The effect of platelet transfusion in patients with traumatic brain injury and concomitant antiplatelet use: a systematic review and meta-analysis

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The prescription of oral antiplatelet agents has increased over recent years in response to an aging population and the rising prevalence of cardiovascular diseases. Fifty percent of adults aged over 75 years in the United Kingdom report taking antiplatelet agents.1,2 These agents are frequently prescribed for primary prophylaxis and risk reduction in cardiovascular and cerebrovascular diseases. Antiplatelet medications, or platelet aggregation inhibitors, primarily act through the inhibition of platelet activation pathways, thereby reducing platelet aggregation and subsequently clot formation. Aspirin and clopidogrel are the two most commonly prescribed antiplatelet medications.3 While these medications have proven benefits with respect to the prevention of thromboembolic events within appropriate indications, their use may result in worsening or inhibiting clot formation and platelet aggregation in the setting of trauma, in particular in traumatic brain injury (TBI) with complicating intracerebral hemorrhage (ICH).

Several studies have investigated the effects of antiplatelet therapy on mortality, hospital length of stay, and hemorrhage progression in patients with TBI with varying results. Farsi et al.4 demonstrated a higher risk of mortality at 30 days after TBI if concomitant antiplatelet therapy pre-existed, as well as prolonged hospitalization. However, a systematic review by Batchelor and Grayson5 reported that a higher mortality risk existed only for TBI patients over 65 years of age with antiplatelet premedication. This is corroborated by Stead et al.,6 who showed in a cohort of 2246 TBI patients that preceding antiplatelet and anticoagulant therapy was present in older patients and associated with higher 3-month mortality, more frequent readmissions to hospital within 30 days, and a greater need for neurosurgical interventions.

Exogenous administration of functional platelets via platelet concentrate transfusion is considered a therapeutic means to replace affected platelets.7 It is not clear whether platelet transfusions effectively reduce bleeding risk in these patients or whether there is a mortality benefit from the intervention. Previously published studies suggest there is often no benefit to administering platelet transfusions and there may be transfusion-related harms. In this systematic review and meta-analysis, we aimed to investigate the impact of platelet transfusion on mortality in patients with TBI and preinjury antiplatelet therapy compared to control TBI cases and to clarify whether there is a reasonable indication for providing this costly, supply-limited, and potentially harmful treatment.

METHODS

Search strategy
We identified relevant studies by searching Ovid MEDLINE (1946 to July 30, 2018) and Ovid EMBASE (1980 to July 30, 2018) with a repeat search on January 30, 2019. The search was conducted in accordance with the 2015 PRISMA statement8 (see Appendix S1, available as supporting information in the online version of this paper). We combined the concepts "traumatic brain injury" and "platelet transfusion" using AND to link concepts and OR to link synonyms. We reviewed titles and abstracts to identify relevant manuscripts, and then obtained full texts and evaluated their appropriateness for

ABBREVIATIONS: ICH = intracranial hemorrhage; TBI = traumatic brain injury; TEG-PM = thromboelastography platelet mapping.

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inclusion. Additional articles were identified by reading reference lists of pertinent manuscripts and reviewing significant studies. For one study, we contacted the lead author and requested additional information. The reviewers established the described plan for the search strategy, study selection, and bias assessment before commencing the review. The authors adhered to the AMSTAR quality criteria where possible.9

Study selection was performed by two independent reviewers. Disagreements around whether to include a study were resolved by a third senior reviewer. The search strategy used is available in Appendix S2, available as supporting information in the online version of this paper.

Study selection
Manuscripts were assessed based on the study type, population characteristics, and intervention being investigated. Included studies:

- were randomized controlled trials or cohort studies;
- included adult patients on preinjury antiplatelet agents (aspirin, clopidogrel, or prasugrel) with or without preinjury anticoagulant agents (warfarin, heparin) who had sustained a head injury resulting in TBI;
- included patients who had received a computed tomography scan of the brain to diagnose ICH;
- had a study group that included patients who were transfused at least one unit of platelets, while the control group patients were not given a platelet transfusion; and
- compared the outcome of mortality between the study and control groups.

The primary outcome of interest was mortality. We included studies that compared in-hospital or 28-day mortality in patients who had received a platelet transfusion with patients who had not.

We assessed the risk of bias with the Newcastle-Ottawa Tool for assessing the quality of cohort studies, which is available in Appendix S2, available as supporting information in the online version of this paper. Studies of sufficiently high quality and with sufficiently low risk of bias were included in the systematic review. Only studies published in English were included.

Fig. 1. Study inclusion and exclusion process. Diagram demonstrating the inclusion and exclusion process for this systematic review. Articles written in languages other than English (non-English), articles involving animal models (non-human), and articles not pertaining to the review question (not relevant) were excluded during title/abstract screening. Articles that investigated an exposure other than platelet transfusion (wrong exposure) or an outcome other than mortality (wrong outcome), or studies that used a study design other than randomized controlled trial or cohort study (wrong study design), were excluded during full-text screening.
Statistical analysis
We performed a meta-analysis for pooled odds ratios (ORs). We calculated 95% confidence intervals (CIs) for all the summary risk ratios (RRs). We calculated inverse-variance random effects meta-analyses using the modified Hartung-Knapp method and the Paule-Mandel between-study heterogeneity estimator. Statistical heterogeneity was quantified with $I^2$. Because we observed heterogeneity, we calculated 95% prediction intervals. We performed the analysis with the R package metan.11

RESULTS
A total of 10 manuscripts were identified that met the defined inclusion criteria.12–21 Figure 1 shows the process of inclusion and exclusion of the study. Eight manuscripts described retrospective studies, and two described prospective cohort studies. Seven studies investigated traumatic ICH in patients on aspirin or P2Y12 inhibitors (clopidogrel, ticagrelor, or prasugrel). Two of the seven included patients with concomitant warfarin use.12,20 One study investigated patients only on aspirin; one study investigated patients only on P2Y12 inhibitors; and one study investigated patients on aspirin, clopidogrel, or warfarin. The latter study included 30 patients who received only warfarin and no antiplatelet agents, who we were unable to isolate.13 A total of 1368 cases from 14 hospitals (12 Level 1 trauma centers and two Level 2 trauma centers) were analyzed in the included studies, and 529 (39%) of these cases were transfused with at least one unit of platelet concentrates.

Table 1 shows the results of the Newcastle-Ottawa Tool for assessing the quality of cohort studies for each of the studies. Eight of the studies were judged to be of good quality, while two were of fair quality. Two studies, Jehan et al.17 and Lee et al.18 received full marks.

Key information about each included study is given in Table 2. The sample size of studies ranged from 66 (with 23 transfused) to 328 (with 166 transfused), and the mean sample size was 137 with 53 transfused. Four studies included only patients aged 50 years or older, one study included only patients aged 65 years or older, four studies included all adult patients, and one study included patients aged 15 years or older. The mean age of patients ranged from 55.5 years to 78.3 years. Eight of the studies required computed tomography confirmation or diagnosis of ICH for inclusion. All studies required documented preinjury use of antiplatelet or anticoagulant agents. In most of the included studies, the control and study groups were similar in demographics. Notable exceptions are shown in Table 3. Two studies reported the mean number of platelet units transfused; in Holzmacher’s transfused cohort, the average number of units was 1.2 ± 0.39; and in Washington’s, the average was 1.1 ± 0.9.

The route by which the decision was made to administer platelet concentrates was inconsistent among studies. In three of the studies, the decision was based on a predefined laboratory test result: Downey et al.12 used a platelet function analyzer (PFA-100, Dade-Behring, Miami, FL); Guillotte et al.14 used adenosine diphosphate inhibition on thromboelastography platelet mapping; and Lindblad et al.19 used multiple electrode aggregometry to guide platelet transfusion. In all other studies, the decision was at the physician’s or surgeon’s discretion. An outcome of interest in each study was mortality: in six studies, the mortality rate was assessed on hospital discharge (i.e., in-hospital mortality), in one study, mortality at 12 months was used; and in three studies, the time point was not specified. Several studies recorded other sequelae as primary or secondary outcomes, including hospital or intensive care unit length of stay, need for neurosurgical intervention, change in laboratory parameters, or ICH progression on follow-up computed tomography.

Among the included studies in this review, the mortality in patients transfused with platelet concentrates ranged between 4.5% and 41.7% (mean, 18.4%), and the mortality in non-transfused patients ranged between 0.0% and 21.7% (mean, 11.2%). Three of the 10 studies displayed a statistically significant (p < 0.05) difference in mortality for the cohorts included. Figure 2 shows a forest plot demonstrating the comparison and meta-analysis of included studies. The pooled RR indicated a higher mortality with the use of platelet transfusion (RR, 1.50; 95% CI, 0.93-2.42; $I^2$, 43%; prediction interval, 0.49-4.58).

### Table 1. Newcastle-Ottawa bias assessment for cohort studies

|                | Selection | Comparability | Outcome | Quality |
|----------------|-----------|---------------|---------|---------|
| Downey 2009    | ****      | *             | **      | Good    |
| Fortuna 2008   | ****      | *             | **      | Fair    |
| Guillotte 2018 | ****      | **            | **      | Good    |
| Holzmacher 2017| ****      | *             | **      | Good    |
| Ivascu 2008    | ***       | **            | **      | Good    |
| Jehan 2019     | ****      | **            | **      | Good    |
| Lee 2017       | **        | ***           | Good    |         |
| Lindblad 2018  | *         | **            | Good    |         |
| Ohm 2005       | **        | *             |        | Fair    |
| Washington 2011| ****      | *             | **      | Good    |

A point is awarded for each criterion of the assessment tool which is met. The maximum overall score, as set out in the score template, is 9, with a possible 4 stars for selection, 2 for comparability, and 3 for outcome.
| Author, date | Study design | Patient groups | Key results | Study weaknesses |
|--------------|--------------|----------------|-------------|------------------|
| Downey et al., 2009 | Retrospective database review of two Level 1 trauma centers (MVH and UC). | 328 patients aged >50 years old with CT-confirmed traumatic ICH treated between January 1, 2003 and December 31, 2006, with documented preinjury aspirin or clopidogrel use. | Mortality rate was insignificantly higher for transfused patients (29/166; 17.5%) versus non-transfused patients (27/162, 16.7%; p = 0.85). Hospital length of stay was insignificantly longer: 7.5 ± 8.7 days versus 6.4 ± 7.6 days (p = 0.22). | MVH transfused patients who had laboratory platelet dysfunction, while UC transfused based on clinical impression. 27 patients were taking warfarin as well, and warfarin users had a higher mortality. The timing of platelet administration was not standardized. |
| Fortuna et al., 2008 | Retrospective registry review at one trauma center. | 166 patients aged ≥50 years old diagnosed with TBI and hemorrhagic brain injury admitted between January 2003 and October 2006. Patients were on clopidogrel, aspirin, warfarin, or heparin at the time of injury. | Mortality rate was significantly higher for transfused patients (20/66, 30%) versus non-transfused patients (16/100, 16%; p = 0.01). Hospital length of stay was significantly longer for transfused patients: 12 ± 2 days versus 7 ± 0.4 days; p = 0.007. | The primary aim of the study was to investigate the impact of age and anticoagulant use on TBI. Patients who were transfused were older, more severely injured, and had a lower initial GCS. The decision to transfuse was on a case-by-case rather than per-protocol basis. |
| Guillote et al., 2018 | Prospective single-center observational study | 80 patients aged ≥18 years old presenting with history of blunt head trauma and CT evidence of TBI on preinjury aspirin or clopidogrel. | Mortality rate was significantly higher for transfused patients (3/16, 16%) versus non-transfused patients (1/61, 2%; p = 0.04). Hospital length of stay was longer for transfused patients (12.6 vs. 8.0) days for non-transfused. More transfused patients received neurosurgical intervention (5/19, 26%) compared with non-transfused patients (4/61, 7%; p = 0.15). | The primary aim of the study was to characterize platelet dysfunction; mortality was a secondary outcome. The study was performed at a single center, on a small cohort of transfused patients. Cohorts were very similar, and the decision to transfuse platelets was based on protocol. |
| Holzmacher et al., 2017 | Retrospective multcenter (six centers) cohort study | 66 adult patients who had a radiographically evident blunt TBI and were on preinjury aspirin or clopidogrel between January 8, 2015, and December 31, 2016, and underwent TEG-PM testing. | Mortality rate was insignificantly higher in transfused patients (2/23, 8.7%) than in non-transfused patients (1/32, 3.2%; p = 0.28). Transfused patients had a longer hospital length of stay (7.8 ± 4.8 vs. 3.5 ± 2.8 days; p < 0.01), a longer ICU length of stay (3.9 ± 2.6 vs. 0.7 ± 1.1; p < 0.01) and higher proportion of craniotomy/craniectomy (26.1% vs 0%; p < 0.01). In ISS ≥15, transfused patients had 9.1% mortality versus 4.2% in non-transfused (p = 0.50). | Mortality was not the main outcome in this study. The study cohort and mortality rate were small. Although an attempt was made to stratify results by major injury only, no other confounders were controlled for. There was significant variability between protocols for transfusion of platelets between centers, the result of which was that the proportion of transfused patients was vastly different between centers. Injury severity was higher in transfused patients. |
| Ivascu et al., 2008 | Retrospective review of the William Beaumont Hospital trauma registry | 109 patients with CT-confirmed ICH who were taking aspirin, clopidogrel, or both before injury between August 1999 and November 2004. | Mortality rate was insignificantly higher in transfused patients (11/40, 28%) than in non-transfused patients (9/69, 13%; p = 0.064). More transfused patients were taken to theater (9/40 vs. 8/69; p = 0.137). | Retrospective study. Platelet transfusions were administered at the discretion of the physician. GCS and hemorrhage severity predicted mortality independent of platelets. |
| Author, date       | Study design                  | Patient groups                                                                 | Key results                                                                                                                                        | Study weaknesses                                                                                                     |
|-------------------|-------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Jehan et al., 2019 | Prospective database review of one Level 1 trauma center (University of Arizona) | 243 patients aged ≥18 years old who were admitted between 2013 and 2016 with TBI and ICH and were taking P2Y12 inhibitors (clopidogrel, ticagrelor or prasugrel) before injury. | Mortality rate was insignificantly lower in non-transfused patients (25/179, 14%) than in transfused patients (5/64, 8%; p = 0.26). OR of mortality was 0.85; p = 0.04. Hemorrhage progression was more common in non-transfused patients (64% vs. 23%; OR = 0.68; p < 0.01). | Retrospective, thus no randomization. Administration of platelets was based on physician's discretion. Only P2Y12 inhibitors; no aspirin or anticoagulants. Mortality was not the primary outcome. |
| Lee et al., 2017   | Retrospective database review of one Level 1 trauma center (Harborview Medical Center). | 171 patients aged ≥65 years old who required emergency neurosurgery for traumatic ICH and were on preinjury aspirin between January 1, 2008, and December 31, 2012. | Mortality rate was insignificantly higher in transfused patients (4/38, 10.5%) than in non-transfused patients (5/49, 10.2%; p = 0.73). Transfused patients had an insignificantly longer hospital length of stay (12 days vs. 9 days; p = 0.25), a longer ICU length of stay (10 vs. 7 days; p = 0.28). | Mortality was not the main outcome in this study. Few patients were transfused platelets. The decision to transfuse platelets preoperatively was made by the neurosurgeons. Only patients requiring neurosurgery were included. |
| Lindblad et al., 2018 | Retrospective observational study at Karolinska University Hospital | 91 patients ≥15 years old who had been admitted to the ICU with a traumatic intracranial lesion and were on preinjury aspirin or clopidogrel between February 2010 and May 2014. | Mortality rate (12 months GOSE = 1) was insignificantly lower in patients who were transfused with platelets (9/45, 20%) than in patients who were not transfused (10/46, 22%; p = 0.84). | Retrospective review with small sample size. Assessing effect of platelet transfusion in patients on antiplatelet agents was not the primary aim of the study. |
| Ohm et al., 2005   | Retrospective chart review at a Level 1 trauma center (William Beaumont Hospital) | 90 patients >50 years with a diagnosis of ICH and concomitant use of aspirin, clopidogrel, or both (+/- warfarin) treated between January 1, 1999, and December 31, 2002. | Mortality was significantly higher in patients who were transfused with platelets (10/24, 42%) than patients who were not transfused (14/69, 20%; p = 0.013). | A small number of patients received platelets. There was no protocol in place regarding platelet administration. This study's main focus was not on assessing effects of platelet transfusion. |
| Washington et al., 2011 | Retrospective review at a Level 1 trauma center (Washington University School of Medicine) | 108 patients with GCS ≥13 and history of isolated head injury and CT-confirmed ICH and on preinjury aspirin or clopidogrel between January 2007 and December 2008. | 2 (5%) patients died following platelet transfusion while no patients in the non-transfused group died (p = 0.16). Two transfused patients required neurosurgical intervention while no non-transfused patients did (p = 0.16). | Retrospective review. There was no protocol guiding platelet transfusion. Only patients with mild TBI were included, hence lower overall mortality than the other studies. |

CT = computed tomography; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale Extended; ICH = intracranial hemorrhage; ICU = intensive care unit; ISS = injury severity scale; OR = odds ratio; TBI = traumatic brain injury; TEG-PM = thromboelastography platelet mapping.
We summarized the body of evidence pertaining to the impact of platelet transfusion on mortality in TBI patients with pre-injury antiplatelet medication. Of the studies identified and analyzed in this systematic review, none showed a statistically significant benefit of platelet transfusion on mortality, although the included studies were all small in size, with cohorts ranging from 66 to 328 patients. Notably, three studies showed significant evidence of harm. The present meta-analysis shows an insignificant trend favoring no transfusion.

The transfusion of platelet concentrates in TBI patients on preinjury antiplatelet agents reflects a pathophysiology-based rather than an evidence-based approach for emergency reversal. A systematic review published in 2009 on the management of prehospital antiplatelet and anticoagulant therapy in TBI indicated three possible options for the reversal of antiplatelet therapy: 1) platelet transfusion, 2) desmopressin, or 3) recombinant factor VIIa. For desmopressin, there is a lack of consistent evidence as a monotherapy or adjunct to other coagulation-targeted treatments. A retrospective observational study of 4284 patients with TBI, of whom 129 received recombinant factor VIIa, showed no difference in mortality between the study groups.

A randomized controlled trial published in 2016 demonstrated increased mortality rates among platelet-transfused patients who were receiving antiplatelet therapy and had a spontaneous ICH (adjusted OR, 2.05; 95% CI, 1.18–3.56; p = 0.0114). We were unable to identify evidence of an equal standard pertaining to traumatic ICH. A major limitation of this systematic review is the reliance on retrospective observational data, the lack of randomization and hence the absence of controlling for confounding factors. Matching of study and control cases with regard to their vital signs, injury severity, and medications would increase the reliability of results.

Systematic reviews on the topic of platelet transfusion in TBI were performed previously. However, the present study reflects, to our knowledge, the largest in size to date and includes several studies that have not been included previously in systematic reviews. Nishijima et al. found too much heterogeneity between studies to produce a meta-analysis, but the mortality RR for platelet transfusion ranged from 0.21 (95% CI, 0.05–0.95) to 2.42 (95% CI, 1.18–4.96). Batchelor et al. produced a pooled OR for survival of 0.773 (95% CI, 0.414–1.442) from four studies insignificantly favoring no transfusion.

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**DISCUSSION**

**TABLE 3. Notable differences between study and control groups in included studies**

| Author     | Variable     | Study group | Control group | p value |
|------------|--------------|-------------|---------------|---------|
| Downey     | Age          | 77.4        | 73.0          | <0.001  |
|            | Clopidogrel use | 47.8%      | 27.9%         | 0.038   |
| Fortuna    | ISS          | 28 ± 1      | 24 ± 1        | 0.001   |
|            | Initial GCS  | 11 ± 1      | 13 ± 0.2      | 0.007   |
| Holzmacher | ISS          | 23.4 ± 9.4  | 17.4 ± 10.44  | 0.02    |
| Jehan      | Emergency SBP| 105 ± 21    | 115 ± 12      | <0.01   |
| Lindblad   | ISS          | 26.2 ± 12.6 | 20.5 ± 8.33   |         |

Values given as mean ± standard deviation.

GCS = Glasgow Coma Scale; ISS = injury severity scale; SBP = systolic blood pressure.

**Fig. 2. Forest plot and meta-analysis of included studies.** [Color figure can be viewed at wileyonlinelibrary.com]
Leong et al.\textsuperscript{26} produced a pooled OR for in-hospital mortality among four studies of 1.77 (95% CI, 1.00-3.13). Despite the insignificant result of the present study, it adds to the concerns around administering platelet transfusions to TBI patients on preinjury antiplatelet agents.

The most recent study discussed in the present review was published by Jehan et al.\textsuperscript{17} Although this was a retrospective observational study, the study and the control groups were well matched for demographics. The authors also performed a multivariate regression analysis to reduce confounding, with the result being an OR of 0.85 (95% CI, 0.4-0.9; \(p = 0.04\)) for mortality in patients transfused with platelet concentrates. The same study also reported improved rates of neurosurgical intervention and hemorrhage progression in transfused patients. These results differ from most previous studies, as more effort has been undertaken to reduce bias where possible.

A higher degree of clarity for indication, timing, and dosing of platelet transfusion would increase the comparability of studies. Due to the lack of clear evidence surrounding emergency antiplatelet reversal, the decision of whether to administer platelet concentrates to TBI patients on preinjury antiplatelet agents was often at the treating physicians’ discretion. This could have led to significant selection bias, with the sicker patients being more likely to receive a transfusion or, alternatively, patients more likely to recover being preferentially administered platelet transfusions. The development and implementation of clinical practice guidelines or randomization may serve as an approach to overcome this problem.

The role of assessing platelet function and subsequently administering platelet concentrates only in the presence of proven platelet dysfunction is not yet known. None of the studies included in this review and meta-analysis has investigated if preinjury antiplatelet therapy included single, dual, or even triple platelet inhibition strategies, which may have affected the individual response to platelet transfusion. Under some circumstances, metabolites from antiplatelet agents may display prolonged activity and thereby may partially inactivate newly transfused platelets as well.\textsuperscript{30} Even in the absence of preinjury antiplatelet medication, there may be soluble plasma species that downregulate endogenous or transfused platelets in the context of trauma.\textsuperscript{29} The spiking experiments by Verni and coworkers have demonstrated an inhibitory effect of plasma from trauma patients on washed healthy platelets through a significant reduction in calcium mobilization. Platelets stored for transfusion may also perform less effectively than native platelets due to the development of “platelet storage lesions.”\textsuperscript{30} If platelets are stored, they can undergo a time-dependent degradation of function that mimics platelet activation and subsequent exhaustion with the deterioration of mitochondrial respiration and function with 2 days of storage.\textsuperscript{30–33}

Three of the included studies measured platelet function with diagnostic devices (multiple electrode aggregometry, PFA-100, and thromboelastography platelet mapping) and used results to guide the administration of platelet transfusion.\textsuperscript{12,14,19} More consistent use of these tests would increase comparability of studies and reduce selection bias; however, the technology is not available everywhere, and implementation is not presently feasible.

Among the included studies, there was also inconsistency in the timing of measurement of the outcome. The utility of measuring outcome at 12 months in this group of patients is difficult to judge, as it provides a more thorough assessment of long-term consequences; however, it may capture outcomes that are unrelated to the ICH. There are also likely to be more patients lost to follow-up over a 12-month period than a 28-day or in-hospital period.\textsuperscript{34} This particular inconsistency may be attributable to the fact that investigating the effect on mortality of platelet transfusions was not the primary aim of several of the included studies. Thirty patients were included who were not taking antiplatelet agents at all. This is a limitation of this study; however, the proportion of the overall cohort (2.8%) is decidedly small, and we agreed that the overall benefit of including the study outweighed this.

Finally, as with all blood products, there also may be harmful effects associated with the transfusion of platelet concentrates. Platelets are collected from a single donor, in a 1- to 2-hour procedure, or pooled from whole blood donations by multiple donors.\textsuperscript{35} Platelet concentrate units contain small numbers of white blood cells, plasma, and red blood cells. This translates into a risk of transfusion reactions including allergic reactions, transfusion-related acute lung injury, transfusion-associated graft-versus-host disease, Rh alloimmunization, and bacterial infection.\textsuperscript{21,36,37} Platelet transfusions carry greater risks of infection, sepsis, and death than any other blood product, owing primarily to bacterial contamination.\textsuperscript{37} The risks of bacterial contamination of platelets and transfusion-transmitted infections have been mitigated significantly, but not eliminated, by improvements in prevention and detection strategies. Between 1 in 1000 and 1 in 2500 platelet units are still bacterially contaminated.\textsuperscript{38}

**CONCLUSION**

This systematic review demonstrates a lack of clear evidence of mortality benefit of platelet transfusion in patients who sustain a traumatic ICH while on antiplatelet therapy, although the studies included in this meta-analysis were mostly small and observational and thus not able to provide gold-standard evidence. Our review provides clinical equipoise for randomized controlled trials investigating the effect of platelet transfusion in these patients, which will drive the creation of good-quality, evidence-based treatment guidelines in this very high-risk population. Potential harms and risks with the transfusion of platelet concentrates to TBI patients need to be considered.

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CONFLICT OF INTEREST
The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix S1. PRISMA 2009 Checklist.
Appendix S2. OVID Medline Search Strategy 30/07/2018.