

Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation (Review)

Estcourt L, Stanworth S, Doree C, Hopewell S, Murphy MF, Tinmouth A, Heddle N



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Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation (Review)
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[Intervention Review]

Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

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ABSTRACT

Background

Platelet transfusions are used in modern clinical practice to prevent and treat bleeding in thrombocytopenic patients with bone marrow failure. Although considerable advances have been made in platelet transfusion therapy in the last 40 years, some areas continue to provoke debate especially concerning the use of prophylactic platelet transfusions for the prevention of thrombocytopenic bleeding.

Objectives

To determine the most effective use of platelet transfusion for the prevention of bleeding in patients with haematological disorders undergoing chemotherapy or stem cell transplantation.

Search methods

This is an update of a Cochrane review first published in 2004. We searched for randomised controlled trials (RCTs) in the Cochrane Central Register of Controlled Trials (CENTRAL Issue 4, 2011), MEDLINE (1950 to Nov 2011), EMBASE (1980 to Nov 2011) and CINAHL (1982 to Nov 2011), using adaptations of the Cochrane RCT search filter, the UKBTS/SRI Transfusion Evidence Library, and ongoing trial databases to 10 November 2011.

Selection criteria

RCTs involving transfusions of platelet concentrates, prepared either from individual units of whole blood or by apheresis, and given to prevent bleeding in patients with haematological disorders. Four different types of prophylactic platelet transfusion trial were included.

Data collection and analysis

In the original review one author initially screened all electronically derived citations and abstracts of papers, identified by the review search strategy, for relevancy. Two authors performed this task in the updated review. Two authors independently assessed the full text of all potentially relevant trials for eligibility. Two authors completed data extraction independently. We requested missing data from the original investigators as appropriate.

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Main results

There were 18 trials that were eligible for inclusion, five of these were still ongoing. Thirteen completed published trials (2331 participants) were included for analysis in the review. The original review contained nine trials (718 participants). This updated review includes six new trials (1818 participants). Two trials (205 participants) in the original review are now excluded because fewer than 80% of participants had a haematological disorder.

The four different types of prophylactic platelet transfusion trial, that were the focus of this review, were included within these thirteen trials.

Three trials compared prophylactic platelet transfusions versus therapeutic-only platelet transfusions. There was no statistical difference between the number of participants with clinically significant bleeding in the therapeutic and prophylactic arms but the confidence interval was wide (RR 1.66; 95% CI 0.9 to 3.04). The time taken for a clinically significant bleed to occur was longer in the prophylactic platelet transfusion arm. There was a clear reduction in platelet transfusion usage in the therapeutic arm. There was no statistical difference between the number of participants in the therapeutic and prophylactic arms with platelet refractoriness, the only adverse event reported.

Three trials compared different platelet count thresholds to trigger administration of prophylactic platelet transfusions. No statistical difference was seen in the number of participants with clinically significant bleeding (RR 1.35; 95% CI 0.95 to 1.9), however, this type of bleeding occurred on fewer days in the group of patients transfused at a higher platelet count threshold (RR 1.72; 95% CI 1.33 to 2.22). The lack of a difference seen for the number of participants with clinically significant bleeding may be due to the studies, in combination, having insufficient power to demonstrate a difference, or due to masking of the effect by a higher number of protocol violations in the groups of patients with a lower platelet count threshold. Using a lower platelet count threshold led to a significant reduction in the number of platelet transfusions used. There were no statistical differences in the number of adverse events reported between the two groups.

Six trials compared different doses of prophylactic platelet transfusions. There was no evidence to suggest that using a lower platelet transfusion dose increased: the number of participants with clinically significant (WHO grade 2 or above) (RR 1.02; 95% CI 0.93 to 1.11), or life-threatening (WHO grade 4) bleeding (RR 1.87; 95% CI 0.86 to 4.08). A higher platelet transfusion dose led to a reduction in the number of platelet transfusion episodes, but an increase in total platelet utilisation. Only one adverse event, wheezing after transfusion, had a significantly higher incidence when standard and high dose transfusions were compared but this difference was not seen when low dose and high dose transfusions were compared. It is therefore likely to be a type I error (false positive).

One small trial compared prophylactic platelet transfusions versus platelet-poor plasma. The risk of a significant bleed was decreased in the prophylactic platelet transfusion arm (RR 0.47; 95% CI 0.23 to 0.95) and this was statistically significant.

All studies had threats to validity; the majority of these were due to methodology of the studies not being described in adequate detail.

Although it was not the main focus of the review, it was interesting to note that in one of the pre-specified sub-group analyses (treatment type) two studies showed that patients receiving an autologous transplant have a lower risk of bleeding than patients receiving intensive chemotherapy or an allogeneic transplant (RR 0.73, 95% CI 0.65 to 0.82).

Authors' conclusions

These conclusions refer to the four different types of platelet transfusion trial separately. Firstly, there is no evidence that a prophylactic platelet transfusion policy prevents bleeding. Two large trials comparing a therapeutic versus prophylactic platelet transfusion strategy, that have not yet been published, should provide important new data on this comparison. Secondly, there is no evidence, at the moment, to suggest a change from the current practice of using a platelet count of $10 \times 10^9/L$. However, the evidence for a platelet count threshold of $10 \times 10^9/L$ being equivalent to $20 \times 10^9/L$ is not as definitive as it would first appear and further research is required. Thirdly, platelet dose does not affect the number of patients with significant bleeding, but whether it affects number of days each patient bleeds for is as yet undetermined. There is no evidence that platelet dose affects the incidence of WHO grade 4 bleeding. Prophylactic platelet transfusions were more effective than platelet-poor plasma at preventing bleeding.

PLAIN LANGUAGE SUMMARY

Platelet transfusions are used to prevent bleeding in patients with low platelet counts due to treatment-induced bone marrow failure

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This review was undertaken to determine the best use of platelet transfusions for the prevention of bleeding in patients who have haematological disorders and are receiving intensive (myelosuppressive) chemotherapy or stem cell transplantation. The review aimed to look at three main topics. One, what is the evidence to indicate if platelet transfusions should be given to prevent bleeding as compared to a strategy aimed at transfusion when bleeding occurs? Second, if platelet transfusions are given to prevent bleeding, when should they be given, for example, at what level of platelet count when measured in a blood sample? Three, if platelet transfusions are given what platelet dose should be used? We are unable to answer the first question, however new data from two large studies should be available when this review is updated in approximately two years time. With regard to the second question, there is no evidence to suggest a change from the current practice of using a platelet count of $10 \times 10^9/\text{L}$ to trigger the use of platelet transfusions to prevent bleeding. However, more research is required to clarify this issue. The final question can be answered. Using a lower platelet dose did not lead to an increased risk of bleeding and fewer platelets were required. The reduction in the number of platelets used should, theoretically, reduce the risk of adverse events although no true differences were seen in the studies. However, adverse events are uncommon and therefore a statistically significant difference may not be seen.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Prophylactic platelet transfusion compared to non prophylactic or therapeutic platelet transfusion for prevention of haemorrhage after chemotherapy and stem cell transplantation						
Patient or population: Patients with a haematological disorder Settings: Patients receiving intensive chemotherapy or a stem cell transplantation Intervention: Non-prophylactic or therapeutic platelet transfusions Comparison: Prophylactic platelet transfusions						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk					
	prophylactic transfusions	platelet non prophylactic or therapeutic platelet transfusions				
Bleeding: Numbers of patients with at least one significant bleeding event	286 per 1000	475 per 1000 (257 to 869)	RR 1.66 (0.9 to 3.04)	56 (1 study)	⊕⊕○○ low ^{1,2}	Only one of the studies reported on bleeding that did not cause death
Bleeding: Number of days on which a significant bleeding event occurred ³	5 per 1000 ³	4 per 1000 ³ (3 to 7)	RR 0.9 (0.62 to 1.32)	34212 ³ (1 study)	⊕⊕○○ low ^{1,2,4}	This reported the total number of days with clinically significant bleeding in either arm of the study
Mortality: Secondary to bleeding	58 per 1000	63 per 1000 (13 to 293)	RR 1.08 (0.23 to 5.06)	85 (2 studies)	⊕⊕○○ low ^{2,5,6}	
Number of platelet transfusions		The mean Number of platelet transfusions in the intervention groups was 15.8 lower (19.2 to 12.4 lower)		85 (2 studies)	⊕⊕⊕○ moderate ⁵	This was measured per course of chemotherapy

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ This study was conducted over 30 years ago and there have been dramatic changes in patient management since that time

² This was a small study

³ This was the total number of days recorded within the study rather than participants

⁴ There were only a small number of events leading to imprecision

⁵ These studies were conducted over 30 years ago and there have been major changes to patient management in that time

⁶ These were small studies and this may have led to some inconsistency in the results

BACKGROUND

Description of the condition

Platelet transfusions are used in modern clinical practice to prevent and treat bleeding in thrombocytopenic patients with bone marrow failure secondary to chemotherapy or stem cell transplantation. The ready availability of platelet concentrates has undoubtedly made a major contribution in allowing the development of intensive treatment regimens for haematological disorders (malignant and non-malignant) and other malignancies.

The first demonstration of the effectiveness of transfusions of platelets was performed in 1910 (Duke 1910). However, it was not until the 1970s and 1980s that the use of platelet transfusions became standard treatment for thrombocytopenic patients with bone marrow failure (Blajchman 2008). Alongside changes in supportive care, the routine use of platelet transfusions in patients with haematological disorders since that time has led to a marked decrease in the number of haemorrhagic deaths associated with thrombocytopenia (Slichter 1980), however this has led to a considerable increase in the demand for platelet concentrates. Currently, platelet concentrates are the second most frequently used blood component. About 266,000 adult doses per year are transfused in the UK (Taylor 2010), costing about £50 million per year. Administration of platelet transfusions to patients with haematological disorders now constitute a significant proportion (up to 67%) of all platelets issued (Cameron 2007; Greeno 2007; Pendry 2011), and the majority of these (69%) are given to prevent bleeding (Estcourt 2011a).

Description of the intervention

Despite the obvious beneficial effect that platelet transfusions have had on the management of patients with haematological malignancies with severe thrombocytopenia who are actively bleeding, questions still remain on how this limited resource should be used to prevent severe and life-threatening bleeding (Estcourt 2011b). Prophylactic platelet transfusions for patients with chemotherapy-induced thrombocytopenia became standard practice following the publication of several, small, randomised controlled trials in the late 1970s and early 1980s (Higby 1974; Murphy 1982; Solomon 1978). This review does not focus on the absolute need for platelet transfusions in this patient population but instead reviews the transfusion strategies that most effectively balance the benefits of their use against their risks. This review focused on four different types of prophylactic platelet transfusion trial.

Prophylactic platelet transfusions versus therapeutic-only platelet transfusions

The standard practice in most haematology units across the developed world has been to use prophylactic transfusions, in line

with guidelines (BCSH 2003; Slichter 2007). The experimental intervention was to only give platelet transfusions when bleeding occurred.

Prophylactic platelet transfusion threshold

Prophylactic platelet transfusions are typically given when blood platelet counts fall below a given trigger level. Studies compared different platelet count thresholds to trigger the administration of prophylactic platelet transfusions. The current consensus is that patients should receive a platelet transfusion when the platelet count is $<10 \times 10^9/L$, unless there are other risk factors for bleeding, such as sepsis, concurrent use of antibiotics or other abnormalities of haemostasis (BCSH 2003; Schiffer 2001; Slichter 2007). The experimental interventions were higher or lower platelet transfusion thresholds.

Dose of prophylactic platelet transfusions

This is the number of platelets given (platelet dose) during a standard platelet transfusion. For adults, the usual dose given is a single apheresis unit or a pool of four to six whole blood-derived platelets, with the absolute number of platelets in the range of 300×10^9 to 600×10^9 (Stanworth 2005). The experimental interventions were low dose or high dose platelet transfusion strategies.

Platelet transfusions versus alternative treatments (such as artificial platelet substitutes/platelet-poor plasma/ recombinant factor VIIa (rFVIIa)/ fibrinogen)

The standard practice in most haematology units across the developed world has been to use prophylactic transfusions, in line with guidelines (BCSH 2003; Slichter 2007). The experimental intervention was to give an alternative treatment, such as artificial platelet substitutes, platelet-poor plasma, rFVIIa or fibrinogen.

How the intervention might work

Prophylactic platelets versus therapeutic-only platelet transfusions

A retrospective review of almost 3000 thrombocytopenic adult patients over a 10-year period showed no relationship between the first morning platelet count, or the lowest platelet count of the day, and the risk of bleeding (Friedmann 2002). This has raised the question as to whether a threshold-defined prophylactic platelet transfusion approach is appropriate.

Further support for the absence of a relationship between the severity of thrombocytopenia and bleeding came from a review of case reports of severe intracranial haemorrhage. These cases were described in trials of prophylactic platelet transfusions. No clear evidence could be found for an association between the occurrence of

major intracranial bleeding and absolute platelet count just prior to the onset of severe bleeding (Stanworth 2005).

Thus, the overall benefit of a prophylactic platelet transfusion policy over a policy to use platelets only therapeutically, using a platelet count threshold, has not been established.

A recent study, using an historical control, assessed a therapeutic platelet transfusion strategy after autologous transplantation. Only 19% of the patients had clinically relevant bleeding of minor or moderate severity, and no severe or life-threatening bleeding was documented, this was a comparable rate to the historical control (20%). One-third of all transplants, and 47% after high-dose melphalan, were performed without any platelet transfusion. The numbers of platelet transfusions were reduced by 50% compared with their historical control (Wandt 2006). In an interim report of a randomised controlled trial (Wandt 2009), platelet transfusions could be significantly reduced (by 27%) in the therapeutic transfusion arm compared with prophylactic transfusion. 46% of patients in the therapeutic arm did not need any platelet transfusions. However, the incidence of clinically relevant bleeding was significantly higher (28.7% vs 9.5%), this is not surprising as this was the trigger for transfusion in the experimental arm.

Therefore a therapeutic platelet transfusion strategy may be safe and feasible. A large randomised controlled trial that hopes to answer this question has just completed recruitment of patients - TOPPs trial (Blajchman 2008; Stanworth 2010).

Optimal dose of prophylactic platelets

The dose of the platelet product transfused was based upon the perceived need to raise the patient's platelet count above a certain safe threshold. Over the years, our understanding of bleeding in thrombocytopenic patients has advanced and there is now evidence to suggest that patients require only approximately 7100 platelets/ μ L per day to maintain haemostasis (Hanson 1985). Platelets have been shown to provide an endothelial supportive function by plugging gaps in the endothelium of otherwise intact blood vessels. Animal studies have shown that thrombocytopenia is associated with the gradual thinning of the vessel wall endothelium over time, and that, if thrombocytopenia persists, gaps gradually occur between adjacent endothelial cells (Blajchman 1981; Kitchens 1975; Nachman 2008). This thinning and fenestration of the endothelium is accompanied with the on-going and increased use of circulating platelets to prevent the loss of red blood cells (RBCs) through these gaps.

A mathematical model predicted that smaller, more frequent doses of platelets would be as effective as higher doses of platelets in maintaining patients' platelet counts above an agreed threshold (Hersh 1998). This raised the question of whether thrombocytopenic bleeding could be prevented with a lower platelet dose (Tinmouth 2003). Such a strategy has potential economic and resource advantages, as fewer platelet transfusions might be required and donor exposures might be reduced.

Several smaller studies tried to address this question but only one of them used bleeding as a primary outcome measure (Tinmouth 2004). This showed that the low-dose prophylactic regimen was just as effective as the standard dose and resulted in a 25% reduction in the number of platelets transfused.

There have been two recent larger trials. One was stopped early because of an excess of WHO grade 4 bleeding (Heddle 2009), and the large PLADO trial confirmed the earlier finding by Tinmouth (Slichter 2010).

Prophylactic platelet threshold

Efforts were also made to establish a threshold for the use of prophylactic transfusions based on the platelet count. It became standard practice to transfuse platelets at platelet counts below $20 \times 10^9/L$, in an attempt to prevent bleeding (Beutler 1993). This practice was partly based on the findings of non-randomised studies, such as Gaydos 1962. This showed that gross haemorrhage (haematuria, haematemesis and melaena) was present more frequently at platelet counts below $5 \times 10^9/L$ than when the platelet count was between $5 \times 10^9/L$ and $100 \times 10^9/L$. This study and others like it did not clearly support the use of a threshold for prophylactic platelet transfusion of $20 \times 10^9/L$, nor was any threshold effect seen.

The routine use of platelet transfusions from the 1970s, in patients with haematological malignancies, resulted in a decreased mortality rate due to bleeding (less than 1% of patients) (Slichter 1980). However, the widespread use of a threshold platelet count of $20 \times 10^9/L$ for prophylactic platelet transfusions led to a marked growth in demand for platelet concentrates (Sullivan 2002).

This stimulated research to address whether the threshold could be safely lowered to $10 \times 10^9/L$ (Rebulla 1997, reviewed in Stanworth 2004). The consensus formulated from these trials was that patients should receive a platelet transfusion when the platelet count is $<10 \times 10^9/L$, unless there are other risk factors for bleeding, such as sepsis, concurrent use of antibiotics or other abnormalities of haemostasis (BCSH 2003; Schiffer 2001; Slichter 2007).

There have been calls for a further reduction in the threshold to $5 \times 10^9/L$. In the 1970s it had been shown, using faecal blood loss as an indicator of bleeding, that the increased risk of bleeding was at the $5 \times 10^9/L$ threshold (Slichter 1978). However, the ability to decrease the platelet threshold to this level may be compromised by the inaccuracy of automated platelet counters at very low platelet counts (Segal 2005).

Although platelet mass has been used as a transfusion trigger for neonatal platelet transfusions (Gerday 2009), different platelet count thresholds have been the only known trigger used in patients with a haematological disorder.

Platelet transfusions versus alternative treatments (such as artificial platelet substitutes/platelet-poor plasma/ rFVIIa/ fibrinogen)

Most clinical research has focused on the optimal dose for platelet transfusion or the threshold level of platelet counts for prophylactic platelet transfusions, rather than questioning the underlying assumption that prophylactic platelet transfusions are necessary or effective. The most recent RCTs have established that many patients develop bleeding at some stage during the period of greatest risk, frequently defined as a period of thrombocytopenia (Heddle 2009; Slichter 2010). This bleeding covers a spectrum of bleeding, from skin changes to, less commonly, intracranial haemorrhage. In Slichter 2010, patients had similar rates of bleeding (17%) with morning platelet counts within the range of 6 to 80 x 10⁹/L. This means that there are a significant number of bleeding episodes that are not being effectively treated by prophylactic platelet transfusions. Treatments that target other parts of the clotting cascade may be as effective at treating bleeding as prophylactic platelet transfusions.

Assessment of bleeding

A bleeding assessment has been seen as a more clinically relevant measure of the effect of platelet transfusions than surrogate markers such as platelet increment.

Any review that uses bleeding as a primary outcome measure needs to assess the way that the trials have recorded bleeding. Unfortunately, the way bleeding has been recorded and assessed has varied markedly between trials (Cook 2004; Heddle 2003). Retrospective analysis of bleeding leads to a risk of bias because bleeding events may be missed, and only more severe bleeding is likely to have been documented. Prospective bleeding assessment forms provide more information and are less likely to miss bleeding events. However, different assessors may grade the same bleed differently and it is very difficult to blind the assessor to the intervention.

The majority of trials have used the WHO system for grading bleeding, or a modification of this system (Koreth 2004). One limitation of all the scoring systems that have been based on the WHO system is that the categories are relatively broad and subjective. This means that a small change in a patient's bleeding risk may not be detected. Another limitation is that the modified WHO categories are partially defined by whether a bleeding patient requires a blood transfusion. The threshold for intervention may vary between clinicians and institutions and so the same level of bleeding could be graded differently in different institutions. The definition of what constitutes clinically significant bleeding has varied between studies, although the majority of more recent platelet transfusion studies (Heddle 2009; Stanworth 2010; Slichter 2010) now classify it as WHO grade 2 or above there has been greater heterogeneity in the past (Cook 2004; Koreth 2004). The difficulties with assessing and grading bleeding may limit the ability to compare results between studies and this needs to be kept in mind when reviewing the evidence for the effectiveness of prophylactic platelet transfusions.

Why it is important to do this review

Although considerable advances have been made in platelet transfusion therapy in the last 40 years, three major areas continue to provoke debate.

Firstly, what is the optimal prophylactic platelet dose to prevent thrombocytopenic bleeding?

Secondly, which threshold should be used to trigger the transfusion of prophylactic platelets?

Thirdly, are prophylactic platelet transfusions superior to therapeutic platelet transfusions for the prevention and/or control of life-threatening thrombocytopenic bleeding?

The initial formulation of this Cochrane review attempted to answer these questions, but there was insufficient evidence available at the time for any definitive conclusions to be drawn (Stanworth 2004). This update of the review reassessed the literature, to ascertain whether any recent studies can provide us with the evidence to answer those questions. There has been another recent systematic review of the optimal dose for prophylactic platelets (Cid 2007), but this is now out-dated because several new large studies have recently been completed.

This review did not assess whether there are any differences in the efficacy of apheresis versus whole-blood derived platelet products, nor did it assess differences between ABO identical and ABO non-identical platelet transfusions. This is because both these topics have been covered by recent systematic reviews (Heddle 2008; Shehata 2009).

OBJECTIVES

To determine the most effective use of platelet transfusion for the prevention of bleeding (prophylactic platelet transfusion) in patients with haematological disorders and undergoing myelosuppressive chemotherapy or stem cell transplantation.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) have been included in this review.

Types of participants

Patients with haematological disorders receiving treatment with myelosuppressive chemotherapy and/or stem cell transplantation. All ages were included. If trials consisted of mixed populations

of patients, with diagnoses of solid tumours, only data from the haematological subgroups were used. If subgroup data for haematological patients was not provided (after contacting the authors of the trial), the trial was excluded if fewer than 80% of participants had a haematological disorder. Any patients that are not being treated with intensive chemotherapy or a stem cell transplant are by definition excluded. Patients with non-malignant haematological disorders (e.g. aplastic anaemia, congenital bone marrow failure syndromes) that are being treated with an allogeneic stem cell transplant are therefore included within the study.

Types of interventions

Transfusions of platelet concentrates, prepared either from individual units of whole blood or by apheresis, and given prophylactically to prevent bleeding. Prophylactic platelet transfusions are typically given when blood platelet counts fall below a given trigger level. There was no restriction on dose or frequency of platelet transfusion but we took this information into account in the analysis, where available. Similarly, there was no restriction on trigger level, although again we took this information into account in the analysis where available.

We included the following comparisons:

- prophylactic platelet transfusions versus therapeutic platelet transfusions (on-demand triggered by bleeding)
- prophylactic platelet transfusion with one trigger level versus prophylactic platelet transfusion with another trigger level
- prophylactic platelet transfusion with one dose schedule versus prophylactic platelet transfusion with another dose schedule
- platelet transfusions (prophylactic or on-demand) versus alternative treatments (such as artificial platelet substitutes/ platelet-poor plasma/ rFVIIa/ fibrinogen).

Types of outcome measures

Primary outcomes

Number and severity of bleeding episodes.

- The number of patients with at least one bleeding episode.
- The number of days on which bleeding occurred.

Secondary outcomes

- Mortality (all causes)
- Mortality secondary to bleeding
- Number of platelet transfusions
- Number of red cell transfusions
- Disease-free survival
- Proportion of patients achieving complete remission
- Time in hospital

- Adverse effects of treatments (transfusion reactions, thromboembolism, development of platelet antibodies).

Search methods for identification of studies

We formulated search strategies in collaboration with the Cochrane Haematological Malignancies Group.

Electronic searches

Bibliographic databases

We searched for randomised controlled trials in the following databases:

- MEDLINE (Ovid, 1950 to 10 November 2011)
- EMBASE (Ovid, 1980 to 10 November 2011)
- CENTRAL (*The Cochrane Library*, Issue 4, 2011)
- CINAHL (NHS Evidence, 1982 to 10 November 2011)
- UKBTS/SRI Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1980 to 10 November 2011)
- LILACS (BIREME/PAHO/WHO, 1982 to 10 November 2011)
- KoreaMed (KAMJE, 1997 to 10 November 2011)
- PakMediNet (2001 to 10 November 2011)
- IndMed (ICMR-NIC, 1985 to 10 November 2011)
- Conference Proceedings Citation Index-Science (CPCI-S) (Web of Science (Thomson Reuters), 1990 to 10 November 2011)

Searches were updated from the original search in January 2002, first in November 2009, then in May 2010, then in March 2011 and finally on 10 November 2011. Searches in MEDLINE, EMBASE and CINAHL were combined with adaptations of the Cochrane RCT search filters, as detailed in the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre 2011). Search strategies for both the original and update searches are presented in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), [Appendix 5](#), [Appendix 6](#) and [Appendix 7](#).

Databases of ongoing trials

We also searched ClinicalTrials.gov (<http://clinicaltrials.gov/ct2/search>), the ISRCTN Register (<http://www.controlled-trials.com/isrctn/>) and the World Health Organization International Clinical Trials Registry (ICTRP) (<http://apps.who.int/trialsearch/>) on 10 November 2011 in order to identify ongoing trials.

Searching other resources

We augmented database searching by:

Handsearching of references

We checked references of all identified trials, relevant review articles, and current treatment guidelines for further literature. These searches were limited to the first generation reference lists.

Personal contacts

We contacted authors of relevant studies, study groups and experts worldwide known to be active in the field for unpublished material or further information on ongoing studies.

Data collection and analysis

Selection of studies

Two independent review authors (LE, CD) initially screened all electronically derived citations and abstracts of papers identified by the review search strategy for relevancy. Studies clearly irrelevant were excluded at this stage.

The full texts of all potentially relevant trials were then formally assessed for eligibility by two independent review authors (LE, SS) against the criteria outlined above. All disagreements were resolved by discussion with a third review author (MM). Further information was sought from a study author because the article contained insufficient data to make a decision about eligibility (Zumberg 2002). This study was excluded after the author supplied the additional information. A study eligibility form was designed for trials of platelet transfusion to help in the assessment of relevance, which included ascertaining whether the participants had haematological disorders, and whether two groups could be defined in the trial on the basis of differences in symptomatic triggers, platelet count triggers, or platelet dose schedules. The reasons why studies failed to meet the eligibility criteria were recorded.

Data extraction and management

Two review authors (LE, SS) conducted data extraction according to the guidelines proposed by the Cochrane Collaboration (Higgins 2011a). Potential disagreements between the review authors were resolved by consensus. The review authors were not blinded to names of authors, institutions, journals, or the outcomes of the trials. The data extraction forms were piloted on three studies with all disagreements resolved by consensus, thereafter the two authors (LE, SS) extracted data independently for all the studies. The following data were extracted:

General information

Review author's name, date of data extraction, study ID, reference manager number, first author of study, author's contact address (if available), citation of paper, objectives of the trial.

Trial details

Trial design, location, setting, sample size, power calculation, treatment allocation, randomisation, blinding, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow up, stratification, stopping rules described, statistical analysis, results, conclusion, and funding.

Characteristics of participants

Age, gender, ethnicity, total number recruited, total number randomised, total number analysed, types of haematological disease, lost to follow-up numbers, drop outs (percentage in each arm) with reasons, protocol violations, previous treatments, current treatment, prognostic factors.

Interventions

Experimental and control interventions, type of platelet given, timing of intervention, dosage of platelet given, compliance to interventions, additional interventions given especially in relation to red cell transfusions, any differences between interventions.

Outcomes measured

Number and severity of bleeding episodes. Mortality (all causes), and mortality due to bleeding. Disease-free survival. Proportion of patients achieving complete remission. Time in hospital. Number of platelet transfusions. Number of red cell transfusions. Adverse effects of treatments (e.g. transfusion reactions, thromboembolism, development of platelet antibodies)

Both full-text versions and abstracts including additional information (for example slides) of eligible studies were used to retrieve the data. Publications reporting on more than one trial were extracted using one data extraction form for each trial. Trials reported in more than one publication were extracted on one form only. Nine study authors were contacted for additional information, two study authors no longer had access to the original data and two study authors supplied the information requested.

Assessment of risk of bias in included studies

Two review authors (LE, SS) assessed all included studies for possible risk of bias (as described in the Cochrane Handbook (Higgins 2011c)). The assessment included information about the design, conduct and analysis of the trial. Each criterion was evaluated on a three-point scale: low risk of bias, high risk of bias, or unclear. To assess risk of bias, the following questions were included in the risk of bias table for each included study:

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?
- Were incomplete outcome data adequately addressed (for every outcome separately)?

- Are reports of the study free of selective outcome reporting?
- Was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect

For dichotomous outcomes the number of outcomes in treatment and control groups were recorded and the treatment effect measures across individual studies were estimated as the relative effect measures (relative risk (RR) with 95% confidence intervals (CI)). For continuous outcomes, the mean and standard deviations were recorded. For continuous outcomes measured using the same scale the effect measure was the mean difference (MD) with 95% confidence intervals, or the standardised mean difference (SMD) for outcomes measured using different scales.

Dealing with missing data

This was performed according to the recommendations in the Cochrane Handbook (Higgins 2011b). Nine authors were contacted in order to obtain information not reported in the publications of the trials. Four authors supplied the missing data (Heckman 1997; Heddle 2009; Rebulla 1997; Tinmouth 2004). Two further authors searched for missing data but it was no longer available (Diedrich 2005; Sintnicolaas 1982).

In trials that included patients with haematological disorders as well as patients with solid tumours or non-malignant haematological disorders. Data were extracted for the malignant haematology subgroup from the general trial data; This could not be done in one study (Zumberg 2002). The author was contacted in order to retrieve information on malignant haematology patients but was unable to supply the requested data. All five authors of the ongoing trials were contacted, two responded (Stanworth 2010; Wandt 2009).

Within an outcome, when there was missing data, the preferred analysis was an intention-to-treat analysis (ITT). The number of patients lost to follow-up was recorded for each trial.

Assessment of heterogeneity

The decision about whether or not to combine the results of individual studies depended on an assessment of heterogeneity. If studies were considered sufficiently homogenous in their study design, a meta-analysis was carried out and the statistical heterogeneity assessed. Statistical heterogeneity of treatment effects between trials was assessed using a Chi² test with a significance level at $P < 0.1$. The I² statistic was used to quantify possible heterogeneity (I² > 30% moderate heterogeneity, I² > 75% considerable heterogeneity). Potential causes of heterogeneity were explored by sensitivity and subgroup analyses if possible.

Assessment of reporting biases

None of the meta-analyses contained more than 10 trials, therefore potential publication bias (small trial bias) was not explored by the generation of a funnel plot (Sterne 2011).

Data synthesis

Analyses were performed according to the recommendations of the Cochrane Collaboration (Deeks 2011). Aggregated data was used for analysis. For statistical analysis, data was entered into Review Manager 2011. Data entry into software was done by one review author and was checked for accuracy by a second review author. Meta-analyses were performed using a fixed-effect model (for example the generic inverse variance method for survival data outcomes); results of the random-effects model were also examined. GRADEprofiller was used to create summary of finding tables as suggested in the Cochrane Handbook (Schünemann 2011).

The following types of comparisons were performed separately:

1. Prophylactic platelet transfusions versus therapeutic platelet transfusions (on-demand triggered by bleeding)
2. Prophylactic platelet transfusion with one trigger level versus prophylactic platelet transfusion with another trigger level
3. Prophylactic platelet transfusion with one dose schedule versus prophylactic platelet transfusion with another dose schedule
4. Platelet transfusions (prophylactic or on-demand) versus alternative treatments (such as artificial platelet substitutes/platelet-poor plasma/rFVIIa/fibrinogen concentrate)

In the discussion, consideration was taken into translating the results of the included studies into recommendations for action. All review authors were involved in drawing conclusions and making specific recommendations for future research.

Subgroup analysis and investigation of heterogeneity

Two sub-group analyses were pre-specified prior to updating the review, these were fever and patients' diagnostic and treatment sub-groups.

The pre-specified sub-group analyses were only reported on in a minority of studies. If data were available it has been reported. Meta-regression was not performed because no sub-group contained more than ten studies (Deeks 2011). Differences between sub-groups were compared using a random-effects model when the two sub-groups were independent following the guidance in Chapter 9 of the Cochrane Handbook (Deeks 2011). If this was not possible then differences would be commented on narratively.

Sensitivity analysis

Robustness of the overall results were assessed by sensitivity analysis with respect to those trials deemed at high risk of bias.

RESULTS

Results of the search

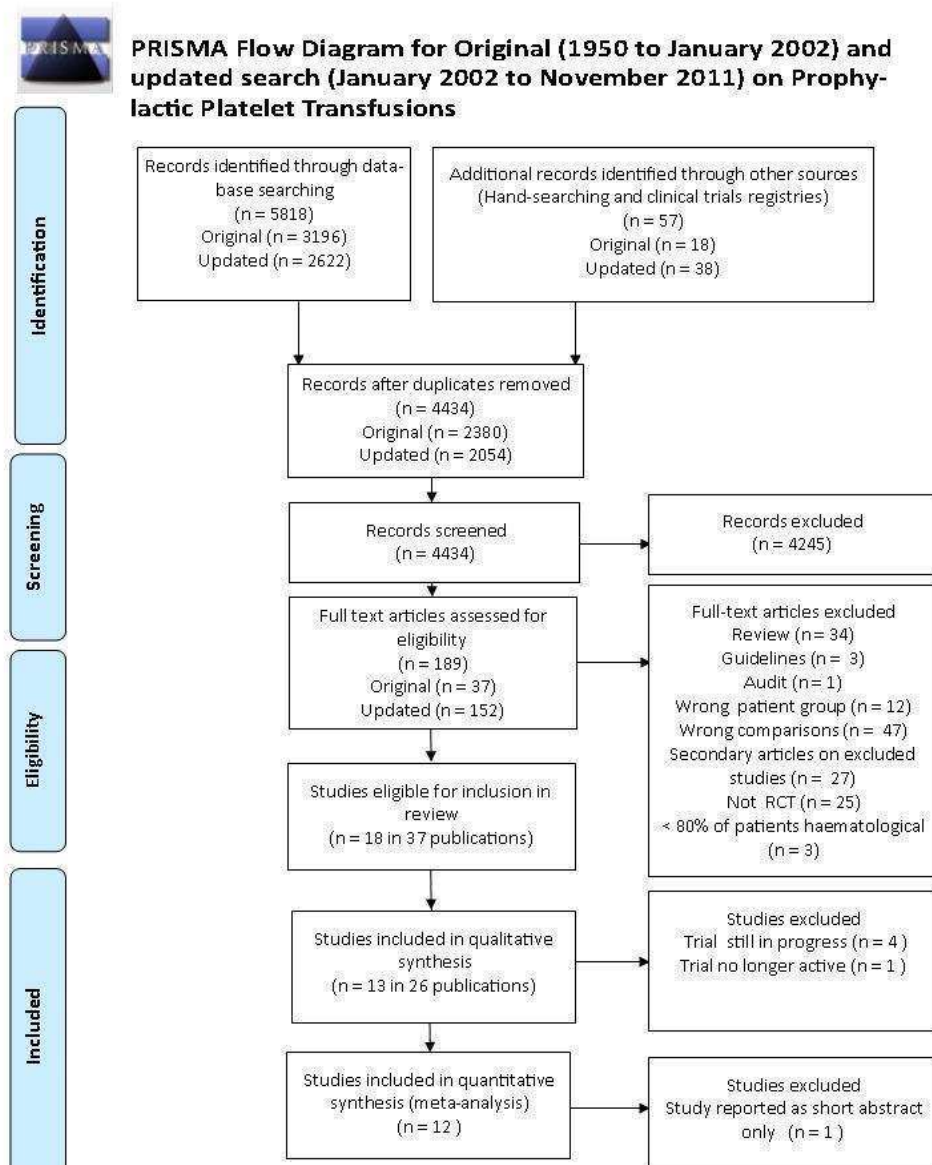
Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); and [Characteristics of ongoing studies](#).

See PRISMA Flow Diagram [Figure 1](#) The original search (conducted January 2002) identified a total of 3196 potentially relevant citations. There were 2380 citations after duplicates were removed. 2343 records were able to be excluded on the basis of the abstract. This was performed by one review author.

Figure 1. PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews*

The update searches (conducted November 2009, May 2010, March 2011 and November 2011) identified a total of 2622 potentially relevant citations. There were 2054 citations after duplicates were removed. 1865 records were able to be excluded on the basis of the abstract by two review authors (CD & LE). In this update, 152 full text articles were retrieved for relevance and the previous systematic review (Stanworth 2004) identified 37 studies which appeared relevant on the basis of their full text of abstract or paper using the original inclusion/exclusion criteria (Stanworth 2004). These 189 citations were reviewed by two review authors (LE & SS).

Included studies

See [Characteristics of included studies](#) for full details of each study. There were 18 studies eligible for inclusion, five of these studies were ongoing studies.

Ongoing studies

The updated review identified five ongoing studies within 11 abstracts or database records. The original review identified one ongoing study that is not currently recruiting patients (Franklin 1995). However, no further information were available from the trialists. Searches of databases of ongoing trials and abstracts identified four further potentially relevant trials (Lu 2011; NCT00180986; Stanworth 2010; Wandt 2009). NCT00180986 is not actively recruiting patients at the moment (no further information available from the author). Lu 2011; Stanworth 2010; Wandt 2009 have now completed recruitment of patients but results have not yet been published. See [Characteristics of ongoing studies](#) for further details.

Studies contributing to the main outcome

The 13 remaining RCTs (26 publications) were published between 1973 and 2010. There were 13 secondary citations of included studies (cited as secondary references for the relevant included studies).

There were six new studies (Diedrich 2005; Heddle 2009; Sensebe 2004; Slichter 2010; Steffens 2002; Tinmouth 2004) included in this updated review, and they were published between 2002 and 2010. Nine studies were identified in the original review (Heckman 1997; Higby 1974; Klumpp 1999; Murphy 1982; Rebulla 1997; Roy 1973; Sintnicolaas 1982; Solomon 1978; Zumberg 2002). Two studies that had previously been included in the review were excluded because fewer than 80% of participants had a haematological disorder and no subgroup data could be identified (Klumpp 1999; Zumberg 2002).

The thirteen RCTs included were distributed across the four review sub-categories as follows:

- Three trials evaluated the effect of a prophylactic platelet transfusion policy versus a therapeutic platelet transfusion policy (Murphy 1982; Sintnicolaas 1982; Solomon 1978);
- Three trials evaluated the effect of a prophylactic platelet transfusion policy with one trigger level versus a prophylactic platelet transfusion policy with another trigger level (Diedrich 2005; Heckman 1997; Rebulla 1997);
- Six trials evaluated the effect of a prophylactic platelet transfusion with one dose schedule versus a prophylactic platelet transfusion with another dose schedule (Heddle 2009; Roy 1973; Sensebe 2004; Slichter 2010; Steffens 2002; Tinmouth 2004);
- One trial evaluated the effect of prophylactic platelet transfusions versus platelet-poor plasma (Higby 1974).

In the remainder of this review these sub-categories will be described in separate sections.

Prophylactic platelet transfusions versus therapeutic platelet transfusions

See [Table 1](#) for study characteristics, including number and type of participants, type of intervention, duration of study, type of platelet product and primary outcome.

Three RCTs were identified in this comparison. All were single centre parallel RCTs. The number of patients randomised ranged from 12 in Sintnicolaas 1982 to 56 in Murphy 1982. Two studies were conducted in the USA in the 1970's, although one study was not published until 1982, some years after recruitment had been completed (Murphy 1982). One study was conducted in the Netherlands (Sintnicolaas 1982).

Sintnicolaas 1982 was only reported as a short abstract, and no further information was available from the author, therefore this study will be excluded from any quantitative analysis (12 participants were randomised, but the numbers in each arm of the study were not stated).

Participants

In total 99 participants were randomised, and of these, 97 were included in the analysis. Two patients were excluded from Solomon 1978 because they died from an intra-cranial haemorrhage on the first day of the study. The study populations varied slightly. In Solomon 1978, patients were previously untreated adults with acute myeloid leukaemia (AML); patients with acute promyelocytic leukaemia (APL) were excluded. In Murphy 1982, patients were previously untreated children with either AML or acute lymphoblastic leukaemia (ALL); no exclusion criteria were reported. In Sintnicolaas 1982, patients had acute leukaemia and were severely thrombocytopenic; no exclusion criteria were reported.

Intervention

All three studies compared prophylactic platelet transfusions with a platelet threshold of $20 \times 10^9/L$ with a therapeutic platelet transfusion regime (platelet transfusion given for clinically significant bleeding). However, in [Solomon 1978](#), platelet transfusions were also given in the therapeutic (“specific indications”) arm if there had been a 50% fall in platelets to below $20 \times 10^9/L$ over the previous 24 hrs.

Co-interventions

None of the studies had any reported co-interventions. None of the studies reported a red cell transfusion policy.

Outcomes

Only one of the three studies defined a primary outcome; this was survival ([Murphy 1982](#)). Only one study commented on bleeding outcomes apart from death from bleeding ([Murphy 1982](#)). Two studies reported on platelet transfusion requirements ([Murphy 1982](#); [Solomon 1978](#)). Two studies commented on adverse events (platelet refractoriness) ([Murphy 1982](#); [Sintnicolaas 1982](#)). None of the studies commented on transfusion reactions or thromboembolic disease.

Prophylactic platelet transfusion with one trigger level versus prophylactic platelet transfusion with another trigger level

See [Table 2](#) for study characteristics including: number and type of participants; type of intervention (actual thresholds used); duration of study; type of platelet product; and primary outcome. Three parallel RCTs were identified in this comparison. Two were single-centre studies ([Diedrich 2005](#); [Heckman 1997](#)), and one was a multicentre study ([Rebulla 1997](#)). The number of patients randomised ranged from 78 in [Heckman 1997](#) to 276 in [Rebulla 1997](#). The studies were conducted in Italy, Sweden and the USA.

Participants

In total 520 participants were randomised, of these, 499 were included in the analysis. Twenty one patients randomised in [Rebulla 1997](#) were excluded from analysis (16 no study records received; two received non-myeloablative chemotherapy; three died (two within 24 hours of enrolment into the study). Two of the studies examined adult patients with acute leukaemia; one included ALL and AML patients ([Heckman 1997](#)); and the other included only patients with AML ([Rebulla 1997](#)). Both excluded patients with APL. The third study included both adults and children undergoing an allogeneic stem cell transplant ([Diedrich 2005](#)).

Intervention

Two studies compared a prophylactic transfusion threshold of $10 \times 10^9/L$ with a threshold of $20 \times 10^9/L$ ([Heckman 1997](#); [Rebulla 1997](#)). One study compared a threshold of $10 \times 10^9/L$ with a threshold of $30 \times 10^9/L$ ([Diedrich 2005](#)).

Co-interventions

In two of the three studies ([Diedrich 2005](#); [Rebulla 1997](#)) a red cell transfusion policy was stated. Both studies transfused red cells when the haemoglobin was less than 80g/L.

Outcomes

Two of the three studies defined a primary outcome ([Diedrich 2005](#); [Rebulla 1997](#)). [Rebulla 1997](#) defined the frequency and severity of bleeding as the primary outcome, with the number of platelet transfusions as a secondary outcome. Whereas [Diedrich 2005](#) defined the number of platelet transfusions as the primary outcome with bleeding as one of the secondary outcomes. The third study, [Heckman 1997](#), stated that its main aims were to look at platelet use and bleeding complications. All three studies commented on adverse events associated with platelet transfusions.

Prophylactic platelet transfusion with one dose schedule versus prophylactic platelet transfusion with another dose schedule

See [Table 3](#) for study characteristics including number and type of participants, type of intervention (actual doses used), prophylactic platelet transfusion thresholds used, duration of study, type of platelet product and primary outcome.

Six RCTs were identified in this type of platelet transfusion study. Three were single-centre studies ([Roy 1973](#); [Steffens 2002](#); [Tinmouth 2004](#)) and three were multi-centre studies ([Heddle 2009](#); [Sensebe 2004](#); [Slichter 2010](#)). The number of patients randomised ranged from 54 in [Steffens 2002](#) to 1351 in [Slichter 2010](#). The studies were conducted in Canada, France, UK and USA.

Participants

In total 1808 participants were randomised, of these, 1714 were included in the analysis. Ninety one patients (7 in [Heddle 2009](#), 5 in [Sensebe 2004](#), and 79 in [Slichter 2010](#)) were excluded from these studies because they did not receive a platelet transfusion. Three further patients were excluded from the [Heddle 2009](#) study because there were no bleeding assessment data available. Three of the studies included only adult patients ([Heddle 2009](#); [Steffens 2002](#); [Tinmouth 2004](#)). Two of the studies included both adults and children ([Sensebe 2004](#); [Slichter 2010](#)). One study included only children with acute leukaemia ([Roy 1973](#)). All of the patients

had hypoproliferative thrombocytopenia but the cause of this varied between studies. All of the studies included patients with acute leukaemia, however only four of the studies specifically stated that APL was an exclusion criteria (Heddle 2009; Sensebe 2004; Slichter 2010; Tinmouth 2004). Four of the studies included patients receiving an autologous stem cell transplant (Heddle 2009; Sensebe 2004; Slichter 2010; Tinmouth 2004). Three of the studies included patients receiving an allogeneic stem cell transplant (Heddle 2009; Slichter 2010; Steffens 2002).

Intervention

Two studies (Heddle 2009; Tinmouth 2004) compared low versus standard dose platelet transfusions (as defined by the individual studies). Three studies compared standard versus high dose platelet transfusions (Roy 1973; Sensebe 2004; Steffens 2002). Slichter 2010 performed a comparison between low dose, standard dose, and high dose platelet transfusions.

Co-interventions

There were no reported co-interventions in any of the studies. Four of the six studies did not report a red cell transfusion policy and two studies (unpublished data of Heddle 2009; Slichter 2010) reported that local practice at each centre determined the red cell transfusion policy.

Outcomes

Four of the six studies defined a primary outcome (Heddle 2009; Sensebe 2004; Slichter 2010; Tinmouth 2004). In three of these studies bleeding was the primary outcome measure (Heddle 2009; Slichter 2010; Tinmouth 2004), whereas in the fourth study the primary outcome was the time between the first platelet transfusion and the daily platelet count reaching $20 \times 10^9/L$ (Sensebe 2004), with bleeding reported as an adverse event. Only one of the six studies reported on adverse events associated with platelet transfusions (Slichter 2010).

Prophylactic platelet transfusions versus alternative treatments (such as artificial platelet substitutes/platelet-poor plasma/ rFVIIa/ fibrinogen)

There was only one study in this sub-category (Higby 1974). It was a small (21 patients) parallel RCT conducted in the USA in the 1970s.

Participants

In total 21 participants were randomised (18 patients were randomised once and three were randomised twice). Three of the randomisation episodes were not included in the analysis because patients had spontaneous recovery of their platelet counts within 48 hours of study entry. The study included adults with AML.

Intervention

Patients received either platelets (3 units/m²) or an equivalent volume of platelet-poor plasma twice weekly. The study stopped if the patient had a significant bleed, developed significant sepsis or there was recovery of the platelet count.

Co-interventions

This study had no reported co-interventions.

Outcomes

No primary outcome was mentioned, but outcomes mentioned were the frequency of bleeding and average platelet count during the study. This study commented on the development of HLA antibodies as an adverse effect of platelet transfusions.

Excluded studies

See [Characteristics of excluded studies](#) for further details.

- Twelve studies compared different participant groups

(Andrew 1993; Arnold 2006; Bai 2004; Fanning 1995; Gajic 2006; Gerday 2009; Hilbom 2008; Johansson 2007; Julmy 2009; Reed 1986; Speiss 2004; Vadhan-Raj 2002).

- Forty seven studies compared different types of platelet formulations with outcome measures not relevant to the eligibility criteria

(Agliaastro 2006; Akk  k 2007; Anderson 1997; Arnold 2004; Bentley 2000; Blumberg 2002; Blundell 1996; Carr 1990; Couban 2002; de Wildt-Eggen 2000; Diedrich 2009; Dumont 2011; Gmur 1983; Goodrich 2008; Gurkan 2007; Harrup 1999; Heal 1993; Heddle 1994; Heddle 1999; Heddle 2002; Kakaiya 1981; Kerkhoffs 2010; Lapierre 2003; Leach 1991; Lee 1989; Lozano 2010; Lozano 2011; ISRCTN49080246; McCullough 2004; Messerschmidt 1988; Mirasol 2010; Murphy 1986; Oksanen 1991; Oksanen 1994; Schiffer 1983; Shanwell 1992; Singer 1988; Sintnicolaas 1995; Slichter 2006; Strindberg 1996; Sweeney 2000; TRAP 1997; Van Marwijk 1991; van Rhenen 2003; Wang 2002; Williamson 1994; Zhao 2002).

- Three citations were guidelines (Follea 2004; Samama 2005; Tosetto 2009).
- One citation was an audit (Qureshi 2007).
- Thirty four citations were reviews (including 3 systematic reviews: Cid 2007; Heddle 2003; Shehata 2009).
- Twenty five studies were not randomised controlled trials

(Aderka 1986; Callow 2002; Cameron 2007; Chaoui 2005; Decaudin 2004; Eder 2007; Elting 2002; Elting 2003; Friedmann 2002; Gil-Fernandez 1996; Gmur 1991; Greeno 2007; Hardan 1994; Lawrence 2001; Navarro 1998; Nevo 2007; Norol 1998; Paananen 2009; Sagmeister 1999; Verma 2008; Wandt 1998; Wandt 2005; Wandt 2006; Weigand 2009; Zahur 2002).

- Twenty seven were secondary citations of excluded studies (cited as secondary references for the relevant excluded studies).
- Three studies were studies in which fewer than 80% of the participants were haematological patients and no data were available on the haematological subgroup ([Goodnough 2001](#); [Klumpp 1999](#); [Zumberg 2002](#)). [Klumpp 1999](#) and [Zumberg 2002](#) had been included in the previous review [Stanworth 2004](#) but have now been excluded because these were studies in which fewer than 80% of the participants were haematological patients and no data were available on the haematological subgroup.

Risk of bias in included studies

See [Figure 2](#) for further details.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): Assessor of bleeding assessment	Blinding (performance bias and detection bias): Physician/Medical Staff	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Protocol Deviation balanced?
Diedrich 2005	?	?	+	-	?	?	+	?
Heckman 1997	?	?	-	-	?	?	?	-
Heddle 2009	+	+	+	-	-	-	-	-
Higby 1974	?	+	?	+	+	?	-	?
Murphy 1982	?	?	?	?	?	-	-	?
Rebulla 1997	+	+	-	-	+	?	+	-
Roy 1973	?	?	+	?	+	-	-	?
Sensebe 2004	?	?	?	-	+	?	+	?
Sintricolaas 1982	?	?	?	?	?	?	?	?
Slichter 2010	+	?	-	-	-	+	+	-
Solomon 1978	?	?	?	?	?	?	?	?
Steffens 2002	?	?	?	?	?	-	?	?
Tinmouth 2004	+	+	-	-	+	?	+	-

Prophylactic platelet transfusions versus therapeutic platelet transfusions

All studies ([Murphy 1982](#); [Sintnicolaas 1982](#); [Solomon 1978](#)) had some threats to validity. The majority of these potential risks were due to a lack of detail provided on the specific criteria and were thus judged as “unclear” using the Cochrane grading system.

Sequence generation and allocation concealment

None of the studies reported on the method of sequence generation or allocation concealment.

Blinding

All studies were likely to be at risk of detection bias. No mechanisms were mentioned to blind outcome assessors or clinicians to the intervention. This might have been particularly problematic with respect to outcomes with potentially very high levels of subjectivity - such as enumerating significant bleeding events.

Incomplete outcome data

Loss to follow-up was generally low. In [Solomon 1978](#) analysis was not by intention-to-treat as two patients (randomised to the prophylactic arm) that died from cerebral haemorrhages on day one of the study were not included in the analysis.

Selective reporting

It was unclear whether any of the studies were free of selective reporting as study protocols were not available.

Protocol deviation

No study reported on protocol deviation.

Other potential sources of bias

The small numbers of participants in the studies compromised the likelihood that there was equivalence of participants at baseline. All studies are therefore potentially at risk of significant bias.

Prophylactic platelet transfusion with one trigger level versus prophylactic platelet transfusion with another trigger level

All three studies had some threats to validity ([Diedrich 2005](#); [Heckman 1997](#); [Rebulla 1997](#)). The majority of these potential risks were due to a lack of detail provided on the specific criteria

and were thus judged as “unclear” using the Cochrane grading system.

Sequence generation

Only one of the studies had adequate sequence generation ([Rebulla 1997](#)), the methods used in the other two studies were unclear.

Allocation concealment

Only one of the studies had adequate allocation concealment ([Rebulla 1997](#)), whether this was achieved in the other studies was unclear.

Blinding

In one of the studies there was adequate blinding of the bleeding assessor ([Diedrich 2005](#)), but other medical staff were unblinded to the treatment arm. In the other two studies ([Heckman 1997](#); unpublished data of [Rebulla 1997](#)), the bleeding assessors and medical staff were unblinded.

Incomplete outcome data

[Rebulla 1997](#) did not perform an intention to treat analysis. Twenty one of the randomised patients were excluded from analysis (16 no study records received; two received non-myeloablative chemotherapy. Three died (two within 24 hours of enrolment into the study); two of the three deaths were due to an intra-cerebral haemorrhage. However, the number of participants with missing outcome data were balanced across the intervention groups.

Selective reporting

It was unclear whether any of the studies were free of selective reporting as study protocols were not available.

Protocol deviation

In two of the three studies there were more protocol deviations in the intervention arm of the study ([Heckman 1997](#); [Rebulla 1997](#)). The third study was insufficiently reported for an adequate assessment to be made ([Diedrich 2005](#)). In [Heckman 1997](#), there was a statistically significant difference between the two arms. 14 out of 37 patients with a transfusion threshold of $10 \times 10^9/L$ were affected by protocol deviations whereas only 6 out of 41 patients with a transfusion threshold of $20 \times 10^9/L$ were affected. In [Rebulla 1997](#), the pre-transfusion platelet count was higher than indicated in the protocol in 5.4% of platelet transfusions with a transfusion threshold of $10 \times 10^9/L$, but only 2% of platelet transfusions with a higher transfusion trigger were transfused outside

the protocol guidelines, whether this was statistically significant was not reported.

Other potential sources of bias

Two of the three studies (Diedrich 2005; Rebull 1997) appeared to be free of other sources of significant bias. The third study was insufficiently reported for an adequate assessment to be made (Heckman 1997).

Two of the three studies are potentially at risk of bias due to the higher numbers of protocol violations in the intervention arms of the studies. The third study could not be adequately assessed for this risk.

Prophylactic platelet transfusion with one dose schedule versus prophylactic platelet transfusion with another dose schedule

All six studies had some threats to validity (Heddle 2009; Roy 1973; Sensebe 2004; Slichter 2010; Steffens 2002; Tinmouth 2004).

Sequence generation

Three of the studies described reliable methods of sequence generation with computer generated block design (Heddle 2009; Slichter 2010; Tinmouth 2004). The other three studies were insufficiently reported for an adequate assessment to be made (Roy 1973; Sensebe 2004; Steffens 2002).

Allocation concealment

Two of the studies described adequate allocation concealment (Heddle 2009; Tinmouth 2004). Heddle 2009 used a secure web-based randomisation system and Tinmouth 2004 used a sealed envelope system administered by blood bank staff. The other four studies were insufficiently reported for an adequate assessment to be made.

Blinding

In two of the six studies (Sensebe 2004; Tinmouth 2004), the medical staff were not blinded to the intervention. A further two studies could not be assessed for blinding of medical staff due to lack of information (Roy 1973; Steffens 2002). The final two studies had been designed as blinded studies, but the authors of both of these studies raised the suspicion that blinding was inadequate (Heddle 2009; Slichter 2010). In Heddle 2009 this suspicion was raised because of unbalanced early withdrawal of patients from the study by physicians (seven patients were withdrawn early from the study; one in the standard dose arm and six in the low dose arm). In Slichter 2010 it was noted that differences in the volume of platelets transfused led to loss of blinding.

Three studies were designed so that the bleeding assessors were blinded to the intervention (Heddle 2009; Roy 1973; Slichter 2010), but the authors of two of these studies (Heddle 2009; Slichter 2010) raised the suspicion that blinding was inadequate. Two studies did not provide sufficient information to determine whether bleeding assessors were blinded to the intervention (Sensebe 2004; Steffens 2002). In one study (Tinmouth 2004), the bleeding assessor was unblinded to the outcome measure. In four of the six studies (Heddle 2009; Roy 1973; Slichter 2010; Tinmouth 2004), the final allocation of bleeding grade was performed by individuals blinded to the intervention (Heddle 2009; Roy 1973; Tinmouth 2004), or by the use of a computer algorithm (Slichter 2010). Sensebe 2004 and Steffens 2002 did not provide sufficient information to determine whether individuals who graded bleeding were blinded to the intervention.

Incomplete outcome data

Two of the studies were at risk of significant bias due to an imbalance in the amount of missing data between the arms of the study (Heddle 2009; Slichter 2010). In Slichter 2010 complete data were available on 71%, 82% and 83% of platelet transfusions in the low, medium and high dose arms of the study respectively (this was a statistically significant difference). In Heddle 2009 more participants were withdrawn early from the study in the low dose arm.

Three of the studies were not at risk of bias due to incomplete outcome data (Roy 1973; Sensebe 2004; Tinmouth 2004). The sixth study was not reported in enough detail for this to be assessed (Steffens 2002).

Selective reporting

Only one of the six studies was free of selective reporting (Slichter 2010). In two further studies (Sensebe 2004; Tinmouth 2004), an assessment could not be made due to a lack of information. Three of the studies were at risk of significant bias due to selective reporting (Heddle 2009; Roy 1973; Steffens 2002). In Heddle 2009 not all of the pre-specified outcomes were reported (including platelet response; pre- and post-transfusion bleeding grade in response to dose of therapeutic platelets transfused; cost analysis). In Roy 1973 a large amount of data had been collected as demonstrated by the sentence that states: "*No correlation of the incidence of bleeding with sex, pre-transfusion haematocrit, concomitant corticosteroid therapy or the use of anti-neoplastic drugs was found*". However, none of these results were reported. Steffens 2002 has only ever been reported as an abstract, however, it mentions within this that further outcomes (such as clinical efficacy and bleeding episodes) would be reported in more detail in the future.

Protocol deviation

Three of the six studies were at risk of bias due to an imbalance in protocol deviations between the different arms of the studies

(Heddle 2009; Slichter 2010; Tinmouth 2004). The other three studies were not reported in enough detail for an assessment to be made (Roy 1973; Sensebe 2004; Steffens 2002).

In Heddle 2009, the platelet count that triggered a transfusion was higher in the low-dose treatment group (35.9% of transfusions (158/440) given at a trigger of $16 \times 10^9/L$ or more) than in the standard dose group (24.7% of transfusions (66/267) given at a trigger of $16 \times 10^9/L$ or more). In Slichter 2010, a significantly smaller proportion of transfusions were within the assigned dose range when platelet counts were compared between low dose and medium dose groups (71% vs. 80%) and between high dose and medium dose groups (70% vs. 80%). In Tinmouth 2004, a total of 15 out of 164 transfusions contravened the protocol in the low dose arm but only 3 out of 147 transfusions contravened the protocol in the standard dose arm.

Other potential sources of bias

Only two of the six studies had further potential sources of bias (Roy 1973; Heddle 2009). Three of the studies were free of any other obvious sources of bias (Sensebe 2004; Slichter 2010; Tinmouth 2004), and the sixth study was reported in insufficient detail for an assessment to be made (Steffens 2002).

In Roy 1973, there was a marked difference in population age groups between the two arms of the study, other baseline characteristics were not reported in sufficient detail for an assessment to be made. In Heddle 2009, discrepancies in the adjudication of bleeding grade occurred in 39% (433 out of 1150) of the bleeding days analysed with most of these discrepancies occurring between the grade 1 and grade 2 classifications. Although, through consensus, agreement could eventually be reached in most cases. Heddle 2009 was also stopped early due to a pre-specified stopping guideline.

All of these studies were therefore at risk of bias.

Prophylactic platelet transfusions versus alternative treatments (such as artificial platelet substitutes/platelet-poor plasma/ rFVIIa/ fibrinogen)

Higby 1974 had some significant threats to validity, with differences in the baseline characteristics between the two arms of the study.

Sequence generation and allocation concealment

Methods of randomisation and allocation concealment were not stated.

Blinding

Physicians were blinded to the treatment regimen.

Incomplete outcome data

Analysis was not performed on an intention-to-treat basis. Only 21 of the 24 randomisations were included because an as-treated analysis was performed instead.

Selective reporting

No protocol was available to comment on whether selective reporting had occurred.

Protocol deviation

No protocol deviations were reported.

Other potential sources of bias

There was a difference in baseline characteristics between the two groups of patients. Patients in the platelet-poor plasma arm of the study were significantly younger than those patients in the prophylactic platelet arm of the study.

Risk of bias in the assessment and grading of bleeding

There were ten studies in which bleeding outcomes were reported (Table 4). In four of these it was the primary outcome (Heddle 2009; Rebull 1997; Slichter 2010; Tinmouth 2004). These four studies all reported the method of assessing bleeding and the bleeding severity scale used. However, although in three of these four studies red blood cell usage was used to partially grade bleeding severity, only one study reported a definitive red cell transfusion policy (Rebull 1997), and two studies left the decision to transfuse up to local policies (Heddle 2009; Slichter 2010). Variations in red cell transfusion policies across centres within a trial could affect the assessment of bleeding grade and therefore lead to bias. Also, variations in the use of transfusions between studies could affect the results of any meta-analysis.

Effects of interventions

See: [Summary of findings for the main comparison](#)
Prophylactic platelet transfusion compared to non prophylactic or therapeutic platelet transfusion for prevention of haemorrhage after chemotherapy and stem cell transplantation; [Summary of findings 2](#) Prophylactic platelet transfusion at threshold of 10,000 compared to higher transfusion threshold (20,000 or 30,000) for patients with a haematological disorder; [Summary of findings 3](#) Prophylactic platelet transfusion with one dose schedule compared to prophylactic platelet transfusions with another dose schedule for patients with a haematological disorder; [Summary of findings 4](#) Prophylactic platelet transfusion compared to platelet-poor plasma for patients with a haematological disorder

In all the included studies, the study's own definition of clinically significant bleeding was used, unless otherwise stated. If the study

did not explicitly define clinically significant bleeding it was assumed that WHO grade 2 or above bleeding was clinically significant bleeding because the majority of newer studies have used this as the definition of clinically significant bleeding (Heddle 2009; Slichter 2010; Stanworth 2010).

Prophylactic platelet transfusions versus therapeutic platelet transfusions.

Three studies were included in this type of platelet study (Murphy 1982; Sintnicolaas 1982; Solomon 1978).

Number and severity of bleeding episodes

Bleeding outcomes were only reported for one of the three studies (Murphy 1982).

Number of participants with a significant bleeding event

The number of participants with a significant bleeding event showed a trend towards an increased risk of bleeding in the therapeutic arm (RR 1.66; 95% CI 0.90 to 3.04), however the confidence intervals included 1.0 (no effect) i.e. this was not statistically significant (Analysis 1.1). Murphy 1982 also reported this outcome for cases of AML and ALL separately (Analysis 1.1), but this subgroup analysis also showed no significant difference between the two arms of the study.

Number of days with a significant bleeding event

There was no significant difference between the two arms in the number of days on which significant bleeding occurred (RR 0.9; 95% CI 0.62 to 1.32) (Analysis 1.2). Murphy 1982 also reported this outcome for cases of AML and ALL separately (Analysis 1.2), but this subgroup analysis also showed no significant difference between the two arms of the study.

Time to first significant bleeding event

The time to the first significant bleeding event was only reported graphically (Murphy 1982). Murphy 1982 also reported this outcome for cases of AML and ALL separately. The time to the first significant bleeding event was significantly longer for ALL patients in the prophylactic platelet transfusion arm but there was no significant difference between the two arms of the study for AML patients.

Severity of bleeding episodes

None of the studies reported the number of patients with bleeding that required a red cell transfusion.

None of the studies reported the number of patients with bleeding that caused cardiovascular compromise.

Mortality

All-cause mortality

This was reported in two of the three studies (Murphy 1982; Solomon 1978). Meta-analysis of the data was performed and no significant difference in all-cause mortality (RR 0.97; 95% CI 0.48 to 1.93) was seen between prophylactic and therapeutic platelet transfusions. There was no evidence of heterogeneity in all cause mortality.

Mortality secondary to bleeding

This was reported for all of the studies (Murphy 1982; Sintnicolaas 1982; Solomon 1978). A meta-analysis of the data from two of the studies (Murphy 1982; Solomon 1978) was performed and no significant difference in mortality due to bleeding (RR 1.08, 95% CI 0.23 to 5.06) was seen between prophylactic and therapeutic platelet transfusions (Analysis 1.4). There was the possibility of moderate heterogeneity in mortality due to bleeding ($I^2=41\%$), however this may be explained by the small size of both studies (this could not be explored further using formal statistical analysis due to a lack of data). Although no deaths due to bleeding occurred in Sintnicolaas 1982, a meta-analysis could not be performed because it was unknown how many patients were randomised to each arm of the study.

Number of platelet transfusions

Two of the three studies reported the number of platelet units given (Murphy 1982; Solomon 1978) (see Table 5), but a meta-analysis was unable to be performed because the figures were reported in different units and SDs were not reported by Murphy (Murphy 1982). Despite this limitation, there was evidence of a clear reduction in platelet usage between the prophylactic and therapeutic arms. In Solomon 1978 there was a mean difference (MD) (fixed-effect) of -15.8 platelet units per course of chemotherapy (95% CI -19.2 to -12.4).

Number of red cell transfusions

Only Solomon 1978 reported the mean number of red cell units given per patient (Table 5). There was a small reduction in red

cell usage in the prophylactic arm, but this was not statistically significant (MD (fixed-effect) -0.6 units, 95% CI -1.34 to 0.14).

Disease free survival

Only [Murphy 1982](#) reported disease free or all cause survival rates. However, this was only reported graphically. There was no significant difference seen between the two arms. At 10 months, average survival rate in the therapeutic arm was approximately 86% SD \pm 8% and in the prophylactic arm was approximately 91% SD \pm 8%.

Complete remission

Only [Solomon 1978](#) reported complete or partial remission rates. There was no significant difference between complete remission rates between the two arms of the study (RR 1.06, 95% CI 0.50 to 2.27).

Time in hospital

None of the studies reported the length of time that the patients were in hospital.

Adverse events

Two of the three studies reported any adverse events ([Murphy 1982](#); [Sintnicolaas 1982](#)). The only adverse event reported was platelet refractoriness.

Transfusion reactions

None of the studies reported transfusion reactions.

Thromboembolic disease

None of the studies reported thromboembolic disease.

HLA antibodies/platelet refractoriness

Platelet refractoriness was defined in [Murphy 1982](#) as bleeding for more than 4 days in which thrombocytopenia persists in the face of repeated platelet transfusions. This showed a trend towards a decreased risk of developing platelet refractoriness in patients in

the therapeutic arm but this was not statistically significant (RR 0.33, 95% CI 0.04 to 2.66). In [Sintnicolaas 1982](#), two patients became refractory to platelets (no definition given) one in each arm of the study but it was unknown how many patients were randomised to each arm of the study.

Pre-specified subgroup analysis

Treatment and diagnostic subgroups

These were only reported in [Murphy 1982](#) (see paragraph on number and severity of bleeding episodes above). There was no statistically significant difference between the subgroups of AML and ALL when number of participants with a significant bleeding event were compared ($P=0.1$; $I^2=64.1\%$).

Fever

None of the studies commented on an association between fever and bleeding risk.

Prophylactic platelet transfusion with one trigger level versus prophylactic platelet transfusion with another trigger level

Three studies were included in this type of platelet transfusion study ([Diedrich 2005](#); [Heckman 1997](#); [Rebulla 1997](#)).

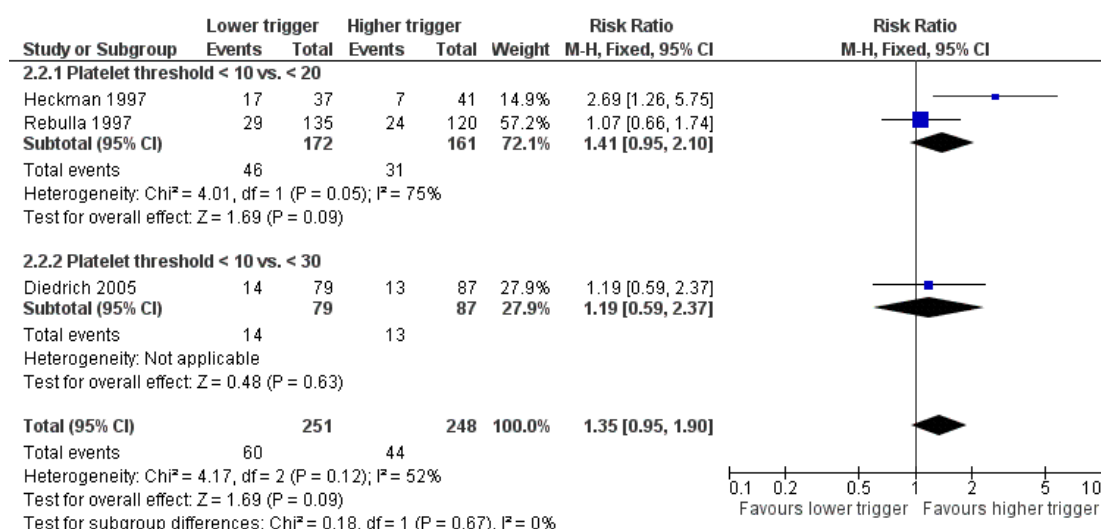
Number and severity of bleeding episodes

Bleeding outcomes were reported for all three studies.

Number of participants with a significant bleeding event

This was reported for two of the three studies ([Diedrich 2005](#); [Rebulla 1997](#)), and data from the third study was supplied by the author ([Heckman 1997](#)). A meta-analysis of this data showed no significant difference between a lower versus a higher transfusion trigger level (RR 1.35, 95% CI 0.95 to 1.90) ([Figure 3](#)), nor was any significant difference seen if the studies comparing a threshold of $10 \times 10^9/L$ versus $20 \times 10^9/L$ were analysed separately (RR 1.41; 95% CI 0.95 to 2.1) ([Heckman 1997](#); [Rebulla 1997](#)), to that compared a threshold of $10 \times 10^9/L$ versus $30 \times 10^9/L$ (RR 1.19, 95% CI 0.59 to 2.37) ([Diedrich 2005](#)).

Figure 3. Forest plot of comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, outcome: 2.2 Numbers of participants with a significant bleeding event.



Number of days with a significant bleeding event

This was reported in [Rebulla 1997](#); data from a second study was supplied by the author ([Heckman 1997](#)). The author of the third study was contacted but this data was no longer available ([Diedrich 2005](#)). A meta-analysis of the available data showed that there was a higher number of days with clinically significant bleeding in the arm with a lower transfusion trigger level and that this result was statistically significant (RR 1.72, 95% CI 1.33 to 2.22) ([Figure 4](#)).

Figure 4. Forest plot of comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, outcome: 2.4 Number of days with a significant bleed.



Time to first significant bleeding event

None of the studies reported the time to first significant bleeding event.

Severity of bleeding episodes

Only [Diedrich 2005](#) reported the number of patients with bleeding that required a red cell transfusion. There was no significant difference between a lower versus a higher transfusion trigger level

(RR 0.65, 95% CI 0.15 to 2.8).

None of the studies reported the number of patients with bleeding that caused cardiovascular compromise.

Two of the studies (Diedrich 2005; Rebulla 1997) reported the number of patients with WHO grade 3 and 4 bleeding. A meta-analysis of this data showed no statistically significant difference between a lower versus a higher trigger level (RR 0.99, 95% CI 0.52 to 1.88).

None of the studies reported the number of patients with WHO grade 4 bleeding alone.

Mortality

All-cause mortality

This was reported for two of the three studies (Heckman 1997; Rebulla 1997). In Heckman 1997, the number of study participants who had died was reported at the time of data analysis rather than those that occurred during the initial study period (Rebulla 1997) because of these differences a meta-analysis was not performed. In Heckman 1997, 25 out of 37 patients died in the lower threshold arm and 29 out of 41 patients died in the higher threshold arm, this was not a statistically significant difference. In Rebulla 1997, 18 out of 135 patients died in the lower threshold arm and 9 out of 120 patients died in the higher threshold arm, this was not a statistically significant difference.

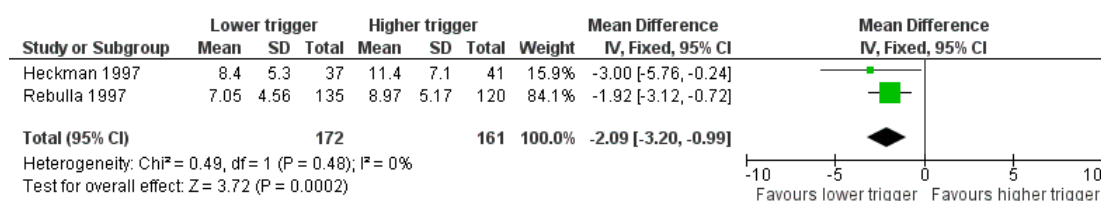
Mortality secondary to bleeding

Death due to bleeding was reported for all three studies, but it was only in the largest study that any deaths occurred (Rebulla 1997). One death due to intracerebral haemorrhage in the lower trigger arm was included in the analysis (RR 2.67, 95% CI 0.11 to 64.91), however two further deaths due to intracerebral haemorrhage (one in each arm of the study) were in patients who were randomised but not included in the analysis. If analysis of the data included all patients randomised then there was still no evidence of a statistically significant difference in death rate between the two arms of the study (RR 1.86, 95% CI 0.17 to 20.26) (assuming that those patients on which no data forms were returned did not die secondary to bleeding).

Number of platelet transfusions

All three studies reported on the number of platelet transfusions required. Diedrich 2005 reported the results as medians and ranges and showed a statistically significant decrease in the median number of platelet transfusions required in the lower trigger level arm (median 4; range 0 to 32 versus median 10; range 0 to 48). A meta-analysis of the other two studies, unpublished data of Heckman 1997 and Rebulla 1997, showed a statistically significant reduction in the mean number of platelet transfusions required in the low threshold arm (MD (fixed-effects) -2.09, 95% CI -3.20 to -0.99) (Figure 5).

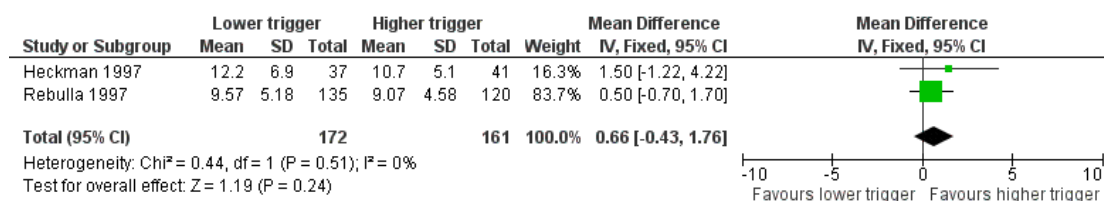
Figure 5. Forest plot of comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, outcome: 2.8 Mean number of platelet transfusions per patient.



Number of red cell transfusions

All three studies reported on the number of red cell transfusions required. One of the studies reported the results as medians and ranges and showed no difference in the red cell transfusion requirement (median 4; range 0 to 26 in the lower trigger arm versus median 4; range 0 to 31 in the higher trigger arm). A meta-analysis of the other two studies, unpublished data of [Heckman 1997](#) and [Rebulla 1997](#), showed no statistically significant difference between the two arms in the mean number of red cell transfusions required (MD (fixed effects) 0.66, 95% CI -0.43 to 1.76) ([Figure 6](#)).

Figure 6. Forest plot of comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, outcome: 2.9 Mean number of red cell transfusions per patient.



Disease free survival

Only [Diedrich 2005](#) reported a Kaplan-Meier probability at 3 years of disease-free survival; and reported no significant difference between the two arms of the study. The three studies reported all-cause survival in various ways and none showed a significant difference between the two arms of the study.

Complete remission

Two of the studies reported the number of patients who had achieved a complete remission ([Heckman 1997](#); [Rebulla 1997](#)). A meta-analysis of this data showed no evidence of a difference between the two arms (RR 0.92, 95% CI 0.78 to 1.09) ([Figure 7](#)).

Figure 7. Forest plot of comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, outcome: 2.10 Remission rates.



Time in hospital

All of the studies reported the length of time that the patients were in hospital. These were all reported as medians with ranges or interquartile ranges (IQR) (Table 6). Therefore, a meta-analysis could not be performed. Two of the studies reported no statistically significant difference in hospital stay between the arms of the study (Diedrich 2005; Heckman 1997), whereas the third study did not report any P values (Rebulla 1997).

Adverse events

All of the studies reported at least one adverse event of platelet transfusions.

Transfusion reactions

Only Heckman 1997 reported on transfusion reactions secondary to platelet transfusions. There was no statistically significant difference between the two arms of the study (RR 0.07, 95% CI 0.00 to 1.09).

Thromboembolic disease

Only Rebulla 1997 reported deaths due to thromboembolic disease. There was one death in each arm of the study.

HLA antibodies/platelet refractoriness.

Only Diedrich 2005 reported on the development of HLA antibodies. There was no statistically significant difference between the two arms of the study (RR 1.10, 95% CI 0.07 to 17.31). Two of the studies reported on the development of platelet refractoriness (Diedrich 2005; Heckman 1997). A meta-analysis of this data showed no significant difference between the different transfusion trigger levels (RR 0.66, 95% CI 0.16 to 2.67).

Pre-specified subgroup analysis

Heterogeneity between the subgroups could not be assessed formally due to a lack of data.

Treatment and diagnostic subgroups

Heckman 1997 performed a subgroup analysis that compared newly diagnosed versus relapsed acute leukaemia patients. The relapsed patients had 2.1 fewer bleeding episodes during the study. However, in a multivariate analysis, performed by the study authors, that included age, disease status and arm of the study this difference was not statistically significant.

Fever

Two of the studies commented on an association between fever and bleeding risk (Heckman 1997; Rebulla 1997).

In Heckman 1997, the authors reported a statistically significant association between the number of febrile days and an increase in the number of platelet transfusions but not between the number of febrile days and the total number of bleeding events.

A retrospective multivariate analysis of the data from Rebulla 1997 by Webert 2006 showed that an increase in body temperature increased the risk of clinically significant bleeding (WHO grade 2 to 4) the following day. After they had controlled for the platelet count (which was the only other factor in their analysis that significantly affected bleeding risk), the presence of an elevated body temperature was associated with an 87% increase in the risk of clinically significant bleeding. This effect was more pronounced at higher body temperatures (> 38.5°C). However, this effect was not seen when they analysed only WHO grade 3 and 4 bleeding events.

Prophylactic platelet transfusion with one dose schedule versus prophylactic platelet transfusion with another dose schedule

Six studies were included in this type of platelet transfusion study (Heddle 2009; Roy 1973; Sensebe 2004; Slichter 2010; Steffens 2002; Tinmouth 2004).

Number and severity of bleeding episodes

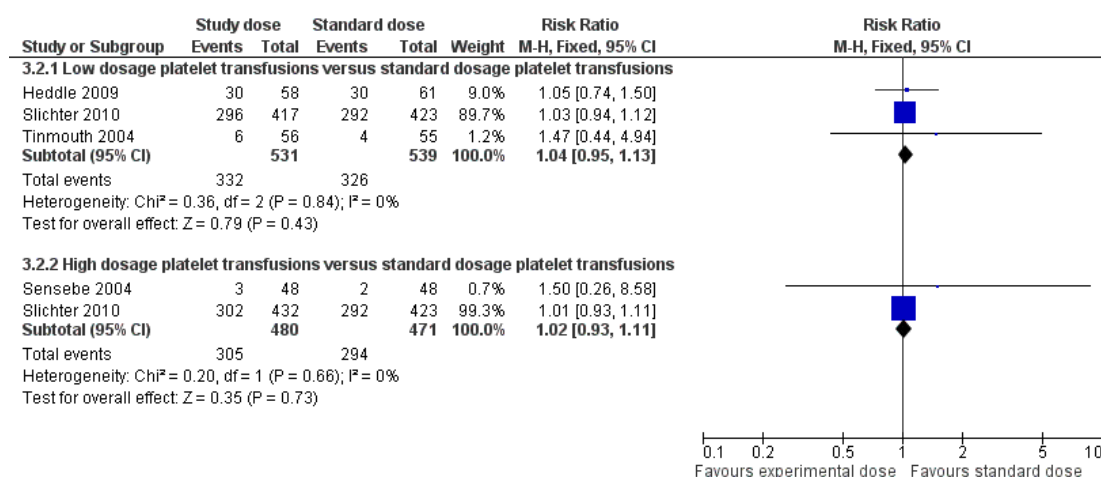
Five of the six studies reported bleeding as an outcome. Three studies compared a low dosage versus standard dosage platelet transfusion. Two studies showed no significant difference in the number or severity of bleeding episodes between low dosage versus standard dosage platelet transfusions (Slichter 2010;

Tinmouth 2004). The third study was stopped early according to a pre-defined stopping rule because of an excessive number of severe bleeding episodes in the low dosage arm (Heddle 2009). Three studies compared standard dosage versus high dosage platelet transfusions (Roy 1973; Sensebe 2004; Slichter 2010). None of these studies showed any significant difference in the number or severity of bleeding episodes.

Number of participants with a significant bleeding event

This was reported for four of the six studies (Figure 8).

Figure 8. Forest plot of comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, outcome: 3.2 Number of participants with a significant bleeding event.



Three studies compared a low dosage versus standard dosage platelet transfusion (Heddle 2009; Slichter 2010; Tinmouth 2004). A meta-analysis of this data showed no statistically significant difference in the number of participants who had clinically significant bleeding (RR 1.04, 95% CI 0.95 to 1.13) with relatively narrow 95% confidence intervals.

Two studies compared a high dosage versus standard dosage platelet transfusion (Sensebe 2004; Slichter 2010). A meta-analysis of this data showed no statistically significant difference in the number of participants who had significant bleeding (RR 1.02, 95% CI 0.93 to 1.11) with relatively narrow 95% confidence intervals.

Number of days with a significant bleeding event

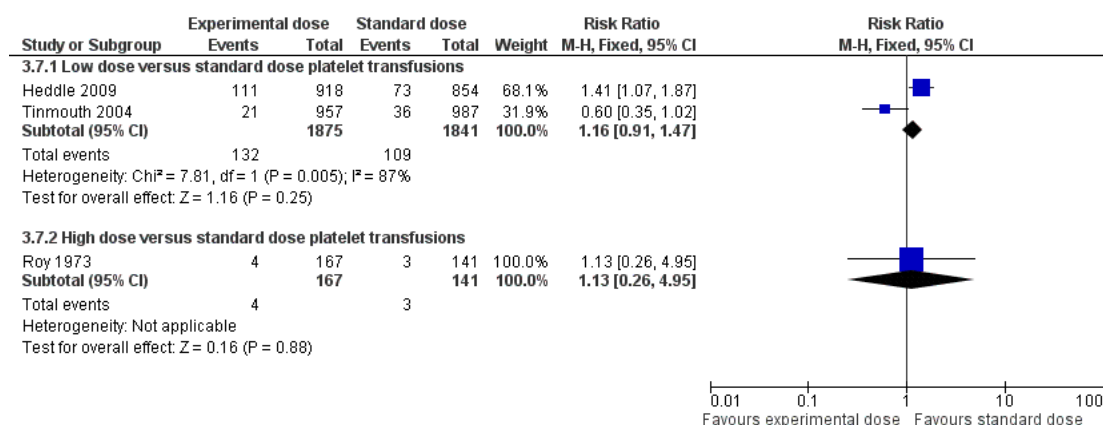
Three of the studies reported on the number of days with a sig-

nificant bleeding event (Roy 1973; Heddle 2009; Slichter 2010, and a fourth study provided unpublished data (Tinmouth 2004). In Slichter 2010, it was reported as the median number of days with WHO grade 2 or above bleeding per patient (Table 7), and no significant difference was seen between the arms of the study. Authors of Heddle 2009 and Tinmouth 2004 studies provided unpublished data on the mean number of days with bleeding. Despite re-classifying significant bleeding in Tinmouth 2004 as the number of days with bleeding that required an intervention or a therapeutic platelet transfusion (rather than the study definition - in an attempt to decrease the differences in how bleeding events were defined between studies) there was still substantial heterogeneity (I²=64%) when an attempt was made to combine the data. A formal analysis of the reasons for this could not be performed but there were several possible reasons. Firstly, Tinmouth

2004 included 24 patients who never received a platelet transfusion, these were specifically excluded from analysis of Heddle 2009. Secondly, Tinmouth 2004 randomised patients at initiation of chemotherapy and the study was stopped when they had a clinically significant bleed, whereas in Heddle 2009, patients were randomised when they received their first prophylactic platelet transfusion and they remained within the study until platelet count recovery or discharge from hospital. Thirdly, the majority of patients in Tinmouth 2004 were patients receiving an autologous stem cell transplant (77/111) whereas in Heddle 2009 the majority of patients had acute leukaemia (103/119). The data was also

skewed and therefore a meta-analysis was not performed. In Roy 1973, Heddle 2009 and Tinmouth 2004 (unpublished data), the total number of days in each arm in which significant bleeding occurred was reported. Again these studies showed substantial heterogeneity (for the reasons above). In Heddle 2009, it showed a significantly larger number of days with bleeding in the low dosage arm of the study (RR 1.41, 95% CI 1.07 to 1.87). In Tinmouth 2004, there was no significant difference between the two arms of the study (RR 0.6, 95% CI 0.35 to 1.02) (in the number of days with bleeding that required an intervention or a therapeutic platelet transfusion) (Figure 9).

Figure 9. Forest plot of comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, outcome: 3.3 Number of days with significant bleeding.



Time to first significant bleeding event

This was reported for two of the six studies (Heddle 2009; Slichter 2010). A meta-analysis was unable to be performed because the data were reported in different formats. In Heddle 2009, there was no significant difference seen in the time taken for patients receiving low dosage or standard dosage platelets to develop bleeding of WHO grade 2 or above. In Slichter 2010, there was no significant difference in the time to first significant bleeding event (Table 8).

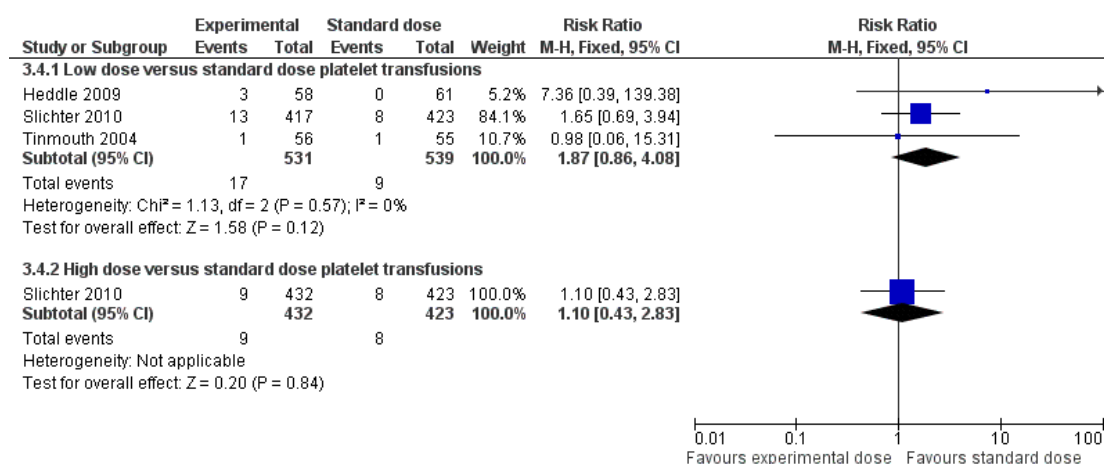
Severity of bleeding

Two of the studies reported the number of patients with WHO grade 3 or 4 bleeding (Heddle 2009; Slichter 2010). A meta-

analysis was performed that compared low dose versus standard dose platelet transfusions and no significant difference was seen (RR 1.33, 95% CI 0.91 to 1.92). In Slichter 2010, no significant difference was seen between high dose and standard dose platelet transfusions in the incidence of grade 3 and 4 bleeding (RR 1.11, 95% CI 0.73 to 1.68).

Three of the studies reported the number of patients who could be classified as having grade 4 bleeding (Heddle 2009; Slichter 2010; Tinmouth 2004). A meta-analysis was performed that compared low dose versus standard dose platelet transfusions and no significant difference was seen (RR 1.87, 95% CI 0.86 to 4.08) (Figure 10). In Slichter 2010, no significant difference was seen between high dose and standard dose platelet transfusions in the incidence of grade 4 bleeding (RR 1.10, 95% CI 0.43 to 2.83).

Figure 10. Forest plot of comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, outcome: 3.6 Number of participants with WHO grade 4 bleeding.



One of the studies reported the number of patients with bleeding that required a red cell transfusion (Heddle 2009). There was no statistically significant difference between the two arms of the study (RR 0.86, 95% CI 0.25 to 3.0).

Mortality

All-cause mortality

Data on all-cause mortality was available for four of the studies. In two of these studies this was published data (Sensebe 2004; Slichter 2010), and in the other two studies this was unpublished data (Heddle 2009; Tinmouth 2004). In Sensebe 2004, three deaths occurred over both arms of the study, all in patients with acute leukaemia, but no further details were given. In the other three studies there was no significant difference in the mortality rates between the low dosage versus standard dosage arms (RR 2.04, 95% CI 0.70 to 5.93). In Slichter 2010, there was no difference between the high dosage versus standard dosage arms of the study (RR 1.71, 95% CI 0.51 to 5.81).

Mortality secondary to bleeding

Four of the six studies reported mortality secondary to bleeding (Heddle 2009; Sensebe 2004; Slichter 2010; Tinmouth 2004). The mortality rate secondary to bleeding was very low. In all four studies there was only one death attributable to bleeding (Slichter 2010), this was a patient in the high platelet dosage arm who died secondary to a pulmonary haemorrhage.

Number of platelet transfusions

All of the studies reported on the number of platelet transfusions (Table 9), however a meta-analysis could not be performed because the data were reported in different ways. Two of the three studies comparing a low dose versus standard dosage platelet transfusion showed a significantly smaller number of platelet transfusion episodes in the standard dosage arm (Heddle 2009; Slichter 2010). Only two of the four studies comparing a high dosage versus standard dosage platelet transfusion reported P values (Sensebe 2004; Slichter 2010). Sensebe 2004 showed a significant difference in the number of platelet transfusion episodes, whereas Slichter 2010 did not. Overall, it appears that higher platelet doses led to fewer platelet transfusion episodes.

Five of the six studies reported on the total platelet utilisation, and the other study reported the number of donor exposures (Table 9), a meta-analysis could not be performed because the data were reported in different ways. Two of the three studies comparing a low dose versus standard dose platelet transfusion strategy showed a significant reduction in the total amount of platelets used (Slichter 2010; Tinmouth 2004). Only two of the four studies comparing a high dosage versus standard dosage platelet transfusion reported P values (Sensebe 2004; Slichter 2010). Slichter 2010 showed a significant difference in the total platelet utilisation, whereas Sensebe 2004 did not. Overall, it appears that higher platelet doses led to a higher total platelet utilisation.

Number of red cell transfusions

Three of the six studies reported on the number of red cell transfusions (Heddle 2009; Slichter 2010; Tinmouth 2004) (Table 9). A meta-analysis could not be performed because the data were

reported in different ways. In [Heddle 2009](#), the mean difference in red cell transfusions per thrombocytopenic day was reported and showed no significant difference between low versus standard dosage platelet transfusions ([Table 9](#)). In [Slichter 2010](#), no significant difference was seen between the various arms of the study in the number of red cell transfusions patients received ([Table 9](#)). In [Tinmouth 2004](#), no formal statistical analysis was reported.

Disease free survival

None of the six studies reported disease free or all cause survival rates.

Complete remission

None of the six studies reported complete or partial remission rates.

Time in hospital

None of the six studies reported the length of time that the patients were in hospital.

Adverse events

Transfusion reactions

Only [Slichter 2010](#) reported on transfusion reactions secondary to platelet transfusions ([Analysis 3.10](#)), and a large number of events that occurred during or within four hours of a platelet transfusion were documented. Wheezing was the only adverse event that occurred significantly more frequently in the high dosage arm of the study compared to the standard dosage arm of the study (RR 6.85, 95% CI 1.57 to 29.98). However, there was no significant difference in the frequency of wheezing when the low dosage arm of the study was compared with the high dosage arm (RR 0.52, 95% CI 0.21 to 1.27) therefore there is the possibility that this a type I error (i.e. a false positive).

Thromboembolic disease

Only one study reported on thromboembolic disease ([Slichter 2010](#)). [Slichter 2010](#) reported three episodes of venous thromboembolism in the low dosage platelet transfusion arm, with no thrombotic episodes reported in the standard or high dosage platelet transfusion arms. There was no significant difference between the arms of the study in the frequency of thromboembolic disease. [Slichter 2010](#) also reported veno-occlusive disease (VOD) of the liver, with six cases in the low dosage arm, five cases in the standard dosage arm and two cases in the high dosage arm. There

was no significant difference in the frequency of VOD between the low dosage and standard dosage arms of the study nor was any significant difference seen between the standard and high dosage arms of the study.

HLA antibodies/platelet refractoriness

None of the six studies reported on the development of HLA antibodies or platelet refractoriness.

Pre-specified subgroup analysis

Treatment and diagnostic subgroups

Two of the studies commented on disease or treatment subgroup and bleeding risk ([Slichter 2010](#); [Tinmouth 2004](#)). In [Tinmouth 2004](#), 8 out of 34 acute leukaemia patients had significant bleeding, whereas only 2 out of 77 patients receiving an autologous transplant had significant bleeding (both of these patients bled when the platelet counts were $> 100 \times 10^9/L$). In [Slichter 2010](#), bleeding of WHO grade 2 or greater occurred in 79% of recipients of allogeneic stem cell transplants (413 patients), 73% of patients with haematological cancers receiving chemotherapy (228 patients), and 57% of patients undergoing autologous or syngeneic stem cell transplantation (245 patients). There was significant heterogeneity between the two studies ($I^2=70\%$), this is likely to be secondary to the different ways in which bleeding was documented and graded between the two studies leading to a much lower rate of significant bleeding in [Tinmouth 2004](#). A meta-analysis was performed because the heterogeneity could be explained, this showed a significantly lower risk of bleeding for autologous transplant patients compared to patients receiving intensive chemotherapy or an allogeneic stem cell transplant (RR 0.73, 95% CI 0.65 to 0.82). There was no heterogeneity between the intensive chemotherapy and allogeneic subgroups ($P=0.97$; $I^2=0\%$).

Fever

None of the studies commented on an association between fever and bleeding risk.

Prophylactic platelet transfusions versus alternative treatments (such as artificial platelet substitutes/platelet-poor plasma/ rFVIIa/ fibrinogen)

Number and severity of bleeding episodes

There was only one study in this type of platelet transfusion study (Higby 1974).

Number of participants with a significant bleeding event

The risk of a significant bleed was decreased in the prophylactic platelet transfusion arm (RR 0.47, 95% CI 0.23 to 0.95) and this was statistically significant.

Number of days with a significant bleeding event

This was not reported by this study.

Time to first significant bleeding event

There was no difference between the two arms of the study in the time to first bleed (MD (fixed-effects) 0.00, 95% CI -7.57 to 7.57).

Severity of bleeding

There was no statistically significant difference in the number of patients with bleeding that required a red cell transfusion (RR 0.38, 95% CI 0.13 to 1.11).

There was no statistically significant difference in the number of patients with bleeding that caused cardiovascular compromise (RR 0.75, 95% CI 0.05 to 10.44).

Mortality

All-cause mortality

All cause mortality was not reported.

Mortality secondary to bleeding

There was no evidence for a difference in the mortality rate due to bleeding between the two arms of the study (RR 2.31, 95% CI 0.1 to 50.85).

Number of platelet transfusions and red cell transfusions

Neither the number of platelet transfusions per patient nor the number of red cell transfusions per patient were reported in the original study.

Complete remission

The rates of complete remission were lower in the prophylactic platelet arm, but this was not a statistically significant finding (RR 0.50, 95% CI 0.2 to 1.26).

Disease free survival

Survival rates were not reported in the study.

Time in hospital

The length of in-patient stay was not reported in the study.

Adverse events

This study did not report on transfusion reactions secondary to platelet transfusions, nor did it comment on any thromboembolic side-effects.

Transfusion reactions

Not reported in this study.

Thromboembolic disease

Not reported in this study.

HLA antibodies/platelet refractoriness

The number of patients who developed HLA antibodies was lower in the prophylactic platelet arm, however there was no evidence for a difference between the two arms of the study (RR 0.38, 95% CI 0.09 to 1.62).

Pre-specified subgroup analysis

Treatment and diagnostic subgroups

This type of subgroup analysis was not performed in the study.

Fever

Four out of the five patients who bled in the prophylactic platelet arm had a fever prior to bleeding and six out of the eight patients who bled in the platelet-poor plasma arm had a fever prior to the bleed. In all of these cases this fever was still present at the time of the bleed.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Prophylactic platelet transfusion at threshold of 10,000 compared to Higher transfusion threshold (20,000 or 30,000) for prevention of haemorrhage after chemotherapy and stem cell transplantation						
Patient or population: Patients with a haematological disorder Settings: Receiving intensive chemotherapy or a stem cell transplant Intervention: Prophylactic platelet transfusion at threshold of 10,000 Comparison: Higher transfusion threshold (20,000 or 30,000)						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk					
	Higher transfusion threshold (20,000 or 30,000)	Prophylactic platelet transfusion at threshold of 10,000				
Bleeding: Numbers of patients with at least one significant bleeding event	177 per 1000	239 per 1000 (168 to 336)	RR 1.35 (0.95 to 1.9)	499 (3 studies)	⊕⊕⊕○ moderate ¹	The definition of clinically significant bleeding varied between studies, because there were differences in the way bleeding was graded
Bleeding: Number of days on which clinically significant bleeding occurred ⁵	20 per 1000 ⁵	34 per 1000 ⁵ (27 to 44)	RR 1.72 (1.33 to 2.22)	9420 ⁵ (2 studies)	⊕⊕⊕○ moderate ^{2,3}	This reported the total number of days with clinically significant bleeding in either arm of the studies
Mortality: secondary to bleeding	0 per 1000	0 per 1000 (0 to 0)	RR 2.67 (0.11 to 64.91)	499 (3 studies)	⊕⊕○○ low ^{1,2,4}	There was only 1 death reported in all three studies. Although two deaths due to bleeding within the Rebutla study were excluded from the analysis

Number of platelet transfusions per patient	The mean Number of platelet transfusions per patient in the intervention groups was 2.09 lower (3.2 to 0.99 lower)	333 (2 studies)	⊕⊕⊕○ moderate ³
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ The number of participants from all three studies may not be large enough to detect a clinically significant difference. The confidence intervals are wide and there is therefore uncertainty about the result.

² The Rebullia study did not perform an intention to treat analysis and excluded two patients who died within 24 hours of entering the study

³ More protocol violations occurred in the lower threshold arm.

⁴ The number of events were very small leading to imprecision

⁵ This was the total number of days recorded within the study rather than participants

Prophylactic platelet transfusion with one dose schedule compared to prophylactic platelet transfusions with another dose schedule for prevention of haemorrhage after chemotherapy and stem cell transplantation						
Patient or population: Patients with a haematological disorder Settings: After chemotherapy or a stem cell transplant Intervention: Prophylactic platelet transfusion with one dose schedule Comparison: Prophylactic platelet transfusions with another dose schedule						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	prophy-lactic platelet transfu-sions with another dose schedule	Prophylactic platelet transfusion with one dose schedule				
Bleed-ing: Number of partici-pants with a significant bleeding event - Low dosage platelet transfu-sions versus standard dosage platelet transfu-sions	605 per 1000	629 per 1000 (575 to 684)	RR 1.04 (0.95 to 1.13)	1070 (3 studies)	⊕⊕⊕⊕⊕ high ¹	
Bleeding Number of par-ticipants with a signif-icant bleeding event - High dosage platelet transfu-sions versus standard dosage platelet transfu-sions	624 per 1000	636 per 1000 (580 to 693)	RR 1.02 (0.93 to 1.11)	951 (2 studies)	⊕⊕⊕⊕⊕ high ¹	

Bleeding Number of days with significant bleeding - Low dosage platelet transfusions versus standard dosage platelet transfusions	See comment	See comment	Not estimable	(3 studies)	See comment	Slichter reported no. of days with significant bleeding/patient and no difference was seen between low dose and standard dose. Unpublished data from Timmouth showed no difference between low dose and standard dose platelets. Heddle 2009 showed a higher number of days with significant bleeding.
Bleeding: Number of days with significant bleeding - High dosage platelet transfusions versus standard dosage platelet transfusions	See comment	See comment	Not estimable	0 (2 studies)	See comment	Slichter 2010 reported number of days with significant bleeding/patient. No difference was seen between high dosage and standard dosage platelet transfusions. Roy 1973 reported no difference in the number of days with significant bleeding
Mortality:sec- ondary to bleeding - Low dosage platelet transfusions versus standard dose platelet transfusions	See comment	See comment	Not estimable	859 (3 studies)	⊕⊕○○ low ^{2,3}	No deaths due to bleeding were reported in any of the studies
Mortality: secondary to bleeding - High dosage platelet transfusions versus standard dosage	0 per 1000	0 per 1000 (0 to 0)	RR 1.47 (0.06 to 35.9)	739 (2 studies)	⊕⊕⊕○ moderate ³	Only one death due to bleeding was reported in the high dosage arm of the Slichter study

platelet transfusions

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Although all the studies had limitations and were at risk of bias the authors did not feel that the largest study (Slichter 2010) which was much larger than any of the other studies was at sufficient risk of bias to down-grade the evidence

² The study had many protocol violations that meant patients in the low dose arm were transfused at higher thresholds. However, this should have decreased any difference between the two arms of the study.

³ The number of cases was very low

Prophylactic platelet transfusion compared to platelet-poor plasma for prevention of haemorrhage after chemotherapy and stem cell transplantation						
Patient or population: Patients with a haematological disorder Settings: Patients receiving intensive chemotherapy or a stem cell transplant Intervention: Prophylactic platelet transfusion Comparison: Platelet-poor plasma						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Platelet-poor plasma	Prophylactic platelet transfusion				
Number of participants with a significant bleeding event	889 per 1000	418 per 1000 (204 to 845)	RR 0.47 (0.23 to 0.95)	21 (1 study)	⊕○○○ very low ^{1,2}	
Mortality: secondary to bleeding	0 per 1000	0 per 1000 (0 to 0)	RR 2.31 (0.1 to 50.85)	21 (1 study)	⊕○○○ very low ^{1,2}	
Number of platelet transfusions	See comment	See comment	Not estimable	0 (1 study)	⊕○○○ very low ³	This was not reported on in the original study
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval; RR: Risk ratio;</p>						
<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>Very low quality: We are very uncertain about the estimate.</p>						

¹ This was a very small study performed more than 35 years ago. There have significant changes in patient care since his time

² The quality of platelet components may have changed since this trial was performed

³ This was not reported

DISCUSSION

The main objective of this review of prophylactic platelet transfusions was to answer certain questions that continue to cause debate.

Firstly, are prophylactic platelet transfusions superior to therapeutic platelet transfusions for the prevention and/or control of life-threatening thrombocytopenic bleeding?

(Studies from the sub-categories of prophylactic platelet transfusions versus therapeutic platelet transfusions and prophylactic platelet transfusions versus alternative treatments will be used to answer this question).

Secondly, which threshold should be used to trigger the transfusion of prophylactic platelets?

Thirdly, what is the optimal prophylactic platelet dose to prevent thrombocytopenic bleeding?

The [Authors' conclusions](#) provide our answers to these questions.

Summary of main results

Eighteen studies met the inclusion criteria for the review, five of these were ongoing studies and thirteen had data available.

Prophylactic platelet transfusions versus therapeutic platelet transfusions

Three trials that compared the effect of a prophylactic versus therapeutic platelet transfusion policy were included in the review, but only two of these studies contained separate data for each arm of the study. All of these studies were at risk of bias mainly due to lack of clarity on the methods of randomisation.

There was no significant difference in the number of participants with clinically significant bleeding. The time to first significant bleed was significantly shorter in the therapeutic arm than the prophylactic arm. There was a significant reduction in the number of platelet units required in the therapeutic transfusion arm. There was no statistically significant effect seen on overall mortality, mortality due to bleeding, red cell transfusion requirements, remission rates, or incidence of platelet refractoriness. However, due to the size of the studies they would not be adequately powered to detect important differences and this was reflected in the wide confidence intervals for any comparison.

Prophylactic platelet transfusion with one trigger level versus prophylactic platelet transfusion with another trigger level

Three trials that compared the effect of platelet transfusions at one platelet count trigger level versus another were included in this review. All of the studies were at risk of bias.

No difference was seen in the number of participants with significant bleeding between the two threshold levels, however this

result may have been affected by the greater number of protocol violations in the lower threshold arm of at least two of the studies. When the number of days with significant bleeding was analysed, there was a significant increase in the number of days with significant bleeding in the group of patients transfused at the lower platelet count threshold. There was no difference seen in the number of patients with severe or life-threatening bleeding between the two threshold levels but the confidence intervals were wide (0.52 to 1.88).

There was a statistically significant reduction in the number of platelet transfusions required using a threshold of $10 \times 10^9/L$.

There were no statistically significant differences between the groups with regards to mortality, red cell transfusion requirements, survival, remission rates, hospital stay or adverse events.

The two studies that reported on fever and bleeding risk reached different conclusions.

Prophylactic platelet transfusion with one dose schedule versus prophylactic platelet transfusion with another dose schedule

Six trials that compared the effect of platelet transfusion dosage were included in the review. Three compared a low dose versus standard dose platelet transfusion, whereas four compared a standard dose versus a high dose platelet transfusion strategy. All of the studies were at risk of bias.

There was no evidence to suggest that using a lower platelet transfusion dose increased the number of participants with clinically significant (WHO grade 2 or above), or life-threatening (WHO grade 4) bleeding.

Although a formal meta-analysis was not performed, two of the three studies did not show an increase in the total number of days with clinically significant bleeding, or an increase in the number of days per patient with clinically significant bleeding ([Slichter 2010](#); [Tinmouth 2004](#)).

Overall the trials of platelet dose showed that a low dose transfusion policy reduced patients' total platelet requirements, but at the expense of a higher number of platelet transfusions.

There were no statistically significant differences between the groups with regards to mortality, red cell transfusion requirements, survival, remission rates or hospital stay. The only adverse event that showed a significant difference between standard and high dose platelet transfusions (wheezing) was not seen when low dose and high dose platelet transfusions were compared and is therefore likely to be a type I error (i.e. a false positive).

Of interest, in those studies that reported treatment subgroups autologous transplantation was associated with a lower risk of clinically significant bleeding compared to those patients receiving myelosuppressive chemotherapy or allogeneic transplantation. However, this is an additional finding and not the focus of this review.

Prophylactic platelet transfusions versus alternative treatments (such as artificial platelet substitutes/platelet-poor plasma/ rFVIIa/ fibrinogen)

This small study was at risk of bias due to differences in the baseline characteristics of the patients as well as lack of clarity on the method of randomisation (Higby 1974). It showed a reduction in the rate of significant bleeding in those patients receiving prophylactic platelet transfusions. There was no significant difference in any of the other outcomes, including adverse events, within this comparison. In this study, fever was associated with an increased risk of bleeding. However, aspirin was still used in the 1970s as an anti-pyretic (because its anti-platelet effects were unknown at that time) and therefore this may have been a confounding factor in this study.

Overall completeness and applicability of evidence

Are prophylactic platelet transfusions superior to therapeutic platelet transfusions for the prevention and/or control of life-threatening thrombocytopenic bleeding?

Studies of prophylactic platelet transfusions versus therapeutic platelet transfusions

The two reports of controlled trials that addressed the question of a prophylactic versus therapeutic platelet transfusion policy contained small numbers of patients and were undertaken over 30 years ago. These studies were performed at a time when different quality control measures for the platelet product were applied. The possibility that the platelets in use in the 1970's would have differed in quality from those in use today does need to be considered if attempting to generalise results to the present day. Other factors that also need to be taken in to consideration are that the patients in these studies probably received less optimal supportive therapy (e.g. prophylaxis and treatment of infection), and may have received aspirin and other compounds for fever that affect platelet function (potentially increasing the risk of bleeding).

Also, one study may not actually represent a strict comparison of prophylactic versus therapeutic platelet transfusions because platelet transfusions were also given if there had been a significant reduction in the platelet count on the preceding day (Solomon 1978).

Studies of prophylactic platelet transfusions versus alternative treatments (such as artificial platelet substitutes/platelet-poor plasma/ rFVIIa/ fibrinogen)

One small study that compared prophylactic platelet transfusions versus platelet-poor plasma was conducted over 35 years ago

(Higby 1974). As in the other older studies there is concern over the ability to generalise the findings from this study to the present day. This is due to potential differences in the quality of the platelets and changes in the management of patients with haematological malignancies. It is very unlikely that a similar study will be performed again due to the fact that the control arm was still exposing patients to a transfusion product that might harm the patient but was not expected to benefit the patient and hence would be ethically unacceptable. Newer studies instead compare a therapeutic versus prophylactic platelet transfusion policy.

We are therefore unable to answer this question at the moment.

Which threshold should be used to trigger the transfusion of prophylactic platelets?

Studies of prophylactic platelet transfusion with one trigger level versus prophylactic platelet transfusion with another trigger level

No statistically significant difference was demonstrated in the number of participants with clinically significant bleeding, but the 95% confidence interval (0.95 to 1.9) demonstrates that a clinically important difference in the proportion of patients with bleeding could have been missed. The studies, when combined, were not adequately powered to detect a difference. In Rebutta 1997, which included 255 patients, the power calculations were based on the assumption that the rate of WHO grade 2 or above bleeding was 30%, but the actual rate in this study was 20%. If we assume the rate of bleeding was similar in all three studies, to detect a 50% increase in the rate of bleeding (i.e. from 20% to 30%) with 80% power would require 293 participants per arm of the study (586 in total) and to detect a 25% increase in the rate of bleeding (i.e. from 20% to 25%) with 80% power would require 1098 participants per arm of the study (2196 in total). As there were only 499 participants within all three studies, the meta-analysis would not be sufficiently powered to detect a 50% increase in the rate of bleeding in the restrictive transfusion arm. Additionally, there were important differences between the studies that might affect the degree of confidence that can be placed on the assertion of equivalence between liberal (20 or 30 x 10⁹/L) and restrictive (10 x 10⁹/L) platelet count thresholds for prophylactic platelet transfusions. The treatment protocols for administration of platelets varied, particularly the circumstances for which platelet transfusions could be given. In Rebutta 1997, platelets could be given to patients in the 10 x 10⁹/L threshold arm if the platelet count was in the range of 10 to 20 x 10⁹/L and the patient's temperature was above 38°C. This meant that 22.6% of platelet transfusions were given above the threshold of 10 x 10⁹/L. In Diedrich 2005 and Heckman 1997, there were no changes in the transfusion threshold in the presence of fever.

What is the optimal prophylactic platelet dose to prevent thrombocytopenic bleeding?

Studies of prophylactic platelet transfusion with one dose schedule versus prophylactic platelet transfusion with another dose schedule

The large number of patients within these studies provided strong evidence that there was no difference in the proportion of participants with bleeding between low dose, standard dose and high dose platelet transfusions. This was reflected in the narrow confidence intervals around the point estimates.

Although [Heddle 2009](#) did not demonstrate any difference in donor exposures between the two arms of the trial, caution needs to be taken when drawing conclusions from this trial. This is because of the large number of protocol deviations within the trial. Patients in the low dose arm were transfused at higher platelet counts, and this may explain why there was no difference in the number of donor exposures.

Also, although [Heddle 2009](#) and [Slichter 2010](#) both used a WHO grading system for bleeding the categorisation of bleeding varied between the studies. In [Slichter 2010](#), less severe bleeding was categorised as Grade 2. For example, in [Heddle 2009](#) epistaxis that lasted for more than an hour or required packing was classed as grade 2 bleeding, whereas in [Slichter 2010](#) if a patient had epistaxis that lasted for more than 30 minutes in any given 24 hour period it was classified as grade 2 bleeding. Also, in [Heddle 2009](#), ecchymoses larger than 10cm in size were classified as grade 2 bleeding, whereas in [Slichter 2010](#) purpura greater than 2.54cm (1 inch) in diameter were classified as grade 2 bleeding.

Quality of the evidence

The ability to assess the quality of the evidence was limited by most of the studies not reporting study methodology in adequate detail. For example, allocation concealment was adequate in four studies and unclear in nine studies.

Two of the four studies that blinded the bleeding assessor documented compromise to the blinding process ([Heddle 2009](#); [Slichter 2010](#)). This is likely to reflect the inherent difficulties with blinding platelet transfusion trials. Platelet dose trials have difficulties with blinding due to the different volumes of platelets to be transfused. Obviously, trials that compare therapeutic versus prophylactic transfusions or differing transfusion thresholds cannot blind the medical staff caring for the patient.

Overall, the highest quality of evidence was from the platelet dose study sub-category ([Summary of findings 3](#)). We felt that evidence from future trials would be likely to affect the results in all other sub-categories ([Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 4](#)).

Potential biases in the review process

There were no obvious biases within the review process. A wide search was conducted, the relevance of each paper identified was carefully assessed, and no restrictions were made for the language in which the paper was originally published.

AUTHORS' CONCLUSIONS

Implications for practice

Are prophylactic platelet transfusions superior to therapeutic platelet transfusions for the prevention and/or control of life-threatening thrombocytopenic bleeding?

We are still unable to answer this question. There is no evidence to change current practice at the moment, and the results from the trials that have just completed recruitment are awaited ([Stanworth 2010](#); [Wandt 2009](#)).

Which threshold should be used to trigger the transfusion of prophylactic platelets?

The evidence does not clearly show equivalence of a threshold of $10 \times 10^9/L$ or $20 \times 10^9/L$. However, without further evidence it is reasonable to continue with the current practice of a platelet transfusion threshold of $10 \times 10^9/L$ in the absence of other risk factors for bleeding. This practice reduces platelet utilisation and donor exposure.

What is the optimal prophylactic platelet dose to prevent thrombocytopenic bleeding?

Most published guidelines do not suggest an optimal platelet dose for transfusion. The use of low dose prophylactic platelet transfusions for intensively treated in-patients and medium to high dose for outpatients could be considered. This would decrease the total platelet utilisation for inpatients. For out-patients it would decrease the frequency of day-unit attendances for transfusions, which could not only improve a patient's quality of life but also have resource and budget implications.

Implications for research

Are prophylactic platelet transfusions superior to therapeutic platelet transfusions for the prevention and/or control of life-threatening thrombocytopenic bleeding?

We are awaiting evidence from the two trials in progress at the moment that compare a therapeutic versus prophylactic transfusion policy (Stanworth 2010; Wandt 2009). It is unlikely that any future trials will compare a policy of prophylactic platelet transfusions versus platelet-poor plasma.

Which threshold should be used to trigger the transfusion of prophylactic platelets?

The evidence for use of a platelet count threshold of $10 \times 10^9/L$ needs to be re-addressed. Conclusions on the non-inferiority of a platelet count threshold of $10 \times 10^9/L$ compared to $20 \times 10^9/L$ or $30 \times 10^9/L$ have been based on under-powered studies. However, whether the morning platelet count should be used to guide prophylactic platelet transfusions at all has recently been brought into question (Gerday 2009). Friedmann 2002 performed a large retrospective analysis that demonstrated no relationship between morning platelet count and bleeding risk and in the recent PLADO study the number of days on which WHO grade 2 or above bleeding occurred was similar (17%) at platelet counts between $6 \times 10^9/L$ and $80 \times 10^9/L$.

What is the optimal prophylactic platelet dose to prevent thrombocytopenic bleeding?

If possible, further data are required from Slichter 2010 to assess whether there is an increase in the number of days with clinically significant bleeding at a low platelet transfusion dose. If this confirms that there is no difference in the number of days with bleeding overall and the mean number of days with bleeding per patient then no further studies are required.

Assessment of bleeding in future trials

One of the difficulties within this review was the variability between studies in assessing and grading bleeding. The WHO classification of bleeding, although widely used, has never been validated, and therefore the assumption that all grade 2 bleeding is clinically significant has been brought into question. For future studies an agreed international consensus on assessing and grading bleeding would greatly enhance the ability to compare platelet transfusion trials. This would need to be validated and to take into account the impact bleeding has upon the patient from both a medical perspective and with regard to their quality of life. It is acknowledged that blinding in platelet transfusion trials is difficult. However, whenever possible, the bleeding assessor should be blinded to the intervention.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Diedrich 2005

Methods	Parallel RCT (enrolled September 1996 to September 2001). Single centre. Sweden	
Participants	Inclusion criteria: Patients undergoing an allogeneic haematopoietic stem cell transplant. All ages Exclusion criteria: Patients with a known bleeding disorder or coagulopathy N = 166 (All included in analysis) Arm 1 N = 79 (acute leukaemia N = 47; chronic leukaemia N = 20; non-malignant haematological disorder N = 4; other malignancy N = 8) Arm 2 N = 87 (acute leukaemia N = 36; chronic leukaemia N = 24; non-malignant haematological disorder N = 11; other malignancy N = 16)	
Interventions	Comparison between prophylactic platelets with different transfusion triggers Arm 1 (Low transfusion trigger): If platelet count < 10 x 10 ⁹ /L Arm 2 (High transfusion trigger): If platelet count < 30 x 10 ⁹ /L In both arms prior to an operation or a biopsy, a platelet count > 50 x 10 ⁹ /L was aimed for. Platelet dose (mean ± S.D.): <ul style="list-style-type: none">• (buffy coat) approximately 410 x 10⁹ ± 20 x 10⁹• (apheresis) approximately 380 x 10⁹ ± 20 x 10⁹ Platelet type: pooled random donor platelets (buffy coat) 85% of platelet transfusions given; apheresis 15% of platelet transfusions given. All were ABO matched, irradiated and leuco depleted	
Outcomes	Primary outcome: - Number of platelet transfusions Secondary outcomes included: <ul style="list-style-type: none">• RBC transfusions• Haemorrhages• GvHD• Transplantation related mortality• Survival Average number of days patients on study Not reported	
Notes	Patients randomised: documentation for study started 7 days prior to transplant Follow-up: until 30 days post stem cell transplant. Stopping rules: not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomised after stratification, method of randomisation not stated

Diedrich 2005 (Continued)

Allocation concealment (selection bias)	Unclear risk	Patients were randomised after stratification, method of allocation concealment not stated
Blinding (performance bias and detection bias) Assessor of bleeding assessment	Low risk	Nurses from the ward, blinded to treatment arm, performed daily (inpatients) or twice a week (outpatients) bleeding assessment and reported this. A special research nurse collected all data for the study
Blinding (performance bias and detection bias) Physician/Medical Staff	High risk	All platelet units were ordered by a different nurse in charge of and responsible for the patient. He or she was not blinded, for practical reasons, to the treatment arm
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make an assessment
Selective reporting (reporting bias)	Unclear risk	No protocol available to assess whether all pre-specified outcomes have been reported
Other bias	Low risk	The study appears to be free of other sources of bias
Protocol Deviation balanced?	Unclear risk	In patients with WHO grade 2-4 bleeding, violations of the protocol occurred in 4/14 patients in Arm 1 and 3/13 patients in Arm 2. The number of transfusions in which a protocol deviation occurred was not reported. Whether there were any protocol deviations in those patients that did not bleed was not reported

Heckman 1997

Methods	Parallel RCT (enrolled April 1991 to November 1995). Single centre. USA
Participants	<p>Inclusion criteria: - Unequivocal diagnosis of acute leukaemia (AML, ALL in relapse, acute undifferentiated leukaemia or MDS transformed to AML). Age > 17yrs. Patient undergoing initial induction chemotherapy, or re-induction following relapse</p> <p>Exclusion criteria: - APL. Inherited clotting disorder. Uncontrolled infection at randomisation. History of a bleeding diathesis. DIC at randomisation into the study. Prior entry into the study. Concomitant malignancy or AIDs diagnosis. History of platelet refractory status</p> <p>N=82 entered into study; 4 ineligible (2 delayed cytogenetic diagnosis of APL. 2 not assessable, transferred to ITU within 24 hrs of registration with severe infections).</p> <p>Arm 1: N=37</p> <p>Arm 2: N= 41</p>

Interventions	Comparison between prophylactic platelets with different transfusion triggers Arm 1 (Low transfusion trigger). If platelet count $\leq 10 \times 10^9/L$ Arm 2 (High transfusion trigger). If platelet count $\leq 20 \times 10^9/L$ Platelets given in both arms if serious or life-threatening bleeding and for procedures at discretion of physician Platelet dose: 1 apheresis unit (approximately $4\text{-}4.9 \times 10^{11}$ of platelets) Platelet type: apheresis. Leucodepleted.	
Outcomes	Main or primary outcome not stated Outcomes mentioned <ul style="list-style-type: none">• Survival (at time of analysis)• Remission rates (time period not stated)• Bleeding episodes per patient• Transfusion requirements (platelets, red cells)• Hospital stay• Adverse events Number of days patients on study (median): Arm 1: 24 days Arm 2: 24 days	
Notes	Patients randomised: no definition Follow-up of patients: until unsupported platelet count $> 30 \times 10^9/L$ for 2 days OR transfer to intensive care for > 2 days OR discharge from hospital OR death Stopping guideline: not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation "by selecting randomised cards from envelopes". No comment on how cards were randomised Randomisation stratified by four groups [new diagnosis <60 y; new diagnosis = 60 y; relapse <60 y; relapse =60y]
Allocation concealment (selection bias)	Unclear risk	Attempt to conceal allocation not described. It was not mentioned whether envelopes were opaque or sealed
Blinding (performance bias and detection bias) Assessor of bleeding assessment	High risk	Assessor of bleeding was variable. Doctors and nurses would know randomisation because of having to treat depending on a threshold
Blinding (performance bias and detection bias) Physician/Medical Staff	High risk	Authors felt doctors may be more prone to treat minor bleeding with platelet transfusions in $<10,000$ group

Heckman 1997 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting to allow assessment.
Selective reporting (reporting bias)	Unclear risk	No study protocol available and outcomes not clearly stated.
Other bias	Unclear risk	Insufficient information to assess.
Protocol Deviation balanced?	High risk	In Arm 1 30/311 transfusions deviated from the protocol whereas in Arm 2 only 7/457 transfusions deviated from the protocol. This affected 14/37 patients in Arm 1 and 6/41 patients in Arm 2 (P = 0.02)

Heddle 2009

Methods	Parallel RCT (enrolled October 2003-June 2007). Multi-national study (Canada 3 centres, Norway 1 centre, USA 2 centres)
Participants	<p>Inclusion Criteria: Hypoproliferative thrombocytopenia where platelet count was expected to be $< 10 \times 10^9/L$ for ≥ 10 days; receiving treatment as an in-patient; weight between 40-100kg; minimum age 17 yrs</p> <p>Exclusion Criteria: APL; pregnant; history or current diagnosis of ITP, TTP or HUS; evidence of \geq WHO grade 2 bleeding at time of study assessment; indication for bedside leukoreduced platelet components</p> <p>N = 129 randomised; 119 included in analysis (6 did not require platelet transfusions; 1 withdrew from trial before receiving platelets; 3 no bleeding assessment data)</p> <p>Arm 1 N = 58 (acute leukaemia N = 51; lymphoma N = 4; carcinoma N = 1; MDS N = 1; plasma cell dyscrasia N = 1)</p> <p><i>N = 7 withdrew early (1 patient decision; 6 physician decision)</i></p> <p>Arm 2 N = 61 (acute leukaemia N = 52; chronic leukaemia N = 2; lymphoma N = 3; MDS N = 2; plasma cell dyscrasia N = 1; other N = 1)</p> <p><i>N = 3 withdrew early (2 patient decision; 1 physician decision)</i></p>
Interventions	<p>Comparison between prophylactic platelet transfusions with different platelet dosages</p> <p>Arm 1 Low dose (1.5 to 3.0×10^{11} platelets/product)</p> <p>Arm 2 Standard dose (3.0 to 6.0×10^{11} platelets/product)</p> <p>Transfusion thresholds: Prophylactic platelet transfusion threshold depended on local transfusion trigger. Most centres used trigger of $10 \times 10^9/L$. Higher triggers were used in special circumstances (e.g. sepsis) at the discretion of the treating physician</p> <p>Type of platelet transfusion: Both US sites used leucodepleted apheresis platelets. Canadian sites used both apheresis and random donor pooled platelets (both leucodepleted). Norwegian site used apheresis and random donor pooled platelets</p>
Outcomes	<p>Primary outcome: -Occurrence of a WHO grade 2 or higher bleed</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Frequency of individual grades of bleeding (grades 1-4) • Time to first bleed

	<ul style="list-style-type: none">• Duration of thrombocytopenia• Platelet transfusions requirements• Red cell transfusion requirements• Interval between platelet transfusions• Modeling the recurrent event analysis to determine the mean number of bleeding days over time per 100 patients Number of days of thrombocytopenia (mean ± SD) Arm 1 = 15.8 ± 9.3 Arm 2 = 14.0 ± 9.0	
Notes	Patients randomised at: time of first prophylactic platelet transfusion. (usually when platelet count < 10 x 10 ⁹ /L - depended on local trigger). Followed up of patients: until bone marrow recovery (unsupported platelet count > 50 x 10 ⁹ /L) OR 30 days from randomisation OR discharge from hospital OR patient withdrawal OR death Stopping guideline: Study to be stopped if difference in the proportion of grade 4 bleeding between the 2 treatment arms exceeded 5% at any time after 50 patients had been enrolled per arm	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated, stratified by centre and diagnostic group. Block randomisation was used with variable block sizes within strata to help conceal treatment allocation
Allocation concealment (selection bias)	Low risk	Allocated through a secure central web-based randomisation system. Block randomisation was used with variable block sizes within strata to help conceal treatment allocation
Blinding (performance bias and detection bias) Assessor of bleeding assessment	Low risk	Bleeding assessment was performed each morning during the period of thrombocytopenia by personnel who were blinded to the platelet dose assigned to the patient
Blinding (performance bias and detection bias) Physician/Medical Staff	High risk	Although study was meant to be blinded authors were concerned that this was not always the case. 7 patients withdrawn from the study early 1 in standard dose arm and 6 in low dose arm
Incomplete outcome data (attrition bias) All outcomes	High risk	2 patients in standard group and 1 patient in low risk group had missing data (not included in analysis). 10 patients withdrew from the study early for the following rea-

Heddle 2009 (Continued)

		sons; patient decision to withdraw (N = 3: 2 standard dose; 1 low dose); physician decision to withdraw (N = 7: 1 standard dose; 6 low dose). Therefore early withdrawal unbalanced between the two groups
Selective reporting (reporting bias)	High risk	Not all of the pre-specified outcomes were reported. Including platelet response; pre and post transfusion bleeding grade in response to dose of therapeutic platelets transfused; cost analysis
Other bias	High risk	Discrepancies in adjudication of bleeding grade between the first 2 adjudicators in 39% (433/1150) of the bleeding days adjudicated. However, through consensus, agreement could be reached. Most of the discrepancies occurred between the grade 1 and grade 2 classifications Trial stopped early due to a pre-specified stopping guideline. Higher rate of grade 4 bleeding in patients receiving low dose prophylactic platelet transfusions. Frequency of grade 4 bleeding 5.2% (3/58) in low dose arm and 0% (0/61) in standard-dose arm. Risk of incomplete randomisation blocks
Protocol Deviation balanced?	High risk	The triggers used for prophylactic platelet transfusions tended to be higher in the low-dose treatment group with 35.9% of transfusions (158/440) given at a trigger of $16 \times 10^9/L$ or more compared with 24.7% (66/267) in the standard dose group In the low dose arm 27.4% of the prophylactic platelet transfusions were outside the predesignated range: 2.7% below 150×10^9 platelets/product (n = 10) and 24.7% above 300×10^9 platelets/product (N = 91) In the standard dose arm 20% of the prophylactic platelet transfusions were outside the predesignated range: 6.7% below 300×10^9 platelets/product (n = 17) and 13.3% above 600×10^9 platelets/product (N = 34)

Higby 1974

Methods	Parallel RCT (enrolment period not stated). Single centre. USA
Participants	<p>Inclusion Criteria: - Afebrile; thrombocytopenic - platelet count $< 30 \times 10^9/L$; patients with Acute Myeloid Leukaemia (adults)</p> <p>Exclusion Criteria: - Haematological remission of leukaemia; evidence of bleeding; evidence of haemolysis</p> <p>N = 21 participants, 24 episodes of chemotherapy induced thrombocytopenia. (18 patients randomised once; 3 randomised twice)</p> <p>Arm 1: N=12 episodes; 12 patients</p> <p>Arm 2: N= 12 episodes; 12 patients, 3 not entered into analysis (recovered from thrombocytopenia within 48hrs of entry into trial)</p>
Interventions	<p>Comparison between prophylactic platelet transfusions and platelet-poor plasma</p> <p>Arm 1 (Prophylactic). Platelets (3 units/m^2 body surface area = approximately 3×10^{11} platelets /m^2)</p> <p>Arm 2 (Placebo). Plasma infusion (platelet-poor) of equal volume</p> <p>Platelets or platelet-poor plasma given twice weekly.</p> <p>Type of platelet transfusion: random donor pooled platelets</p>
Outcomes	<p>Main or primary outcome not stated</p> <p>Outcomes mentioned</p> <ul style="list-style-type: none"> • Frequency of haemorrhage • Average platelet count <p>Number of days patients on study (mean \pm SD):</p> <p>Arm 1: 12.3 ± 6.9</p> <p>Arm 2: 14.9 ± 10.8</p>
Notes	<p>Patients randomised at: platelet count $< 30 \times 10^9/L$</p> <p>Follow-up of patients: until unsupported platelet count $>30 \times 10^9/L$ for 2 days; OR patient had a significant haemorrhage; OR patient developed septic shock/ significant sepsis</p> <p>Stopping guidelines: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients "were assigned at random to one of two groups" Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'
Allocation concealment (selection bias)	Low risk	"Eligible patients were allocated to treatment regimen in the blood bank and without knowledge of the attending physicians"

Higby 1974 (Continued)

Blinding (performance bias and detection bias) Assessor of bleeding assessment	Unclear risk	The method of performing the bleeding assessment and the person performing the bleeding assessment were not stated
Blinding (performance bias and detection bias) Physician/Medical Staff	Low risk	“Eligible patients were allocated to a treatment regimen in the blood bank and were treated in the manner assigned without the knowledge of the attending physicians”
Incomplete outcome data (attrition bias) All outcomes	Low risk	“as treated analysis. No missing outcome data”
Selective reporting (reporting bias)	Unclear risk	Protocol not available to make assessment.
Other bias	High risk	There was a significant difference between the ages of the patients in the two groups (mean \pm SD) 53.3 \pm 18.5 (arm 1) vs. 43.8 \pm 19.4 (arm 2) ($P < 0.05$ (t-test))
Protocol Deviation balanced?	Unclear risk	Not stated

Murphy 1982

Methods	Parallel RCT (conducted from July 1st 1972 to Jan 1st 1976). Single Centre. USA
Participants	<p>Inclusion criteria: Children with previously untreated acute leukaemia cared for at the Children's Hospital of Philadelphia</p> <p>Exclusion criteria: Not stated.</p> <p>N=56 children</p> <p>Arm 1: N=35 (Acute lymphocytic leukaemia (ALL) =28, Acute leukaemia excluding ALL (AnonLL) =7)</p> <p>Arm 2: N=21 (ALL=15, AnonLL=6)</p>
Interventions	<p>Comparison between prophylactic and therapeutic platelet transfusions</p> <p>Arm 1 (Prophylactic): Aim to maintain platelet count above $20 \times 10^9/L$</p> <p>Arm 2 (Therapeutic): Only given platelets in presence of five clinical indications</p> <ol style="list-style-type: none"> 1. Epistaxis not controlled by initial packing 2. Gross gastrointestinal bleeding 3. Gross genitourinary tract bleeding 4. Any central nervous system bleeding 5. Any bleeding episode felt to be life- threatening <p>Unclear whether platelets were given in both arms if clinical indications occurred and platelet count $>20 \times 10^9/L$</p> <p>Platelet dose: 4 units /m². Number of platelets/unit not stated.</p> <p>Platelet type: pooled random donor platelets</p>

Outcomes	Primary outcome: Survival Secondary outcomes <ul style="list-style-type: none">• Number, duration and dates of serious bleeding events (bleeds) during study.• Total number of days on which bleeding was present.• Platelet transfusion requirements in first 10 months (number of patients transfused; number of transfusions given; number of units given; number of patients bleeding; number of days with bleeding) Number of months patients on study Arm 1: Mean length of follow-up 19.9 months (ALL = 20.7 months; AnonLL = 16.6 months) Arm 2: Mean length of follow-up 20.4 months (ALL = 21.6 months; AnonLL = 17.7 months)	
Notes	Patients randomised at: not reported Follow-up of patients: until death or until 1st July 1976. Stopping guidelines: not reported	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random allocation not described. Randomisation was performed separately for acute lymphoblastic and acute non lymphoblastic leukaemia. Initially randomisation 1:1; changed to 2:1 after interim analysis 2 years after start of trial, since a preliminary analysis indicated that “the incidence of bleeding might be reduced in the prophylactic group” (further details of numbers enrolled prior to change in method of allocation not provided)
Allocation concealment (selection bias)	Unclear risk	Attempt to conceal allocation not mentioned.
Blinding (performance bias and detection bias) Assessor of bleeding assessment	Unclear risk	No mechanisms mentioned to blind outcome assessors (presumed also to be clinicians) to treatment after allocation
Blinding (performance bias and detection bias) Physician/Medical Staff	Unclear risk	No mechanisms mentioned to blind physicians to treatment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting to allow assessment

Murphy 1982 (Continued)

Selective reporting (reporting bias)	High risk	Reported in text that there was “no correlation of the incidence of bleeding with sex, pre-transfusion haematocrit, concomitant corticosteroid therapy or the use of specific antineoplastic drugs”. None of these were reported further
Other bias	High risk	Unbalanced numbers between groups with a greater proportion of AnonLL in therapeutic group. Age and gender of patients not reported for each group
Protocol Deviation balanced?	Unclear risk	Not reported

Rebulla 1997

Methods	Parallel RCT (enrolled from March 1994 to March 1996). Multi-centre study (21 centres). Italy
Participants	<p>Inclusion Criteria: Patients with acute myeloid leukaemia (AML); adolescents and adults (aged 16 -70yrs); admitted to hospital for 1st course of induction chemotherapy</p> <p>Exclusion Criteria: Patients diagnosed with promyelocytic leukaemia or secondary AML; patients who had received a blood transfusion prior to diagnosis of AML</p> <p>N = 329 patients screened for trial. 276 randomised. (37 secondary leukaemia; 10 blood transfusion prior to diagnosis; 4 did not meet age criteria; 2 declined to give consent)</p> <p>Arm 1: N=144; 9 not included in analysis; 8 alive at discharge (no study records received); 1 death on day 5 (cerebral haemorrhage) (no study records received)</p> <p>Arm 2: N= 132; 12 not included in analysis; 8 alive at discharge (no study records received); 2 died within 24 hours of admission (1 cerebral haemorrhage, 1 cardiac arrest); 2 received non-myeloablative course of chemotherapy</p>
Interventions	<p>Comparison between prophylactic platelets with different transfusion triggers</p> <p>Arm 1 (Low transfusion trigger). If platelet count < $10 \times 10^9/L$ if temperature (T) < 38 °C, OR 10 to $20 \times 10^9/L$ if T > 38°C or in presence of major or minor bleeding or if invasive procedures were necessary</p> <p>Arm 2 (High transfusion trigger). If platelet count < $20 \times 10^9/L$</p> <p>Platelet dose: 1 unit of platelet rich plasma or buffy coat concentrate per 10kg body weight or 1 apheresis concentrate given. Number of platelets per transfusion (apheresis) median 280×10^9 (range 110 to 588), pooled concentrate median 217×10^9 (range 140 to 555)</p> <p>Platelet type: Apheresis platelets given to 50% of patients in Arm 1 and 42% of patients in Arm 2</p>
Outcomes	<p>Primary outcome: Frequency and severity of haemorrhage</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Mortality rates • Rates of complete remission • Number of red cell transfusions

Rebulla 1997 (Continued)

	<ul style="list-style-type: none">• Number of platelet transfusions All outcomes measured to end of study Number of days patients on study (mean) Arm 1 = 29.7 days Arm 2 = 27.8 days	
Notes	Patients randomised at: diagnosis Follow-up of patients: until platelet count > 100 x 10 ⁹ /L OR discharge from hospital OR occurrence of complete remission OR resistance to chemotherapy OR death Stopping guidelines: The trial was scheduled to be stopped if the rate of outcome events reached statistical significance (P < 0.01 by the chi-square test) Acetaminophen was used as an anti-pyretic agent	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients underwent randomisation as soon as the diagnosis and other inclusion criteria were communicated by telephone to the central randomisation centre at the GIMEMA secretariat in Rome. A random permuted block design was used in the individual centres
Allocation concealment (selection bias)	Low risk	The people who handled randomisation, data management, and statistical analysis were not involved in the treatment of the patients
Blinding (performance bias and detection bias) Assessor of bleeding assessment	High risk	Bleeding assessors were not blinded to the intervention (unpublished, supplied by the author)
Blinding (performance bias and detection bias) Physician/Medical Staff	High risk	Medical staff routinely involved in the care of the patient were the bleeding assessors and were not blinded to the intervention (unpublished, supplied by the author)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Study protocol not available to allow judgement.
Other bias	Low risk	The study appears to be free of other sources of bias.

Rebulla 1997 (Continued)

Protocol Deviation balanced?	High risk	Pre-transfusion platelet count higher than indicated in the protocol in 5.4% of platelet transfusions in Arm 1 and 2% of platelet transfusions in Arm 2
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Roy 1973

Methods	Parallel RCT (enrolment period not stated). Single centre. USA	
Participants	Inclusion Criteria: Hospitalised leukaemia patients (paediatric); platelet count $\leq 25 \times 10^9/L$; no active bleeding within the previous 5 days Exclusion Criteria: Not stated N = 62 patients Arm 1: N = 30 patients having 167 transfusion episodes (age 0-4 yrs = 14; age 5-9 yrs = 14; age 10-14 yrs = 2) Arm 2: N = 32 patients having 141 transfusion episodes (age 0-4 yrs = 5; age 5-9 yrs = 12; age 10-14 yrs = 15)	
Interventions	Comparison between prophylactic platelet transfusions with different platelet dosages Arm 1. 'higher dose' platelets (dose: 0.06 - 0.07 units/lb) = 0.9 to 1.1×10^{11} platelets/10kg Arm 2. 'lower dose' platelets (dose: 0.03 units/lb) = 0.46×10^{11} platelets/10kg (the average platelet yield reported in the study was 7×10^{10} platelets per unit) Transfusion thresholds: Prophylactic platelet transfusions given when platelet count $\leq 25 \times 10^9/L$ When bleeding occurred despite prophylaxis, the patient was treated with larger platelet transfusions until all bleeding was arrested Platelet transfusion type: ABO identical pooled platelets	
Outcomes	Main or Primary outcome not stated. Aims of the trial: - <ul style="list-style-type: none">To assess the dose-response relationship between transfused platelets and prevention of haemorrhageTo investigate the needs and desirability of prophylactic platelet transfusion Number of days on study Patients were followed up for 24 hours after platelet transfusion	
Notes	Patients randomised at: platelet count $\leq 25 \times 10^9/L$ Follow up of patients: for 24 hours after platelet transfusion. Stopping guideline: not reported If patient required further platelet transfusions during the same hospital admission patient kept initial randomisation. On re-admission to hospital patients were re-randomised	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Roy 1973 (Continued)

Random sequence generation (selection bias)	Unclear risk	Patients were assigned randomly to either dosage group by drawing sealed envelopes. Does not say how patients were randomised
Allocation concealment (selection bias)	Unclear risk	Patients were assigned randomly to either dosage group by drawing sealed envelopes. Does not say whether envelopes were opaque
Blinding (performance bias and detection bias) Assessor of bleeding assessment	Low risk	They were studied over each 24 hours following transfusion for signs of bleeding by an investigator who was unaware of the platelet dosage received
Blinding (performance bias and detection bias) Physician/Medical Staff	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	High risk	No protocol available to assess this, but in the report a lot of data has been collected but not reported on. "No correlation of the incidence of bleeding with sex, pre-transfusion haematocrit, concomitant corticosteroid therapy or the use of anti-neoplastic drugs was found". None of these results were reported
Other bias	High risk	Marked difference between population age groups. Other baseline characteristics not stated adequately to assess
Protocol Deviation balanced?	Unclear risk	Not reported

Sensebe 2004

Methods	Parallel RCT (enrolled from May 1999 - October 2001). Multicentre (4 centres). France
Participants	<p>Inclusion criteria: Patients who had not undergone transfusion who had acute leukaemia undergoing first line treatment; Patients undergoing autologous hematopoietic stem cell transplantation without criteria impairing platelet efficiency</p> <p>Exclusion criteria: Patients diagnosed with AML M3</p> <p>N = 101 patients randomised (98 included in analysis; 5 patients never transfused)</p> <p>Arm 1 = 50 (acute leukaemia (AL) = 17; autologous transplant (AT) = 33) (2 AT never transfused)</p> <p>Arm 2 = 51 (AL = 14; AT = 37) (2 AL never transfused; 1 AT never transfused)</p>

Interventions	Comparison between prophylactic platelet transfusions with different platelet dosages Arm 1: Single dose (0.5 x 10 ¹¹ /10kg) Arm 2: Double dose (1.0 x 10 ¹¹ /10kg) Platelet transfusion thresholds: Prophylactic platelet transfusions given if platelet count < 20 x 10 ⁹ /L. Therapeutic platelet transfusion trigger not stated. Platelet transfusion type: Leucodepleted, ABO compatible apheresis platelets	
Outcomes	Primary outcome: Time between first transfusion and daily platelet reaching 20 x 10 ⁹ /L (allowed for calculating the risk of re-transfusion and theoretical time between first and second transfusions) Secondary outcomes: <ul style="list-style-type: none">Corrected count increment (CCI) calculated as:<ul style="list-style-type: none">(post-transfusion count - pre-transfusion count x body surface area (m²)/platelet dose (x 10¹¹))Number of transfusionsNumber of transfused platelets Number of days on study Not reported	
Notes	Patients randomised at: not reported Follow-up of patients: until platelet count > 25 x 10 ⁹ /L and stable OR discharge from hospital OR death Stopping guideline: not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not commented on.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not commented on.
Blinding (performance bias and detection bias) Assessor of bleeding assessment	Unclear risk	Bleeding was assessed daily, but it was not stated how bleeding was assessed not who assessed the bleeding
Blinding (performance bias and detection bias) Physician/Medical Staff	High risk	Physicians and patients were not blinded to the randomisation arm
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to say. No protocol available

Sensebe 2004 (Continued)

Other bias	Low risk	The study appears to be free of other sources of biases.
Protocol Deviation balanced?	Unclear risk	Protocol deviations or violations were not commented on.

Sintnicolaas 1982

Methods	Randomised (enrolment period not reported). Study performed by haematological supportive care group in Netherlands	
Participants	Inclusion criteria: patients with acute leukaemia and severe thrombocytopenia N = 12	
Interventions	Comparison between prophylactic and therapeutic platelet regimens Arm 1: Prophylactic platelets to maintain platelet count above $20 \times 10^9/L$ Arm 2: Transfusion for 'haemorrhage only' Platelet dose: 4×10^{11} platelets/transfusion	
Outcomes	No primary or secondary outcomes reported. Reported decreased morbidity in the prophylactic group (no deaths due to bleeding) Reported 2 patients became refractory to platelets (1 in each arm)	
Notes	Published in abstract form only	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding (performance bias and detection bias) Assessor of bleeding assessment	Unclear risk	Not reported
Blinding (performance bias and detection bias) Physician/Medical Staff	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only reported as an abstract
Selective reporting (reporting bias)	Unclear risk	Only reported as an abstract

Other bias	Unclear risk	Only reported as an abstract
Protocol Deviation balanced?	Unclear risk	Not reported

Slichter 2010

Methods	Parallel RCT (enrolled from 2004-2007). Multicentre (26 centres). USA
Participants	<p>Inclusion Criteria: Inpatients of any age; receiving a stem cell transplant (for any diagnosis) or chemotherapy (for haematological cancers or solid tumours) and were expected to have a platelet count $\leq 10 \times 10^9/L$ for ≥ 5 days. Weight 10kg-135kg. PT & APTT $< 1.3 \times$ upper limit of normal. Fibrinogen $\geq 100\text{mg/dl}$. No previous platelet transfusions related to the current or planned course of therapy</p> <p>Exclusion Criteria: Evidence of WHO \geq grade 2 bleeding; receiving antithrombotic/antiplatelet medications; bedside platelet leucoreduction; platelet refractoriness within previous 30 days; acute promyelocytic leukaemia; idiopathic or thrombotic thrombocytopenic purpura; haemolytic-uraemic syndrome; major surgery within previous 2 weeks; pregnancy; planned prophylactic transfusion of platelets at platelet counts $> 10 \times 10^9/L$. N = 1351 patients randomised (1272 patients received at least 1 platelet transfusion - data analysis only on these patients)</p> <p>Arm 1 N = 417(Acute leukaemia = 202; lymphoma = 91; myeloma = 39; chronic leukaemia = 24; MDS = 16; other = 45)</p> <p>Arm 2 N = 423(Acute leukaemia = 186; lymphoma = 89; myeloma = 59; chronic leukaemia = 24; MDS = 26; other = 39)</p> <p>Arm 3 N = 432(Acute leukaemia = 185; lymphoma = 84; myeloma = 56; chronic leukaemia = 33; MDS = 14; other = 60)</p>
Interventions	<p>Comparison between prophylactic platelet transfusions with different platelet dosages</p> <p>Arm 1: $1.1 \times 10^{11}/\text{m}^2$ body surface area/transfusion $\pm 25\%$</p> <p>Arm 2: $2.2 \times 10^{11}/\text{m}^2$ body surface area/transfusion $\pm 25\%$</p> <p>Arm 3: $4.4 \times 10^{11}/\text{m}^2$ body surface area/transfusion $\pm 25\%$</p> <p>Platelet transfusion thresholds: Prophylactic platelet transfusions given when platelet count $\leq 10 \times 10^9/L$. Patient's physician could alter transfusion trigger or threshold if required by clinical indications. Therapeutic platelet transfusion trigger not reported</p> <p>Platelet transfusion type: apheresis and random donor pooled products</p>
Outcomes	<p>Primary outcome: Grade 2 or higher bleeding as determined by the Platelet Dose Trial Bleeding Scale</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Platelet utilisation rates (total number of platelets transfused $\times 10^{11}$) • Number of platelet transfusion events (frequency of transfusions) • Highest category of bleeding during time of study • Bleeding severity based on number of days with bleeding, intensity of bleeding, and number of sites with bleeding <p>Number of days on study</p> <p>1272 patients were observed for a total of 24,309 days. Mean number of days 19.1</p>

Notes	Patients randomised at: not reported Follow-up of patients: until a 10 day period without a platelet transfusion OR 30 days from first platelet transfusion OR discharge from hospital OR withdrawal from study OR death Stopping guideline: Stopping boundaries for the comparison of the primary end-point between each pair of treatment groups were calculated with the use of an alpha spending function similar to O'Brien-Fleming boundaries	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned in a 1:1:1 ratio, by means of computer-generated permuted blocks, to receive platelets at one of three doses. Treatment groups were balanced within trial sites with the use of dynamic balancing
Allocation concealment (selection bias)	Unclear risk	Not explicitly reported
Blinding (performance bias and detection bias) Assessor of bleeding assessment	High risk	Site staff were not told the patient's assigned dose but differences in transfusion volume prevented complete blinding. However, a computer algorithm assigned the final bleeding grade from the collected data, and this part of the process was at a low risk of bias
Blinding (performance bias and detection bias) Physician/Medical Staff	High risk	Site staff were not told the patient's assigned dose but differences in transfusion volume prevented complete blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Analysis of the number of platelet transfusions per patient was limited to patients who had no missing data on the number of transfusion events and number of platelets transfused (71%, 82% and 83% of data were complete on low, medium and high dose patients respectively)
Selective reporting (reporting bias)	Low risk	Study protocol is available and has been reported in the prespecified way
Other bias	Low risk	The study appears to be free of other sources of bias

Slichter 2010 (Continued)

Protocol Deviation balanced?	High risk	A significantly smaller proportion of transfusions were within the assigned dose range when the “at-issue” platelet counts were compared between low dose and medium dose groups (71% vs. 80% (P = 0.007)) and between high dose and medium dose groups (70% vs. 80% (P < 0.001))
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Solomon 1978

Solomon 1978		
Methods	Parallel RCT (period of enrolment not reported). Single centre. USA	
Participants	Inclusion Criteria: previously untreated non-lymphoblastic acute leukaemia (adults) Exclusion Criteria: promyelocytic leukaemia N = 31 successive patients receiving induction chemotherapy Arm 1: N=19 patients; 17 patients included in analyses (2 died on day 1 of study from cerebral haemorrhage) Arm 2: N=12 patients receiving 17 courses of chemotherapy	
Interventions	Comparison of a prophylactic platelet regime versus a therapeutic platelet regime Arm 1 (Prophylactic):If platelet count $<20 \times 10^9/L$ Arm 2 (Specific indications): clinically significant bleeding or 50% fall in platelets to below $20 \times 10^9/L$ occurred over 24 hrs. Both arms received platelets when there was clinically significant bleeding Platelet dose: not reported Platelet type: random donor pooled platelets	
Outcomes	Primary outcome not reported Outcomes reported <ul style="list-style-type: none">Deaths (within 1 month of chemotherapy course)Deaths due to bleeding (within 1 month of chemotherapy course)Complete remission rates (time period not stated)Transfusion requirements (platelets, red cells) per course of chemotherapy Number of days on study Not reported.	
Notes	Patients randomised at: not reported Follow-up of patients: not reported Stopping guideline: not reported Main author died before full publication	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Solomon 1978 (Continued)

Random sequence generation (selection bias)	Unclear risk	Method of random allocation not described - "17 randomly selected patients were given platelet transfusions .."
Allocation concealment (selection bias)	Unclear risk	Attempt to conceal allocation not mentioned.
Blinding (performance bias and detection bias) Assessor of bleeding assessment	Unclear risk	No mechanisms mentioned to blind outcome assessors (presumed also to be clinicians) to treatment after allocation
Blinding (performance bias and detection bias) Physician/Medical Staff	Unclear risk	No mechanisms mentioned to blind clinicians
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study not sufficiently reported
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Not enough information to assess
Protocol Deviation balanced?	Unclear risk	Not reported

Steffens 2002

Methods	Parallel RCT (period of enrolment not stated). Single centre. UK
Participants	<p>Inclusion criteria: Patients aged > 16yrs receiving intensive chemotherapy for AML and SCT conditioning for allogeneic SCT</p> <p>Exclusion criteria: Patients with HLA antibodies Patients with cardiovascular disease unable to tolerate a volume load</p> <p>N = 54 Arm 1: N = 28 patients. AML (21) Allogeneic stem cell transplant (7) Arm 2: N = 26 patients. AML (19) Allogeneic stem cell transplant (7)</p>
Interventions	<p>Comparison between prophylactic platelet transfusions with different platelet dosages Arm 1: single adult unit ($2.4 \times 10^{11}/L$)</p> <p>Arm 2: three single adult units</p> <p>Transfusion thresholds: platelet count $\leq 10 \times 10^9/L$ or higher if the patient was bleeding or febrile.</p> <p>Type of platelet transfusion: single donor apheresis platelets</p>

Steffens 2002 (Continued)

Outcomes	No primary or secondary outcomes stated. Aim: compare the efficacy of single donor platelets given as either a single adult dose or a triple adult dose	
Notes	Patients randomised at : initiation of chemotherapy Patients followed up until: platelet transfusion independent (not further defined) Stopping guideline: not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random allocation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding (performance bias and detection bias) Assessor of bleeding assessment	Unclear risk	Method of blinding assessor not reported
Blinding (performance bias and detection bias) Physician/Medical Staff	Unclear risk	Method of blinding clinician not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficiently reported to allow an assessment to be made
Selective reporting (reporting bias)	High risk	No protocol available. However mentions study will reported in more detail in future including clinical efficacy, bleeding episodes, red cell requirements and complication
Other bias	Unclear risk	Study not reported sufficiently to enable a comment to be made
Protocol Deviation balanced?	Unclear risk	Not reported

Tinmouth 2004

Methods	Phase II Bayesian approach study (Feb 2001 to Mar 2002 (unpublished)). Single centre. Canada
Participants	<p>Inclusion Criteria: Consecutive patients > 16 yrs of age. Undergoing autologous stem cell transplant or induction chemotherapy for ALL or AML</p> <p>Exclusion Criteria: APL, active bleeding, abnormal coagulation tests, history of a bleeding diathesis, ITP, refractory to platelet transfusions, receiving anticoagulants, antifibrinolytics, desmopressin or antiplatelet medication</p> <p>N = 111 patients enrolled</p> <p>Arm 1: N = 56. Acute leukaemia (17); Autologous transplant (39)</p> <p>55 patients completed assessment (1 allergic transfusion reaction). 14 patients did not require any platelet transfusions</p> <p>Arm 2: N = 55. Acute leukaemia (17); Autologous transplant (38).</p> <p>51 patients completed assessment (2 withdrawn when required antifibrinolytic or anti-coagulant; 2 withdrawn when bleeding initially categorised as major was reclassified as minor). 10 patients did not require any platelet transfusions</p>
Interventions	<p>Comparison between prophylactic platelet transfusions with different platelet dosages</p> <p>Arm 1: 3 units/half single apheresis unit = $1.9 - 2.5 \times 10^{11}$ platelets/transfusion</p> <p>Arm 2: 5 units/full single apheresis unit = $3.4 - 4.4 \times 10^{11}$ platelets/transfusion</p> <p>Platelet yields were 6.73×10^{10} to 8.5×10^{10} per whole blood derived platelet unit and 3.85×10^{11} to 4.06×10^{11} per apheresis platelet unit</p> <p>Platelet transfusion thresholds: Prophylactic platelet threshold < $10 \times 10^9/L$. If minor bleeding platelet threshold < $20 \times 10^9/L$. Prior to invasive procedures platelet threshold < $50 \times 10^9/L$.</p> <p>Platelet transfusion type: Random donor pooled platelets (PRP method). Leucodepleted. Apheresis platelets only used if no whole blood derived platelets available</p>
Outcomes	<p>Hypothesis: Lower dose of platelets would be safe and effective in preventing major bleeding events and would decrease total utilisation of platelets</p> <p>Stopping criteria:</p> <p>Absolute increase in major bleeding in the low-dose group of $\leq 10\%$ was considered the range of equivalence</p> <p>1) a high probability (greater than 80%) of equivalence (i.e., the increase in major bleeding events with low-dose PLT transfusions was less than 10%)</p> <p>2) a moderately high probability (greater than 60%) of nonequivalence (i.e., that the increase in major bleeding events was greater than 10%)</p> <p>Number of days on study</p> <p>Median time from start of chemotherapy to termination of the transfusion protocol was 15 days</p>
Notes	<p>Patient randomisation: within 72 hours of starting chemotherapy</p> <p>Follow up of patients: until platelet count > $20 \times 10^9/L$ for 2 days spontaneously OR major bleeding event (determined by treating physician) OR refractoriness to platelet transfusions OR discharge from hospital OR transfer to intensive care unit OR administration of further chemotherapy OR failure of engraftment OR death</p>
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated, stratified by diagnostic group. Block randomisation was used with variable block sizes within strata to help conceal treatment allocation (unpublished, information supplied by the author)
Allocation concealment (selection bias)	Low risk	Sealed, consecutively numbered envelopes containing information about the platelet dose group were opened by the hospital blood bank staff who were not involved in the study design, clinical management or data collection for the trial (unpublished, information supplied by the author)
Blinding (performance bias and detection bias) Assessor of bleeding assessment	High risk	Clinicians collected the data on bleeding and they were unblinded to the dose of platelets transfused. "Ajudication committee of three physicians blinded to the platelet dose and physician assigned bleeding grade independently reviewed all bleeding events and assigned the final bleeding grade." Therefore the allocation of a bleeding grade was at a low risk of bias
Blinding (performance bias and detection bias) Physician/Medical Staff	High risk	Medical and nursing staff were not blinded to the dose of platelet transfused
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced withdrawal across groups
Selective reporting (reporting bias)	Unclear risk	No protocol available to assess
Other bias	Low risk	The study appears to be free of other sources of bias
Protocol Deviation balanced?	High risk	15/164 transfusions contravened protocol in Arm 1 3/147 transfusions contravened protocol in Arm 2

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aderka 1986	A non-randomised retrospective study
Agliastro 2006	Comparison of apheresis vs. buffy coat platelet transfusions (Abstract)
Akkök 2007	Comparison of apheresis vs. buffy coat platelet transfusions
Anderson 1997	Comparison of apheresis versus buffy coat derived versus platelet rich plasma derived platelet products
Andrew 1993	Wrong patient group - premature infants
Arnold 2004	Comparison of apheresis versus whole blood derived platelet transfusions
Arnold 2006	Wrong patient group - ITU
Bai 2004	Wrong patient group - solid tumours
Bentley 2000	Comparison of autologous versus allogeneic platelet transfusions
Blumberg 2002	Comparison of washed versus standard platelet transfusions
Blundell 1996	Comparison of standard versus pathogen inactivated platelets
Callow 2002	A non-randomised prospective study with historical control
Cameron 2007	A non-randomised prospective study
Carr 1990	Comparison of ABO-matched versus mismatched platelet products
Chaoui 2005	Observational prospective study
Cid 2007	Systematic review of differing platelet transfusion doses
Couban 2002	Comparison of plasma reduction and leucodepletion
de Wildt-Eggen 2000	Comparison of platelet concentrates in plasma versus additive solution
Decaudin 2004	Non-randomised prospective study
Diedrich 2009	Comparison of platelet products stored 1-5 versus 6-7 days
Dumont 2011	Comparison of buffy coat versus platelet rich plasma platelet concentrates
Eder 2007	Non-randomised observational study

(Continued)

Elting 2002	Retrospective analysis - lymphoma and solid tumours
Elting 2003	Non-randomised retrospective cohort - lymphoma and solid tumours
Fanning 1995	Wrong patient group - gynaecological cancer
Follea 2004	Guideline
Friedmann 2002	A non-randomised retrospective analysis
Gajic 2006	Wrong patient group - ITU
Gerday 2009	Wrong patient group - neonates
Gil-Fernandez 1996	A non-randomised retrospective historical control study (different platelet transfusion thresholds)
Gmur 1983	Comparison of single donor versus pooled platelet products
Gmur 1991	A non-randomised prospective cohort observational study (different platelet transfusion thresholds)
Goodnough 2001	Fewer than 80% of patients diagnosed with a haematological disorder - different platelet doses
Goodrich 2008	Comparison of pathogen inactivated versus standard apheresis platelets
Greeno 2007	A non-randomised prospective observational study (different platelet transfusion thresholds)
Gurkan 2007	Comparison of apheresis vs. pooled platelet products
Hardan 1994	A non-randomised observational study, (therapeutic platelets only), historical control reported only as an abstract
Harrup 1999	Comparison of buffy coat plasma or T-sol platelet transfusions
Heal 1993	Comparison of ABO compatible versus mismatched platelet transfusions
Heddle 1994	Comparison of plasma from platelet concentrates versus platelets
Heddle 1999	Comparison of plasma removal versus leucodepletion
Heddle 2002	Comparison of plasma removal versus leucodepletion
Heddle 2003	Systematic review - methods of assessing bleeding outcome
Hilbom 2008	Wrong patient group - intracerebral haemorrhage
ISRCTN49080246	Comparison of 1-5 vs. 6-7 day old platelet transfusions

(Continued)

Johansson 2007	Wrong patient group - ruptured abdominal aortic aneurysm
Julmy 2009	Wrong patient group - ruptured abdominal aortic aneurysm
Kakaiya 1981	Comparison of apheresis versus pooled platelet concentrates
Kerkhoffs 2010	Comparison of standard platelets versus pathogen inactivated platelets versus platelets stored in PAS II media
Klumpp 1999	A randomised cross-over study. This study was included within the previous systematic review. However because of stricter inclusion/exclusion criteria this study has now been excluded from the review Only laboratory outcomes were reported. 37% of patients had a non-haematological malignancy (breast cancer)
Lapierre 2003	Comparison of standard apheresis platelet products versus a donor reduction policy
Lawrence 2001	A non-randomised retrospective historical control study (different platelet transfusion thresholds)
Leach 1991	Comparison of warmed versus standard platelet transfusions
Lee 1989	Comparison of ABO matched versus mis-matched platelet transfusions
Lozano 2010	Efficacy of older platelet transfusions
Lozano 2011	Comparison of pathogen inactivated vs. conventional platelet products
McCullough 2004	Comparison of pathogen inactivated vs conventional apheresis platelets
Messerschmidt 1988	Comparison of HLA matched versus mismatched platelet transfusions
Mirasol 2010	Comparison of pathogen inactivated vs. conventional platelet products
Murphy 1986	Comparison of HLA matched and leucodepleted blood products
Navarro 1998	A non-randomised retrospective historical control observational study (different platelet transfusion thresholds)
Nevo 2007	A non-randomised retrospective analysis (different platelet thresholds)
Norol 1998	A non-randomised prospective comparison (three different doses of platelets)
Oksanen 1991	Comparison of pre versus post storage leucodepletion of PRP derived platelet transfusions
Oksanen 1994	Comparison of leucodepleted buffy coat derived platelet transfusions versus historical control
Paananen 2009	Non-randomised study (unclear whether prospective or retrospective)
Qureshi 2007	Audit of platelet transfusions in the UK

(Continued)

Rabinowitz 2010	Review
Reed 1986	Wrong patient group - massive transfusion
Sagmeister 1999	A non-randomised retrospective study (aplastic anaemia)
Samama 2005	Guideline
Schiffer 1983	Comparison of leucodepleted versus standard platelet concentrates
Shanwell 1992	Comparison of fresh versus stored platelets
Shehata 2009	Systematic review - ABO identical versus non-identical platelet transfusions
Singer 1988	Single donor HLA matched versus random donor platelets
Sintnicolaas 1995	Comparison of leucocyte depleted versus standard platelets
Slichter 2006	Comparison of pathogen inactivated vs conventional apheresis platelets
Speiss 2004	Wrong patient group - cardiac
Strindberg 1996	Comparison of apheresis versus buffy coat platelet products
Sweeney 2000	Comparison of pre-storage leucodepleted versus bed-side leucodepleted platelets
Tosetto 2009	Guideline
TRAP 1997	Comparison of standard pooled platelet product vs. irradiated pooled platelet product vs. leucodepleted pooled platelet product vs. apheresis platelet product
Vadhan-Raj 2002	Wrong patient group - gynaecological malignancy
Van Marwijk 1991	Comparison of leucodepleted platelet products prepared by filtration or centrifugation
van Rhenen 2003	Comparison of pathogen inactivated versus standard buffy coat derived platelet transfusions
Verma 2008	A non-randomised observational study
Wandt 1998	A non-randomised prospective cohort study (not randomised at the participant level)
Wandt 2005	A non-randomised prospective study with an historical case control (therapeutic vs. prophylactic platelet transfusions)
Wandt 2006	A non-randomised prospective study with an historical case control (therapeutic vs. prophylactic platelet transfusions)

(Continued)

Wang 2002	A comparison of acetaminophen and diphenhydramine vs. placebo as premedication for platelet transfusions
Weigand 2009	Prospective observational study
Williamson 1994	Comparison of standard versus bedside leucodepleted platelet products
Zahur 2002	Prospective observational study
Zhao 2002	Comparison of leucodepleted versus standard platelet transfusions
Zumberg 2002	This study was included within the previous systematic review. However because of stricter inclusion/exclusion criteria this study has now been excluded from the review 31% of patients had a non-haematological malignancy (breast cancer)

Characteristics of ongoing studies [ordered by study ID]

Franklin 1995

Trial name or title	Clinical efficacy of platelet transfusions in relation to platelet dose given
Methods	Open versus blinded study (unknown). Single centre versus multicentre (unknown)
Participants	Patients undergoing BMT
Interventions	
Outcomes	Response to platelets
Starting date	1995
Contact information	Prof I Franklin, Glasgow, UK
Notes	Not actively recruiting patients at the moment Author contacted but did not supply any further information.

Lu 2011

Trial name or title	Effect of reducing prophylactic platelet transfusion dose on bleeding in thrombocytopenic patients
Methods	Single centre. Randomised Controlled Trial. Open versus blinded study (unknown)
Participants	Hospitalised patients undergoing haematopoietic stem-cell transplantation or chemotherapy for haematological cancers or solid tumours

Lu 2011 (Continued)

Interventions	Eligible patients randomised to receive low dose ($1.1 \times 10^{11} / \text{m}^2$) or standard dose ($2.2 \times 10^{11} / \text{m}^2$) prophylactic platelet transfusions when the morning platelet count was $\leq 10 \times 10^9 / \text{L}$
Outcomes	Primary outcome: percentage of patients with bleeding of grade 2 or higher (as defined on the basis of World Health Organization criteria) Secondary outcomes: incidence of higher grades of bleeding; number of platelet transfusions/patient; number of platelets/patient
Starting date	Not reported
Contact information	Dr Fa Qiang Lu faqianglu@yahoo.com
Notes	Study completed but not published Author contacted but did not supply any further information.

NCT00180986

Trial name or title	Randomized Trial Of Platelet Transfusion Policies After Blood Stem Cells Transplantation In Young Children: Reduction Of Number Of Single Platelet Concentrate Donors Per Child
Methods	Open-label, parallel, randomised controlled trial. Single centre versus multicentre (unknown)
Participants	Children weighing 30 kg or less with a diagnosis of haematological malignancy or solid tumour, who were candidates for HSCT were eligible for inclusion in the study. Children were excluded if they had an anti-HLA and/or anti-HPA antibody, if they were prior included in this study or if the parents declined to participate
Interventions	Different platelet transfusion policies
Outcomes	The primary end point of the study was to compare the number of platelet concentrates donors who were implicated in platelet transfusion supportive after HSCT
Starting date	October 1995
Contact information	
Notes	NCT00180986 Not actively recruiting but ongoing Author contacted but did not supply any further information.

Stanworth 2010

Trial name or title	A randomised controlled trial of prophylactic versus no-prophylactic platelet transfusions in patients with haematological malignancies
Methods	Open-label, parallel, multicentre, randomised controlled trial

Stanworth 2010 (Continued)

Participants	<p>Inclusion Criteria: They are aged 16 years or over; they have a confirmed diagnosis of a haematological malignancy; they are receiving or are going to receive myelosuppressive chemotherapy on this hospital admission with or without haematopoietic stem cell support (this includes patients undergoing haematopoietic stem cell transplantation - autograft or allograft); they are thrombocytopenic or expected to become thrombocytopenic with a platelet count of less than $50 \times 10^9/L$ for at least five days; they are able to comply with treatment and monitoring</p> <p>Exclusion Criteria: They have had a World Health Organisation (WHO) Grade three or four bleed (refer to Modified WHO Bleeding Criteria) during any stage of their treatment to date; during the current admission, they have experienced or are currently experiencing a WHO Grade two or greater bleed; they have any inherited clotting disorder (e.g. haemophilia); they need to remain on regular aspirin (or related drugs), or will require regular therapeutic doses of anticoagulants (heparin), during the whole period of thrombocytopenia; they have acute promyelocytic leukaemia; they have known HLA antibodies; they are pregnant; they have previously been randomised in this trial at any stage of their treatment</p>
Interventions	Eligible patients will be randomised to receive either prophylactic platelet transfusions if the platelet count is less than $10 \times 10^9/L$, or no prophylaxis with therapeutic transfusions given only after documented signs or symptoms of bleeding
Outcomes	<p>Primary outcome: percentage of patients who develop a WHO Grade two, three or four bleeding event up to 30 days from randomisation. The percentage of patients a WHO Grade two, three or four bleed by day 30 will be calculated for each arm</p> <p>Secondary outcomes: Logistic regression for proportion developing grade 3 or 4 bleed - subsidiary outcome measure: Cox proportional hazards regression model for time to first WHO grade two, three, or four bleed; time from randomisation to second grade two bleed; period in hospital; poisson regression for the rate of bleeding events</p>
Starting date	July 2006
Contact information	Dr Simon Stanworth simon.stanworth@nhsbt.nhs.uk
Notes	ISRCTN08758735 Study completed but not published

Wandt 2009

Trial name or title	Prospective Randomized Trial Comparing a Prophylactic With a Therapeutic Platelet Transfusion Strategy in Two Groups: 1) In Patients With Acute Myeloid Leukemia After Intensive Chemotherapy and 2) After Autologous Blood Stem Cell Transplantation
Methods	Open-label, parallel, multicentre, randomised controlled trial
Participants	<p>Inclusion Criteria</p> <p>(AML Group): Inclusion in studies of the DSIL or OSHO group for AML; AML M3/M3v can be included only when in complete remission; age 16 - 80 years</p> <p>(Autologous Group): AML and ALL patients in first or second remission; low grade or high grade Non-Hodgkin lymphoma or morbus Hodgkin or multiple myeloma; conditioning regime: TBI 8-12 Gy/Cy 120 or BEAM or BU/CY or Melphalan 140-200mg/m² or a similarly intensive chemotherapy regime; age 16 -</p>

Wandt 2009 (Continued)

	65 years Exclusion Criteria <i>(Both Groups):</i> known refractoriness to platelet transfusion; known major bleeding with thrombocytopenia when the reason for bleeding is still ongoing known plasmatic coagulation disorder; patient unable to give informed consent <i>(Autologous Group):</i> patients with pulmonal or cerebral lesions due to infection or neoplasm; patients with AL-amyloidosis
Interventions	In the therapeutic platelet transfusion arm: platelet transfusion is only required if bleeding occurs (more than petechial) or in case of pulmonary infections with or without sepsis In the prophylactic platelet transfusion arm: platelet transfusion has to be performed when platelet count is below 10,000/ μ L in any case and when bleeding (more than petechial) occurs
Outcomes	Primary Outcome: reduction in numbers of platelet transfusion by 25 % in the experimental arm (therapeutic transfusion strategy) compared with the standard arm (prophylactic transfusion strategy) Secondary Outcomes: incidence and duration of clinically relevant bleeding - numbers of red blood cell transfusion - side effects of transfusions - duration of thrombocytopenia below 10,000/ μ L and below 20,000/ μ L - duration of hospitalisation
Starting date	September 2004
Contact information	Hannes Wandt, Dr. MD wandt@klinikum-nuernberg.de Kerstin Schäfer-Eckart, Dr. schaefer@klinikum-nuernberg.de
Notes	NCT00521664 Study completed but not published

DATA AND ANALYSES

Comparison 1. Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Numbers of participants with a significant bleeding event	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.90, 3.04]
1.1 Patients with ALL	1	43	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [1.00, 6.83]
1.2 Patients with AML	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.45, 1.95]
2 Number of days with significant bleeding	1	34213	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.62, 1.32]
2.1 Patients with ALL	1	27516	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.43, 1.52]
2.2 Patients with AML	1	6697	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.60, 1.54]
3 Mortality from all causes	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.48, 1.93]
4 Mortality from bleeding	2	85	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.23, 5.06]
5 Mean number of platelet transfusions per course of chemotherapy	2	85	Mean Difference (IV, Fixed, 95% CI)	-15.80 [-19.20, -12.40]
6 Mean number of red cell transfusions per patient	1	29	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.14, 1.34]
7 Remission rates	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.50, 2.27]
8 Number of participants with platelet refractoriness	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.66]

Comparison 2. Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with any bleeding event	1	78	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.92, 1.19]
2 Numbers of participants with a significant bleeding event	3	499	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.95, 1.90]
2.1 Platelet threshold < 10 vs. < 20	2	333	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.95, 2.10]
2.2 Platelet threshold < 10 vs. < 30	1	166	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.59, 2.37]
3 Number of participants with WHO Grade 3 or 4 bleeding	2	421	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.52, 1.88]
3.1 Platelet threshold < 10 vs. < 20	1	255	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.58, 2.54]
3.2 Platelet threshold < 10 vs. < 30	1	166	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.14, 2.13]

4 Number of participants with bleeding requiring a red cell transfusion	1	166	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.16, 2.68]
5 Number of days with any bleeding	1	7336	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.10, 1.46]
6 Number of days with a significant bleed	2	9420	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.33, 2.22]
7 Mortality from all causes	2	333	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.85, 1.60]
8 Mortality from bleeding	3	499	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.11, 64.91]
9 Mean number of platelet transfusions per patient	2	333	Mean Difference (IV, Fixed, 95% CI)	-2.09 [-3.20, -0.99]
10 Mean number of red cell transfusions per patient	2	333	Mean Difference (IV, Fixed, 95% CI)	0.66 [-0.43, 1.76]
11 Remission rates	2	333	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.78, 1.09]
12 Numbers of participants with platelet transfusion reactions	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.09]
13 Number of participants with thromboembolic disease	1	255	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.06, 14.06]
14 Number of participants requiring HLA-matched platelets	1	166	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.07, 17.31]
15 Number of participants with platelet refractoriness	2	244	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.16, 2.67]

Comparison 3. Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with any bleeding event	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Low dosage platelet transfusion versus standard dose platelet transfusions	1	119	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.00, 1.35]
1.2 High dosage platelet transfusion versus standard dose platelet transfusion	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.54]
2 Number of participants with a significant bleeding event	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Low dosage platelet transfusions versus standard dosage platelet transfusions	3	1070	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.95, 1.13]
2.2 High dosage platelet transfusions versus standard dosage platelet transfusions	2	951	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.11]
3 Number of participants with WHO Grade 3 or 4 bleeding	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Low dose vs. standard dose	2	959	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.91, 1.92]

3.2 High dose vs. Standard dose	1	855	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.73, 1.68]
4 Number of participants with WHO grade 4 bleeding	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Low dose versus standard dose platelet transfusions	3	1070	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [0.86, 4.08]
4.2 High dose versus standard dose platelet transfusions	1	855	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.43, 2.83]
5 Number of participants with bleeding requiring a red cell transfusion	1	119	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.28, 2.72]
6 Number of participants with bleeding causing cardiovascular compromise	1	111	Risk Ratio (M-H, Fixed, 95% CI)	2.95 [0.12, 70.82]
7 Number of days with significant bleeding	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Low dose versus standard dose platelet transfusions	2	3716	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.91, 1.47]
7.2 High dose versus standard dose platelet transfusions	1	308	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.26, 4.95]
8 Mortality from all causes	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Low dose vs. standard dose	3	1070	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.70, 5.93]
8.2 High dose vs. standard dose	1	855	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.51, 5.81]
9 Mortality from bleeding	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Low dosage platelet transfusions versus standard dose platelet transfusions	3	859	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 High dosage platelet transfusions versus standard dosage platelet transfusions	2	739	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.06, 35.90]
10 Number of participants with platelet transfusion reactions	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Allergic reaction or hypersensitivity: Low dosage platelet transfusions versus standard dosage platelet transfusions	1	840	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.55, 1.26]
10.2 Allergic reaction or hypersensitivity: High dosage platelet transfusions versus standard dosage platelet transfusions	1	855	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.86, 1.79]
10.3 Hypotension: Low dosage platelet transfusions versus standard dosage platelet transfusions	1	840	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.81, 2.21]

10.4 Hypotension: High dosage platelet transfusions versus standard dosage platelet transfusions	1	855	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.65, 1.85]
10.5 Dyspnoea: Low dosage platelet transfusions versus standard dosage platelet transfusions	1	840	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.47, 1.61]
10.6 Dyspnoea: High dosage platelet transfusions versus standard dosage platelet transfusions	1	855	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.60, 1.91]
10.7 Hypoxia: Low dosage platelet transfusions versus standard dosage platelet transfusions	1	840	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.44, 1.80]
10.8 Hypoxia: High dosage platelet transfusions versus standard dosage platelet transfusions	1	855	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.53, 2.03]
10.9 Wheezing: Low dosage platelet transfusions versus standard dosage platelet transfusions	1	840	Risk Ratio (M-H, Fixed, 95% CI)	3.55 [0.74, 16.99]
10.10 Wheezing: High dosage platelet transfusions versus standard dosage platelet transfusions	1	855	Risk Ratio (M-H, Fixed, 95% CI)	6.85 [1.57, 29.98]
10.11 Wheezing: Low dosage platelet transfusions versus high dosage platelet transfusions	1	849	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.21, 1.27]
10.12 Haemolysis: Low dosage platelet transfusions versus standard dosage platelet transfusions	1	840	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.18, 22.29]
10.13 Haemolysis: High dosage platelet transfusions versus standard dosage platelet transfusions	1	855	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [0.18, 21.52]
10.14 Rigors or chills: Low dosage platelet transfusions versus standard dosage platelet transfusions	1	840	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.57, 1.33]
10.15 Rigors or chills: High dosage platelet transfusions versus standard dosage platelet transfusions	1	855	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.77, 1.67]
10.16 Fever: Low dosage platelet transfusions versus standard dosage platelet transfusions	1	840	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.95, 1.39]

10.17 Fever: High dosage platelet transfusions versus standard dosage platelet transfusions	1	855	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.30]
10.18 Infection: Low dosage platelet transfusions versus standard dosage platelet transfusions	1	840	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.30, 3.48]
10.19 Infection: High dosage platelet transfusions versus standard dosage platelet transfusions	1	855	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.44, 4.29]
11 Thromboembolic disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Low dosage platelet transfusions versus standard dose platelet transfusions	1	840	Risk Ratio (M-H, Fixed, 95% CI)	7.10 [0.37, 137.04]
11.2 High dosage platelet transfusions versus standard dosage platelet transfusions	1	855	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Number of participants with a significant bleeding episode	2	998	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.65, 0.82]
12.1 Autologous transplantation versus chemotherapy	2	463	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.61, 0.86]
12.2 Autologous transplantation versus Allogeneic transplantation	1	535	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.62, 0.85]
13 Time to first significant bleeding event	1	119	Mean Difference (IV, Fixed, 95% CI)	1.5 [-1.66, 4.66]
14 Number of days with WHO grade 2 or above bleeding per patient	2	230	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.51, 0.16]

Comparison 4. Prophylactic platelet transfusion versus platelet-poor plasma

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with a significant bleeding event	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.95]
2 Time to first bleed	1	21	Mean Difference (IV, Fixed, 95% CI)	0.0 [-7.57, 7.57]
3 Number of participants with bleeding requiring a red cell transfusion	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.13, 1.11]
4 Number of participants with bleeding causing cardiovascular compromise	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.05, 10.44]
5 Mortality from bleeding	1	21	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [0.10, 50.85]
6 Complete remission	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.20, 1.26]

Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation (Review) 87

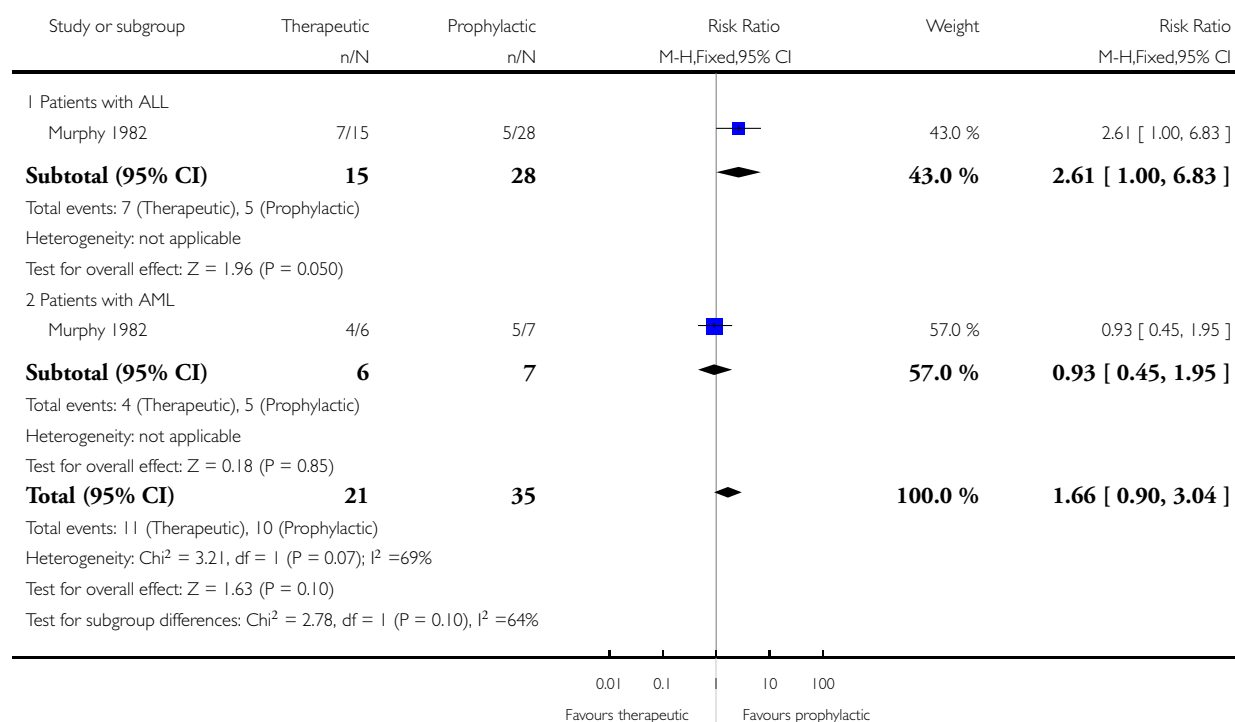
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Analysis 1.1. Comparison 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion, Outcome 1 Numbers of participants with a significant bleeding event.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion

Outcome: 1 Numbers of participants with a significant bleeding event

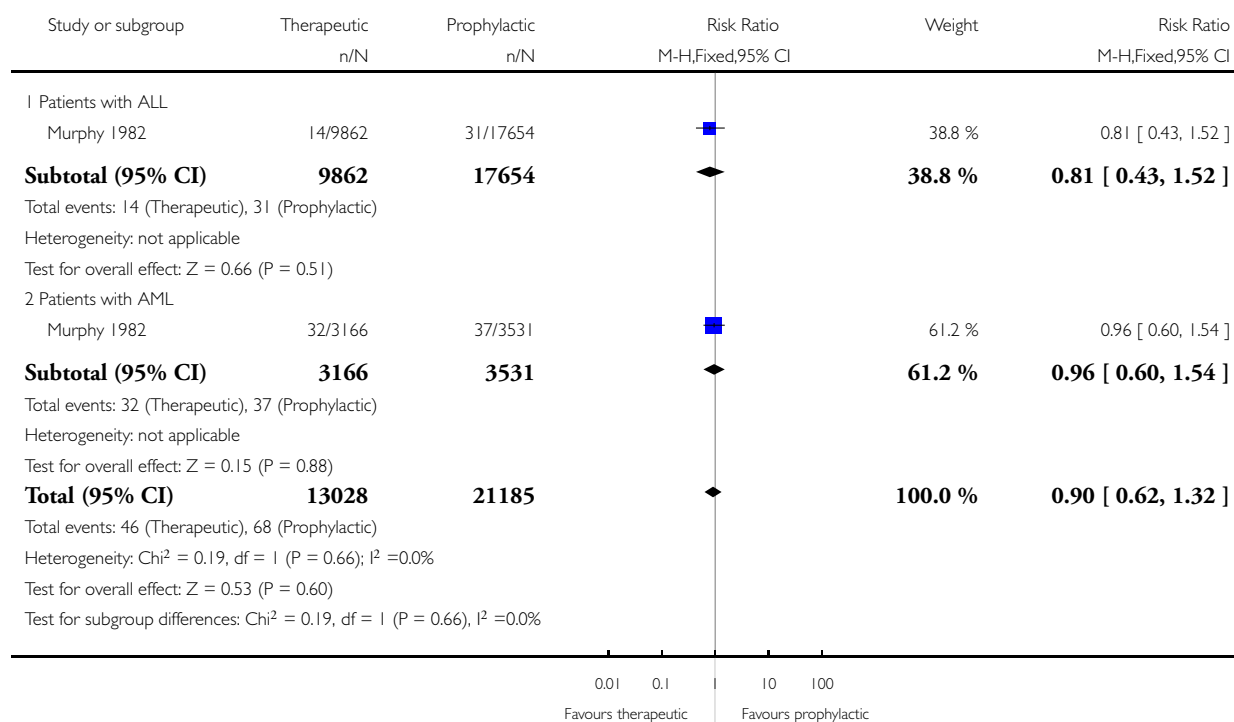


Analysis 1.2. Comparison 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion, Outcome 2 Number of days with significant bleeding.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion

Outcome: 2 Number of days with significant bleeding

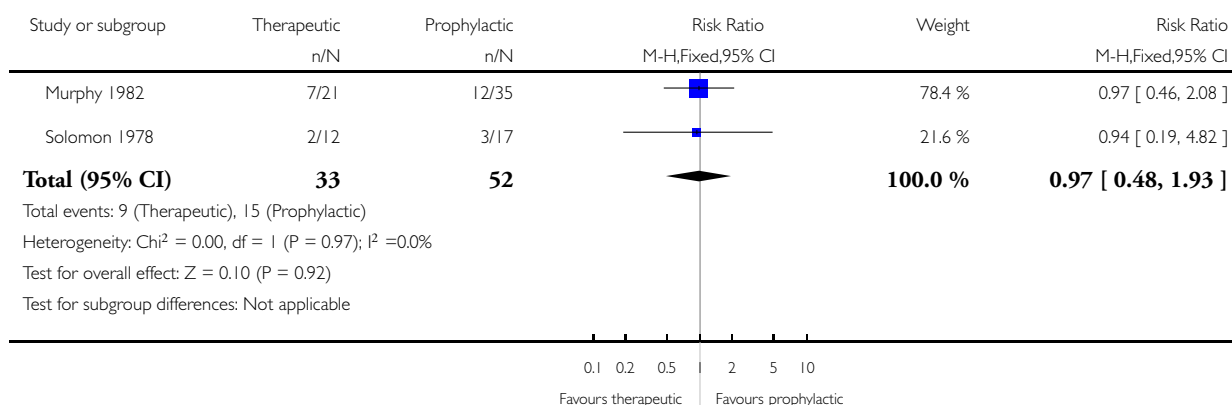


Analysis 1.3. Comparison 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion, Outcome 3 Mortality from all causes.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion

Outcome: 3 Mortality from all causes

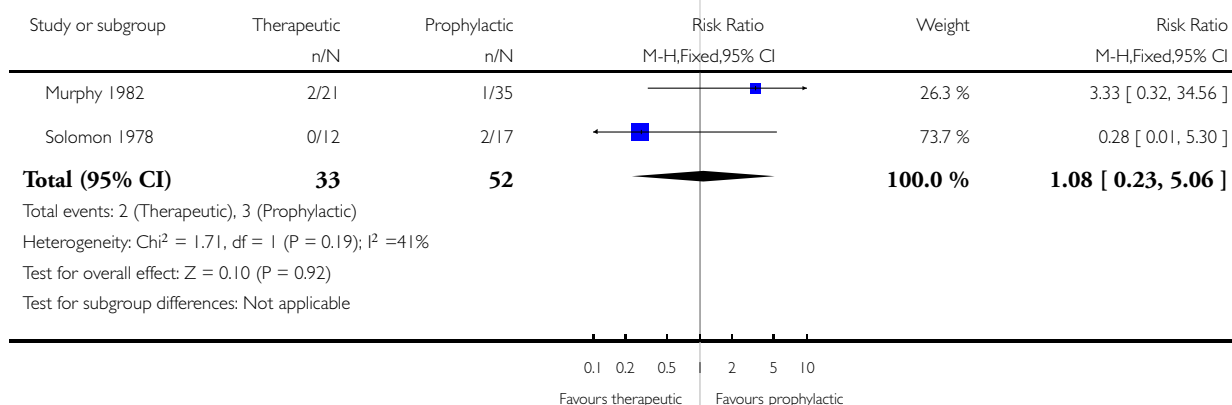


Analysis 1.4. Comparison 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion, Outcome 4 Mortality from bleeding.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion

Outcome: 4 Mortality from bleeding

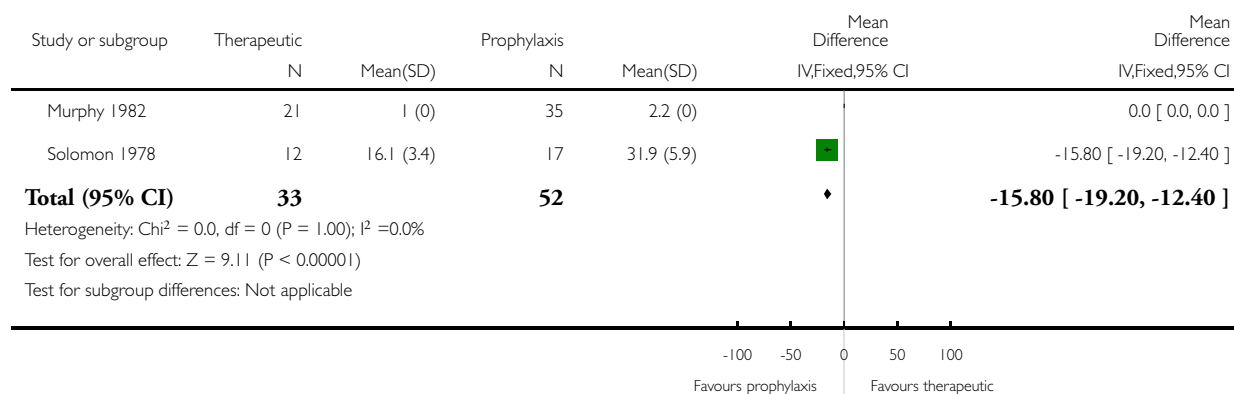


Analysis 1.5. Comparison 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion, Outcome 5 Mean number of platelet transfusions per course of chemotherapy.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion

Outcome: 5 Mean number of platelet transfusions per course of chemotherapy

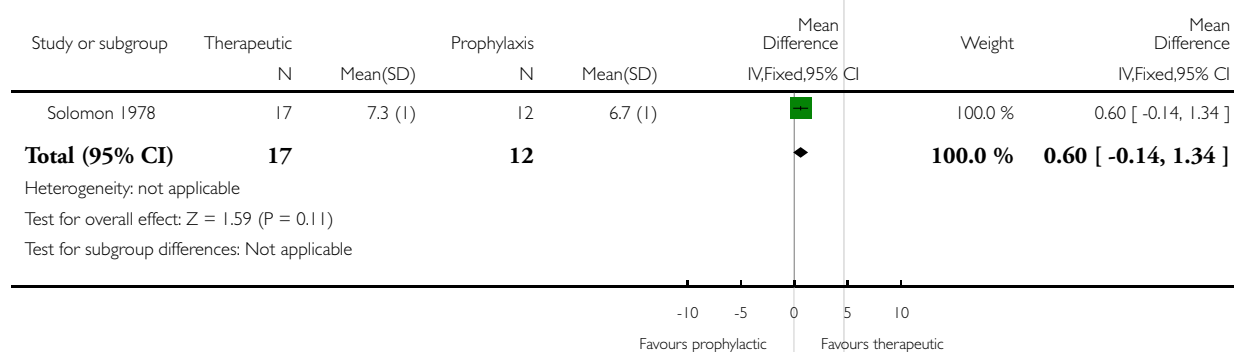


Analysis 1.6. Comparison 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion, Outcome 6 Mean number of red cell transfusions per patient.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion

Outcome: 6 Mean number of red cell transfusions per patient

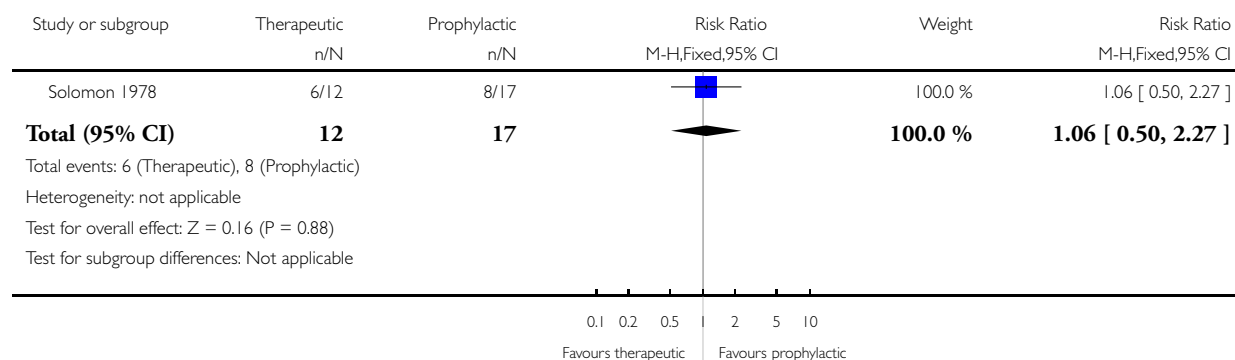


Analysis 1.7. Comparison 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion, Outcome 7 Remission rates.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion

Outcome: 7 Remission rates

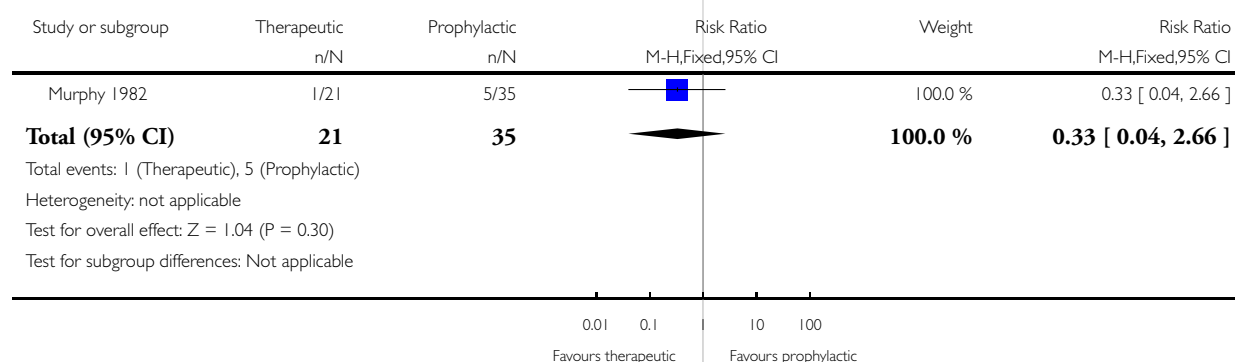


Analysis 1.8. Comparison 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion, Outcome 8 Number of participants with platelet refractoriness.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion versus non prophylactic or therapeutic transfusion

Outcome: 8 Number of participants with platelet refractoriness

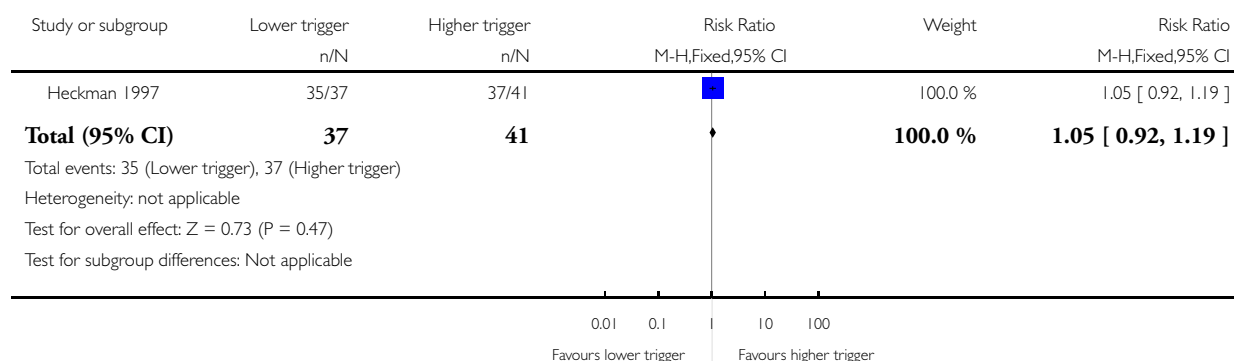


Analysis 2.1. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 1 Number of participants with any bleeding event.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 1 Number of participants with any bleeding event

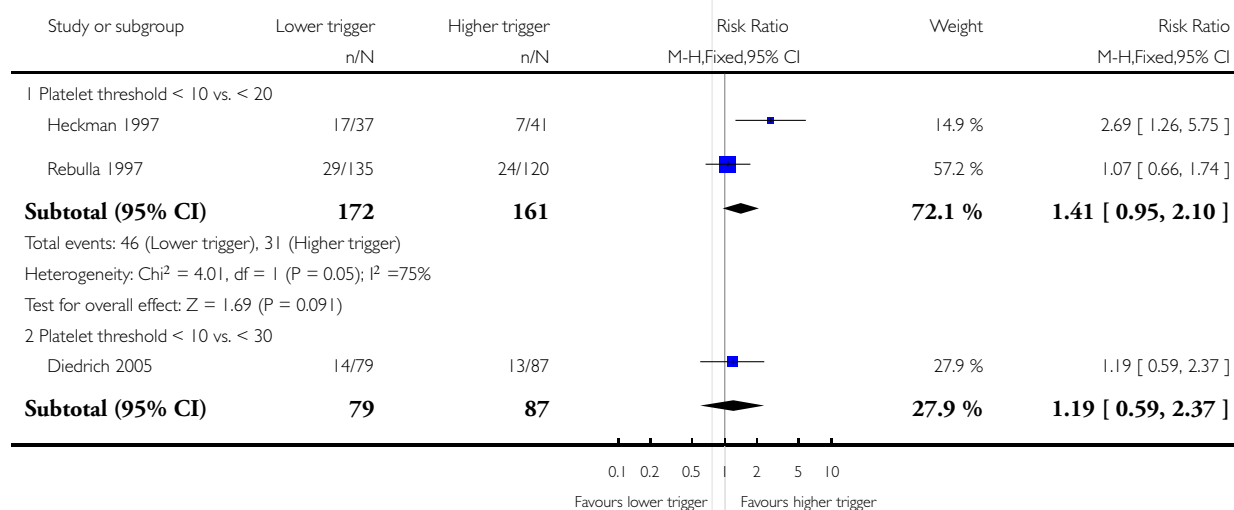


Analysis 2.2. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 2 Numbers of participants with a significant bleeding event.

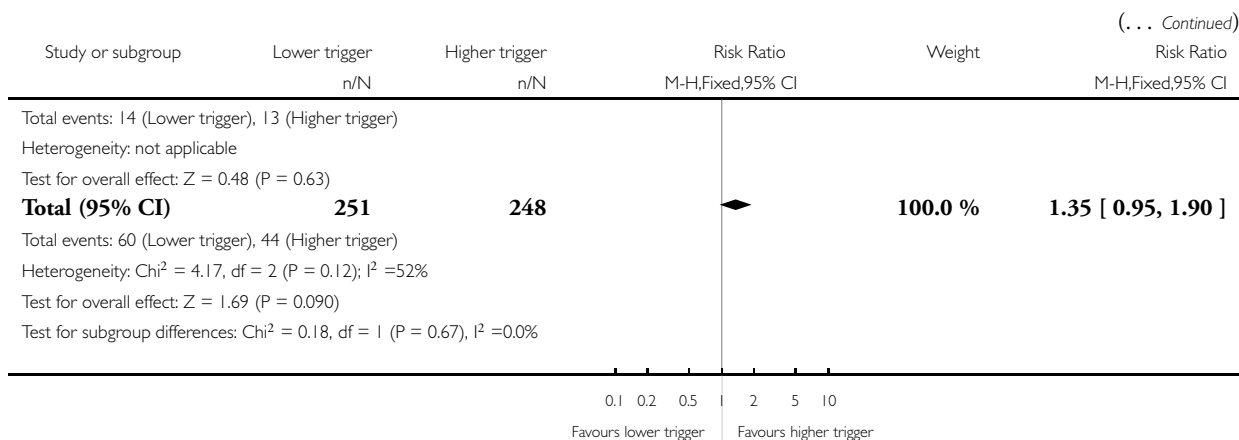
Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 2 Numbers of participants with a significant bleeding event



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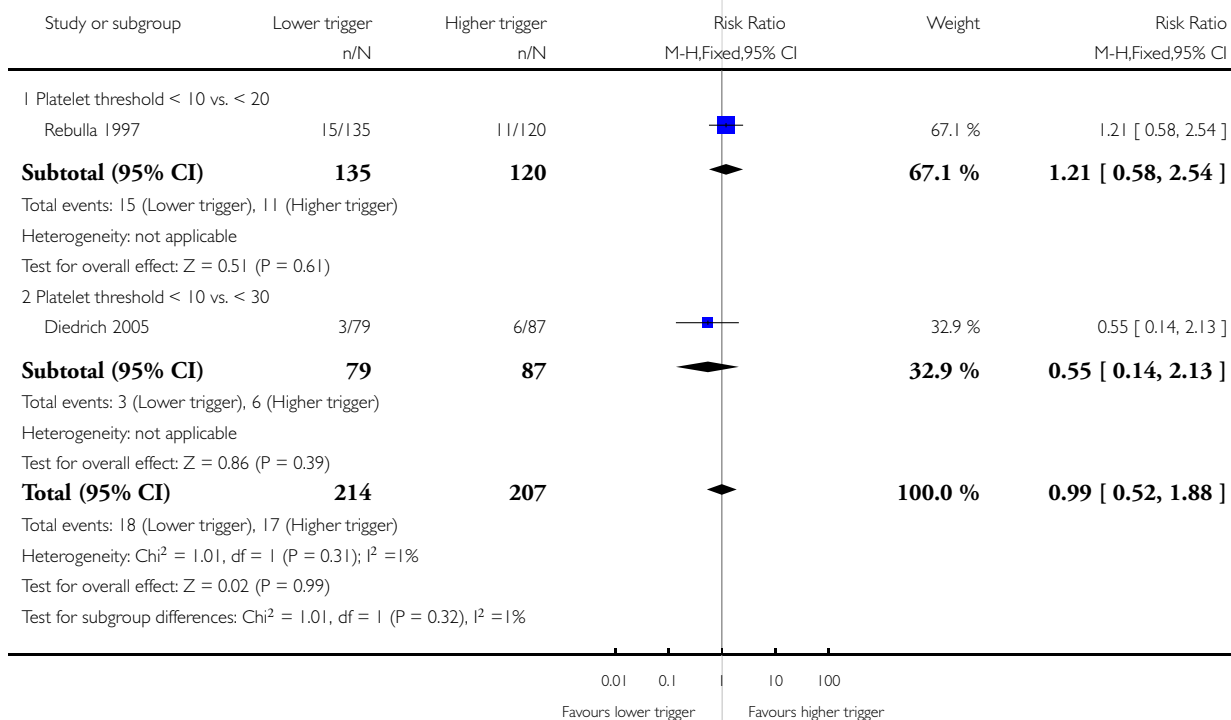


Analysis 2.3. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 3 Number of participants with WHO Grade 3 or 4 bleeding.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 3 Number of participants with WHO Grade 3 or 4 bleeding

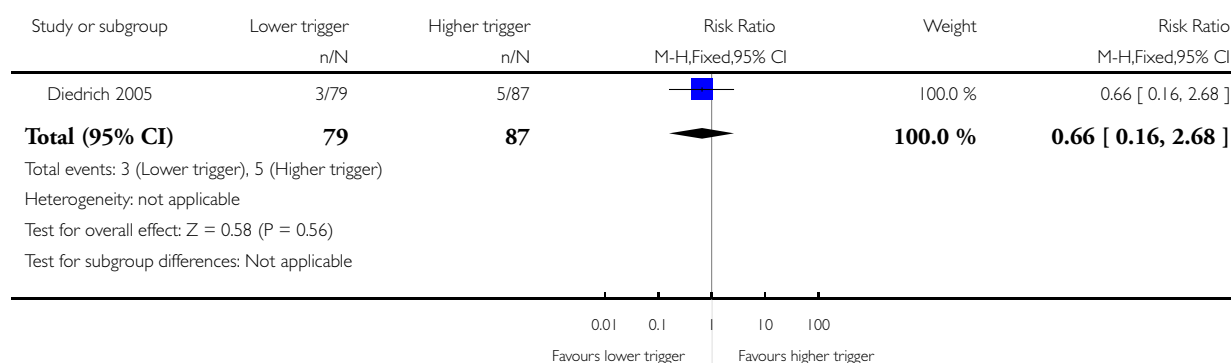


Analysis 2.4. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 4 Number of participants with bleeding requiring a red cell transfusion.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 4 Number of participants with bleeding requiring a red cell transfusion

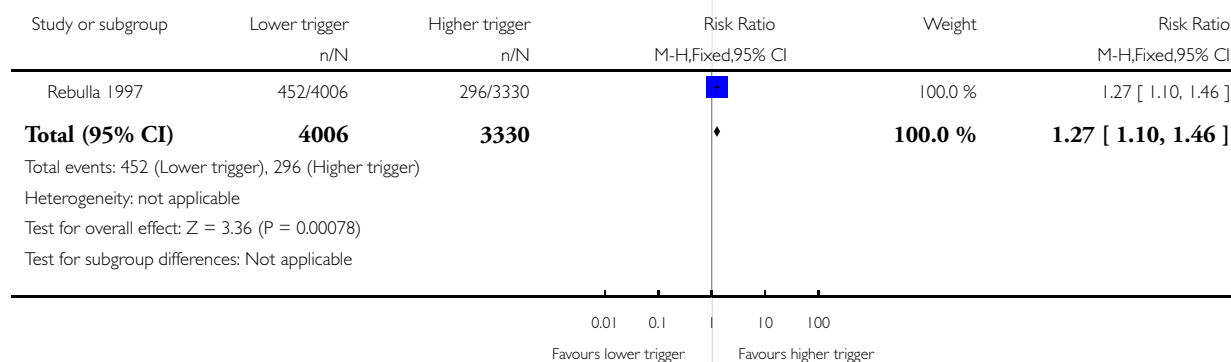


Analysis 2.5. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 5 Number of days with any bleeding.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 5 Number of days with any bleeding

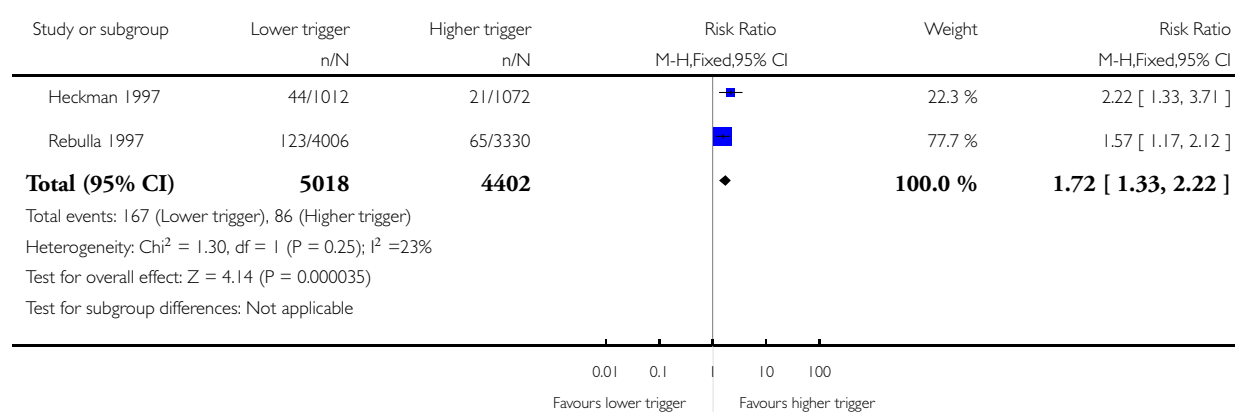


Analysis 2.6. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 6 Number of days with a significant bleed.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 6 Number of days with a significant bleed

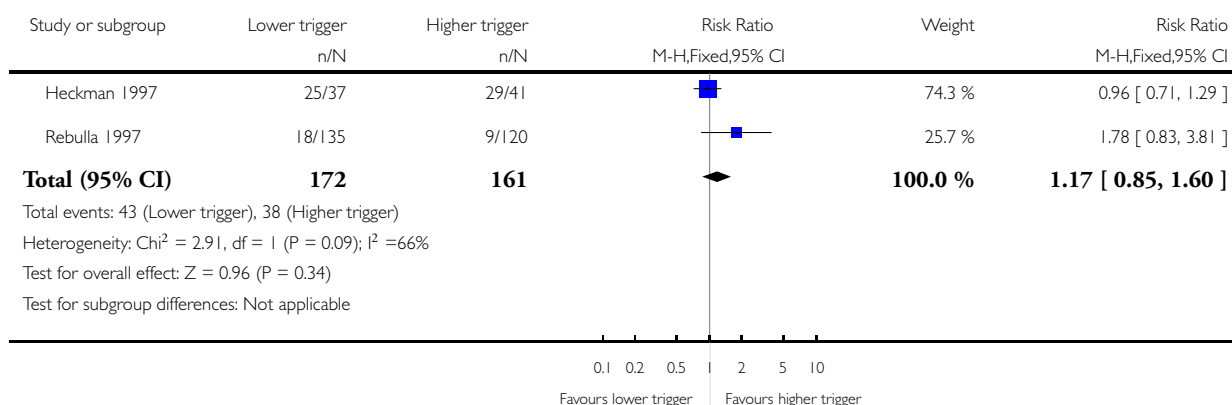


Analysis 2.7. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 7 Mortality from all causes.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 7 Mortality from all causes

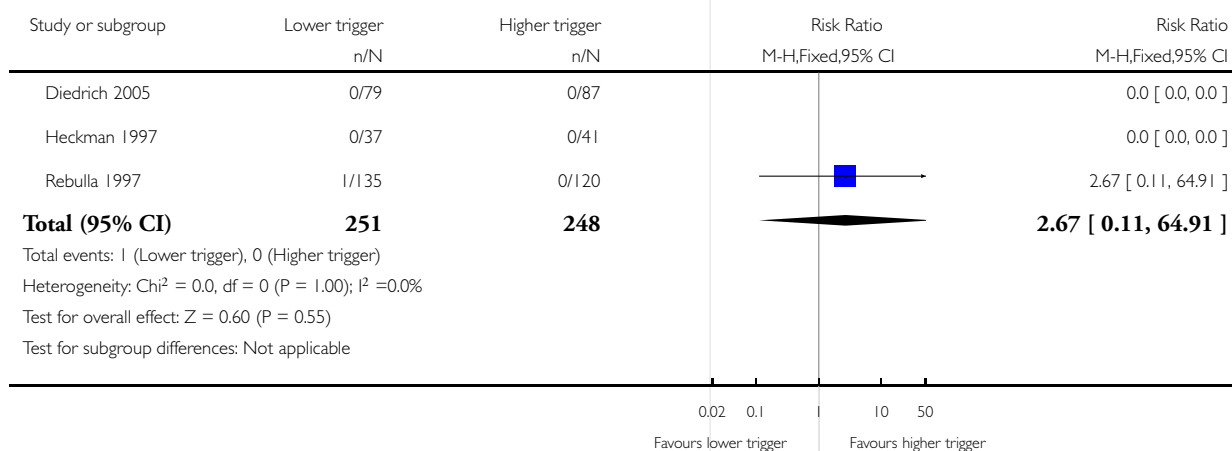


Analysis 2.8. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 8 Mortality from bleeding.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 8 Mortality from bleeding

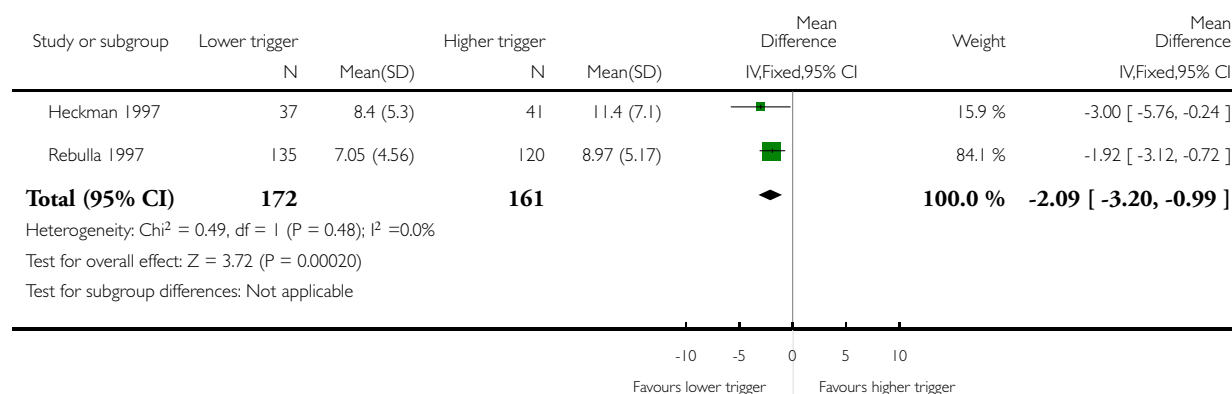


Analysis 2.9. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 9 Mean number of platelet transfusions per patient.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 9 Mean number of platelet transfusions per patient

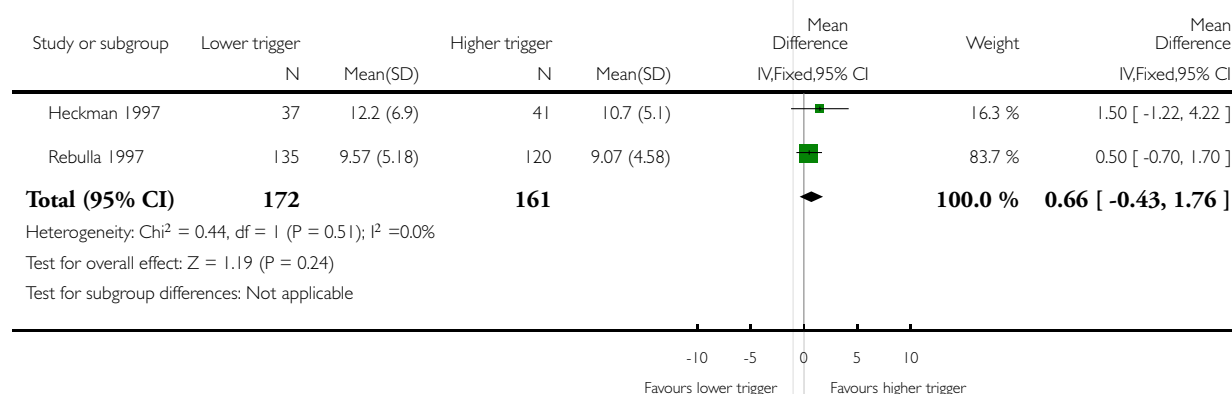


Analysis 2.10. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 10 Mean number of red cell transfusions per patient.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 10 Mean number of red cell transfusions per patient

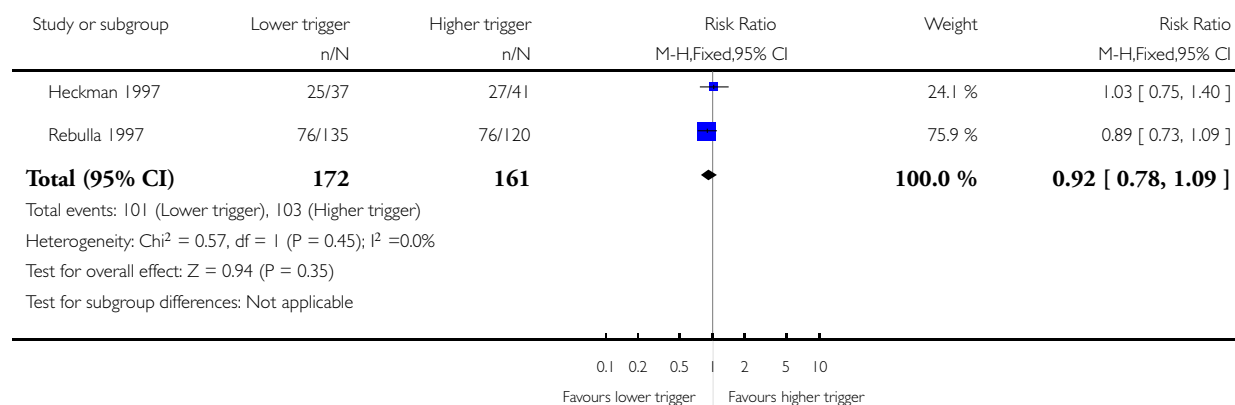


Analysis 2.11. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 11 Remission rates.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 11 Remission rates

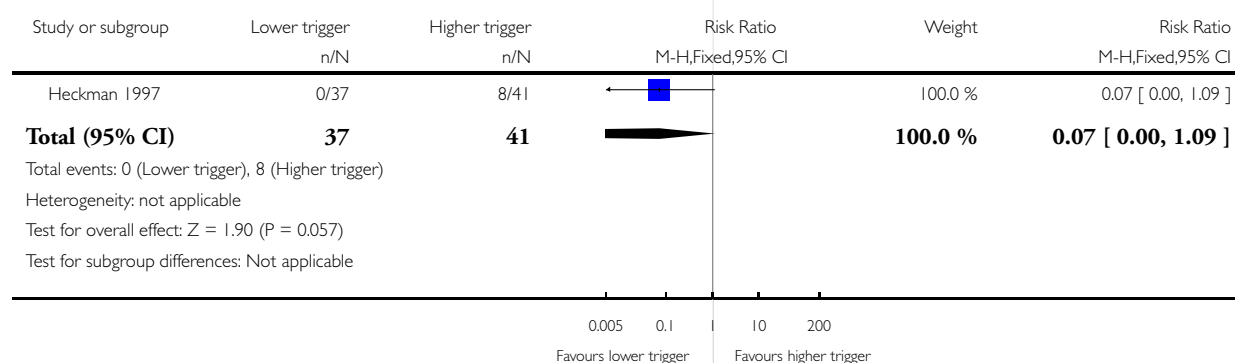


Analysis 2.12. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 12 Numbers of participants with platelet transfusion reactions.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 12 Numbers of participants with platelet transfusion reactions

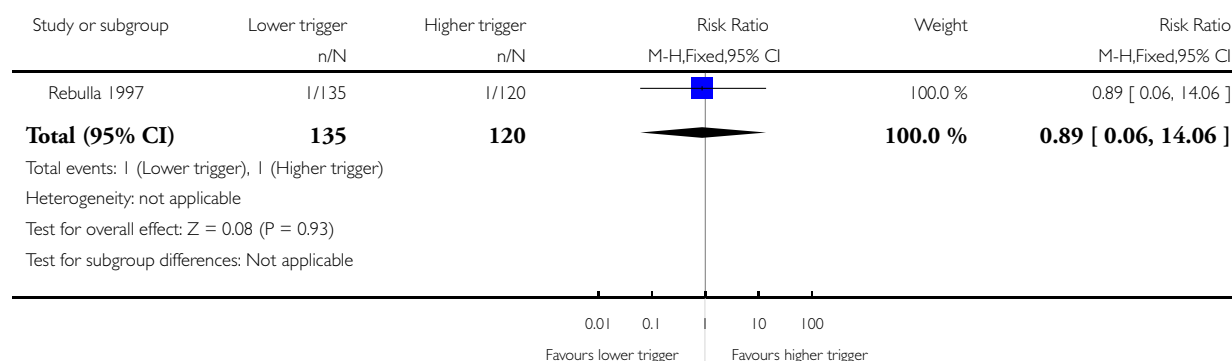


Analysis 2.13. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 13 Number of participants with thromboembolic disease.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 13 Number of participants with thromboembolic disease

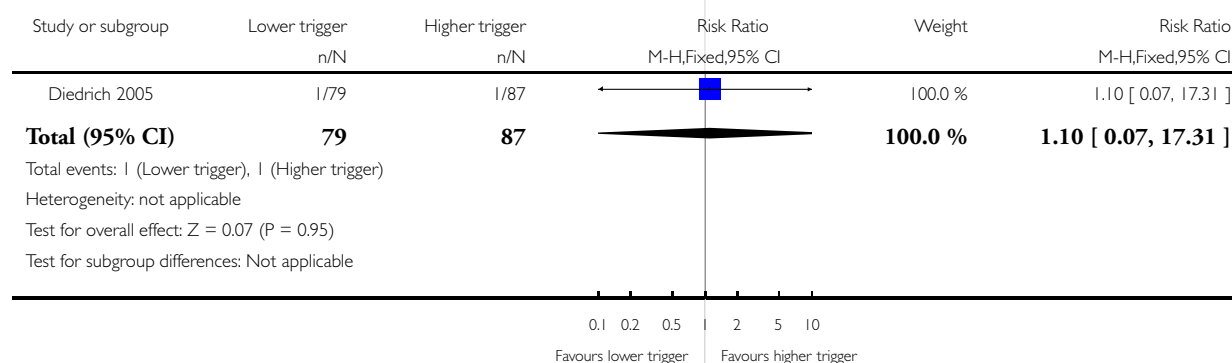


Analysis 2.14. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 14 Number of participants requiring HLA-matched platelets.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 14 Number of participants requiring HLA-matched platelets

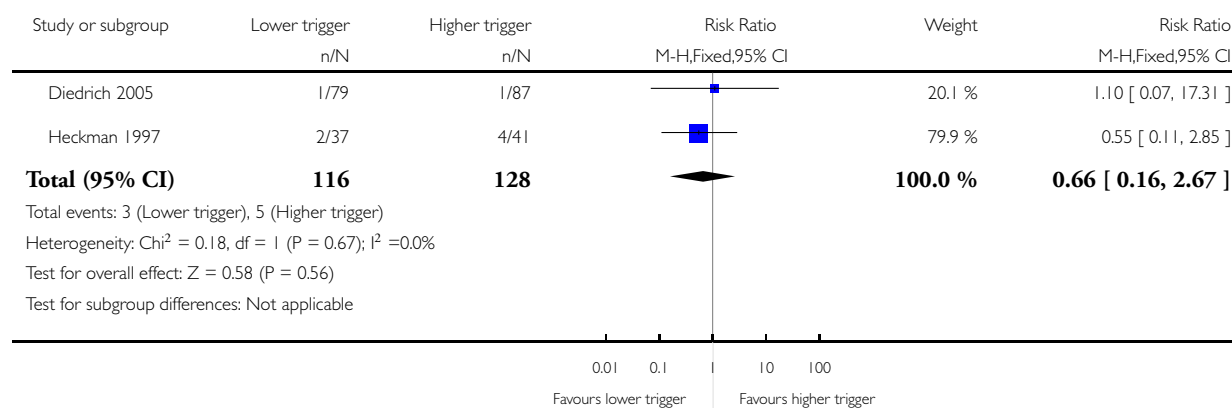


Analysis 2.15. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 15 Number of participants with platelet refractoriness.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 15 Number of participants with platelet refractoriness

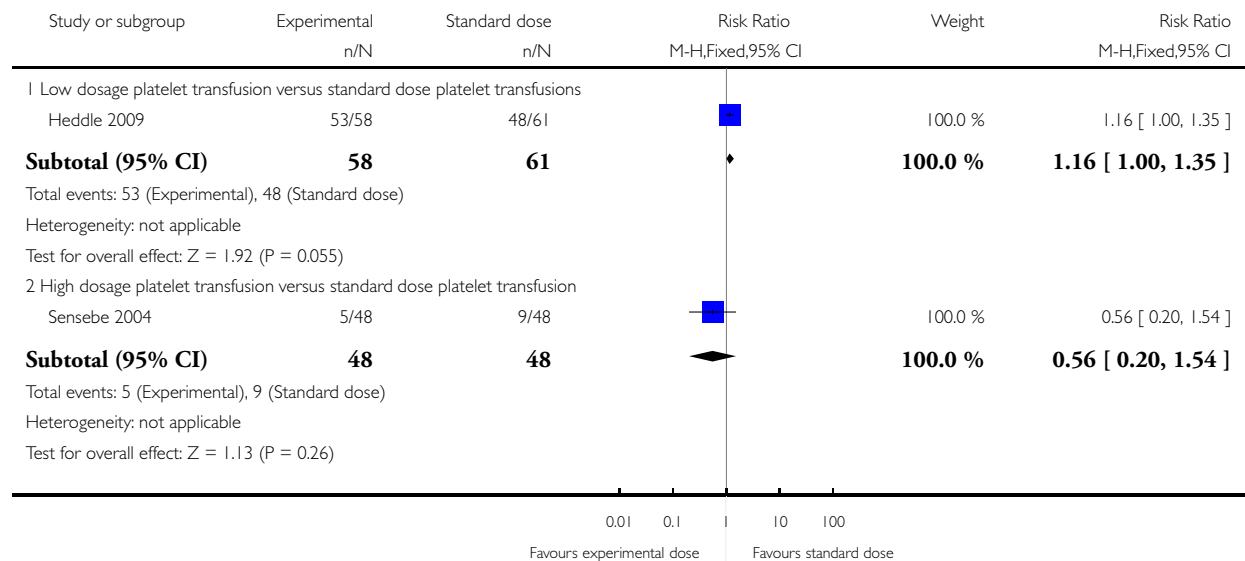


Analysis 3.1. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 1 Number of participants with any bleeding event.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 1 Number of participants with any bleeding event

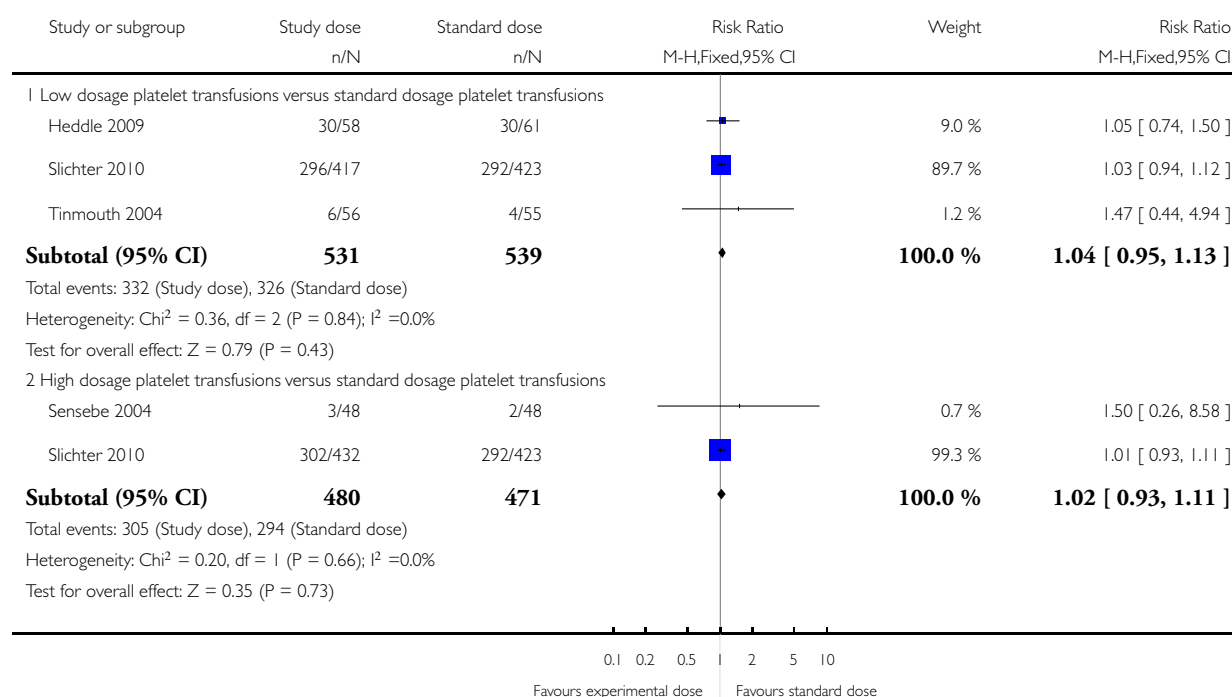


Analysis 3.2. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 2 Number of participants with a significant bleeding event.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 2 Number of participants with a significant bleeding event

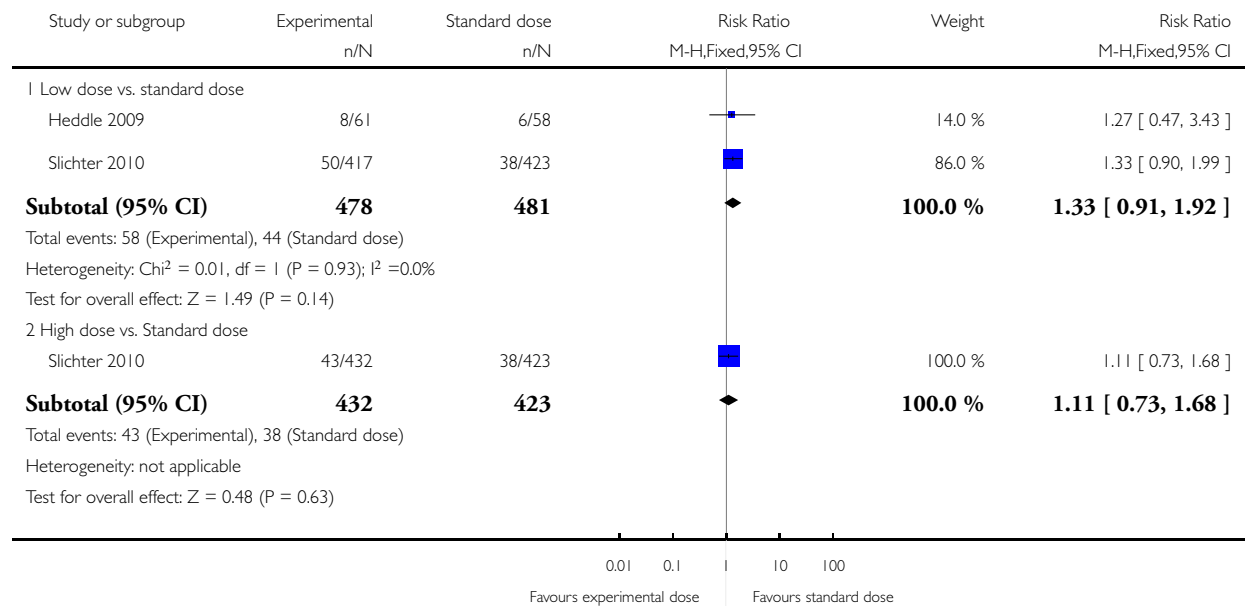


Analysis 3.3. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 3 Number of participants with WHO Grade 3 or 4 bleeding.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 3 Number of participants with WHO Grade 3 or 4 bleeding

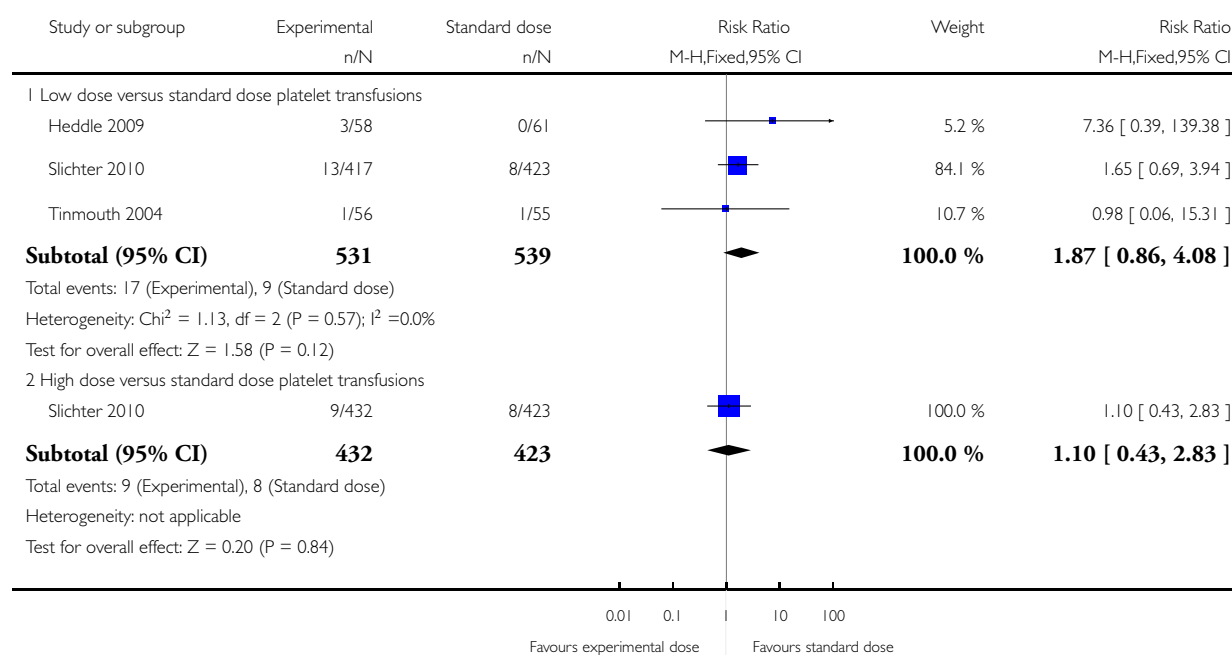


Analysis 3.4. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 4 Number of participants with WHO grade 4 bleeding.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 4 Number of participants with WHO grade 4 bleeding

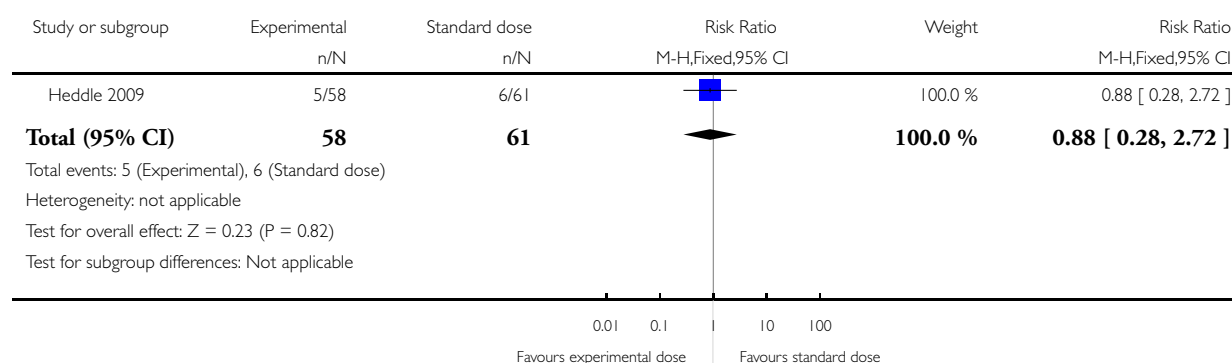


Analysis 3.5. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 5 Number of participants with bleeding requiring a red cell transfusion.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 5 Number of participants with bleeding requiring a red cell transfusion

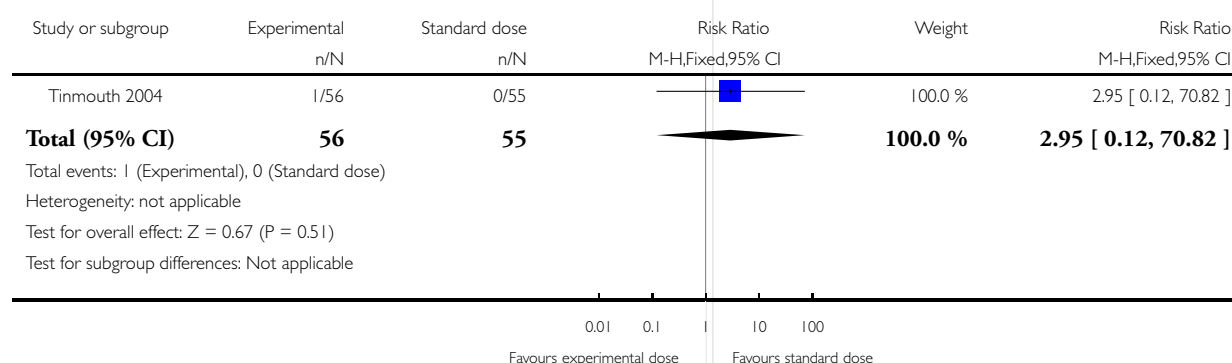


Analysis 3.6. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 6 Number of participants with bleeding causing cardiovascular compromise.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 6 Number of participants with bleeding causing cardiovascular compromise

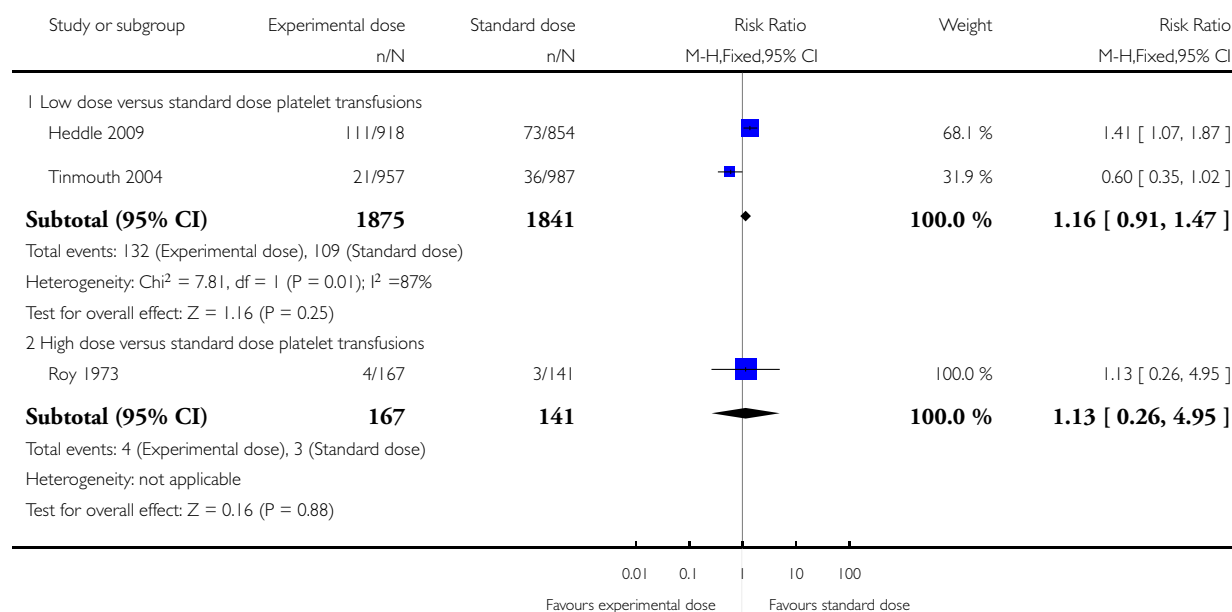


Analysis 3.7. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 7 Number of days with significant bleeding.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 7 Number of days with significant bleeding

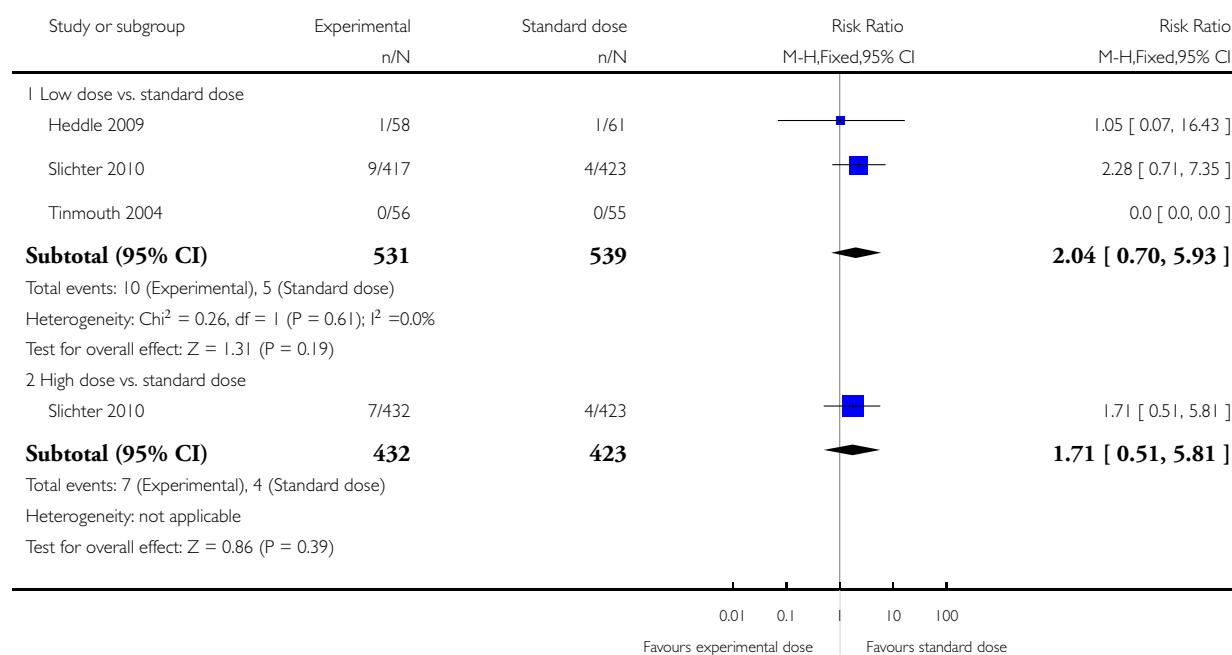


Analysis 3.8. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 8 Mortality from all causes.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 8 Mortality from all causes

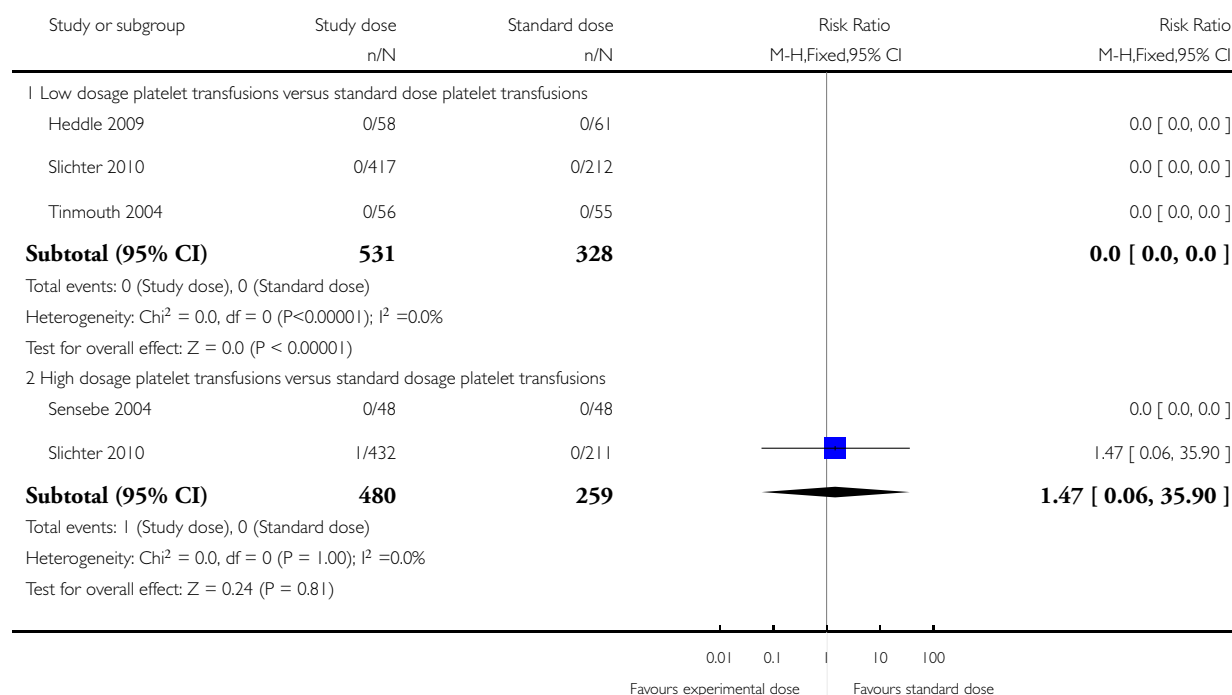


Analysis 3.9. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 9 Mortality from bleeding.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 9 Mortality from bleeding

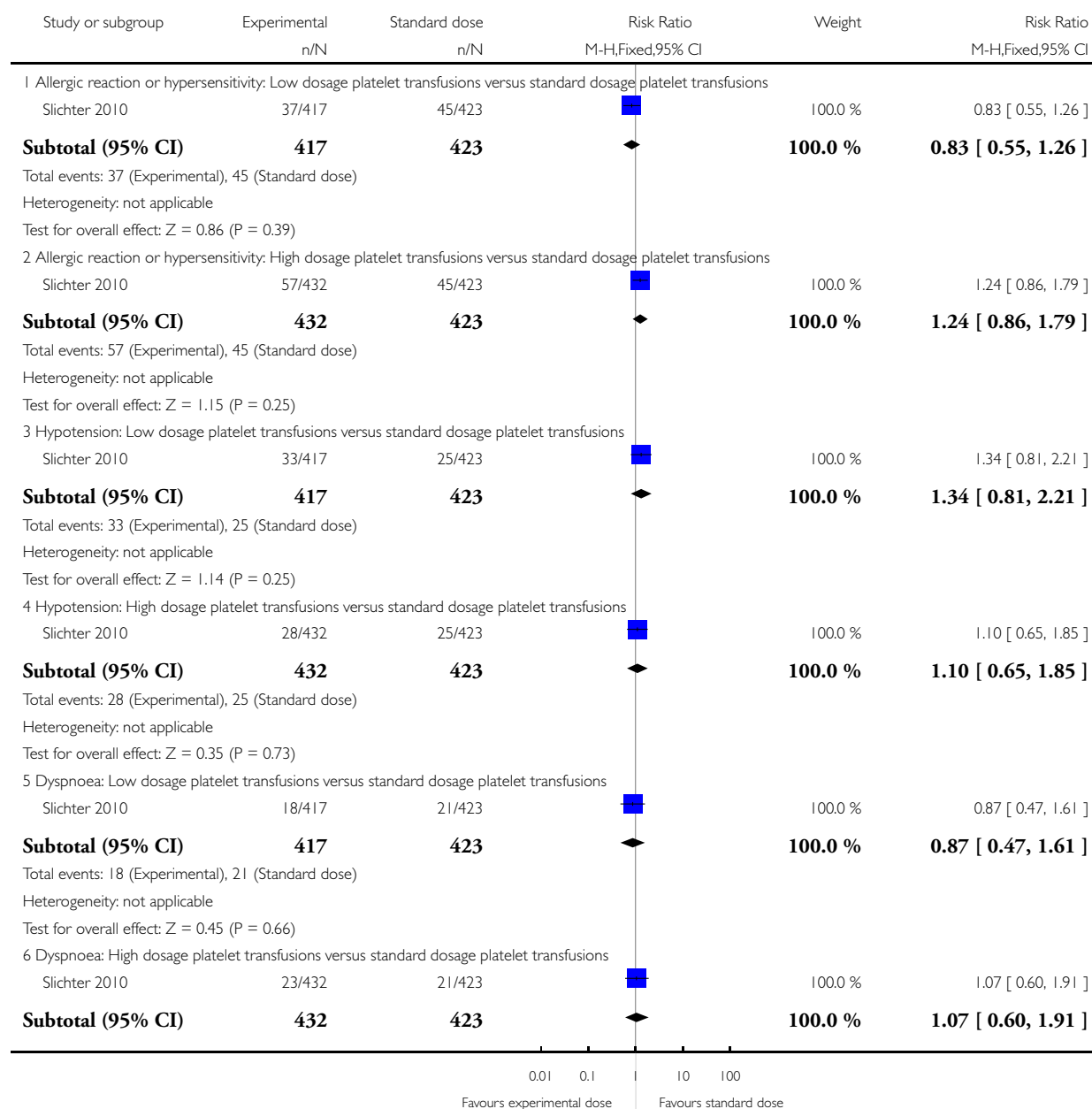


Analysis 3.10. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 10 Number of participants with platelet transfusion reactions.

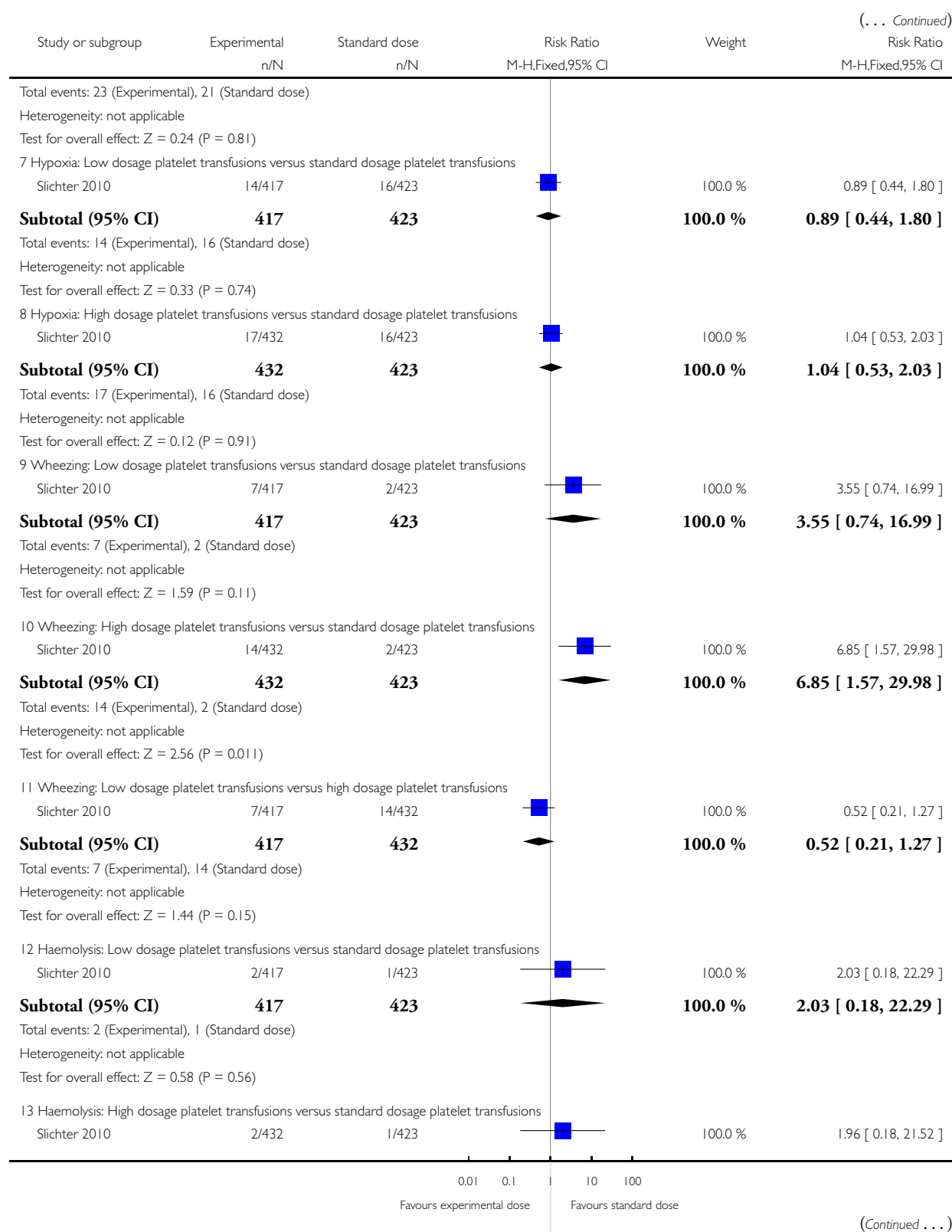
Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

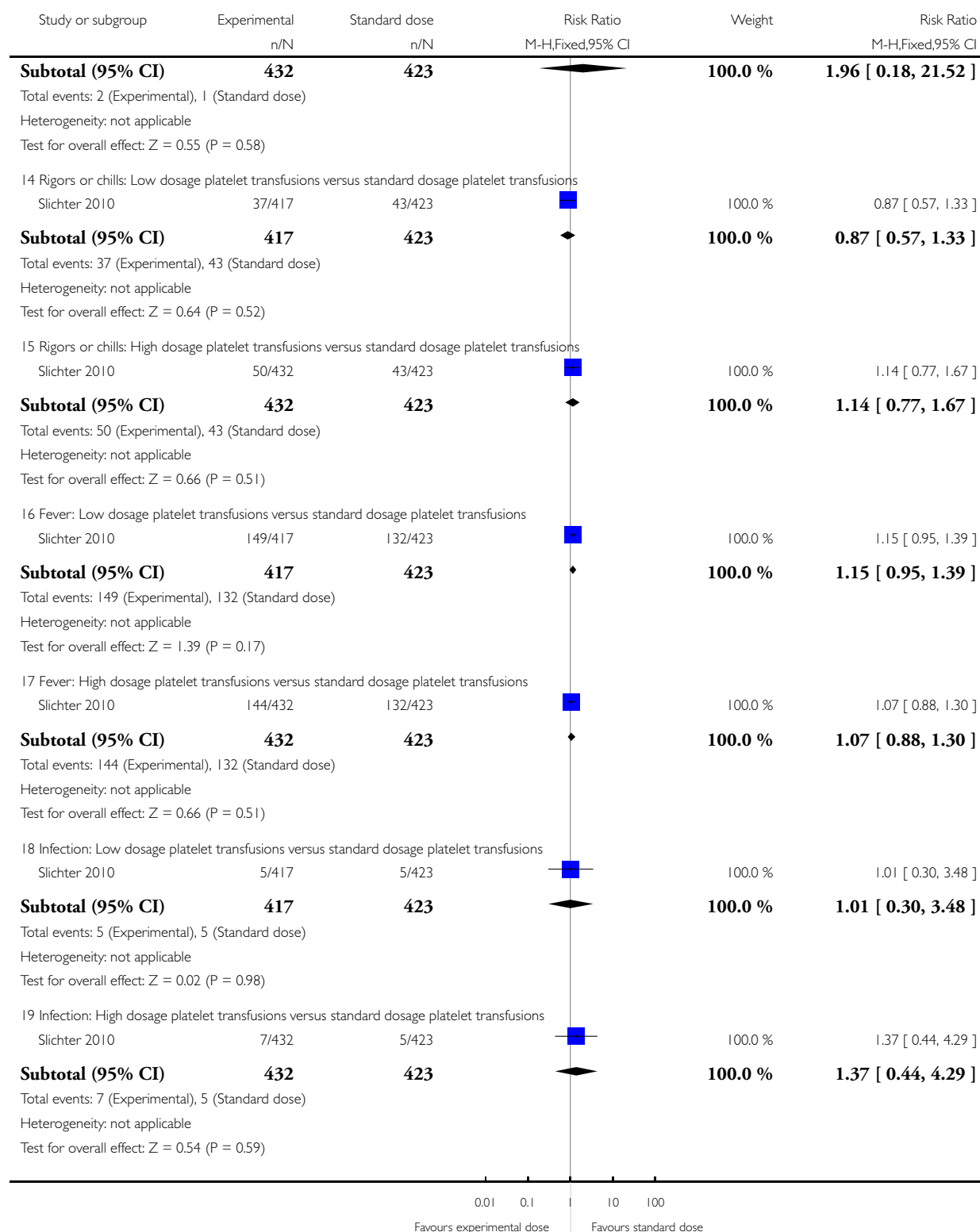
Outcome: 10 Number of participants with platelet transfusion reactions



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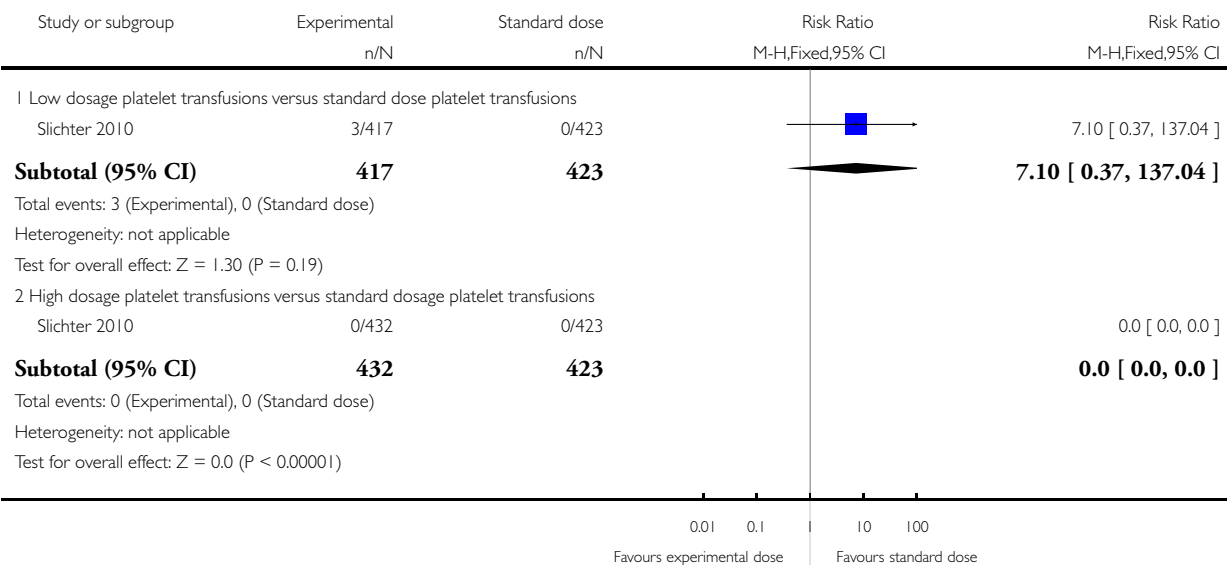


Analysis 3.11. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 11 Thromboembolic disease.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 11 Thromboembolic disease

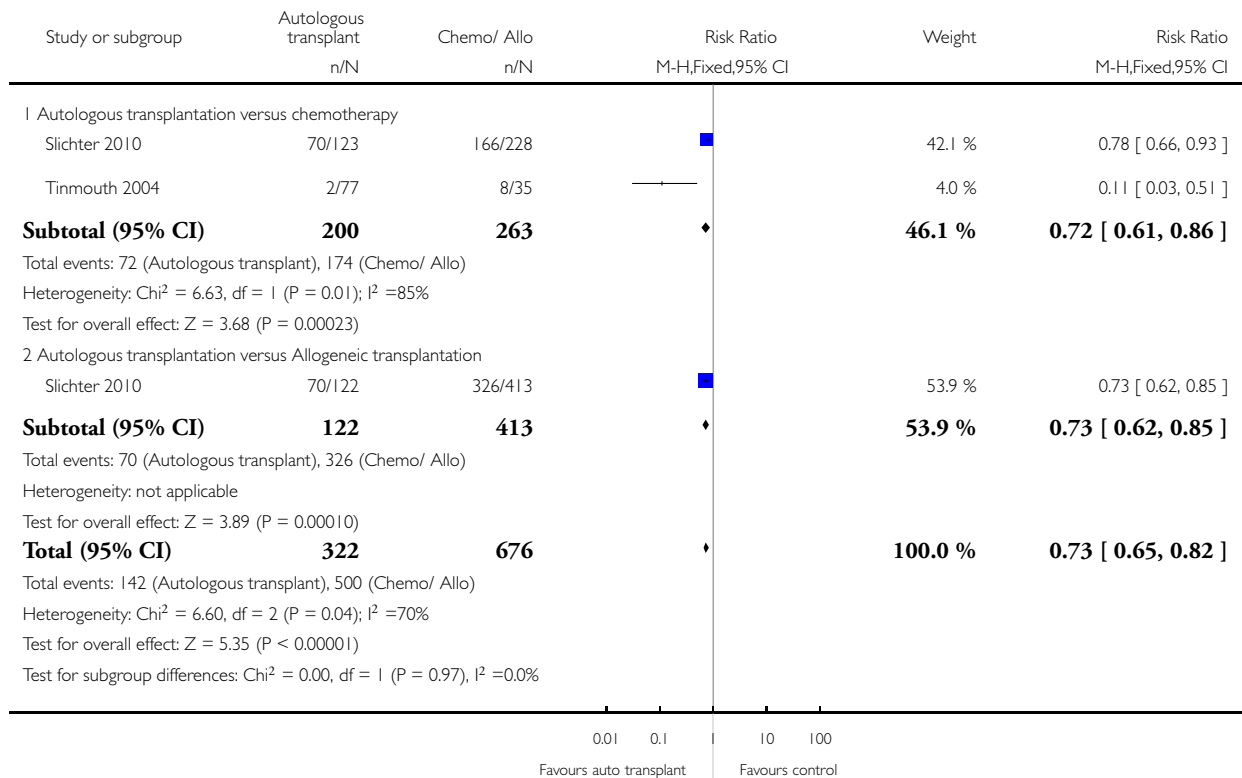


Analysis 3.12. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 12 Number of participants with a significant bleeding episode.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 12 Number of participants with a significant bleeding episode

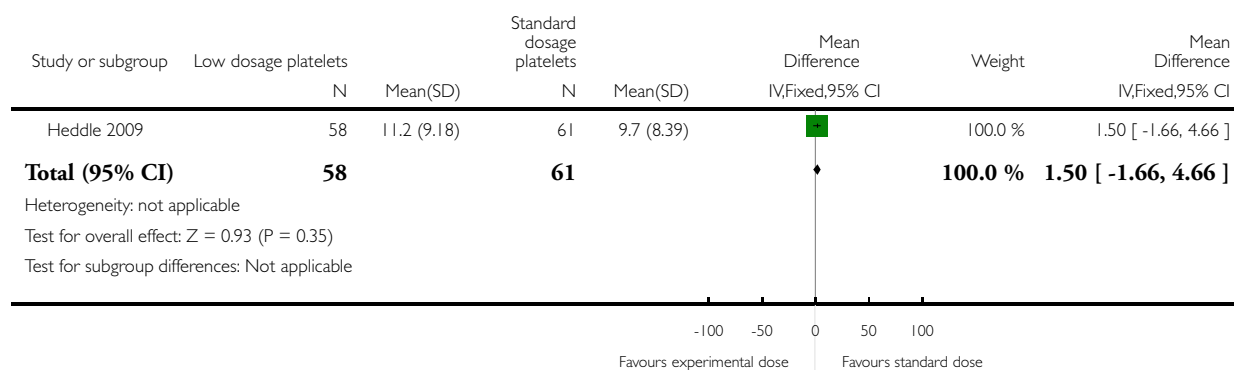


Analysis 3.13. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 13 Time to first significant bleeding event.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 13 Time to first significant bleeding event

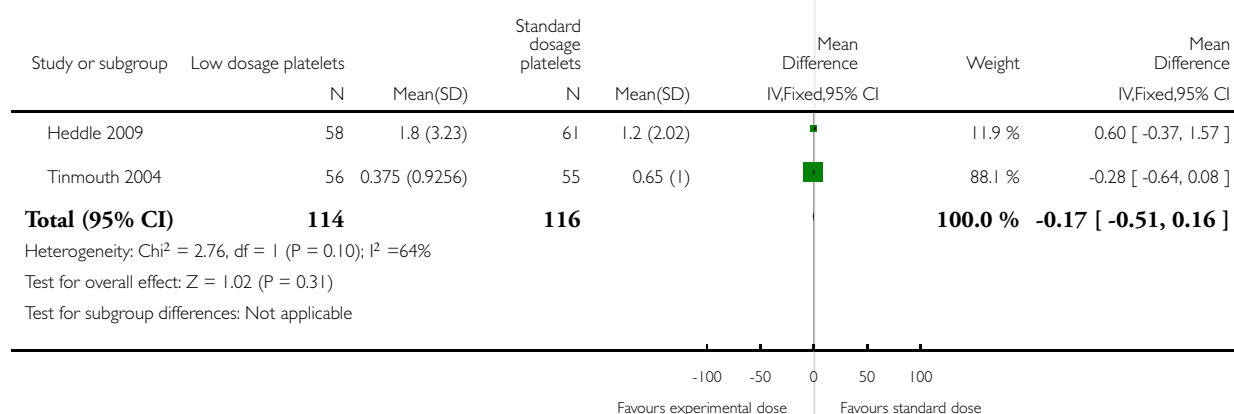


Analysis 3.14. Comparison 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule, Outcome 14 Number of days with WHO grade 2 or above bleeding per patient.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 3 Prophylactic platelet transfusion with one dose schedule versus another dose schedule

Outcome: 14 Number of days with WHO grade 2 or above bleeding per patient

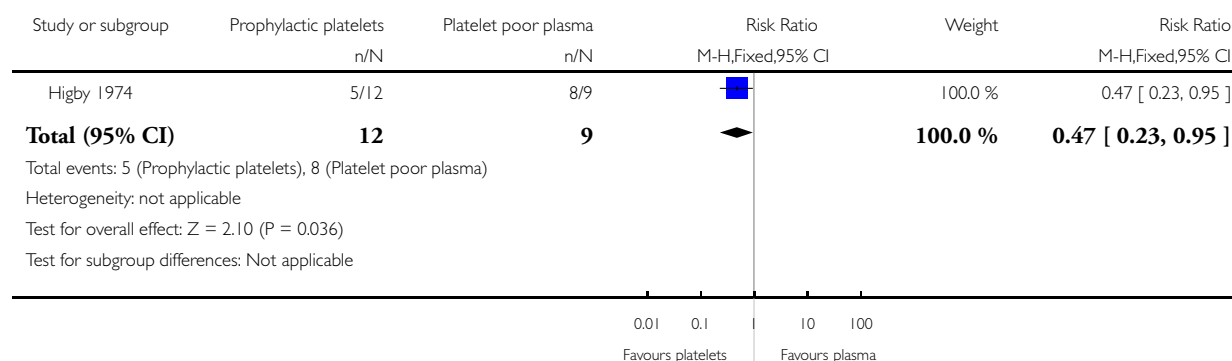


Analysis 4.1. Comparison 4 Prophylactic platelet transfusion versus platelet-poor plasma, Outcome 1 Number of participants with a significant bleeding event.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 4 Prophylactic platelet transfusion versus platelet-poor plasma

Outcome: 1 Number of participants with a significant bleeding event

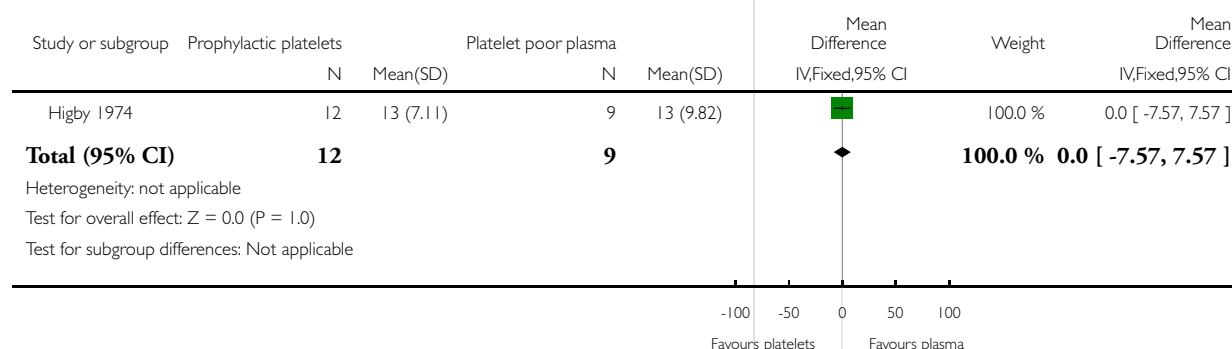


Analysis 4.2. Comparison 4 Prophylactic platelet transfusion versus platelet-poor plasma, Outcome 2 Time to first bleed.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 4 Prophylactic platelet transfusion versus platelet-poor plasma

Outcome: 2 Time to first bleed

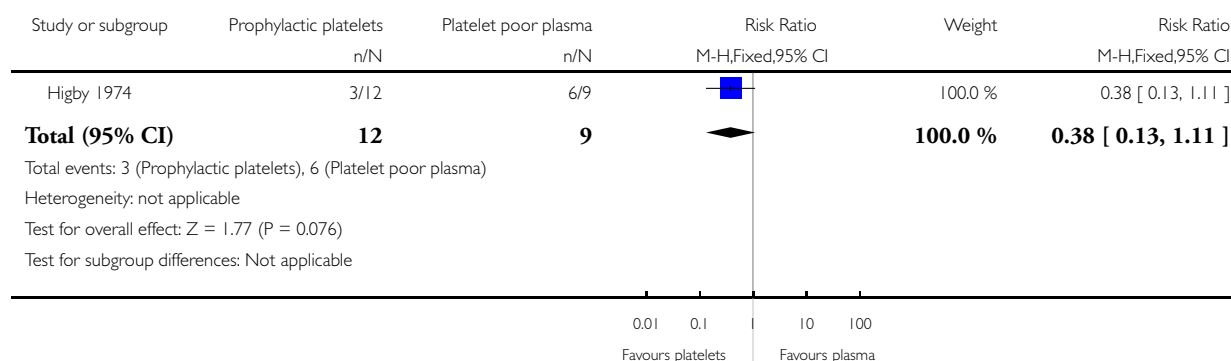


Analysis 4.3. Comparison 4 Prophylactic platelet transfusion versus platelet-poor plasma, Outcome 3 Number of participants with bleeding requiring a red cell transfusion.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 4 Prophylactic platelet transfusion versus platelet-poor plasma

Outcome: 3 Number of participants with bleeding requiring a red cell transfusion

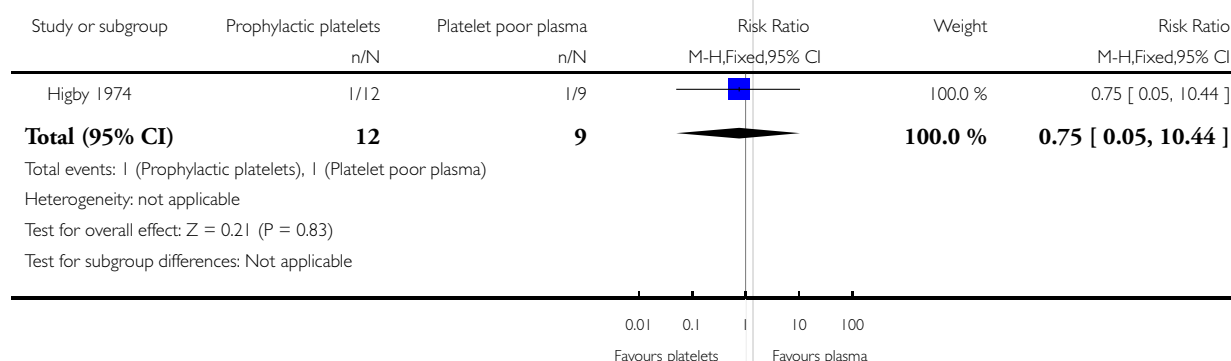


Analysis 4.4. Comparison 4 Prophylactic platelet transfusion versus platelet-poor plasma, Outcome 4 Number of participants with bleeding causing cardiovascular compromise.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 4 Prophylactic platelet transfusion versus platelet-poor plasma

Outcome: 4 Number of participants with bleeding causing cardiovascular compromise

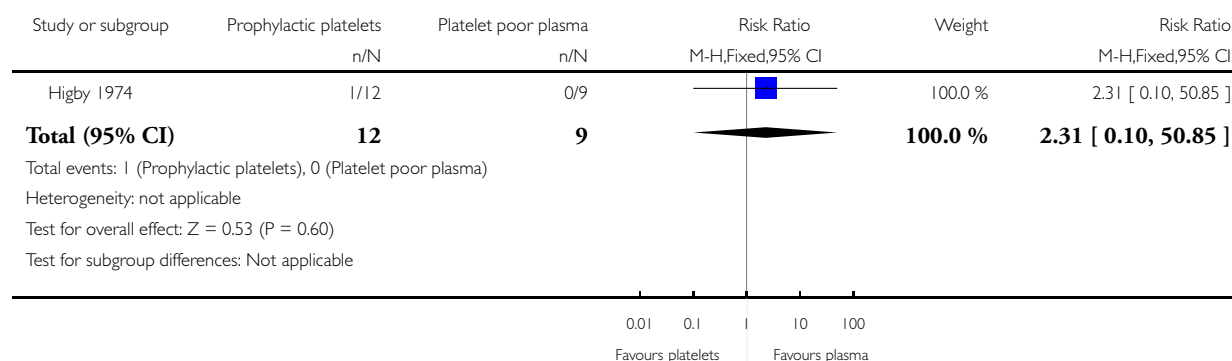


Analysis 4.5. Comparison 4 Prophylactic platelet transfusion versus platelet-poor plasma, Outcome 5 Mortality from bleeding.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 4 Prophylactic platelet transfusion versus platelet-poor plasma

Outcome: 5 Mortality from bleeding

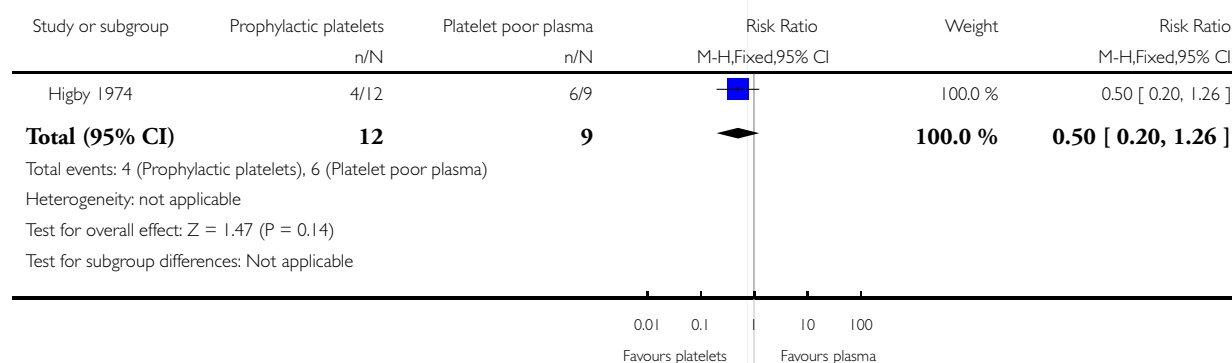


Analysis 4.6. Comparison 4 Prophylactic platelet transfusion versus platelet-poor plasma, Outcome 6 Complete remission.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 4 Prophylactic platelet transfusion versus platelet-poor plasma

Outcome: 6 Complete remission

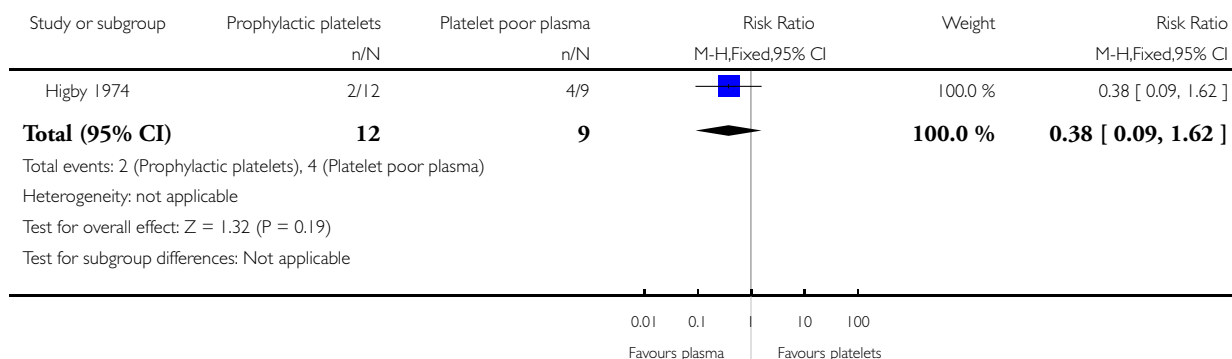


Analysis 4.7. Comparison 4 Prophylactic platelet transfusion versus platelet-poor plasma, Outcome 7 Development of HLA Antibodies.

Review: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation

Comparison: 4 Prophylactic platelet transfusion versus platelet-poor plasma

Outcome: 7 Development of HLA Antibodies



ADDITIONAL TABLES

Table 1. Prophylactic versus Therapeutic Platelet Transfusion Studies - Characteristics of Studies

Study	Participants	Number	Intervention	Duration of study	Type of platelet product	Primary Outcome
Murphy 1982	Children with acute leukaemia	56	Pro-phylactic plt transfusion if plt count $< 20 \times 10^9/L$ versus Plt transfusion given in presence of 5 clinical indicators of bleeding	19.9 to 20.4 months	Random donor	Survival
Sintnicolaas 1982	Patients with acute leukaemia	12	Pro-phylactic plt transfusion if plt count $< 20 \times 10^9/L$ versus Plt transfusion given in presence of haemorrhage	Not reported	ABO compatible Single donor	Not reported

Table 1. Prophylactic versus Therapeutic Platelet Transfusion Studies - Characteristics of Studies (Continued)

Solomon 1978	Adults with AML	31	Pro-phylactic plt transfusion if plt count $< 20 \times 10^9/L$ versus Plt transfusion given if clinically significant bleeding OR $> 50\%$ fall in plts to $< 20 \times 10^9/L$ in previous 24 hours	Not reported	Random donor	Not reported
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Table 2. Prophylactic Platelet transfusion Studies with Varying Transfusion Trigger Levels - Characteristics of Studies

Study	Participants	Number	Intervention	Duration of study	Type of platelet product	Primary Outcome
Diedrich 2005	All ages undergoing an allogeneic stem cell transplant	166	Pro-phylactic plt transfusion if plt count $< 10 \times 10^9/L$ versus Pro-phylactic plt transfusion if plt count $< 30 \times 10^9/L$	Not reported	Leucodepleted ABO matched Irradiated Pooled random donor platelets (Buffy coat) 85% Apheresis 15%	Number of platelet transfusions
Heckman 1997	Adults with acute leukaemia	82	Pro-phylactic plt transfusion if plt count $\leq 10 \times 10^9/L$ versus Pro-phylactic plt transfusion if plt count $\leq 20 \times 10^9/L$	Median 24 days	Leucodepleted Apheresis	Not reported
Rebulla 1997	Adolescents and adults with AML	276	Pro-phylactic plt transfusion if plt count $< 10 \times 10^9/L$ versus Pro-phylactic plt transfusion if plt count $< 20 \times 10^9/L$	Not reported	Apheresis and Pooled products	Frequency and severity of haemorrhage

Table 3. Prophylactic Platelet Transfusion Studies with Varying Platelet Transfusion Doses - Characteristics of Studies

Study	Participants	Number	Intervention	Prophylactic Platelet transfusion threshold	Duration of study	Type of platelet product	Primary Outcome
Heddle 2009	Adults with hypoproliferative thrombocytopenia	129	Low dose (1.5 to 3.0×10^{11} platelets/product) versus Standard dose (3.0 to 6.0×10^{11} platelets/product)	Depended on local transfusion trigger. Usually $10 \times 10^9/L$	Mean of 14 to 15.8 days	Apheresis and Pooled platelet products	Occurrence of a WHO grade 2 bleed or above
Roy 1973	Children with acute leukaemia	62	Standard dose (0.46×10^{11} platelets/10kg) versus High dose (0.9 to $1.1 \times 10^{11}/10\text{kg}$)	Plt count $\leq 25 \times 10^9/L$	Follow-up for 24 hours post platelet transfusion	ABO identical Pooled products	Not reported
Sensebe 2004	Patients with acute leukaemia or patients undergoing autologous SCT	101	Standard dose ($0.5 \times 10^{11}/10\text{kg}$) versus High dose ($1.0 \times 10^{11}/10\text{kg}$)	Plt count $< 20 \times 10^9/L$	Not stated	Leucodepleted ABO compatible Apheresis	Time between first transfusion and daily platelet count reaching $20 \times 10^9/L$
Slichter 2010	Patients of any age receiving stem cell transplant or myeloablative chemotherapy	1351	Low dose ($1.1 \times 10^{11}/\text{m}^2$ BSA) versus Intermediate dose ($2.2 \times 10^{11}/\text{m}^2$ BSA) versus High dose ($4.4 \times 10^{11}/\text{m}^2$ BSA)	Plt count $\leq 10 \times 10^9/L$	Mean number of days 19.1	Apheresis and pooled platelet products	Grade 2 or higher bleeding
Steffens 2002	Patients aged > 16yrs with AML or undergoing an allogeneic SCT	54	Standard dose (single apheresis unit) versus High dose (triple apheresis unit)	Plt count $\leq 10 \times 10^9/L$	Median time for AML patients 25.1 to 25.8 days Median time for SCT 14.1 to 15.9 days	Apheresis	Not reported

Table 3. Prophylactic Platelet Transfusion Studies with Varying Platelet Transfusion Doses - Characteristics of Studies (*Continued*)

Tinmouth 2004	Patients age > 16yrs with acute leukaemia or receiving an autologous SCT	111	Low dose (1.9 to 2.5×10^{11} platelets/transfusion) versus Standard dose (3.4 to 4.4×10^{11} platelets/transfusion)	Plt count < $10 \times 10^9/L$	Median time 15 days	Leucodepleted Random donor pooled platelets (PRP method)	Bayesian design. Lower dose of platelets would be safe and effective in preventing major bleeding events and would decrease total utilisation of platelets
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BSA = body surface area

SCT = stem cell transplant

Table 4. Studies that reported bleeding as an outcome measure- Bleeding Assessment and Grading

Study	Bleeding primary outcome of study	Method of bleeding assessment reported	Bleeding severity scale used	RBC usage part of bleeding severity assessment	RBC transfusion policy
Heddle 2009	Yes	Yes	Adapted WHO	Yes	Local practice at each centre (unpublished)
Rebulla 1997	Yes	Yes	New scale developed by Rebulla	Yes	Haemoglobin < 80g/L
Slichter 2010	Yes	Yes	Adapted WHO	Yes	Local practice at each centre
Tinmouth 2004	Yes	Yes	Adapted Rebulla	No	Not reported
Heckman 1997	Not reported	Yes	Ajani 1990	Yes	Not reported
Higby 1974	Not reported	No	Study specific	Yes	Not reported
Roy 1973	Not reported	Yes	Study specific	No	Not reported
Diedrich 2005	No	Yes	WHO 1979	No	Haemoglobin < 80g/L
Murphy 1982	No	No	Study specific	No	Not reported
Sensebe 2004	No	No	WHO 1979	No	Not reported

RBC = red blood cell

Table 5. Prophylactic versus Therapeutic Platelet Transfusion Studies - Number of platelet units and red cell transfusions

Study	Intervention	Number of patients in each arm	Platelet dose/ transfusion	Number of platelet units	P value	Number of red cell transfusions/ patient	P value
Murphy 1982	Prophylactic	35	4 units/m ²	8.1/ patient*	Not reported	Not reported	Not reported
	Therapeutic	21		4.8/ patient*			
Solomon 1978	Prophylactic	17	Not reported	Mean 31.9 (S. D. \pm 5.9)/ course of chemotherapy	Not reported	Mean 6.7 (S. D. \pm 1.0)	Not reported
	Therapeutic	12		Mean 16.1 (S. D. \pm 3.4)/ course of chemotherapy		Mean 7.3 (S. D. \pm 1.0)	

* = Not specified in article whether this figure is a mean or a median (author has died).

SD = standard deviation

Table 6. Prophylactic Platelet Transfusion Studies with Varying Platelet Transfusion Thresholds - Duration of Hospital Stay

Study	Intervention (Transfusion threshold)	Number of patients in each arm	Number of days in hospital (median)	P value
Diedrich 2005	< 10 x 10⁹/L	79	23 Range 9 to 89	Not significant
	< 30 x 10⁹/L	87	23 Range 14 to 140	
Heckman 1997	≤ 10 x 10⁹/L	37	38 IQR 30 to 42	0.25*
	≤ 20 x 10⁹/L	41	32 IQR 27 to 45	
Rebulla 1997	< 10 x 10⁹/L	135	29 Range 3 to 64	Not reported
	< 20 x 10⁹/L	120	28 Range 4 to 54	

IQR = Interquartile range

* = P value is not statistically significant

Table 7. Prophylactic Platelet Transfusion Studies with Varying Platelet Transfusion Dosages - Number of days with a significant bleeding event/patient

Study	Low dose		P value Low dose vs. standard dose	Standard dose		P value Standard dose vs. high dose	High dose	
	Num- ber of par- ticipants	Days		Num- ber of par- ticipants	Days		Num- ber of par- ticipants	Days
Heddle 2009	58	Mean 1.8 ± S.D. 3.23 [#]	Not reported	61	Mean 1.2 ± S.D. 2.02 [#]	NA	NA	NA
Slichter 2010	417	Median 1 IQR 0 to 4	0.9*	423	Median 1 IQR 0 to 4	0.91*	432	Median 1 IQR 0 to 4
Tinmouth 2004[@]	56	Mean 0.375 ± SD 0.93 [#]	Not reported	55	Mean 0.65 ± SD 1.0 [#]	NA	NA	NA

IQR = Interquartile range

NA = Not applicable

* = P value is not statistically significant

[#] = unpublished data

[@] = To improve comparison with the other studies significant bleeding in this analysis was the number of days with bleeding that required a therapeutic platelet transfusion or local intervention. This differs from the study's definition of significant bleeding.

Table 8. Prophylactic Platelet Transfusion Studies with Varying Platelet Transfusion Dosages - Time to first significant bleeding event

Study	Low dose		P value Low dose vs. standard dose	Standard dose		P value Standard dose vs. high dose	High dose	
	Num- ber of par- ticipants	Days		Num- ber of par- ticipants	Days		Num- ber of par- ticipants	Days
Heddle 2009	58	Mean 11.2 ± SD 9.18 [#]	Not reported	61	Mean 9.7 ± SD 8.39 [#]	NA	NA	NA
Slichter 2010	417	Median 7 IQR 3 to 18	0.85*	423	Median 7 IQR 3 to 19	0.66*	432	Median 8 IQR 3 to 19

IQR = Interquartile range

NA = Not applicable

* = P value is not statistically significant

[#] = unpublished data

Table 9. Prophylactic Platelet Transfusion Studies with Varying Platelet Transfusion Doses - Number of platelet transfusions and red cell transfusions

Study	Intervention	Number of participants	Number of platelet transfusion episodes/ patient	P value	Total platelet utilisation	P value	Number of red cell transfusions/ patient	P value
Low dosage versus standard dosage platelets								
Heddle 2009	Low dose 1.5 - 3 x 10 ¹¹ platelets/ transfusion	58	Mean 9.5 ± SD 7.8	< 0.001	Number of donor exposures MD 4.1; 95% CI -4.3 to 12.4	0.335*	Mean 6.1 ± SD 4.19 [#]	Not reported
	Standard dose 3 - 6 x 10 ¹¹ platelets/ transfusion	61	Mean 5.3 ± SD 3.2				Mean 5.23 ± SD 3.58 [#]	
Slichter 2010	Low dose 1.1 x 10 ¹¹ platelets/ m ² ± 25%	417	Median 5 IQR 3 to 9	< 0.001	Median 9.3 x 10 ¹¹ IQR 4.9 to 17.9	0.002	Median 4 IQR 2 to 8	0.62*
	Standard dose 2.2 x 10 ¹¹ platelets/ m ² ± 25%	423	Median 3 IQR 2 to 6		Median 11.3 x 10 ¹¹ IQR 7.0 to 22.8		Median 4 IQR 2 to 8	
Tinmouth 2004	Low dose 1.9 - 2.6 x 10 ¹¹ platelets/ transfusion	56	Median 1 IQR 0.75 to 5	Not reported	Median 3 WBD units Range 0 to 49	Bayesian analysis 89 % probability low-dose platelets reduce total number of units transfused per patient.	Median 4.5 Range 0 to 16	Not reported
	Standard dose 3.4 - 4.4 x 10 ¹¹ platelets/ transfusion	55	Median 1 IQR 1 to 4		Median 5 WBD units Range 0 to 110		Median 4 Range 0 to 12	
Standard dosage versus High dosage platelets								
Roy 1973	Standard dose 0.46 x 10 ¹¹ platelets/	32	Mean 4.4	Not reported	Mean 11.5 WBD units	Not reported	Not reported	Not reported

Table 9. Prophylactic Platelet Transfusion Studies with Varying Platelet Transfusion Doses - Number of platelet transfusions and red cell transfusions (Continued)

	10kg							
	High dose 0.9 - 1.1 x 10¹¹ platelets/10kg	30	Mean 5.6		Mean 19.0 WBD units		Not reported	
Sensebe 2004	Standard dose 0.5 x 10¹¹ platelets/10kg	48	Median 3 Range 1 to 12	0.037	Mean 14.9 x 10 ¹¹	0.156*	Not reported	Not reported
	High dose 1.0 x 10¹¹ platelets/10kg	48	Median 2 Range 1 to 13		Mean 18.5 x 10 ¹¹		Not reported	
Slichter 2010	Standard dose 2.2 x 10¹¹ platelets/m² ± 25%	423	Median 3 IQR 2 to 6	0.09*	Median 11.3 x 10 ¹¹ IQR 7.0 to 22.8	< 0.001	Median 4 IQR 2 to 8	0.70*
	High dose 4.4 x 10¹¹ platelets/m² ± 25%	432	Median 3 IQR 2 to 6		Median 19.6 x 10 ¹¹ IQR 10.6 to 37.4		Median 4 IQR 2 to 8	
Steffens 2002	Standard dose (Single apheresis unit)	28	Median 6 Range 1 to 14	Not reported	Mean 6.0 units Range 1 to 14	Not reported	Not reported	Not reported
	High dose (Triple apheresis unit)	26	Median 3.23 Range 1 to 8		Mean 9.7 units Range 3 to 23		Not reported	

IQR = Interquartile range

MD = mean difference

SD = standard deviation

WBD = whole blood derived

* = P value is not statistically significant

= unpublished data

APPENDICES

Appendix 1. MEDLINE search strategy (1996 to Jan 2002)

1. Platelet Transfusion.mh.
2. platelet\$ adj10 (substitute\$ or transfusion\$ or prophyla\$).tw.
3. 1 or 2
4. haemorrhage.mh.
5. platelet\$.tw.
6. 4 and 5
7. exp Blood Transfusion/
8. 5 and 7
9. 3 or 6 or 8
10. randomised controlled trial.pt.
11. controlled clinical trial.pt.
12. randomised controlled trials/
13. random allocation/
14. double blind method/
15. single blind method/
16. clinical trial.pt.
17. exp clinical trials/
18. (clinic\$ adj25 trial\$).ti, ab.
19. cross-over studies/
20. (crossover or cross-over or cross over).tw.
21. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti, ab.
22. placebos/
23. placebo\$.ti, ab.
24. random\$.ti, ab.
25. research design/
26. or/10-25
27. 9 and 26
28. animal/ not (animal/ and human/)
29. 27 not 28

Appendix 2. MEDLINE (Ovid) search strategy (Jan 2002-Nov 2011)

1. BLOOD PLATELETS/
2. (platelet* or thrombocyte*).tw.
3. 1 or 2
4. exp BLOOD TRANSFUSION/
5. transfus*.tw.
6. 4 or 5
7. 3 and 6
8. PLATELET TRANSFUSION/
9. ((platelet* or thrombocyte*) adj5 (transfus* or infus* or administ* or requir*)).tw.
10. or/7-9
11. (prophylactic* or prophylax* or prevent*).tw.
12. 10 and 11
13. RANDOMIZED CONTROLLED TRIAL.pt.
14. CONTROLLED CLINICAL TRIAL.pt.
15. exp CLINICAL TRIAL/
16. MULTICENTER STUDY.pt.
17. CLINICAL TRIALS AS TOPIC/

18. CLINICAL TRIALS PHASE III AS TOPIC/
19. CLINICAL TRIALS PHASE IV AS TOPIC/
20. exp CONTROLLED CLINICAL TRIALS AS TOPIC/
21. RANDOM ALLOCATION/
22. DOUBLE BLIND METHOD/
23. SINGLE BLIND METHOD/
24. CROSSOVER STUDIES/
25. PLACEBOS/
26. or/13-25
27. (controlled adj3 (trial* or stud*)).ti,ab.
28. (blind* or mask*).ti,ab.
29. (placebo* or random* or factorial*).ti,ab.
30. (crossover or (cross adj over)).ti,ab.
31. aleatori*.ti,ab.
32. (treatment adj arm*).ti,ab.
33. ((phase adj iii) or (phase adj three) or (phase adj '3')).ti,ab.
34. (latin adj square).ti,ab.
35. or/27-34
36. 26 or 35
37. ANIMALS/ NOT (HUMANS/ AND ANIMALS/)
38. 36 not 37
39. 12 AND 38

Appendix 3. EMBASE (Ovid) search strategy (1980 to Jan 2002)

1. random\$.ti,ab.
2. factorial\$.ti,ab.
3. (crossover\$ or crossover\$ or crossover\$).ti,ab.
4. placebo\$.ti,ab.
5. (double\$ adj blind\$).ti,ab.
6. (singl\$ adj blind\$).ti,ab.
7. assign\$.ti,ab.
8. allocat\$.ti,ab.
9. volunteer\$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE-BLIND PROCEDURE.sh
14. versus.ti,ab,sh.
15. factorial.ti,ab.
16. latin square design.sh.
17. latine square.mp.
18. aleatoric.ab.
19. aleatory.ti,ab.
20. aleatorized.ab.
21. aleatorily.ab.
22. multicenter.ti,ab.
23. multicenter study.sh.
24. multicentered.ti,ab.
25. multicenters.ti,ab.
26. multicenterstudy.ti,ab.
27. multicenterstudie.ti.

28. multicenterstudies.ab.
29. multicentre.ti,ab.
30. multicentred.ti,ab.
31. multacentral.ti,ab.
32. multicentres.ti,ab.
33. or/1-32
34. ANIMAL/or NONHUMAN/ or ANIMAL EXPERIMENT
35. HUMAN
36. 35 and 34
37. 34 not 36
38. 33 not 37
39. THROMBOCYTE TRANSFUSION/
40. 38 and 39

Appendix 4. EMBASE (Ovid) search strategy (Jan 2002-Nov 2011)

1. THROMBOCYTE/
2. (platelet* or thrombocyte*).tw.
3. 1 or 2
4. exp BLOOD TRANSFUSION/
5. transfus*.tw.
6. 4 or 5
7. 3 and 6
8. THROMBOCYTE TRANSFUSION/
9. ((platelet* or thrombocyte*) adj5 (transfus* or infus* or administ* or requir*)).tw.
10. or/7-9
11. (prophylactic* or prophylax* or prevent*).tw.
12. 10 and 11
11. random*.ti,ab.
12. factorial*.ti,ab.
13. (crossover* OR cross over* OR cross-over*).ti,ab.
14. placebo*.ti,ab.
15. (double* adj blind*).ti,ab.
16. (singl* adj blind*).ti,ab.
17. (assign* or allocat*).ti,ab.
18. (latin square or aleator*).ti,ab.
19. volunteer*.ti,ab.
20. CROSSOVER PROCEDURE/
21. DOUBLE BLIND PROCEDURE/
22. RANDOMIZED CONTROLLED TRIAL/
23. SINGLE BLIND PROCEDURE/
24. or/11-23
25. exp ANIMAL/ OR NONHUMAN/ OR exp ANIMAL EXPERIMENT/
26. exp HUMAN/
27. 25 NOT 26
28. 24 NOT 27
29. 12 AND 28

Appendix 5. CENTRAL search strategy (Issue 4, 2011)

#1 MeSH descriptor Blood Platelets explode all trees
#2 platelet* or thrombocyte*
#3 (#1 OR #2)
#4 MeSH descriptor Blood Transfusion explode all trees
#5 transfus*
#6 (#4 OR #5)
#7 (#3 AND #6)
#8 MeSH descriptor Platelet Transfusion explode all trees
#9 (platelet* or thrombocyte*) NEAR/5 (transfus* or infus* or administ* or requir*)
#10 (#7 OR #8 OR #9)
#11 prophylactic* or prophylax* or prevent*
#12 (#10 AND #11)

Appendix 6. CINAHL (NHS Evidence) search strategy (Jan 2002-Nov 2011)

1. BLOOD PLATELETS/
2. (platelet* or thrombocyte*).ti,ab
3. 1 or 2
4. exp BLOOD TRANSFUSION/
5. transfus*.ti,ab
6. 4 or 5
7. 3 and 6
8. PLATELET TRANSFUSION/
9. ((platelet* adj5 transfus*) or (platelet* adj5 infus*) or (platelet* adj5 administ*) or (platelet* adj5 requir*)).ti,ab
10. ((thrombocyte* adj5 transfus*) or (thrombocyte* adj5 infus*) or (thrombocyte* adj5 administ*) or (thrombocyte* adj5 requir*)).ti,ab
11. 7 or 8 or 9 or 10
12. (prophylactic* or prophylax* or prevent*).ti,ab
13. 11 and 12
14. "CLINICAL TRIAL"/
15. ((controlled adj trial*) OR (clinical adj trial*)).ti,ab
16. ((singl* adj blind*) OR (doubl* adj blind*) OR (trebl* adj blind*) OR (singl* adj mask*) OR (doubl* adj mask*) OR (tripl* adj mask*)).ti,ab
17. RANDOM ASSIGNMENT/
18. ("phase III" OR "phase 3" OR "phase three").ti,ab
19. (random* adj1 allocat*).ti,ab
20. (random* adj1 assign*).ti,ab
21. PLACEBOS/
22. 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21
23. 13 AND 22

Appendix 7. Free text search strategy for other databases

(platelet* OR thrombocyte*) AND (transfus* OR infus* OR administ* OR requir*) AND (prophylactic* OR prophylaxis OR prevent OR prevention OR preventing)

WHAT'S NEW

Last assessed as up-to-date: 14 November 2011.

Date	Event	Description
14 November 2011	New citation required and conclusions have changed	Authors changed (new authors S Hopewell and A Tinmouth) Outcomes are now divided into primary and secondary outcomes. Bleeding is the primary outcome Pre-specified subgroup analyses (type of disease and treatment) and fever
10 November 2011	New search has been performed	New search Inclusion/exclusion criteria altered - only includes studies that contain at least 80% haematology patients or a subgroup of haematology patients can be identified

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 4, 2004

CONTRIBUTIONS OF AUTHORS

Lise Estcourt: protocol development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis and content expert.

Simon Stanworth: protocol development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis and content expert.

Carolyn Doree: protocol development, searching and selection of studies

Sally Hopewell: protocol development and methodological expert.

Mike Murphy: protocol development and content expert.

Alan Tinmouth: content expert.

Nancy Heddle: protocol development and content expert.

All review authors contributed to the preparation of the final review.

DECLARATIONS OF INTEREST

Lise Estcourt: none declared

Simon Stanworth: none declared

Carolyn Doree: none declared

Sally Hopewell: none declared

Mike Murphy: none declared

Alan Tinmouth: none declared

Nancy Heddle: none declared

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This updated review has changed from the previous review ([Stanworth 2004](#)). The inclusion/exclusion criteria are more restrictive so that only studies that include at least 80% haematology patients were included in the review. This led to the exclusion of two studies that were included in the previous review ([Klump 1999](#); [Zumberg 2002](#)). A primary outcome was pre-specified prior to performing the updated review, to comply with the current Cochrane recommendations. One of the secondary outcomes, cost of treatments, was no longer included in the updated review because none of the studies in the original review reported this outcome. Two subgroup analyses were pre-specified prior to updating the review, these were fever and patients diagnostic and treatment subgroups.

INDEX TERMS

Medical Subject Headings (MeSH)

*Platelet Transfusion; *Stem Cell Transplantation; Hemorrhage [prevention & control; *therapy]; Randomized Controlled Trials as Topic; Thrombocytopenia [*complications]

MeSH check words

Humans