Appendix A: Summary of evidence from surveillance

Original review question		
We updated the literature search used to answer the following question included original guideline: What is the best clinical decision rule for selecting adults, infants and children with head injury for CT head scan who have no history of amnesia or loss of consciousness who are on anticoagulant or antiplatelet therapy?		
Review strategy		
	Included	**Excluded**
Population	Adults, infants and children WITH blunt head injury AND no history of amnesia or loss of consciousness AND are on anticoagulant treatment with: Warfarin Direct oral anticoagulants (DOACs) including dabigatran etexilate, rivaroxaban, apaxiban, edoxaban. Setting: assessment in the emergency department and hospital	Adults, infants and children WITH Head injury AND on antiplatelet treatment
Prognosis factor	Treatment with DOACs	
Outcomes	Intracranial bleeding risk (intracranial haemorrhage [ICH]) Mortality	
Search strategy	Language: Restrict to English only Date limits: from 31 January 2013 to 4 June 2019	

Study design	Randomised controlled trials Cohort studies Systematic reviews and meta-analyses of the above Cost-effectiveness studies	
Other criteria	Population size: No limitations on sample size.	

Summary of the results

The original search strategy was adapted, focusing on people having warfarin or DOACs as anticoagulant treatment. We followed a pragmatic approach to select the relevant studies. We initially identified systematic reviews (SR) that directly answered the question. Then, we identified all relevant studies published after the date of the last search of the SRs included. Cost-effectiveness studies were included if they were available and were considered relevant to the UK context.

A total of 401 references were identified. We found two SRs relevant to the question (Minhas H et al. 2018; Fuller GW et al. 2019). The first SR assessed the incidence of initial and delayed intracranial bleeding in people on anticoagulant treatment (warfarin, DOACs or low molecular heparin) with a minor head injury (Glasgow Coma Score [GCS] of 15 at triage) in hospital emergency settings (Minhas H et al. 2018). Only prospective studies that included consecutive patients were considered for inclusion. A total of five studies (n=4080) with a moderate risk of bias were included. The included studies varied in the mechanism of injury (motor vehicle collision, fall from height, direct blow, assault, among others) as well as in the follow-up of the patients (ST head scan repeated after 24 hours, telephone survey at 14 days, review of electronic health records for 30 days or 10 weeks). One study assessed coumarins, three warfarin and one different type of anticoagulants (vitamin K antagonists [VKA], DOACS, and enoxaparin). The proportion of patients with an ICH diagnosed in the emergency department or at the follow-up varied between 4% to 22% in the studies included. The pooled incidence of ICH (initial or delayed) was 8.9% (95% confidence interval [95%CI] 5.0 to 13.8%; I^2=93%). Authors stated that this incidence is higher than the incidence reported by other studies in non-anticoagulated patients (between 4% and 7%);

however, the results identified were heterogeneous. Given the lack of data available, no conclusions were made regarding patients receiving DOACs.

The second SR assessed the risk of adverse outcome in people receiving DOACs with a mild traumatic head injury (GCS score 13-15) within three months of the hospital attendance (Fuller GW et al. 2019). An adverse outcome was defined as any adverse outcome related to the traumatic brain injury such as clinically significant ICH, neurosurgery, disability, reattendance or mortality. Retrospective and prospective studies were included. A total of seven retrospective and prospective cohort studies (n= 346) with a high risk of bias were included. All the studies assessed dabigatran, and four of them assessed other types of DOACs (rivaroxaban, apixaban, and edoxaban). The definition of a mild traumatic head injury varied between the studies included (GCS score 13-15, GCS score 15 plus symptoms or GCS score 14-15). Two studies included only patients that were transported by emergency services. The adverse outcomes assessed were ICH in CT head scan, neurosurgery, readmission and mortality. The follow-up also varied between studies with some of them assessing the outcomes within 6 hours, during the hospitalisation, or at one month of follow-up. The incidence of adverse outcome reported by the studies included was between 0% and 8%. The pooled risk of adverse outcome was 3.7% (95% CI 1.7% to 5.8%; I^2=3.3%). Authors considered that the quality of the evidence was low due to the high risk of bias, imprecision, and indirectness. It was not possible to determine the risk of adverse outcome in asymptomatic patients given the limited of data available.

We identified seven additional studies published since 2018[1]. All them but one (Jeanmonod R et al. 2018) were retrospective studies, and all with a high risk of bias.
The first study assessed the presence of delayed intracranial bleeding in patients with blunt trauma on anticoagulant or antiplatelet treatment and a negative first CT head scan (Hill JH et al. 2018). A total of 338 patients receiving aspirin, clopidogrel, or warfarin (or combinations of those) were included. The mean GCS was 15, 27.2% reported loss of consciousness and 55% had signs of head trauma. The incidence of a delayed ICH was 2.4% (95% CI not reported). None of the patients included needed additional treatment. Authors

[1] Hill JH et al. 2018; Marcia L et al. 2018; Prexl O et al. 2018; Verschoof M et al. 2018; Yuquero O et al. 2018; Vedin T et al. 2018; Jeanmonod R et al. 2018

concluded that given the low incidence of adverse outcomes, there is no need of a second CT head scan after an initial negative one in this population.
The second study evaluated the risk factors associated with a delayed head bleeding in people with suspected traumatic brain injury and receiving antiplatelets or anticoagulants (warfarin or DOACs) (Marcia L et al. 2018). A total of 110 patients were included. Mechanical fall was the most common mechanism of injury (93.6%). Most of the patients received aspirin (42.7%) and warfarin (31.8%). Nineteen patients received treatment with DOACs (17.2%). Fifty per cent of the patients included had a positive finding in the first CT head scan, and 20.9% of patients developed new bleeding (1.8%) or a worsening of the initial intracranial hemorrhage (19.1%). Having a higher mean of the Injury Severity Score was the only risk factor associated with an increased risk of progression of the head bleeding (or delayed presentation).

Prexl O et al. 2018 assessed the risk of head bleeding in patients having treatment with DOACs and with a traumatic brain injury. They included a total of 186 patients aged 60 years and over admitted to the intensive care unit (ICU): 80 patients did not receive any anticoagulant treatment, 41 patients received antiplatelet therapy, 32 patients received VKA, and 33 patients received DOACs. The most common mechanism of injury was falling < 1 meter. The mean GCS was 14. People receiving VKA treatment had a higher risk of progression of head bleeding (p=0.023) and in-hospital mortality compared (p=0,047) with the other groups assessed (results not adjusted). Authors concluded that DOACs have a safer profile compared to VKA in this population, but more studies are needed.

In a retrospective multicenter study, Verschoof M et al. 2018 assessed the need of a second CT head scan in people receiving anticoagulants with a mild traumatic brain injury and with a normal initial CT head scan within 24 hours after the trauma. A total of 905 patients were included: 874 received VKA, 14 low molecular weight heparin, and 17 DOACs. Atrial fibrillation was the main indication for receiving anticoagulant treatment. The most common mechanism of injury was ground-level falls. No delayed ICH cases were identified during the first day after the trauma. Three patients had a delayed ICH. Given the low number of patients with a delayed ICH, no further analyses were done. Authors also conducted a review of the literature to assess the risk of delayed ICH in the population included in the

study. Nine observational studies were included, and only one study included patients receiving DOACs. The overall pooled risk of delayed (or delayed diagnosis) of ICH was 1.2% (95% CI 0.6 to 2.2). Authors concluded that the risk of symptomatic ICH in people receiving anticoagulants with a mild head injury and with a normal initial CT head scan is very low, so there is no need of routine hospitalisation in this population after a reliable evaluation of the initial CT head scan.

Yuquero O et al. 2018 assessed the incidence of adverse outcome in patients with a traumatic brain injury and receiving antiplatelet or anticoagulant treatment. A total of 243 patients were included, and most of them had a normal initial CT head scan (62.3%). The mortality was 5.8%, and it was associated with loss of consciousness, a decrease in GCS and comorbidities. No differences were identified in the mortality rates between those receiving antiplatelet or anticoagulant treatment and those not treated.
In a retrospective study, Vedin T et al. 2018 evaluated the risk factors associated with the development of ICH in adults after a head injury. A total of 1638 patients were included (mean age 58 years). Male, age, new neurological deficits, and mild trauma injuries were associated with an increased risk of ICH. The overall incidence of ICH was 4.3%, the incidence of ICH in patients receiving anticoagulants was 8.6%, and for those receiving antiplatelet treatment was 11.8%.

Finally, a prospective cohort study assessed the factors associated with an increased risk of head bleeding in older patients (≥65 years) after a fall (Jeanmonod R et al. 2018). A total of 723 patients were included (median age 83 years), 10% had a GCS <15, 21% had dementia, and 56% were receiving anticoagulant treatment. Loss of consciousness and signs of head trauma were associated with an increased risk of ICH in this population.

Summary

We identified only one study specifically answering the review question. It was a SR of observational studies which assessed the risk of adverse outcomes in people receiving DOACs with a mild head injury. Results of this SR showed a pooled adverse outcome risk of 3.7%. Authors considered that the quality of evidence was low given the high or unclear risk of bias, imprecision and indirectness (Fuller GW et al. 2019). We identified other relevant

evidence assessing risk of adverse outcomes in people on anticoagulants (mostly warfarin), and risk factors associated to ICH after a head injury. Only one study provided data on DOACs, and showed that they have a lower risk of adverse outcomes compared with warfarin (Prexl O et al. 2018). This study has a high risk of bias. No relevant economic studies were identified.