Does pre-injury clopidogrel use increase the risk of intracranial haemorrhage post head injury in adult patients? A systematic review and meta-analysis

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ABSTRACT

Background Several current guidelines do not include antiplatelet use as an explicit indication for CT scan of the head following head injury. The impact of individual antiplatelet agent use on rates of intracranial haemorrhage is unclear. The primary objective of this systematic review was to assess if clopidogrel monotherapy was associated with traumatic intracranial haemorrhage (tICH) on CT of the head within 24 hours of presentation following head trauma compared with no antithrombotic controls.

Methods Eligible studies were non-randomised studies with participants aged ≥18 years old with head injury. Studies had to have conducted CT of the head within 24 hours of presentation and contain a no antithrombotic control group and a clopidogrel monotherapy group. Eight databases were searched from inception to December 2020. Assessment of identified studies against inclusion criteria and data extraction were carried out independently and in duplicate by two authors. Quality assessment and risk of bias (ROB) were assessed using the Newcastle–Ottawa Quality Assessment tool and Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool. Meta-analysis was conducted using a random-effects model and reported as an OR and 95% CI.

Results Seven studies were eligible for inclusion with a total of 21 898 participants that were incorporated into the meta-analysis. Five studies were retrospective. Clopidogrel monotherapy was not significantly associated with an increase in risk of tICH compared with no antithrombotic controls (OR 0.97, 95% CI 0.54 to 1.75). Heterogeneity was high with an I^2 of 75%. Sensitivity analysis produced an I^2 of 21% and did not show a significant association between clopidogrel monotherapy and risk of tICH (OR 1.16, 95% CI 0.87 to 1.55). All studies scored for moderate to serious ROB on categories in the ROBINS-I tool.

Conclusion Included studies were vulnerable to confounding and several were small-scale studies. The results should be interpreted with caution given the ROB identified. This study does not provide statistically significant evidence that clopidogrel monotherapy patients are at increased risk of tICH after head injury compared with no antithrombotic controls.

PROSPERO registration number CRD42020223541.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A systematic review and meta-analysis of antiplatelet agents (as a whole class including dual antiplatelet use) in head injury by van den Brand *et al* demonstrated an increased risk of intracranial haemorrhage associated with these agents. However, the risk for individual agents was not assessed. International guidelines vary in whether they consider antiplatelet therapy a risk factor that should trigger a CT scan of the head.

WHAT THIS STUDY ADDS

⇒ This systematic review and meta-analysis focuses on the antiplatelet agent clopidogrel as a monotherapy and if it increases the risk of traumatic intracranial haemorrhage after head injury. Our study suggests that clopidogrel monotherapy may not increase the risk of traumatic intracranial haemorrhage after head injury.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The finding of this systematic review and meta-analysis are not sufficient to change current practice or policy. More research is required to determine the risk of intracranial haemorrhage post head injury for patients using individual antiplatelet agents especially in those without concurrent indications for CT scanning.

BACKGROUND

Considerable controversy remains regarding the impact of pre-injury treatment with anticoagulation[1] or antiplatelet agents[2] on outcomes after head injury (HI). Current decision-making rules such as the Canadian CT rules[3] and the New Orleans criteria[4] were based on studies excluding those on anticoagulants. The UK's National Institute for Health and Care Excellence (NICE) guidelines[5] consider anticoagulation as an independent risk factor and indication for CT within 8 hours of injury but do not address antiplatelet therapy. Scandinavian guidelines[6] on the other hand do include antiplatelet use as a risk factor. A 2017 systematic review and meta-analysis by van den Brand *et al*[2] demonstrated a statistically significant increased risk of traumatic intracranial haemorrhage (tICH) in patients with mild HI on all forms of antiplatelet therapy but the degree to which individual antiplatelet agents affect risk remains unclear.

The antiplatelet agent clopidogrel is often used as part of dual antiplatelet therapy. Clopidogrel can

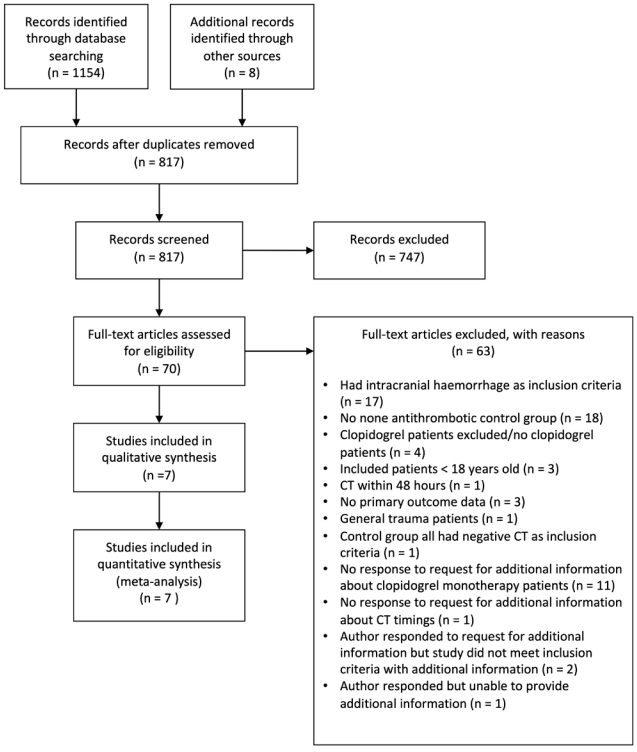

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses chart.

be used as a monotherapy to prevent occlusive vascular events in peripheral arterial disease/multivascular disease or post-myocardial infarction if aspirin cannot be tolerated or is contra-indicated.[7] Clinicians have to decide on the need to scan patients with HI on clopidogrel monotherapy (who do not have other independent indications for CT of the head) in the absence of clear evidence.

The aim of this systematic review was to determine if the rate of CT-proven tICH is higher in patients with HI on clopidogrel monotherapy in the 24-hour period post-presentation compared with patients on no antithrombotic therapy. The secondary aims were to determine if 28-day mortality and the requirement for neurosurgical intervention are higher in patients with HI on clopidogrel monotherapy.

METHOD

Search strategy

Eight databases—Medline (using PubMed), Embase, Web of Science, Google Scholar, Cochrane Central, OpenGrey, SCOPUS and ClinicalTrials.gov—were searched from their inception to 13 December 2020. Details of the search strategy are shown in online supplemental appendix 1. Reference lists from identified studies were searched for studies meeting the inclusion criteria. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[8] was used as the reporting method for this systematic review (figure 1). The review was registered on the PROSPERO register (CRD42020223541).

Inclusion and exclusion criteria

This study included non-randomised studies of the effects of interventions (NRSIs) with human participants aged ≥18 years old who had sustained an HI. NRSIs were selected rather than randomised trials as pre-injury clopidogrel use cannot be randomly assigned. Studies had to have conducted CT of the head within 24 hours of presentation and contain a no anti-thrombotic control group and a clopidogrel monotherapy group. If the clopidogrel monotherapy patients were included in a combined antiplatelet group, the study was included if the clopidogrel monotherapy data could be extracted or if the authors could provide data on being contacted. Any study where it was not possible to extract data for the primary outcome of tICH or obtain this information from the authors was excluded. Studies in which secondary outcomes were not available were included provided primary outcome data were available. Non-English-language studies were excluded.

The primary outcome was tICH on CT of the head within 24 hours of presentation following HI. The secondary outcomes were requirement for neurosurgical intervention and mortality up to 28 days.

Screening and selection

Abstracts of identified studies were assessed independently and in duplicate against the inclusion criteria by two authors (SM and SV). Disagreements were resolved through discussion/consensus with remaining dispute being resolved by the third author (PV). Remaining studies underwent full-text screening independently and in duplicate by SM and SV with disputes resolved through discussion/consensus and unresolved disputes being settled by PV. For studies where full information was not available to allow assessment, attempts were made to contact the authors for additional information.

Data extraction and quality assessment

Data were extracted from the included studies to a pre-prepared Microsoft Excel spreadsheet independently and in duplicate by SM and SV. Quality assessment and risk of bias (ROB) assessment were conducted using the Newcastle–Ottawa Quality Assessment tool (NOS)[9] and Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I)[10] tool, respectively.

Meta-analysis

Synthesis and analysis were conducted using Review Manager (V.5.4) from the Cochrane Collaboration.[11] Pooled OR and 95% CI were calculated using a random-effects model. Heterogeneity was evaluated using I^2 score and risk of publication bias assessed with a funnel plot diagram.

RESULTS

Search strategy

The search of Medline, Embase, Web of Science, Google Scholar, Cochrane Central, OpenGrey, SCOPUS and ClinicalTrials.gov identified 415, 107, 372, 171, 10, 16, 44 and 19 results, respectively. Manual search of reference lists identified eight potentially relevant studies.

After removal of duplicates, 817 studies remained. Screening by title and abstract left 70 studies for full-text assessment. Of these, 48 were excluded based on the full-text assessment and attempts made to contact authors for additional information for 21. One study met all the inclusion criteria without requiring any additional information from the authors. There was no response to our attempts to contact authors of 12 studies, nine replied and the additional information provided revealed that they did not meet our criteria in three studies. This left a total of seven studies[12–18] that were included in our systematic review. Study characteristics are displayed in table 1.

Table 1 Study characteristics

Study	Location	Centre	Study design	Inclusion age (years)	Inclusion GCS	tICH clopidogrel monotherapy group	tICH no antithrombotic group	Neurosurgical intervention clopidogrel monotherapy group	Neurosurgical intervention no antithrombotic group	28-day mortality clopidogrel monotherapy group	28-day mortality no antithrombotic group
Ahmed *et al*[12]	USA	Single centre ▶ Trauma centre	Retrospective cohort study	≥18	3–15	4/7	18/52	–	–	–	–
Dunham *et al*[13]	USA	Single centre ▶ Level 1 trauma centre	Retrospective consecutive study	≥60	3–15	9/18	23/72	–	–	–	–
Fakhry *et al*[14] 2021	USA	Multicentre ▶ 90 hospitals ▶ 46% level 1 and 2 trauma centres	Retrospective cohort study	≥65	3–15	309/1078	3748/13 029	25/1339	354/17 679	29/1339 (in-hospital mortality)	442/17 679 (in-hospital mortality)
Gangavati *et al*[15]	USA	Single centre ▶ Academic teaching hospital	Retrospective cohort study	≥65	–	2/45	18/32	–	–	–	–
Nishijima *et al*[16]	USA	Multicentre ▶ 5× EMS agencies ▶ 1× level 1 trauma centre ▶ 3× level 2 trauma centres ▶ 7× non-trauma centres	Prospective observational study	≥55	3–15	8*/84*	65/713	–	–	–	–
Probst *et al*[17]	USA	Multicentre ▶ 2× level 1 trauma centres ▶ 1× level 2 trauma centre	Prospective observational study	≥18	3–15	3/109	210/5715	1/109	85/5715	–	–
Uccella *et al*[18]	Switzerland	Single centre	Retrospective consecutive study	≥18	15	11*/96*	56/848	–	–	–	–

*Information supplied in correspondence with study authors.
EMS, emergency medical services; tICH, traumatic intracranial haemorrhage.

Table 2 Newcastle–Ottawa scores

Study	Selection				Comparability		Outcome			
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Study controls for most important factor	Study controls for additional factors	Assessment of outcome	Was follow-up long enough for outcome to occur?	Adequacy of follow-up of cohorts	Total score
Ahmed *et al*[12]	★	★	★	–	★	★	★	★	★	8/9
Dunham *et al*[13]	★	★	★	–	★	★	★	★	★	8/9
Fakhry *et al* 2020	★	★	★	–	★	★	★	★	★	8/9
Gangavati *et al*[15]	★	★	★	–	★	–	★	★	★	7/9
Nishijima *et al*[16]	★	★	★	–	★	★	★	★	★	8/9
Probst *et al*[17]	★	★	★	–	★	★	★	★	★	8/9
Uccella *et al*[18]	★	★	★	–	★	★	★	★	★	8/9

Quality assessment

Quality of included studies and ROB were assessed using NOS and ROBINS-I (tables 2 and 3). All studies scored highly on the three domains of the NOS due to the strict inclusion criteria used for this systematic review. All studies contained cohorts representative of patients with HI in the general population (on either clopidogrel monotherapy or no antithrombotic medication). Follow-up time (CT within 24 hours of presentation), adequacy of follow-up and assessment of outcome (via CT report/medical records) were also high quality in all studies. None of the included studies could objectively measure compliance with clopidogrel therapy.

ROB/limitations of included studies

There is considerable ROB due to confounding in all included studies.[12–18] All clopidogrel monotherapy patients would have comorbidities requiring clopidogrel use. It is unclear if these comorbidities influence outcome or risk of falls. Patients on antiplatelets were generally older than those on no antithrombotic medication.[14 16 17] No study had a particularly robust method of adjusting for age or comorbidities. Probst *et al*[17] found that the median age of their clopidogrel monotherapy group was 81.3 years old while the median of all their participants was 54.8 years old. Rates of tICH are generally higher in older patients post-HI.[19 20] However, this confounding would likely favour the no antithrombotic group and is not reflected in the individual results of the majority of the included studies.

There is substantial clinical heterogeneity between the identified studies in terms of included participants and mechanism of injury. Three studies[12 14 15] included only patients injured in ground level falls/falls from standing. One study[13] included both falls from standing and road traffic collisions. Two studies[17 18] included all patients with blunt HI and the remaining study included all patients with HI.[16] The inclusion age of patients varied between studies. Three[12 17 18] included patients ≥18 years old, one[16] ≥55 years old, one[13] ≥60 years old and two[14 15] ≥65 years old. Uccella *et al*[18] only included patients with a GCS of 15 with the remaining studies[12–14 16 17] including patients with GCS ranging from 3 to 15 (with the exception of Gangavati *et al*[15] where it is not clear which GCS scores were included). The interpretation of CT scans and criteria defining a positive CT result was relatively consistent across all studies.

In terms of methodological variation, the heterogeneity is less substantial. This is due to the narrow inclusion criteria of this systematic review and is demonstrated by the narrow range of scoring on the NOS tool. Most of the studies were retrospective studies[12–15 18] with the exception of two prospective studies[16 17] but they were otherwise very similar in terms of method.

All included studies had conflict of interest statements and disclosed sources of funding (when received). Two authors of the Dunham *et al*[13] study declared potential conflicts of interest. The first was employed by a pharmaceutical company and had worked for a medical technology company and the second author was on the advisory board of two pharmaceutical companies. The lead author of the Nishijima *et al*[16] study declared that they reported for a pharmaceutical company in an unpaid role. A funnel plot demonstrated minor asymmetry and did not provide evidence of publication bias (figure 2).

The majority of the studies identified were not primarily designed to compare rate of tICH in clopidogrel monotherapy patients versus no antithrombotic patients. Additionally, five[12–15 18] of the studies were retrospective studies and suffered from the limitations of this study type. Of the retrospective

Table 3 ROBINS-I score

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in the selection of the reported results	Overall bias
Ahmed *et al*[12]	Moderate	Low	Low	Moderate	?	Moderate	Moderate	Moderate
Dunham *et al*[13]	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Fakhry *et al* 2020	Serious	Low	Low	Moderate	Moderate	Moderate	Low	Moderate
Gangavati *et al*[15]	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Nishijima *et al*[16]	Serious	Low	Low	Moderate	Moderate	Moderate	Low	Moderate
Probst *et al*[17]	Serious	Low	Low	Moderate	Moderate	Low	Moderate	Moderate
Uccella *et al*[18]	Moderate	Low	Low	Low	Low	Moderate	Moderate	Low

ROBINS-I, Risk Of Bias In Non-randomised Studies of Interventions.

studies identified in this systematic review, the majority included patients from trauma registries[12–14] which are unlikely to include all patients with HI because patients presenting with less severe injuries may not be recorded in these registries. These patients may be at lower risk of tICH so these studies have the potential to overestimate the rate of tICH.

It is not possible to determine how many of the included patients would have had concurrent indicators to undergo CT scan of the head within current guidelines. The range of included patients' GCS across all studies was 3–15.[12–18] The Canadian CT of the head rules,[3] NICE guidelines[5] and the New Orleans criteria[4] would have identified many of these patients as requiring a CT of the head due to reduced GCS. Only Uccella *et al*[18] assessed patients solely with a GCS of 15. This study did find a statistically significant difference in rate of tICH in patients on all forms of antiplatelet therapy (including dual antiplatelet therapy) versus the general population and concluded that in mild traumatic brain injury, all patients on antiplatelet medication should have a CT of the head. This study did not originally look at clopidogrel monotherapy but the lead author did respond to a request to provide their data for patients on clopidogrel monotherapy. The OR calculated from this data for risk of tICH in clopidogrel monotherapy patient versus no antithrombotic use is 1.83 with a 95% CI of 0.92 to 3.63 (this has been included in the meta-analysis below). Patients with a GCS of 15 were included in the Uccella *et al*[18] study if they had witnessed loss of consciousness, disorientation or amnesia which would have been an indication for many of them to undergo CT of the head under current guidelines regardless of antithrombotic status.[3–5]

Four studies[13 15–17] clearly stated that the decision to conduct CT of the head was at the clinician's discretion. This may have introduced a degree of selection bias by not including all patients with HI. Three studies[15–17] made attempts to address this. Nishijima *et al*[16] conducted an enrolment audit and found that only 49% of eligible patients were enrolled in their study. Gangavati *et al*[15] conducted a convenience sample which showed 93.5% of eligible patients received a CT scan and Probst *et al*[17] carried out follow-up interviews at 3 months with 368 consecutive patients who had not received CT of the head and found none of these patients had any missed intracranial injury.

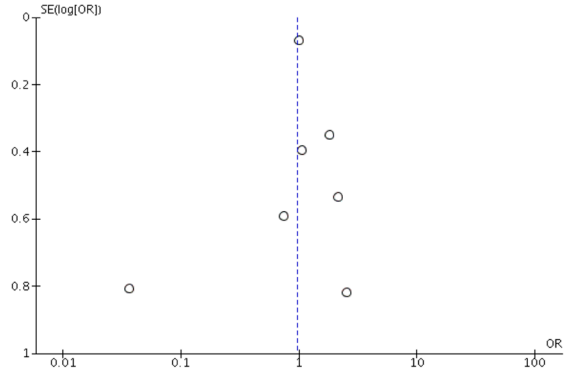

Figure 2 Funnel plot.

Meta-analysis

The pooled results for the seven studies[12–18] identified included 1437 patients on clopidogrel monotherapy and 20461 controls not on antithrombotics. The pooled OR for risk of tICH for clopidogrel monotherapy versus no antithrombotic agents was 0.97 (95% CI 0.54 to 1.75). The forest plot for the individual studies shows the CIs for the ORs bridging 1, with the exception of Gangavati *et al*[15] which showed a significantly lower risk of bleeding for those on clopidogrel. The I^2 for the analysis is 75%, showing high statistical heterogeneity. A sensitivity analysis excluding the Gangavati *et al*[15] study included 1392 patients on clopidogrel monotherapy and 20429 controls not on antithrombotics. The I^2 was lower at 21% with a non-significant OR (OR 1.16, 95% CI 0.87 to 1.55, p=0.31).

It was not possible to extract secondary outcome data from the majority of the included studies. Two studies[14 17] provided secondary outcome data (in a format that could be used) for the requirement for neurosurgical intervention and only one[14] reported mortality in a format where the mortality rate in clopidogrel monotherapy patients could be determined. The study reporting mortality in a format where the rate in clopidogrel monotherapy patients could be determined reported on in-hospital mortality. Pooled analysis of the two studies that provided data on requirement for neurosurgical intervention gave an OR of 0.92 (95% CI 0.61 to 1.37, p=0.67, I^2=0%). Figure 3 shows forest plots for the pooled results.

DISCUSSION

The results of this study do not demonstrate a statistically significant difference between rates of tICH between patients on clopidogrel monotherapy and those on no antithrombotic medication within 24 hours of presentation after HI. This result is consistent after sensitivity analysis which removed the Gangavati *et al*[15] study to reduce statistical heterogeneity. The limited pooled result about rates of neurosurgical intervention does not show any difference between clopidogrel monotherapy and no antithrombotic medication groups. There was not sufficient information to provide pooled results for mortality. These results

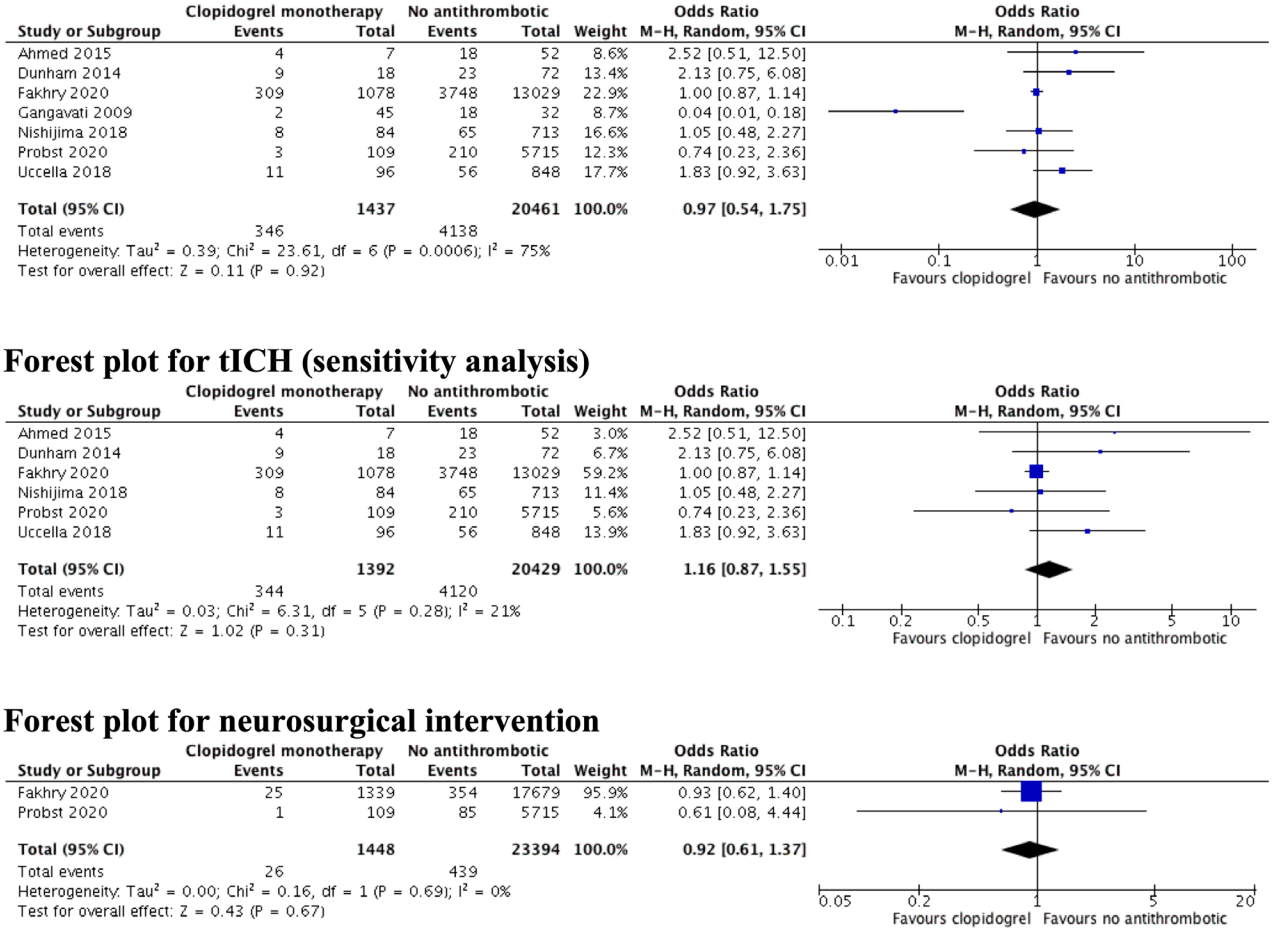

Figure 3 Forrest plots. tICH, traumatic intracranial haemorrhage.

should be interpreted with caution due to the limitations of included studies and the considerable variation in patient characteristics. Most of the included studies have small sample sizes and the quality of included studies was variable. The included studies were primarily designed to investigate anticoagulation or antiplatelet use (as a whole class) in HI and data about clopidogrel monotherapy have been either described as a subgroup or obtained through correspondence with the authors.

The role of antiplatelet agents in tICH post-HI is controversial. A number of studies (that did not meet the inclusion criteria for this systematic review and meta-analysis) have found a statistically significant increase in the rate of tICH in patients using antiplatelet drugs.[21–25] Van den Brand *et al*[2] found that antiplatelet use did increase risk of tICH. The difference between our review results and the van den Brand *et al*[2] results may be due to that research including patients on all forms of antiplatelet therapy rather than investigation of a single antiplatelet agent. There are several studies looking at differences in outcome or mortality in pre-injury antiplatelet patients that do not show any significant difference compared with no antithrombotic controls (again not meeting our inclusion criteria). Grandhi *et al*[26] found that antiplatelet agents did not influence neurosurgical intervention rates or mortality in patients ≥65 years old after closed HI. A 2021 retrospective study of 844 neurointensive care patients in Sweden[27] did not show an association between antiplatelet use and mortality or poor outcomes after multiple regression analysis. In terms of studies included in this systematic review, Gangavati *et al*[15] found a reduced rate of tICH in patients on pre-injury clopidogrel and as there is not a biologically plausible mechanism for this the difference is likely due to confounding or bias that cannot be identified from the published information. Gangavati *et al*[15] also found lower rates of tICH in patients taking pre-injury aspirin and they suggested that patients on pre-injury antiplatelet medication were more likely to present post-minor HI and receive a negative CT scan thus reducing the incidence rate in those groups.

Limitations

There are several limitations to this systematic review. The inclusion of only NRSI increases the risk of confounding and selection bias. This was unavoidable due to it not being possible to randomise pre-injury clopidogrel use. This systematic review also had strict inclusion criteria in terms of only including patients aged ≥18 years old and with CT performed within 24 hours of presentation. This limited the number of included studies. During the search, four potentially relevant studies were identified that might have strengthened our results but were slightly outside of our inclusion criteria. Three of these[21 22 28] included patients with ages just outside our inclusion criteria (≥14 and

≥16 years old), and one[29] included patients who had CT of the head within 48 hours of presentation. The decision to limit included studies to those conducting CT of the head within 24 hours of presentation was made based on this being the time used in a similar systematic review looking at antiplatelet use as a whole (rather than clopidogrel monotherapy) by van den Brand *et al*[2] so that our results were directly comparable. The results of some studies that may have met the inclusion criteria may be absent due to unsuccessful attempts to contact the authors or those authors not responding. This systematic review was also limited in that it only included English-language studies.

This systematic review's primary aim was to identify if clopidogrel was a risk factor for tICH; however, in reality, outcomes such as need for neurosurgical intervention, complications and mortality are all more important measures of outcome. Only two studies[14 17] reported neurosurgical intervention in a format that could be used. Only one study[14] reported mortality in a format that could be used (in-hospital mortality). Due to the limited data identified by the systematic review, it has not been able to draw any firm conclusions about whether clopidogrel use increases risk of neurosurgical intervention or mortality.

CONCLUSION

This systematic review and meta-analysis does not provide statistically significant evidence that clopidogrel use is associated with tICH or that it should be an independent indication for CT of the head in adult patients on initial presentation post-HI. The results are limited by the quality of included studies and should be interpreted with caution. Based on the results, we cannot recommend any changes to current practice. There is a need for specific prospective research into the incidence rate of tICH in patients with HI with pre-injury clopidogrel use and a GCS of 15 without other criteria for CT of the head in order to inform guidelines.

Contributors SM designed and led this systematic review and meta-analysis and carried out the search, data extraction, data analysis and wrote the paper. SV conducted independent duplicate assessment of the identified studies against the inclusion criteria and independently duplicated data extraction. PV was project supervisor for this systematic review and meta-analysis. SM is the guarantor for this paper and accepts full responsibility for the conduct of the study.

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