hypertension: OR 1.21 (95% CI 0.68-2.14) Dementia: OR 1.08 (95% CI 0.64-1.79) Antiplatelet therapy: OR 1.07 (95% CI 0.64-1.79) Loss of consciousness: OR 1.03 (95% CI 0.55-1.94) Previous stroke or TIA: OR 1.02(95% CI 0.58-1.79) Diabetes: OR 1.01 (95% CI 0.61-1.67) Age, per year: OR 0.98 (95% CI 0.96-1.01) Anticoagulation therapy: OR 0.87 (95% CI 0.48-1.59) Congestive heart failure: OR 0.53 (95% CI 0.25-1.15) New abnormalities found on neurologic examination, head laceration or bruise, CKD , reduced GCS compared to normal were associated with intra cranial bleeding. No association between all the other variables and intracranial bleeding including current anticoagulant use or antiplatelet use

Reference	**De Wit 2020 [9]**
Limitations	Risk of bias (QUIPS): 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Indirectness: no indirectness
Comments	

Reference	**Dunham 2014 [12]**
Study type and analysis	A retrospective, consecutive investigation of patients with signs of external head trauma and age ≥60 years. Adjusting data for brain atrophy occurrence, composite brain atrophy, platelet inhibitor agent status, warfarin status, admission major neurologic dysfunction using multivariate analysis to adjust the changes. USA
Number of participants and characteristics	N=198 (36% were antithrombotic-negative and 64% antithrombotic-positive) **Inclusion criteria:** age ≥60 years, fall from standing height or motor vehicular crash, physical evidence for head trauma (facial fracture, skull fracture, scalp soft tissue injury, facial soft tissue injury, or cervical spine injury), and trauma centre admission. **Exclusion criteria:** none stated **Population characteristics:**

Reference	Dunham 2014 [12]
	• Age mean (SD): 78.46 (10) years • Male: Female = not stated • Admission Glasgow Coma Score 3–12 n (%): 15 (7.6) **Population source:** Trauma registry, Ohio, USA
Clinical variables	Admission major neurologic dysfunction, n (%): 19 (9.6%) Antithrombotic-negative n (%): 72 (36.4) Antithrombotic-positive n (%): 126 (63.6) Preinjury brain atrophy n (%): 98 (49.5) Intracranial haemorrhage n (%): 72 (36) Intracranial haemorrhage with brain compression n (%): 12 (6.1) Intracranial haemorrhage complication n (%): 8 (4.0) Neurologic complication n (%): 13 (6.6) Intracranial haemorrhage-neurologic complication n (%): 16 (8.1)
Confounders	Multivariable analysis Factors included in the adjusted multivariate analysis: brain atrophy occurrence, composite brain atrophy, platelet inhibitor agent status, warfarin status, admission major neurologic dysfunction No adjustment for key confounders of age and GCS No description of excluded patients, no accounting for participant drop-out,
Outcomes and effect sizes	Multivariate analysis showed that intercranial haemorrhage (ICH) correlated with composite brain atrophy ($p < 0.0001$), but not AT agent status ($p = 0.9293$) ($n = 192$ AT-positive or AT-negative patients). ICH correlated with composite brain atrophy ($p < 0.0001$), but not platelet inhibitor agent status ($p = 0.3205$) ($n = 143$ AT-negative or platelet inhibitor-positive patients). ICH correlated with composite brain atrophy ($p < 0.0001$), but not warfarin status ($p = 0.2733$) ($n = 114$ AT-negative or warfarin-positive patients). ICH had an independent association with composite brain atrophy ($p < 0.001$) and admission major neurologic dysfunction ($p < 0.001$), but not AT status ($p = 0.9774$) or age ($p = 0.8566$). Multivariate logistic regression analysis indicated that ICH neurologic complications were independently associated with admission major neurologic dysfunction ($p < 0.001$) and ICH ($p = 0.0218$), but not AT status ($p = 0.8953$). ICH-neurologic complications were independently associated with admission major neurologic dysfunction ($p > 0.001$) and ICH ($p = 0.0202$), but not with platelet inhibitor-status ($p = 0.7055$). ICH-neurologic complications were independently associated with admission major neurologic dysfunction (p <

Reference	Dunham 2014 [12]
	0.001) and ICH (p = 0.0209), but not with warfarin-status (p = 0.7219). In the 72 patients with ICH, the ICH-neurologic complication rate was similar for the AT-negative (17.4% [4/23]) and AT-positive (20.4% [10/49]; p = 1.0) groups. Multivariate logistic regression analysis, ICH-neurologic complication was independently associated with admission major neurologic dysfunction (p < 0.001) and ICH (p = 0.0216), but not with AT-positive status (p = 0.9966) or coagulation intervention (p = 0.4160).
Limitations	Risk of bias (QUIPS): 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: not all participants on anti-thrombotics
Comments	

Reference	Galliazzo, 2019 [15]
Study type and analysis	Single centre retrospective cohort study multivariate logistic regression analysis was performed to examine patients' clinical factors associated with an acute intracranial bleeding complication. Italy
Number of participants and characteristics	N= 1846 (n=459 CT not performed; n=1387 CT performed) **Inclusion criteria:** GCS score ranging from 13 to 15 upon ED presentation after a referred TBI and age over 18 years old. **Exclusion criteria:** Patients receiving any regimen of low molecular weight heparin were excluded. **Population characteristics:** Sex, male: 926 (50.2%) Age > 65 years: 1042 (56.5%) median age was 71 years (IQR 46–83) GCS score 15: 1811 (98.1%) 14: 29 (1.6%) 13: 6 (0.3%) INR >3: 36 (2%) 1222 (66.2%) patients in group 1 (no antithrombotic therapy prior to the index event), 407 (22.0%) in group 2 (one antiplatelet agent), 120 (6.5%) in group 3 (VKAs), 51 (2.8%) in group 4 (DOACs) and 46 (2.5%) in group 5 (double antithrombotic therapy). **Population source:** all consecutive adult patients admitted to the ED of the Teaching Hospital of Varese, Italy, between January 2015 and September 2017 because of a mild TBI. Patients were detected by querying ED medical electronic registry with the following descriptive diagnosis: minor TBI, minimal TBI, mild TBI, minor/minimal/mild TBI on anticoagulation therapy/VKA/DOACs and minor/minimal/mild TBI on antiplatelet therapy.
Clinical variables	Antithrombotic drug, antiplatelet, VKA, DOACs, Double therapy, Age (years) <65 and ≥65, Sex , GCS score (15 and <15), Loss of consciousness, Amnesia , Neurological signs, Seizure , Headache, Vomiting, Clinical signs of cranial fracture, Complicated contused

Reference	Galliazzo, 2019 [15]
	lacerated wound, Critical dynamic, History of epilepsy, Previous stroke/TIA/neurosurgery, Drug/alcohol intoxication, History of cerebral neoplasia, scalp lesions
Confounders	multivariate logistic regression analysis Age older than 65 years, any ongoing antithrombotic treatment, history of epilepsy, history of TIA/stroke/neurosurgery, history of cerebral neoplasia and drug/alcohol intoxication as patient baseline risk factors; GCS score < 15, LOC, amnesia, vomiting, neurological signs, seizure, headache, clinical signs of skull fracture, complicated contused lacerated wound, other scalp lesions
Outcomes and effect sizes	Outcome: acute intra cranial bleeding complications <u>Association between patients' clinical findings and intracranial bleedings. Logistic regression model, overall sample.</u> Antithrombotic drug Antiplatelet: OR 1.93(95% CI 0.98–3.80) VKA: OR 1.58 (95% CI 0.55–4.54) DOACs: OR 1.54(95% CI 0.33–7.16) Double therapy: OR 2.11 (95% CI 0.51–8.67) Age (years) <65: OR 1 (NR) Age ≥65: OR 1.89 (95% CI 0.92–3.87) Sex male: OR 1 (NR) Female: OR 1.13 (95% CI 0.65–1.97) GCS score 15: OR 1 (NR) <15: OR 7.95 (95% CI 3.12–20.28) Loss of consciousness (yes): OR 1.31 (95% CI 0.42–4.04) Loss of consciousness (no): OR 1 (NR) Amnesia (yes): OR 6.49 (95% CI 3.57–11.82) Amnesia (no): OR 1 (NR) Neurological signs (yes): 1.04 0.09–11.56 Neurological signs (no): OR 1 (NR) Seizure (yes): not estimable Seizure (no): OR 1 (NR) Headache (yes): OR 1.11 (95% CI 0.13–9.4) Headache (no): OR 1 (NR)

Reference	Galliazzo, 2019 [15]
	Vomiting (yes): OR 4.45 (95% CI 1.47–13.50) Vomiting (no): OR 1 (NR) Clinical signs of cranial fracture (yes): OR 8.41 (95% CI 2.12–33.33) Clinical signs of cranial fracture (no): OR 1 (NR) Complicated contused lacerated wound (yes): OR 1.01 (95% CI 0.28–3.61) Complicated contused lacerated wound (no): OR 1 (NR) Critical dynamic (yes) : OR 3.03 (95% CI 0.96–9.60) Critical dynamic (no): OR 1 (NR) History of epilepsy (yes) : OR 2.46 (95% CI 0.51–11.79) History of epilepsy (no): OR 1 (NR) Previous stroke/TIA/neurosurgery (yes) : OR 1.57 (95% CI 0.61–4.09) Previous stroke/TIA/neurosurgery (no): OR 1 (NR) Drug/alcohol intoxication (yes) : OR 1.13 (95% CI 0.30–4.25) Drug/alcohol intoxication (no): OR 1 (NR) History of cerebral neoplasia (yes): NOT ESTIMABLE History of cerebral neoplasia (no): OR 1 (NR) scalp lesions (yes): OR 2.31 (95% CI 1.09–4.89) scalp lesions (no): OR 1 (NR) Association between patients' clinical findings and intracranial bleedings. Logistic regression model, only patients with CT performed. Antithrombotic drug Antiplatelet: OR 1.70 (95% CI 0.87–3.33)

Reference	Galliazzo, 2019 [15]
	VKA: OR 1.33 (95% CI 0.47–3.77) DOACs: OR 1.28 (95% CI 0.28–5.88) Double therapy: OR 1.84 (95% CI 0.46–7.44) Age (years) <65 – OR 1 (NR) Age ≥65: OR 1.38 (95% CI 0.67–2.83) Sex Male: OR 1.15 (95% CI 0.66–2.00) Female: OR 1 (NR) GCS score 15: OR 1 (NR) GCS score <15: OR 6.69 (95% CI 2.67–16.77) Loss of consciousness (yes): OR 1.10 (95% CI 0.36–3.37) Loss of consciousness (no): OR 1 (NR) Amnesia (yes): OR 5.62 (95% CI 3.07–10.26) Amnesia (no): OR 1 (NR) Neurological signs (yes): OR 0.92 (95% CI 0.09–9.92) Neurological signs (no): OR 1 (NR) Seizure (yes): not estimable Headache (yes): OR 0.91 (95% CI 0.10–8.02) Headache (no): OR 1 (NR) Vomiting (yes): OR 4.33 (95% CI 1.43–3.11) Vomiting (no): OR 1 (NR) Clinical signs of cranial fracture (yes): OR 7.36 (95% CI 1.88–28.91) Clinical signs of cranial fracture (no): OR 1 (NR) Complicated contused lacerated wound (yes): OR 1.04 (95% CI 0.30–3.60) Critical dynamic (yes): OR 2.38 (95% CI 0.76–7.48) Critical dynamic (no): OR 1 (NR) History of epilepsy (yes): OR 2.15 (95% CI 0.45–10.25) History of epilepsy (no): OR 1 (NR) Previous stroke/TIA/neurosurgery (yes): OR 1.47 (95% CI 0.57–3.77) Previous stroke/TIA/neurosurgery (no): OR 1 (NR) Drug/alcohol intoxication (yes): OR 0.96 (95% CI 0.26–3.58)

Reference	Galliazzo, 2019 [15]
	Drug/alcohol intoxication (no): OR 1 (NR) History of cerebral neoplasia (yes): not estimable History of cerebral neoplasia (no): OR 1 (NR) scalp lesions (yes): OR 2.20 (95% CI 1.03–4.68) scalp lesions (no): OR 1 (NR) At multivariable analysis performed in the whole study population, the following clinical characteristics were independently associated with acute intracranial bleeding complications: GCS < 15 (OR 7.95 CI 95%: 3.12–20.28), post traumatic amnesia (OR 6.49; CI 95%: 3.57–11.82), vomiting (OR 4.45 CI 95%: 1.47–13.50), clinical signs of cranial fractures (OR 8.41 CI 95%: 2.12–33.33), and evidence of other clinical scalp lesions (OR 2.31 CI 95%: 1.09–4.89). Treatment with single antiplatelet (OR=1.93 CI 95%: 0.98–3.80), VKAs (OR=1.58 CI 95%: 0.55–4.54), DOACs (OR=1.54 CI 95%: 0.33–7.16) or double antithrombotic drugs (OR=2.11 CI 95%: 0.51–8.67) was not significantly associated with an increased risk of intracranial bleeding. These findings, with the exception for the variable “other scalp lesions”, were confirmed at the multivariable analysis performed by considering only patients who underwent CT scan.
Limitations	Risk of bias (QUIPS): 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS LOW Indirectness: serious Not all participants on anti-thrombotic therapy
Comments	Among patients who underwent brain CT, 68 (4.9% CI 95%: 3.9–6.2) had acute intracranial bleeding: 36 (4.6%; 95% CI: 3.2–6.3) in group 1, 22 (5.7%; 95% CI: 3.6–8.5) in group 2, 5 (4.2%; 95% CI: 1.4–9.5) in group 3, 2 (3.9%; 95%: 0.5–13.5) in group 4 and 3 (7.0%; 95%CI: 1.5–19.1) in group 5. Intracranial bleeding prevalence was similar among patient groups. ICH prevalence increased as the number of overall concurrent risk factors increased. An INR value greater than three was documented in 2 out of 5 cases of intracranial bleeding on VKAs. None of the intracranial bleeding lesions required a neurosurgical treatment. Overall, only 1 patient died. He belonged to group 4 and was on dabigatran.

Reference	**Gelernter, 2018 [16]**
Study type and analysis	Retrospective chart review of infants less than 24 months old Logistic regression model Israel
Number of participants and characteristics	N= 344 cases were analysed, 68 with late presentation. **Inclusion criteria:** All files of children younger than 24 months with head injury who underwent CT from January 2004 to December 2014, were retrospectively reviewed. The study group included children with late presentation, i.e. their injury occurred at least 24 h prior to CT performance. Patients evaluated by a physician immediately after head injury who presented to the ED later, and those who were admitted without initial CT and underwent CT later, were also included. The control group included children with early presentation, who underwent CT within 24 h of their injury. **Exclusion criteria:** Children with non-trauma indication for head CT, highly suspected non-accidental trauma, penetrating trauma, and those with pre-existing neurological disorders complicating assessment, were excluded. Files with no documentation of the time of injury were also excluded from the study. **Population characteristics:** **Factor** — **After 24 h (n = 68)** — **Within 24 h (n = 275)** Age, months (mean (SD)): 11.4 (5.6) — 10.5 (7.0) Gender (n (%) male): 34 (50%) — 171(62%) GCS<15 (n (%) : 10 (15%) — 49 (18%) Hematoma (n (%): 53 (78%) — 170 (62%) Severe mechanism of injury (n (%): 14 (22%) — 157 (58%) Type of Mechanism Fall (n (%) : 63 (98%) — 238 (88%) motor vehicle accident: 0 (0%) 21(8%) other : 1 (2%) — 12(4%) Readmittance to Emergency Room: 10 (15%) — 2 (1%)

Reference	Gelernter, 2018 [16]
	Population source: A retrospective chart review of infants less than 24 months old referred for head CT because of traumatic brain injury from January 2004 to December 2014 in Assaf-Harofeh medical centre was conducted.
Clinical variables	Age, gender, GCS, hematoma, duration of injury
Confounders	A logistic regression model was used to determine the effect of different variables (including time of presentation) on the risk for significant TBI. Demographic and clinical variables were included in the model based on data from previous studies. Age, gender, GCS, hematoma, duration of injury. Adjusted for key confounders
Outcomes and effect sizes	Outcome: - Variables associated with increased risk for significant TBI on CT [Significant TBI on CT includes any of the following descriptions: any intracranial bleeding, pneumocephalus, cerebral oedema, skull fracture depressed by at least the thickness of skull, or diastasis of the skull] - Variables associated with increased risk for any TBI on CT [any TBI on CT as any finding on CT related to the injury (e.g. linear skull fracture)] PECARN definitions of TBI on CT to define significant CT findings. <u>Variables associated with increased risk for significant TBI on CT.</u> Factor OR (95% CI) Age, months: 0.91 (0.86–0.96) Male gender: 1.34 (0.72–2.49) GCS<15: 5.88 (2.69–13.02) Hematoma: 4.39 (1.91–10.10) Duration from injury >24 h: 1.63 (0.79–3.44) <u>Variables associated with increased risk for any TBI on CT.</u> Factor OR (95% CI) Age, months :0.90 (0.86–0.94) Male gender: 1.51 (0.89–2.58) GCS<15: 2.44 (1.17–5.26) Haematoma: 7.69 (4.00–14.26) Duration from injury >24 h: 2.77 (1.40–5.55)

Reference	Gelernter, 2018 [16]
	In the model, younger age, presence of scalp hematoma and GCS (Glasgow Coma Scale)<15 predicted significant TBI on CT, while time of presentation following injury did not. Exploring the relationship between patient characteristics and any finding on CT by logistic regression demonstrated that late presentation, as well as the three characters mentioned above, predicted any TBI on CT.
Limitations	Risk of bias (QUIPS): 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS LOW Indirectness: indirectness Included infants with <and > 24 hours after injury Note from study: Documentation of time of injury was lacking in several cases and was estimated by the author. However, study included only cases in which we could determine if the injury occurred within 24 h to presentation or later. In this study, included only children with a late presenting head injury that underwent CT and not those who did not receive imaging studies. That makes those who were chosen to undergo CT a selected high-risk group. Additionally, children that did not have CT scans preformed may have had serious intracranial pathology that failed to present to the ED and may have been missed. We did not follow children that had an initial negative CT, or did not have a CT at all, to see if they presented to other ED's or suffered late complications. However, as this was a regional hospital, patients tend to readmit it in case they need
Comments	There were no significant differences in age and gender between children with late and early presentation. Significant differences between the groups were found in the frequency of scalp hematoma (OR 2.18, CI 1.17– 4.06), severe mechanism (OR 0.20, CI 0.10–0.39), as well as in type of injury. Difference in frequency of readmission to ER was also found to be significant, but with a very wide CI (OR 23.62, CI 5.04–110.66). Total of 344 CT scans were available for the study. Of the 344 included CT scans, 68 were for patients presenting after 24 h from injury (study group). Overall, 159 scans demonstrated any TBI, from which 68 were significant. There were no significant differences between

Reference	Gelernter, 2018 [16]
	the groups in the incidence of significant TBI (22% vs 19%, p = 0.61), clinically important TBI and neurosurgery intervention. Any TBI on CT were found in 43 (63%) patients with late presentation compared with 116 (42%) patients with early presentation (p = 0.002, OR 2.37, 95% CI 1.37–4.1). There was no significant difference in hospitalisation duration between children with late and early presentation (mean 2.5 (SD 2.4) days vs 2.3 (SD 3.3) days, p = 0.84). There was borderline significant difference in intensive care unit admission between the groups (15% vs 26%, p = 0.057, OR 0.47 (CI 0.23–0.98)).

Reference	Hall, 2019 [18]
Study type and analysis	Retrospective cohort study multivariate Cox regression models were used to model readmission and mortality as a function of variables of interest USA
Number of participants and characteristics	N= 173 (n=115 on OAC/OAP; n= 58 not on OAC/OAP) **Inclusion criteria:** Patients were included in the analysis if their age was 80 years and they underwent a head CT in the ED at the index fall assessment. **Exclusion criteria:** Only patients with active malignancy or age <80 years were excluded. **Population characteristics:** OAP/OAC (n = 115) / No OAP/OAC (n= 58) Age (years): 86.9 ± 5.0 / 87.1 ± 4.7 Female: 67 (58%) / 40 (69%) Intracranial haemorrhage: 16 (14%) / 6 (10%) Oral antiplatelet: 100 (87%) / - Oral anticoagulant: 26 (23%) / - In the OAP group, 75 patients took aspirin and 25 patients took clopidogrel. In the OAC group, 22 patients took warfarin, 2 took rivaroxaban, 1 took dabigatran, and 1 took apixaban.

Reference	**Hall, 2019** [18]
	Population source: Patients who had suffered a fall were selected from a database of all blunt trauma patients seen in the ED from January 2014 to January 2016, including cases of falls, motor vehicle collisions, and motorcycle.
Clinical variables	OAC , OAP, presence of intracranial haemorrhage on the initial head CT scan, disposition from the ED, and patient-specific comorbidities. These included dementia, hypertension, hyperlipidemia, diabetes, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, and history of stroke or cerebrovascular disease
Confounders	Multivariate analysis Presence of intracranial haemorrhage on the initial head CT scan, disposition from the ED, and patient-specific comorbidities Not adjusted for key founders of age and GCS
Outcomes and effect sizes	Outcome: 30-day, 6-month, and overall mortality <u>Multivariate analysis for 30-day, 6-month, and overall mortality</u> <u>30 -day mortality</u> Variable ICH: HR 6.8 (95% CI 2.6–17.4) OAP/OAC: HR 1.5 (95% CI 0.5–5.3) <u>6-month mortality</u> Rockwood: HR 1.8 (95% CI 1.3–2.4) Disposition to-ICU: HR 5.7 (95% CI 2.2–14.3) Atrial fibrillation: HR 2.0 (95% CI 1.0–3.8) OAP/OAC: HR 0.8 (95% CI 0.4–1.5) <u>Overall mortality</u> Rockwood: HR 1.6 (95% CI 1.3–2.0) CHF: HR 1.8 (95% CI 1.1–3.0) OAP/OAC: HR 0.9 (95% CI 0.5–1.4)
Limitations	Risk of bias (QUIPS): 1. Study participation LOW

Reference	Hall, 2019 [18]
	2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Indirectness: serious Not all participants on anti-coagulants/anti-platelets
Comments	Delayed intracranial haemorrhage did not occur in any patient discharged from the ED after the initial fall. However, 28 patients were readmitted to the hospital within 30 days of their sentinel fall, for an overall readmission rate of 17.5% (95% confidence interval [CI], 11.4–23.2). This group had a higher 6-month mortality (43%) than the group that did not get readmitted (16%, P=0.01). OAP/OAC status was also included in the multivariate analysis because it was a variable of interest in the study. Multivariate analysis demonstrated that the hazard ratio for 30-day readmission was 2.9 times higher for patients living at home compared to those in a nursing facility (P = 0.02; 95% CI, 1.28–7.31). OAP/OAC status did not have a significant impact on 30-day readmission (hazard ratio 1.28; P =0.35; 95% CI, 0.58–3.10). Mortality rates at 1, 6, 12, and 24 months were 8.9% (95% CI, 4.5–13.1), 22.6% (95% CI, 15.9–28.8), 28.0% (95% CI, 20.7–34.7), and 46.7% (95% CI, 36.7–55.2), respectively. Univariate and multivariate analyses were performed to determine patient-specific risk factors for 30-day, 6-month, and overall mortality. Risk factors for mortality were time dependent. For 6-month mortality, each unit of the Rockwood Frailty Score increased the hazard ratio by 76%. For overall mortality, each unit of the Rockwood Frailty Score increased the hazard ratio by 60%. As demonstrated in the multivariate analyses, OAP/OAC status did not have a significant impact on 30-day, 6-month, and overall mortality. Among the patients, 9% had a Rockwood Score of 3; 26%, 4; 29%, 5; 25%, 6; and 11%, 7. Study did not identify any patients with a score of <3, and 36% of patients included in the study had a score 6. The Kaplan-Meier curve showed that patients over 80 years old with higher Rockwood frailty scores were much more likely to die following a fall compared to their less frail counterparts (P < 0.01).

Reference	Mason, 2017 [24] AHEAD study
Study type and analysis	Multicentre, observational study Multivariable analysis. Adjusted for age and sex. UK
Number of participants and characteristics	N= 3566 (aged ≥16 years) who had suffered blunt head injury and were currently taking warfarin. **Inclusion criteria:** Adults (≥16 years) attending the ED in a participating hospital site between September 2011 and March 2013 presenting with head trauma who were currently taking warfarin were included **Exclusion criteria:** patients with a penetrating injury or head trauma following a spontaneous intracranial event. **Population characteristics:** Males : 1738 (49.2) Age group, years <60: 251 (7.1) 60–69: 313 (8.9) 70–79: 925 (26.2) 80–89: 1674 (47.4) 90+: 371 (10.5) Symptoms, type Amnesia: 341 (9.6) 1464 (41.4) Vomiting: 163 (4.6) 900 (25.5) Loss of consciousness: 425 (12.0) 620 (17.5) Headache: 535 (15.1) 1511 (42.8) Admitted Yes : 2216 (62.7) Glasgow Coma Scale

Reference	Mason, 2017 [24] AHEAD study
	15 : 2871 (81.2) 14 : 275 (7.8) 13: 23 (0.7) <13: 60 (1.7) Not recorded at site: 305 (8.6) INR: <2: 741 (21.0) 2–4: 1941 (54.9) >4: 252 (7.1) CT scan performed Yes: 2114 (59.8) Time to scan (from ED attendance) <1 hour: 199 (9.4) 1–4 hours: 1210 (57.2) 4+ hours : 610 (28.9) CT grading Intracranial abnormality likely to be due to injury: 192 (5.4) Other abnormality likely to be due to injury (eg, scalp haematoma, uncomplicated fracture): 417 (11.8) Other abnormality unlikely to be due to injury: 909 (25.7) Normal CT scan: 461 (13.0) Reversal therapy: Yes: 189 (5.3) Prothrombin complex: 30 (0.8) Intravenous vitamin K: 100 (2.8) Oral vitamin K: 16 (0.5) Other* : 42 (1.2) Neurosurgical procedures

Reference	Mason, 2017 [24] AHEAD study
	Yes: 18 (0.5) Further hospital attendances: Head injury-related to original attendance: 37 (1.0) **Population source:** 33 EDs in England and Scotland
Clinical variables	four neurological symptoms (headache, vomiting, amnesia and loss of consciousness)
Confounders	Age and gender Not adjusted for key conder of GCS
Outcomes and effect sizes	Outcome: Predictors (neurological outcomes) of death or neurosurgery resulting from the initial injury <u>Relative risk in patients GCS=15 associated with neurological symptoms (compared with no symptoms) following multiple imputation (n=2871)</u> <u>Multivariable joint analysis</u> Amnesia: RR 3.48 (95% CI 2.13 to 5.70) p<0.001 Vomiting: RR 1.80 (95% CI 0.97 to 3.36) p=0.063 Loss of consciousness (LOC): RR 1.75 (95% CI 1.03 to 2.99) p=0.039 Headache: RR 1.30 (95% CI 0.76 to 2.22) p=0.331 When all four symptoms were included in the same model amnesia was the strongest predictor with vomiting or loss of consciousness associated with slightly lower relative risks and headache associated with the lowest relative risk
Limitations	Risk of bias (QUIPS): 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH

Reference	Mason, 2017 [24] AHEAD study
	Indirectness: None
Comments	Adverse event rate by Glasgow Coma Scale (GCS) and neurological symptoms GCS=15 and no neurological symptoms (n=2243): adverse event=2.8% (n=65) GCS=15 and one neurological symptom (n=384): adverse event=9.0% (n=38) GCS=15 and two neurological symptoms (n=109): adverse event=13.5% (n=17) GCS=15 and three neurological symptoms (n=15): adverse event=26.7% (n=4) GCS<15 (n=358): adverse event=20.9% (n=75)

Reference	Nishijima, 2018 [27]
Study type and analysis	Prospective cohort study Random-effects multivariate logistic regression model. Adjusted results. USA
Number of participants and characteristics	N= 1140 **Inclusion criteria:** patients 55 years and older with head trauma who were transported to a hospital by the participating EMS agencies from August 1, 2015 to September 30, 2016. Age 55 years and older was chosen as the study population based on the current field triage definition of older adults **Exclusion criteria:** patients transferred by emergency medical services (EMS) from another receiving facility (interfacility transport), patients transported to a non-participating hospital, and patients with penetrating head trauma. Also excluded patients for whom it was unable to link hospital data to EMS data

Reference	Nishijima, 2018 [27]
	Population characteristics: Age, median (Q1, Q3): 73 (63, 84) years Male sex: 610 (47) Race White: 919 (70) Black: 115 (9) Asian: 117 (9) American Indian/Alaskan Native: 9 (0.7) Pacific Islander/Native Hawaiian: 20 (1) Other: 135 (10) Unknown: 22 (2) Ethnicity Hispanic 113: (9) Advanced Life Support transport: 839 (64) Initial pre-hospital Glasgow Coma Scale (GCS) score GCS score 15: 1003 (77) GCS score 14: 203 (16) GCS score 13: 32 (2) GCS score <13: 58 (4) Anticoagulant/antiplatelet medication use (may have more than one medication) Warfarin: 102 (8) Direct oral anticoagulant: 53 (4) Aspirin: 279 (21) Other antiplatelet (clopidogrel and others): 89 (7) More than one anticoagulant or antiplatelet medication: 53 (4) None: 887 (68) International normalized ratio, median (Q1, Q3): 2.39 (1.81, 2.90) Platelet count, median (Q1, Q3): 214 (173, 261)

Reference	Nishijima, 2018 [27]
	Injury severity score, median (Q1, Q3): 6 (4, 14) Isolated head injury: 1224 (94) **Population source:** a county-wide, prospective study at five EMS agencies and 11 hospitals in Northern California.
Clinical variables	Ten variables: age 80 years or older [ideal Cut-point based on receiver operating curve], male sex, an abnormal initial EMS GCS score [GCS score <15], a mechanism of injury other than a fall from standing height or less, a history of loss of consciousness or amnesia, anticoagulant or antiplatelet use, evidence of trauma above the clavicles, a history of vomiting, a history of headache, and the presence of physiological, anatomical, or mechanism of injury trauma triage criteria [Step 1 to 3 criteria]) were defined a priori and entered into a random-effects multivariate logistic regression model to account for random variation.
Confounders	multi-variate logistic regression risk factors study reports adjusted for numerous demographic and clinical variables in the adjusted analysis.
Outcomes and effect sizes	Outcome: Predict the Incidence of Traumatic Intracranial haemorrhage (ICH) on Initial Cranial CT Scan N=434 (33%) patients had anticoagulant or antiplatelet use and 112 (10%) had traumatic ICH. <u>Adjusted Analysis to Predict the Incidence of Traumatic Intracranial haemorrhage on Initial Cranial CT Scan, n = 1140 Variable OR (95% CI)</u> History of vomiting: 6.65 (2.61–16.96) Evidence of trauma above the clavicles: 2.55 (1.33–4.88) Abnormal EMS GCS score, initial: 2.06 (1.27–3.35) Mechanism of injury other than a fall from standing height or less: 1.92 (1.17–3.15) Loss of consciousness or amnesia: 1.63 (1.02–2.61) Any anticoagulant or antiplatelet use: 1.53 (0.99–2.38) Age 80 years or older: 1.53 (0.96–2.43) History of headache: 1.11 (0.44–2.76) Male sex: 1.00 (0.65–1.53)

Reference	Nishijima, 2018 [27]
	On adjusted analysis, a history of vomiting, evidence of trauma above the clavicles, an abnormal initial EMS GCS score, a mechanism of injury other than a fall from standing height or less and a history of loss of consciousness or amnesia were independent risk factors for the incidence of traumatic ICH on initial cranial CT scan. A history of anticoagulant or antiplatelet use was not identified as an independent risk factor for traumatic ICH. The sensitivity analysis demonstrated that ‘‘warfarin use and INR level 2.0 or higher’’ was not an independent risk factor for the incidence of traumatic ICH (OR 1.18, 95% CI 0.48–2.87).
Limitations	Risk of bias (QUIPS): 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS LOW Indirectness: serious Not all participants on anti-coagulants/anti-platelets
Comments	Of the 1304 patients enrolled, 1147 (88%) received a cranial CT scan and were eligible for outcome analysis. Of these patients receiving a cranial CT scan, there were 112 (9.8%) with a traumatic ICH and 22(1.9%) with in-hospital neurosurgery or death due to trauma. Four hundred and thirty-four of 1304 patients (33.3%) had anticoagulant or antiplatelet use. There was no difference in the incidence of traumatic ICH in patients with (47/434; 10.8%, 95% CI 8.1%– 14.1%) and without (65/713; 9.1%, 95% CI 7.1%–11.5%) anticoagulant or antiplatelet use. There was also no difference in the incidence of in-hospital neurosurgery or death due to trauma in patients with (6/434; 1.4%, 95% CI 0.5%–3.0%) and without (16/713; 2.2%, 95% CI 1.3%–3.6%) anticoagulant or antiplatelet use. The incidence of traumatic ICH and in-hospital neurosurgery or death due to trauma also did not differ when compared across specific anticoagulant or antiplatelet medications.

Reference	Nishijima 2013 [28]
Study type and analysis	Prospective observational study between April 2009 and January 2011. Multivariable analysis adjusting data for age 65 years or older, warfarin use, clopidogrel use, concomitant aspirin use, non-ground level fall mechanism of injury, headache, vomiting, loss of consciousness (LOC) or amnesia, drug or alcohol intoxication, evidence of trauma above the clavicles, abnormal mental status. USA
Number of participants and characteristics	N=982 **Inclusion criteria:** adult (≥ 18 years old) ED patients with pre-injury warfarin or clopidogrel use (within the prior seven days) and mild blunt head trauma (initial ED Glasgow Coma Scale (GCS) score 13 to 15). **Exclusion criteria:** patients who did not receive cranial CT scans during the index ED visit **Population characteristics:** • Age mean (SD): 75.4 years (12.6) years • Male:Female = 464/518 • Admission Glasgow Coma Score: 13 to 15 **Population source:** Two trauma centres and four community hospitals in Northern California, USA
Clinical variables	Warfarin use n (%): 714 (72.7) Clopidogrel use n (%): 279 (28.4) Concomitant aspirin use n (%): 45 (4.6) Vomiting n (%): 41 (4.2) Headache n (%): 349 (35.5) Loss of consciousness or amnesia n (%): 187 (19.0) Any evidence of trauma above the clavicles n (%):696 (70.9) Normal mental status (GCS 15) n (%): 879 (89.5) Admitted to hospital n (%): 346 (33.1)
Confounders	Multivariable analysis using both binary recursive partitioning and logistic regression

Reference	Nishijima 2013 [28]
	Factors included in the adjusted multivariate analysis: age 65 years or older, warfarin use, clopidogrel use, concomitant aspirin use, non-ground level fall mechanism of injury, headache, vomiting, LOL or amnesia, drug or alcohol intoxication, evidence of trauma above the clavicles, abnormal mental status. Not adjusted for key confounder of GCS
Outcomes and effect sizes	Outcome: predictors of traumatic intracranial haemorrhage Adjusted risk for traumatic intracranial haemorrhage (multivariable analysis) Warfarin use 0.62 (0.70–5.49) Clopidogrel use 1.68 (0.19–14.72) Vomiting 3.68 (1.55–8.76) Headache 1.60 (0.93–2.77) Drug or alcohol intoxication 1.61 (0.50–5.16) Abnormal mental status 3.08 (1.60–5.94) Multivariable logistic regression identified vomiting (adjusted odds ratio (aOR) 3.68; 95% CI = 1.55 to 8.76) and abnormal mental status (aOR 3.08; 95% CI = 1.60 to 5.94) as associated with immediate traumatic intracranial haemorrhage (tICH). No association for clopidogrel use, warfarin use, headache, drug or alcohol intoxication.
Limitations	Risk of bias (QUIPS): 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Indirectness: no indirectness

Reference	Nishijima 2013 [28]
Comments	

Reference	Turcato 2019 [36]
Study type and analysis	A retrospective observational study of patients admitted to the Emergency Department of the University Hospital of Verona, Verona, Italy from June 1, 2017 to August 31, 2018, due to mild traumatic brain injury. Adjusting data for VKA treatment, pre-trauma conditions (previous neurosurgery high-energy impact, alcohol abuse, antiplatelet treatment), post-trauma symptoms (amnesia, loss of consciousness, post-trauma seizures, vomiting, GCS < 15, worsening headache, trauma beyond clavicles, presence of cranial fracture) using multivariate analysis to adjust the changes. Italy
Number of participants and characteristics	N=451 (n= 268 were on vitamin K antagonists (VKAs) and n=183 on direct oral anticoagulants ((DOACs) **Inclusion criteria:** patients treated with anticoagulants, GCS score of 13–15, regardless of the presence of loss of consciousness or amnesia immediately after the injury. **Exclusion criteria:** none stated **Population characteristics:** • Age median (IQR): 83 (78–88) years • Male:Female = 212:238 • GCS: not stated **Population source:** Emergency Department of the University Hospital of Verona, Verona, Italy
Clinical variables	Direct oral anticoagulants (DOAC): n (%) 183 (40.6) Vitamin K antagonists (VA): n (%) 268 (59.4) High-energy impact: n (%) 14 (3.1)

Reference	Turcato 2019 [36]
	Indication to anticoagulation VA vs DOAC n (%): atrial fibrillation: 232 (86.6) vs 171 (93.4) mechanical valve: 19 (7.1) vs 0 (0.0) venous thromboembolism 17 (6.3) vs 11 (6.0) Intracranial bleeding, n (%) VA vs DOAC global: 40 (14.9) vs 14 (7.7) immediate: 31 (11.6) vs 10 (5.5) delayed: 31 (11.6) vs 10 (5.5)
Confounders	Multivariable analysis Factors included in the adjusted multivariate analysis: VKA treatment, pre-trauma conditions and post trauma conditions
Outcomes and effect sizes	Independent predictors for global ICH in patients on anticoagulant therapy: VKA therapy: OR 2.327, 95% CI 1.117 to 4.847, p = 0.024 High-energy impact: OR 11.229, 95% CI 3.265 to 38.617 Amnesia: OR 2.814, 95% CI 1.102 to 6.556, p = 0.017 Loss of consciousness: OR 5.286, 95% CI 1.102 to 25.348, p = 0.037 GCS score < 15: OR 4.719, 95% CI 1.938 to 11.492, p = 0.001 Presence of an objective lesion above the clavicles: OR 2.742, 95% CI 1.297 to 5.797, p = 0.008
Limitations	Risk of bias (QUIPS): 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS LOW Indirectness: no indirectness

Reference	**Turcato 2019 [36]**
Comments	DOAC-treated patients had a lower overall ICH rate compared with theVKA-treated patients. In fact, only 7.7% (14/183) of DOAC-treated patients presented overall bleeding compared with the 14.9% (40/268) of VKA-treated patients (p = 0.026), whereas early bleeding was present in 5.5% (10/183) of DOAC-treated patients comparedwith the 11.6% (31/268) of VKA-treated patients (p = 0.030). No difference was found for delayed bleeding (3.8 vs. 2.3, p = 0.570). Globally, 1.6% of patients (7/451) required neurosurgical treatment; 0.7% of the patients (3/451) died as a result of ICH. There was no difference between the DOAC and VKA treatment groups

Appendix E – Forest plots

Adults

People on anticoagulants only

Independent predictors for intra cranial haemorrhage in people on anticoagulant therapy (all participants on VKA and DOACs)

Figure 2: Vitamin K antagonists (VKA) therapy

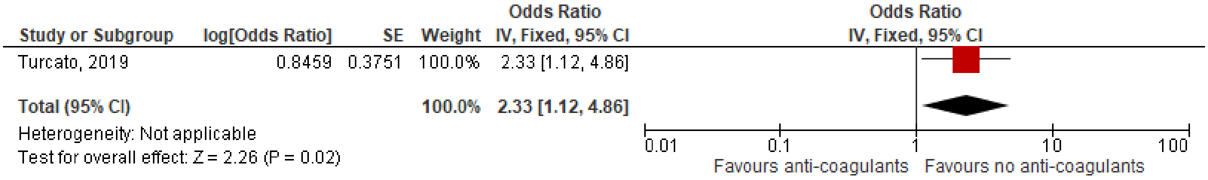


Figure 3: vitamin K antagonists (VKAs) treatment

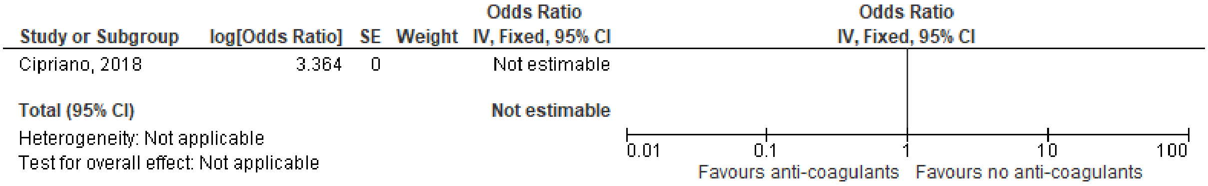


Figure 4: Amnesia

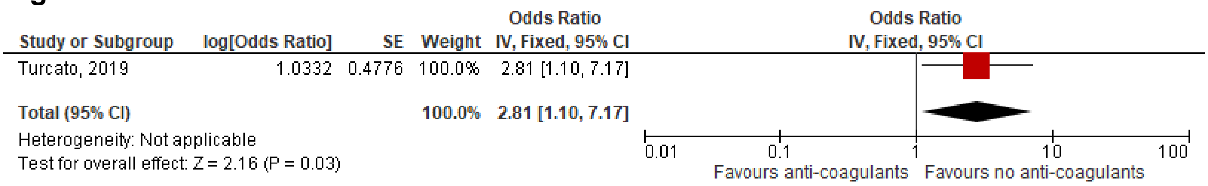


Figure 5: Post-traumatic amnesia

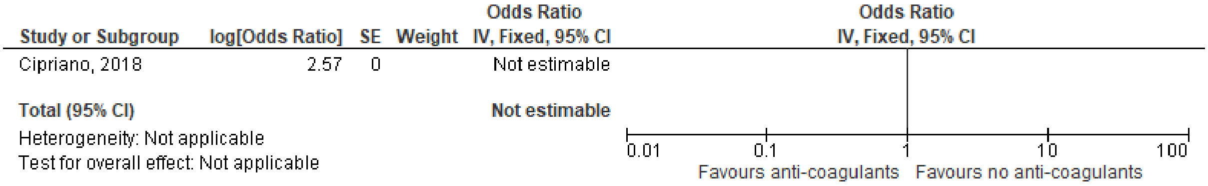


Figure 6: Loss of consciousness

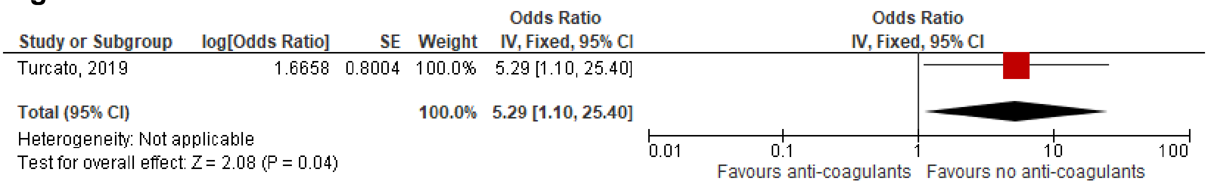


Figure 7: GCS<15

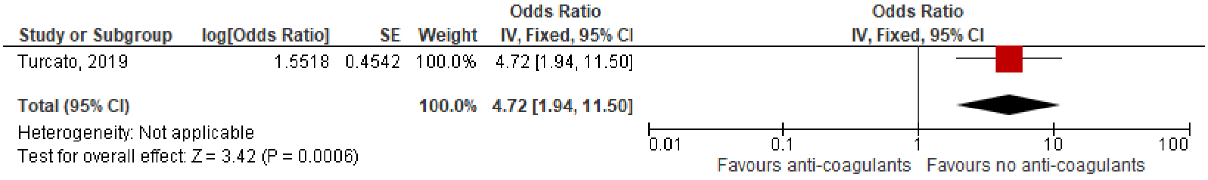
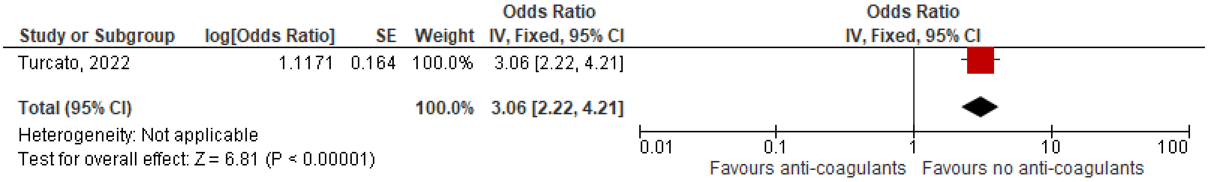


Figure 8: GCS<15



Predictors (neurological symptoms) of death or neurosurgery resulting from the initial injury- Compared with no symptoms. - people taking warfarin (in people with GCS 15)

Figure 9: Amnesia

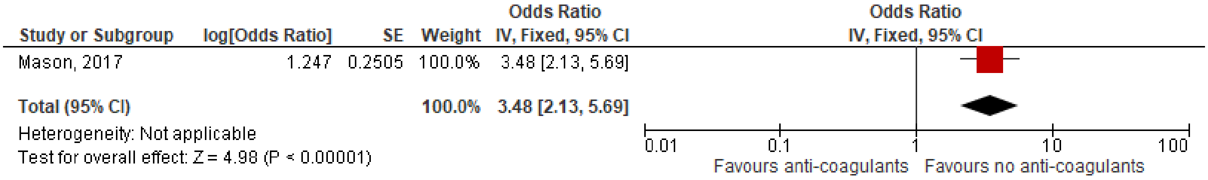


Figure 10: vomiting

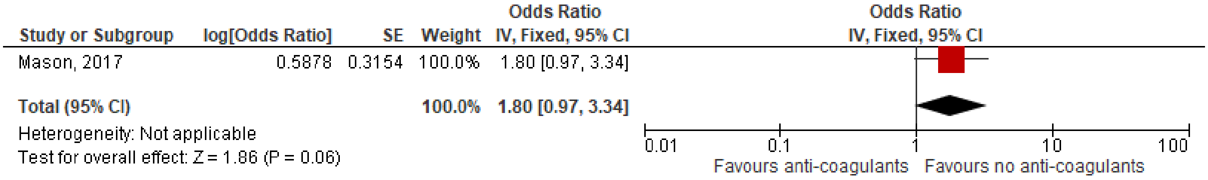


Figure 11: loss of consciousness

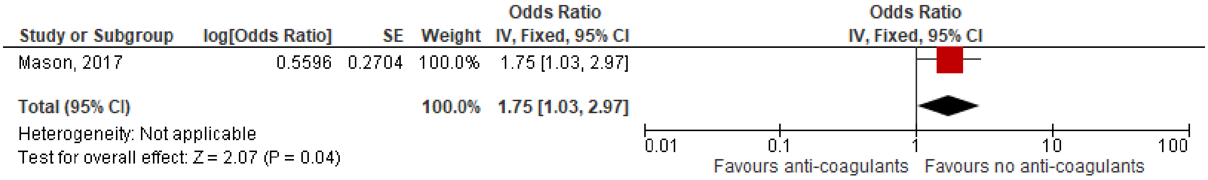
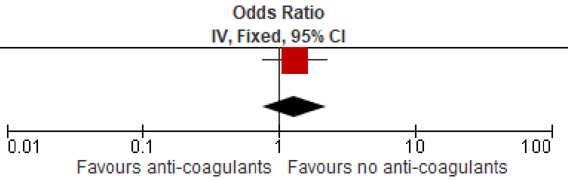


Figure 12: headache

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Mason, 2017	0.2624	0.2739	100.0%	1.30 [0.76, 2.22]
Total (95% CI)			**100.0%**	**1.30 [0.76, 2.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)



Anti-coagulants and anti-platelets

Predictors of immediate traumatic intracranial haemorrhage- People on anticoagulant or antiplatelet (All participants on anticoagulant or antiplatelet therapy)

Figure 13: clopidogrel use

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Nishijima, 2013	0.5188	1.112	100.0%	1.68 [0.19, 14.85]
Total (95% CI)			**100.0%**	**1.68 [0.19, 14.85]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

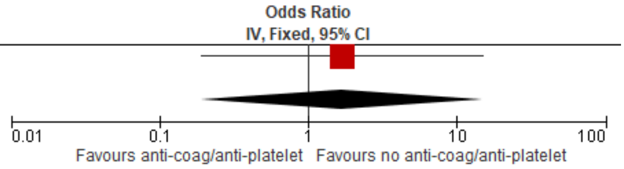


Figure 14: warfarin use

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Nishijima, 2013	-0.478	1.1128	100.0%	0.62 [0.07, 5.49]
Total (95% CI)			**100.0%**	**0.62 [0.07, 5.49]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)

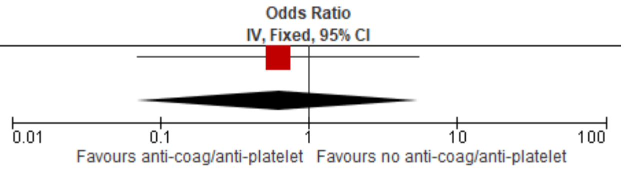


Figure 15: vomiting

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Nishijima, 2013	1.3029	0.4412	100.0%	3.68 [1.55, 8.74]
Total (95% CI)			**100.0%**	**3.68 [1.55, 8.74]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.95 (P = 0.003)

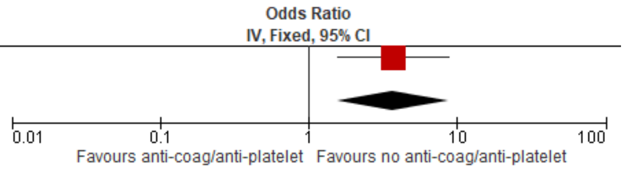


Figure 16: abnormal mental status

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Nishijima, 2013	1.1249	0.3342	100.0%	3.08 [1.60, 5.93]
Total (95% CI)			**100.0%**	**3.08 [1.60, 5.93]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.37 (P = 0.0008)

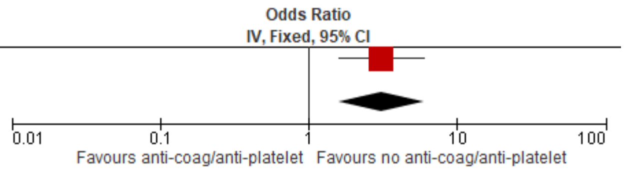
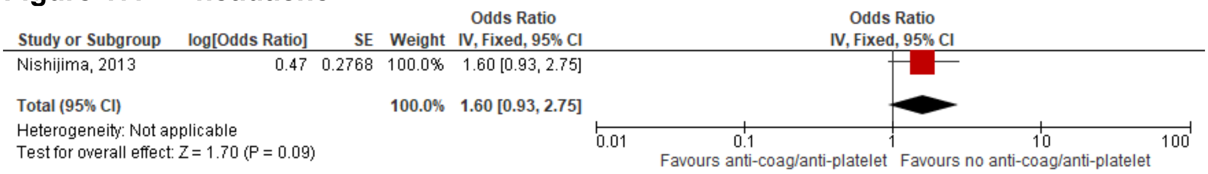


Figure 17: headache



Predictors of acute intra cranial bleeding complications (overall sample)-[anti-thrombotic therapy + people not on anti-thrombotic therapy in Galliazzo 2019 and anti-coagulant+antiplatelet in Nishijima 2018]

Figure 18: anti-platelet use

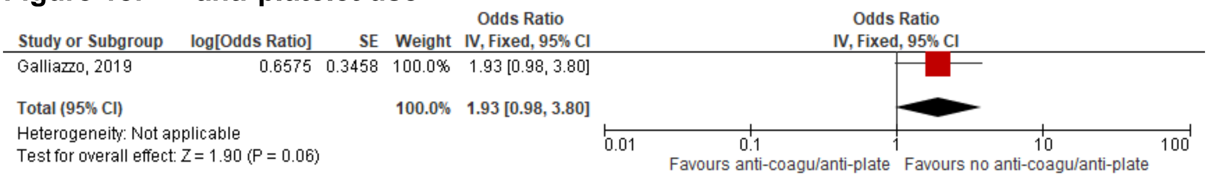


Figure 19: vitamin K antagonist

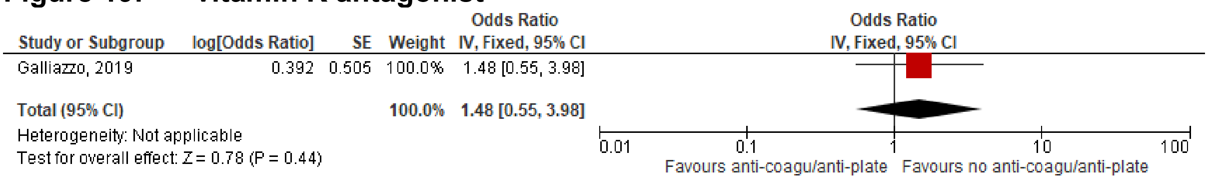


Figure 20: Direct oral anticoagulants (DOACs)

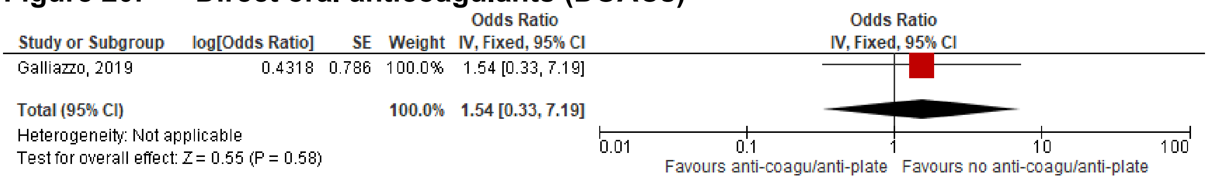


Figure 21: Double therapy

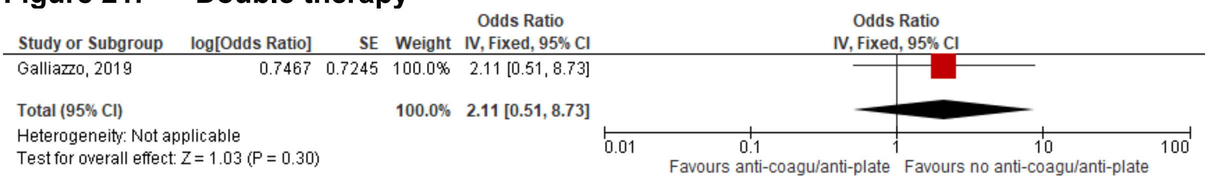


Figure 22: any anti-platelet or anti-coagulant use

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Nishijima, 2018	0.4253	0.2221	100.0%	1.53 [0.99, 2.36]
Total (95% CI)			**100.0%**	**1.53 [0.99, 2.36]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)

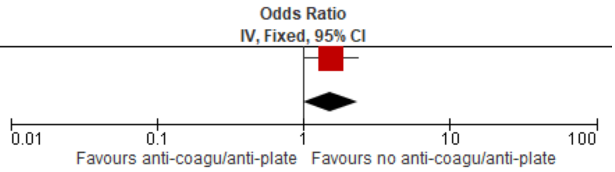


Figure 23: Age>65 years

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	0.6366	0.3673	100.0%	1.89 [0.92, 3.88]
Total (95% CI)			**100.0%**	**1.89 [0.92, 3.88]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)

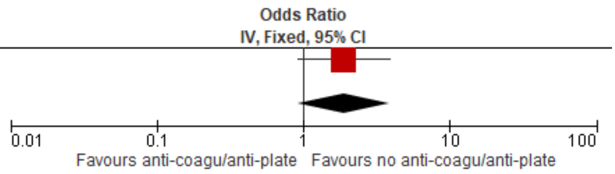


Figure 24: Age>80 years

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Nishijima, 2018	0.4253	0.2378	100.0%	1.53 [0.96, 2.44]
Total (95% CI)			**100.0%**	**1.53 [0.96, 2.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)

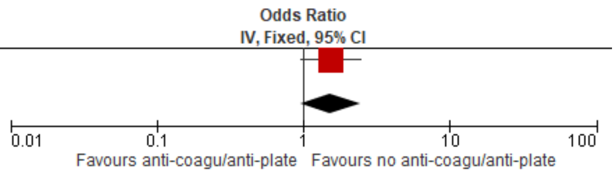


Figure 25: GCS<15

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	2.0732	0.4772	100.0%	7.95 [3.12, 20.26]
Total (95% CI)			**100.0%**	**7.95 [3.12, 20.26]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.34 (P < 0.0001)

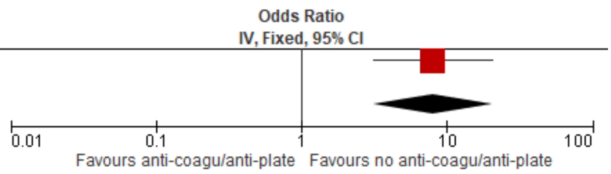


Figure 26: GCS<15

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Nishijima, 2018	0.7227	0.2468	100.0%	2.06 [1.27, 3.34]
Total (95% CI)			**100.0%**	**2.06 [1.27, 3.34]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.93 (P = 0.003)

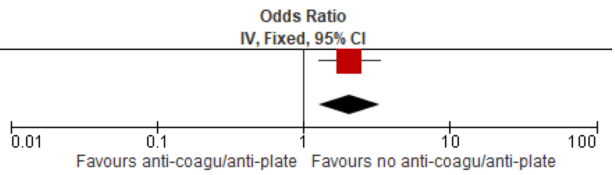


Figure 27: Loss of consciousness

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	0.27	0.5804	100.0%	1.31 [0.42, 4.09]
Total (95% CI)			**100.0%**	**1.31 [0.42, 4.09]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

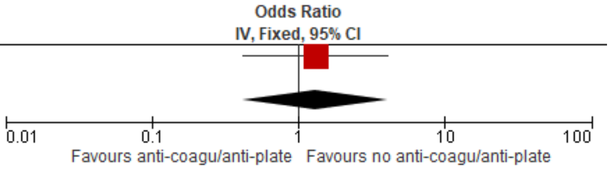


Figure 28: Loss of consciousness or amnesia

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Nishijima, 2018	0.4886	0.2392	100.0%	1.63 [1.02, 2.60]
Total (95% CI)			**100.0%**	**1.63 [1.02, 2.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)

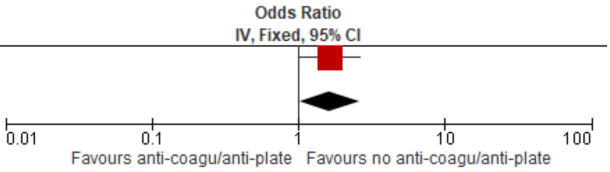


Figure 29: amnesia

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	1.8703	0.305	100.0%	6.49 [3.57, 11.80]
Total (95% CI)			**100.0%**	**6.49 [3.57, 11.80]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.13 (P < 0.00001)

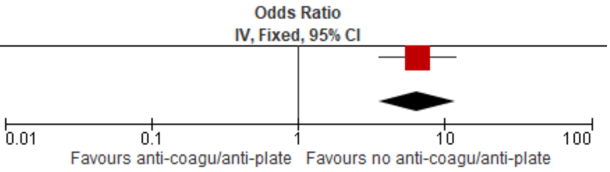


Figure 30: neurological signs

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	0.0392	1.2486	100.0%	1.04 [0.09, 12.02]
Total (95% CI)			**100.0%**	**1.04 [0.09, 12.02]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)

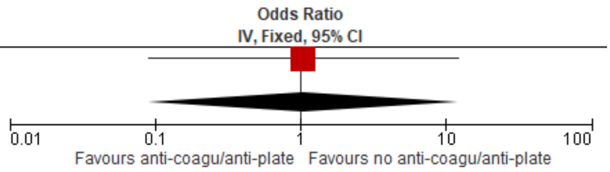


Figure 31: seizure

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	0	0		Not estimable
Total (95% CI)				**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

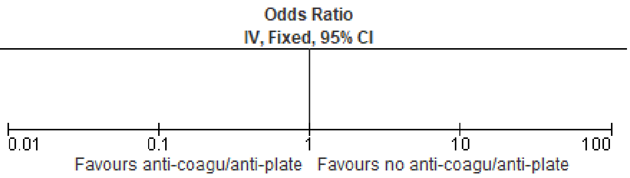


Figure 32: headache

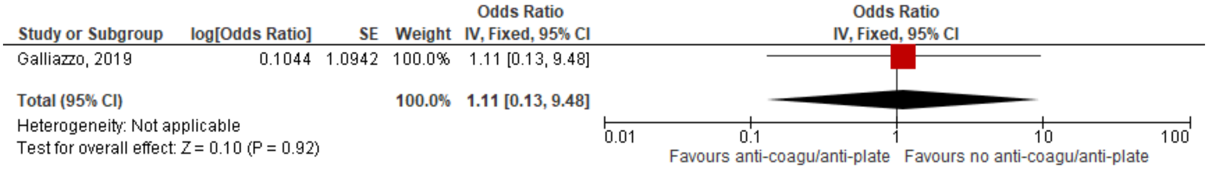


Figure 33: history of headache

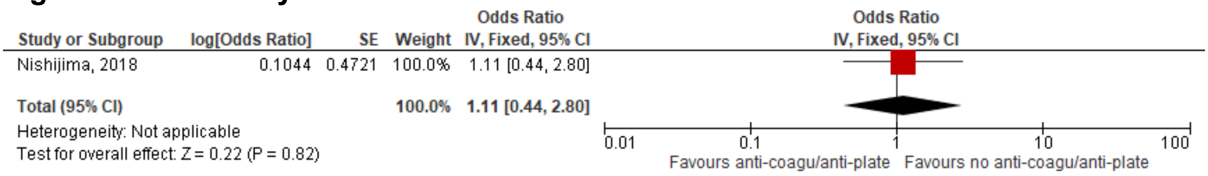


Figure 34: vomiting

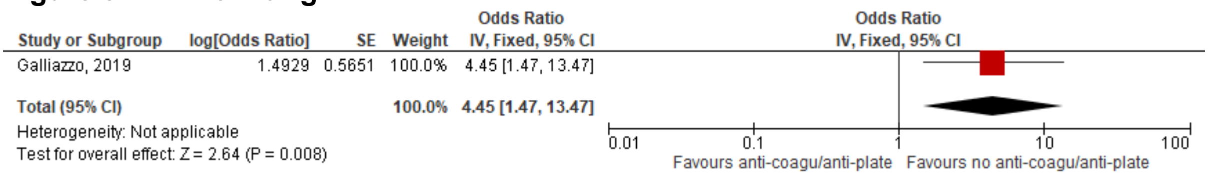


Figure 35: history of vomiting

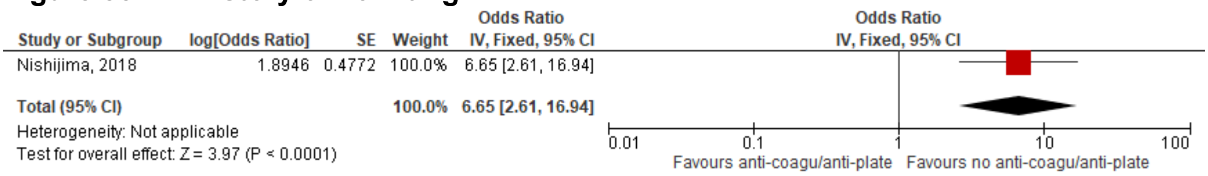
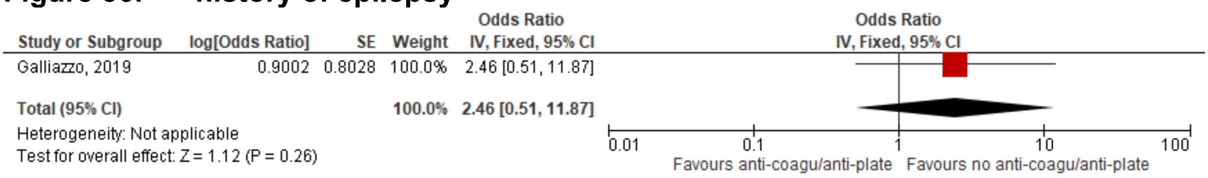


Figure 36: history of epilepsy



Predictors for intracranial bleedings. only patients with CT performed (n=1387 CT performed) - people on anti-thrombotic therapy + people not on anti-thrombotic therapy

Figure 37: anti-platelet

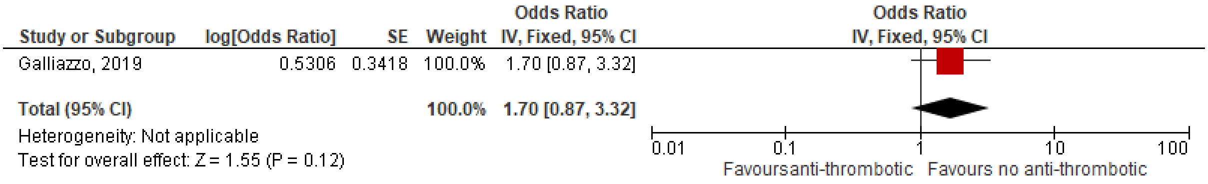


Figure 38: vitamin K antagonist

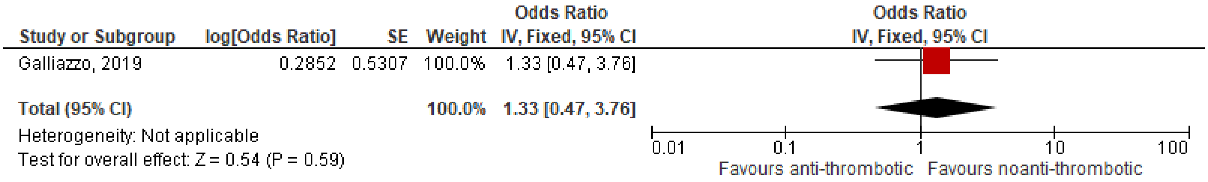


Figure 39: Direct oral anticoagulants (DOACs)

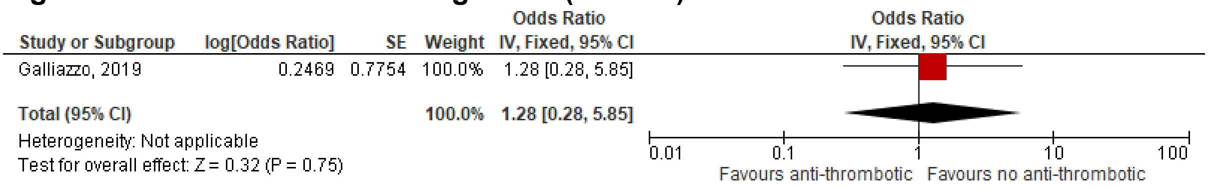


Figure 40: Double therapy

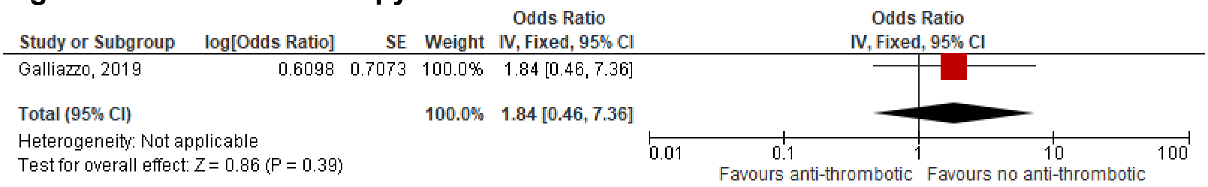


Figure 41: Age>65 years

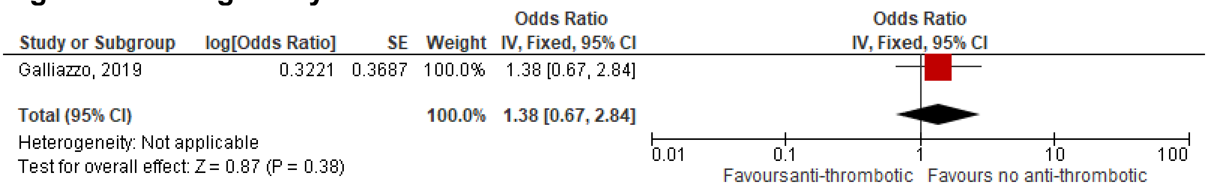


Figure 42: GCS<15

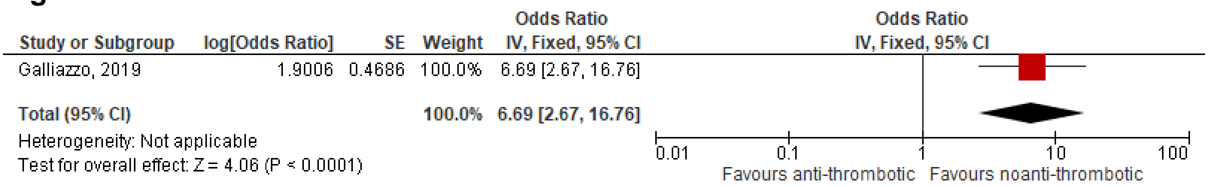


Figure 43: Loss of consciousness

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	0.0953	0.5699	100.0%	1.10 [0.36, 3.36]
Total (95% CI)			**100.0%**	**1.10 [0.36, 3.36]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.87)

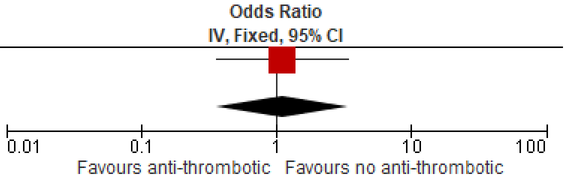


Figure 44: amnesia

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	1.7263	0.3085	100.0%	5.62 [3.07, 10.29]
Total (95% CI)			**100.0%**	**5.62 [3.07, 10.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.60 (P < 0.00001)

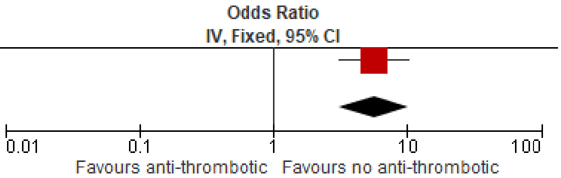


Figure 45: neurological signs

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	-0.0834	1.186	100.0%	0.92 [0.09, 9.40]
Total (95% CI)			**100.0%**	**0.92 [0.09, 9.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.94)

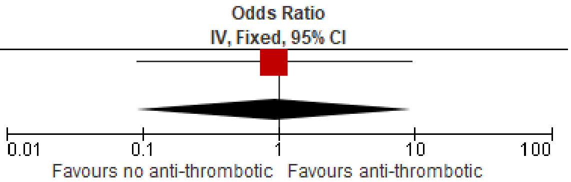


Figure 46: seizure

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	0	0		Not estimable
Total (95% CI)				**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

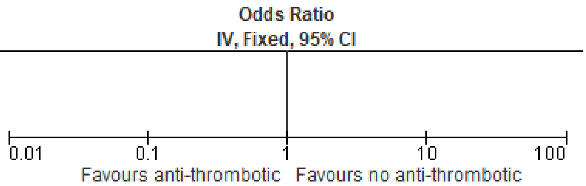


Figure 47: headache

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	-0.0943	1.1267	100.0%	0.91 [0.10, 8.28]
Total (95% CI)			**100.0%**	**0.91 [0.10, 8.28]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.93)

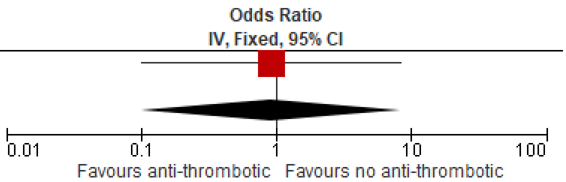


Figure 48: vomiting

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	1.4656	0.6023	100.0%	4.33 [1.33, 14.10]
Total (95% CI)			**100.0%**	**4.33 [1.33, 14.10]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.43 (P = 0.01)				

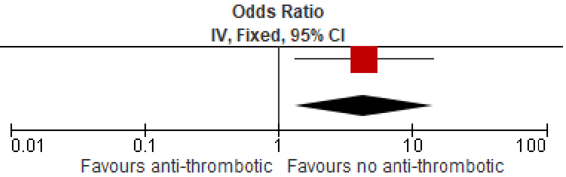
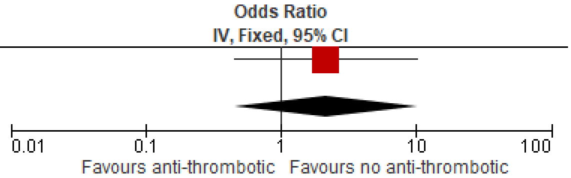


Figure 49: history of epilepsy

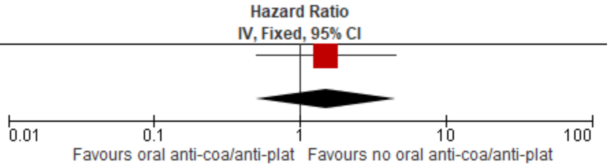
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Galliazzo, 2019	0.7655	0.798	100.0%	2.15 [0.45, 10.27]
Total (95% CI)			**100.0%**	**2.15 [0.45, 10.27]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.96 (P = 0.34)				



Predictors of 30-day mortality - oral antiplatelet and oral anticoagulant + not on oral antiplatelet and oral anticoagulant

Figure 50: Oral antiplatelet and oral anticoagulant (OAP/OAC)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Hall, 2019	0.4055	0.5605	100.0%	1.50 [0.50, 4.50]
Total (95% CI)			**100.0%**	**1.50 [0.50, 4.50]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.72 (P = 0.47)				



Predictors of 6-month mortality- oral antiplatelet and oral anticoagulant + not on oral antiplatelet and oral anticoagulant

Figure 51: Higher Rockwood score

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Hall, 2019	0.5878	0.166	100.0%	1.80 [1.30, 2.49]
Total (95% CI)			**100.0%**	**1.80 [1.30, 2.49]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.54 (P = 0.0004)				

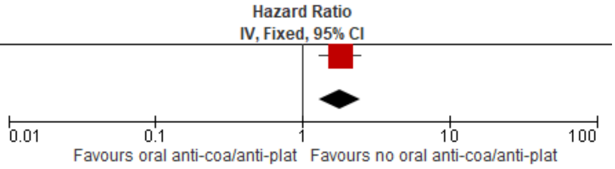
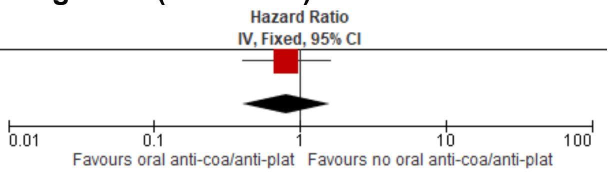


Figure 52: Oral antiplatelet and oral anticoagulant (OAP/OAC)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Hall, 2019	-0.2231	0.3537	100.0%	0.80 [0.40, 1.60]
Total (95% CI)			**100.0%**	**0.80 [0.40, 1.60]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.63 (P = 0.53)				



Predictors of overall mortality- oral antiplatelet and oral anticoagulant + not on oral antiplatelet and oral anticoagulant

Figure 53: Higher Rockwood score

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Hall, 2019	0.47	0.1059	100.0%	1.60 [1.30, 1.97]
Total (95% CI)			**100.0%**	**1.60 [1.30, 1.97]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.44 (P < 0.00001)

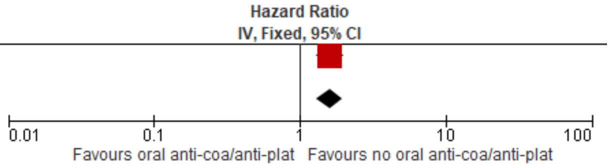
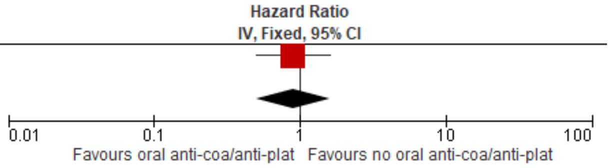


Figure 54: Oral antiplatelet and oral anticoagulant (OAP/OAC)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Hall, 2019	-0.1054	0.2999	100.0%	0.90 [0.50, 1.62]
Total (95% CI)			**100.0%**	**0.90 [0.50, 1.62]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)



People with pre-injury cognitive impairment sustaining injury through low energy impact/ low level falls (fall from standing position)

Risk factors associated with the diagnosis of intracranial bleed (ICB) after a fall from a standing position

Figure 55: Use of aspirin (gender was adjusted)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Ahmed, 2015	0.7747	0.3655	100.0%	2.17 [1.06, 4.44]
Total (95% CI)			**100.0%**	**2.17 [1.06, 4.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.12 (P = 0.03)

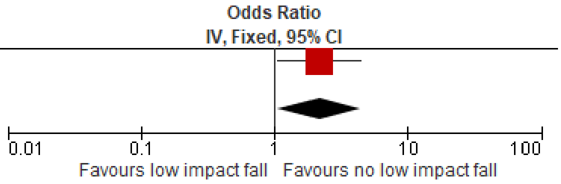


Figure 56: Anticoagulation therapy

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
de Wit, 2020	-0.1393	0.3034	100.0%	0.87 [0.48, 1.58]
Total (95% CI)			**100.0%**	**0.87 [0.48, 1.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)

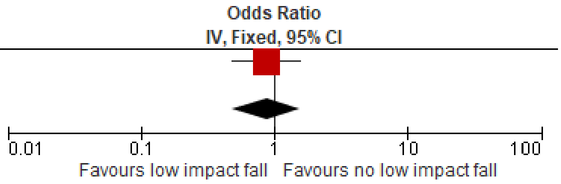


Figure 57: Antiplatelet therapy

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
de Wit, 2020	0.0677	0.2622	100.0%	1.07 [0.64, 1.79]
Total (95% CI)			**100.0%**	**1.07 [0.64, 1.79]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)

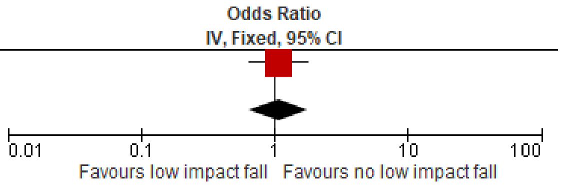
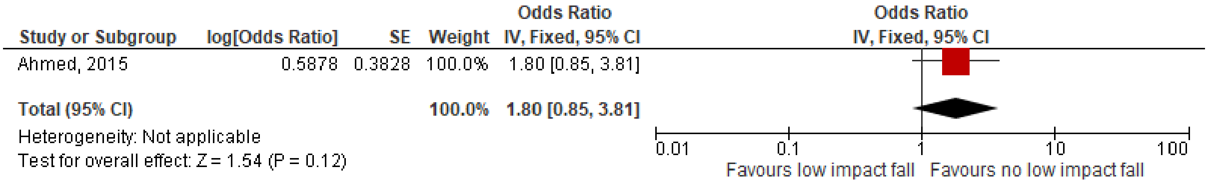
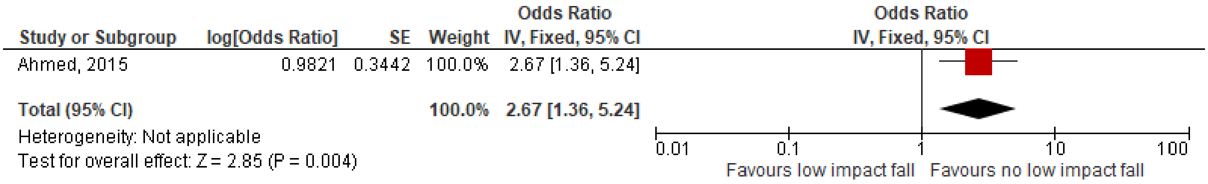


Figure 58: Age ≥70 years (not adjusted for gender)



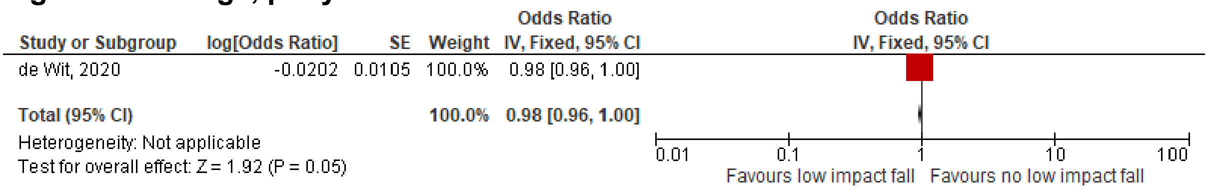
88

Figure 59: Age ≥70 years (gender was adjusted)



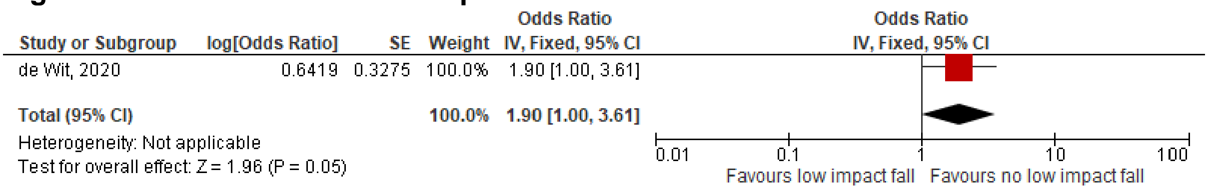
89

Figure 60: Age, per year



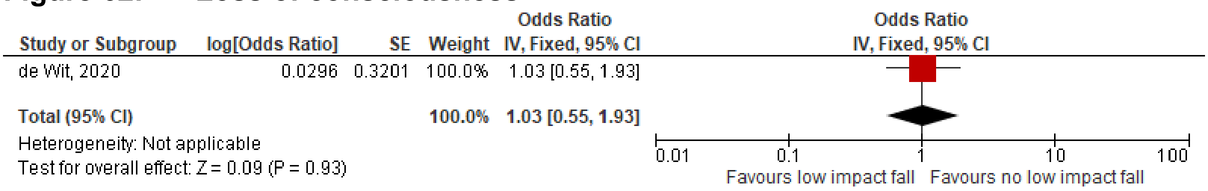
90

Figure 61: Reduced GCS compared to normal



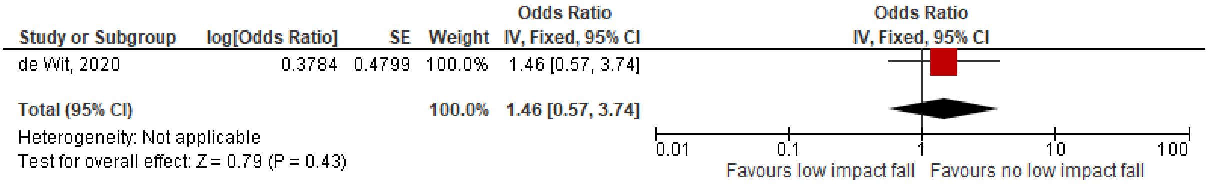
91

Figure 62: Loss of consciousness



92

Figure 63: vomited after fall



Infants with late presentation (> 24 hours post-injury)

Variables associated with increased risk for significant TBI on CT in children with late presentation (> 24 hours + < 24 hours post-injury) [Significant TBI on CT includes any of the following descriptions: any intracranial bleeding, pneumocephalus, cerebral oedema, skull fracture depressed by at least the thickness of skull, or diastasis of the skull]

Figure 64: Age, months - Older age vs younger age

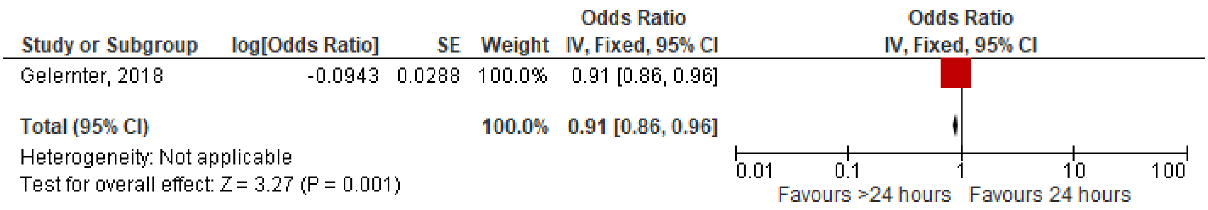


Figure 65: GCS<15

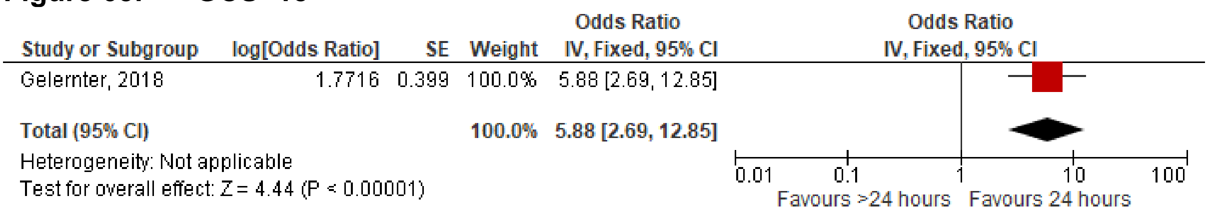
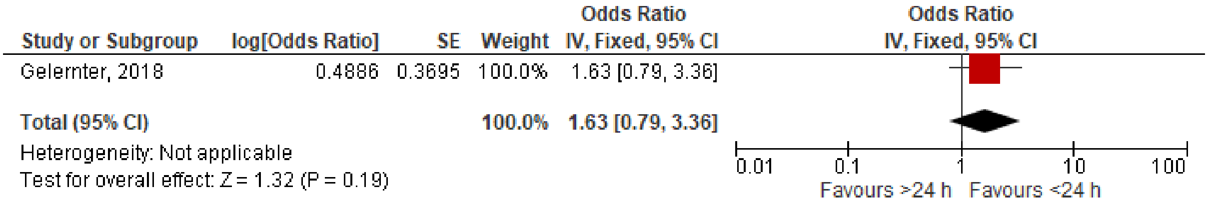


Figure 66: Duration from injury >24 h



Variables associated with increased risk for any TBI on CT in children with late presentation (> 24 hours + < 24 hours post-injury) **[any TBI on CT as any finding on CT related to the injury (e.g. linear skull fracture)]**

Figure 67: Age, months - Older age vs younger age (not specified)

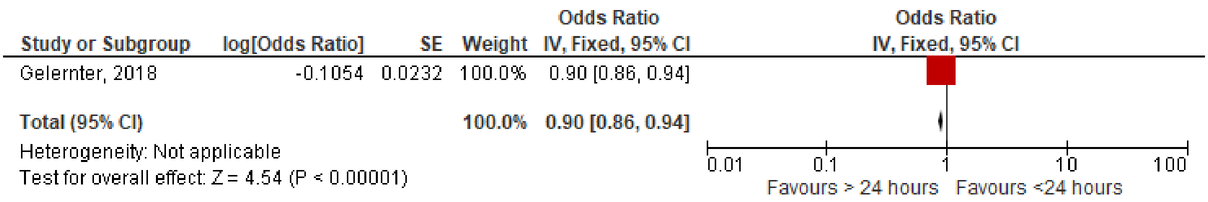


Figure 68: GCS<15

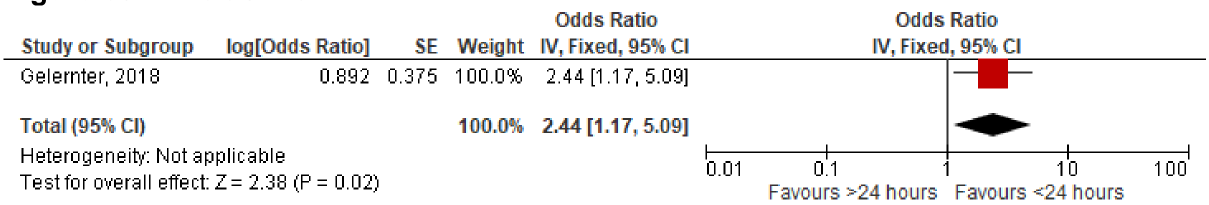
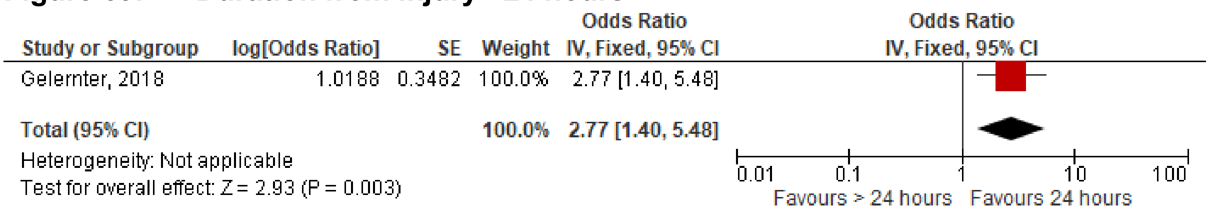
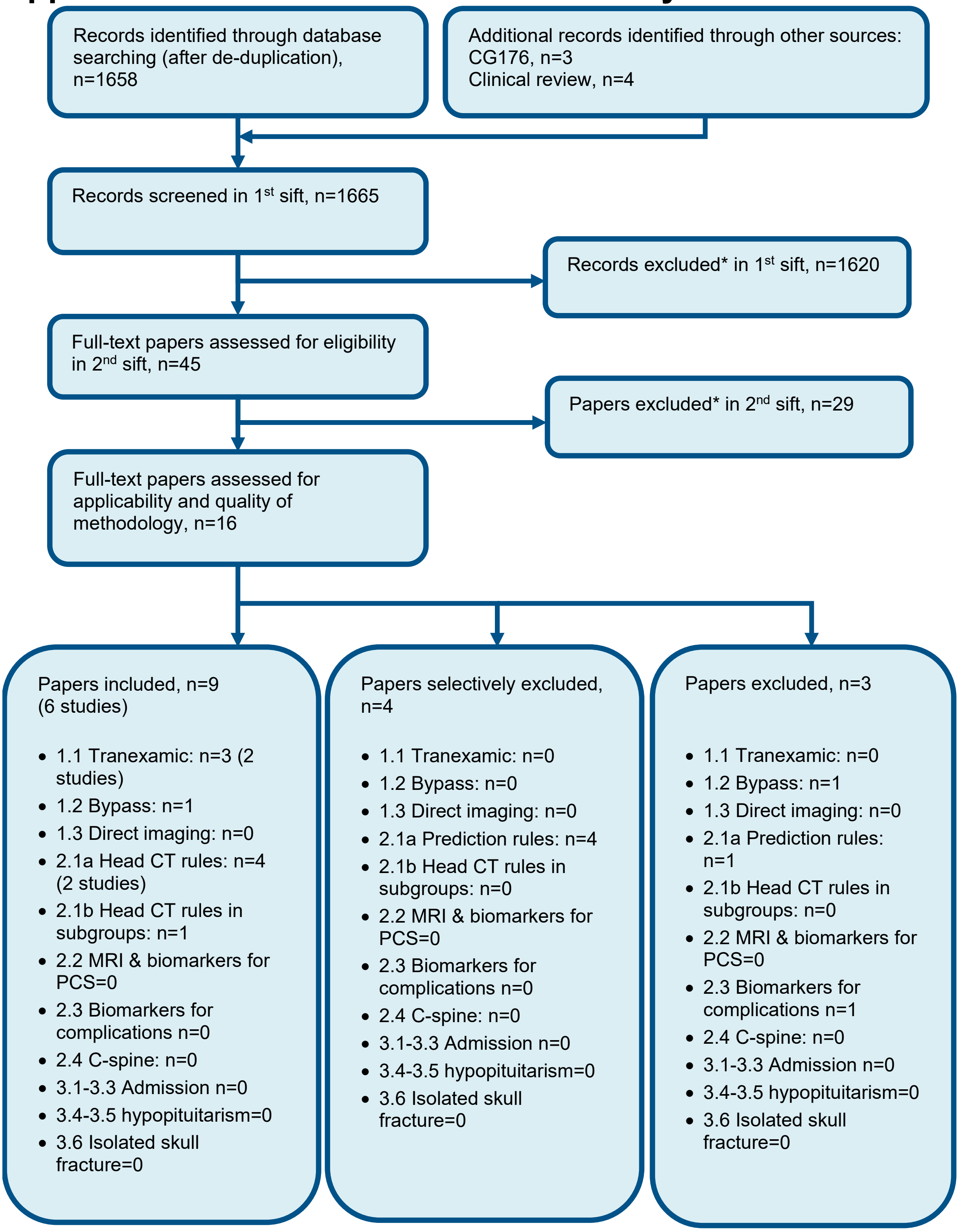


Figure 69: Duration from injury >24 hours



Appendix F – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G – Economic evidence tables

Study	Kuczawski 2016[21]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision analytic model (patient-level simulation) **Approach to analysis:** The analysis is based on AHEAD observational study. People who would have received a CT scan under the new NICE guideline were simulated over their lifetime with their probability of survival and QoL states assessed by two physicians **Perspective:** UK NHS **Time horizon:** Lifetime **Discounting:** Costs: 3.5%	**Population:** People with head injury who were taking warfarin and presented to a hospital emergency department (ED) **Cohort settings:** Median age: NR Male: NR **Intervention 1:** CT scan following head injury to people with coagulopathy (including those currently treated with warfarin) only if they report amnesia or loss of consciousness following injury (NICE guidance 2007) **Intervention 2:** CT scan following head injury to all patients with coagulopathy (including those currently treated with warfarin) (NICE update 2014)	**Total costs:** Incremental (2−1): £346,741 (95% CI: NR; p=NR) **Currency & cost year:** 2014 UK pounds **Cost components incorporated:** CT scan, neurosurgery, GOS state, inpatient stay	**QALYs:** Incremental (2−1): 3.41 QALYs (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £94,895 per QALY gained 95% CI: NR **Threshold analysis:** 67% of the inpatient attendances (<48 hours) would need to be avoided for intervention 2 to be cost effective (£30,000 threshold) **Analysis of uncertainty:** Probabilistic sensitivity analysis not conducted. Scenario analysis conducted on expert opinion (assuming that one of the physicians was correct) and on GOS being 1 level higher if the patient survives. The ICER did not go below the threshold £30,000

Outcomes: 3.5%				
Data sources				
Health outcomes: Treatment effects were informed using expert opinion. An average value of the estimates of the probability of survival provided by two different physicians was used in the base case scenario. The estimate of GOS if the patient survives was provided by a single physician. The probability of GOS increasing by 1 for people who were found later to have brain injury was estimated by two physicians. Mortality was assumed to be the same of the general population if the patient survives and was based on UK 2010-2012 life tables. GOS or other events do not affect mortality. **Quality-of-life weights:** General UK population for people with GOS=5. Based on Pandor 2011[31] for those with GOS<5 **Cost sources:** NHS Reference costs for Neurosurgery, CT scan and inpatient stay. Pandor 2011[31] and PSSRU for costs associated with GUS state.				
Comments				
Source of funding: This study was sponsored by Sheffield Teaching Hospitals NHS Foundation Trust. **Limitations:** Relative treatment effects were estimated through expert opinion only and not through published trials or evidence arguably as there was none available. The patient-level simulation model was based on a very small number of patients who did not receive CT and that would have benefit with intervention 2: four who died and three that were re-admitted with a positive CT. No probabilistic sensitivity analysis was conducted. The population was people taking warfarin only so the results may not be transferable to people under other anticoagulative treatment. **Other:** None				
Overall applicability:[(a)] Directly applicable **Overall quality:**[(b)] Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; CUA= cost utility analysis; CT = Computed tomography; GOS = Glasgow outcome scale; ICER= incremental cost-effectiveness ratio; NA = not applicable; NR= not reported; QALYs= quality-adjusted life years.
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix H – Economic model

Model specification

Population: Adults with mild head injury who were on warfarin and have no other indication for head CT scan (that is, without amnesia or loss of consciousness).

Comparison: Head CT vs no Head CT

Outcomes: NHS cost, Quality-adjusted life-years (QALYs), Cost per QALY gained

Model inputs and methods

Model approach

The model was based on the model described above by Kuczawski 2016[21]. Patient-level simulation model based on UK observational data, AHEAD study. The cost of CT was attributed to all patients in the CT arm of the model. Health outcomes and care costs were modelled only for those patients that have an intracranial abnormality. The treatment benefits of CT and subsequent earlier intervention were based on the expert opinion, as reported in Kuczawski 2016[21].

- The (corrected) results of Kuczawski 2016 were replicated.
- Costs and utilities in the model were updated to be consistent with those in our tranexamic acid model (the base case analysis).
- Sensitivity analyses were conducted around the incidence of intracranial abnormalities and the magnitude of the treatment benefits for those with an intracranial abnormality.

Prevalence of intracranial abnormalities

The prevalence of intracranial abnormality in the base case was 7 out of 1420 (0.49%) from the AHEAD study, as used in Kuczawski 2016. In sensitivity analyses the prevalence was increased to 5%.

Treatment effects for people that have an intracranial abnormality

The main benefit of CT scanning in the model was assumed to be due to earlier neurosurgery for those patients that have an intracranial abnormality. CT is likely to detect almost all intracranial abnormalities that require surgery but not all surgery will be successful. For the base case we used the estimates of benefit from Kuczawski 2016[21]. These were based by expert opinion for 7 patients that had an intracranial abnormality in the AHEAD study – see columns 1-7 of .

Table 14: Outcomes for 7 patients that had an adverse event in the AHEAD study: Predicted improvements had they had a CT scan

Patient	Age	Sex	Probability of survival			Estimated GOS if survived	Actual outcome		Outcomes if survive		Change (Survive-Actual)	
			Clinician 1	Clinician 2	Combined		Costs	QALYs	Costs	QALYs	Costs	QALYs
Patients that died												
1	81	M	75%	75%	75%	3	£0	0.00	£121,877	2.44	£91,408	1.83
2	74	M	25%	15%	20%	2	£0	0.00	£358,752	-0.58	£71,750	-0.12
3	90	M	0%	0%	0%	2	£0	0.00	£358,752	-0.58	£0	0.00
4	88	M	75%	75%	75%	4	£0	0.00	£27,940	2.72	£20,955	2.04
Patient	**Age**	**Sex**	**Probability of GOS increase (+1)**			**Lower GOS score**	**Actual outcome**		**Outcomes if improve**		**Change (Improve-actual)**	
			Clinician 1	**Clinician 2**	**Combined**		**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**
Patients that survived												
5	76	M	25%	50%	38%	4	£36,033	5.68	£285	6.51	-£13,406	0.31
6	77	F	25%	0%	13%	4	£37,141	6.09	£537	6.41	-£4,575	0.04
7	82	M	25%	0%	13%	4	£31,592	4.06	£453	4.54	-£3,892	0.06
Mean							**£14,967**	**2.26**	**£124,085**	**3.06**	**£23,177**	**0.59**

NHS health technology assessment reports[22, 31] were used to identify alternative treatment effects for Immediate vs delayed neurosurgery in terms of Glasgow Outcome Scale. Five estimates of effect were identified, and the extracted outcomes are in :

- Pandor 2011[31] – NHS HTA evaluating decision rules for Head CT for minor head injury
  - For the outcome of immediate surgery, 5 studies were pooled together (n=177, Cheung 2007[5], Cook 1985[7], Gerlach 2009[17], Haselsberger 1988[19], and Lee 1998)[23]. For the treatment effect of immediate surgery versus delayed surgery they seem to have used Deverill 2007[11].
- Deverill 2007[11] (Cited in Pandor 2011[31])

  - A series of patients requiring surgery for extradural haemorrhage from 10 centres in Queensland, Australia. Forty-six patients underwent interhospital transfer before decompressive craniotomy; their median time interval from presentation to operation was 8 h 5 min. This delay was significantly greater than that for 25 patients admitted directly to neurosurgical centres (median 4 h 19).
- Haselsberger 1988[19] (Cited in Pandor 2011[31])
  - A series of 171 patients suffering acute subdural haemorrhage or epidural haemorrhage after closed head injury at the University Hospital of Graz in Austria. They compared timing of surgery - <2 hours vs >2 hours from injury.
- Lecky 2016[22] – NHS HTA feasibility study investigating transportation straight to neurosurgery.
  - For secondary transfer they used the outcomes for 87 patients in the Nottingham Head Injury Register (Fuller 2011[14]) with moderate or severe TBI who were transferred to the Queen's Medical Centre for neurosurgery. For the treatment effect a proportional odds ratio for an unfavourable outcome (GOS<4) of 0.53 was applied based on expert opinion.
- Smits 2010[33]
  - 92 patients with a lesion on CT after minor head injury and GOS data at >1 year from the CHIP (CT in Head Injury Patients) multicentre study (Smits 2008[34]). Outcomes for missed lesions were from Cordobes 1981[8] –41 patients with epidural haematoma before the advent of CT.

Table 15: Alternative treatment outcomes used in sensitivity analyses

	Pandor 2011[31]			Deverill 2007[31]			Haselsberger 1988[19]			Lecky 2016[22]			Smits 2010[33]		
	Immed	Delay	Diff	Immed	Delay	Diff	Immed	Delay	Diff	Immed	Delay	Diff	Immed	Delay	Diff
Good recovery	81%	57%	24%	70%	68%	1%	33%	7%	27%	32%	23%	9%	63%	39%	24%
Moderate disability	9%	7%	3%	22%	11%	10%	33%	7%	27%	30%	22%	8%	31%	22%	9%
Severe disability	3%	12%	-9%	9%	9%	0%	17%	27%	-10%	9%	13%	-4%	0%	10%	-10%
Vegetative state	3%	10%	-7%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Dead	4%	14%	-11%	0%	11%	-11%	17%	60%	-43%	29%	41%	-12%	6%	29%	-23%
	100%	100%		100%	100%		100%	100%		100%	100%		100%	100%	

Immed=immediate surgery; Delay=delayed surgery; Diff=immediate surgery minus delayed surgery

Longer-term survival after neurosurgery

Two of the patients were in a vegetative state. The Multi-Society Task Force on Persistent Vegetative State reported the mean length of survival for adults in a vegetative state as 3.6 years. (stated in Pandor 2011[31]).

For the other 5 patients, in the base case analysis, survival was assumed to be the same as the general population for their age and sex. Age-specific annual mortality rates were used to estimate life expectancy using ONS lifetables for England 2017-19[29].

For the sensitivity analyses where alternative treatment effects were used, general population mortality was used assuming an average age of 81 at the time of injury and 85% male (based on the 7 patients with an intracranial abnormality).

Intervention and admission costs

The cost of the CT (£88) was assumed to be a scan of one area with no contrast taken from NHS national schedule of costs 2019/20[26] - see 1.1.10.

Neurosurgery was not costed as this was assumed to be the same in both model arms.

Admission was included but only in a threshold sensitivity analysis. The cost of the admission (£521) was a short stay from NHS national schedule of costs 2019/20[26].

Utilities (quality of life scores) and costs by Glasgow Outcome Scale state

Utilities (EQ-5D from Fuller2017[37]) and health state costs inflated to 2020/21 (Beecham 2009[3] And Formsby 2015[13]) were the same as for the guideline model evaluating tranexamic acid - . Please check Evidence report A and full model report appendix.

For patients in good recovery, age and sex-specific utility estimates from the Health Survey for England were used.[20]

Table 16: Unit costs and utilities

	Kuczawski 2016[21].	Guideline models
Costs by Glasgow Outcome Scale state		
First year - Good recovery	£0	£313
First year - Moderate disability	£18,837	£22,361
First year - Severe disability	£37,214	£44,176
First year - Vegetative state	£94,269	£109,475
Subsequent years - Good recovery	£0	£28
Subsequent years - Moderate disability	£0	£1,843
Subsequent years - Severe disability	£37,214	£14,404
Subsequent years - Vegetative state	£46,595	£109,475
Other unit costs		
CT scan	£92	£88
Surgery	£3,994	£7,299
Short stay	£615	£521
Utilities by Glasgow Outcome Scale state		
Moderate disability	0.51	0.68
Severe disability	0.15	0.38
Vegetative state	0.00	-0.18

1 The parameters used in the base case analysis are listed in

2 Table 17 with the distributions used in the probabilistic analysis.

3 **Table 17: Overview of parameters and parameter distributions used in the base case**
4 **model**

Input	Data	Source	Probability distribution
Perspective	UK NHS & personal social services	NICE reference case[25]	n/a
Time horizon	Lifetime	NICE reference case[25]	n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case[25]	n/a
Baseline demographics for 7 people experiencing an adverse event			
Median age (range)	81 (74-90)	AHEAD study Kuczawski 2016[21]	n/a
Proportion male	6/7	AHEAD study Kuczawski 2016[21]	n/a
Adverse events and admissions			
Head injury-related adverse outcome	0.49%	AHEAD study Kuczawski 2016[21]	Beta Alpha=7 Beta=1413
Admission	51.3%	AHEAD study Kuczawski 2016[21]	Beta Alpha=728 Beta=692
Glasgow outcome scale at 6 months for 7 people experiencing adverse event			
GOS with delayed surgery	Dead=4 Moderate disability=3	AHEAD study Kuczawski 2016[21]	n/a
GOS with immediate surgery	Dead=2.3 Vegetative state=0.20 Severe disability=0.75 Moderate disability=3.13 Good recovery=0.63	Expert opinion Kuczawski 2016[21]	n/a
Mortality – see Economic analysis report on Tranexamic acid			
Vegetative state (VS) per year	24%	Derived from Pandor 2011[32] – Life expectancy = 3.6 years for children	n/a
Mortality (not VS)	National Life Tables 2017 - 2019	Office for National Statistics[29]	n/a
Health-related quality of life (utilities) – see Economic analysis report on Tranexamic acid			
Full health	1.000	By definition	n/a
Good recovery	0.894	Fuller 2017[37]	Gamma for decrement vs full health Alpha=575, Beta=0.00
Moderate disability	0.675	Fuller 2017[37]	Gamma for decrement vs GR Alpha=605, Beta=0.00
Severe disability	0.382	Fuller 2017[37]	Gamma for decrement vs MD

Input	Data	Source	Probability distribution
			Alpha=439, Beta=0.00
Vegetative state	-0.178	Fuller 2017[37]	Gamma for decrement vs SD Alpha=51, Beta=0.01
Dead	0.000	By definition	n/a
Costs			
Intervention costs			
Computed tomography scan	£88	NHS reference costs 2019/20[26]	Gamma Alpha=25, Beta=4
Admission	£521	Estimated based on data from NHS reference costs 2017/18[10] and NHS reference costs 2019/20[26]	Gamma Alpha=25, Beta=21
Post-discharge costs – see Economic analysis report on Tranexamic acid			
First year – Good recovery	£313	Reported in Williams 2020[38], derived from Beecham 2009[3]	Gamma Alpha=25, Beta=13
First year – Moderate disability	£22,361	Williams 2020[38], derived from Beecham 2009[3]	Gamma Alpha=25, Beta=894
First year – Severe disability	£44,176	Williams 2020[38], derived from Beecham 2009[3]	Gamma Alpha=25, Beta=1767
Subsequent years – Good recovery	£28	Williams 2020[38]	Gamma Alpha=25, Beta=1
Subsequent years – Moderate disability	£1,843	Williams 2020[38]	Gamma Alpha=25, Beta=74
Subsequent years – Severe disability	£14,404	Williams 2020[38]	Gamma Alpha=25, Beta=576
Vegetative state (first and subsequent years)	£109,475	Formby 2015[13]	Gamma Alpha=25, Beta=4379

Appendix I – Excluded studies

Clinical studies

Table 18: Studies excluded from the clinical review

Study	Code [Reason]
Acar, E., Demir, A., Alatas, O. D. et al. (2016) Evaluation of hematological markers in minor head trauma in the emergency room. European Journal of Trauma & Emergency Surgery 42(5): 611-616	- Population not relevant to this review protocol *People with isolated minor head trauma. In appropriate comparison- people with pathologies on head scan vs people with no pathologies on head scan. outcome-relationship between haematoligical biomarkers and CT scan*
Ahmed, N., Bialowas, C., Kuo, Y. H. et al. (2009) Impact of preinjury anticoagulation in patients with traumatic brain injury. Southern Medical Journal 102(5): 476-80	- No multi-variate analysis
Aldridge, P., Castle, H., Phillips, C. et al. (2020) Head home: a prospective cohort study of a nurse-led paediatric head injury clinical decision tool at a district general hospital. Emergency Medicine Journal 37(11): 680-685	- Population not relevant to this review protocol *patients with head injury. Study asses the nurse led application of a paediatric head injury clinical decision tool*
Alharthy, N., Al Queflie, S., Alyousef, K. et al. (2015) Clinical manifestations that predict abnormal brain computed tomography (CT) in children with minor head injury. Journal of Emergencies Trauma & Shock 8(2): 88-93	- Study design not relevant to this review protocol *cross sectional study* - Population not relevant to this review protocol *children with blunt head injury.*
Alter, S. M., Mazer, B. A., Solano, J. J. et al. (2020) Antiplatelet therapy is associated with a high rate of intracranial hemorrhage in patients with head injuries. Trauma Surgery & Acute Care Open 5(1): e000520	- No multi-variate analysis
Anandalwar, S. P., Mau, C. Y., Gordhan, C. G. et al. (2016) Eliminating unnecessary routine head CT scanning in neurologically intact mild traumatic brain injury patients: implementation and evaluation of a new protocol. Journal of Neurosurgery 125(3): 667-73	- No relevant clinical variables *neurologic observation without repeat head CT (NORH) for mild head injury* - Population not relevant to this review protocol *mild head injury*

Study	Code [Reason]
Anonymous (2007) Summaries for patients. Predicting intracranial traumatic findings on computed tomography in patients with minor head injury: the CHIP prediction rule. Annals of Internal Medicine 146(6): i55	- No relevant clinical variables *CHIP prediction rule for mild TBI* - Population not relevant to this review protocol *minor head injury*
Antoni, A., Schwendenwein, E., Binder, H. et al. (2019) Delayed intracranial hemorrhage in patients with head trauma and antithrombotic therapy. Journal of Clinical Medicine 8(11)	- No multi-variate analysis
Aras, M. and Oral, S. (2020) Management of intracranial hemorrhage in hemophilia A patients. Childs Nervous System 36(9): 2041-2046	- Population not relevant to this review protocol *management of intracranial haemorrhage in haemophilia A patients. Paediatric patients.*
Baig, A., Drabkin, M. J., Khan, F. et al. (2021) Patients with falls from standing height and head or neck injury may not require body CT in the absence of signs or symptoms of body injury. Emergency Radiology 28(2): 239-243	- Population not relevant to this review protocol *Included patients who already had initial CT scan.*
Barmparas, G., Kobayashi, L., Dhillon, N. K. et al. (2019) The risk of delayed intracranial hemorrhage with direct acting oral anticoagulants after trauma: A two-center study. American Journal of Surgery 217(6): 1051-1054	- No relevant clinical variables
Barrow, A.; Ndikum, J.; Harris, T. (2012) Late presentations of minor head injury. Emergency Medicine Journal 29(12): 983-8	- Population not relevant to this review protocol *patients with minor head injury presenting more than 4 h from insult to the ED*
Barton, C. A., Oetken, H. J., Hall, N. L. et al. (2022) Incidence of traumatic intracranial hemorrhage expansion after stable repeat head imaging: A retrospective cohort study. American Journal of Surgery 04: 04	- No multi-variate analysis
Battle, B.; Sexton, K. W.; Fitzgerald, R. T. (2018) Understanding the Value of Repeat Head CT in Elderly Trauma Patients on Anticoagulant or Antiplatelet Therapy. Journal of the American College of Radiology 15(2): 319-321	- No relevant clinical variables *The purpose of this study was to examine the risk for a delayed ICH in patients on DOACs who are at risk for a TBI and who have a negative admission CT of the brain.*
Bauman, Z. M., Ruggero, J. M., Squindo, S. et al. (2017) Repeat Head CT? Not Necessary for Patients with a Negative Initial Head CT on	- No multi-variate analysis

Study	Code [Reason]
Anticoagulation or Antiplatelet Therapy Suffering Low-Altitude Falls. American Surgeon 83(5): 429-435	
Bee, T. K., Magnotti, L. J., Croce, M. A. et al. (2009) Necessity of repeat head CT and ICU monitoring in patients with minimal brain injury. Journal of Trauma-Injury Infection & Critical Care 66(4): 1015-8	- Population not relevant to this review protocol *Mild TBI. study evaluated the use of repeat head scans and ICU monitoring in mild TBI*
Bent, C., Lee, P. S., Shen, P. Y. et al. (2015) Clinical scoring system may improve yield of head CT of non-trauma emergency department patients. Emergency Radiology 22(5): 511-6	- Population not relevant to this review protocol *ED non-trauma patients. study evaluated predictors of positive head CT scan in non-trauma patients*
Bonnier, C., Nassogne, M. C., Saint-Martin, C. et al. (2003) Neuroimaging of intraparenchymal lesions predicts outcome in shaken baby syndrome. Pediatrics 112(4): 808-14	- No multi-variate analysis - No relevant clinical variables *study describes clinical and imaging features in children with non-accidental head injury.*
Bonow, R. H., Friedman, S. D., Perez, F. A. et al. (2017) Prevalence of Abnormal Magnetic Resonance Imaging Findings in Children with Persistent Symptoms after Pediatric Sports-Related Concussion. Journal of Neurotrauma 34(19): 2706-2712	- Population not relevant to this review protocol *study describes MRI findings in children with concussion*
Borczuk, P. (1995) Predictors of intracranial injury in patients with mild head trauma. Annals of Emergency Medicine 25(6): 731-6	- Population not relevant to this review protocol *study determined the prevalence of abnormal computed tomography (CT) scans and defined high-risk clinical variables in patients with mild head injury.* - No relevant clinical variables
Borland, M. L., Dalziel, S. R., Phillips, N. et al. (2019) Delayed Presentations to Emergency Departments of Children With Head Injury: A PREDICT Study. Annals of Emergency Medicine 74(1): 1-10	- No multi-variate analysis *Bivariate analyses only*
Borst, J., Godat, L. N., Berndtson, A. E. et al. (2021) Repeat head computed tomography for anticoagulated patients with an initial negative scan is not cost-effective. Surgery 170(2): 623-627	- No multi-variate analysis

Study	Code [Reason]
Bressan, S., Monagle, P., Dalziel, S. R. et al. (2020) Risk of traumatic intracranial haemorrhage in children with bleeding disorders. Journal of Paediatrics & Child Health 56(12): 1891-1897	- No MV analysis
Brown, A. J.; Witham, M. D.; George, J. (2011) Development of a risk score to guide brain imaging in older patients admitted with falls and confusion. The British journal of radiology 84(1004): 756-7	- Population not relevant to this review protocol *Older confused fallers* - No relevant clinical variables - No multi-variate analysis
Burrows, P., Trefan, L., Houston, R. et al. (2015) Head injury from falls in children younger than 6 years of age. Archives of Disease in Childhood 100(11): 1032-7	- No relevant clinical variables *Study described describe the object fallen from, the neurophysiological status and CT scan findings in children younger than 6 years.* - Study design not relevant to this review protocol *cross-sectional study*
Chang, W., Yin, D., Li, C. et al. (2022) Increased relative risk of delayed hemorrhage in patients taking anticoagulant/antiplatelet medications with concurrent aspirin therapy: implications for clinical practice based on 3-year retrospective analysis in a large health system. Emergency Radiology 29(2): 353-358	- No multi-variate analysis
Chao, A., Pearl, J., Perdue, P. et al. (2001) Utility of routine serial computed tomography for blunt intracranial injury. Journal of Trauma-Injury Infection & Critical Care 51(5): 870-5; discussion 875	- No multi-variate analysis - No relevant clinical variables *Study aimed to determine the utility of routine serial head computed tomography (H-CT) for predicting need for invasive neurosurgical intervention in patients with blunt intracranial injuries*
Chauny, J. M., Marquis, M., Bernard, F. et al. (2016) Risk of Delayed Intracranial Hemorrhage in Anticoagulated Patients with Mild Traumatic Brain Injury: Systematic Review and Meta-	- Systematic review. Screened for relevant references

Study	Code [Reason]
Analysis. Journal of Emergency Medicine 51(5): 519-528	
Chenoweth, J. A., Gaona, S. D., Faul, M. et al. (2018) Incidence of Delayed Intracranial Hemorrhage in Older Patients After Blunt Head Trauma. JAMA Surgery 153(6): 570-575	- No relevant clinical variables *Study aimed to investigate the incidence of delayed traumatic intracranial haemorrhage in older adults with head trauma, including those taking anticoagulant and antiplatelet medications.*
Chenoweth, J. A., Johnson, M. A., Shook, L. et al. (2017) Prevalence of Intracranial Hemorrhage after Blunt Head Trauma in Patients on Pre-injury Dabigatran. The Western Journal of Emergency Medicine 18(5): 794-799	- No relevant clinical variables *study aimed to determine the prevalence of intracranial haemorrhage for patients on dabigatran presenting to a Level I trauma centre.*
Chhabra, G., Sharma, S., Subramanian, A. et al. (2013) Coagulopathy as prognostic marker in acute traumatic brain injury. Journal of Emergencies Trauma & Shock 6(3): 180-5	- Population not relevant to this review protocol *Adult patients with isolated moderate and severe head injury.* - No relevant clinical variables
Choe, D. W., Reiter, M., Morley, E. et al. (2016) Comparison of severity of intracranial hemorrhage in patients on warfarin or a novel oral anticoagulant. Annals of Emergency Medicine 68(4 Supplement 1): 103	- Conference abstract
Claudia, C., Claudia, R., Agostino, O. et al. (2011) Minor head injury in warfarinized patients: indicators of risk for intracranial hemorrhage. Journal of Trauma-Injury Infection & Critical Care 70(4): 906-9	- No multi-variate analysis *No MV analysis for risk factors in anticoagulated patients*
Cocca, A. T., Privette, A., Leon, S. M. et al. (2019) Delayed Intracranial Hemorrhage in Anticoagulated Geriatric Patients After Ground Level Falls. Journal of Emergency Medicine 57(6): 812-816	- No relevant clinical variables - No multi-variate analysis
Cohan, C. M., Beattie, G., Bowman, J. A. et al. (2020) Repeat computed tomography head scan is not indicated in trauma patients taking novel anticoagulation: A multicenter study. The Journal of Trauma and Acute Care Surgery 89(2): 301-310	- Population not relevant to this review protocol *Assessing the need for repeat CT after initial negative CT to detect delayed intracranial haemorrhage in people on anticoagulants.*

Study	Code [Reason]
Cohan, C. M., Beattie, G., Dominguez, D. A. et al. (2020) Routine Repeat CT Head Does Not Change Management in Trauma Patients on Novel Anticoagulants. Journal of Surgical Research 249: 114-120	- Population not relevant to this review protocol *Assessing the need for repeat CT after initial negative CT to detect delayed intracranial haemorrhage in people on anticoagulants.*
Cohen, D. B.; Rinker, C.; Wilberger, J. E. (2006) Traumatic brain injury in anticoagulated patients. Journal of Trauma-Injury Infection & Critical Care 60(3): 553-7	- No multi-variate analysis
Colas, L., Graf, S., Ding, J. et al. (2021) Limited benefit of systematic head CT for mild traumatic brain injury in patients under antithrombotic therapy. Journal of Neuroradiology.	- No multi-variate analysis
Colombo, G., Bonzi, M., Fiorelli, E. et al. (2021) Incidence of delayed bleeding in patients on antiplatelet therapy after mild traumatic brain injury: a systematic review and meta-analysis. Scandinavian Journal of Trauma, Resuscitation & Emergency Medicine 29(1): 123	- Systematic review. Screened for relevant references
Covino, M., Manno, A., della Pepa, G. M. et al. (2021) Delayed intracranial hemorrhage after mild traumatic brain injury in patients on oral anticoagulants: Is the juice worth the squeeze?. European Review for Medical and Pharmacological Sciences 25(7): 3066-3073	- No multi-variate analysis
Cui, W., Shi, Y., Zhao, B. et al. (2020) Computed tomographic parameters correlate with coagulation disorders in isolated traumatic brain injury. International Journal of Neuroscience.	- Population not relevant to this review protocol *TBI induced coagulopathy*
Dawson, E. C., Montgomery, C. P., Frim, D. et al. (2012) Is repeat head computed tomography necessary in children admitted with mild head injury and normal neurological exam?. Pediatric Neurosurgery 48(4): 221-4	- Population not relevant to this review protocol *children with mild head injury and normal neurological exam. Not population specified in the protocol .*
de Wit, K., Merali, Z., Kagoma, Y. K. et al. (2020) Incidence of intracranial bleeding in seniors presenting to the emergency department after a fall: A systematic review. Injury 51(2): 157-163	- Systematic review. Screened for relevant references
De Wit, K., Merali, Z., Kagoma, Y. et al. (2019) The incidence of intracranial bleeding following a fall on level ground in geriatric patients.	- Conference abstract

Study	Code [Reason]
Canadian Journal of Emergency Medicine 21(Supplement 1): 12	
Della Pepa, G. M., Covino, M., Menna, G. et al. (2022) Are oral anticoagulants a risk factor for mild traumatic brain injury progression? A single-center experience focused on of direct oral anticoagulants and vitamin K antagonists. Acta Neurochirurgica 164(1): 97-105	- Population not relevant to this review protocol *included people already had admission CT scan.*
Donovan, L. M., Kress, W. L., Strnad, L. C. et al. (2015) Low likelihood of intracranial hemorrhage in patients with cirrhosis and altered mental status. Clinical Gastroenterology & Hepatology 13(1): 165-9	- Population not relevant to this review protocol *patients with cirrhosis of the liver presenting to the ED with altered mental status not head injury.*
Dusenberry, M. W.; Brown, C. K.; Brewer, K. L. (2017) Artificial neural networks: Predicting head CT findings in elderly patients presenting with minor head injury after a fall. American Journal of Emergency Medicine 35(2): 260-267	- No relevant clinical variables *The objective was to build a preliminary artificial neural network model that could predict the presence of CT findings in patients ≥ 65 years old who presented to the ED with minor head injury after a fall.*
Dybiec, E., Wieczorek, P., Osemlak, P. et al. (1999) CT imaging of the evolution of the post-traumatic intracerebral haematoma in children. Annales Universitatis Mariae Curie-Sklodowska - Sectio d - Medicina 54: 319-25	- Population not relevant to this review protocol *children with intra cerebral haematoma* - Study design not relevant to this review protocol *case series*
Echlin, H. V.; Rahimi, A.; Wojtowicz, M. (2021) Systematic Review of the Long-Term Neuroimaging Correlates of Mild Traumatic Brain Injury and Repetitive Head Injuries. Frontiers in neurology 12: 726425	- Systematic review. Screened for relevant references
Ethridge, M.; Keller, J.; Edhayan, E. (2021) Risk of delayed intracranial hemorrhage in patients on anticoagulation with negative initial imaging. American Journal of Surgery 221(3): 606-608	- No relevant clinical variables - No multi-variate analysis
Evans, E., Asuzu, D., Cook, N. E. et al. (2018) Traumatic Brain Injury-Related Symptoms Reported by Parents: Clinical, Imaging, and Host Predictors in Children with Impairments in Consciousness Less than 24 Hours. Journal of Neurotrauma 35(19): 2287-2297	- Population not relevant to this review protocol *children with TBI. This study examined the relationship between acute neuroimaging, host and injury factors, and parent-reported TBI-related symptoms in children with non-critical head injury at two weeks and three months after injury*

Study	Code [Reason]
Fabbri, A., Servadei, F., Marchesini, G. et al. (2013) Antiplatelet therapy and the outcome of subjects with intracranial injury: the Italian SIMEU study. Critical Care (London, England) 17(2): r53	- Population not relevant to this review protocol *Included people with TBI and had positive head CT at their first evaluation in ED.*
Falcone, G. J., Brouwers, H. B., Biffi, A. et al. (2014) Warfarin and statins are associated with hematoma volume in primary infratentorial intracerebral hemorrhage. Neurocritical Care 21(2): 192-9	- Population not relevant to this review protocol *Adults with primary and warfarin-related intracerebral hemorrhage. study excluded trauma patients.*
Fiorelli, E. M., Bozzano, V., Bonzi, M. et al. (2020) Incremental Risk of Intracranial Hemorrhage After Mild Traumatic Brain Injury in Patients on Antiplatelet Therapy: Systematic Review and Meta-Analysis. Journal of Emergency Medicine 59(6): 843-855	- Systematic review. Screened for relevant references
Flashburg, E., Ong, A. W., Muller, A. et al. (2019) Fall downs should not fall out: Blunt cerebrovascular injury in geriatric patients after low-energy trauma is common. The Journal of Trauma and Acute Care Surgery 86(6): 1010-1014	- No relevant clinical variables *risk factors for blunt cerebrovascular injury. No multivariate analysis*
Folkerson, L. E., Sloan, D., Cotton, B. A. et al. (2015) Predicting progressive hemorrhagic injury from isolated traumatic brain injury and coagulation. Surgery 158(3): 655-61	- Population not relevant to this review protocol *isolated TBI* - No relevant clinical variables
Franschman, G., Boer, C., Andriessen, T. M. et al. (2012) Multicenter evaluation of the course of coagulopathy in patients with isolated traumatic brain injury: relation to CT characteristics and outcome. Journal of Neurotrauma 29(1): 128-36	- Population not relevant to this review protocol *people with isolated head injury. This study investigated the association of the course of coagulation abnormalities with initial CT characteristics and outcome in patients with isolated traumatic brain injury (TBI).*
Franschman, G., Greuters, S., Jansen, W. H. et al. (2012) Haemostatic and cranial computed tomography characteristics in patients with acute and delayed coagulopathy after isolated traumatic brain injury. Brain Injury 26(12): 1464-71	- Population not relevant to this review protocol *patients with moderate and severe isolated TBI*
Fujimoto, K., Otsuka, T., Yoshizato, K. et al. (2014) Predictors of rapid spontaneous resolution of acute subdural hematoma. Clinical Neurology & Neurosurgery 118: 94-7	- Population not relevant to this review protocol

Study	Code [Reason]
	The aim of the study was to identify factors predictive of spontaneous acute subdural haematoma resolution.
Fuller, G. W., Evans, R., Preston, L. et al. (2019) Should Adults With Mild Head Injury Who Are Receiving Direct Oral Anticoagulants Undergo Computed Tomography Scanning? A Systematic Review. Annals of Emergency Medicine 73(1): 66-75	- Systematic review. Screened for relevant references
Fuller, G., Evans, R., Preston, L. et al. (2019) Should adults with mild head injury taking direct oral anticoagulants undergo CT scanning? A systematic review. Emergency Medicine Journal 36(12): 805	- Systematic review. Screened for relevant references
Fuller, G., Sabir, L., Evans, R. et al. (2020) Risk of significant traumatic brain injury in adults with minor head injury taking direct oral anticoagulants: a cohort study and updated meta-analysis. Emergency Medicine Journal 37(11): 666-673	- No relevant clinical variables - Systematic review. Screened for relevant references *Paper included a cohort study and updated meta-analysis*
Ganetsky, M., Lopez, G., Coreanu, T. et al. (2017) Risk of Intracranial Hemorrhage in Ground-level Fall With Antiplatelet or Anticoagulant Agents. Academic Emergency Medicine 24(10): 1258-1266	- No relevant clinical variables
Gangavati, A. S., Kiely, D. K., Kulchycki, L. K. et al. (2009) Prevalence and characteristics of traumatic intracranial hemorrhage in elderly fallers presenting to the emergency department without focal findings. Journal of the American Geriatrics Society 57(8): 1470-4	- No multi-variate analysis *No MV analysis of risk factors for people on anti-coagulants* - Population not relevant to this review protocol *People aged 65 and older presenting with a fall to the ED*
Garra, G.; Nashed, A. H.; Capobianco, L. (1999) Minor head trauma in anticoagulated patients. Academic Emergency Medicine 6(2): 121-4	- No relevant clinical variables
Gebel, J. M., Sila, C. A., Sloan, M. A. et al. (1998) Thrombolysis-related intracranial hemorrhage: a radiographic analysis of 244 cases from the GUSTO-1 trial with clinical correlation. Global Utilization of Streptokinase	- Population not relevant to this review protocol *Patients suffering symptomatic intra cranial haemorrhage (ICH). The study reviewed radiographic features of cases of*

Study	Code [Reason]
and Tissue Plasminogen Activator for Occluded Coronary Arteries. Stroke 29(3): 563-9	*symptomatic ICH complicating thrombolysis for acute myocardial infarction in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial, correlated these observations with clinical data, and speculated on hemorrhage pathogenesis*
Gebel, J. M., Sila, C. A., Sloan, M. A. et al. (1998) Thrombolysis-related intracranial hemorrhage: A radiographic analysis of 244 cases from the GUSTO-1 trial with clinical correlation. Stroke 29(3): 563-569	- Population not relevant to this review protocol *Adults patients with symptomatic intra cranial haemorrhage complicating thrombolysis for acute myocardial infarction* - No relevant clinical variables *The study reviewed radiographic features of cases of symptomatic ICH complicating thrombolysis for acute myocardial infarction in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial, correlated these observations with clinical data, and speculated on haemorrhage pathogenesis.*
Gittleman, A. M., Ortiz, A. O., Keating, D. P. et al. (2005) Indications for CT in patients receiving anticoagulation after head trauma. Ajnr: American Journal of Neuroradiology 26(3): 603-6	- No multi-variate analysis
Godbout, B. J., Lee, J., Newman, D. H. et al. (2011) Yield of head CT in the alcohol-intoxicated patient in the emergency department. Emergency Radiology 18(5): 381-4	- Population not relevant to this review protocol *alcohol-intoxicated patients presenting to the emergency department (ED).*
Gomez, P. A., Lobato, R. D., Ortega, J. M. et al. (1996) Mild head injury: differences in prognosis among patients with a Glasgow Coma Scale score of 13 to 15 and analysis of factors associated with abnormal CT findings. British Journal of Neurosurgery 10(5): 453-60	- Population not relevant to this review protocol *All people with mild head injury.*
Granata, R. T.; Castillo, E. M.; Vilke, G. M. (2017) Safety of deferred CT imaging of intoxicated patients presenting with possible traumatic brain injury. American Journal of Emergency Medicine 35(1): 51-54	- Population not relevant to this review protocol *alcohol-intoxicated patients presenting to the emergency department (ED).*
Grandhi, R., Harrison, G., Voronovich, Z. et al. (2015) Preinjury warfarin, but not antiplatelet medications, increases mortality in elderly	- Population not relevant to this review protocol *Included elderly people with TBI with evidence of brain haemorrhage on CT.*

Study	Code [Reason]
traumatic brain injury patients. The Journal of Trauma and Acute Care Surgery 78(3): 614-21	
Grenander, A., Bredbacka, S., Rydvall, A. et al. (2001) Antithrombin treatment in patients with traumatic brain injury: a pilot study. Journal of Neurosurgical Anesthesiology 13(1): 49-56	- Study design not relevant to this review protocol *RCT. Study determined if early administration of antithrombin concentrate to patients with traumatic brain injury (TBI) can inhibit or significantly shorten the time of coagulopathy.*
Greuters, S., van den Berg, A., Franschman, G. et al. (2011) Acute and delayed mild coagulopathy are related to outcome in patients with isolated traumatic brain injury. Critical Care (London, England) 15(1): r2	- Population not relevant to this review protocol *Adults patients with isolated TBI. The aim of the present study was to investigate the incidence of early and delayed coagulopathy in patients with isolated TBI and an extracranial Abbreviated Injury Score less than three.*
Guillamondegui, O. D., Richards, J. E., Ely, E. W. et al. (2011) Does hypoxia affect intensive care unit delirium or long-term cognitive impairment after multiple trauma without intracranial hemorrhage?. Journal of Trauma-Injury Infection & Critical Care 70(4): 910-5	- Population not relevant to this review protocol *people with multiple injuries (ISS >15) with no intracranial haemorrhage. People had hypoxic events in ICU. Study examined relationship between hypoxic events in ICU to ICU delirium or long term cognitive impairment*
Gupta, A., Sellers, W., Toy, F. et al. (2018) The Necessity for Observation after Traumatic Loss of Consciousness. American Surgeon 84(9): e426-e427	- No relevant clinical variables - Study design not relevant to this review protocol *Brief report* - Population not relevant to this review protocol *Mild TBI*
Hagiwara, Y. and Inoue, N. (2020) The Effect of an Observation Unit on Pediatric Minor Head Injury. Pediatric Emergency Care 36(10): e564-e567	- Study does not contain an intervention relevant to this review protocol *study compared CT use before and after observation unit.* - Study design not relevant to this review protocol *before-after study*

Study	Code [Reason]
Hanna, A., Gill, I., Imam, Z. et al. (2021) Low yield of head CT in cirrhotic patients presenting with hepatic encephalopathy. BMJ Open Gastroenterology 8(1): 06	- Population not relevant to this review protocol *Not TBI. Study investigated the utility of head CT in hepatic encephalopathy (HE). Only 13% of CT scans due to fall, trauma or syncope.*
Haque, A., Dhanani, Z., Ali, A. et al. (2018) Outcome Of Traumatic Brain Injury In Children By Using Rotterdam Score On Computed Tomography. Journal of Ayub Medical College, Abbottabad: JAMC 30(1): 140-142	- Population not relevant to this review protocol *Children with TBI. The objective of the study was to assess the outcome of children with TBI admitted in paediatric intensive care unit (PICU) of a tertiary care, university hospital by using Rotterdam score..* - No relevant clinical variables
Hardy, J. E. and Brennan, N. (2008) Computerized tomography of the brain for elderly patients presenting to the emergency department with acute confusion. Emergency Medicine Australasia 20(5): 420-4	- No relevant clinical variables
Harris, L., Axinte, L., Campbell, P. et al. (2019) Computer Tomography (CT) for head injury: adherence to the National Institute for Health and Care Excellence (NICE) criteria. Brain Injury 33(12): 1539-1544	- Population not relevant to this review protocol *People with TBI. This is quality improvement project to improve adherence to NICE CT head scan guidelines following head injury.* - No relevant clinical variables
Hatefi, M., Dastjerdi, M. M., Ghiasi, B. et al. (2016) Association of serum uric acid level with the severity of brain injury and patient's outcome in severe traumatic brain injury. Journal of Clinical and Diagnostic Research 10(12): OC20-OC24	- Population not relevant to this review protocol *adults with TBI. The aim of the study was to investigate the relationship between serum uric acid levels and prognosis of patients with TBI during hospitalisation and six months after discharge.* - No relevant clinical variables
Hayashi, T., Kameyama, M., Imaizumi, S. et al. (2007) Acute epidural hematoma of the posterior fossa--cases of acute clinical deterioration. American Journal of Emergency Medicine 25(9): 989-95	- Study design not relevant to this review protocol *case-control review* - Population not relevant to this review protocol

Study	Code [Reason]
	People with Posterior fossa epidural hematoma (PFEDH)
Haydel, M. J. and Shembekar, A. D. (2003) Prediction of intracranial injury in children aged five years and older with loss of consciousness after minor head injury due to nontrivial mechanisms. Annals of Emergency Medicine 42(4): 507-14	- No relevant clinical variables *The objective of the study was to determine whether a clinical decision rule developed for adults could be used in children aged 5 years and older.* - Study design not relevant to this review protocol *questionnaire*
Heidari, K., Asadollahi, S., Jamshidian, M. et al. (2015) Prediction of neuropsychological outcome after mild traumatic brain injury using clinical parameters, serum S100B protein and findings on computed tomography. Brain Injury 29(1): 33-40	- Population not relevant to this review protocol *outcome is prediction of post-concussion syndrome. No population specified in the protocol. No relevant clinical variables*
Heidari, K., Vafaee, A., Rastekenari, A. M. et al. (2015) S100B protein as a screening tool for computed tomography findings after mild traumatic brain injury: Systematic review and meta-analysis. Brain Injury 29(10): 1146-1157	- No relevant clinical variables *S 100 B for predicting intra cranial lesions after mild TBI.*
Hemachandran, N., Meena, S., Kumar, A. et al. (2021) Utility of admission perfusion CT for the prediction of suboptimal outcome following uncomplicated minor traumatic brain injury. Emergency Radiology 28(3): 541-548	- Population not relevant to this review protocol *All people with uncomplicated mild TBI. No relevant clinical variables.*
Hemphill, R. R.; Santen, S. A.; Kleinschmidt, P. E. (1999) Delayed presentation after head injury: is a computed tomography scan necessary?. Academic Emergency Medicine 6(9): 957-60	- No multi-variate analysis
Hennes, H., Lee, M., Smith, D. et al. (1988) Clinical predictors of severe head trauma in children. American Journal of Diseases of Children 142(10): 1045-7	- Population not relevant to this review protocol *children with severe head trauma. No relevant clinical variables*
Heuer, G. G., Smith, M. J., Elliott, J. P. et al. (2004) Relationship between intracranial pressure and other clinical variables in patients with aneurysmal subarachnoid hemorrhage. Journal of Neurosurgery 101(3): 408-16	- Population not relevant to this review protocol *people with aneurysmal subarachnoid haemorrhage*

Study	Code [Reason]
Heydari, F.; Golban, M.; Majidinejad, S. (2020) Traumatic Brain Injury in Older Adults Presenting to the Emergency Department: Epidemiology, Outcomes and Risk Factors Predicting the Prognosis. Advanced Journal of Emergency Medicine 4(2): e19	- Study design not relevant to this review protocol *cross-sectional study* - Population not relevant to this review protocol *all TBI patients with a minimum age of 60 years presenting to the ED*
Hickey, S., Hickman, Z. L., Conway, J. et al. (2021) The Effect of Direct Oral Anti-Coagulants on Delayed Traumatic Intracranial Hemorrhage After Mild Traumatic Brain Injury: A Systematic Review. Journal of Emergency Medicine 60(3): 321-330	- Systematic review. Screened for relevant references
Hill JH, Bonner P, O'Mara MS et al. (2018) Delayed intracranial hemorrhage in the patient with blunt trauma on anticoagulant or antiplatelet agents: routine repeat head computed tomography is unnecessary. Brain injury 32(6): 735-738	- No multi-variate analysis
Hirsch, W., Schobess, A., Eichler, G. et al. (2002) Severe head trauma in children: cranial computer tomography and clinical consequences. Paediatric Anaesthesia 12(4): 337-44	- Population not relevant to this review protocol *Children with severe head trauma. No relevant clinical variables*
Ho, K. M.; Burrell, M.; Rao, S. (2010) Extracranial injuries are important in determining mortality of neurotrauma. Critical Care Medicine 38(7): 1562-8	- No relevant clinical variables *No relevant clinical variables. Inappropriate population-Adult neurotrauma patients. Study aimed to assess the significance of extra cranial injuries on mortality of neurotrauma*
Hofbauer, M., Kdolsky, R., Figl, M. et al. (2010) Predictive factors influencing the outcome after gunshot injuries to the head-a retrospective cohort study. Journal of Trauma-Injury Infection & Critical Care 69(4): 770-5	- No relevant clinical variables *no relevant clinical variables. Not appropriate population- people with gun shot injuries to the head.*
Hollander, J. E., Go, S., Lowery, D. W. et al. (2003) Interrater reliability of criteria used in assessing blunt head injury patients for intracranial injuries. Academic Emergency Medicine 10(8): 830-5	- No relevant clinical variables *sub study of NEXUS II study. Study aimed to determine the interrater reliability of potential predictor variables that may be used to construct a clinical decision rule for emergency computed tomography of the head in blunt head injury victims*

Study	Code [Reason]
Holshouser, B., Pivonka-Jones, J., Nichols, J. G. et al. (2019) Longitudinal Metabolite Changes after Traumatic Brain Injury: A Prospective Pediatric Magnetic Resonance Spectroscopic Imaging Study. Journal of Neurotrauma 36(8): 1352-1360	- Population not relevant to this review protocol *children with TBI. The study aimed to evaluate longitudinal metabolite changes in traumatic brain injury (TBI) subjects and determine whether early magnetic resonance spectroscopic imaging (MRSI) changes in discrete brain regions predict 1- year neuropsychological outcomes.*
Homer, C. J. and Kleinman, L. (1999) Technical report: minor head injury in children. Pediatrics 104(6): e78	- Review article but not a systematic review
Honda, M., Tsuruta, R., Kaneko, T. et al. (2010) Serum glial fibrillary acidic protein is a highly specific biomarker for traumatic brain injury in humans compared with S-100B and neuron-specific enolase. Journal of Trauma-Injury Infection & Critical Care 69(1): 104-9	- No relevant clinical variables *serum GFAP vs serum NSE to predict abnormalities on CT in people with severe trauma*
Howard, J. L., 2nd, Cipolle, M. D., Horvat, S. A. et al. (2009) Preinjury warfarin worsens outcome in elderly patients who fall from standing. Journal of Trauma-Injury Infection & Critical Care 66(6): 1518-22; discussion 1523	- No multi-variate analysis
Howard, M. A., 3rd, Gross, A. S., Dacey, R. G., Jr. et al. (1989) Acute subdural hematomas: an age-dependent clinical entity. Journal of Neurosurgery 71(6): 858-63	- Population not relevant to this review protocol *people with acute subdural haematoma*
Howard, M. A.; Bell, B. A.; Uttley, D. (1993) The pathophysiology of infant subdural haematomas. British Journal of Neurosurgery 7(4): 355-65	- No relevant clinical variables *study examines pathophysiology of infants with subdural haematomas*
Howard, R. S., Holmes, P. A., Siddiqui, A. et al. (2012) Hypoxic-ischaemic brain injury: imaging and neurophysiology abnormalities related to outcome. Qjm 105(6): 551-61	- Population not relevant to this review protocol *patients with hypoxic-ischaemic brain injury (HIBI)*
Hsiao, A. K.; Michelson, S. P.; Hedges, J. R. (1993) Emergent intubation and CT scan pathology of blunt trauma patients with Glasgow Coma Scale scores of 3-13. Prehospital & Disaster Medicine 8(3): 229-36	- No relevant clinical variables *No relevant clinical variables. CT scan pathology and emergent intubation in people in GCS 3-13*
Hu, G. W., Lang, H. L., Guo, H. et al. (2017) A risk score based on admission characteristics to predict progressive hemorrhagic injury from	- Population not relevant to this review protocol *children with TBI. The objective of the study was to develop and validate a prognostic model that*

Study	Code [Reason]
traumatic brain injury in children. European Journal of Pediatrics 176(6): 689-696	*uses the information available at admission to determine the likelihood of progressive haemorrhagic injury occurrence after TBI in children*
Huang GS, Dunham CM, Chance EA et al. (2020) Detecting delayed intracranial hemorrhage with repeat head imaging in trauma patients on antithrombotics with no hemorrhage on the initial image: A retrospective chart review and meta-analysis. American journal of surgery 220(1): 55-61	- No multi-variate analysis
Hughes, P. G., Alter, S. M., Greaves, S. W. et al. (2021) Acute and Delayed Intracranial Hemorrhage in Head-Injured Patients on Warfarin versus Direct Oral Anticoagulant Therapy. Journal of Emergencies Trauma & Shock 14(3): 123-127	- No multi-variate analysis
Hukkelhoven, C. W., Steyerberg, E. W., Rampen, A. J. et al. (2003) Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. Journal of Neurosurgery 99(4): 666-73	- No relevant clinical variables *no relevant clinical variables. Not appropriate population- people with severe head injury*
Husson, E. C., Ribbers, G. M., Willemse-van Son, A. H. et al. (2010) Prognosis of six-month functioning after moderate to severe traumatic brain injury: a systematic review of prospective cohort studies. Journal of Rehabilitation Medicine 42(5): 425-36	- Systematic review. Screened for relevant references
Ibanez Perez De La Blanca, M. A., Fernandez Mondejar, E., Gomez Jimenez, F. J. et al. (2018) Risk factors for intracranial lesions and mortality in older patients with mild traumatic brain injuries. Brain Injury 32(1): 99-104	- Population not relevant to this review protocol *People with mild TBI. Not specific populations as specified in the protocol*
Ibanez, J., Arikan, F., Pedraza, S. et al. (2004) Reliability of clinical guidelines in the detection of patients at risk following mild head injury: results of a prospective study. Journal of Neurosurgery 100(5): 825-34	- Population not relevant to this review protocol *all people with mild head injury not specific population as in protocol. No relevant clinical variables.*
Ilves, P., Lintrop, M., Talvik, I. et al. (2010) Predictive value of clinical and radiological findings in inflicted traumatic brain injury. Acta Paediatrica 99(9): 1329-36	- Population not relevant to this review protocol *Infants with inflicted traumatic brain injury. No relevant clinical variables*
Imen, R. B., Olfa, C., Kamilia, C. et al. (2015) Factors predicting early outcome in patients	- Population not relevant to this review protocol

Study	Code [Reason]
admitted at emergency department with severe head trauma. Journal of Acute Disease 4(1): 68-72	*People with severe head trauma* - No relevant clinical variables
Ingebrigtsen, T., Romner, B., Marup-Jensen, S. et al. (2000) The clinical value of serum S-100 protein measurements in minor head injury: a Scandinavian multicentre study. Brain Injury 14(12): 1047-55	- No relevant clinical variables *S100 B for predicting post-concussion syndrome.*
Ingebrigtsen, T., Waterloo, K., Jacobsen, E. A. et al. (1999) Traumatic brain damage in minor head injury: relation of serum S-100 protein measurements to magnetic resonance imaging and neurobehavioral outcome. Neurosurgery 45(3): 468-75; discussion 475	- Full text paper not available
Jacobs, B., Beems, T., Stulemeijer, M. et al. (2010) Outcome prediction in mild traumatic brain injury: age and clinical variables are stronger predictors than CT abnormalities. Journal of Neurotrauma 27(4): 655-68	- Population not relevant to this review protocol *Adults with mild TBI. The study aimed to identify the demographic, clinical, and CT characteristics associated with unfavourable outcome at 6 months after mild TBI.*
Jacobs, B., Beems, T., van der Vliet, T. M. et al. (2010) The status of the fourth ventricle and ambient cisterns predict outcome in moderate and severe traumatic brain injury. Journal of Neurotrauma 27(2): 331-40	- Population not relevant to this review protocol *Adults with moderate and severe TBI. This study describes the prognostic value of the appearance of individual cisterns and ventricles in relation to that of the basal cisterns* - No relevant clinical variables
Jamous, M. A. (2020) The safety of early thromboembolic prophylaxis in closed traumatic intracranial hemorrhage. Open Access Emergency Medicine 12: 81-85	- Population not relevant to this review protocol *People with closed traumatic intracranial bleeding receiving early (ie, within 72 hours) venous thromboembolic prophylaxis with 40 mg of enoxaparin*
Jha, R. M., Puccio, A. M., Chou, S. H. et al. (2017) Sulfonylurea Receptor-1: A Novel Biomarker for Cerebral Edema in Severe Traumatic Brain Injury. Critical Care Medicine 45(3): e255-e264	- No relevant clinical variables *Sulfonylurea Receptor-1(Sur1) after severe brain injury.*
Jiang, Y., Sun, X., Gui, L. et al. (2007) Correlation between APOE -491AA promoter in epsilon4 carriers and clinical deterioration in	- Population not relevant to this review protocol *adults with TBI. The objective of this work was to investigate the relationship between*

Study	Code [Reason]
early stage of traumatic brain injury. Journal of Neurotrauma 24(12): 1802-1810	*apolipoprotein E (APOE) promoters (G-219T, C-427T, A-491T) polymorphisms and the clinical deterioration in early stage of traumatic brain injury (TBI)*
Jonsdottir, G. M., Lund, S. H., Snorradottir, B. et al. (2017) A population-based study on epidemiology of intensive care unit treated traumatic brain injury in Iceland. Acta Anaesthesiologica Scandinavica 61(4): 408-417	- No relevant clinical variables *study aimed to describe population based data on ICU admission treated people with TBI in Iceland for 15 years*
Joseph, B., Aziz, H., Zangbar, B. et al. (2014) Acquired coagulopathy of traumatic brain injury defined by routine laboratory tests: which laboratory values matter?. The Journal of Trauma and Acute Care Surgery 76(1): 121-5	- Population not relevant to this review protocol *People had initial CT scan.*
Julien, J., Alsideiri, G., Marcoux, J. et al. (2017) Antithrombotic agents intake prior to injury does not affect outcome after a traumatic brain injury in hospitalized elderly patients. Journal of Clinical Neuroscience 38: 122-125	- No relevant outcomes *hospital length of stay (LOS) and The Extended Glasgow Outcome Scale (GOSE)*
Kandasamy, R., Kanti Pal, H., Swamy, M. et al. (2013) Cerebrospinal fluid nitric oxide metabolite levels as a biomarker in severe traumatic brain injury. International Journal of Neuroscience 123(6): 385-91	- Population not relevant to this review protocol *adults with severe TBI. The study investigated the changes in nitric oxide metabolite (NO x) levels in cerebrospinal fluid (CSF) and their correlation with factors associated with severity and prognosis after severe TBI* - No relevant clinical variables
Karlsborg, M., Smed, A., Jespersen, H. et al. (1997) A prospective study of 39 patients with whiplash injury. Acta Neurologica Scandinavica 95(2): 65-72	- Population not relevant to this review protocol *people with whiplash injury. No relevant clinical variables.*
Karni, A., Holtzman, R., Bass, T. et al. (2001) Traumatic head injury in the anticoagulated elderly patient: a lethal combination. American Surgeon 67(11): 1098-100	- No multi-variate analysis - No relevant clinical variables
Kiflie, A., Alias, N. A., Abdul-Kareem, M. M. et al. (2006) The prognostic value of early follow-up computerized tomography of the brain in adult traumatic brain injury. Medical Journal of Malaysia 61(4): 466-73	- Population not relevant to this review protocol *Adults with moderate and severe TBI. The study aimed to evaluate prognostic value of early follow-up CT of the Brain in adult TBI* - No relevant clinical variables

Study	Code [Reason]
Kim, B. J., Park, K. J., Park, D. H. et al. (2014) Risk factors of delayed surgical evacuation for initially nonoperative acute subdural hematomas following mild head injury. Acta Neurochirurgica 156(8): 1605-13	- Population not relevant to this review protocol *People with acute subdural hematomas (aSDHs) following mild head injury. study aimed to determine the risk factors associated with delayed hematoma enlargement leading to surgery in patients with aSDHs who did not initially require surgical intervention* - No relevant clinical variables
Kim, J., Gearhart, M. M., Zurick, A. et al. (2002) Preliminary report on the safety of heparin for deep venous thrombosis prophylaxis after severe head injury. Journal of Trauma-Injury Infection & Critical Care 53(1): 38-42; discussion 43	- Population not relevant to this review protocol *people with severe head injury. study assessed safety of heparin for VTE prophylaxis in after TBI. No relevant clinical variables*
Kisat, M., Zafar, S. N., Latif, A. et al. (2012) Predictors of positive head CT scan and neurosurgical procedures after minor head trauma. Journal of Surgical Research 173(1): 31-7	- Population not relevant to this review protocol *Adults presenting to the ED with a history of blunt head injury and a normal GCS of 15* - No relevant clinical variables
Klora, M., Zeidler, J., Bassler, S. et al. (2019) Frequency of neuroimaging for pediatric minor brain injury is determined by the primary treating medical department. Medicine 98(28): e16320	- Population not relevant to this review protocol *children and adolescents with mild TBI. This study analysed the use of neuroimaging in children and adolescents with minor traumatic brain injuries in paediatric and non-paediatric departments in Germany.* - No relevant clinical variables
Kocyigit, A., Serinken, M., Ceven, Z. et al. (2014) A strategy to optimize CT use in children with mild blunt head trauma utilizing clinical risk stratification; could we improve CT use in children with mild head injury?. Clinical Imaging 38(3): 236-40	- Population not relevant to this review protocol *Children with isolated paediatric mild head trauma.* - No relevant clinical variables
Koelfen, W., Freund, M., Dinter, D. et al. (1997) Long-term follow up of children with head injuries-classified as "good recovery" using the Glasgow Outcome Scale: neurological, neuropsychological and magnetic resonance	- Population not relevant to this review protocol *children 6–15 years of age at the time of testing who received an initial CT scan at the time of their head injury and who had been injured at least 12 months prior to the follow up test. The*

Study	Code [Reason]
imaging results. European Journal of Pediatrics 156(3): 230-5	*primary issues addressed in this study were; (1) determination of the significance of the classification ‘‘good outcome’’ utilising the GOS in children at least 1 year brain injury as compared to the abilities of healthy children; (2) detection of residual lesions of brain parenchyma in these children upon follow up MRI; and (3) detection of relationships between neuropsychological test performance and MRI results.* - No relevant clinical variables
Koerte, I. K., Bahr, R., Filipcik, P. et al. (2022) REPIMPACT - a prospective longitudinal multisite study on the effects of repetitive head impacts in youth soccer. Brain Imaging & Behavior 16(1): 492-502	- Population not relevant to this review protocol *Repetitive head impacts (RHI) are common in youth athletes*
Koiso, T., Goto, M., Terakado, T. et al. (2021) The effects of antithrombotic therapy on head trauma and its management. Scientific Reports 11(1): 20459	- No relevant outcomes *risk factors for modified Rankin Scale (mRS)*
Korfias, S., Stranjalis, G., Boviatsis, E. et al. (2007) Serum S-100B protein monitoring in patients with severe traumatic brain injury. Intensive Care Medicine 33(2): 255-60	- Population not relevant to this review protocol *Severe TBI.* - No relevant clinical variables *The study examined the relationship between serum S-100B concentrations and injury severity, clinical course, survival, and treatment efficacy after severe TBI.*
Kou, Z., Wu, Z., Tong, K. A. et al. (2010) The role of advanced MR imaging findings as biomarkers of traumatic brain injury. Journal of Head Trauma Rehabilitation 25(4): 267-82	- Review article but not a systematic review
Kuczawski, M., Stevenson, M., Goodacre, S. et al. (2016) Should all anticoagulated patients with head injury receive a CT scan? Decision-analysis modelling of an observational cohort. BMJ Open 6(12): e013742	- Study to be considered for inclusion in HE part of the review
Kuppermann, N., Holmes, J. F., Dayan, P. S. et al. (2009) Identification of children at very low risk of clinically-important brain injuries after	- Population not relevant to this review protocol

Study	Code [Reason]
head trauma: a prospective cohort study. Lancet 374(9696): 1160-70	*patients younger than 18 years presenting within 24 h of head trauma with Glasgow Coma Scale scores of 14-15* - No relevant clinical variables
Lai, P. M. and Du, R. (2016) Association between S100B Levels and Long-Term Outcome after Aneurysmal Subarachnoid Hemorrhage: Systematic Review and Pooled Analysis. PloS one 11(3): e0151853	- No relevant clinical variables *Study evaluated associations between S100B protein in serum and cerebrospinal fluid (CSF) with radiographic vasospasm, delayed ischemic neurologic deficit (DIND), delayed cerebral infarction, and Glasgow Outcome Scale (GOS) outcome*
Lannsjo, M., Backheden, M., Johansson, U. et al. (2013) Does head CT scan pathology predict outcome after mild traumatic brain injury?. European Journal of Neurology 20(1): 124-9	- Population not relevant to this review protocol *people with TBI. Study assessed effect of head can pathology on self-reported symptoms or global function 3 months after TBI. No relevant clinical variables*
Laribi, S., Kansao, J., Borderie, D. et al. (2014) S100B blood level measurement to exclude cerebral lesions after minor head injury: the multicenter STIC-S100 French study. Clinical Chemistry & Laboratory Medicine 52(4): 527-36	- No relevant clinical variables *validation of S100B for mild head injury diagnosis*
Lee, H. J., Kim, Y. J., Seo, D. W. et al. (2018) Incidence of intracranial injury in orbital wall fracture patients not classified as traumatic brain injury. Injury 49(5): 963-968	- Population not relevant to this review protocol *This study aimed to evaluate the incidence and risk factors of intracranial injury in patients with orbital wall fracture (OWF), who were classified with a chief complaint of facial injury rather than TBI.* - No relevant clinical variables - Study design not relevant to this review protocol *case-control study*
Lee, T. T., Aldana, P. R., Kirton, O. C. et al. (1997) Follow-up computerized tomography (CT) scans in moderate and severe head injuries: correlation with Glasgow Coma Scores (GCS), and complication rate. Acta Neurochirurgica 139(11): 1042-7; discussion 1047	- Population not relevant to this review protocol *moderate and severe TBI* - No relevant clinical variables

Study	Code [Reason]
	study investigated the correlation between CT scans and Glasgow coma score (GCS), and complication rate during follow-up CT scans
Levin, H. S., Temkin, N. R., Barber, J. et al. (2021) Association of Sex and Age With Mild Traumatic Brain Injury-Related Symptoms: A TRACK-TBI Study. JAMA Network Open 4(4): e213046	- Population not relevant to this review protocol *Patients with mild TBI* - No relevant clinical variables *Study aimed to identify sex-related differences in symptom recovery from mild TBI and to explore age differences within women, who demonstrate poorer outcomes after TBI.*
Levy, A. S., Salottolo, K., Bar-Or, R. et al. (2010) Pharmacologic thromboprophylaxis is a risk factor for hemorrhage progression in a subset of patients with traumatic brain injury. Journal of Trauma-Injury Infection & Critical Care 68(4): 886-94	- Population not relevant to this review protocol *Included people who already had initial CT.*
Lewis, L. M., Papa, L., Bazarian, J. J. et al. (2020) Biomarkers May Predict Unfavorable Neurological Outcome after Mild Traumatic Brain Injury. Journal of Neurotrauma 37(24): 2624-2631	- Population not relevant to this review protocol *mild TBI* - No relevant clinical variables *The objective of this study was to determine if initial or repeat measurements of serum concentrations of glial fibrillary acidic protein (GFAP) or ubiquitin C-terminal hydrolase L1 (UCH-L1) are predictive of an acute unfavourable neurological outcome in patients who present to the emergency department (ED) with brain injury and an initial Glasgow Coma Scale Score (GCS) of 14–15*
Lewis, L. M., Schloemann, D. T., Papa, L. et al. (2017) Utility of Serum Biomarkers in the Diagnosis and Stratification of Mild Traumatic Brain Injury. Academic Emergency Medicine 24(6): 710-720	- Population not relevant to this review protocol *Blunt closed head injury* - No relevant clinical variables *The objective of the study was to compare test characteristics of a single serum concentration of glial fibrillary acidic protein (GFAP), S-100beta, and ubiquitin carboxyl terminal hydrolase L1 (UCH-L1), obtained within 6 hours of head injury, to diagnose mild traumatic brain injury in head-injured subjects.*

Study	Code [Reason]
Lewis, R. J., Yee, L., Inkelis, S. H. et al. (1993) Clinical predictors of post-traumatic seizures in children with head trauma. Annals of Emergency Medicine 22(7): 1114-8	- Population not relevant to this review protocol *Children with head trauma* - No relevant clinical variables *Study aimed to determine the clinical characteristics associated with early post-traumatic seizures in children with head trauma.*
Lipper, M. H., Kishore, P. R., Enas, G. G. et al. (1985) Computed tomography in the prediction of outcome in head injury. AJR. American Journal of Roentgenology 144(3): 483-6	- Population not relevant to this review protocol *Adults with severe TBI* - No relevant clinical variables *Study aimed to determine the prognostic significance of CT findings in people with severe head injury.*
Lorente, L., Martin, M. M., Perez-Cejas, A. et al. (2021) Low blood caspase-8 levels in survivor patients of traumatic brain injury. Neurological Sciences 23: 23	- Population not relevant to this review protocol *Isolated and severe TBI* - No relevant clinical variables *study examines if blood caspase-8 concentrations are associated with mortality in TBI patients*
Lv, L. Q., Hou, L. J., Yu, M. K. et al. (2010) Prognostic influence and magnetic resonance imaging findings in paroxysmal sympathetic hyperactivity after severe traumatic brain injury. Journal of Neurotrauma 27(11): 1945-50	- Population not relevant to this review protocol *severe TBI* - No relevant clinical variables *The study determined prevalence, magnetic resonance imaging (MRI) presentation, influence on the clinical course in the intensive care unit (ICU), and effect on neurological recovery of Paroxysmal sympathetic hyperactivity in patients with severe traumatic brain injury (TBI).*
Mack, L. R., Chan, S. B., Silva, J. C. et al. (2003) The use of head computed tomography in elderly patients sustaining minor head trauma. Journal of Emergency Medicine 24(2): 157-62	- Population not relevant to this review protocol *adults 65 and older with minor head trauma. Not specific population as specified in the protocol*

Study	Code [Reason]
Majdan, M., Steyerberg, E. W., Nieboer, D. et al. (2015) Glasgow coma scale motor score and pupillary reaction to predict six-month mortality in patients with traumatic brain injury: Comparison of field and admission assessment. Journal of Neurotrauma 32(2): 101-108	- Population not relevant to this review protocol *moderate and severe TBI* - No relevant clinical variables *The study aimed to compare the GCS motor score and pupillary reactivity assessed in the field and at hospital admission and assess their prognostic value for 6-month mortality in patients with moderate or severe TBI.*
Major, J. and Reed, M. J. (2009) A retrospective review of patients with head injury with coexistent anticoagulant and antiplatelet use admitted from a UK emergency department. Emergency Medicine Journal 26(12): 871-6	- No multi-variate analysis
Mandera, M., Wencel, T., Bazowski, P. et al. (2000) How should we manage children after mild head injury?. Childs Nervous System 16(3): 156-60	- Population not relevant to this review protocol *children with mild TBI. No relevant clinical variables*
Mann, N., Welch, K., Martin, A. et al. (2018) Delayed intracranial hemorrhage in elderly anticoagulated patients sustaining a minor fall. BMC Emergency Medicine 18(1): 27	- No multi-variate analysis
Manzano, S., Holzinger, I. B., Kellenberger, C. J. et al. (2016) Diagnostic performance of S100B protein serum measurement in detecting intracranial injury in children with mild head trauma. Emergency Medicine Journal 33(1): 42-6	- No relevant clinical variables *study aimed to assess the accuracy of S100B serum level to detect intracranial injury in children with mild traumatic brain injury.*
Marincowitz, C.; Allgar, V.; Townend, W. (2016) CT head imaging in patients with head injury who present after 24 h of injury: a retrospective cohort study. Emergency Medicine Journal 33(8): 538-42	- No multi-variate analysis results reported
Marincowitz, C., Gravesteijn, B., Sheldon, T. et al. (2021) Performance of the Hull Salford Cambridge Decision Rule (HSC DR) for early discharge of patients with findings on CT scan of the brain: A CENTER-TBI validation study. Emergency Medicine Journal	- No relevant clinical variables *Study included in review 3.3. validation of the Hull Salford Cambridge Decision Rule (HSC DR) and the Brain Injury Guidelines (BIG) criteria to select low-risk patients for discharge from the emergency department.*
Marincowitz, C.; Smith, C. M.; Townend, W. (2015) The risk of intra-cranial haemorrhage in	- Systematic review. Screened for relevant references

Study	Code [Reason]
those presenting late to the ED following a head injury: a systematic review. Systematic Reviews 4: 165	
Marques, R. S. F., Antunes, C., Machado, M. J. et al. (2019) Reappraising the need for a control CT in mild head injury patients on anticoagulation. European Journal of Trauma & Emergency Surgery 17: 17	- No multi-variate analysis
Marques-Matos, C., Alves, J. N., Marto, J. P. et al. (2017) POST-NOAC: Portuguese observational study of intracranial hemorrhage on non-vitamin K antagonist oral anticoagulants. International Journal of Stroke 12(6): 623-627	- Population not relevant to this review protocol *patients with acute non-traumatic intracranial haemorrhage*
Marton, E., Mazzucco, M., Nascimben, E. et al. (2007) Severe head injury in early infancy: analysis of causes and possible predictive factors for outcome. Childs Nervous System 23(8): 873-80	- Population not relevant to this review protocol *study analyses causes and prognostic factors for outcome in severe head injury in infants. No relevant clinical variables.*
Mathieu, F., Guting, H., Gravesteijn, B. et al. (2020) Impact of Antithrombotic Agents on Radiological Lesion Progression in Acute Traumatic Brain Injury: A CENTER-TBI Propensity-Matched Cohort Analysis. Journal of Neurotrauma 37(19): 2069-2080	- No relevant clinical variables *The primary aim of this study was to quantify the impact of antithrombotic agent use on radiological lesion progression in acute TBI*
Matsukawa, H., Shinoda, M., Fujii, M. et al. (2012) Intraventricular hemorrhage on computed tomography and corpus callosum injury on magnetic resonance imaging in patients with isolated blunt traumatic brain injury. Journal of Neurosurgery 117(2): 334-9	- Population not relevant to this review protocol *People with blunt TBI. study aimed to investigate whether intra ventricular haemorrhage found on CT predicts corpus callosum injury on MRI. No relevant clinical variables*
McCammack, K. C., Sadler, C., Guo, Y. et al. (2015) Routine repeat head CT may not be indicated in patients on anticoagulant/antiplatelet therapy following mild traumatic brain injury. The Western Journal of Emergency Medicine 16(1): 43-9	- No multi-variate analysis *No MV analysis data reported*
McCullagh, S., Oucherlony, D., Protzner, A. et al. (2001) Prediction of neuropsychiatric outcome following mild trauma brain injury: an examination of the Glasgow Coma Scale. Brain Injury 15(6): 489-97	- Population not relevant to this review protocol *People with mild TBI. study examines relationship between GCS and neuropsychiatric outcomes in people with mild TBI.*
McIntyre, M. K., Kumar, N. S., Tilley, E. H. et al. (2020) Clinical Characteristics Predict the Yield	- Population not relevant to this review protocol *Trauma patients with alcohol intoxication.*

Study	Code [Reason]
of Head Computed Tomography Scans among Intoxicated Trauma Patients: Implications for the Initial Work-up. Journal of Emergencies Trauma & Shock 13(2): 135-141	
Medzon, R., Bracken, M., Rathlev, N. K. et al. (2010) Clinically suspected coagulopathy in blunt head trauma. Journal of Emergency Medicine 39(4): 399-405	- No relevant clinical variables
Menditto, V. G., Lucci, M., Polonara, S. et al. (2012) Management of minor head injury in patients receiving oral anticoagulant therapy: a prospective study of a 24-hour observation protocol. Annals of Emergency Medicine 59(6): 451-5	- Study design not relevant to this review protocol *case series*
Miller, M. M., Lowe, J., Khan, M. et al. (2019) Clinical and Radiological Characteristics of Vitamin K Versus Non-Vitamin K Antagonist Oral Anticoagulation-Related Intracerebral Hemorrhage. Neurocritical Care 31(1): 56-65	- Population not relevant to this review protocol *patients acute non-traumatic intra cranial haemorrhage on oral anticoagulation therapy*
Moore, M. M.; Pasquale, M. D.; Badellino, M. (2012) Impact of age and anticoagulation: need for neurosurgical intervention in trauma patients with mild traumatic brain injury. The Journal of Trauma and Acute Care Surgery 73(1): 126-30	- No relevant clinical variables - No multi-variate analysis *No MV analysis for people on anti-coagulation*
Mourad, M.; Senay, A.; Kharbutli, B. (2021) The utility of a second head CT scan after a negative initial CT scan in head trauma patients on new direct oral anticoagulants (DOACs). Injury 52(9): 2571-2575	- No relevant clinical variables - No multi-variate analysis
Muller, K., Townend, W., Biasca, N. et al. (2007) S100B serum level predicts computed tomography findings after minor head injury. Journal of Trauma-Injury Infection & Critical Care 62(6): 1452-6	- No relevant clinical variables *S100b for selecting mild TBI patients for CT .* - Population not relevant to this review protocol *People with mild TBI*
Murillo-Cabezas, F., Munoz-Sanchez, M. A., Rincon-Ferrari, M. D. et al. (2010) The prognostic value of the temporal course of S100beta protein in post-acute severe brain injury: A prospective and observational study. Brain Injury 24(4): 609-19	- No relevant clinical variables *prognostic value of S100 for severe TBI* - Population not relevant to this review protocol

Study	Code [Reason]
	Severe TBI
Murray, G. D., Butcher, I., McHugh, G. S. et al. (2007) Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. Journal of Neurotrauma 24(2): 329-37	- Population not relevant to this review protocol *All patients with TBI* - No relevant clinical variables
Naeimi, Z. S., Weinhofer, A., Sarahrudi, K. et al. (2006) Predictive value of S-100B protein and neuron specific-enolase as markers of traumatic brain damage in clinical use. Brain Injury 20(5): 463-8	- No relevant clinical variables *predictive value of S100B and NSE for TBI* - Population not relevant to this review protocol *TBI patients*
Nakhjavan-Shahraki, B., Yousefifard, M., Hajighanbari, M. J. et al. (2017) Pediatric Emergency Care Applied Research Network (PECARN) prediction rules in identifying high risk children with mild traumatic brain injury. European Journal of Trauma & Emergency Surgery 43(6): 755-762	- Population not relevant to this review protocol *children with mild TBI* - No relevant clinical variables *study was designed to assess the value of PECARN rule in identification of children with clinically important TBI*
Ng, S. M.; Toh, E. M.; Sherrington, C. A. (2002) Clinical predictors of abnormal computed tomography scans in paediatric head injury. Journal of Paediatrics & Child Health 38(4): 388-92	- No relevant clinical variables *study aimed to evaluate if if clinical features associated with head injury in children can be co-related with abnormal CT scans* - Population not relevant to this review protocol *children with acute head injury*
Nishijima DK, Offerman SR, Ballard DW et al. (2012) Immediate and delayed traumatic intracranial hemorrhage in patients with head trauma and preinjury warfarin or clopidogrel use. Annals of emergency medicine 59(6): 460	- No multi-variate analysis
Nishijima, D. K., Shahlaie, K., Sarkar, K. et al. (2013) Risk of unfavorable long-term outcome in older adults with traumatic intracranial hemorrhage and anticoagulant or antiplatelet use. American Journal of Emergency Medicine 31(8): 1244-7	- No relevant clinical variables

Study	Code [Reason]
Norwood, S. H., Berne, J. D., Rowe, S. A. et al. (2008) Early venous thromboembolism prophylaxis with enoxaparin in patients with blunt traumatic brain injury. Journal of Trauma-Injury Infection & Critical Care 65(5): 1021-6; discussion 1026	- No relevant clinical variables *Study aimed to determine the safety of early enoxaparin for venous thromboembolism (VTE) prophylaxis in patients with blunt traumatic brain injury (TBI).*
O'Neill, K. M., Jean, R. A., Savetamal, A. et al. (2020) When to Admit to Observation: Predicting Length of Stay for Anticoagulated Elderly Fall Victims. Journal of Surgical Research 250: 156-160	- No relevant clinical variables *study aimed to determine what factors were associated with a stay consistent with observational status.* - No multi-variate analysis - No relevant outcomes *length of stay*
Ohbuchi, H., Hagiwara, S., Hirota, K. et al. (2017) Clinical Predictors of Intracranial Injuries in Infants with Minor Head Trauma. World Neurosurgery 98: 479-483	- Population not relevant to this review protocol *Infants with mild head trauma* - No relevant clinical variables *The aim of this study was to identify clinical predictors of intracranial injuries in infants with minor head trauma.*
Okonkwo, D. O., Puffer, R. C., Puccio, A. M. et al. (2020) Point-of-Care Platform Blood Biomarker Testing of Glial Fibrillary Acidic Protein versus S100 Calcium-Binding Protein B for Prediction of Traumatic Brain Injuries: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury Study. Journal of Neurotrauma 37(23): 2460-2467	- No relevant clinical variables *biomarkers S 100 B and GFAP for prediction ofTBI*
Olivero, W. C., Wang, H., Farahvar, A. et al. (2017) Predictive (subtle or overlooked) initial head CT findings in patients who develop delayed chronic subdural hematoma. Journal of Clinical Neuroscience 42: 129-133	- Population not relevant to this review protocol *patients who underwent surgery for chronic subdural hematoma.*
Oris, C., Pereira, B., Durif, J. et al. (2018) The Biomarker S100B and Mild Traumatic Brain Injury: A Meta-analysis. Pediatrics 141(6): 06	- No relevant clinical variables *Biomarkers for TBI*

Study	Code [Reason]
Palchak, M. J., Holmes, J. F., Vance, C. W. et al. (2003) A decision rule for identifying children at low risk for brain injuries after blunt head trauma. Annals of Emergency Medicine 42(4): 492-506	- No relevant clinical variables *study aimed to derive a decision rule for identifying children at low risk for traumatic brain injuries.* - Population not relevant to this review protocol *children with blunt head trauma*
Papa, L., Ramia, M. M., Kelly, J. M. et al. (2013) Systematic review of clinical research on biomarkers for pediatric traumatic brain injury. Journal of Neurotrauma 30(5): 324-38	- No relevant clinical variables *Biomarkers for paediatric TBI*
Parmar, K. A.; Rao, S.; Abu-Zidan, F. M. (2006) Head injuries in warfarinised patients. Singapore Medical Journal 47(8): 676-8	- No multi-variate analysis
Peck, K. A., Calvo, R. Y., Schechter, M. S. et al. (2014) The impact of preinjury anticoagulants and prescription antiplatelet agents on outcomes in older patients with traumatic brain injury. The Journal of Trauma and Acute Care Surgery 76(2): 431-6	- Population not relevant to this review protocol *Included people with acute ICH on CT*
Pelinka, L. E., Kroepfl, A., Leixnering, M. et al. (2004) GFAP versus S100B in serum after traumatic brain injury: relationship to brain damage and outcome. Journal of Neurotrauma 21(11): 1553-61	- No relevant clinical variables *S 100B and GFAP in TBI*
Piazza, O., Storti, M. P., Cotena, S. et al. (2007) S100B is not a reliable prognostic index in paediatric TBI. Pediatric Neurosurgery 43(4): 258-64	- No relevant clinical variables *S100B in paediatric TBI*
Pieracci, F. M., Eachempati, S. R., Shou, J. et al. (2007) Degree of anticoagulation, but not warfarin use itself, predicts adverse outcomes after traumatic brain injury in elderly trauma patients. Journal of Trauma-Injury Infection & Critical Care 63(3): 525-30	- No multi-variate analysis
Pillai, S., Praharaj, S. S., Mohanty, A. et al. (2001) Prognostic factors in children with severe diffuse brain injuries: a study of 74 patients. Pediatric Neurosurgery 34(2): 98-103	- No relevant clinical variables *Study analysed prognostic factors for children with severe diffuse brain injury*

Study	Code [Reason]
Poli-de-Figueiredo, L. F., Biberthaler, P., Simao Filho, C. et al. (2006) Measurement of S-100B for risk classification of victims sustaining minor head injury--first pilot study in Brazil. Clinics (Sao Paulo, Brazil) 61(1): 41-6	- No relevant clinical variables *S100B for minor head injury*
Prat, R. and Calatayud-Maldonado, V. (1998) Prognostic factors in postraumatic severe diffuse brain injury. Acta Neurochirurgica 140(12): 1257-60; discussion 1261	- No relevant clinical variables *Prognostic factors in post-traumatic severe diffuse brain injury*
Puzio, T. J., Murphy, P. B., Kregel, H. R. et al. (2021) Delayed Intracranial Hemorrhage After Blunt Head Trauma While on Direct Oral Anticoagulant: Systematic Review and Meta-Analysis. Journal of the American College of Surgeons	- Systematic review. Screened for relevant references
Raabe, A., Grolms, C., Sorge, O. et al. (1999) Serum S-100B protein in severe head injury. Neurosurgery 45(3): 477-83	- Full text paper not available
Rendell, S. and Batchelor, J. S. (2013) An analysis of predictive markers for intracranial haemorrhage in warfarinised head injury patients. Emergency Medicine Journal 30(1): 28-31	- No multi-variate analysis
Riccardi, A., Frumento, F., Guiddo, G. et al. (2013) Minor head injury in the elderly at very low risk: a retrospective study of 6 years in an Emergency Department (ED). American Journal of Emergency Medicine 31(1): 37-41	- No multi-variate analysis
Riccardi, A., Spinola, B., Minuto, P. et al. (2017) Intracranial complications after minor head injury (MHI) in patients taking vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs). American Journal of Emergency Medicine 35(9): 1317-1319	- No multi-variate analysis
Ronning, P., Helseth, E., Skaansar, O. et al. (2021) Impact of Preinjury Antithrombotic Therapy on 30-Day Mortality in Older Patients Hospitalized With Traumatic Brain Injury (TBI). Frontiers in neurology [electronic resource]. 12: 650695	- No relevant clinical variables *Study aimed to describe the frequency of antithrombotic drug use in elderly, hospitalized patients with TBI compared to the general elderly Norwegian population and to assess the association between preinjury antithrombotic therapy and 30-day mortality*
Saadat, S., Ghodsi, S. M., Naieni, K. H. et al. (2009) Prediction of intracranial computed	- Population not relevant to this review protocol

Study	Code [Reason]
tomography findings in patients with minor head injury by using logistic regression. Journal of Neurosurgery 111(4): 688-94	*people with mild TBI*
Saboori, M.; Ahmadi, J.; Farajzadegan, Z. (2007) Indications for brain CT scan in patients with minor head injury. Clinical Neurology & Neurosurgery 109(5): 399-405	- No relevant clinical variables *The aim of this study was to find clinical signs and symptoms which help to predict the indications for brain CT scan following minor head injury.* - Population not relevant to this review protocol *minor head injury*
Santing, J. A. L.; Van den Brand, C. L.; Jellema, K. (2021) Traumatic Brain Injury in Patients Receiving Direct Oral Anticoagulants. Journal of Emergency Medicine 60(3): 285-291	- No multi-variate analysis
Sapin, V., Gaulmin, R., Aubin, R. et al. (2021) Blood biomarkers of mild traumatic brain injury: State of art. Neuro-Chirurgie 67(3): 249-254	- No relevant clinical variables *Blood biomarkers in TBI*
Sauter, T. C., Ziegenhorn, S., Ahmad, S. S. et al. (2016) Age is not associated with intracranial haemorrhage in patients with mild traumatic brain injury and oral anticoagulation. Journal of Negative Results in Biomedicine 15(1): 12	- No multi-variate analysis
Scantling D, Fischer C, Gruner R et al. (2017) The role of delayed head CT in evaluation of elderly blunt head trauma victims taking antithrombotic therapy. European journal of trauma and emergency surgery : official publication of the European Trauma Society 43(6): 741-746	- No multi-variate analysis
Scavarda, D., Gabaudan, C., Ughetto, F. et al. (2010) Initial predictive factors of outcome in severe non-accidental head trauma in children. Childs Nervous System 26(11): 1555-61	- Population not relevant to this review protocol *children with severe non accidental trauma*
Schneider Soares, F. M., Menezes de Souza, N., Liborio Schwarzbold, M. et al. (2012) Interleukin-10 is an independent biomarker of severe traumatic brain injury prognosis. Neuroimmunomodulation 19(6): 377-85	- Population not relevant to this review protocol *severe TBI* - No relevant clinical variables *IL-10 in severe TBI*

Study	Code [Reason]
Schreiber, M. A., Aoki, N., Scott, B. G. et al. (2002) Determinants of mortality in patients with severe blunt head injury. Archives of Surgery 137(3): 285-90	- No relevant clinical variables *Predictive variables for mortality after severe head injury* - Population not relevant to this review protocol *severe blunt head injury*
Seligman, E., Aslam, U., Psoter, K. J. et al. (2022) Factors Associated With Repeat Emergency Department Visits in a State-wide Cohort of Pediatric Patients With Mild Traumatic Brain Injury. Pediatric Emergency Care 38(2): e683-e689	- Population not relevant to this review protocol *paediatric patients treated in the ED for mild traumatic brain injury*
Sert, E. T.; Mutlu, H.; Kokulu, K. (2020) The Use of PECARN and CATCH Rules in Children With Minor Head Trauma Presenting to Emergency Department 24 Hours After Injury. Pediatric emergency care. 10	- No relevant clinical variables *PECARN and CATCH rules in children with mild TBI* - Population not relevant to this review protocol *children with mild TBI*
Sezer, A. A., Akinci, E., Ozturk, M. et al. (2012) The role of blood S100B and lactate levels in minor head traumas in children and adults and correlation with brain computerized tomography. Ulusal Travma ve Acil Cerrahi Dergisi 18(5): 411-416	- No relevant clinical variables *blood S100B and lactate and to determine any correlation with brain computerised tomography in minor head traumas in children and adults.*
Sherer, M., Stouter, J., Hart, T. et al. (2006) Computed tomography findings and early cognitive outcome after traumatic brain injury. Brain Injury 20(10): 997-1005	- Population not relevant to this review protocol *People with TBI. Study examines relationship between CT abnormalities and early neuropsychological outcome after TBI*
Shimoni, Z., Danilov, V., Hadar, S. et al. (2021) Head Computed Tomography Scans in Elderly Patients with Low Velocity Head trauma after a Fall. Israel Medical Association Journal: Imaj 23(6): 359-363	- No multi-variate analysis
Singh, R., Venkateshwara, G., Nair, K. P. et al. (2014) Agitation after traumatic brain injury and predictors of outcome. Brain Injury 28(3): 336-40	- Population not relevant to this review protocol *Study measures incidence of agitation after TBI*

Study	Code [Reason]
Smits, M., Hunink, M. G., van Rijssel, D. A. et al. (2008) Outcome after complicated minor head injury. Ajnr: American Journal of Neuroradiology 29(3): 506-13	- Population not relevant to this review protocol *adults with complicated minor head injury presenting within 24 hours of injury*
So, W. H.; Chan, H. F.; Li, M. K. (2018) Investigation of risk factors of geriatric patients with significant brain injury from ground-level fall: A retrospective cohort study in a local Accident and Emergency Department setting. Hong Kong Journal of Emergency Medicine 25(6): 305-312	- No multi-variate analysis *Only univariate analysis*
Soleimani, T., Mosher, B., Ochoa-Frongia, L. et al. (2021) Delayed Intracranial Hemorrhage After Blunt Head Injury With Direct Oral Anticoagulants. Journal of Surgical Research 257: 394-398	- No multi-variate analysis
Spano, P. J., 2nd, Shaikh, S., Boneva, D. et al. (2020) Anticoagulant chemoprophylaxis in patients with traumatic brain injuries: A systematic review. The Journal of Trauma and Acute Care Surgery 88(3): 454-460	- systematic not relevant to reveiw question *anticoagulant chemoprophylaxis regimens in TBI patients*
Spinola MB, Riccardi A, Minuto P et al. (2019) Hemorrhagic risk and intracranial complications in patients with minor head injury (MHI) taking different oral anticoagulants. The American journal of emergency medicine 37(9): 1677-1680	- No multi-variate analysis
Stanitsas L, Huang G, Emerick E, Chance E HB (2016) 1563: if the initial head Ct of a trauma patient on antithrombotics is negative, is a second Ct necessary?. Crit Care Med.: 466	- Conference abstract
Stephen, S., Wong, E. W. W., Idris, A. M. et al. (2019) Intracranial haemorrhage detected by cerebral computed tomography after falls in hospital acute medical wards. BMC Health Services Research 19(1): 792	- Population not relevant to this review protocol *patients with falls in hospital acute care wards* - No relevant clinical variables *The study describes the use of brain computed tomography (CT) following inpatient falls, and determine the incidence and potential risk factors for intracranial haemorrhage*
Sun, Y., Xi, C., Wang, E. et al. (2011) Disseminated intravascular coagulation scores as predictors for progressive hemorrhage and	- Population not relevant to this review protocol

Study	Code [Reason]
neurological prognosis following traumatic brain injury. Neural Regeneration Research 6(2): 136-142	*people with Isolated head injury. study excludes people on anti-coagulants/liver cirrhosis.*
Swap C, Sidell M, Ogaz R et al. (2016) Risk of Delayed Intracerebral Hemorrhage in Anticoagulated Patients after Minor Head Trauma: The Role of Repeat Cranial Computed Tomography. The Permanente journal 20(2): 14-16	- No relevant clinical variables *Study aimed to identify the frequency of delayed traumatic ICH in patients receiving warfarin or clopidogrel.*
Tabrizi, S.; Zafar, E.; Rafiei, H. (2021) A cohort retrospective study on computed tomography scan among pediatric minor head trauma patients. International Journal of Surgery Open 29: 50-54	- Population not relevant to this review protocol *children with minor head trauma* - No relevant clinical variables *The aim of this study was to evaluate the incidence of positive CT findings in children with minor head trauma*
Tao, C., Hu, X., Wang, J. et al. (2017) Admission neutrophil count and neutrophil to lymphocyte ratio predict 90-day outcome in intracerebral hemorrhage. Biomarkers in Medicine 11(1): 33-42	- Population not relevant to this review protocol *patients with spontaneous intra cranial haemorrhage*
Tauber M, Koller H, Moroder P et al. (2009) Secondary intracranial hemorrhage after mild head injury in patients with low-dose acetylsalicylate acid prophylaxis. The Journal of trauma 67(3): 521-5; discussion 525	- No multi-variate analysis
Taylor K, Lymburner P CJ (2012) Medical imaging in emergency medicine: assessing the use of serial imaging to screen for delayed intracranial haemorrhage in patients on anticoagulant and antiplatelet therapy. Med Imaging Radiat Oncol: 146	- Conference abstract
Thaler, H. W., Schmidsfeld, J., Pusch, M. et al. (2015) Evaluation of S100B in the diagnosis of suspected intracranial hemorrhage after minor head injury in patients who are receiving platelet aggregation inhibitors and in patients 65 years of age and older. Journal of Neurosurgery 123(5): 1202-8	- No relevant clinical variables *S100B in the diagnosis of suspected intracranial haemorrhage*
Thelin, E. P., Johannesson, L., Nelson, D. et al. (2013) S100B is an important outcome predictor in traumatic brain injury. Journal of Neurotrauma 30(7): 519-28	- No relevant clinical variables *S100B for TBI*

Study	Code [Reason]
	- Population not relevant to this review protocol *people with TBI*
Thelin, E. P.; Nelson, D. W.; Bellander, B. M. (2014) Secondary peaks of S100B in serum relate to subsequent radiological pathology in traumatic brain injury. Neurocritical Care 20(2): 217-29	- No relevant clinical variables *serum levels of S100B and their relation to potential subsequent radiological pathology present on CT/MRI-scans.*
Thelin, E. P., Zibung, E., Riddez, L. et al. (2016) Assessing bicycle-related trauma using the biomarker S100B reveals a correlation with total injury severity. European Journal of Trauma & Emergency Surgery 42(5): 617-625	- No relevant clinical variables *Study aimed to investigate how S100B could be used when assessing injuries in patients suffering from bicycle trauma injury*
Thelin, E., Al Nimer, F., Frostell, A. et al. (2019) A Serum Protein Biomarker Panel Improves Outcome Prediction in Human Traumatic Brain Injury. Journal of Neurotrauma 36(20): 2850-2862	- No relevant clinical variables *Study aimed to determine how concentrations of six different protein biomarkers, measured in samples collected during the first weeks after TBI, relate to injury severity and outcome.*
Timmons, S. D., Bee, T., Webb, S. et al. (2011) Using the abbreviated injury severity and Glasgow Coma Scale scores to predict 2-week mortality after traumatic brain injury. Journal of Trauma-Injury Infection & Critical Care 71(5): 1172-8	- No relevant clinical variables *using GCS and AIS to predict 2 week mortality after TBI* - Population not relevant to this review protocol *TBI patients*
Tollefsen, M. H., Vik, A., Skandsen, T. et al. (2018) Patients with Moderate and Severe Traumatic Brain Injury: Impact of Preinjury Platelet Inhibitor or Warfarin Treatment. World Neurosurgery 114: e209-e217	Population not relevant to this review protocol [Includes moderate and severe TBI.]
Tong, W. S., Zheng, P., Zeng, J. S. et al. (2012) Prognosis analysis and risk factors related to progressive intracranial haemorrhage in patients with acute traumatic brain injury. Brain Injury 26(9): 1136-42	- No relevant clinical variables *risk factors for progressive intracranial haemorrhage in patients with acute TBI* - Population not relevant to this review protocol *acute TBI*

Study	Code [Reason]
Townend, W. and Ingebrigtsen, T. (2006) Head injury outcome prediction: a role for protein S-100B?. Injury 37(12): 1098-108	- No relevant clinical variables *S 100 B in head injury*
Travers, B., Jones, S., Bastani, A. et al. (2021) Assessing geriatric patients with head injury in the emergency department using the novel level III trauma protocol. American Journal of Emergency Medicine 45: 149-153	- No relevant clinical variables *The purpose of this study was to assess the impact of the novel Level III trauma protocol on resource utilisation and patient outcome.*
Tremblay, S., Desjardins, M., Bermudez, P. et al. (2019) Mild traumatic brain injury: The effect of age at trauma onset on brain structure integrity. NeuroImage Clinical 23: 101907	- No relevant clinical variables *Study aimed to determine whether patients who sustain a mild TBI earlier in life fare better than patients who sustain a mild TBI at an older age*
Uccella, L., Zoia, C., Bongetta, D. et al. (2018) Are Antiplatelet and Anticoagulants Drugs A Risk Factor for Bleeding in Mild Traumatic Brain Injury?. World Neurosurgery 110: e339-e345	- No multi-variate analysis
Uccella, L., Zoia, C., Perlasca, F. et al. (2016) Mild Traumatic Brain Injury in Patients on Long-Term Anticoagulation Therapy: Do They Really Need Repeated Head CT Scan?. World Neurosurgery 93: 100-3	- No relevant clinical variables
Uchino, Y., Okimura, Y., Tanaka, M. et al. (2001) Computed tomography and magnetic resonance imaging of mild head injury--is it appropriate to classify patients with Glasgow Coma Scale score of 13 to 15 as "mild injury"?. Acta Neurochirurgica 143(10): 1031-7	- Population not relevant to this review protocol *mild TBI* - No relevant clinical variables *The purpose of this study is to examine the relation between Glasgow Coma Scale (GCS) score and findings on computed tomography (CT) and magnetic resonance (MR) imaging of patients with mild head injury presenting GCS scores between 13 and 15.*
Unden, J., Astrand, R., Waterloo, K. et al. (2007) Clinical significance of serum S100B levels in neurointensive care. Neurocritical Care 6(2): 94-9	- No relevant clinical variables *S100B for monitoring in neuro intensive care in patients with head injury or cerebrovascular insults* - Population not relevant to this review protocol *head injury or cerebrovascular insults*

Study	Code [Reason]
Unden, J. and Romner, B. (2010) Can low serum levels of S100B predict normal CT findings after minor head injury in adults?: an evidence-based review and meta-analysis. Journal of Head Trauma Rehabilitation 25(4): 228-40	- systematic not relevant to reveiw question *S100B in adults with minor head injury*
Valiuddin, H., Calice, M., Alam, A. et al. (2021) Incidence of Traumatic Delayed Intracranial Hemorrhage Among Patients Using Direct Oral Anticoagulants. Journal of Emergency Medicine 23: 23	- No multi-variate analysis
van den Brand, C. L., Tolido, T., Rambach, A. H. et al. (2017) Systematic Review and Meta-Analysis: Is Pre-Injury Antiplatelet Therapy Associated with Traumatic Intracranial Hemorrhage?. Journal of Neurotrauma 34(1): 1-7	- Systematic review. Screened for relevant references
Vaniyapong, T., Patumanond, J., Ratanalert, S. et al. (2019) Clinical indicators for traumatic intracranial findings in mild traumatic brain injury patients. Surgical Neurology International 10(64): 1-5	- Population not relevant to this review protocol *mild TBI* - No relevant clinical variables
Vedantam, A., Brennan, J., Levin, H. S. et al. (2021) Early versus Late Profiles of Inflammatory Cytokines after Mild Traumatic Brain Injury and Their Association with Neuropsychological Outcomes. Journal of Neurotrauma 38(1): 53-62	- No relevant clinical variables *Study describes the profile of plasma inflammatory cytokines and explore associations between these cytokines and neuropsychological outcomes after mild TBI*
Vos, P. E., Jacobs, B., Andriessen, T. M. et al. (2010) GFAP and S100B are biomarkers of traumatic brain injury: an observational cohort study. Neurology 75(20): 1786-93	- Population not relevant to this review protocol *GFAP and S100 in TBI*
Vos, P. E., Lamers, K. J., Hendriks, J. C. et al. (2004) Glial and neuronal proteins in serum predict outcome after severe traumatic brain injury. Neurology 62(8): 1303-10	- Population not relevant to this review protocol *GFAP, NSE and S100 in severe TBI*
Wilson, C. L., Hearps, S. J., Tavender, E. J. et al. (2021) Factors predictive for computed tomography use and abnormality in paediatric head injuries in Australia and New Zealand. Emergency Medicine Australasia 33(1): 157-160	- No relevant clinical variables *Study aimed to investigate patient-level factors predictive for computed tomography of the brain (CTB) use and abnormality in head injured children*

Study	Code [Reason]
Winter, C., Bell, C., Whyte, T. et al. (2015) Blood-brain barrier dysfunction following traumatic brain injury: correlation of K(trans) (DCE-MRI) and SUVR (99mTc-DTPA SPECT) but not serum S100B. Neurological Research 37(7): 599-606	- Population not relevant to this review protocol *Post-traumatic blood brain barrier was assessed suing MRI, SPECT and serum S100b in people with TBI*
Yavasi, O., Unluer, E. E., Gun, C. et al. (2011) Do we routinely need cranial computed tomography for mild head injuries in Turkey?. European Journal of Emergency Medicine 18(4): 238-40	- Population not relevant to this review protocol *People with mild TBI. study aimed to determine role of clinical parameters in detecting intra cranial injury and if CT is needed routinely in mild TBI.*
Yogo, N., Toida, C., Muguruma, T. et al. (2021) Simplified Clinical Decision Rule Using Clinically Important Events for Risk Prediction in Pediatric Head Injury: A Retrospective Cohort Study. Journal of Clinical Medicine 10(22): 11	- Population not relevant to this review protocol *Paediatric head injury. Not relevant clinical variables*
Yuan, F., Ding, J., Chen, H. et al. (2012) Predicting progressive hemorrhagic injury after traumatic brain injury: derivation and validation of a risk score based on admission characteristics. Journal of Neurotrauma 29(12): 2137-42	- No relevant clinical variables *The objective of this study was to develop and validate a prognostic model that uses information available at admission to determine the likelihood of progressive haemorrhagic injury after TBI*
Yue, J. K., Winkler, E. A., Sharma, S. et al. (2017) Temporal profile of care following mild traumatic brain injury: predictors of hospital admission, follow-up referral and six-month outcome. Brain Injury 31(1314): 1820-1829	- Population not relevant to this review protocol *people with mild TBI. Study evaluates the clinical management and follow-up of patients with mild TBI*
Yuguero, O., Guzman, M., Castan, T. et al. (2018) Characteristics and prognosis of patients admitted to a hospital emergency department for traumatic brain injury and with anticoagulant or antiplatelet treatment. Neurocirugia (Astur : Engl Ed) 29(5): 233-239	- Full text paper not available
Yuksen, C., Sittichanbuncha, Y., Patumanond, J. et al. (2018) Clinical predictive score of intracranial hemorrhage in mild traumatic brain injury. Therapeutics and Clinical Risk Management 14: 213-218	- Population not relevant to this review protocol *Asian population with mild TBI* - No relevant clinical variables *This study aimed to evaluate which clinical factors are associated with intracranial haemorrhage in Asian population*

Study	Code [Reason]
Zhang, W., Wu, H., Zhang, S. et al. (2021) Can S100B Predict and Evaluate Post-Traumatic Hydrocephalus. World Neurosurgery 149: e931-e934	- Population not relevant to this review protocol *Post-traumatic hydrocephalus* - No relevant clinical variables *S100B to predict Post-traumatic hydrocephalus*
Zwahlen, R. A., Labler, L., Trentz, O. et al. (2007) Lateral impact in closed head injury: a substantially increased risk for diffuse axonal injury--a preliminary study. Journal of Cranio-Maxillo-Facial Surgery 35(3): 142-6	- No relevant clinical variables *Study aimed to assess whether location of impact causing different facial fracture patterns was associated with diffuse axonal injury in patients with severe closed head injury.*

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix J Research recommendations

J.1 Research recommendation

What is the risk of any intracranial bleeding or intracranial bleeding associated with clinical deterioration after head injury in people with a pre-injury coagulopathy? This includes medical conditions such as liver failure or haemophilia, or taking anticoagulants or antiplatelets in people who:

- have a Glasgow Comma Scale score of 15 at 2 hours after the head injury and medium risk factors for intracranial bleeding, or
- loss of consciousness or amnesia with no additional risk factors (that is, they are under 65, had a low energy transfer injury and any retrograde amnesia has lasted for less than 30 minutes), or
- there is no loss of consciousness or amnesia?

J.1.1 Why this is important

There is a recognition that anticoagulant therapy increases the risk of progression of intracranial injuries following TBI. It is therefore rational to hypothesise that other forms of coagulopathy (both congenital and acquired) can also increase the risk of progression of intracranial bleeding. The committee reviewed the literature in this regard; however, there is insufficient literature to allow us to make a recommendation. On this basis, we have made a research recommendation.

J.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Coagulation abnormalities have the potential to increase the risk or intracranial bleeding, both identification on initial assessment, and progression of existing lesions.
Relevance to NICE guidance	There is a broad range of therapeutic anti-coagulants and anti-platelet agents, some of which have been licensed since the last NICE Guideline (CG176), whose risk of intracranial haemorrhage following head injury have not been assessed. There is the potential to identify further high risk groups following TBI that require a different threshold for imaging at initial assessment.
Relevance to the NHS	If coagulation abnormalities result in higher risk to the patient, there is a risk of missed diagnoses, or subsequent deterioration. This requires systems to be put in place to identify and treat this patient cohort.
National priorities	None identified
Current evidence base	There was evidence from 5 observational studies in adults for anti-coagulants only and 5 observational studies in adults on anticoagulants and anti-platelets. In the studies on anti-coagulants only, all 5 studies included only users (there were no non-users in the studies). In the studies on anti-coagulants and anti-platelets, only one study included people on anti-coagulants and anti-platelets only (there were no non-users in the studies). Other 4

	studies were mixed population [people with (users) and without anti-coagulants/anti-platelets (non -users)]. The proportion of users in the studies varied from 30-70%. These studies included use of anticoagulants/anti-platelets as variables along with other variables such as age, GCS etc in the analysis. Data was not stratified separately for users and non-users in these studies. The evidence was considered to be indirect as risk factors in these studies were applicable to the overall population rather than just the population on anticoagulants/anti-platelets. There was no evidence for pre-injury coagulopathy due to medical conditions. .
Equality considerations	None identified

J.13 Modified PICO table

Population	Studies should include patients in subgroups: (i) medical conditions associated with coagulopathy such as liver failure, haemophilia (ii) patients on anticoagulant medication (VitKA, DOACs, heparin) (iii) antiplatelets (example clopidogrel, ticagrelor, prasugrel) and patients on preinjury aspirin across all 3 risk strata (A) medium risk factors for ICH (B) LOC or amnesia with no additional risk factors (i.e they are aged <65 with a low energy transfer injury and any retrograde amnesia is<30 minutes duration) (C) no loss of consciousness or amnesia Studies should also include head injury patients with no medical conditions or medication associated with coagulopathy across strata to allow comparison to non-users and assessment of the additional risk associated with each drug / medical condition. Patients with head injury who are high risk for intracranial injury (any of GCS < 13, GCS <15 at 2 hours after injury, >1 vomit, focal neurology, seizure, signs of complex skull fracture) would be excluded

J.2 Research recommendation

What are the indications for selecting people of any age who present more than 24 hours after a head injury for a CT or MRI head scan?

J.2.1 Why this is important

The previous NICE guideline on early management of head injury (CG176) did not distinguish between people presenting immediately following head injury and those presenting in a delayed fashion. If people have delayed presentation because they have been in a good clinical state, this may reduce the risk of having an intracranial injury on CT scan. Alternatively, if people present in a delayed fashion because they have been deteriorating, this may increase the risk of having an intracranial injury on CT scan.

J.2.2 Rationale for research recommendation

Importance to 'patients' or the population	It is not clear whether people with head injuries presenting in a delayed fashion have an increased or decreased risk of injury. This can lead to this group being over- or under-investigated.
Relevance to NICE guidance	In the absence of evidence and variation in clinical practice, no recommendations could be made. Future evidence will therefore enable recommendations to be made.
Relevance to the NHS	NHS providers need advice on how to investigate this cohort of patients, and when the at-risk period is following a head injury.
National priorities	One of the aims of the NHS long term plan (2021) is to reduce pressure on emergency services. Identifying which patients need imaging will support the most clinically and cost-effective use of resources.
Current evidence base	One retrospective cohort study with a small proportion of infants presenting more than 24 hrs after injury was identified.
Equality considerations	There are no specific equality considerations.

J.2.3 Modified PICO table

Population	Inclusion: Infants, children and adult with suspected or confirmed head injury presenting more than 24 hours after injury Strata: • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • Infants (aged <1 year) Exclusion: Adults, young people and children (including infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury.
Prognostic variable(s) under consideration	• Age (below 65 years and over 65 years for adults). There is no age-cut off children GCS (13 to 15)

	• neurological injury severity* • Patient’s blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels, platelet count
Confounding factors	Key confounders: Age GCS Other confounders: Neurological injury severity Blood measures of coagulopathy
Outcomes	• Any traumatic intracranial abnormality detected by CT or MR imaging or autopsy • Any intracranial abnormality that causes death, neurosurgical intervention or neuro critical care.
Study design	Cohort studies (prospective and retrospective)
Timeframe	Medium term – required for when the guidance is updated
Additional information	None identified

J.3 Research recommendation

What are the indications for selecting for imaging adults, young people, children and babies with a head injury sustained through a low energy fall and with suspected pre-injury cognitive impairment when loss of consciousness or amnesia is difficult to assess or the pre-injury Glasgow Coma Scale score is not 15?

J.3.1 Why this is important

The basis of clinical assessment following head injury is the Glasgow Coma Score. In the groups identified in the research recommendation, the baseline GCS is not 15, or the ability to accurately assess GCS is impaired. There is therefore a need to either modify the guidelines, or provide alternative modes of assessment.

J.3.2 Rationale for research recommendation

Importance to 'patients' or the population	These patient groups are not adequately assessed with the current guidance as there are specific limitations to current modes of assessment.
Relevance to NICE guidance	Future NICE guidance should ideally stipulate the assessments and indications for investigation or imaging in these difficult to assess patient cohorts. This may require specific assessment tools stratified by age for the paediatric population or pre-existing cognitive impairment. Alternatively, factors such as the mechanism of injury may take on a more important role in decision making.
Relevance to the NHS	The NHS is increasingly treating patients with cognitive impairment who have specialised needs for assessment.
National priorities	None identified
Current evidence base	There was no evidence for people with pre-existing cognitive impairment.
Equality considerations	There is the need to recognise these groups within the NICE guidance to provide the same high quality evidence for management of head injury.

J.3.3 Modified PICO table

Population	Inclusion: Adults, young people, children and infants with a head injury sustained through a low energy fall and with suspected pre-injury cognitive impairment where loss of consciousness or amnesia is difficult to assess or where pre-injury GCS is not 15 Strata: • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • Infants (aged <1 year) Exclusion:

	Adults, young people and children (including infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury.
Prognostic variables under consideration	• Age (below 65 years and over 65 years for adults). There is no age-cut off children • GCS (13 to 15) • neurological injury severity* • Patient’s blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels, platelet count • other indicators of presence and severity of pre-injury disease such as American Society of Anaesthesiology scale (ASA-PS), Charlson comorbidity index (CCI) or single disease grades such as severity of liver/ Chronic kidney disease • indicators of frailty if available such as Rockwood Clinical Frailty Scale or Electronic Frailty Index (for adults only – not applicable for children)
Outcomes	• Any traumatic intracranial abnormality detected by CT or MR imaging or autopsy • Any intracranial abnormality that causes death, neurosurgical intervention or neuro critical care.
Study design	Cohort study Key confounders: Age GCS Other confounders: Neurological injury severity Blood measures of coagulopathy
Timeframe	Medium term – required for when the guidance is updated
Additional information	None

J.4 Research recommendation

What is the risk of intracranial injuries in people with a history of recurrent head injuries, including sports and falls, and no other indications for CT scan?

J.4.1 Why this is important

Mild TBI is the commonest presentation of TBI and is common following sports injuries. Particularly in the context of sports injuries, these can be repeated and lead to cumulative risks to the individual. As this is a large cohort of people, it can have significant health economic implications.

J.4.2 Rationale for research recommendation

Importance to 'patients' or the population	Repeated mild TBI is a common presentation. Each presentation is addressed on its merits but does not account for cumulative morbidity or cumulative risk of intracranial injury.
Relevance to NICE guidance	Current NICE guidance was not able to make recommendations on this area, despite it being a common presentation. Future guidance may take into account the cumulative burden of injury, or the possibility that those who have had an initial head injury have an increased risk of subsequent head injury.
Relevance to the NHS	As thiscohort is large, it is important for the NHS not to over- (costs of imaging) or under- (risk of deterioration or cumulative morbidity to the patient) investigate.
National priorities	None identified
Current evidence base	There was no evidence for people sustaining recurrent head injuries
Equality considerations	There are no specific equality considerations.

J.4.3 Modified PICO table

Population	
Prognostic variables under consideration	Inclusion: Infants, children and adult with a history of recurrent head injuries including sports and falls and no other indications for CT scan? Strata: • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • Infants (aged <1 year) Exclusion: Adults, young people and children (including infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury.
Prognostic variables under consideration	• Age (below 65 years and over 65 years for adults). There is no age-cut off children

	• GCS (13 to 15) • neurological injury severity* • Blood measures of coagulopathy prior to CT such as International Normalised Ration (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen levels • other indicators of presence and severity of pre-injury disease such as American Society of Anaesthesiology scale (ASA-PS), Charlson comorbidity index (CCI) or single disease grades such as severity of liver/ Chronic kidney disease, platelet count • indicators of frailty if available such as Rockwood Clinical Frailty Scale or Electronic Frailty Index
Outcomes	• Any traumatic intracranial abnormality detected by CT or MR imaging or autopsy • Any intracranial abnormality that causes death, neurosurgical intervention or neuro critical care.
Study design	Cohort study Key confounders: Age GCS (Glasgow Coma Scale) Other confounders: Neurological injury severity Blood measures of coagulopathy
Timeframe	Medium term
Additional information	None