National Institute for Health and Care Excellence

Final

Head Injury: assessment and management

[I] Evidence review for admission and observation in hospital of people with head injury who are on anticoagulant or antiplatelet therapy after normal brain imaging or no indication for early imaging

NICE guideline NG232

Evidence reviews underpinning recommendation 1.9.1 to 1.9.5 in the NICE guideline

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Contents

1 Admission and observation in hospital of people with head injury who are on anticoagulant or antiplatelet therapy after normal brain imaging or no indication for early imaging

1.1 How long should people with head injury who are on anticoagulant or antiplatelet therapy be observed in hospital after normal brain imaging or no indication for early imaging?

1.1.1 Introduction

People with TBI and pre-injury anticoagulant or antiplatelet use are at high risk for intracranial haemorrhage. It was identified at scoping that recommendations were required for early care of those with head injury who are on anticoagulant (including DOACs) or antiplatelet therapy as there was uncertainty in the provision of care. There is a need for guidance on admission or discharge of this group, particularly following up those who had no indication for an initial CT scan or had a negative initial CT scan as they may be overlooked. This question aims to investigate how long people on anticoagulants or antiplatelets should be observed after a normal brain scan or where it was not indicated. This will be investigated by comparing these groups to people who are not on pre-injury anticoagulant or antiplatelet therapy in relation to the time it took for certain outcomes to occur.

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	People with head injury on anticoagulant or antiplatelet therapy after normal brain imaging or no indication for early imaging Inclusion: Infants, children and adults with traumatic brain injury (TBI) 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. Further notes: • this population will include people with Glasgow Coma Scale score (GCS) 15 or back to baseline

Interventions	People on pre-injury anticoagulant and/or antiplatelet therapy, split into strata listed below:
	
	• Anticoagulant
	  ○ Warfarin
	  ○ Direct oral anti-coagulants (DOACs)
	  ○ Low molecular weight heparin
	  ○ Sinthrome (acenocoumarol)

	○ Enoxaparin ○ Dalteparin • Antiplatelet (examples below) ○ Aspirin ○ Clopidogrel/prasugrel ○ Dual anti-platelet therapy • Mixed strata: There will be group of patients with both anti-coagulants and anti-platelets It was noted that the different class of anticoagulants/antiplatelets differ pharmacologically. Hence all drugs will be analysed in separate strata.
Comparison	People not on pre-injury anticoagulant or antiplatelet therapy
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Rate of delayed intracranial bleeding (30 days) • Time after injury when bleeding was detected • Time to diagnosis of intracranial injury on CT/MRI/clinical follow-up or autopsy • Re-admission as a result of delayed diagnosis of intracranial injury (30 days) • Serious adverse events within 2 weeks • TBI related mortality (30 days) • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended Glasgow Outcome Score (GOS-E) - at 3 months or more For rate of delayed intracranial bleeding, re-admission and TBI mortality, follow-up ideally 30 days but could accept shorter follow up periods (minimum 7 days)
Study design	• Randomised controlled trials (RCTs) • Systematic reviews of RCTs • If no RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders, starting with prospective cohort studies • If there are no comparative non-randomised studies we will consider inclusion of single arm/non-comparative studies (prospective and retrospective cohort studies) of people on pre-injury anticoagulant or antiplatelet therapy (a minimum sample size for non-comparative studies was set at 1000 people) Key confounders for non-randomised comparative studies: • Age • Diabetes mellitus • Hypertension

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 Effectiveness evidence

1.1.4.1 Included studies

A search was conducted for randomised trials and non-randomised comparative studies, as well as non-comparative studies which would be considered if no comparative evidence was identified, comparing outcomes between those taking pre-injury anticoagulants and/or antiplatelets and those not taking these drugs prior to injury.

Six non-randomised studies (n=2 prospective and n=4 retrospective) were included in the review;[1-5, 7] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Tables 3-10).

Interventions

Most of the evidence for individual antithrombotic drugs was for comparing either warfarin (with some studies using warfarin or another VKA also included in this group based on most using warfarin) or DOACs to no antithrombotic treatment (n=4 studies each). One study also reported results for an aspirin group compared to no antithrombotic treatment and the remaining comparisons were mixed groups or dual therapies, for example an 'other antiplatelet' group included those taking aspirin, ticlopidine, indobufen, clopidogrel, prasugel or ticagrelor in one study and two studies reported results for an intervention consisting of more than one antiplatelet or anticoagulant (dual antithrombotic therapy).

There was no individual/separate evidence for the following drugs (though some may have been included in the mixed intervention groups mentioned in the previous paragraph, for example clopidogrel):

- Low molecular weight heparin
- Sinthrome (acenocoumarol)
- Enoxaparin
- Dalteparin
- Clopidogrel/prasugrel
- Dual anti-platelet therapy

Population

Three studies included those ≥18 years old while another two studies used higher thresholds for age (55 and 65 years, respectively) and the remaining study did not report an age threshold for inclusion. Despite different age thresholds for inclusion, mean/median age in the studies was >65 years in all studies where this was reported, though often characteristics for the specific drug groups or populations analysed were not provided and this was for the overall intervention/population only.

As the aim of this review protocol was to look at the population of people with head injury that had no indication for an initial CT scan or had a negative initial CT scan, results for this subgroup were extracted from studies where possible. Definitions of the populations subsequently included varied, as follows:

- No traumatic haemorrhage on initial cranial CT scan/negative initial CT at admission (n=4 studies)
- Subgroup of those with mild TBI having a second CT scan (n=1 study, delayed bleeding reported for this specific group)
- Presenting to ED with head trauma where 5.9% had haemorrhage at first CT and delayed bleeding was reported (n=1, included as only small proportion had positive initial CT)

In terms of severity of injury (based on GCS), studies varied in how much detail they provided and whether or not any inclusion criteria were based on GCS:

- One study did not report it as an inclusion criterion and reported that ~20% in two group had a pre-hospital GCS score of 15
- Two studies used mild TBI as an inclusion criterion (including GCS score 13-15); one reported that small proportions across two main groups had GCS score <15 at 6 h (1.4 vs. 6.9%) and the other study reported that 97.6% to 100.0% across two main groups were GCS score 15
- One study limited the population further to only include those with GCS score 15
- One study included mild-severe head injury (including GCS score 3-15), with ~60% of the two main groups reported to have mild (GCS score 13-15) head injury
- One study did not report GCS as an inclusion criterion and also did not report the proportion with specific GCS scores or any average values

Degree of anticoagulation was not well reported in studies, but three studies did provide a measure of this:

- Median (IQR) INR was reported to be 2.4 (1.98 to 2.90) for those taking warfarin in one study
- One study reported that 25.0%, 10.9% and 0.8% had INR >3 in the VKA, double antithrombotic treatment and no antithrombotic treatment groups, respectively

Pre-existing cognitive impairment was reported in some studies but this was limited to the proportion with specific conditions rather than a formal assessment of cognition:

- One study reported that 6.0-11.1% across groups had dementia
- 8.6-8.8% had neurodegenerative disease and 9.5-11.9% had cerebrovascular disease across two groups in one study
- <1.0% in all groups had a history of cerebral neoplasia while 3.4-9.8% across groups had stroke/TIA/neurosurgery in one study
- One study showed a higher proportion with some conditions that could affect cognition, including 26.3-33.6% with dementia and 13.3-24.1% with ischaemic stroke or TIA; lower rates were reported for Parkinson's disease (3.4-4.5%) and haemorrhagic stroke (2.0-2.9%)

Outcomes/time-points

Across included studies, most data obtained was for the outcome of delayed bleeding. Although the time-point of 30 days was specified in the protocol as ideal, no studies reported the event specifically at this time-point, with time-points that were reported being either much shorter time-points (such as 24 h or 14 days) or much longer time-points (90 days).

Some data was also available for mortality, though fewer studies reported this outcome. TBI-related mortality was available from two studies and only data for any mortality was available from a further study. One study did report the outcome at the ideal time-point of 30 days but for other studies the time-point was shorter or longer than the 30-day time-point.

One study reported data for neurosurgical intervention which was extracted as it may cover 'readmission as a result of delayed diagnosis of intracranial injury' listed in the protocol, with the time-point being unclear but possibly much longer than the ideal 30-day time-point, as the longest time-point mentioned in the paper was 6 months.

For the following remaining outcomes in the protocol, no data in a form that could be analysed was obtained but as much information as possible was extracted for outcomes related to timing of events: time after injury when bleeding was detected; time to diagnosis of intracranial injury on CT/MRI/clinical follow-up or autopsy; serious adverse events within 2 weeks; and objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS at 3 months or more

Confounding factors

Although in the absence of RCTs the aim was to identify and include non-randomised comparative studies that had adjusted for the key confounder of age, all of the six included studies had issues with confounding with either clear differences between groups demonstrated and not adjusted for or limited reports of these characteristics for the specific drug groups meaning they could not be compared between groups.

For groups where characteristics could be compared, age was often significantly different between groups. Two studies did perform propensity score matching, but as a subpopulation from the study was used for analysis it is unclear whether the matching of characteristics held for the subpopulation as characteristics for these subgroups were not reported separately. Rather than excluding studies, in the absence of other comparative evidence studies were included and confounding issues taken into account in the risk of bias assessment.

Note that hypertension and diabetes had initially been considered as possible key confounders however upon reflection it was agreed they should not be key confounders, with only age being a key confounder.

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

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Chenoweth 2018[1] N=859 Conducted in USA Prospective	Anticoagulant or antiplatelet use pre-injury, with results reported separately for: • Warfarin alone (n=75) • Direct oral anticoagulants (DOACs; n=37)	Aged ≥55 years, blunt head trauma with **no traumatic haemorrhage on initial cranial CT scan** and transported to hospital by emergency services Median (IQR) age: 79 (70-88)	Delayed traumatic intracranial haemorrhage on follow-up CT – **14 days** TBI-related mortality – **follow-up call 14-28 days**	Confounding: • Age: median values >70 in both groups but no P-value provided **Note data not reported to compare between**

Study	Intervention and comparison	Population	Outcomes	Comments
	• Aspirin alone (n=156) • Other antiplatelet (n=41) • >1 anticoagulant or antiplatelet (n=34) vs. No anticoagulant or antiplatelet use pre-injury (n=516)	vs. 71 (61-81) years GCS: 19.8% vs. 20.5% with initial pre-hospital GCS score of 15 Degree of anticoagulation: median (IQR) INR for those taking warfarin was 2.4 (1.98 to 2.90) Pre-existing cognitive impairment: 11.1% vs. 6.0% with reported dementia CT scan: yes, all with negative initial CT Note that characteristics above given for antithrombotic group vs. no antithrombotic, with data for individual drug groups not reported		**individual drug groups and no treatment group** Other antiplatelet alone group included: clopidogrel bisulfate, ticlopidine hydrochloride, prasugrel, dipyridamole, cilostazol or ticagrelor
Covino 2021[2] N=685 Conducted in Italy Retrospective	Anticoagulant use pre-injury, with results reported separately for: • Vitamin K antagonists (VKAs; n=111) • DOACs (n=99) vs. No anticoagulant use pre-injury (n=475) Note: 10.5% vs. 25.9% were taking aspirin, 2.4% vs.	Aged ≥18 years admitted to emergency department with mild TBI as chief complaint **with negative initial CT at admission** and repeated CT 24 h later Median (IQR) age: 83 (78-88) vs. 76 (54-85) years GCS: all GCS score 13-15 to be included; 1.4% vs.	Delayed/late intracranial haemorrhage – **24 h (time of control/repeat CT scan)**	Confounding: • Age: not adjusted for and appears to be a significant difference between groups **Note data not reported to compare between individual drug groups and no treatment group**

Study	Intervention and comparison	Population	Outcomes	Comments
	6.9% were taking clopidogrel, 11.0% vs. 30.5% were taking aspirin/clopidogrel combined and 0.1% vs. 5.1% were taking low-molecular weight heparin in the anticoagulant vs. no anticoagulant groups (proportions for VKA and DOAC groups separately not reported)	6.9% with GCS score <15 at 6 h Degree of anticoagulation: not reported Pre-existing cognitive impairment: 8.6% vs. 8.8% with neurodegenerative disease; 11.9% vs. 9.5% with cerebrovascular disease CT scan: yes, all with negative initial CT Note that characteristics above given for anticoagulation group vs no anticoagulation group, with data for individual drug groups not reported		Note: unclear proportion taking warfarin/other VKAs in the VKA group Mild TBI defined as: GCS score 13-15, loss of consciousness <30 min and post-traumatic amnesia <24 h
Galliazzo 2019[3] N=412 (subgroup with second CT performed) Conducted in Italy Retrospective	Antithrombotic drug use pre-injury, with results reported separately for: • Single antiplatelet therapy (n=131) • VKAs (n=86) • DOACs (n=29) • Double antithrombotic therapy (n=28) vs. No antithrombotic drug use pre-injury (n=135)	Aged >18 years presenting to ED with mild TBI – for purpose of this review only group with second CT included as only group where delayed bleeding outcome was reported Proportion >65 years ranged from 37.9% to 95.8% across groups – all antithrombotic groups had >90% while no treatment group was 37.9% GCS: all GCS score 13-15 to be included; across groups, 97.6% to	Delayed bleeding on repeat CT – 24 h (unclear if same in all people but performed during observation and 24 h mentioned in some cases)	Confounding: • Age: not adjusted for and appears to be a significant difference between treatment and no treatment groups Note data not reported to compare between individual drug groups within the second CT subgroup that was analysed (characteristics only provided for the overall population)

Study	Intervention and comparison	Population	Outcomes	Comments
		100.0% were GCS score 15 Degree of anticoagulation: For VKA, double antithrombotic treatment group and no antithrombotic group, 25.0%, 10.9% and 0.8% had INR >3; 0% for other groups or NA. Pre-existing cognitive impairment: <1.0% in all groups with history of cerebral neoplasia; previous stroke/TIA/neurosurgery in 3.4% to 9.8% across groups CT scan: yes, subgroup with negative initial CT included Note that characteristics above given for whole population as data for the specific subgroup with a second CT were not provided		Single antiplatelet therapy included: aspirin, ticlopidine, indobufen, clopidogrel, prasugrel and ticagrelor VKA use included: warfarin and acenocumarol DOACs included: apixaban, dabigatran, edoxaban and rivaroxaban Double antithrombotic therapy included: dual antiplatelet therapy or antiplatelet + anticoagulant
Grewal 2021[4] N=77,834 Conducted in Canada Retrospective	Anticoagulant use pre-injury, with results reported separately for: • Warfarin (n=3703) • DOACs (n=9214) vs. No anticoagulant use pre-injury (n=64917)	Aged ≥65 years presenting to ED with triage complaint of head injury or trauma – 5.9% reported to have ICH at index visit/CT and not relevant to review population Median (IQR) age: 85 (79-90), 84 (79-89) and 80 (72-87) in	Mortality – 30 days (not specifically TBI-related) Delayed intracranial haemorrhage – within 90 days	Confounding: • Age: not adjusted for and appears to be a significant difference between anticoagulant groups and the no anticoagulant group

Study	Intervention and comparison	Population	Outcomes	Comments
	Note that 2.2%, 2.0% and 8.0% were using clopidogrel in warfarin, DOAC and no anticoagulant groups	warfarin, DOAC and no anticoagulant groups Age >80 years: 69.2%, 68.1% and 47.8% in warfarin, DOAC and no anticoagulant groups GCS: not reported Degree of anticoagulation: not reported Pre-existing cognitive impairment: 26.3% to 33.6% across groups with dementia; 3.4% to 4.5% with Parkinson's disease across groups; stroke or TIA (ischaemic) ranged from 13.3% to 24.1%, with lowest proportion in no anticoagulant group (other two both >20%); haemorrhagic stroke similar between groups (2.0-2.9%) CT scan: 90.2%, 90.6% and 72.4% had CT in ED in warfarin, DOAC and no anticoagulant groups – 8.2%, 5.9% and 5.8% had haemorrhage identified at index visit, respectively Note that characteristics above given for		Note although a propensity score matched population is reported, results for outcomes relevant to the negative initial CT/no initial CT population are not provided in this analysis

Study	Intervention and comparison	Population	Outcomes	Comments
		whole population as data for the specific subgroup with a second CT were not provided		
Mathieu 2020[5] N=34 (subgroup with negative initial CT relevant to review protocol) Conducted in 60 centres across Europe Prospective	Antiplatelet/anticoagulant use pre-injury (n=18), including any of the following (no results given separately for individual drugs within the relevant subpopulation): • antiplatelets (aspirin, ADPR-inhibitors, dual treatment or other) • anticoagulants (VKAs, DOAC and other) • combination of antiplatelet and anticoagulation vs. No pre-injury antiplatelet or anticoagulant treatment (n=16) Note that the proportion taking each drug listed above is unclear for the specific subgroup of those with a negative CT where data was analysed for this review	Aged ≥18 years with blunt mechanism of head injury of mild-severe severity (GCS score 3-15). Initial CT scan performed on admission and repeat scan within 7 days of injury – results specifically from the subgroup with a negative initial CT were relevant to this review protocol Mean (SD) age: 67.9 (12.9) vs. 67.9 (11.6) years GCS: mild-severe GCS score (3-15) to be included, with ~60% in both groups having GCS score 13-15 Degree of anticoagulation: not reported Pre-existing cognitive impairment: not reported CT scan: all had CT to be included, for purpose of this review only included results from subgroup with negative initial CT Note that characteristics above given for whole population	New intracranial haemorrhage on repeat CT – within 7 days Neurosurgical intervention due to new intracranial haemorrhage on repeat CT – 6 months/unclear (unclear but was longest time-point/follow-up mentioned in the paper)	CENTER-TBI study Confounding: • Age: propensity matching demonstrated similar between groups for whole cohort, but unclear if this was maintained within negative CT subgroup as characteristic not reported for this group separately Note although a propensity score matched population is reported, it is unclear if this matching is maintained when looking specifically at the negative CT subgroup as data is not reported

Study	Intervention and comparison	Population	Outcomes	Comments
		as data for the specific subgroup with a negative initial CT were not provided		
Uccella 2016[7] N=865 (subgroup with negative baseline CT) Conducted in Italy Retrospective	Anticoagulant use pre-injury (n=69), with results not reported separately for different types of anticoagulants – proportions using different types not reported vs. No pre-injury anticoagulant use (n=796) Note: those taking single or dual antiplatelet treatments were excluded	Presenting to ED with traumatic head injury, mild TBI with GCS score 15 and having CT performed – results for subgroup with negative CT extracted in line with review protocol Mean (range) age: 67.5 (18-98) years for whole cohort GCS: all had GCS score 15 to be included Degree of anticoagulation: not reported Pre-existing cognitive impairment: not reported CT scan: yes, extracted results for those with negative initial CT Note that characteristics above given for whole population as data for the specific subgroup with a negative initial CT were not provided	Delayed haemorrhage on control CT scan – 24 h/unclear (repeat CT performed after 24 h observation in anticoagulant group but unclear how/if those in no treatment group were followed up for delayed bleeds/other events)	Confounding: • Age: significant difference between the two groups in whole population Note that characteristics not given specifically for those in the negative CT subgroup

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Warfarin/VKA alone vs. no antithrombotic treatment

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no antithrombotic treatment	Risk difference with Warfarin/VKA alone
Delayed traumatic intracranial haemorrhage follow-up: 24 h - 90 days	70018 (4 RCTs)	⊕◯◯◯ Very low[a,b,c]	RR 1.69 (1.29 to 2.20)	Moderate	
				8 per 1,000	6 more per 1,000 (2 more to 10 more)
TBI-related mortality follow-up: 14-28 days	591 (1 RCT)	⊕⊕◯◯ Low[a,d]	RD 0.00 (-0.02 to 0.02)	0 per 1,000	0 fewer per 1,000 (20 fewer to 20 more)[e]
Mortality (not specific to TBI) follow-up: 30 days	68620 (1 RCT)	⊕◯◯◯ Very low[a,f]	RR 2.11 (1.85 to 2.42)	28 per 1,000	32 more per 1,000 (24 more to 40 more)

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as point estimate of one study opposes direction of the other three studies and no clear differences between studies that could explain this. Also no subgrouping strategies prespecified in protocol.

c. Downgraded by 1 increment as time-point in all of the studies is either <30 days (24 h or 14 days) or much longer than 30 days

d. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

e. Absolute effect calculated using risk difference as zero events in both arms of a single study

f. Downgraded by 1 increment as the outcome was not specifically TBI-related mortality as in the protocol

Table 4: Clinical evidence summary: DOACs alone vs. no antithrombotic treatment

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no antithrombotic treatment	Risk difference with DOACs alone
Delayed traumatic intracranial haemorrhage follow-up: 24 h - 90 days	75422 (4 RCTs)	⨁◯◯◯ Very low[a,b,c,d]	RR 1.33 (0.66 to 2.69)	Moderate	
				8 per 1,000	3 more per 1,000 (3 fewer to 14 more)
TBI-related mortality follow-up: 14 - 28 days	553 (1 RCT)	⨁⨁◯◯ Low[a,e]	RD 0.00 (-0.04 to 0.04)	0 per 1,000	0 fewer per 1,000 (40 fewer to 40 more)[f]
Mortality (not specific to TBI) follow-up: 30 days	74131 (1 RCT)	⨁◯◯◯ Very low[a,g]	RR 1.49 (1.34 to 1.65)	Moderate	
				29 per 1,000	14 more per 1,000 (10 more to 19 more)

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as there is variation in point estimate position on Forest plot across studies , with one being on centre line and others towards right of graph, and no clear differences between studies that could explain this. Also no subgrouping strategies prespecified in protocol.

c. Downgraded by 1 increment as time-point in all of the studies is either <30 days (24 h or 14 days) or much longer than 30 days

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

f. Absolute effect calculated using risk difference as zero events in both arms of a single study

g. Downgraded by 1 increment as the outcome was not specifically TBI-related mortality as in the protocol

Table 5: Clinical evidence summary: Aspirin alone vs. no antithrombotic treatment

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no antithrombotic treatment	Risk difference with Aspirin alone
Delayed traumatic intracranial haemorrhage follow-up: 14 days	672 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	OR 0.27 (0.01 to 7.25)	4 per 1,000	0 fewer per 1,000 (10 fewer to 10 more)[d]
TBI-related mortality follow-up: 14-28 days	672 (1 RCT)	⊕⊕◯◯ Low[a,e]	RD 0.00 (-0.01 to 0.00)	0 per 1,000	0 fewer per 1,000 (10 fewer to 10 more)[f]

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as outcome reported at 14-day time-point rather than 30 days as in protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Absolute effect calculate using risk difference as zero events in one arm of a single study

e. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

f. Absolute effect calculate using risk difference as zero events in both arms of a single study

Table 6: Clinical evidence summary: Other antiplatelet alone (clopidogrel bisulfate, ticlopidine hydrochloride, prasugrel, dipyridamole, cilostazol, or ticagrelor) vs. no antithrombotic treatment

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no antithrombotic treatment	Risk difference with Other antiplatelet alone (clopidogrel bisulfate, ticlopidine hydrochloride, prasugrel, dipyridamole, cilostazol, or ticagrelor)
Delayed traumatic intracranial	557 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	OR 0.34 (0.00 to 68.76)	4 per 1,000	0 fewer per 1,000 (40 fewer to 30 more)[d]

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no antithrombotic treatment	Risk difference with Other antiplatelet alone (clopidogrel bisulfate, ticlopidine hydrochloride, prasugrel, dipyridamole, cilostazol, or ticagrelor)
haemorrhage follow-up: 14 days					
TBI-related mortality follow-up: 14-28 days	557 (1 RCT)	⨁⨁◯◯ Low[a,e]	RD 0.00 (-0.03 to 0.03)	0 per 1,000	0 fewer per 1,000 (30 fewer to 30 more)[f]

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as outcome reported at 14-day time-point rather than 30 days as in protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Absolute effect calculated using risk difference as zero events in one arm of a single study

e. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

f. Absolute effect calculated using risk difference as zero events in both arms of a single study

Table 7: Clinical evidence summary: >1 anticoagulant or antiplatelet/double antithrombotic treatment vs. no antithrombotic treatment

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no antithrombotic treatment	Risk difference with >1 anticoagulant or antiplatelet/double antithrombotic treatment
Delayed traumatic intracranial haemorrhage follow-up: 24 h - 14 days	713 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	OR 0.32 (0.01 to 15.08)	5 per 1,000	10 fewer per 1,000 (40 fewer to 30 more)[d]

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no antithrombotic treatment	Risk difference with >1 anticoagulant or antiplatelet/double antithrombotic treatment
TBI-related mortality - 14-28 days	550 (1 RCT)	⨁⨁◯◯ Low[a,e]	RD 0.00 (-0.04 to 0.04)	0 per 1,000	0 fewer per 1,000 (40 fewer to 40 more)[f]

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as both studies report at time-points <30 days (24 h or 14 days)

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Absolute effect calculated using risk difference as zero events in one arm of both studies

e. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

f. Absolute effect calculated using risk difference as zero events in both arms of a single study

Table 8: Clinical evidence summary: Single antiplatelet use (including aspirin, ticlopidine, indobufen, clopidogrel, prasugel and ticagelor) vs. no antithrombotic treatment

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no antithrombotic treatment	Risk difference with Single antiplatelet use (including aspirin, ticlopidine, indobufen, clopidogrel, prasugel and ticagelor)
Delayed bleeding repeat CT - 24 h follow-up: 24 h	266 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	RR 2.06 (0.19 to 22.46)	Moderate	
				7 per 1,000	8 more per 1,000 (6 fewer to 159 more)

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as outcome reported at ~24 h rather than 30 days as in protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 9: Clinical evidence summary: Antiplatelet/anticoagulant use vs. no antithrombotic treatment

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no antithrombotic treatment	Risk difference with Antiplatelet/anticoagulant use
New intracranial haemorrhage on repeat CT follow-up: 7 days	34 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	OR 7.99 (1.02 to 62.61)	0 per 1,000	220 more per 1,000 (10 more to 430 more)[d]
Neurosurgical intervention due to new ICH on repeat CT follow-up: 6 months/unclear	34 (1 RCT)	⨁◯◯◯ Very low[a,e]	RD 0.00 (-0.11 to 0.11)	0 per 1,000	0 fewer per 1,000 (110 fewer to 110 more)[f]

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as outcome reported at 7 days rather than 30 days as in protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Absolute effect calculated using risk difference as zero events in a one arm of a single study

e. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

f. Absolute effect calculated using risk difference as zero events in both arms of a single study

Table 10: Clinical evidence summary: Anticoagulant use vs. no anticoagulant use (those using single and dual antiplatelets also excluded)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no anticoagulant use	Risk difference with Anticoagulant use
Delayed haemorrhage follow-up: 24 h/unclear	865 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	RD 0.00 (-0.02 to 0.02)	0 per 1,000	0 fewer per 1,000 (20 fewer to 20 more)[d]
TBI-related mortality follow-up: 24 h/unclear	865 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	RD 0.00 (-0.02 to 0.02)	0 per 1,000	0 fewer per 1,000 (20 fewer to 20 more)[d]

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as the outcome was reported at 24 h/unclear time-point rather than 30 days as in the protocol

c. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

d. Absolute effect calculated using risk difference as zero events in both arms of a single study

Table 11: Matrix summary table

Worse outcome in AC/AP group Better outcome in AC/AP group **Bold = no imprecision**

		Outcome			
Comparison		Delayed/new traumatic intracranial haemorrhage (time-point varies depending on study/comparison)	Neurosurgical intervention due to new ICH on repeat CT at unclear/6 months	TBI-related mortality (time-point varies depending on study/comparison)	Mortality (not specific to TBI) at 30 days
	Warfarin/VKA alone vs. no antithrombotic treatment	*24 h – 90 days – n=70,018* **RR 1.69 (1.29 to 2.20) – 6 more per 1000 (2 more to 10 more)**	-	*14-28 days – n=591* **RD 0.00 (-0.02 to 0.02) – 0 more per 1000 (20 fewer to 20 more)**	*N=68,620* **RR 2.11 (1.85 to 2.42) – 32 more per 1000 (24 more to 40 more)**
	DOACs alone vs. no antithrombotic treatment	*24 h – 90 days – n=75,422* RR 1.33 (0.66 to 2.69) – 3 more per 1000 (3 fewer to 14 more)	-	*14-28 days – n=553* **RD 0.00 (-0.04 to 0.04) – 0 more per 1000 (40 fewer to 40 more)**	*N=74,131* **RR 1.49 (1.34 to 1.65) – 14 more per 1000 (10 more to 19 more)**
	Aspirin alone vs. no antithrombotic treatment	*14 days – n=672* OR 0.27 (0.01 to 7.25) – 0 fewer per 1000 (10 fewer to 10 more)	-	*14-28 days – n=672* **RD 0.00 (-0.01 to 0.00) – 0 more per 1000 (10 fewer to 10 more)**	-
	Other antiplatelet alone[a] vs. no antithrombotic treatment	*14 days – n=557* OR 0.34 (0.00 to 68.76) – 0 fewer per 1000 (40 fewer to 30 more)	-	*14-28 days – n=557* **RD 0.00 (-0.03 to 0.03) – 0 more per 1000 (30 fewer to 30 more)**	-
	>1 anticoagulant or antiplatelet/double antithrombotic treatment vs. no antithrombotic treatment	*24 h – 14 days – n=713* RR 0.32 (0.01 to 15.08) – 10 fewer per 1000 (40 fewer to 30 more)	-	*14-28 days – n=550* **RD 0.00 (-0.04 to 0.04) – 0 more per 1000 (40 fewer to 40 more)**	-
	Single antiplatelet use[b] vs. no antithrombotic treatment	*24 h – n=266* RR 2.06 (0.19 to 22.46) – 8 more per 1000 (6 fewer to 159 more)	-	-	-
	Antiplatelet/anticoagulant use vs. no antithrombotic treatment	*7 days – n=34* RR 7.99 (1.02 to 62.61) – 220 more per 1000 (10 more to 430 more)	*N=34* RD 0.00 (-0.11 to 0.11) – 0 fewer per 1000 (110 fewer to 110 more)	-	-

	Anticoagulant use vs. no anticoagulant use (those using single and dual antiplatelets also excluded)	*24 h/unclear – n=865* **RD 0.00 (-0.02 to 0.02) – 0 fewer per 1000 (20 fewer to 20 more)**	-	*24 h/unclear – n=865* **RD 0.00 (-0.02 to 0.02) – 0 fewer per 1000 (20 fewer to 20 more)**	-

[a]Including clopidogrel bisulfate, ticlopidine hydrochloride, prasugrel, dipyridamole, cilostazol, or ticagrelor
[b]Including aspirin, ticlopidine, indobufen, clopidogrel, prasugel and ticagelor

See Appendix F for full GRADE tables

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

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 G.

1.1.8 Summary of included economic evidence

None.

1.1.9 Unit costs

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

National Schedule of NHS Costs - Year 2019-20 version 2 - NHS trusts and NHS foundation trusts NON ELECTIVE SHORT STAY				
Code	**Description**	**Number of Finished consultant episodes**	**National Average Unit Cost**	
AA26C	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 15+	5,469	£1,256	
AA26D	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 12-14	8,639	£654	
AA26E	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 9-11	14,996	£580	
AA26F	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 6-8	23,237	£520	
AA26G	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 3-5	33,460	£465	
AA26H	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-2	31,230	£386	
AA26	**Weighted average**	**117,031**	**£521**	

1.1.10 Evidence statements

Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

All outcomes are considered equally important for decision making and therefore have all been rated as critical. The following outcomes were included in the protocol:

- Rate of delayed intracranial bleeding (30 days)
- Time after injury when bleeding was detected
- Time to diagnosis of intracranial injury on CT/MRI/clinical follow-up or autopsy
- Re-admission as a result of delayed diagnosis of intracranial injury (30 days)
- Serious adverse events within 2 weeks
- TBI related mortality (30 days)
- Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more

However, most evidence was identified for rate of delayed intracranial bleeding with the only other two outcomes data was available for being TBI-related mortality and overall mortality, which was included given there was limited evidence for TBI-related mortality with only zero events reported across arms.

1.1.11.2 The quality of the evidence

Six non-randomised studies (n=2 prospective and n=4 retrospective) were included in the review.

All included evidence was graded low-very low quality based on GRADE. This was taken into account when deciding not to make a recommendation. There was some evidence from one very large study (~70,000) that was propensity matched and possibly better in terms of confounding than other included studies, showing only a very small difference in terms of absolute effect between warfarin and no anticoagulant groups and direct oral anticoagulant (DOAC) and no anticoagulant groups. However, other limitations associated with retrospective and non-randomised studies were still present for this review, such as selection of participants and deviation from interventions being unclear. The other included studies were much smaller in comparison and often effects were decided by a difference of only one event between the two groups, leading to imprecision and uncertainty. In meta-analyses that included the larger study, the pooled effect was largely influenced by this study given its size and increased number of events compared to the smaller studies. Based on the available data, the committee agreed that there was enough evidence of no or no clinically important difference for delayed bleeding between those on anticoagulation treatments and those not on any anticoagulation prior to the head injury not to include it as an indication for admission in existing recommendations. In addition, they also agreed that limitations with the evidence meant they could not make a 'do not admit solely based on anticoagulation status' recommendation. Evidence for mortality was limited as although for general mortality there were increased events in the antithrombotic treatment arms, it was noted that it would be difficult to attribute this to head injury as there may have been underlying conditions leading to these deaths that differed between groups, for example the reasons that people were taking anticoagulation. For TBI-related mortality evidence was also limited as the only available data was zero events in each arm of comparisons. Evidence for antiplatelets vs. no treatment pre-injury was more limited as there were no large studies meaning this could not be commented on either in the recommendations. The committee considered making a

research recommendation for further evidence but agreed that this was not a priority considering there was already information from a large study of ~70,000 for anticoagulation and that studies in this area would always be limited to non-randomised retrospective comparisons given the fact that the effect of pre-injury treatments in those with a head injury is being assessed.

It was also noted that there was no evidence specific to the paediatric population, but that usually in terms of admission guidance would be extrapolated from adults to children.

1.1.11.3 Benefits and harms

Warfarin/vitamin K antagonists (VKA) and DOACs vs. no antithrombotic treatment

The outcome with evidence from the most studies/participants was delayed traumatic intracranial haemorrhage at 24 h – 90 days, with the time-point varying across studies. At least 70,000 participants were analysed across four studies in these meta-analyses for warfarin/VKA and DOACs and although the results indicated more events in the anticoagulation group in both cases, the committee agreed that they did not consider the size of the absolute effect to be clinically important. The committee further explained that they were aware of non-comparative evidence that even when delayed bleeding occurs in this group it is rare for them to be significant bleeds requiring anything other than observation and reversal of anticoagulation, with deaths also being rare. It was also noted that the effect was smaller for DOACs than for the warfarin/VKA group with uncertainty in the direction of effect for DOACs.

The only other outcomes reported for these two comparisons were TBI-related mortality and any mortality. Data for TBI-related mortality was only available from one study and was limited to zero events in both arms for both comparisons. Although a possible harm of anticoagulation was identified in both cases in terms of any mortality, the committee noted that this is difficult to interpret and could be influenced by the reasons for taking anticoagulation in the anticoagulation group which would have been difficult or not possible to adjust for even for the propensity-matched study.

Given there was some indication of no clinically important difference between anticoagulation or no anticoagulation pre-injury in terms of delayed bleeding and evidence included at least one very large study with ~70,000 people analysed that was propensity matched, the committee agreed that it would not be appropriate to include anticoagulation status as a sole indicator for admission in those with negative initial CT. However, given the existing limitations with the included evidence, the committee also agreed that evidence was not strong enough to be able to make a ‘do no admit solely based on anticoagulation status’ recommendation.

The committee also highlighted that admitting people solely based on anticoagulation status if there is not a large increase in risk of delayed bleeding, and if these events when they do occur are usually not clinically significant, could cause harm in a group of patients that are already vulnerable for example due to frailty or underlying conditions in terms of hospital-acquired infections and/or delirium.

The committee considered making a research recommendation for further evidence but agreed that this was not a priority considering there was already information from a large study of ~70,000 for anticoagulation and that studies in this area would always be limited to non-randomised retrospective comparisons given the fact that the effect of pre-injury treatments in those with a head injury is being assessed.

Antiplatelets

Evidence for antiplatelet comparisons was more limited compared to that described above for warfarin/VKA and DOACs. There were no large studies reporting data for antiplatelets,

and all reported effects were based on a difference of only 1-2 events between the two groups per study. For this reason, it was not possible to make reference to antiplatelets as a sole indicator for admission in those with a negative initial CT or no indication for a CT. The committee did not make a research recommendation for this group this as they did not consider it to be a priority for research recommendation.

Other comparisons

Other comparisons reported included >1 anticoagulant or antiplatelet combined, any antiplatelet/anticoagulant treatment and any anticoagulant use vs. people not on any antithrombotic treatment. Evidence for these comparisons were again too limited to inform any recommendations, for example due to zero events in both arms, very small study sample size (n=34), only 1-2 event difference between arms and/or imprecision in the size and/or direction of effect.

People with pre-injury cognitive impairment

Some studies reported the proportion of people with pre-injury cognitive impairment such as dementia, Parkinson's disease, stroke etc. However, they did not report the effect of pre-injury cognitive impairment on the outcomes. 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 and medication side effects.

The committee noted from their experience that pre-existing conditions affecting cognition are less likely to recognise and raise alarm about the early signs of a late intracranial bleed such as severe headache, drowsiness, vomiting than someone without pre-existing cognitive impairment. Hence, in current practice they are arranged a short overnight admission for observation where no supervision at home is available. If they are to be discharged from ED, they will need to be appropriately supervised and monitored to ensure that their symptoms are not worsening . The committee noted that at discharge, it is important for people and their carers to be given a written copy of the head injury discharge advice (rec 1.9.8).

1.1.11.4 Cost effectiveness and resource use.

Currently most people on anticoagulant or antiplatelet therapy at the time of head injury will not be admitted and observed unless they have an additional indication, such as an intracranial haematoma observed on a CT scan. Therefore, admission and observation of these people would potentially lead to an increase in cost to the NHS.

Economic evaluations were not identified for this question and so the average cost of a short stay for head injury in the NHS was presented to the committee.

The cost of admission and observation might be justified but only if it allowed a significant number of people who would have deteriorated to be identified and operated on more quickly.

The clinical review did not find any evidence for improved mortality. There was evidence of a raised risk of delayed traumatic intracranial haemorrhage for people on anticoagulants but risk was small and the proportion of these that would be clinically important was thought to be smaller still.

Any benefit needs to be balanced against the harms as well as the NHS costs. There are always risks with admitting people, especially the frail, who might count for a substantial proportion of people on anticoagulant and antiplatelet therapy. The cost effectiveness of admitting and observing these people is uncertain but the committee concluded that it was highly unlikely to be cost effective. Therefore, they did not recommend that these people be admitted and observed unless they had additional risk factors, as already outlined in this guideline.

1.1.11.5 Other factors the committee took into account

Another factor discussed by the committee in terms of not adding anticoagulation status as a standalone indication for admission in the recommendations was that any associated risk of increased bleeding should be covered and managed by existing recommendations in the guideline, such as the recommendation to provide patients with risk factors to look out for in terms of their condition deteriorating and recommendations highlighting that people should not be discharged home unless there is supervision for 24 h, which are detailed under the 'Discharge and Follow-up' section of the guideline.

The committee also noted that anticoagulation is an indication for CT within 8 h in people with head injury, regardless of other risk factors. However, this is not the case for antiplatelets.

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Appendices

Appendix A – Review protocols

Review protocol for admission and observation in hospital of people with head injury who are on anticoagulant or antiplatelet therapy after normal brain imaging or no indication for early imaging

ID	Field	Content
1.	Review title	Admission and observation in hospital of people with head injury who are on anticoagulant or antiplatelet therapy after normal brain imaging or no indication for early imaging
2.	Review question	How long should people with head injury who are on anticoagulant or antiplatelet therapy be observed in hospital after normal brain imaging or no indication for early imaging?
3.	Objective	People with TBI and pre-injury anticoagulant or antiplatelet use are at high risk for intracranial cranial haemorrhage. Hence there is a need for guidance on admission/discharge of this group of people.
4.	Searches	The following databases (from inception) will be searched: • 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	People with head injury on anticoagulant or antiplatelet therapy after normal brain imaging or no indication for early imaging
6.	Population	i) Inclusion: Infants, children and adults with traumatic brain injury 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.
7.	Intervention	People on pre-injury anticoagulant or antiplatelet therapy Strata: o 1. Anticoagulant ▪ A. Warfarin

		▪ B. DOACs ▪ C. Low molecular weight heparin ▪ D. sinthrome (acenocoumarol) ▪ E. Enoxaparin ▪ F. Dalteparin o 2. Antiplatelet (examples below) ▪ A. Aspirin ▪ B. Clopidogrel/prasugrel ▪ C. Dual anti-platelet therapy- 3. Mixed strata: There will be group of patients with both anti-coagulants and anti-platelet It was noted that the different class of anticoagulants/antiplatelets differ pharmacologically. Hence all drugs will be analysed in separate strata.
8.	Comparator	People not on pre-injury anticoagulant or antiplatelet therapy Currently (as per current recs- CG176) we CT all patients with head injury on anticoagulants - There is no current rec on antiplatelets as influencing indications for CT (insufficient evidence for CG 176) so that currently the decision is left to clinical judgement -As per current recs we are not admitting patients taking antiplatelets or anticoagulant meds for observation after normal CT scan unless there is another reason (intoxication, no – one to observe at home, other illnesses or injuries requiring inpatient care)

		-Studies of admitting these patients for observation may have used observation periods of 6-24 hours post normal CT prior to discharge +/- a second CT scan. I think we should just report whichever strategy used by the study team rather than exclude specific strategies
9.	Types of study to be included	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, non-randomised studies will be considered if they are adjusted for key confounders, starting with prospective cohort studies. If there are no comparative non-randomised studies we will consider inclusion of single arm/non-comparative studies (prospective and retrospective cohort studies) of people on pre-injury anticoagulant or antiplatelet therapy. key confounders: • Age- elderly people more vulnerable to intracranial bleeding Note from studies about: • GCS of the population • Degree of anti-coagulation (different regimes will have clotting impaired to a different degree). Blood test measuring coagulation such as INR for patients on warfarin. Other blood tests APTT. • If they have been scanned • Note if Pre-existing cognitive impairment has been assessed. Pre-existing cognitive impairment may alter recs in this group with normal GCS. Pre-existing cognitive impairment may predispose to increase risk of bleeding. It is a subjective measurement This population will include people with GCS score 15 or back to baseline. Minimum number of participants (non-comparative studies): 1000

		Cut-off for participants only for non-comparative studies. The committee wanted us to review data from large cohort studies if there is no evidence from comparative studies. No limit for comparative studies
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.
11.	Context	There is variation in clinical practice regarding admission and discharge of people on anticoagulants/anti-platelet therapy as there is no guidance. Some clinicians will admit such people because of risk of delayed intracranial bleeding. However, some clinicians will discharge if there are no symptoms and there is normal imaging or no indications for imaging. This group includes a huge population, admission of all patients in this group will put a huge pressure on the healthcare system.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Rate of delayed intracranial bleeding (30 days) • time after injury when bleeding was detected • Time to diagnosis of intracranial injury on CT/MRI/clinical follow-up or autopsy • Re-admission as a result of delayed diagnosis of intracranial injury (30 days) • Serious adverse events within 2 weeks • TBI related mortality (30 days)

		• Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more For rate of delayed intracranial bleeding, re-admission and TBI mortality- follow-up ideally 30 days but could accept shorter follow up periods (minimum 7 days) Note for outcome rate of delayed intracranial bleeding: Denominator: Patients who had normal/no CT scan initially Numerator: intracranial bleeding on second CT scan or after deterioration or after discharge or on autopsy.
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. 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	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I
15.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. If there is substantial heterogeneity results will be presented pooled using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. 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/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.			
16.	Analysis of sub-groups	None identified			
17.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
18.	Language	English			
19.	Country	England			
20.	Anticipated or actual start date				
21.	Anticipated completion date				
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 headinjury@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
24.	Review team members	 From the National Guideline Centre: Guideline lead: Sharon Swain Senior systematic reviewer: Sharangini Rajesh Senior systematic reviewer: Julie Neilson		

		Health economist: David Wonderling Information specialist: Joseph Runicles Project manager: Giulia Zuodar
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: 1 (nice.org.uk) .
28.	Other registration details	
29.	Reference/URL for published protocol	
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.	
31.	Keywords	Head injury, follow-up, anticoagulant/antiplatelet therapy	
32.	Details of existing review of same topic by same authors	NA	
33.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	NA	
35.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Table 12: 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).[6] **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.[6]

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.

Table 13: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 22 June 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 22 June 2022	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 CENTRAL to 2022 Issue 6 of 12	Exclusions (conference abstracts)
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.	exp anticoagulants/ or coumarins/ or exp antithrombins/ or exp factor xa inhibitors/ or exp Thrombolytic Therapy/ or exp Fibrinolytic Agents/
27.	(anticoagul* anti-coagul* or antithrom* or anti-thromb* or DOAC or DOACs or thrombolytic*).ti,ab,kf.
28.	(blood adj thin*).ti,ab,kf.
29.	((thrombus or blood clot*) adj3 (prevent* or stop* or inhibit*)).ti,ab,kf.
30.	((thrombin or xa) adj2 inhibitor*).ti,ab,kf.
31.	warfarin.ti,ab,kf.
32.	(coumarin* or coumadin*).ti,ab,kf.
33.	(Edoxaban or Lixiana).ti,ab,kf.
34.	(Dabigatran or Pradaxa).ti,ab,kf.
35.	(Apixaban or Eliquis).ti,ab,kf.
36.	Heparin.ti,ab,kf.
37.	(Rivaroxaban or Xarelto or acetylsalicylic acid).ti,ab,kf.
38.	Phenindione.ti,ab,kf.
39.	(vitamin k adj2 (antagonist* or inhibit*)).ti,ab,kf.
40.	(antivitamin k or anti vitamin k).ti,ab,kf.
41.	(Acenocoumarol or Sinthrome).ti,ab,kf.
42.	exp platelet aggregation inhibitors/
43.	(antiplatlet* or anti-platlet* or antiaggregant* or anti-aggregant*).ti,ab,kf.
44.	(platlet* adj2 (inhibit* or antagonist* or aggregat*)).ti,ab,kf.
45.	aspirin.ti,ab,kf.
46.	(Cangrelor or Kengrexal).ti,ab,kf.
47.	Cilostazol.ti,ab,kf.
48.	Clopidogrel.ti,ab,kf.
49.	(Dipyridamole or Molita).ti,ab,kf.
50.	(Prasugrel or Efient).ti,ab,kf.
51.	(Selexipag or Uptravi or prostacyclin).ti,ab,kf.
52.	(Ticagrelor or Brilique).ti,ab,kf.
53.	(Epoprostenol or Veletri or prostacyclin).ti,ab,kf.
54.	(Eptifibatide or Integrilin).ti,ab,kf.
55.	(Tirofiban or Aggrastat).ti,ab,kf.

56.	or/26-55
57.	25 and 56

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.	exp *anticoagulant agent/
28.	(anticoagul* anti-coagul* or antithromb* or anti-thromb* or DOAC or DOACs or thrombolytic*).ti,ab,kf.
29.	(blood adj thin*).ti,ab,kf.
30.	((thrombus or blood clot*) adj3 (prevent* or stop* or inhibit*)).ti,ab,kf.
31.	exp *antithrombin/ or exp *blood clotting factor 10a inhibitor/ or *blood clotting inhibitor/
32.	((thrombin or xa) adj2 inhibitor*).ti,ab,kf.
33.	warfarin.ti,ab,kf.
34.	*coumarin derivative/
35.	(coumarin* or coumadin*).ti,ab,kf.
36.	(Edoxaban or Lixiana).ti,ab,kf.
37.	(Dabigatran or Pradaxa).ti,ab,kf.
38.	(Apixaban or Eliquis).ti,ab,kf.
39.	Heparin.ti,ab,kf.

40.	(Rivaroxaban or Xarelto or acetylsalicylic acid).ti,ab,kf.
41.	Phenindione.ti,ab,kf.
42.	(vitamin k adj2 (antagonist* or inhibit*)).ti,ab,kf.
43.	(antivitamin k or anti vitamin k).ti,ab,kf.
44.	(Acenocoumarol or Sinthrome).ti,ab,kf.
45.	exp *antithrombocytic agent/
46.	(antiplatlet* or anti-platlet* or antiaggregant* or anti-aggregant*).ti,ab,kf.
47.	(platlet* adj2 (inhibit* or antagonist* or aggregat*)).ti,ab,kf.
48.	aspirin.ti,ab,kf.
49.	(Cangrelor or Kengrexal).ti,ab,kf.
50.	Cilostazol.ti,ab,kf.
51.	Clopidogrel.ti,ab,kf.
52.	(Dipyridamole or Molita).ti,ab,kf.
53.	(Prasugrel or Efient).ti,ab,kf.
54.	(Selexipag or Uptravi or prostacyclin).ti,ab,kf.
55.	(Ticagrelor or Brilique).ti,ab,kf.
56.	(Epoprostenol or Veletri).ti,ab,kf.
57.	(Eptifibatide or Integrilin).ti,ab,kf.
58.	(Tirofiban or Aggrastat).ti,ab,kf.
59.	or/27-58
60.	26 and 59

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.	conference:pt or (clinicaltrials or trialsearch):so
#13.	#11 NOT #12
#14.	MeSH descriptor: [Anticoagulants] explode all trees
#15.	MeSH descriptor: [Coumarins] explode all trees
#16.	MeSH descriptor: [Antithrombins] explode all trees
#17.	MeSH descriptor: [Factor Xa Inhibitors] explode all trees
#18.	MeSH descriptor: [Thrombolytic Therapy] explode all trees
#19.	MeSH descriptor: [Fibrinolytic Agents] explode all trees
#20.	(anticoagul* anti-coagul* or antithrom* or anti-thromb* or DOAC or DOACs or thrombolytic*):ti,ab
#21.	(blood near/1 thin*):ti,ab

#22.	((thrombus or blood clot*) near/3 (prevent* or stop* or inhibit*)):ti,ab
#23.	((thrombin or xa) near/2 inhibitor*):ti,ab
#24.	warfarin:ti,ab
#25.	(coumarin* or coumadin*):ti,ab
#26.	(Edoxaban or Lixiana):ti,ab
#27.	(Dabigatran or Pradaxa):ti,ab
#28.	(Apixaban or Eliquis):ti,ab
#29.	Heparin:ti,ab
#30.	(Rivaroxaban or Xarelto or acetylsalicylic acid):ti,ab
#31.	Phenindione:ti,ab
#32.	(vitamin k near/2 (antagonist* or inhibit*)):ti,ab
#33.	(antivitamin k or anti vitamin k):ti,ab
#34.	(Acenocoumarol or Sinthrome):ti,ab
#35.	MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees
#36.	(antiplatlet* or anti-platlet* or antiaggregant* or anti-aggregant*):ti,ab
#37.	(platlet* near/2 (inhibit* or antagonist* or aggregat*)):ti,ab
#38.	aspirin:ti,ab
#39.	(Cangrelor or Kengrexal):ti,ab
#40.	Cilostazol:ti,ab
#41.	Clopidogrel:ti,ab
#42.	(Dipyridamole or Molita):ti,ab
#43.	(Prasugrel or Efient):ti,ab
#44.	(Selexipag or Uptravi or prostacyclin):ti,ab
#45.	(Ticagrelor or Brilique):ti,ab
#46.	(Epoprostenol or Veletri or prostacyclin):ti,ab
#47.	(Eptifibatide or Integrilin):ti,ab
#48.	(Tirofiban or Aggrastat):ti,ab
#49.	(or #14-#48)
#50.	#13 and #49

Epistemonikos search terms

1.	(title:(((trauma OR traumatic) AND (injury OR injuries))) OR abstract:(((trauma OR traumatic) AND (injury OR injuries)))) OR (title:(((skull OR cranial) AND fracture*)) OR abstract:(((skull OR cranial) AND fracture*))) OR (title:(((head OR brain OR craniocerebral OR cranial OR cerebral OR skull) AND (injur* OR trauma*))) OR abstract:(((head OR brain OR craniocerebral OR cranial OR cerebral OR skull) AND (injur* OR trauma*))))
2.	(title:((anticoagul* anti-coagul* OR antithrom* OR anti-thromb* OR DOAC OR DOACs OR thrombolytic*)) OR abstract:((anticoagul* anti-coagul* OR antithrom* OR anti-thromb* OR DOAC OR DOACs OR thrombolytic*))) OR (title:((blood AND thin*)) OR abstract:((blood AND thin*))) OR (title:(((thrombus OR blood clot*) AND (prevent* OR stop* OR inhibit*))) OR abstract:(((thrombus OR blood clot*) AND (prevent* OR stop* OR inhibit*)))) OR (title:(((thrombin OR xa) AND inhibitor*)) OR abstract:(((thrombin OR xa) AND inhibitor*))) OR (title:((warfarin* OR coumarin* OR coumadin* OR Edoxaban OR Lixiana OR Dabigatran OR Rivaroxaban OR Xarelto OR acetylsalicylic acid OR Phenindione OR antivitamin k OR anti vitamin k OR Acenocoumarol OR Sinthrome)) OR abstract:((warfarin* OR coumarin* OR coumadin* OR Edoxaban OR Lixiana OR Dabigatran OR Rivaroxaban OR Xarelto OR acetylsalicylic acid OR Phenindione OR antivitamin k OR anti vitamin k OR Acenocoumarol OR Sinthrome))) OR (title:((vitamin k AND (antagonist* OR inhibit*))) OR abstract:((vitamin k AND (antagonist* OR inhibit*)))) OR (title:((antiplatlet* OR anti-platlet* OR antiaggregant* OR anti-

	aggregant*)) OR abstract:((antiplatlet* OR anti-platlet* OR antiaggregant* OR anti-aggregant*))) OR (title:((platlet* AND (inhibit* OR antagonist* OR aggregat*))) OR abstract:((platlet* AND (inhibit* OR antagonist* OR aggregat*)))) OR (title:((aspirin OR Cangrelor OR Kengrexal OR Cilostazol OR Clopidogrel OR Dipyridamole OR Molita OR Prasugrel OR Efient OR Selexipag OR Uptravi OR prostacyclin OR Ticagrelor OR Brilique OR Epoprostenol OR Veletri OR prostacyclin OR Eptifibatide OR Integrilin OR Tirofiban OR Aggrastat)) OR abstract:((aspirin OR Cangrelor OR Kengrexal OR Cilostazol OR Clopidogrel OR Dipyridamole OR Molita OR Prasugrel OR Efient OR Selexipag OR Uptravi OR prostacyclin OR Ticagrelor OR Brilique OR Epoprostenol OR Veletri OR prostacyclin OR Eptifibatide OR Integrilin OR Tirofiban OR Aggrastat)))
3.	1 and 2

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 14: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 22 June 2022	
Embase (OVID)	Health Economics 1 January 2014 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 22 June 2022	
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	Inception – 22 June 2022	English language

Database	Dates searched	Search filters and limits applied
Technology Assessment (INAHTA)		

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

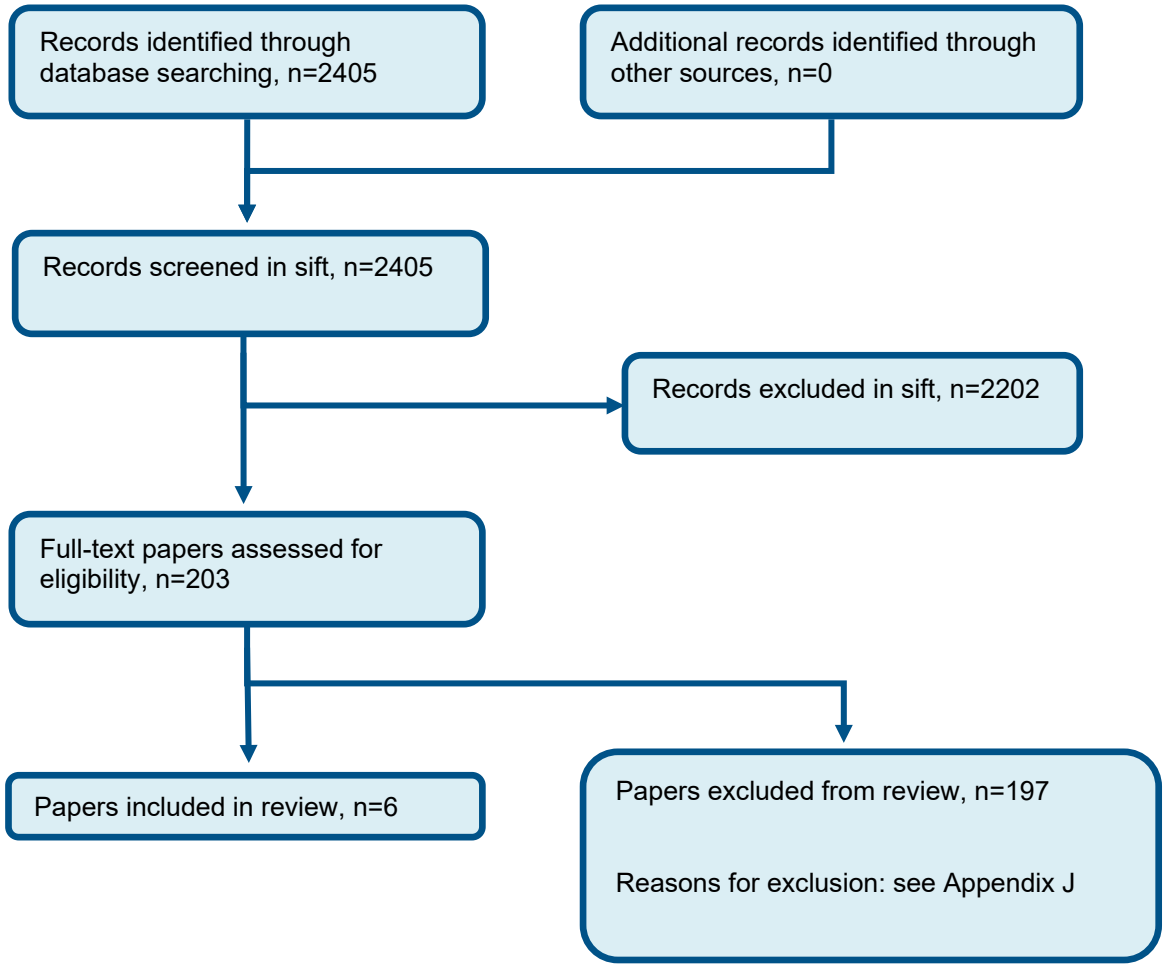
#1.	MeSH DESCRIPTOR Brain Injuries EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Craniocerebral Trauma
#3.	MeSH DESCRIPTOR Coma, Post-Head Injury
#4.	MeSH DESCRIPTOR Head Injuries, Closed EXPLODE ALL TREES
#5.	MeSH DESCRIPTOR Head Injuries, Penetrating
#6.	MeSH DESCRIPTOR Intracranial Hemorrhage, Traumatic EXPLODE 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 – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of admission and observation in hospital of people with head injury who are on anticoagulant or antiplatelet therapy after normal brain imaging or no indication for early imaging



Appendix D – Effectiveness evidence

Chenoweth, 2018

Bibliographic Reference	Chenoweth, J. A.; Gaona, S. D.; Faul, M.; Holmes, J. F.; Nishijima, D. K.; Sacramento County Prehospital Research, Consortium; Incidence of Delayed Intracranial Hemorrhage in Older Patients After Blunt Head Trauma; JAMA Surgery; 2018; vol. 153 (no. 6); 570-575

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	Not reported
Study location	USA
Study setting	Secondary care - 11 hospitals in northern California (four level I/II trauma centres and 7 non-trauma centres)
Study dates	Those transported to participating hospital by emergency services between 1st August 2015 and 30th September 2016 eligible for inclusion.

Sources of funding	Funded by a grant (U01CE002177) from the Centers for Disease Control and Prevention. Dr Nishijima was supported through a Mentored Clinical Research Training Program Award (grant UL1TR000002 and linked award KL2TR000134) from the National Center for Advancing Translational Sciences, a component of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research.
Inclusion criteria	aged ≥55 years; blunt head trauma with no traumatic haemorrhage on initial cranial CT scan; transported to a participating hospital by emergency services.
Exclusion criteria	penetrating head trauma; those with interfacility transfers; intracranial haemorrhage on the initial cranial CT; did not undergo cranial CT at their index emergency department visit; declined consent for a follow-up telephone call and no reliable means for such a call; and people who were incarcerated
Recruitment / selection of participants	Those transported to a participating hospital by emergency services between 1st August 2015 and 30th September 2016 were eligible for inclusion. Oral informed consent obtained from all participants.
Intervention(s)	Anticoagulant or antiplatelet use pre-injury: those using anticoagulants or antiplatelets prior to injury based on data from emergency services and hospital electronic medical records. Anticoagulant use included warfarin or direct-acting oral anticoagulants (DOACs) and antiplatelet medications included aspirin, clopidogrel bisulfate, ticlopidine hydrochloride, prasugrel, dipyridamole, cilostazol, and ticagrelor.
Population subgroups	NA - no subgroups for this review
Comparator	No anticoagulant or antiplatelet use pre-injury: those not using anticoagulants or antiplatelets (including those described above under intervention) prior to injury based on data from emergency services and hospital electronic medical records.
Number of participants	859
Duration of follow-up	14 days - following index ED visit (some may have had follow-up longer but 14 days was used for the outcome)
Indirectness	None - data provided allows results for different types of drug to be calculated.
Additional comments	Key confounders:

	• Age: median values >70 in both groups but no P-value for comparison provided • Diabetes mellitus: unclear, not reported • Hypertension: unclear, not reported Note this is for whole anticoagulant/antiplatelet group combined vs. the group with no drugs taken as characteristics not provided separately for individual drugs (e.g. warfarin or DOACs)

Study arms

Anticoagulant or antiplatelet use pre-injury (N = 343)

No anticoagulant or antiplatelet use pre-injury (N = 516)

Characteristics

Arm-level characteristics

Characteristic	**Anticoagulant or antiplatelet use pre-injury (N = 343)**	**No anticoagulant or antiplatelet use pre-injury (N = 516)**
% Female Sample size	n = 190 ; % = 55.4	n = 280 ; % = 54.3
Mean age (SD) Median (IQR)	79 (70 to 88)	71 (61 to 81)

Characteristic	Anticoagulant or antiplatelet use pre-injury (N = 343)	No anticoagulant or antiplatelet use pre-injury (N = 516)
Race - white Sample size	n = 276 ; % = 80.5	n = 348 ; % = 67.4
Race - Black Sample size	n = 18 ; % = 5.3	n = 52 ; % = 10.1
Race - asian Sample size	n = 17 ; % = 5	n = 48 ; % = 9.3
Race - Native American/Alaskan native Sample size	n = 1 ; % = 0.3	n = 3 ; % = 0.6
Race - Pacific Islander/Native Hawaiian Sample size	n = 6 ; % = 1.8	n = 7 ; % = 1.4
Race - Other Sample size	n = 25 ; % = 7.3	n = 57 ; % = 11
Hispanic ethnicity Missing data in n=15 Sample size	n = 19 ; % = 5.5	n = 51 ; % = 9.9
Reported dementia	n = 38 ; % = 11.1	n = 31 ; % = 6

Characteristic	Anticoagulant or antiplatelet use pre-injury (N = 343)	No anticoagulant or antiplatelet use pre-injury (N = 516)
Sample size		
Reported intoxication Sample size	n = 13 ; % = 3.8	n = 70 ; % = 13.6
Initial prehospital GCS score 15 Missing data in n=6 Sample size	n = 68 ; % = 19.8	n = 106 ; % = 20.5
Mechanism of injury - Direct blow to head Sample size	n = 8 ; % = 2.3	n = 35 ; % = 6.8
Mechanism of injury - Fall from greater than standing height Sample size	n = 14 ; % = 4.1	n = 20 ; % = 3.9
Mechanism of injury - Fall from standing height or lower Sample size	n = 289 ; % = 84.3	n = 357 ; % = 69.2
Mechanism of injury - Motor vehicle crash >35 miles per hour Sample size	n = 8 ; % = 2.3	n = 26 ; % = 5

Characteristic	Anticoagulant or antiplatelet use pre-injury (N = 343)	No anticoagulant or antiplatelet use pre-injury (N = 516)
Mechanism of injury - Motor vehicle crash up to 35 miles per hour Sample size	n = 7 ; % = 2	n = 24 ; % = 4.7
Mechanism of injury - Automobile vs. pedestrian or cyclist Sample size	n = 8 ; % = 2.3	n = 23 ; % = 4.5
Mechanism of injury - Other mechanism Sample size	n = 6 ; % = 1.7	n = 19 ; % = 3.7
Mechanism of injury - Unknown mechanism Sample size	n = 3 ; % = 0.9	n = 12 ; % = 2.3
History - Vomiting Sample size	n = 4 ; % = 1.2	n = 7 ; % = 1.4
History - Headache Sample size	n = 21 ; % = 6.1	n = 26 ; % = 5
History - Loss of consciousness or amnesia Sample size	n = 52 ; % = 15.2	n = 124 ; % = 24

Characteristic	Anticoagulant or antiplatelet use pre-injury (N = 343)	No anticoagulant or antiplatelet use pre-injury (N = 516)
Anticoagulant/antiplatelet use - Warfarin sodium only Sample size	n = 75 ; % = 21.9	n = NA ; % = NA
Anticoagulant/antiplatelet use - DOAC alone Sample size	n = 37 ; % = 10.8	n = NA ; % = NA
Anticoagulant/antiplatelet use - Aspirin alone Sample size	n = 156 ; % = 45.5	n = NA ; % = NA
Anticoagulant/antiplatelet use - Other antiplatelet alone Sample size	n = 41 ; % = 12	n = NA ; % = NA
Anticoagulant/antiplatelet use - >1 anticoagulant or antiplatelet medication Sample size	n = 34 ; % = 9.9	n = NA ; % = NA
International normalised ratio Only applicable for those taking warfarin Median (IQR)	2.4 (1.98 to 2.9)	NA (NA to NA)
Platelet count (x10³/µl) Median (IQR)	207 (168 to 256)	213 (175 to 261)

Characteristic	Anticoagulant or antiplatelet use pre-injury (N = 343)	No anticoagulant or antiplatelet use pre-injury (N = 516)
ED disposition - Discharged home Sample size	n = 212 ; % = 61.8	n = 348
ED disposition - Admitted to observation unit Sample size	n = 11 ; % = 3.2	n = 10 ; % = 1.9
ED disposition - Admitted to floor Sample size	n = 95 ; % = 27.7	n = 107 ; % = 20.7
ED disposition - Admitted to ICU Sample size	n = 14 ; % = 4.1	n = 28 ; % = 5.4
ED disposition - Operating room Sample size	n = 1 ; % = 0.3	n = 5 ; % = 1
ED disposition - Transferred to another hospital Sample size	n = 5 ; % = 1.5	n = 4 ; % = 0.8
ED disposition - Left against medical advice Sample size	n = 4 ; % = 1.2	n = 7 ; % = 1.4
ED disposition - Other Sample size	n = 1 ; % = 0.3	n = 7 ; % = 1.4

Characteristic	Anticoagulant or antiplatelet use pre-injury (N = 343)	No anticoagulant or antiplatelet use pre-injury (N = 516)
Injury Severity Score Calculated in admitted patients only Median (IQR)	5 (2 to 6)	5 (2 to 10)
Isolated head injury If Abbreviated Injury Scale score for all non-head body regions is less than 3 Sample size	n = 324 ; % = 94.5	n = 484 ; % = 93.8

Outcomes

Study timepoints

- 14 day (Within 14 days of index ED visit)

Results - raw data

Outcome	Anticoagulant or antiplatelet use pre-injury, 14 day, N = 343	No anticoagulant or antiplatelet use pre-injury, 14 day, N = 516
Delayed traumatic intracranial haemorrhage Confirmed on follow-up cranial CT scan - use results for individual drugs separately below rather than total combined as stratified in protocol. Delayed ICH occurred 3 and 5	n = 1 ; % = 0.29	n = 2 ; % = 0.39

Outcome	Anticoagulant or antiplatelet use pre-injury, 14 day, N = 343	No anticoagulant or antiplatelet use pre-injury, 14 day, N = 516
days after initial CT scan - unlikely would have been detected even with 24 h observation. No of events		
Warfarin alone vs. no anticoagulant/antiplatelets N=75 in warfarin group and n=516 in no drug group No of events	n = 1 ; % = 1.33	n = 2 ; % = 0.39
DOACs alone vs. no anticoagulant/antiplatelets N=37 in DOACs group and n=516 in no drug group No of events	n = 0 ; % = 0	n = 2 ; % = 0.39
Aspirin alone vs. no anticoagulant/antiplatelets N=156 in aspirin group and n=516 in no drug group No of events	n = 0 ; % = 0	n = 2 ; % = 0.39
Other antiplatelet alone (clopidogrel bisulfate, ticlopidine hydrochloride, prasugrel, dipyridamole, cilostazol, or ticagrelor) vs. no anticoagulant/antiplatelets N=41 in antiplatelet group and n=516 in no drug group No of events	n = 0 ; % = 0	n = 2 ; % = 0.39

Outcome	Anticoagulant or antiplatelet use pre-injury, 14 day, N = 343	No anticoagulant or antiplatelet use pre-injury, 14 day, N = 516
>1 anticoagulant or antiplatelet vs. no anticoagulant/antiplatelets N=34 in combined group and n=516 in no drug group No of events	n = 0 ; % = 0	n = 2 ; % = 0.39
TBI-related mortality (follow-up call 14-28 days) - use results for individual drugs separately below rather than total combined as stratified in protocol reported that none of the deaths were found to be due to delayed bleeding No of events	n = 0 ; % = 0	n = 0 ; % = 0
Warfarin alone vs. no anticoagulant/antiplatelets N=75 in warfarin group and n=516 in no drug group No of events	n = 0 ; % = 0	n = 0 ; % = 0
DOACs alone vs. no anticoagulant/antiplatelets N=37 in DOACs group and n=516 in no drug group No of events	n = 0 ; % = 0	n = 0 ; % = 0
Aspirin alone vs. no anticoagulant/antiplatelets N=156 in aspirin group and n=516 in no drug group No of events	n = 0 ; % = 0	n = 0 ; % = 0
Other antiplatelet alone (clopidogrel bisulfate, ticlopidine hydrochloride, prasugrel, dipyridamole, cilostazol, or ticagrelor) vs. no	n = 0 ; % = 0	n = 0 ; % = 0

Outcome	Anticoagulant or antiplatelet use pre-injury, 14 day, N = 343	No anticoagulant or antiplatelet use pre-injury, 14 day, N = 516
anticoagulant/antiplatelets N=41 in antiplatelet group and n=516 in no drug group No of events		
>1 anticoagulant or antiplatelet vs. no anticoagulant/antiplatelets N=34 in combined group and n=516 in no drug group No of events	n = 0 ; % = 0	n = 0 ; % = 0

Critical appraisal - ROBINS-I checklist

Results_warfarin alone vs. no drug_delayed ICH_14 days

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(time-point of 14 rather than 30 days)*

Results_DOACs alone vs. no drug_delayed ICH_14 days

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(time-point of 14 rather than 30 days)*

Results_aspirin alone vs. no drug_delayed ICH_14 days

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(time-point of 14 rather than 30 days)*

Results_other antiplatelet alone vs. no drug_delayed ICH_14 days

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(time-point of 14 rather than 30 days)*

Results_>1 anticoagulant/antiplatelet drug vs. no drug_delayed ICH_14 days

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(time-point of 14 rather than 30 days)*

Results_warfarin alone vs. no drug_delayed_TBI-related mortality 14-28 days

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Results_DOACs alone vs. no drug_delayed_TBI-related mortality 14-28 days

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Results_aspirin alone vs. no drug_delayed_TBI-related mortality 14-28 days

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Results_other antiplatelet alone vs. no drug_delayed_TBI-related mortality 14-28 days

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Results_>1 anticoagulant/antiplatelet vs. no drug_delayed_TBI-related mortality 14-28 days

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Covino, 2021

Bibliographic Reference	Covino, M.; Manno, A.; Della Pepa, G. M.; Piccioni, A.; Tullo, G.; Petrucci, M.; Navarra, S.; Sardeo, F.; Torelli, E.; Nicolo, R.; Simeoni, B.; Carbone, L.; Gaudino, S.; Franceschi, F.; Delayed intracranial hemorrhage after mild traumatic brain injury in patients on oral anticoagulants: is the juice worth the squeeze?; European Review for Medical & Pharmacological Sciences; 2021; vol. 25 (no. 7); 3066-3073

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	Not reported
Study location	Italy
Study setting	Secondary care - emergency department of single urban teaching hospital, major trauma centre
Study dates	Study conducted over three-year period between 1st January 2016 and 31st December 2018
Sources of funding	Reported to be no funding from private or public institutions

Inclusion criteria	admitted to ED for mild TBI (GCS score 13-15, loss of consciousness <30 min and post-traumatic amnesia <24 h) as chief complaint; negative initial CT scan at admission; and had repeated CT 24 h later
Exclusion criteria	Trauma not classified as mild TBI; <18 years old; pregnant women; known history of inherited coagulation disease; and those with positive findings at first CT assessment
Recruitment / selection of participants	Identified people matching study criteria from ED electronic clinical records, consecutive records assessed
Intervention(s)	Using anticoagulants: those that were using anticoagulants prior to injury, including n=111 (52.8%) using vitamin K antagonists and n=99 (47.2%) using direct oral anticoagulants (DOACs; n=23 dabigatran, n=37 apixaban, n=31 rivaroxaban and n=9 edoxaban). This information was obtained manually from clinical records.
Population subgroups	NA - no subgroups for this review
Comparator	Not using anticoagulants pre-injury: those not using any anticoagulants prior to injury/at time of injury based on data from clinical records.
Number of participants	685 in whole cohort, 350 in propensity-matched cohort but data not used as does not report results for VKA and DOAC groups separately in this smaller population
Duration of follow-up	24 h - control CT scan done within 24 h of index CT
Indirectness	None
Additional comments	Standard ED protocol for the institution indicates a 6 h observation for all mild TBI patients. Head CT scan performed at admission based on emergency physician evaluation. Patients who experience any clinical worsening during the observation period (episode of epilepsy, vomiting ≥ 2 episodes, persistence of GCS score < 15, prolonged amnesia, persistent headache), are prescribed a prolonged

	observation and a 24 h repeat CT scan. All patients on anticoagulant therapy (either VKA or DOAC) receive prolonged observation and a control CT scan at 24 h from the index control. Control CT scan could be anticipated based on evolving clinical findings. Key confounders: • Age: not adjusted for and appears to be a significant difference between groups • Diabetes mellitus: unclear, not reported • Hypertension: unclear, not reported Note this is for whole anticoagulant group combined vs. the group with no drugs taken as characteristics not provided separately for individual drugs (e.g. warfarin or DOACs)

Study arms

Using anticoagulant therapy (N = 210)

Not using anticoagulant therapy (N = 475)

Characteristics

Arm-level characteristics

Characteristic	Using anticoagulant therapy (N = 210)	Not using anticoagulant therapy (N = 475)
% Female Sample size	n = 118 ; % = 56.2	n = 238 ; % = 50.1
Mean age (SD) Median (IQR)	83 (78 to 88)	76 (54 to 85)
Ethnicity Custom value	NR	NR
Other therapy - Aspirin Sample size	n = 22 ; % = 10.5	n = 123 ; % = 25.9
Other therapy - Clopidogrel Sample size	n = 5 ; % = 2.4	n = 33 ; % = 6.9

Characteristic	Using anticoagulant therapy (N = 210)	Not using anticoagulant therapy (N = 475)
Other therapy - Aspirin/clopidogrel Sample size	n = 23 ; % = 11	n = 145 ; % = 30.5
Other therapy - Low-molecular weight heparin Sample size	n = 1 ; % = 0.1	n = 24 ; % = 5.1
Clinical history - Malignancy Sample size	n = 13 ; % = 6.2	n = 55 ; % = 11.6
Clinical history - Neurodegenerative disease Sample size	n = 18 ; % = 8.6	n = 42 ; % = 8.8
Clinical history - Cerebrovascular disease Sample size	n = 25 ; % = 11.9	n = 45 ; % = 9.5
Clinical history - Thrombocytopenia Sample size	n = 1 ; % = 0.5	n = 7 ; % = 1.5
Clinical history - Alcohol abuse Sample size	n = 0 ; % = 0	n = 15 ; % = 3.2
Clinical history - Epilepsy Sample size	n = 3 ; % = 1.4	n = 11 ; % = 2.3

Characteristic	Using anticoagulant therapy (N = 210)	Not using anticoagulant therapy (N = 475)
Other history possibly associated with anticoagulation - Coronary artery disease Sample size	n = 34 ; % = 16.2	n = 27 ; % = 5.7
Other history possibly associated with anticoagulation - Heart failure Sample size	n = 19 ; % = 9	n = 19 ; % = 4
Other history possibly associated with anticoagulation - Intervascular stent Sample size	n = 5 ; % = 2.4	n = 5 ; % = 1.1
Other history possibly associated with anticoagulation - Valvular disease Sample size	n = 14 ; % = 6.7	n = 0 ; % = 0
Other history possibly associated with anticoagulation - Atrial fibrillation Sample size	n = 33 ; % = 15.7	n = 10 ; % = 2.1
Other history possibly associated with anticoagulation - Previous deep venous thrombosis/pulmonary embolism Sample size	n = 5 ; % = 2.4	n = 4 ; % = 0.8
Clinical evaluation - High-energy trauma Sample size	n = 142 ; % = 67.6	n = 309 ; % = 65.1

Characteristic	Using anticoagulant therapy (N = 210)	Not using anticoagulant therapy (N = 475)
Clinical evaluation - Episode of epilepsy Sample size	n = 0 ; % = 0	n = 11 ; % = 2.3
Clinical evaluation - At least 2 vomiting episodes at 6 h Sample size	n = 2 ; % = 1	n = 20 ; % = 4.2
Clinical evaluation - GCS score **<15 at 6 h** Sample size	n = 3 ; % = 1.4	n = 33 ; % = 6.9
Clinical evaluation - Persistent headache Sample size	n = 33 ; % = 15.7	n = 116 ; % = 24.4

Outcomes

Study timepoints

- 24 hour (24 h after admission CT - time that control CT scan was performed)

Results - raw data

Outcome	Using anticoagulant therapy, 24 hour, N = 210	Not using anticoagulant therapy, 24 hour, N = 475
Delayed/late intracranial haemorrhage - VKA vs. no anticoagulation N=111 in VKA group and n=475 in no anticoagulant group No of events	n = 5 ; % = 4.5	n = 6 ; % = 1.26
Delayed/late intracranial haemorrhage - DOAC vs. no anticoagulation N=99 in DOAC group and n=475 in no anticoagulation group. 2 events in those on dabigatran and 2 on apixaban (no events in those on rivaroxaban or edoxaban) No of events	n = 4 ; % = 4.04	n = 6 ; % = 1.26

Critical appraisal - ROBINS-I checklist

Results_delayed/late ICH_VKA vs. no anticoagulation_24 h

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(outcome reported at time-point 24 h rather than 30 days)*

Results_delayed/late ICH_DOAC vs. no anticoagulation_24 h

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(outcome reported at time-point 24 h rather than 30 days)*

Galliazzo, 2019

Bibliographic Reference	Galliazzo, S.; Bianchi, M. D.; Virano, A.; Trucchi, A.; Donadini, M. P.; Dentali, F.; Bertu, L.; Grandi, A. M.; Ageno, W.; Intracranial bleeding risk after minor traumatic brain injury in patients on antithrombotic drugs; Thrombosis Research; 2019; vol. 174; 113-120

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA

Trial name / registration number	Not reported
Study location	Italy
Study setting	Secondary care - people admitted to a single hospital ED
Study dates	People admitted between January 2015 and September 2017 were included retrospectively
Sources of funding	Reported that no specific grant was received from funding agencies in public, commercial or not-for-profit sectors
Inclusion criteria	GCS score 13-15 on ED presentation after a referred mild TBI; aged >18 years - for the purpose of this review data for those receiving a second CT only was used as results for delayed bleeding are given in this group, which is relevant to the review protocol
Exclusion criteria	Those receiving any regimen of low molecular weight heparin
Recruitment / selection of participants	Retrospective inclusion of those meeting inclusion criteria from single centre ED through medical records
Intervention(s)	Anti-platelet use: single antiplatelet use before injury, including aspirin, ticlopidine, indobufen, clopidogrel, prasugrel and ticagrelor. Vitamin K antagonist use: included warfarin and acenocumarol Direct oral anticoagulant use: included apixaban, dabigatran, edoxaban and rivaroxaban

	Double antithrombotic use: included dual antiplatelet therapy or an antiplatelet and oral anticoagulant used in combination Information on antithrombotic use was obtained from medical records
Population subgroups	NA - no subgroups for this review
Comparator	No antithrombotic use: taking no antithrombotic medications prior to injury based on medical records
Number of participants	412 - subgroup with second CT performed, 1846 in whole study population but this includes people having injury diagnosed on first CT and is not relevant to review population (those with no indication for initial CT or negative initial CT)
Duration of follow-up	unclear - during observation as this is when second CTs said to be performed
Indirectness	Population - using subgroup with second CT could mean some without indication for initial CT that went on to have CT are ignored, but this is the only subgroup that delayed bleeding is reported for in the paper
Additional comments	Key confounders: • Age: not adjusted for and appears to be a significant difference between anticoagulant/antiplatelet groups and no treatment group • Diabetes mellitus: unclear, not reported • Hypertension: unclear, not reported Note this is for the whole population as characteristics not provided separately for the subgroup that had a second CT used for analysis

Study arms

Anti-platelet use (N = 131)

Number given is those that had a second CT performed

Vitamin K antagonist use (N = 86)

Number given is those that had a second CT performed

Direct oral anticoagulant use (N = 29)

Number given is those that had a second CT performed

Double antithrombotic use (N = 28)

Number given is those that had a second CT performed

No antithrombotic use (N = 135)

Number given is those that had a second CT performed

Characteristics

Arm-level characteristics

Characteristic	Anti-platelet use (N = 131)	Vitamin K antagonist use (N = 86)	Direct oral anticoagulant use (N = 29)	Double antithrombotic use (N = 28)	No antithrombotic use (N = 135)
% Female Custom value	236 (58.0%)	68 (56.7%)	22 (43.1%)	22 (47.8%)	572 (46.8%)
Aged >65 years Custom value	115 (95.8%)	376 (92.4%)	46 (90.2%)	42 (91.3%)	463 (37.9%)
TBI rating - Minimal Custom value	365 (89.7%)	10.9 (90.8%)	47 (92.2%)	43 (93.5%)	1056 (86.4%)
TBI rating - Mild Custom value	42 (10.3%)	11 (9.2%)	4 (7.8%)	3 (6.5%)	166 (13.6%)
GCS score 15 Custom value	402 (98.8%)	120 (100.0%)	50 (98.0%)	46 (100.0%)	1193 (97.6%)
GCS score 14 Custom value	5 (1.2%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	23 (1.9%)

Characteristic	Anti-platelet use (N = 131)	Vitamin K antagonist use (N = 86)	Direct oral anticoagulant use (N = 29)	Double antithrombotic use (N = 28)	No antithrombotic use (N = 135)
GCS score 13 Custom value	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.5%)
Loss of consciousness Custom value	9 (2.2%)	0 (0.0%)	2 (3.9%)	2 (4.4%)	55 (4.5%)
Amnesia Custom value	27 (6.6%)	10 (8.3%)	1 (2.0%)	1 (2.2%)	101 (8.3%)
Neurological signs Custom value	3 (0.7%)	1 (0.8%)	0 (0.0%)	1 (2.2%)	10 (0.8%)
Seizure Custom value	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.3%)
Headache Custom value	5 (1.2%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	25 (2.1%)
Vomiting Custom value	5 (1.2%)	1 (0.8%)	0 (0.0%)	2 (4.4%)	22 (1.8%)

Characteristic	Anti-platelet use (N = 131)	Vitamin K antagonist use (N = 86)	Direct oral anticoagulant use (N = 29)	Double antithrombotic use (N = 28)	No antithrombotic use (N = 135)
Clinical signs of cranial fracture Custom value	3 (0.7%)	0 (0.0%)	1 (2.0%)	2 (4.4%)	6 (0.5%)
INR >3 Custom value	0 (0.0%)	30 (25.0%)	0 (0.0%)	5 (10.9%)	1 (0.8%)
History of epilepsy Custom value	5 (1.2%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	22 (1.8%)
Previous stroke/TIA/neurosurgery Custom value	40 (9.8%)	11 (9.2%)	3 (5.9%)	3 (6.5%)	41 (3.4%)
Drug/alcohol intoxication Custom value	5 (1.2%)	1 (0.8%)	1 (2.0%)	1 (2.2%)	68 (5.6%)
History of cerebral neopalsia Custom value	2 (0.5%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	7 (0.6%)
First CT Custom value	387 (95.1%)	119 (99.2%)	51 (100.0%)	43 (93.5%)	787 (64.4%)

Characteristic	Anti-platelet use (N = 131)	Vitamin K antagonist use (N = 86)	Direct oral anticoagulant use (N = 29)	Double antithrombotic use (N = 28)	No antithrombotic use (N = 135)
Second CT Custom value	131 (32.2%)	86 (71.7%)	29 (54.9%)	28 (60.9%)	135 (11.1%)

Note: characteristics only given for whole population rather than subgroup that had second CT and was used for analysis, and numbers analysed for characteristics are higher than those in the heading of the table: antiplatelet use, n=407; vitamin K antagonist use, n=120; direct oral anticoagulant use, n=51; double antithrombotic use, n=46; and no antithrombotic use, n=1222

Outcomes

Study timepoints

- 24 hour (unclear - during observation as this is when second CTs said to be performed. Said to be within 24 h in some cases but unclear if the case for all repeat CTs.)

Results - raw data

Outcome	Anti-platelet use, 24 hour, N = 131	Vitamin K antagonist use, 24 hour, N = 86	Direct oral anticoagulant use, 24 hour, N = 29	Double antithrombotic use, 24 hour, N = 28	No antithrombotic use, 24 hour, N = 135
Delayed bleeding on repeat CT No of events	n = 2 ; % = 1.53	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 0.74

Critical appraisal - ROBINS-I checklist

Results_delayed bleeding_24 h/second CT scan_all comparisons

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(using subgroup with second CT could mean some without indication for initial CT that went on to have CT are ignored, also time-point 24 h rather than 30 days)*

Grewal, 2021

Bibliographic Reference	Grewal, K.; Atzema, C. L.; Austin, P. C.; De Wit, K.; Sharma, S.; Mittmann, N.; Borgundvaag, B.; McLeod, S. L.; Intracranial hemorrhage after head injury among older patients on anticoagulation seen in the emergency department: A populationbased cohort study; Cmaj; 2021; vol. 193 (no. 40); E1561-E1567

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with	NA

this study included in review	
Trial name / registration number	Not reported
Study location	Canada
Study setting	secondary care - those presenting to emergency departments
Study dates	Retrospective data collection of data between 2016 and 2018
Sources of funding	Study funded by the Canadian Association of Emergency Physicians through an Emergency Medicine Advancement Fund research award and individual authors had funding through specific awards or grants.
Inclusion criteria	aged ≥65 years; presenting to ED with triage complaint of head injury or trauma; and first ED visit for a head injury.
Exclusion criteria	Visits to EDs that were not open 24 h a day; visits to urgent care centres (usually treat lower acuity patients with no access to CT imaging); people leaving ED without being seen or leaving against medical advice; patients dying en route to ED; prescribed heparin during 7 days before ED visit; and patients on dialysis (unlikely to receive DOACs).
Recruitment / selection of participants	retrospective review of data between 2016 and 2018 from province-wide health administrative databases held at Ontario Health
Intervention(s)	Warfarin: those identified as using warfarin at the time of the ED visit from database Direct oral anticoagulant: those identified as using a DOAC at time of the ED visit from database Ontario Drug Benefit database, which contains all medical prescriptions covered by the provincial government, to identify anticoagulant status at the time of the emergency department visit. To be classified as an anticoagulant user, patients must

	have had a filled prescription for an anticoagulant that covered the 2 days before the index emergency department visit for the head injury.
Population subgroups	NA - no subgroups for this review
Comparator	No anticoagulant: those with no record of taking anticoagulants at the time of the ED visit. Ontario Drug Benefit database, which contains all medical prescriptions covered by the provincial government, to identify anticoagulant status at the time of the emergency department visit.
Number of participants	77,834 - note, also includes 4620 (5.9%) that had an ICH at the index visit (therefore not delayed/negative at admission and not relevant to population)
Duration of follow-up	Up to 90 days - longest time-point reported for outcomes
Indirectness	Population - not limited to those with no indication for CT or negative CT on index visit (5.9% were positive for ICH initial visit) - however not downgraded as only small proportion of total included
Additional comments	Key confounders: • Age: not adjusted for and appears to be a significant difference between anticoagulant groups and no treatment group • Diabetes mellitus: unclear, not reported • Hypertension: not adjusted for and appears to be a significant difference between anticoagulant groups and no treatment group Note although a propensity score matched population is reported, results for outcomes relevant to the negative initial CT/no initial CT population are not provided in this analysis

Study arms

Warfarin (N = 3703)

Direct oral anticoagulant (N = 9214)

No anticoagulant (N = 64917)

Characteristics

Arm-level characteristics

Characteristic	Warfarin (N = 3703)	Direct oral anticoagulant (N = 9214)	No anticoagulant (N = 64917)
Mean age (SD) Median (IQR)	85 (79 to 90)	84 (79 to 89)	80 (72 to 87)
Atrial fibrillation Sample size	n = 2914 ; % = 78.7	n = 7633 ; % = 82.8	n = 10137 ; % = 15.6
Cancer Sample size	n = 267 ; % = 7.2	n = 790 ; % = 8.6	n = 4603 ; % = 7.1

Characteristic	Warfarin (N = 3703)	Direct oral anticoagulant (N = 9214)	No anticoagulant (N = 64917)
Coronary artery disease Sample size	n = 1735 ; % = 46.9	n = 4070 ; % = 44.2	n = 15485 ; % = 23.9
Chronic obstructive pulmonary disorder Sample size	n = 670 ; % = 18.1	n = 1722 ; % = 18.7	n = 7592 ; % = 11.7
Congestive heart failure Sample size	n = 1709 ; % = 46.2	n = 3693 ; % = 40.1	n = 7086 ; % = 10.9
Dementia Sample size	n = 1122 ; % = 30.3	n = 3099 ; % = 33.6	n = 17068 ; % = 26.3
Hypertension Sample size	n = 2714 ; % = 73.3	n = 6912 ; % = 75	n = 39771 ; % = 61.3
Liver failure Sample size	n = 48 ; % = 1.3	n = 108 ; % = 1.2	n = 773 ; % = 1.2
Multiple sclerosis Sample size	n = 9	n = 22 ; % = 0.2	n = 294 ; % = 0.5
Parkinson's disease Sample size	n = 126 ; % = 3.4	n = 402 ; % = 4.4	n = 2886 ; % = 4.5

Characteristic	Warfarin (N = 3703)	Direct oral anticoagulant (N = 9214)	No anticoagulant (N = 64917)
Renal failure Sample size	n = 869 ; % = 23.5	n = 1233 ; % = 13.4	n = 6128 ; % = 9.4
Seizure Sample size	n = 131 ; % = 3.5	n = 290 ; % = 3.2	n = 1956 ; % = 3
Stroke or transient ischaemic attack (ischaemic) Sample size	n = 818 ; % = 22.1	n = 2217 ; % = 24.1	n = 8656 ; % = 13.3
Stroke (haemorrhagic) Sample size	n = 109 ; % = 2.9	n = 209 ; % = 2.3	n = 1274 ; % = 2
Venous thromboembolism Sample size	n = 707 ; % = 19.1	n = 1070 ; % = 11.6	n = 1949 ; % = 3
Charlson Comorbidity Score at least 3 Sample size	n = 1310 ; % = 35.4	n = 2902 ; % = 31.5	n = 11110 ; % = 17.1
% Male Sample size	n = 1608 ; % = 43.4	n = 3969 ; % = 43.1	n = 24883 ; % = 38.3
Age >80 years Sample size	n = 2563 ; % = 69.2	n = 6276 ; % = 68.1	n = 31034 ; % = 47.8

Characteristic	Warfarin (N = 3703)	Direct oral anticoagulant (N = 9214)	No anticoagulant (N = 64917)
Clopidogrel use Sample size	n = 80 ; % = 2.2	n = 180 ; % = 2	n = 5211 ; % = 8
Head CT scan in ED Sample size	n = 3341 ; % = 90.2	n = 8347 ; % = 90.6	n = 47002 ; % = 72.4
Intracranial haemorrhage at index visit Sample size	n = 303 ; % = 8.2	n = 545 ; % = 5.9	n = 3772 ; % = 5.8

Outcomes

Study timepoints

- 30 day (30-day time-point reported for mortality in whole population (including 5.9% with ICH on initial ED visit))
- 90 day (90-day time-point used for reporting delayed ICH in whole population (including 5.9% with ICH on initial ED visit))

Results - raw data

Outcome	Warfarin, 30 day, N = 3703	Warfarin, 90 day, N = 3703	Direct oral anticoagulant, 30 day, N = 9214	Direct oral anticoagulant, 90 day, N = 9214	No anticoagulant, 30 day, N = 64917	No anticoagulant, 90 day, N = 64917
30-day mortality Not specific to TBI-related	n = 223 ; % = 6	n = NR ; % = NR	n = 390 ; % = 4.2	n = NR ; % = NR	n = 1849 ; % = 2.9	n = NR ; % = NR

Outcome	Warfarin, 30 day, N = 3703	Warfarin, 90 day, N = 3703	Direct oral anticoagulant, 30 day, N = 9214	Direct oral anticoagulant, 90 day, N = 9214	No anticoagulant, 30 day, N = 64917	No anticoagulant, 90 day, N = 64917
mortality. Includes 5.9% with ICH at initial visit. No of events						
Delayed ICH within 90 days Intracranial haemorrhage. Included all types of intracranial bleeds. No of events	n = NR ; % = NR	n = 54 ; % = 1.5	n = NR ; % = NR	n = 78 ; % = 0.9	n = NR ; % = NR	n = 586 ; % = 0.9

Critical appraisal - ROBINS-I checklist

Results_mortality 30 days_warfarin vs. no anticoagulant

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(not specifically TBI-related mortality)*

Results_mortality 30 days_DOAC vs. no anticoagulant

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(not specifically TBI-related mortality)*

Results_delayed ICH 90 days_warfarin vs. no anticoagulant

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(5.9% with positive initial CT however not downgraded as only small proportion of total included, time-point of 90 days much longer than 30 days in protocol)*

Results_delayed ICH 90 days_DOAC vs. no anticoagulant

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(5.9% with positive initial CT however not downgraded as only small proportion of total included, time-point of 90 days much longer than 30 days in protocol)*

Mathieu, 2020

Bibliographic Reference	Mathieu, F.; Guting, H.; Gravesteijn, B.; Monteiro, M.; Glocker, B.; Kornaropoulos, E. N.; Kamnistas, K.; Robertson, C. S.; Levin, H.; Whitehouse, D. P.; Das, T.; Lingsma, H. F.; Maegele, M.; Newcombe, V. F. J.; Menon, D. K.; Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury, Investigators; Participants; Impact of Antithrombotic Agents on Radiological Lesion Progression in Acute Traumatic Brain Injury: A CENTER-TBI Propensity-Matched Cohort Analysis; Journal of Neurotrauma; 2020; vol. 37 (no. 19); 2069-2080

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	CENTER-TBI study
Study location	60 centres across Europe
Study setting	secondary care - those presenting and having CT on initial admission for head injury
Study dates	analysed data collected between December 2014 and December 2017
Sources of funding	CENTER-TBI study was supported by European Union 7th Framework program and individual authors describe funding from various scholarships or grants. Infrastructure support from National Institute for Health Research (NIHR) Cambridge Biomedical Research Center (BRC).

Inclusion criteria	CENTER-TBI participants with initial CT scan performed on admission and a repeat scan within 7 days of injury; aged 18 years or over; and blunt-mechanism mild-severe TBI (GCS score 3-15). For purpose of this review, results for the population that had an initially negative CT scan were extracted.
Exclusion criteria	Not reported.
Recruitment / selection of participants	Retrospective analysis of data collected as part of the CENTER-TBI study between December 2014 and December 2017
Intervention(s)	Antiplatelet/anticoagulant use: of those analysed, this included n=96 on antiplatelets (n=70 aspirin, n=7 ADPR-inhibitors, n=13 dual treatment and n=6 other), n=47 on anticoagulants (n=30 vitamin K antagonist, n=8 direct oral anticoagulant and n=8 other), and n=3 on a combination of antiplatelet and anticoagulation. Note that the numbers given above are for the whole population and breakdown is not reported for the smaller subgroup that had a negative initial CT. Also, results for each antiplatelet/anticoagulant are not reported separately and only given as a whole group vs. no treatment.
Population subgroups	NA - no subgroups for this review
Comparator	Control - no treatment: group that was not receiving preinjury anticoagulants or antiplatelets
Number of participants	34 (group relevant to protocol which had negative initial CT), 316 enrolled in total but included many with positive initial CT not relevant to review protocol

Duration of follow-up	Up to 6 months - longest time-point mentioned in the paper for certain outcomes
Indirectness	Population, none - includes mild-severe GCS but likely that within those with negative initial CT, most would be within mild range Intervention - groups multiple anticoagulants/antiplatelets as a single group and does not report results separately for individual drugs as in protocol
Additional comments	Key confounders: • Age: propensity adjusted population for original cohort demonstrates identical scores between groups - however, details for negative CT group not given and selecting this group may break the matching • Diabetes mellitus: not reported but propensity matching performed for original cohort - however, details for negative CT group not given and selecting this group may break the matching • Hypertension: not reported but propensity matching performed for original cohort - however, details for negative CT group not given and selecting this group may break the matching Note although a propensity score matched population is reported, characteristics specifically for the CT negative group are not given and it is unclear if selecting this group may break the matching.

Study arms

Antiplatelet/anticoagulant use (N = 18)
Note number differs from total included in whole population as data for the subgroup with initial negative result has been extracted, as per the protocol

Control - no treatment (N = 16)
Note number differs from total included in whole population as data for the subgroup with initial negative result has been extracted, as per the protocol

Characteristics

Arm-level characteristics

Characteristic	Antiplatelet/anticoagulant use (N = 18)	Control - no treatment (N = 16)
% Female Custom value	55 (34.8%)	56 (35.4%)
Mean age (SD) Mean (SD)	67.9 (12.9)	67.9 (11.6)
Mechanism of injury - High velocity Custom value	28 (17.7%)	28 (17.7%)
Mechanism of injury - Ground level falls Custom value	70 (44.3%)	65 (41.1%)
Mechanism of injury - Falls >1 m height	31 (19.6%)	39 (24.7%)

Characteristic	Antiplatelet/anticoagulant use (N = 18)	Control - no treatment (N = 16)
Custom value		
Mechanism of injury - Direct blow to head (other) Custom value	29 (18.4%)	26 (16.5%)
Baseline GCS score **13-15** Custom value	95 (60.1%)	90 (60.0%)
Baseline GCS score **9-12** Custom value	21 (13.3%)	25 (15.8%)
Baseline GCS score **3-8** Custom value	39 (24.7%)	37 (23.4%)
Baseline GCS score **not assessed** Custom value	3 (1.9%)	6 (3.8%)
Pupils (uni or bilateral unreactive) Custom value	18 (11.4%)	15 (9.5%)
Injury Severity Score (ISS) Median (range)	20 (1-75)	25 (1-75)
Systolic blood pressure on ED arrival	149 (31)	148 (35)

Characteristic	Antiplatelet/anticoagulant use (N = 18)	Control - no treatment (N = 16)
Mean (SD)		
Negative on initial CT scan Group relevant to the review protocols and for which results were extracted Custom value	18 (11.4%)	16 (10.1%)

Note that characteristics are not given for the two groups within the specific subgroup of those with a negative CT, and represent characteristics for n=158 in each group that were initially propensity matched in the whole population

Outcomes

Study timepoints

- 7 day (7-days - time-point used for delayed bleeding as repeat scan was performed within 7 days of initial CT. In the whole population, mean (SD) timing of initial CT scan was 3.6 (4.2) h vs. 4.0 (7.3) h and of repeat CT scan was 37.1 (36.5) h vs. 36.8 (43.5) h. Not given for negative CT group but suggests overall timing was just over 30 h since initial CT. Unclear if the same applies for negative CT subgroup.)
- 6 month (6- months - possible time-point for neurosurgery but unclear if this was the time-point for these two outcomes. Longest time-point mentioned in the paper.)

Results - raw data

Outcome	Antiplatelet/anticoagulant use, 7 day, N = 18	Antiplatelet/anticoagulant use, 6 month, N = 18	Control - no treatment, 7 day, N = 16	Control - no treatment, 6 month, N = 16
New intracranial haemorrhage In specific subgroup with negative initial CT. Repeat head CT within 7 days. Noted that all were<2 ml in size with none requiring neurosurgery. No of events	n = 4 ; % = 22.2	n = NR ; % = NR	n = 0 ; % = 0	n = NR ; % = NR
Neurosurgical intervention due to new ICH on repeat CT Reported that none of those with delayed haemorrhage required neurosurgical intervention. No of events	n = NR ; % = NR	n = 0 ; % = 0	n = NR ; % = NR	n = 0 ; % = 0

Critical appraisal - ROBINS-I checklist

Results_new intracranial haemorrhage_7 days

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Partially Applicable *(grouping of anticoagulants/antiplatelet drugs no separate results, also time-point of 7 days rather than 30 days)*

Results_neurosurgical intervention due to new ICH_6 months

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Partially Applicable *(grouping of anticoagulants/antiplatelet drugs no separate results, also time-point unclear)*

Uccella, 2016

Bibliographic Reference	Uccella, L.; Zoia, C.; Perlasca, F.; Bongetta, D.; Codeca, R.; Gaetani, P.; Mild Traumatic Brain Injury in Patients on Long-Term Anticoagulation Therapy: Do They Really Need Repeated Head CT Scan?; World Neurosurgery; 2016; vol. 93; 100-3

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	Not reported
Study location	Italy
Study setting	secondary care - from emergency department of single hospital
Study dates	Data collected from those presenting to ED between April 2012 and April 2013
Sources of funding	Not reported
Inclusion criteria	presenting to ED with traumatic head injury; mild TBI; matching Canadian head CT rules for performing a head CT scan; and GCS score 15 - for the purpose of this review results for those whose initial CT scan was negative have been extracted
Exclusion criteria	Those taking single or double antiplatelet treatment.
Recruitment / selection of participants	Retrospective analysis of data collected between April 2012 and April 2013 in database from single ED
Intervention(s)	Anticoagulation: those reported to be taking anticoagulants prior to injury from records.

	Note that this group had baseline CT scan after at least 2 h from arrival and a repeat scan after an observation period of 24 h
Population subgroups	NA - no subgroups for this review
Comparator	No anticoagulation: those not reported to be taking anticoagulants prior to injury from records. Note that this group only had one baseline CT scan, which was at least 2 h after arrival at the hospital. No details about how any readmissions or delayed bleeding might have been detected in this group.
Number of participants	865 - subgroup with negative baseline CT (relevant to this review protocol), 908 in whole population of study
Duration of follow-up	unclear, repeat CT in anticoagulation group performed after 24 h but unclear how/if those in non-anticoagulation group were followed up to detect for delayed bleeds
Indirectness	Intervention - groups multiple anticoagulants as a single group and does not report results separately for individual drugs as in protocol
Additional comments	Key confounders: • Age: not adjusted for and appears to be a significant difference between anticoagulant group and no treatment group in whole population (not given specifically for those with negative initial CT) • Diabetes mellitus: unclear, not reported • Hypertension: unclear, not reported

	Note that characteristics are not reported separately to compare the two groups when specifically looking at those that were CT negative on first scan

Study arms

Anticoagulation (N = 69)

Note number does not match those originally included as have extracted data for those without a positive CT on initial CT scan

No anticoagulation (N = 796)

Note number does not match those originally included as have extracted data for those without a positive CT on initial CT scan

Characteristics

Study-level characteristics

Characteristic	**Study (N = 908)**
% Female Sample size	n = 470 ; % = 51.7
Mean age (SD)	67.5 (18-98) years

Characteristic	Study (N = 908)
Mean (range)	
Triage risk code - White, no risk Sample size	n = 9 ; % = 1
Triage risk code - Green, non-urgent situation Sample size	n = 689 ; % = 75.8
Triage risk code - Yellow, urgent situation Sample size	n = 206 ; % = 22.6
Triage risk code - Red, emergency situation Sample size	n = 4 ; % = 0.4
Cause of trauma - Accidental fall Sample size	% = 69
Cause of trauma - Bicycle accident Sample size	% = 4.4
Cause of trauma - Car vs. pedestrian accident Sample size	% = 3.8
Cause of trauma - Car crash Sample size	% = 6.2

Characteristic	Study (N = 908)
Cause of trauma - Motorcycle crash Sample size	% = 4.3
Cause of trauma - Assault Sample size	% = 4
Cause of trauma - Fall from height Sample size	% = 2.1
Cause of trauma - Other Sample size	% = 5.4

Arm-level characteristics

Characteristic	Anticoagulation (N = 69)	No anticoagulation (N = 796)
Suspected open or depressed skull fracture Sample size	n = 2 ; % = 2.7	n = 11 ; % = 1.3
Any sign of basilar skull fracture Sample size	n = 0 ; % = 0	n = 14 ; % = 1.7
At least 2 episodes of vomiting	74 (8.9%)	0 (0.0%)

Characteristic	Anticoagulation (N = 69)	No anticoagulation (N = 796)
Custom value		
Aged at least 65 years Custom value	510 (61.2%)	67 (90.5%)
Retrograde amnesia to the event at least 30 min Custom value	71 (8.5%)	7 (9.5%)
Dangerous mechanism Custom value	45 (5.4%)	6 (8.1%)

Note that characteristics are only given for the whole population (n=74 in anticoagulation group and n=834 in non-anticoagulation group) and not for the subgroup specifically with negative initial CT

Outcomes

Study timepoints

- 24 hour (Unclear, repeat CT in anticoagulation group performed after 24 h but unclear how/if those in non-anticoagulation group were followed up to detect for delayed bleeds or other events such as surgery/mortality)

Results - raw data

Outcome	Anticoagulation, 24 hour, N = 69	No anticoagulation, 24 hour, N = 796
Delayed haemorrhage On control scan for those in anticoagulant group who had a second CT scan after 24 h observation. Those in non-anticoagulation group that were negative were discharged, unclear how or if they assessed for delayed haemorrhage in this group. Assume zero events as none mentioned. No of events	n = 0 ; % = 0	n = 0 ; % = 0
TBI-related mortality No events reported for mortality in whole population. No of events	n = 0 ; % = 0	n = 0 ; % = 0

Critical appraisal - ROBINS-I checklist

Results_delayed haemorrhage_24 h

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious

Section	Question	Answer
Overall bias	Directness	Indirectly Applicable *(combines different anticoagulant groups together rather than reporting separately as was ideal in the protocol for this review, also time-point of 24 h/unclear rather than 30 days)*

Results_TBI-related mortality_unclear time-point

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable *(combines different anticoagulant groups together rather than reporting separately as was ideal in the protocol for this review, also time-point of 24 h/unclear rather than 30 days)*

Appendix E – Forest plots

E.1 Warfarin/VKA alone vs. no antithrombotic treatment

Figure 2: Delayed traumatic intracranial haemorrhage - 24 h - 90 days

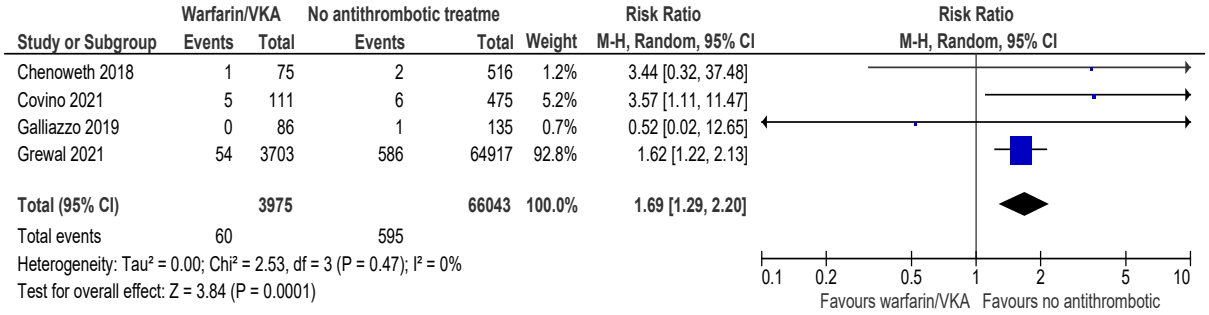


Figure 3: TBI-related mortality – 14-28 days

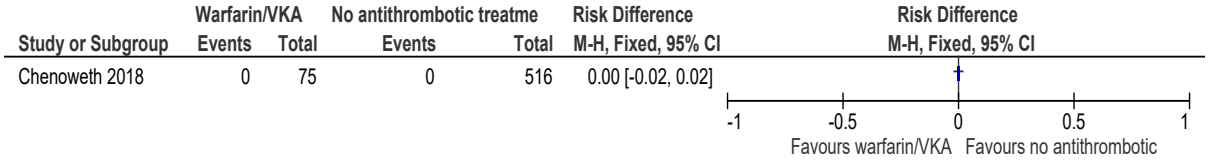
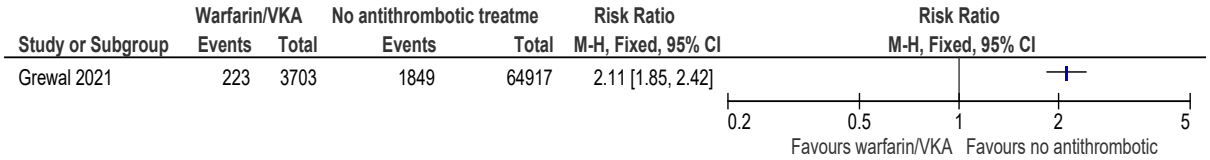


Figure 4: Mortality (not specific to TBI) – 30 days



E.2 DOACs alone vs. no antithrombotic treatment

Figure 5: Delayed traumatic intracranial haemorrhage - 24 h - 90 days

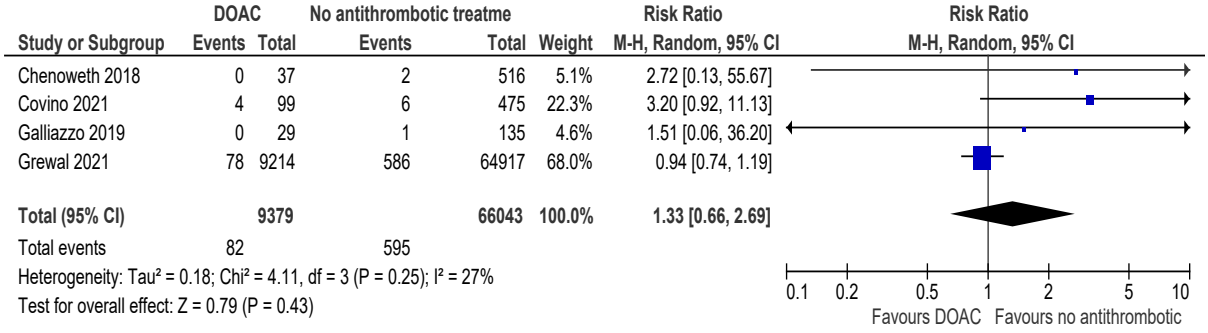


Figure 6: TBI-related mortality - 14-28 days

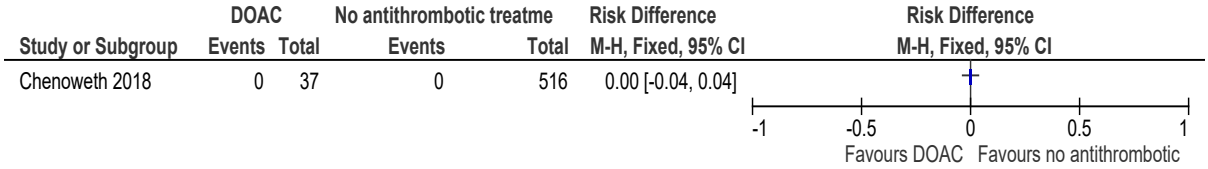
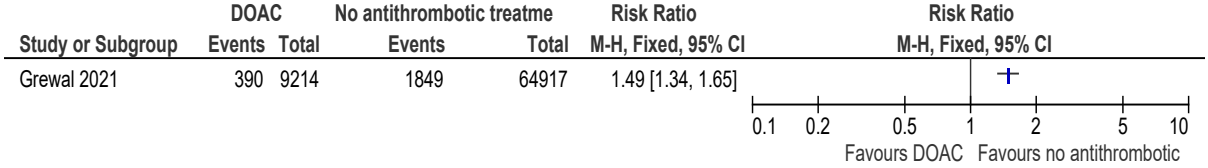


Figure 7: Mortality (not specific to TBI) – 30 days



E.3 Aspirin alone vs. no antithrombotic treatment

Figure 8: Delayed traumatic intracranial haemorrhage - within 14 days

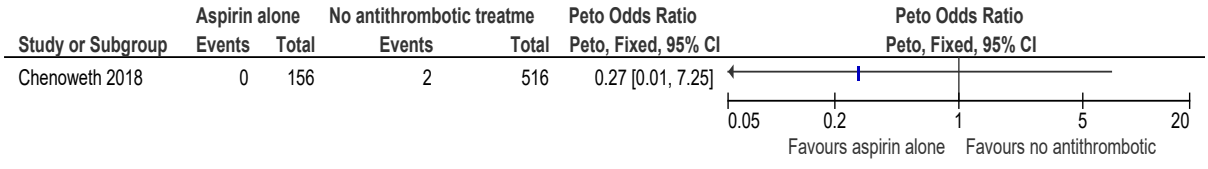
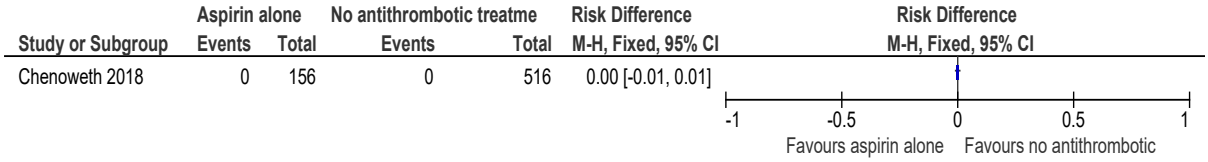


Figure 9: TBI-related mortality - 14-28 days



E.4 Other antiplatelet alone (clopidogrel bisulfate, ticlopidine hydrochloride, prasugrel, dipyridamole, cilostazol, or ticagrelor) vs. no antithrombotic treatment

Figure 10: Delayed traumatic intracranial haemorrhage - within 14 days

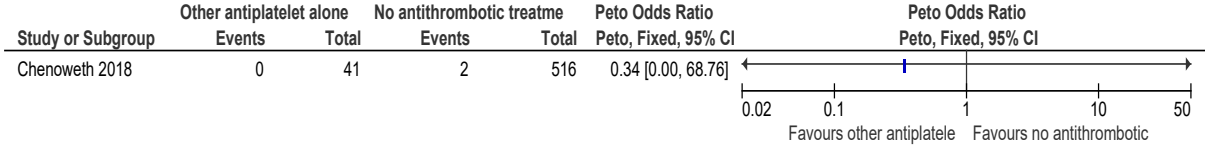
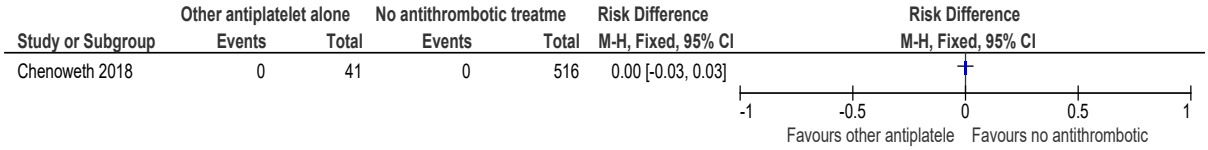


Figure 11: TBI-related mortality - 14-28 days



E.5 >1 anticoagulant or antiplatelet/double antithrombotic treatment vs. no antithrombotic treatment

Figure 12: Delayed traumatic intracranial haemorrhage - 24 h - 14 days

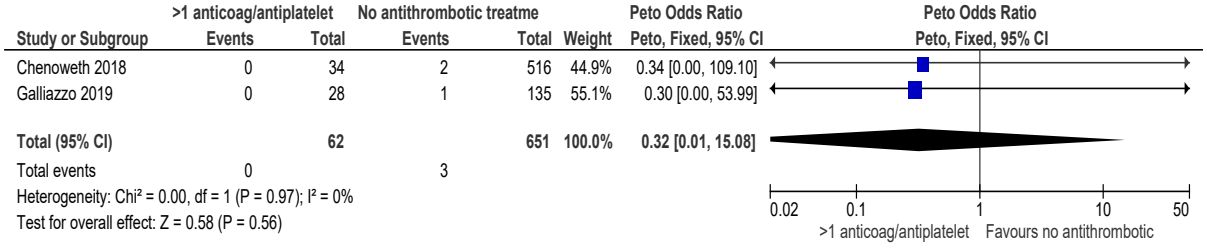
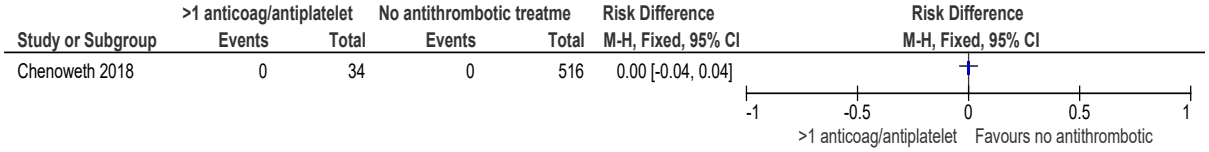
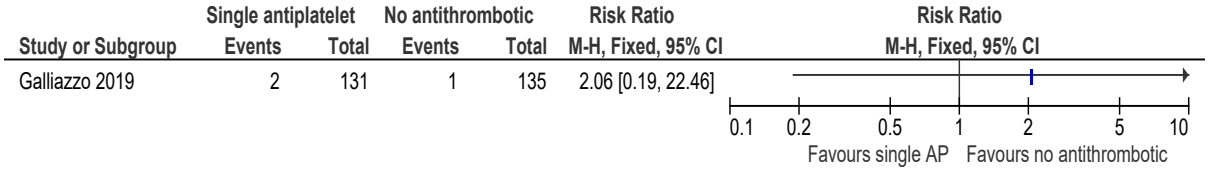


Figure 13: TBI-related mortality - 14-28 days



E.6 Single antiplatelet use (including aspirin, ticlopidine, indobufen, clopidogrel, prasugel and ticagelor) vs. no antithrombotic treatment

Figure 14: Delayed bleeding repeat CT - 24 h



E.7 Antiplatelet/anticoagulant use vs. no antithrombotic treatment

Figure 15: New intracranial haemorrhage on repeat CT - 7 days

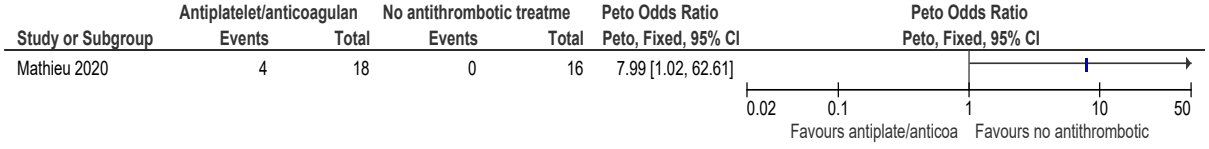
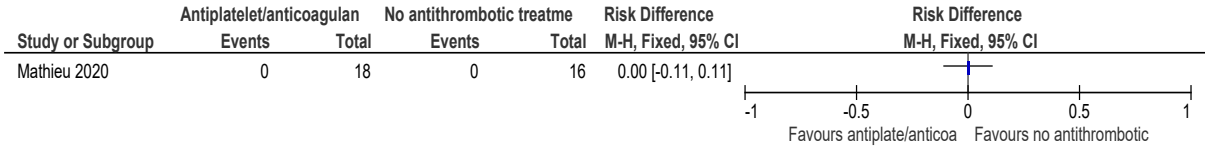


Figure 16: Neurosurgical intervention due to new ICH on repeat CT - 6 months/unclear



E.8 Anticoagulant use vs. no anticoagulant use (those using single and dual antiplatelets also excluded)

Figure 17: Delayed haemorrhage - 24 h/unclear

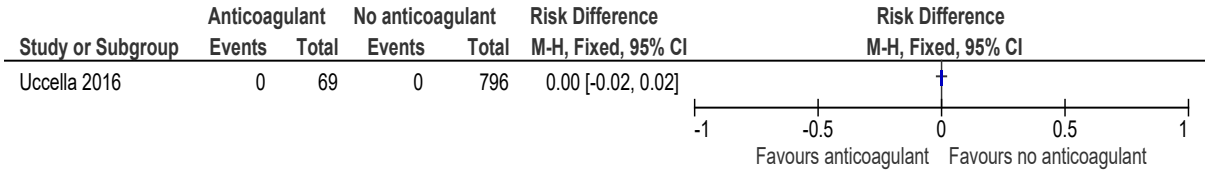
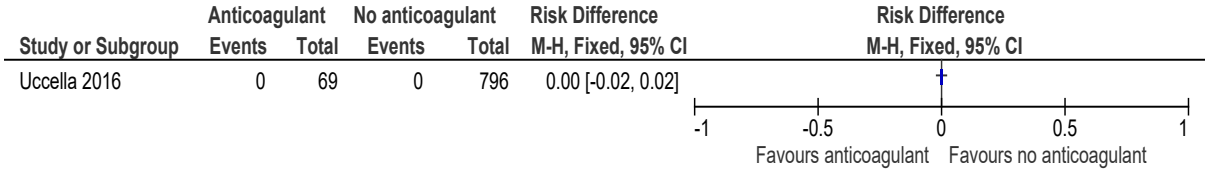


Figure 18: TBI-related mortality - 24 h/unclear



Appendix F – GRADE tables

Table 14: Clinical evidence profile: Warfarin/VKA alone vs. no antithrombotic treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Warfarin/VKA alone	no antithrombotic treatment	Relative (95% CI)	Absolute (95% CI)		
Delayed traumatic intracranial haemorrhage (follow-up: 24 h - 90 days)												
4	randomised trials	very serious[a]	serious[b]	serious[c]	not serious	none	60/3975 (1.5%)	0.8%	**RR 1.69** (1.29 to 2.20)	**6 more per 1,000** (from 2 more to 10 more)	⨁◯◯◯ Very low	CRITICAL
TBI-related mortality (follow-up: 14-28 days)												
1	randomised trials	very serious[a]	not serious	not serious	not serious[d]	none	0/75 (0.0%)	0/516 (0.0%)	**RD 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more)[e]	⨁⨁◯◯ Low	CRITICAL
Mortality (not specific to TBI) (follow-up: unclear - 30 days)												
1	randomised trials	very serious[a]	not serious	serious[f]	not serious	none	223/3703 (6.0%)	1849/64917 (2.8%)	**RR 2.11** (1.85 to 2.42)	**32 more per 1,000** (from 24 more to 40 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as point estimate of one study opposes direction of the other three studies and no clear differences between studies that could explain this. Also no subgrouping strategies prespecified in protocol.

c. Downgraded by 1 increment as time-point in all of the studies is either <30 days (24 h or 14 days) or much longer than 30 days

d. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

e. Absolute effect calculated using risk difference as zero events in both arms of a single study

f. Downgraded by 1 increment as the outcome was not specifically TBI-related mortality as in the protocol

Table 15: Clinical evidence profile: DOACs alone vs. no antithrombotic treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs alone	no antithrombotic treatment	Relative (95% CI)	Absolute (95% CI)		
Delayed traumatic intracranial haemorrhage (follow-up: 24 h - 90 days)												
4	randomised trials	very serious[a]	serious[b]	serious[c]	very serious[d]	none	82/9379 (0.9%)	0.8%	**RR 1.33** (0.66 to 2.69)	**3 more per 1,000** (from 3 fewer to 14 more)	⨁◯◯◯ Very low	CRITICAL
TBI-related mortality (follow-up: 14 - 28 days)												
1	randomised trials	very serious[a]	not serious	not serious	not serious[e]	none	0/37 (0.0%)	0/516 (0.0%)	**RD 0.00** (-0.04 to 0.04)	**0 fewer per 1,000** (from 40 fewer to 40 more)[f]	⨁⨁◯◯ Low	CRITICAL
Mortality (not specific to TBI) (follow-up: 30 days)												
1	randomised trials	very serious[a]	not serious	serious[g]	not serious	none	390/9214 (4.2%)	2.9%	**RR 1.49** (1.34 to 1.65)	**14 more per 1,000** (from 10 more to 19 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as there is variation in point estimate position on Forest plot across studies , with one being on centre line and others towards right of graph, and no clear differences between studies that could explain this. Also no subgrouping strategies prespecified in protocol.

c. Downgraded by 1 increment as time-point in all of the studies is either <30 days (24 h or 14 days) or much longer than 30 days

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

f. Absolute effect calculated using risk difference as zero events in both arms of a single study

g. Downgraded by 1 increment as the outcome was not specifically TBI-related mortality as in the protocol

Table 16: Clinical evidence profile: Aspirin alone vs. no antithrombotic treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin alone	no antithrombotic treatment	Relative (95% CI)	Absolute (95% CI)		
Delayed traumatic intracranial haemorrhage (follow-up: 14 days)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	0/156 (0.0%)	2/516 (0.4%)	**OR 0.27** (0.01 to 7.25)	**0 fewer per 1,000** (from 10 fewer to 10 more)[d]	⨁◯◯◯ Very low	CRITICAL
TBI-related mortality (follow-up: 14-28 days)												
1	randomised trials	very serious[a]	not serious	not serious	not serious[e]	none	0/156 (0.0%)	0/516 (0.0%)	**RD 0.00** (-0.01 to 0.00)	**0 fewer per 1,000** (from 10 fewer to 10 more)[f]	⨁⨁◯◯ Low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as outcome reported at 14-day time-point rather than 30 days as in protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Absolute effect calculate using risk difference as zero events in one arm of a single study

e. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

f. Absolute effect calculate using risk difference as zero events in both arms of a single study

Table 17: Clinical evidence profile: Other antiplatelet alone (clopidogrel bisulfate, ticlopidine hydrochloride, prasugrel, dipyridamole, cilostazol, or ticagrelor) vs. no antithrombotic treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Other antiplatelet alone (clopidogrel bisulfate, ticlopidine hydrochloride, prasugrel, dipyridamole, cilostazol, or ticagrelor)	no antithrombotic treatment	Relative (95% CI)	Absolute (95% CI)		
Delayed traumatic intracranial haemorrhage (follow-up: 14 days)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	0/41 (0.0%)	2/516 (0.4%)	**OR 0.34** (0.00 to 68.76)	**0 fewer per 1,000** (from 40 fewer to 30 more)[d]	⨁◯◯◯ Very low	CRITICAL
TBI-related mortality (follow-up: 14-28 days)												
1	randomised trials	very serious[a]	not serious	not serious	not serious[e]	none	0/41 (0.0%)	0/516 (0.0%)	**RD 0.00** (-0.03 to 0.03)	**0 fewer per 1,000** (from 30 fewer to 30 more)[f]	⨁⨁◯◯ Low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as outcome reported at 14-day time-point rather than 30 days as in protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Absolute effect calculated using risk difference as zero events in one arm of a single study

e. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

f. Absolute effect calculated using risk difference as zero events in both arms of a single study

Table 18: Clinical evidence profile: >1 anticoagulant or antiplatelet/double antithrombotic treatment vs. no antithrombotic treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>1 anticoagulant or antiplatelet/double antithrombotic treatment	no antithrombotic treatment	Relative (95% CI)	Absolute (95% CI)		
Delayed traumatic intracranial haemorrhage (follow-up: 24 h - 14 days)												
2	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	0/62 (0.0%)	3/651 (0.5%)	**OR 0.32** (0.01 to 15.08)	**10 fewer per 1,000** (from 40 fewer to 30 more)[d]	⨁◯◯◯ Very low	CRITICAL
TBI-related mortality - 14-28 days												
1	randomised trials	very serious[a]	not serious	not serious	not serious[e]	none	0/34 (0.0%)	0/516 (0.0%)	**RD 0.00** (-0.04 to 0.04)	**0 fewer per 1,000** (from 40 fewer to 40 more)[f]	⨁⨁◯◯ Low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as both studies report at time-points <30 days (24 h or 14 days)

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Absolute effect calculated using risk difference as zero events in one arm of both studies

e. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

f. Absolute effect calculated using risk difference as zero events in both arms of a single study

Table 19: Clinical evidence profile: Single antiplatelet use (including aspirin, ticlopidine, indobufen, clopidogrel, prasugel and ticagelor) vs. no antithrombotic treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single antiplatelet use (including aspirin, ticlopidine, indobufen, clopidogrel, prasugel and ticagelor)	no antithrombotic treatment	Relative (95% CI)	Absolute (95% CI)		
Delayed bleeding repeat CT - 24 h (follow-up: 24 h)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	2/131 (1.5%)	0.7%	**RR 2.06** (0.19 to 22.46)	**8 more per 1,000** (from 6 fewer to 159 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as outcome reported at ~24 h rather than 30 days as in protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 20: Clinical evidence profile: Antiplatelet/anticoagulant use vs. no antithrombotic treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet/anticoagulant use	no antithrombotic treatment	Relative (95% CI)	Absolute (95% CI)		
New intracranial haemorrhage on repeat CT (follow-up: 7 days)												
1	randomised trials	very serious[a]	not serious	serious[b]	serious[c]	none	4/18 (22.2%)	0/16 (0.0%)	**OR 7.99** (1.02 to 62.61)	**220 more per 1,000** (from 10 more to 430 more)[d]	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet/anticoagulant use	no antithrombotic treatment	Relative (95% CI)	Absolute (95% CI)		
Neurosurgical intervention due to new ICH on repeat CT (follow-up: 6 months/unclear)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[e]	none	0/18 (0.0%)	0/16 (0.0%)	**RD 0.00** (-0.11 to 0.11)	**0 fewer per 1,000** (from 110 fewer to 110 more)[f]	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as outcome reported at 7 days rather than 30 days as in protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Absolute effect calculated using risk difference as zero events in a one arm of a single study

e. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

f. Absolute effect calculated using risk difference as zero events in both arms of a single study

Table 21: Clinical evidence profile: Anticoagulant use vs. no anticoagulant use (those using single and dual antiplatelets also excluded)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anticoagulant use	no anticoagulant use	Relative (95% CI)	Absolute (95% CI)		
Delayed haemorrhage (follow-up: 24 h/unclear)												
1	randomised trials	very serious[a]	not serious	serious[b]	not serious[c]	none	0/69 (0.0%)	0/796 (0.0%)	**RD 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more)[d]	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anticoagulant use	no anticoagulant use	Relative (95% CI)	Absolute (95% CI)		
TBI-related mortality (follow-up: 24 h/unclear)												
1	randomised trials	very serious[a]	not serious	serious[b]	not serious[c]	none	0/69 (0.0%)	0/796 (0.0%)	**RD 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more)[d]	⨁◯◯◯ Very low	CRITICAL

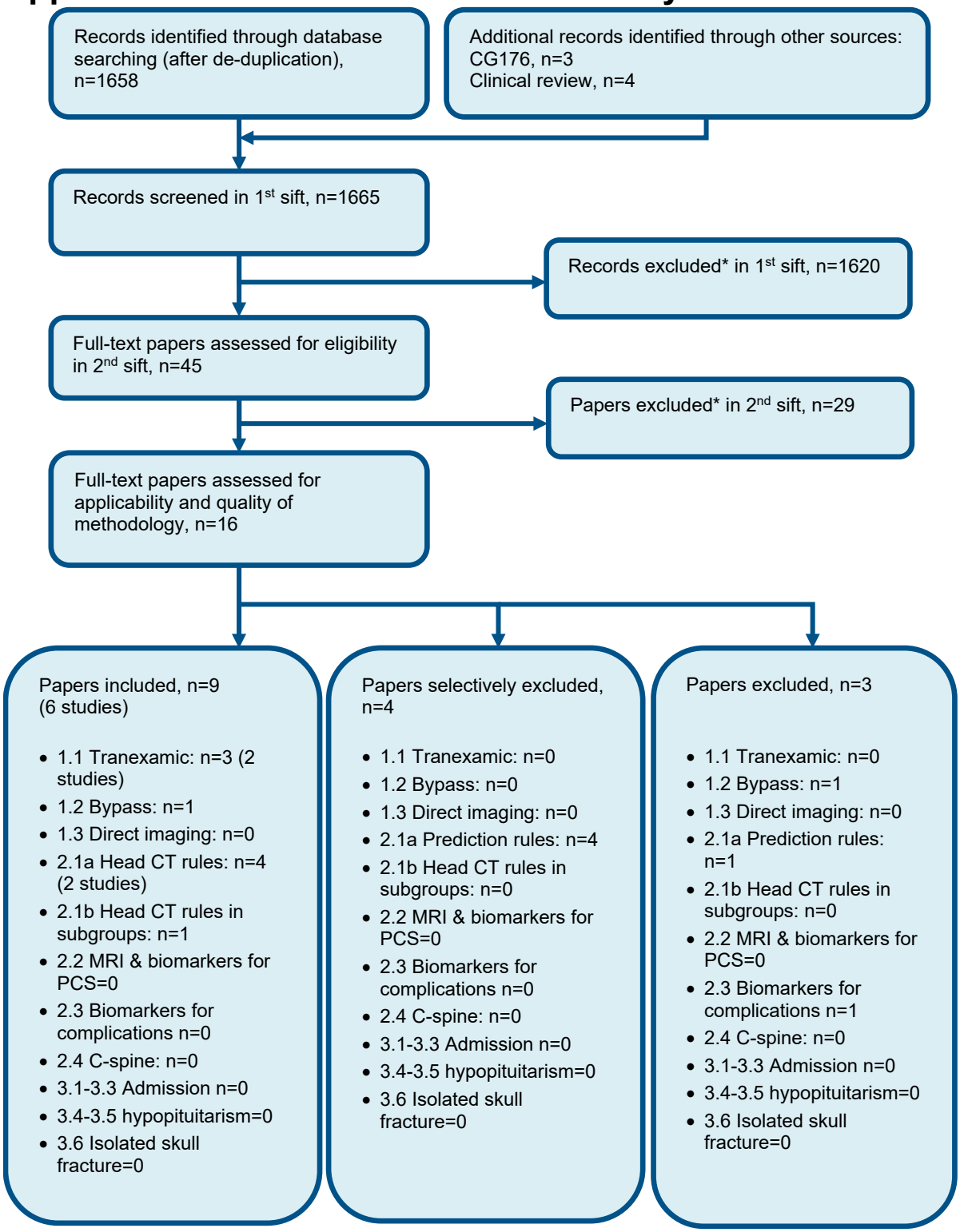
a. Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of the evidence was at serious risk of bias based on ROBINS-I checklist

b. Downgraded by 1 increment as the outcome was reported at 24 h/unclear time-point rather than 30 days as in the protocol

c. Imprecision was assessed based on sample size as there were zero events in both arms of a single study. Downgrading by 2 increments if sample size was <70, by 1 increment if sample size was >70 but <350 and no downgrading if sample size was >350.

d. Absolute effect calculated using risk difference as zero events in both arms of a single study

Appendix G – Economic evidence study selection



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

Appendix H – Economic evidence tables

None.

Appendix I – Health economic model

Modelling was not undertaken for this review.

Appendix J – Excluded studies

Clinical studies

Table 22: Studies excluded from the clinical review

Study	Code [Reason]
Afaneh, A., Ford, J., Gharzeddine, J. et al. (2018) Head injury on Warfarin: likelihood of delayed intracranial bleeding in patients with negative initial head CT. BMC Research Notes 11(1): 183	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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	- All or most had abnormality on initial head imaging
Alrajhi, K. N.; Perry, J. J.; Forster, A. J. (2015) Intracranial bleeds after minor and minimal head injury in patients on warfarin. Journal of Emergency Medicine 48(2): 137-42	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Ang, D., Kurek, S., McKenney, M. et al. (2017) Outcomes of Geriatric Trauma Patients on Preinjury Anticoagulation: A Multicenter Study. American Surgeon 83(6): 527-535	- Any trauma - not specific to 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): 25	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Bahl, A. and Schafer, S. (2018) Utility of Abdominal Computed Tomography in Geriatric Patients on Warfarin with a Fall from Standing. Journal of Emergencies Trauma & Shock 11(2): 88-91	- Abdominal trauma - not head injury
Bansal, V., Fortlage, D., Lee, J. et al. (2011) A new clopidogrel (Plavix) point-of-care assay: rapid determination of antiplatelet activity in trauma patients. Journal of Trauma-Injury Infection & Critical Care 70(1): 65-9; discussion 69	- Full text paper not available

Study	Code [Reason]
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Barrera, D., Sercy, E., Orlando, A. et al. (2020) Associations of Antithrombotic Timing and Regimen with Ischemic Stroke and Bleeding Complications in Blunt Cerebrovascular Injury. Journal of Stroke & Cerebrovascular Diseases 29(6): 104804	- All or most had abnormality on initial head imaging - Study does not contain an intervention relevant to this review protocol
Batchelor, J. S. and Grayson, A. (2013) A meta-analysis to determine the effect of preinjury antiplatelet agents on mortality in patients with blunt head trauma. British Journal of Neurosurgery 27(1): 12-8	- Systematic review used as source of primary studies
Batchelor, J. and Jibuike, O. (2013) A meta-analysis to determine the risk of intracranial haemorrhage posed by pre-injury use of aspirin or clopidogrel in patients with blunt head trauma. Trauma (United Kingdom): 339-340	- Abstract only
Batey, M., Hecht, J., Callahan, C. et al. (2018) Direct oral anticoagulants do not worsen traumatic brain injury after low-level falls in the elderly. Surgery 164(4): 814-819	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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 Anticoagulation or Antiplatelet Therapy Suffering Low-Altitude Falls. American Surgeon 83(5): 429-435	- No comparison to a group with no anticoagulant/antiplatelet therapy and at least 1000 participants included, but comparative data available from other studies
Benko, M. J., Abdulla, S. G., Cuoco, J. A. et al. (2019) Short- and Long-Term Geriatric Mortality After Acute Traumatic Subdural Hemorrhage. World Neurosurgery 130: e350-e355	- All or most had abnormality on initial head imaging

Study	Code [Reason]
Beynon, C., Hertle, D. N., Unterberg, A. W. et al. (2012) Clinical review: Traumatic brain injury in patients receiving antiplatelet medication. Critical Care (London, England) 16(4): 228	- Review article but not a systematic review
Beynon, C., Potzy, A., Sakowitz, O. W. et al. (2015) Rivaroxaban and intracranial haemorrhage after mild traumatic brain injury: A dangerous combination?. Clinical Neurology & Neurosurgery 136: 73-8	- All or most had abnormality on initial head imaging
Bialkowski, W., Tan, S., Mast, A. E. et al. (2020) Equivalent inpatient mortality among direct-acting oral anticoagulant and warfarin users presenting with major hemorrhage. Thrombosis Research 185: 109-118	- All or most had abnormality on initial head imaging - Any trauma - not specific to head injury
Billings, J. D., Khan, A. D., McVicker, J. H. et al. (2020) Preinjury Antiplatelet Use Does Not Increase the Risk of Progression of Small Intracranial Hemorrhage. American Surgeon 86(8): 991-995	- All or most had abnormality on initial head imaging
Billings, J. D., Khan, A. D., McVicker, J. H. et al. (2020) Newer and Better? Comparing Direct Oral Anticoagulants to Warfarin in Patients With Traumatic Intracranial Hemorrhage. American Surgeon 86(9): 1062-1066	- All or most had abnormality on initial head imaging
Boltz, M. M., Podany, A. B., Hollenbeak, C. S. et al. (2015) Injuries and outcomes associated with traumatic falls in the elderly population on oral anticoagulant therapy. Injury 46(9): 1765-71	- Any trauma - not specific to head injury - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Bonville, D. J., Ata, A., Jahraus, C. B. et al. (2011) Impact of preinjury warfarin and antiplatelet agents on outcomes of trauma patients. Surgery 150(4): 861-8	- Outcome - injury based on initial CT rather than follow-up after an initial negative CT - Population - not limited to those with normal imaging or no indication for imaging
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 comparison to a group with no anticoagulant/antiplatelet therapy and at least 1000 participants included, but comparative data available from other studies
Brewer, E. S., Reznikov, B., Liberman, R. F. et al. (2011) Incidence and predictors of	- Population - not limited to those with normal imaging or no indication for imaging

Study	Code [Reason]
intracranial hemorrhage after minor head trauma in patients taking anticoagulant and antiplatelet medication. Journal of Trauma-Injury Infection & Critical Care 70(1): E1-5	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Callahan, Z. M., Gadomski, S. P., 2nd, Koganti, D. et al. (2020) Geriatric patients on antithrombotic therapy as a criterion for trauma team activation leads to over triage. American Journal of Surgery 219(1): 43-48	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Campiglio, L., Bianchi, F., Cattalini, C. et al. (2017) Mild brain injury and anticoagulants: Less is enough. Neurology: Clinical Practice 7(4): 296-305	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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-Analysis. Journal of Emergency Medicine 51(5): 519-528	- Systematic review used as source of primary studies
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Chrastina, J., Hrabovsky, D., Zvarova, M. et al. (2014) The effect of anticoagulation and anti-aggregation treatment on the extent, development and prognosis of acute craniocerebral injury. Acta Chirurgiae Orthopaedicae et Traumatologiae Cechoslovaca 81(1): 77-84	- Study not reported in English
Cipriano, A., Park, N., Pecori, A. et al. (2021) Predictors of post-traumatic complication of mild brain injury in anticoagulated patients: DOACs are safer than VKAs. Internal & Emergency Medicine 16(4): 1061-1070	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Cipriano, A., Pecori, A., Bionda, A. E. et al. (2018) Intracranial hemorrhage in anticoagulated patients with mild traumatic brain injury: significant differences between direct oral anticoagulants and vitamin K antagonists. Internal & Emergency Medicine 13(7): 1077-1087	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included

Study	Code [Reason]
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	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Cohan, C. M., Beattie, G., Dominguez, D. A. et al. (2020) Routine Repeat Head CT Does Not Change Management in Trauma Patients on Novel Anticoagulants. Journal of Surgical Research 249: 114-120	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Collins, C. E., Witkowski, E. R., Flahive, J. M. et al. (2014) Effect of preinjury warfarin use on outcomes after head trauma in Medicare beneficiaries. American Journal of Surgery 208(4): 544-549.e1	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
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 used as source of primary studies
Cull, J. D., Sakai, L. M., Sabir, I. et al. (2015) Outcomes in traumatic brain injury for patients presenting on antiplatelet therapy. American Surgeon 81(2): 128-32	- Population - not limited to those with normal imaging or no indication for imaging

Study	Code [Reason]
	- Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Della Pepa, G. M., Covino, M., Menna, G. et al. (2021) 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 30: 30	- All or most had abnormality on initial head imaging
DiFiori, M. M., Lamb, L. C., Calavan, L. L. et al. (2018) Readmissions in Patients with Anticoagulated Intracranial Hemorrhage: A Retrospective Review. World Neurosurgery 110: e305-e309	- Full text paper not available
Docimo, S., Jr.; Demin, A.; Vinces, F. (2014) Patients with blunt head trauma on anticoagulation and antiplatelet medications: can they be safely discharged after a normal initial cranial computed tomography scan?. American Surgeon 80(6): 610-3	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included - All or most had abnormality on initial head imaging
Eibinger, N., Halvachizadeh, S., Hallmann, B. et al. (2020) Is the Regular Intake of Anticoagulative Agents an Independent Risk Factor for the Severity of Traumatic Brain Injuries in Geriatric Patients? A Retrospective Analysis of 10,559 Patients from the TraumaRegister DGU R. Brain Sciences 10(11): 12	- Population included only those with moderate or severe TBI (likely not GCS score 15 or back to baseline)
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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	- All or most had abnormality on initial head imaging
Fakhry, S. M., Morse, J. L., Garland, J. M. et al. (2021) Antiplatelet and anticoagulant agents have minimal impact on traumatic brain injury incidence, surgery, and mortality in geriatric ground level falls: A multi-institutional analysis of 33,710 patients. The Journal of Trauma and Acute Care Surgery 90(2): 215-223	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT

Study	Code [Reason]
Falzon, C. M., Celenza, A., Chen, W. et al. (2013) Comparison of outcomes in patients with head trauma, taking preinjury antithrombotic agents. Emergency Medicine Journal 30(10): 809-14	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Farsi, D., Karimi, P., Mofidi, M. et al. (2017) Effects of Pre-Injury Anti-Platelet Agents on Short-Term Outcome of Patients with Mild Traumatic Brain Injury: A Cohort Study. Bulletin of Emergency & Trauma 5(2): 110-115	- Population - not limited to those with normal imaging or no indication for imaging
Feeney, J. M., Neulander, M., DiFiori, M. et al. (2017) Direct oral anticoagulants compared with warfarin in patients with severe blunt trauma. Injury 48(1): 47-50	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included - Any trauma - not specific to head injury
Feeney, J. M., Santone, E., DiFiori, M. et al. (2016) Compared to warfarin, direct oral anticoagulants are associated with lower mortality in patients with blunt traumatic intracranial hemorrhage: A TQIP study. The Journal of Trauma and Acute Care Surgery 81(5): 843-848	- All or most had abnormality on initial head imaging
Fernando, S. M., Mok, G., Rochwerg, B. et al. (2021) Preadmission Antiplatelet Use and Associated Outcomes and Costs Among ICU Patients With Intracranial Hemorrhage. Journal of Intensive Care Medicine 36(1): 70-79	- All or most had abnormality on initial head imaging
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 used as source of primary studies
Fleming, B. (2001) Emergency case: Head injury in patients using warfarin. Canadian Family Physician 47(APR.): 727-728	- Review article but not a systematic review
Franko, J., Kish, K. J., O'Connell, B. G. et al. (2006) Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. Journal of Trauma-Injury Infection & Critical Care 61(1): 107-10	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT

Study	Code [Reason]
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 used as source of primary studies
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	- Systematic review used as source of primary studies
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	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
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	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Garra, G.; Nashed, A. H.; Capobianco, L. (1999) Minor head trauma in anticoagulated patients. Academic Emergency Medicine 6(2): 121-4	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Goto, H., Ishikawa, O., Nomura, M. et al. (2015) Magnetic resonance imaging findings predict the recurrence of chronic subdural hematoma. Neurologia Medico-Chirurgica 55(2): 173-8	- All or most had abnormality on initial head imaging - No relevant outcomes
Gottlieb, M.; Thottathil, S. M.; Holton, J. P. (2019) What Is the Incidence of Intracranial Hemorrhage Among Anticoagulated Patients With Minor Head Trauma?. Annals of emergency medicine 74(1): 98-100	- Review article but not a systematic review - All or most had abnormality on initial head imaging

Study	Code [Reason]
Grandhi, R., Duane, T. M., Dechert, T. et al. (2008) Anticoagulation and the elderly head trauma patient. American Surgeon 74(9): 802-5	- All or most had abnormality on initial head imaging
Grandhi, R., Harrison, G., Voronovich, Z. et al. (2015) Preinjury warfarin, but not antiplatelet medications, increases mortality in elderly traumatic brain injury patients. The Journal of Trauma and Acute Care Surgery 78(3): 614-21	- All or most had abnormality on initial head imaging
Guly, H. R.; Jones, L. O.; Nokes, T. J. C. (2005) Trauma in the anticoagulated patient. Trauma 7(3): 155-161	- Review article but not a systematic review
Harland, T. A., Prabhala, T., Nardolillo, A. et al. (2021) Does Pre-existing Anticoagulation or Antiplatelet Therapy Increase the Risk of Traumatic Subarachnoid Hemorrhage Progression?. Neurosurgery 24: 24	- Population - not limited to those with normal imaging or no indication for imaging - No relevant outcomes
Hecht, J. P., LaDuke, Z. J., Cain-Nielsen, A. H. et al. (2020) Effect of Preinjury Oral Anticoagulants on Outcomes Following Traumatic Brain Injury from Falls in Older Adults. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy 40(7): 604-613	- Population - not limited to those with normal imaging or no indication for imaging - Population included only those with moderate or severe TBI (likely not GCS score 15 or back to baseline)
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 used as source of primary studies
Hill, J. H., Bonner, P., O'Mara, M. S. 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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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	- Population - not limited to those with normal imaging or no indication for imaging
Huang, G. S., Dunham, C. M., Chance, E. A. et al. (2020) Detecting delayed intracranial hemorrhage with repeat head imaging in trauma	- Systematic review used as source of primary studies

Study	Code [Reason]
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	
Huang, J. L., Woehrle, T. A., Conway, P. et al. (2019) Evaluation of a protocol for early detection of delayed brain hemorrhage in head injured patients on warfarin. European Journal of Trauma & Emergency Surgery 45(3): 481-487	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Hughes, P., Alter, S., Greaves, S. et al. (2021) Acute and delayed intracranial hemorrhage in head-injured patients on warfarin versus direct oral anticoagulant therapy. Journal of Emergencies, Trauma and Shock 14(3): 123-127	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Inamasu, J., Nakatsukasa, M., Kuramae, T. et al. (2010) Influence of age and anti-platelet/anti-coagulant use on the outcome of elderly patients with fall-related traumatic intracranial hemorrhage. Neurologia Medico-Chirurgica 50(12): 1051-5	- All or most had abnormality on initial head imaging
Inamasu, J., Nakatsukasa, M., Miyatake, S. et al. (2012) Influence of warfarin and low-dose aspirin on the outcomes of geriatric patients with traumatic intracranial hemorrhage resulting from ground-level fall. Geriatrics & gerontology international 12(4): 667-72	- All or most had abnormality on initial head imaging
Ivascu, F. A., Howells, G. A., Junn, F. S. et al. (2008) Predictors of mortality in trauma patients with intracranial hemorrhage on preinjury aspirin or clopidogrel. Journal of Trauma-Injury Infection & Critical Care 65(4): 785-8	- All or most had abnormality on initial head imaging
Ivascu, F. A., Janczyk, R. J., Junn, F. S. et al. (2006) Treatment of trauma patients with intracranial hemorrhage on preinjury warfarin. Journal of Trauma-Injury Infection & Critical Care 61(2): 318-21	- All or most had abnormality on initial head imaging
Jehan, F., Zeeshan, M., Kulvatunyou, N. et al. (2019) Is There a Need for Platelet Transfusion After Traumatic Brain Injury in Patients on P2Y12 Inhibitors?. Journal of Surgical Research 236: 224-229	- All or most had abnormality on initial head imaging
Jentzsch, T., Moos, R. M., Neuhaus, V. et al. (2018) Is rivaroxaban associated with higher	- Population - not limited to those with normal imaging or no indication for imaging

Study	Code [Reason]
morbidity and mortality in patients with traumatic head injuries? A retrospective cohort study comparing rivaroxaban, no anticoagulation, and phenprocoumon. Clinical Neurology & Neurosurgery 169: 116-120	- Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Jones, K., Sharp, C., Mangram, A. J. et al. (2006) The effects of preinjury clopidogrel use on older trauma patients with head injuries. American Journal of Surgery 192(6): 743-5	- Outcome - injury based on initial CT rather than follow-up after an initial negative CT - Population - not limited to those with normal imaging or no indication for imaging
Joseph, B., Aziz, H., Pandit, V. et al. (2014) Low-dose aspirin therapy is not a reason for repeating head computed tomographic scans in traumatic brain injury: a prospective study. Journal of Surgical Research 186(1): 287-91	- All or most had abnormality on initial head imaging
Joseph, B., Pandit, V., Aziz, H. et al. (2014) Clinical outcomes in traumatic brain injury patients on preinjury clopidogrel: a prospective analysis. The Journal of Trauma and Acute Care Surgery 76(3): 817-20	- All or most had abnormality on initial head imaging
Joseph, B., Pandit, V., Sadoun, M. et al. (2013) A prospective evaluation of platelet function in patients on antiplatelet therapy with traumatic intracranial hemorrhage. The Journal of Trauma and Acute Care Surgery 75(6): 990-4	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included - All or most had abnormality on initial head imaging
Joseph, B., Sadoun, M., Aziz, H. et al. (2014) Repeat head computed tomography in anticoagulated traumatic brain injury patients: still warranted. American Surgeon 80(1): 43-7	- All or most had abnormality on initial head imaging
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	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Kaen, A., Jimenez-Roldan, L., Arrese, I. et al. (2010) The value of sequential computed tomography scanning in anticoagulated patients suffering from minor head injury. Journal of Trauma-Injury Infection & Critical Care 68(4): 895-8	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included

Study	Code [Reason]
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	- All or most had abnormality on initial head imaging
Kerr, K., Wilkerson, C., Shepard, S. et al. (2016) Use of anti-platelet agents after traumatic intracranial hemorrhage. Clinical Neurology & Neurosurgery 140: 85-90	- All or most had abnormality on initial head imaging
Kerschbaum, M., Lang, S., Henssler, L. et al. (2021) Influence of oral anticoagulation and antiplatelet drugs on outcome of elderly severely injured patients. Journal of Clinical Medicine 10(8)	- No relevant outcomes - Population - those severely injured with or without head injuries
Kim, S. H., Sul, Y. H., Lee, J. Y. et al. (2020) Does preinjury anticoagulant or antiplatelet medication increase the need for blood transfusions in patients aged older than 65 years with traumatic brain injury?. Critical Care and Shock 23(5): 221-231	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Kinnunen, J., Satopaa, J., Niemela, M. et al. (2021) Coagulopathy and its effect on treatment and mortality in patients with traumatic intracranial hemorrhage. Acta Neurochirurgica 163(5): 1391-1401	- All or most had abnormality on initial head imaging
Kobayashi, L., Barmparas, G., Bosarge, P. et al. (2017) Novel oral anticoagulants and trauma: The results of a prospective American Association for the Surgery of Trauma Multi-Institutional Trial. The Journal of Trauma and Acute Care Surgery 82(5): 827-835	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
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	- All or most had abnormality on initial head imaging
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 design not relevant to this review protocol
Lampart, A., Kuster, T., Nickel, C. H. et al. (2020) Prevalence and Severity of Traumatic Intracranial Hemorrhage in Older Adults with	- Population - not limited to those with normal imaging or no indication for imaging

Study	Code [Reason]
Low-Energy Falls. Journal of the American Geriatrics Society 68(5): 977-982	- Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Lavoie, A., Ratte, S., Clas, D. et al. (2004) Preinjury warfarin use among elderly patients with closed head injuries in a trauma center. Journal of Trauma-Injury Infection & Critical Care 56(4): 802-7	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Lee, Z. X., Lim, X. T., Ang, E. et al. (2020) The effect of preinjury anticoagulation on mortality in trauma patients: A systematic review and meta-analysis. Injury 51(8): 1705-1713	- Systematic review used as source of primary studies
Leiblich, A. and Mason, S. (2011) Emergency management of minor head injury in anticoagulated patients. Emergency Medicine Journal 28(2): 115-8	- Review article but not a systematic review
Levine, M., Wyler, B., Lovecchio, F. et al. (2014) Risk of intracranial injury after minor head trauma in patients with pre-injury use of clopidogrel. American Journal of Emergency Medicine 32(1): 71-4	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
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	- All or most had abnormality on initial head imaging
Li, J.; Brown, J.; Levine, M. (2001) Mild head injury, anticoagulants, and risk of intracranial injury. Lancet 357(9258): 771-772	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Lim, B. L.; Manauis, C.; Asinas-Tan, M. L. (2016) Outcomes of warfarinized patients with minor head injury and normal initial CT scan. American Journal of Emergency Medicine 34(1): 75-8	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Lim, X. T., Ang, E., Lee, Z. X. et al. (2021) Prognostic significance of preinjury anticoagulation in patients with traumatic brain injury: A systematic review and meta-analysis.	- Systematic review used as source of primary studies

Study	Code [Reason]
The Journal of Trauma and Acute Care Surgery 90(1): 191-201	
Macedo, M., Grima, J., Yangouyian, M. et al. (2017) Delayed Intracranial Hemorrhage in Patients Taking Warfarin with Head Trauma. Spartan Medical Research Journal 1(2): 5127	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included - Outcome - injury based on initial CT rather than follow-up after an initial negative CT - Population - not limited to those with normal imaging or no indication for imaging
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Marcia, L., Moazzez, A., Plurad, D. S. et al. (2018) Utility of Repeat Head CT in Patients on Preinjury Antithrombotic Medications. American Surgeon 84(10): 1626-1629	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included - Population - not limited to those with normal imaging or no indication for imaging
Marques, R. S. F., Antunes, C., Machado, M. J. et al. (2021) Reappraising the need for a control CT in mild head injury patients on anticoagulation. European Journal of Trauma & Emergency Surgery 47(5): 1461-1466	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Marquez, B. D. P.; Gine, G. T.; Rosich, M. R. (2015) A patient with mild head injury taking anticoagulant and antiplatelet medications. FMC Formacion Medica Continuada en Atencion Primaria 22(10): 564-567	- Study not reported in English
Mason, S., Kuczawski, M., Teare, M. D. et al. (2017) AHEAD Study: an observational study of the management of anticoagulated patients who suffer head injury. BMJ Open 7(1): e014324	- Outcome - injury based on initial CT rather than follow-up after an initial negative CT - Population - not limited to those with normal imaging or no indication for imaging

Study	Code [Reason]
	- No comparison to a group with no anticoagulant/antiplatelet therapy and at least 1000 participants included, but comparative data available from other studies
Mathiesen, T., Benediktsdottir, K., Johnsson, H. et al. (1995) Intracranial traumatic and non-traumatic haemorrhagic complications of warfarin treatment. Acta Neurologica Scandinavica 91(3): 208-14	- All or most had abnormality on initial head imaging - No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Maung, A. A., Bhattacharya, B., Schuster, K. M. et al. (2016) Trauma patients on new oral anticoagulation agents have lower mortality than those on warfarin. The Journal of Trauma and Acute Care Surgery 81(4): 652-7	- Any trauma - not specific to head injury - Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Maurer, P., Conrad-Hengerer, I., Hollstein, S. et al. (2013) Orbital haemorrhage associated with orbital fractures in geriatric patients on antiplatelet or anticoagulant therapy. International Journal of Oral & Maxillofacial Surgery 42(12): 1510-4	- All or most had abnormality on initial head imaging
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
McMillian, W. D. and Rogers, F. B. (2009) Management of prehospital antiplatelet and anticoagulant therapy in traumatic head injury: a review. Journal of Trauma-Injury Infection & Critical Care 66(3): 942-50	- Review article but not a systematic review
Meade, M. J., Tumati, A., Chantachote, C. et al. (2021) Antithrombotic Agent Use in Elderly Patients Sustaining Low-Level Falls. Journal of Surgical Research 258: 216-223	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT

Study	Code [Reason]
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	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Mesa Galan, L. A., Egea-Guerrero, J. J., Quintana Diaz, M. et al. (2016) The effectiveness and safety of pharmacological prophylaxis against venous thromboembolism in patients with moderate to severe traumatic brain injury: A systematic review and meta-analysis. The Journal of Trauma and Acute Care Surgery 81(3): 567-74	- Systematic review used as source of primary studies
Miller, J., Lieberman, L., Nahab, B. et al. (2015) Delayed intracranial hemorrhage in the anticoagulated patient: A systematic review. The Journal of Trauma and Acute Care Surgery 79(2): 310-3	- Systematic review used as source of primary studies
Mina, A. A., Bair, H. A., Howells, G. A. et al. (2003) Complications of preinjury warfarin use in the trauma patient. Journal of Trauma-Injury Infection & Critical Care 54(5): 842-7	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Mina, A. A., Knipfer, J. F., Park, D. Y. et al. (2002) Intracranial complications of preinjury anticoagulation in trauma patients with head injury. Journal of Trauma-Injury Infection & Critical Care 53(4): 668-72	- All or most had abnormality on initial head imaging
Minhas, H., Welsher, A., Turcotte, M. et al. (2018) Incidence of intracranial bleeding in anticoagulated patients with minor head injury: a systematic review and meta-analysis of prospective studies. British Journal of Haematology 183(1): 119-126	- Systematic review used as source of primary studies
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	- All or most had abnormality on initial head imaging
Mountain, D.; Sistenich, V.; Jacobs, I. G. (2010) Characteristics, management and outcomes of adults with major trauma taking pre-injury	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included

Study	Code [Reason]
warfarin in a Western Australian population from 2000 to 2005: a population-based cohort study. Medical Journal of Australia 193(4): 202-6	- Any trauma - not specific to head injury
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Moustafa, F., Roubin, J., Pereira, B. et al. (2018) Predictive factors of intracranial bleeding in head trauma patients receiving antiplatelet therapy admitted to an emergency department. Scandinavian Journal of Trauma, Resuscitation & Emergency Medicine 26(1): 50	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Narum, S., Brors, O., Stokland, O. et al. (2016) Mortality among head trauma patients taking preinjury antithrombotic agents: a retrospective cohort analysis from a Level 1 trauma centre. BMC Emergency Medicine 16(1): 29	- Population - not limited to those with normal imaging or no indication for imaging
Nederpelt, C. J., van der Aalst, S. J. M., Rosenthal, M. G. et al. (2020) Consequences of pre-injury utilization of direct oral anticoagulants in patients with traumatic brain injury: A systematic review and meta-analysis. The Journal of Trauma and Acute Care Surgery 88(1): 186-194	- Systematic review used as source of primary studies
Nekludov, M., Antovic, J., Bredbacka, S. et al. (2007) Coagulation abnormalities associated with severe isolated traumatic brain injury: cerebral arterio-venous differences in coagulation and inflammatory markers. Journal of Neurotrauma 24(1): 174-80	- Population included only those with moderate or severe TBI (likely not GCS score 15 or back to baseline)
Nishijima, D. K., Gaona, S. D., Waechter, T. et al. (2017) Out-of-Hospital Triage of Older Adults With Head Injury: A Retrospective Study of the Effect of Adding "Anticoagulation or Antiplatelet Medication Use" as a Criterion. Annals of Emergency Medicine 70(2): 127-138.e6	- Population - not limited to those with normal imaging or no indication for imaging
Nishijima, D. K., Gaona, S. D., Waechter, T. et al. (2018) The incidence of traumatic intracranial hemorrhage in head-injured older adults transported by EMS with and without anticoagulant or antiplatelet use. Journal of Neurotrauma 35(5): 750-759	- Population - not limited to those with normal imaging or no indication for imaging

Study	Code [Reason]
Nishijima, D. K., Offerman, S. R., Ballard, D. W. 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): 460-8.e1	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Nishijima, D. K., Offerman, S. R., Ballard, D. W. et al. (2013) Risk of traumatic intracranial hemorrhage in patients with head injury and preinjury warfarin or clopidogrel use. Academic Emergency Medicine 20(2): 140-5	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
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	- All or most had abnormality on initial head imaging
Nishimura, T., Guyette, F. X., Naito, H. et al. (2020) Comparison of direct oral anticoagulant and Vitamin K antagonists on outcomes among elderly and nonelderly trauma patients. Journal of Trauma and Acute Care Surgery 89(3): 514-522	- Any trauma - not specific to head injury
O'Brien, T., Mitra, B., Le Sage, N. et al. (2020) Clinically significant traumatic intracranial hemorrhage following minor head trauma in older adults: a retrospective cohort study. Brain Injury 34(6): 834-839	- Insufficient reporting of data for two groups in those where no initial CT scan required
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Ohm, C., Mina, A., Howells, G. et al. (2005) Effects of antiplatelet agents on outcomes for elderly patients with traumatic intracranial hemorrhage. Journal of Trauma-Injury Infection & Critical Care 58(3): 518-22	- All or most had abnormality on initial head imaging
Ott, M. M., Eriksson, E., Vanderkolk, W. et al. (2010) Antiplatelet and anticoagulation therapies do not increase mortality in the absence of traumatic brain injury. Journal of Trauma-Injury Infection & Critical Care 68(3): 560-3	- Abdominal trauma - not head injury

Study	Code [Reason]
Pakraftar, S., Atencio, D., English, J. et al. (2014) Dabigatran etixilate and traumatic brain injury: Evolving anticoagulants require evolving care plans. World Journal of Clinical Cases 2(8): 362-6	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Pang, C. H.; Lee, S. E.; Yoo, H. (2015) Clinical factors and perioperative strategies associated with outcome in preinjury antiplatelet and anticoagulation therapy for patients with traumatic brain injuries. Journal of Korean Neurosurgical Society 58(3): 262-270	- All or most had abnormality on initial head imaging
Parmar, K. A.; Rao, S.; Abu-Zidan, F. M. (2006) Head injuries in warfarinised patients. Singapore Medical Journal 47(8): 676-8	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included - All or most had abnormality on initial head imaging
Parra, M. W., Zucker, L., Johnson, E. S. et al. (2013) Dabigatran bleed risk with closed head injuries: are we prepared?. Journal of Neurosurgery 119(3): 760-5	- All or most had abnormality on initial head imaging
Parris, R. and Hassan, Z. (2007) Does clopidogrel increase morbidity and mortality after minor head injury. Emergency Medicine Journal 24(6): 435-436	- Review article but not a systematic review
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	- All or most had abnormality on initial head imaging
Peck, K. A., Sise, C. B., Shackford, S. R. et al. (2011) Delayed intracranial hemorrhage after blunt trauma: are patients on preinjury anticoagulants and prescription antiplatelet agents at risk?. Journal of Trauma-Injury Infection & Critical Care 71(6): 1600-4	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Petzl, A., Derndorfer, M., Kollias, G. et al. (2021) Cerebral thromboembolic risk in atrial fibrillation ablation: a direct comparison of vitamin K antagonists versus non-vitamin K-dependent	- Population not relevant to this review protocol

Study	Code [Reason]
oral anticoagulants. Journal of Interventional Cardiac Electrophysiology 60(1): 147-154	
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	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Pokorney, S. D. and Granger, C. B. (2018) Traumatic injury: Another unjustified reason to stop oral anticoagulation for atrial fibrillation. European Heart Journal 39(19): 1706-1708	- Study design not relevant to this review protocol
Pozzessere, A.; Grotts, J.; Kaminski, S. (2015) Dabigatran Use Does Not Increase Intracranial Hemorrhage in Traumatic Geriatric Falls When Compared with Warfarin. American Surgeon 81(10): 1039-42	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Prexl, O., Bruckbauer, M., Voelckel, W. et al. (2018) The impact of direct oral anticoagulants in traumatic brain injury patients greater than 60-years-old. Scandinavian Journal of Trauma, Resuscitation & Emergency Medicine 26(1): 20	- All or most had abnormality on initial head imaging
Probst, M. A., Gupta, M., Hendey, G. W. et al. (2020) Prevalence of Intracranial Injury in Adult Patients With Blunt Head Trauma With and Without Anticoagulant or Antiplatelet Use. Annals of Emergency Medicine 75(3): 354-364	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
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 232(6): 1007-1016.e5	- Systematic review used as source of primary studies
Qiu, L., Han, J. X., See, A. A. Q. et al. (2019) Effects of anticoagulant and antiplatelet agents in severe traumatic brain injury in an asian population - A matched case-control study. Journal of Clinical Neuroscience 70: 61-66	- Population included only those with moderate or severe TBI (likely not GCS score 15 or back to baseline) - All or most had abnormality on initial head imaging

Study	Code [Reason]
Reddy, S., Sharma, R., Grotts, J. et al. (2014) Incidence of intracranial hemorrhage and outcomes after ground-level falls in geriatric trauma patients taking preinjury anticoagulants and antiplatelet agents. American Surgeon 80(10): 975-8	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT - No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Rendell, S. (2010) Towards evidence-based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 2. Observation is recommended even following a normal CT brain in warfarinised head injuries. Emergency Medicine Journal 27(11): 874-5	- Review article but not a systematic review
Rendell, S. and Sultan, L. (2014) Towards evidence-based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 3: Observation is unnecessary following a normal CT brain in warfarinised head injuries: an update. Emergency Medicine Journal 31(4): 339-42	- Review article but not a systematic review
Reymond, M. A., Marbet, G., Radu, E. W. et al. (1992) Aspirin as a risk factor for hemorrhage in patients with head injuries. Neurosurgical Review 15(1): 21-25	- All or most had abnormality on initial head imaging - Population included only those with moderate or severe TBI (likely not GCS score 15 or back to baseline)
Reynolds, F. D., Dietz, P. A., Higgins, D. et al. (2003) Time to deterioration of the elderly, anticoagulated, minor head injury patient who presents without evidence of neurologic abnormality. Journal of Trauma-Injury Infection & Critical Care 54(3): 492-6	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included - Outcome - injury based on initial CT rather than follow-up after an initial negative CT

Study	Code [Reason]
Rittenhouse, K., Rogers, A., Clark, E. et al. (2015) The ACT Alert: preliminary results of a novel protocol to assess geriatric head trauma patients on anticoagulation. American Surgeon 81(4): 408-13	- Comparator in study does not match that specified in this review protocol
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	- All or most had abnormality on initial head imaging
Sakr, M. and Wilson, L. (2005) Best evidence topic report. Aspirin and the risk of intracranial complications following head injury. Emergency Medicine Journal 22(12): 891-2	- Review article but not a systematic review
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	- Full text paper not available
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	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Savioli, G., Ceresa, I. F., Luzzi, S. et al. (2021) Mild Head Trauma: Is Antiplatelet Therapy a Risk Factor for Hemorrhagic Complications?. Medicina 57(4): 07	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
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 & Emergency Surgery 43(6): 741-746	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Schoonman, G. G.; Bakker, D. P.; Jellema, K. (2014) Low risk of late intracranial complications in mild traumatic brain injury patients using oral anticoagulation after an initial normal brain computed tomography scan: education instead of hospitalization. European Journal of Neurology 21(7): 1021-5	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included

Study	Code [Reason]
Scotti, P., Seguin, C., Lo, B. W. Y. et al. (2020) Antithrombotic agents and traumatic brain injury in the elderly population: hemorrhage patterns and outcomes. Journal of Neurosurgery 133(2): 486-495	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Seddighi, A. S., Motiei-Langroudi, R., Sadeghian, H. et al. (2013) Factors predicting early deterioration in mild brain trauma: a prospective study. Brain Injury 27(1314): 1666-70	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Shin, S. S., Marsh, E. B., Ali, H. et al. (2020) Comparison of Traumatic Intracranial Hemorrhage Expansion and Outcomes Among Patients on Direct Oral Anticoagulants Versus Vitamin k Antagonists. Neurocritical Care 32(2): 407-418	- All or most had abnormality on initial head imaging
Siracuse, J. J., Robich, M. P., Gautam, S. et al. (2010) Antiplatelet agents, warfarin, and epidemic intracranial hemorrhage. Surgery 148(4): 724-9; discussion 729	- All or most had abnormality on initial head imaging
Smith, K. and Weeks, S. (2012) The impact of pre-injury anticoagulation therapy in the older adult patient experiencing a traumatic brain injury: A systematic review. JBI Library of Systematic Reviewis 10(58): 4610-4621	- Protocol only
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Sotade, O. (2015) Anticoagulation and injurious falls in the elderly: a review. European Orthopaedics and Traumatology 6(4): 405-408	- Review article but not a systematic review
Spektor, S., Agus, S., Merkin, V. et al. (2003) Low-dose aspirin prophylaxis and risk of intracranial hemorrhage in patients older than 60 years of age with mild or moderate head injury: a prospective study. Journal of Neurosurgery 99(4): 661-5	- Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT

Study	Code [Reason]
Spinola, M. B., Riccardi, A., Minuto, P. et al. (2019) Hemorrhagic risk and intracranial complications in patients with minor head injury (MHI) taking different oral anticoagulants. American Journal of Emergency Medicine 37(9): 1677-1680	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included - Population - not limited to those with normal imaging or no indication for imaging - Outcome - injury based on initial CT rather than follow-up after an initial negative CT
Suehiro, E., Fujiyama, Y., Kiyohira, M. et al. (2019) Risk of Deterioration of Geriatric Traumatic Brain Injury in Patients Treated with Antithrombotic Drugs. World Neurosurgery 127: e1221-e1227	- All or most had abnormality on initial head imaging
Sumiyoshi, K., Hayakawa, T., Yatsushige, H. et al. (2017) Outcome of traumatic brain injury in patients on antiplatelet agents: a retrospective 20-year observational study in a single neurosurgery unit. Brain Injury 31(11): 1445-1454	- All or most had abnormality on initial head imaging
Svedung Wettervik, T., Lenell, S., Enblad, P. et al. (2021) Pre-injury antithrombotic agents predict intracranial hemorrhagic progression, but not worse clinical outcome in severe traumatic brain injury. Acta Neurochirurgica 163(5): 1403-1413	- All or most had abnormality on initial head imaging
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. Permanente Journal 20(2): 14-6	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Tauber, M., Koller, H., Moroder, P. et al. (2009) Secondary intracranial hemorrhage after mild head injury in patients with low-dose acetylsalicylate acid prophylaxis. Journal of Trauma-Injury Infection & Critical Care 67(3): 521-5; discussion 525	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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 included only those with moderate or severe TBI (likely not GCS score 15 or back to baseline)

Study	Code [Reason]
Turcato, G., Zaboli, A., Pfeifer, N. et al. (2021) Decision tree analysis to predict the risk of intracranial haemorrhage after mild traumatic brain injury in patients taking DOACs. American Journal of Emergency Medicine 50: 388-393	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Turcato, G., Zaboli, A., Zannoni, M. et al. (2021) Risk factors associated with intracranial bleeding and neurosurgery in patients with mild traumatic brain injury who are receiving direct oral anticoagulants. American Journal of Emergency Medicine 43: 180-185	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Turcato, G., Zannoni, M., Zaboli, A. et al. (2019) Direct Oral Anticoagulant Treatment and Mild Traumatic Brain Injury: Risk of Early and Delayed Bleeding and the Severity of Injuries Compared with Vitamin K Antagonists. Journal of Emergency Medicine 57(6): 817-824	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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	- Population - not limited to those with normal imaging or no indication for imaging
Valiuddin, H., Alam, A., Calice, M. et al. (2020) Utility of INR For Prediction of Delayed Intracranial Hemorrhage Among Warfarin Users with Head Injury. Journal of Emergency Medicine 58(2): 183-190	- No comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
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 comparison to a group with no anticoagulant/antiplatelet therapy and <1000 people included
Valle, E. J., Van Haren, R. M., Allen, C. J. et al. (2014) Does traumatic brain injury increase the risk for venous thromboembolism in polytrauma patients?. The Journal of Trauma and Acute Care Surgery 77(2): 243-50	- Any trauma - not specific to head injury - Population included only those with moderate or severe TBI (likely not GCS score 15 or back to baseline)
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 used as source of primary studies

Study	Code [Reason]
van Erp, I. A., Mokhtari, A. K., Moheb, M. E. et al. (2020) Comparison of outcomes in non-head injured trauma patients using pre-injury warfarin or direct oral anticoagulant therapy. Injury 51(11): 2546-2552	- Population not relevant to this review protocol
Verschoof, M. A., Zuurbier, C. C. M., de Beer, F. et al. (2018) Evaluation of the yield of 24-h close observation in patients with mild traumatic brain injury on anticoagulation therapy: a retrospective multicenter study and meta-analysis. Journal of Neurology 265(2): 315-321	- Systematic review used as source of primary studies
Wojcik, R., Cipolle, M. D., Seislove, E. et al. (2001) Preinjury warfarin does not impact outcome in trauma patients. Journal of Trauma-Injury Infection & Critical Care 51(6): 1147-51; discussion 1151	- Population - not limited to those with normal imaging or no indication for imaging
Wong, D. K.; Lurie, F.; Wong, L. L. (2008) The effects of clopidogrel on elderly traumatic brain injured patients. Journal of Trauma-Injury Infection & Critical Care 65(6): 1303-8	- All or most had abnormality on initial head imaging
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	- Population - not limited to those with normal imaging or no indication for imaging
Zeeshan, M., Jehan, F., O'Keeffe, T. et al. (2018) The novel oral anticoagulants (NOACs) have worse outcomes compared with warfarin in patients with intracranial hemorrhage after TBI. The Journal of Trauma and Acute Care Surgery 85(5): 915-920	- All or most had abnormality on initial head imaging

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.