Prophylactic platelet transfusions vs. no prophylaxis in hospitalized patients with thrombocytopenia – a systematic review with meta-analysis.

Supplement

This supplement has been provided by the authors to give readers additional information about their work.

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Supplement 1 (S1) – Prisma Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p.1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	suppl. p. 6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p.3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p.3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 4-5
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	suppl. p. 9-13
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p. 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 4-5 and suppl. p. 7-8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 6 and suppl. p. 14-17 and 19-34
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p. 7
Synthesis	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention	p. 4-5

Section and Topic	Item #	Checklist item	Location where item is reported
methods		characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 7-10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 7-10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p. 8-9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p. 9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p. 11
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p. 12 and figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	figure 1. Citations not provided
Study characteristics	17	Cite each included study and present its characteristics.	p. 12-13, table 1, table 2 and suppl. 19-34
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p.13, table 3 and suppl. 35-41
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	p. 14-18, figure 2, figure 3 and suppl. p. 42-43
Results of	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	table 3

Section and Topic	Item #	Checklist item	Location where item is reported
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	p. 14-18 and suppl. p. 42-43
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p. 14-18 and suppl. 44-49
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p. 14-18 and suppl. 56-58
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 14-18 and Table 4.
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p. 19-22
	23b	Discuss any limitations of the evidence included in the review.	p. 21
	23c	Discuss any limitations of the review processes used.	p. 21
	23d	Discuss implications of the results for practice, policy, and future research.	p. 21-22
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p. 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p. 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p. 2
Competing interests	26	Declare any competing interests of review authors.	p. 2
Availability of data, code and other materials	27	Report which of the following are **publicly** available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	suppl. 14-17. Data and code not available.

Supplement 2 (S2) – Abstract

Objective

Prophylactic platelet transfusion is recommended to patients with severe thrombocytopenia, but the evidence is primarily derived in hematological settings. We assessed the benefits and harms of prophylactic platelet transfusion in hospitalized patients with thrombocytopenia.

Methods

Systematic review with meta-analysis and trial sequential analysis (TSA). We searched PubMed, CENTRAL, Embase and Epistemonikos for randomized clinical trials (RCTs) assessing prophylactic platelet transfusion vs. no prophylaxis. The primary outcome was mortality at longest follow-up. Secondary outcomes included clinically important bleeding, transfusion-related adverse events, nosocomial infections, thromboembolic events, length of stay and quality of life.

Results

We included 7 RCTs (n=1642 patients) conducted in patients with hematological malignancy or dengue fever. The results for mortality in the low risk of bias trial (relative risk (RR) 0.81; 95% confidence interval (CI) 0.22 to 2.97, P=0.75) and in all trials (RR 0.99; 95% CI 0.58 to 1.68, P=0.97) were uncertain. Clinically important bleeding may be reduced in the prophylaxis group (RR 0.70, 97.5% CI 0.53 to 0.92, P<0.01), but TSA-adjusted CI (0.26 to 1.87) indicated uncertainty. Days with clinically important bleeding were slightly reduced in the prophylaxis group (mean difference 0.5 days, 95% CI 0.1 to 0.9, P=0.01). For other secondary outcomes, results were uncertain. The certainty of evidence was low or very low for all outcomes.

Conclusions

Prophylactic platelet transfusion may reduce clinically important bleeding in hospitalized patients with hematological malignancy or dengue fever, but the evidence is very uncertain. Effects on mortality and adverse events remain uncertain. Data from non-hematological settings are sparse.

Supplement 3 (S3) – Outcomes

Additional details on the definition of outcomes and handling of the composite outcomes are available below and in the protocol[1].

Primary outcome

1. All-cause mortality at longest follow-up

Secondary outcomes

1. Proportion of participants with at least one episode of clinically important bleeding (as defined in the included trials).

2. Number of days with clinically important bleeding (as defined in the included trials).

3. Proportion of participants with at least one nosocomial infection (as defined in the included trials).

4. Proportion of participants with at least one venous or arterial thromboembolism (as defined in the included trials) including but not limited to deep vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction, and mesenteric ischemia.

5. Proportion of participants with at least one transfusion-related adverse event (as defined in the included trials) including but not limited to acute or delayed hemolytic transfusion reaction (AHTR or DHTR), febrile non-hemolytic transfusion reaction (FNHTR), allergic reactions (ranging from mild (urticarial) to severe (anaphylactic) reactions), transfusion-related lung-injury (TRALI), nonimmune mediated hemolysis, transfusion transmitted infections, transfusion-associated circulatory overload (TACO), post-transfusion purpura and transfusion-associated graft versus host disease.

6. Days alive without the use of life support (mechanical ventilation, circulatory support, or renal replacement therapy).

7. Length of hospital stay.

8. Quality of life (any continuous scale).

Handling of composite outcomes

If data on the composite outcomes were unavailable (nosocomial infections, transfusion-related adverse events and venous or arterial thromboembolism), but the individual components within the composite outcome were reported, we added the individual components to comprise the number of patients with the composite outcome for that trial.

Supplement 4 (S4) – Electronic searches

The searches were conducted on March 29th, 2021 and we updated the search in PubMed on February 3rd, 2022. All search strings are available below.

PubMed

#1 thrombocytopenia[MeSH Terms]
#2 thrombocytopen*[Title/Abstract]
#3 #1 OR #2
#4 blood platelets[MeSH Terms]
#5 platelet*[Title/Abstract]
#6 thrombocyte*[Title/Abstract]
#7 #4 OR #5 OR #6
#8 #3 OR #7
#9 platelet transfusion[MeSH Terms]
#10 plateletpheresis[MesH Terms]
#11 transfus*[Title/Abstract]
#12 platelet concentrate*[Title/Abstract]
#13 thrombocyte concentrate*[Title/Abstract]
#14 platelet component*[Title/Abstract]
#15 thrombocyte component*[Title/Abstract]
#16 plateletpheres*[Title/Abstract]
#17 thrombocytopheres*[Title/Abstract]
#18 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19 #8 AND #18
#20 randomized controlled trial[Publication Type]
#21 controlled Clinical Trial[Publication Type]
#22 randomized[Title/Abstract]
#23 drug therapy[MeSH Subheading]
#24 randomly[Title/Abstract]
#25 trial[Title/Abstract]
#26 groups[Title/Abstract]
#27 placebo[Title/Abstract]
#28 cluster randomized[Title/Abstract]
#29 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#30 animals[MesH Terms] NOT humans[Mesh Terms]
#31 #29 NOT #30
#32 #19 AND #31

Cochrane Central Register of Controlled Trials (CENTRAL, Wiley interface)

#1 MeSH descriptor: [Thrombocytopenia] explode all trees
#2 (thrombocytopen*):ti,ab,kw
#3 #1 OR #2
#4 MeSH descriptor: [Blood platelets] explode all trees
#5 (thrombocyte*): ti,ab,kw
#6 (platelet*):ti,ab,kw
#7 #4 OR #5 OR #6
#8 #3 OR #7
#9 MeSH descriptor: [Platelet Transfusion] explode all trees
#10 MeSH descriptor: [Plateletpheresis] explode all trees
#11 (transfus*):ti,ab,kw
#12 (plateletpheres*):ti,ab,kw OR (thrombocytopheres*):ti,ab,kw
#13 (platelet concentrate):ti,ab,kw OR (thrombocyte concentrate*):ti,ab,kw
#14 (platelet component):ti,ab,kw OR (thrombocyte component*):ti,ab,kw
#15 #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16 #8 AND #15

Embase (OVID interface)

1. exp thrombocytopenia/
2. "Thrombocytopen*".m_titl.
3. 1 or 2
4. exp thrombocyte/
5. "platelet*".m_titl.
6. "thrombocyte*".m_titl.
7. 4 or 5 or 6
8. 3 or 7
9. exp thrombocyte transfusion/
10. exp thrombocytopheresis/
11. "transfus*".m_titl.
12. "plateletpheres*".m_titl.
13. "thrombocytopheres*".m_titl.
14. exp thrombocyte concentrate/
15. "platelet concentrate*".m_titl.
16. "thrombocyte concentrate*".m_titl.
17. "platelet component*".m_titl.
18. "thrombocyte component*".m_titl.
19. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 8 and 19
21. exp randomized controlled trial/ or exp controlled study/ or exp clinical trial/
22. randomized.m_titl.
23. randomly.m_titl.
24. trial.m_titl.
25. placebo.m_titl.
26. groups.m_titl.
27. cluster.m_titl.
28. 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 20 and 28
30. limit 29 to human.

Epistemonikos

(title:(platelet* OR thrombocyte* OR thrombocytopen*) OR abstract:(platelet* OR thrombocyte* OR thrombocytopen*)) AND (title:(platelet transfusion OR thrombocyte transfusion OR platelet concentrate* OR thrombocyte concentrate* OR platelet component* OR thrombocyte component* OR plateletpheres* OR thrombocytopheres*) OR abstract:(platelet transfusion OR thrombocyte transfusion OR platelet concentrate* OR thrombocyte concentrate* OR platelet component* OR thrombocyte component* OR plateletpheres* OR thrombocytopheres*)) AND (title:(randomized OR randomly OR placebo OR groups OR trial OR cluster) OR abstract:(randomized OR randomly OR placebo OR groups OR trial OR cluster))

Clinical trial registries:

- **Clinical Trials** (http://clinicaltrials.gov/)
    - Study type: 'Interventional studies (clinical trials)'
    - Intervention/treatment: '(platelet OR thrombocyte) AND transfusion'

- **EU Clinical Trials Register** (https://www.clinicaltrialsregister.eu/)
    - 'platelet transfusion'

- **World Health Organization (WHO) International Clinical Trials Registry** (https://trialsearch.who.int/AdvSearch.aspx)
    - Intervention: (Platelet* or thrombocyte*) AND transfus*

Supplement 5 (S5) – Data extraction template

The full data-extraction template is available below.

Trial identification

Covidence ID	DOI	Author	Year

Trial characteristics

Design	Setting				
	Country	Developed vs. under development	Study period	No. of centers	Treating unit

Participants

Inclusion criteria	Exclusion criteria	Patients randomized (n)	Type of patients (Medical/surgical/mixed)	Age	Sex (% women)	Comorbidities/ disease severity score

Comparison

Intervention				Control		Co-interventions
Description	Type of platelets	Dose	Allocated (n)	Description	Allocated (n)	

Outcomes evaluated in the trial

Primary outcomes	Secondary outcomes	Tertiary outcomes

Primary outcome

All-cause mortality at longest follow-up				
Follow-up	Intervention		Control	
	Events	No. of patients	Events	No. of patients

Secondary outcomes

Clinically important bleeding					
Follow-up	**Outcome definition**	**Intervention**		**Control**	
		Events	No. of patients	Events	No. of patients

Days with clinically important bleeding								
Follow-up	**Intervention**				**Control**			
	No.	Mean (SD)	Median (IQR)	No. of patients	No.	Mean (SD)	Median (IQR)	No. of patients

Nosocomial infection					
Follow-up	**Outcome definition**	**Intervention**		**Control**	
		Events	No. of patients	Events	No. of patients

Venous or arterial thrombo-embolism					
Follow-up	**Outcome definition**	**Intervention**		**Control**	
		Events	No. of patients	Events	No. of patients

Venous or arterial thrombo-embolism					
Follow-up	**Outcome definition**	**Intervention**		**Control**	
		Events	No. of patients	Events	No. of patients

Transfusion related adverse events					
Follow-up	**Outcome definition**	**Intervention**		**Control**	
		Events	No. of patients	Events	No. of patients

Days alive without the use of life-support								
Follow-up	**Intervention**				**Control**			
	No.	Mean (SD)	Median (IQR)	No. of patients	No.	Mean (SD)	Median (IQR)	No. of patients

Length of hospital stay (days)								
Follow-up	**Intervention**				**Control**			
	No.	Mean (SD)	Median (IQR)	No. of patients	No.	Mean (SD)	Median (IQR)	No. of patients

Quality of life (HRQoL)								
Follow-up	**Intervention**				**Control**			
	No.	Mean (SD)	Median (IQR)	No. of patients	No.	Mean (SD)	Median (IQR)	No. of patients

Process variables

No. of platelet transfusions (units)								
Follow-up	**Intervention**				**Control**			
	No.	Mean (SD)	Median (IQR)	No. of patients	No.	Mean (SD)	Median (IQR)	No. of patients

No. of Red Blood Cell transfusions (units)								
Follow-up	**Intervention**				**Control**			
	No.	Mean (SD)	Median (IQR)	No. of patients	No.	Mean (SD)	Median (IQR)	No. of patients

No. of fresh frozen plasma transfusions (units)								
Follow-up	**Intervention**				**Control**			
	No.	Mean (SD)	Median (IQR)	No. of patients	No.	Mean (SD)	Median (IQR)	No. of patients

Sensitivity analyses

Any bleeding					
Follow-up	**Outcome definition**	**Intervention**		**Control**	
		Events	No. of patients	Events	No. of patients

Days with any bleeding								
Follow-up	**Intervention**				**Control**			
	No.	Mean (SD)	Median (IQR)	No. of patients	No.	Mean (SD)	Median (IQR)	No. of patients

Long-term all-cause mortality (> 90 days)					
Follow-up	**Outcome definition**	**Intervention**		**Control**	
		Events	No. of patients	Events	No. of patients

Supplement 6 (S6) – Pre-planned subgroups and hypothesized direction of effect

Additional details on the pre-planned subgroup analyses and the a priori hypothesized directions of subgroup effects are available below and in the protocol[1].

Subgroups

1) Trials with overall low risk of bias versus some concerns versus high risk of bias (as the total no. of trials in the two latter categories were less than 10, we merged these categories as planned in the protocol[1]).
   Hypothesized direction of subgroup effect: increased beneficial intervention effect in high risk of bias trials.
2) Patients with hematological malignancy versus patients with non-hematological cancer versus patients without cancer or hematological malignancy.
   Hypothesized direction of subgroup effect: increased beneficial intervention effect in patient with hematological malignancies, harm in patients with non-hematological cancer.
3) Medical vs surgical vs mixed patient populations.
   Hypothesized direction of subgroup effect: increased beneficial effect in surgical patients.
4) Invasive procedures (e.g., central venous catheters, dialysis catheters, lumbar puncture, epidural catheters, pleural catheters, biopsies, therapeutic and diagnostic punctures) versus no invasive procedures.
   Hypothesized direction of subgroup effect: increased beneficial effect in patients with invasive procedures.
5) Neonates (including preterm) versus pediatric patients versus adult patients. Hypothesized direction of subgroup effect: increased harm in neonates.
6) ICU patients (including high-dependency units) versus non-ICU patients.
   Hypothesized direction of subgroup effect: increased harm in ICU patients.

Supplement 7 (S7) – Detailed characteristics of included trials, ongoing trials and trials awaiting classification

Assir et al 2013 (published data only)[2] Title: Effectiveness of platelet transfusion in dengue fever: a randomized controlled trial.	
Information sources	Published paper only.
Methods	Single center, randomized, parallel-assignment, non-blinded. **Enrolment period**: August 2011 to October 2011.
Setting	Pakistan. High-dependency unit for patients with dengue.
Participants	**Inclusion criteria:** Adults of the age 14 years and above presenting with dengue fever or dengue hemorrhagic fever, platelet counts of less than $30x10^9$/L, and having no or mild bleeding (WHO grade 1 or 2 bleeding). **Exclusion criteria:** Patients with other causes of thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, aplastic anemia), chronic ailments (chronic liver disease, chronic kidney disease, cancers), prior history of platelet transfusion and severe bleeding (WHO grade 3 and 4). N = 87 patients randomized. Median (range) age 34 (15-78) years, Women 35%. Prophylaxis group: N=43, DF=17, DHF=26, DSS=0. No-prophylaxis group: N=44, DF=20, DHF=24, DSS=0. **Notes**: 19 and 20 patients bleed (WHO Grade 1 or 2) at baseline in the prophylaxis group and no-prophylaxis group respectively and were ineligible for this review. Only data on 'any new onset bleeding' was reported separately for the patients who did not bleed at baseline.
Interventions	**Comparison**: Between platelet transfusion and no platelet transfusion. **Prophylaxis group**: Received platelet transfusion at study entry. **No-prophylaxis group:** Did not receive any platelet transfusion. **Platelet type:** Filtered apheresis single donor platelets. **Platelet dose**: 1 unit of ≥ $5x10^{11}$ platelets / unit. **Notes:**
Outcomes	**Primary:** - Post-transfusion platelet increments at 1 hour (for the treatment group) and at 24 and 72h for both groups. **Secondary** - Progression to severe bleeding (WHO Grade 3 and 4). - Any new onset bleeding (WHO Grade 1-4). - Time to cessation of bleeding. - Adverse events including death.
Missing data	Prophylaxis group: 3/43. No-prophylaxis group: 0/44. **Note:** We assumed no missing data for the patients who did not bleed at baseline.
Bleeding scale and definitions	**Bleeding scale:** WHO Grade 1-4. **Definition of clinically important bleeding:** 'Severe bleeding' was defined as WHO Grade 3 and 4. **Definition of any bleeding: '**New onset bleeding' was defined as WHO grade 1-4.

Bleeding assessment	**Assessor**: Not reported. **Assessment:** Patients were assessed for WHO bleeding ever 12 h.
Co-interventions	None reported.
Follow-up	72 hours follow-up for the primary outcome. Follow-up for the secondary outcomes unclear.
Author contact	Corresponding author contacted but did not respond.

Abbreviations: dengue fever (DF), dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS), World Health Organization (WHO).

Grossman et al 1980[3] (published and unpublished data) Title: A Randomized trial of therapeutic vs. prophylactic platelet transfusions, with a comparison of multiple, random donor to selectively mismatched single donor platelets.	
Information sources	Published abstract, unpublished full paper, author contact, published information in a Cochrane review[4].
Methods	Single center, 2x2 factorial randomized, non-blinded trial. **Enrolment period:** Unclear start and end. Total study period was 1.3 years.
Setting	Canada. Hospital ward.
Participants	**Inclusion criteria:** Patients with amegakaryocytic thrombocytopenia admitted to Vancouver General Hospital over a 24-month period with platelet counts less that $50x10^9$L **Exclusion criteria:** Patients known to be refractory to platelet transfusions or no longer candidates for aggressive therapy or thrombocytopenia not expected to last for more than 7 days. N = 100 patients randomized. Women 44%. Prophylaxis group: N=49, ANLL=37, ALL=8, AA=1, Other=3. Mean (range) age: RD 43 (16-73) years, SD 44 (20-77) years. No-prophylaxis group: N=51, ANLL=31, ALL=8, AA=5, Other = 7. Mean (range) age: RD 53 (16-70), SD 45 (14-71). **Notes**:
Interventions	**Comparison**: Comparison between prophylactic and therapeutic-only platelet transfusion. Within these two comparisons, participants were also randomized to receive SD versus RD platelet transfusions. **Prophylaxis group**: Received platelet transfusion to maintain platelet count above 20 x 10^9/L. Platelet transfusions were given at discretion of the treating clinicians prior to invasive procedures and when clinically significant bleeding occurred. **No-prophylaxis group:** Platelet transfusions were given for clinically significant bleeding and prior to invasive procedures. **Platelet type:** Both RD and SD platelets were used. In total 476 RD platelet units and 410 SD units were transfused. **Platelet dose**: SD platelets had a mean of 4.8 x 10^{11} platelets / unit. RD platelets were pooled from 6-8 (mean 6.8) units. The average yield of one unit were $0.8X10^{11}$ platelets per unit. (Per transfusion, 4.8-6.4x10^{11} platelets were transfused).

	Notes: In the prophylactic arm, if alloimmunization occurred, participants were transfused only for significant bleeding, and if they were receiving RD platelets, they were switched to SD platelets. Patients in the SD group occasionally received RD platelets if SD platelets were not available.
Outcomes	**Primary:** Not reported **Secondary:** - Mild and severe bleeding episodes - Number of platelet transfusions received - Platelet increments 1-hour post transfusion - Incidence of platelet refractoriness (alloimmunization) - Mortality due to bleeding
Missing data	Prophylaxis group: 0/49 No-prophylaxis group: 0/51
Bleeding scale and definitions	**Bleeding scale:** Study specific. **Definition of clinically important bleeding:** Severe bleeding (not defined further). **Definition of any bleeding:** Mild bleeds defined as bleeds not requiring active intervention.
Bleeding assessment	**Assessor**: Not reported. **Assessment:** Participants were assessed clinically on a daily basis for signs of bleeding and fundoscopic examination was performed twice daily once the platelet count was less than 20 x 10^9/L.
Co-interventions	None reported.
Follow-up	Patients were followed throughout their initial hospital stay and all subsequent admissions. 'Days on study' was defined as days with a platelet count less than 50 x 109/L. The mean length of days on study was 42 days (41.6 days in the no-prophylaxis group and 42.7 days in the prophylaxis group.)
Author contact	The main author of a recent Cochrane review[4] that included the unpublished trial by Dr. Larry Grossman supplied the unpublished manuscript and her correspondence with the corresponding author Dr. Larry Grossman. Dr. Larry Grossman was successfully contacted and provided additional clarifications.

Abbreviations: acute-non-lymphoid leukemia (ANLL), acute lymphoid leukemia (ALL), aplastic anemia (AA). Random donor platelets (RD), single donor platelets (SD).

Lye et al 2017[5] (published and unpublished data) Title: Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial.	
Information sources	Published paper, supplement to published paper, trial protocol and statistical analysis plan and author contact.
Methods	Multicenter (5), randomized, parallel-assignment, open-label, superiority trial **Enrolment period:** April 29, 2010 to December 9, 2014
Setting	Singapore and Malaysia. Unclear treating unit, assumingly hospital ward.
Participants	**Inclusion criteria:** Adults, age ≥ 21years with confirmed dengue (confirmation of acute dengue by either i) positive polymerase chain reaction (PCR) for viral ribonucleic acid (RNA), or ii) positive NS1 antigen test with a compatible clinical syndrome) OR probable dengue (positive acute dengue

	serology and clinical presentation fulfilling either WHO 1997 or 2009 criteria for probable dengue AND a platelet count of ≤ $20x10^9$/L **Exclusion criteria:** Patients with platelet counts of > $20x10^9$/L, signs of clinical bleeding (epistaxis (persistent / recurrent), hematemesis, hematochezia, melena, menorrhagia or intermenstrual bleeding), previous history of documented severe adverse reaction to blood product transfusion, peptic ulcer disease 3 months prior to study entry, anticoagulant's usages 4 weeks prior to study entry, chronic liver disease, chronic renal failure or hemodialysis, active hematological or autoimmune disease, prior platelet transfusion within the same illness episode. Pregnant and lactating women as well as patients in whom direct or surrogate consent was unobtainable. N = 372 patients randomized. Women 24%. Prophylaxis group: N=188, Severe Dengue=15, DHF/DSS=20. Mean (SD) age: 44.3 (14.1) No-prophylaxis group: N=184, Severe dengue=6, DHF/DSS=27. Mean (SD) age: 45.2 (12.4) **Notes**:
Interventions	**Comparison**: Comparison between prophylactic platelet transfusion plus supportive care and supportive care alone. **Prophylaxis group**: In addition to supportive care, 4 units of pooled platelets was transfused each day if the platelet count was ≤$20x10^9$/L. The intervention lasted up to hospital discharge or 7 days after enrolment, whichever was earlier. **No-prophylaxis group:** Supportive care which consisted of bed rest, fluid therapy, and fever and pain medication. **Platelet type:** Primarily pooled random donor-cross matched platelets, except for 8 patients who received 1 unit of single donor derived platelet because of shortage of platelet transfusion at the time of randomization. **Platelet dose**: Unclear. **Notes:** If patients in any of the treatment arms bled at any time after randomization, the patient was treated as required clinically by the team and transfusions were given according to the policy of the individual participating institutions. It is unclear whether platelets were given prior to invasive procedures in any of the treatment arms.
Outcomes	**Primary:** - Clinical bleeding excluding petechiae up to hospital discharge or 7 days after randomization (whichever was earlier). **Secondary efficacy endpoints:** - Clinical bleeding excluding petechia within 21 days of randomization. - Rate of change of platelet count at 1h, 12h and 24h post transfusion (prophylaxis group only). - Median time to sustained (i.e., >2days) platelet count > $50x10^9$/L. - **Secondary safety end points:** - Plasma leakage (at least 20% change in serum hematocrit, development of pleural effusion or ascites). - Dengue hemorrhagic fever or dengue shock syndrome (as defined in WHO 1997 dengue guidelines). - Admission to intensive care unit. - Death. - Secondary bacterial infection. - Median length of hospital stay. - Adverse events from platelet transfusion. - Severe bleeding.

	Notes: The primary outcome and the secondary efficacy endpoints were analyzed in the intention-to-treat cohort. The secondary safety end points were analyzed in the as-treated cohort.
Missing data	**Intention-to-treat cohort:** Prophylaxis group: 18/185 (3 withdrew consent and were not regarded as missing). No-prophylaxis group: 25/179 (5 withdrew consent and were not regarded as missing). **As-treated-cohort:** 5 patients crossed from the prophylaxis group to the no-prophylaxis group. 6 patients crossed from the no-prophylaxis group to the prophylaxis group. Prophylaxis group: 18/186 (3 withdrew consent and were not missing). No prophylaxis group: 25/178 (5 withdrew consent and were not missing).
Bleeding scale and definitions	**Bleeding scale:** None. **Definition of clinically important bleeding:** Clinical bleeding according to the WHO 2009 dengue guidelines. Includes the any of following bleedings: gum, nose, hemoptysis, hematuria, hematemesis, melena, melena or hematemesis-not controlled by procedure, menorrhagia, menorrhagia or intermenstrual bleeding-not controlled by progesterone, intermenstrual, hematoma, menses, others. **Definition of any bleeding:** No definition.
Bleeding assessment	**Assessor:** Not reported. **Assessment:** Daily clinical assessment from day 1 until day 7 or discharge (whichever is earlier) and day 21 (+/-3). It is unclear how bleeding from day 7 or discharge until follow-up visit day 21(+/-3) was assessed.
Co-interventions	None reported.
Follow-up	21 (+/-3) days.
Author contact	The corresponding author was contacted for further data and clarifications. The author provided clarifications on secondary bacterial infection, which was not nosocomial infections and supplied mean and SD for length of hospital stay which was used in the analyses.

Abbreviations: dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS), World Health Organization (WHO).

Murphy et al 1982[6] (published data only) Title: Indications for platelet transfusion in children with acute leukemia.	
Information sources	Published paper only. **Notes**: An abstract published in 1976 with by the same authors reported seems to have reported on the same patient population, using the same methods, intervention and was conducted in the same period. This abstract however, included 90 children with previously untreated (n=55) AND treated (n=35) acute leukemia but the outcomes presented (serious bleeding episodes per patient and survival) was not reported so that the data could be extracted from the abstract. As the corresponding author died in 2006, we were not able to confirm that the published trial was a subgroup from the population reported in the abstract. We therefore considered the abstract as a 'duplicate' and only use and report data from the published trial.
Methods	Single center, randomized, unblinded trial. **Enrolment period:** July 1, 1972 to July 1, 1976.

Setting	USA. Treating unit unclear, assumingly hospital ward.
Participants	**Inclusion criteria:** Children with previously untreated acute leukemia cared for at the Children's Hospital of Philadelphia. **Exclusion criteria:** Not reported. N = 56 patients randomized. Prophylaxis group: N=35, ALL=28, AnonLL=7 No-prophylaxis group: N=21, ALL= 15, AnonLL=6 **Notes**:
Interventions	**Comparison**: Comparison between routine prophylactic platelet transfusion and therapeutic-only platelet transfusion. **Prophylaxis group**: Platelet transfusions (4 units/m^2 body surface) were given whenever platelet count was < 20,000 per mm^3 irrespective of clinical events. The goal was to maintain a platelet count above 20,000 per mm^3 throughout the patient's course. **No-prophylaxis group:** Platelet transfusion were only given for five clinical conditions: epistaxis not controlled by initial packing, gross gastrointestinal bleeding, gross genitourinary tract bleeding, any central nervous system bleeding and any bleeding episode felt to be life-threatening. **Platelet type:** Pooled random donor platelets. **Platelet dose**: Unclear. **Notes:** It is unclear whether platelets were given in the prophylactic group if clinical indications occurred irrespective of platelet count. Also, it is unclear whether platelets were given prior to invasive procedures in either group.
Outcomes	**Primary:** - Not reported. **Secondary:** - Number, dates and durations of serious bleeding episodes of patients bleeding. - Total number of days in which bleeding was present. - Platelet transfusion requirements within the first 10 months of follow-up.
Missing data	Prophylaxis group: 0/35 No prophylaxis group: 0/21
Bleeding scale and definitions	**Bleeding scale:** None. **Definition of clinically important bleeding:** Serious bleeding episodes (bleeds) were defined as nasal or oral bleeding requiring packing, gross gastrointestinal bleeding, gross genitourinary bleeding, any central nervous system bleeding, or bleeding requiring red blood cell transfusion. Uncomplicated dermal bleeding was not included. **Definition of any bleeding:** No definition.
Bleeding assessment:	**Assessor:** Not reported. **Assessment:** Not reported.
Co-interventions	None reported.
Follow-up	Follow-up from study entry until death or study closure. Prophylaxis group: Mean length of follow-up 19.9 months. No prophylaxis group: Mean length of follow-up 20.4 months.

Author contact	None. The corresponding author died in 2006.

Abbreviations: acute-non-lymphoid leukemia (AnonLL), acute lymphoid leukemia (ALL).

Sintnicolaas et al 1981[7] (published data only) Title: Comparison of 'prophylactic' and 'therapeutic' single-donor platelet transfusions in patients with acute leukemia.	
Information sources	Published abstract only.
Methods	Single center (assumed), randomized trial. **Enrolment period:** Not reported
Setting	Netherlands. Treating unit assumed to be a hospital ward.
Participants	**Inclusion criteria:** Patients with acute leukemia and severe thrombocytopenia **Exclusion criteria:** Not reported. N = 12 patients randomized. Sex and age not reported. Prophylaxis group: N=not reported. No-prophylaxis group: N=not reported. **Notes**:
Interventions	**Comparison**: Comparison between routine prophylactic platelet transfusion and therapeutic-only platelet transfusion. **Prophylaxis group**: Platelet transfusion were given to maintain a platelet count above $20x10^9$/L. **No-prophylaxis group:** Platelet transfusion were given for hemorrhage only. **Platelet type:** Not reported, appears to be both random donor platelets and single donor platelets. **Platelet dose**: $4x10^{11}$ platelets/unit. **Notes: I**t is unclear, in the prophylactic group, whether platelets were given for hemorrhage. It is unclear in both groups whether platelets were given prior to invasive procedures.
Outcomes	**Primary:** - Not reported **Secondary:** - Serological studies: Lymphocytotoxicity-test, platelet-immuno-fluorescence assay. - Morbidity. - Death due to bleeding. - Refractory to random donor platelets.
Missing data	Prophylaxis group: 0/35 No prophylaxis group: 0/21
Bleeding scale and definitions	**Bleeding scale:** None. **Definition of clinically important bleeding:** No definition. **Definition of any bleeding:** No definition.

Bleeding assessment	Assessor: Not reported. Assessment: Not reported.
Co-interventions	None reported.
Follow-up	Not reported.
Author contact	None. No e-mail address of the corresponding author was available.

Solomon et al 1978[8] (published data only) Title: Platelet prophylaxis in acute non-lymphoblastic leukemia.	
Information sources	Published letter to the editor only.
Methods	Single center (assumed), randomized trial. **Enrolment period:** Not reported.
Setting	USA. Treating unit assumed to be a hospital ward.
Participants	**Inclusion criteria:** Previously untreated patients with non-lymphoblastic acute leukemia **Exclusion criteria:** Promyelocytic leukemia. N = 31 patients randomized. Mean age (range) 43 (16-71) years. Prophylaxis group: N=19 No-prophylaxis group: N=12 **Notes**:
Interventions	**Comparison**: Comparison between routine prophylactic platelet transfusion and therapeutic-only platelet transfusion. **Prophylaxis group**: Platelet transfusion were given whenever platelet count was < $20x10^9$/L and when clinically significant bleeding occurred. **No-prophylaxis group:** Platelet transfusion were given only when clinically significant bleeding occurred or when a platelet count < $20x10^9$/L was preceded by a decline of 50% in the platelet count during the preceding 24 hours. **Platelet type:** Pooled random donor platelets. **Platelet dose**: Not reported. **Notes:** It is unclear whether platelets were given prior to invasive procedures.
Outcomes	**Primary:** - Not reported. **Secondary:** - Deaths per chemotherapy course. - Deaths due to bleeding per chemotherapy course. - Complete remission rates. - Platelets packs per chemotherapy course. - Red blood cell packs per chemotherapy course. - Complete and partial remission rates.

Missing data	Prophylaxis group: 0/19 No prophylaxis group: 0/12
Bleeding scale and definition	**Bleeding scale:** None. Bleeding was not assessed. **Definition of clinically important bleeding:** NA. **Definition of any bleeding:** NA.
Bleeding assessment	**Assessor:** NA. **Assessment:** NA.
Co-interventions	None reported.
Follow-up	Patients were followed within 1 month of chemotherapy course.
Author contact	None. Corresponding author has died.

Stanworth et al 2013[9] (published data only) Title: A no-prophylaxis platelet-transfusion strategy for hematologic cancers.	
Information sources	Published paper, supplement to published paper, trial protocol and statistical analysis plan.
Methods	Multicenter (14), randomized, parallel assignment open-label, non-inferiority trial. **Enrolment period:** August 2006 - August 2011
Setting	The United Kingdom and Australia. Hospital ward.
Participants	**Inclusion criteria:** Patients 16 years of age or older, confirmed diagnosis of a hematological malignancy. Have received, are receiving or about to receive myelosuppressive chemotherapy with or without hematological stem cell transplantation (autograft or allograft). Thrombocytopenic (< 50 x 10^9/L) or expected to be so for at least five days. Able to comply with treatment and monitoring. **Exclusion criteria:** Previous WHO grade 3 or 4 bleeding. A WHO grade 2 bleeding during current admission. Inherited hemostatic or thrombotic disorder. Requirement for therapeutic doses of anticoagulant agents. Diagnosis of acute promyelocytic leukemia. Known HLA antibodies. Pregnancy. Prior randomization into the trial. N = 600 patients randomized. Women 35%. Prophylaxis group: N=299, AML=55, ALL=5, CML=1, Lymphoma=102, Myeloma=125, Other=13. Mean (SD) age 55.3 (11.2) years. No-prophylaxis group: N=301, AML=55, ALL=1, CML=2, Lymphoma=104, Myeloma=124, Other=13. Mean (SD) age 55.7 (10.4) years. **Notes**:
Interventions	**Comparison**: Comparison between routine prophylactic platelet transfusion and therapeutic-only platelet transfusion. **Prophylaxis group**: Platelet transfusions were given prophylactically at threshold counts of less than 10x10^9/L and continued daily until the platelet count is greater than 10x10^9/L. **No-prophylaxis group:** Platelets transfusions were not prophylactically given irrespective of platelet counts.

	Platelet type: Pooled random donor buffy coat derived platelets (leucocyte depleted) and apheresis derived platelets. Approximately 80% of the platelets were pooled random donor platelets. **Platelet dose**: A single dose of "one adult unit" was given for prophylactic platelet transfusions and for WHO Grade 2 bleeds. In participants with WHO Grade 3 or 4 bleeding, the attending hematologist decided the dose. UK specifications for pooled buffy coat derived platelets (leucocyte depleted) and apheresis derived were a platelet cell content > 240 x 10^9/L per pool or unit. Australian specifications for pooled buffy coat derived platelets were > 240 x 10^9/L per pool (leucocyte depleted) and apheresis derived platelets > 200 x 109/L per unit (leucocyte depleted) respectively. **Notes:** Both groups were transfused with platelets if a bleeding of WHO grade 2 or more occurred irrespective of platelet count; prior to invasive procedures (prior to lumbar puncture, insertion of indwelling lines, transbronchial biopsy, laparotomy when the platelet count should be raised to at least $50x10^9$/L; for operations in critical sites such as brain or eyes when the platelet count should be raised to at least $100x10^9$/L; at the clinicians discretion (rationale recorded)
Outcomes	**Primary:** - Proportion of patients who experience a (modified) WHO Grade 2, 3, or 4 bleeds, up to 30 days from randomization. **Secondary:** - Proportion of patients developing a WHO Grade 3 or 4 bleed within 30 days of randomization. - All-cause mortality within 30 days of randomization. - Time from randomization to first WHO Grade 2, 3 or 4 bleeds. - The rate of Grade 2, 3, or 4 bleeds within 30 days from randomization. (Calculated as the number of days with a WHO Grade 2 or higher bleed divided by the number of days of follow-up, up to 30 days from randomization). - The proportion of patients who receive at least one platelet transfusion up to 30 days from randomization. - Total number of platelet transfusions up to 30 days from randomization. - Total number of platelet units transfused up to 30 days from randomization. - Total number of red cell transfusions up to 30 days from randomization. - Total number of red cell units transfused up to 30 days from randomization. - Time from randomization to recovery of thrombocytopenia. Recovery of thrombocytopenia is defined as when the platelet count increases to greater than $50x10^9$/l and is maintained for 3 consecutive days unsupported by platelet transfusion. The time of recovery is defined as the 3rd day with a platelet count greater than $50x10^9$/l. - Number of days with platelet count less than 20x109/l, up to 30 days from randomization. - Number of days in hospital, up to 30 days from randomization.
Missing data	Prophylaxis group: 1/299 No prophylaxis group: 1/301
Bleeding scale and definitions:	**Bleeding scale:** Modified WHO Bleeding scale. **WHO Grade 1:** Petechiae/purpura that is localized to 1 or 2 dependent sites, or sparse/non-confluent; oropharyngeal bleeding, epistaxis <30 minutes duration. **WHO Grade 2:** Melena, hematemesis, hemoptysis, fresh blood in stool, musculoskeletal bleeding or soft tissue bleeding not requiring red cell transfusion within 24 hours of onset and without hemodynamic instability; profuse epistaxis or oropharyngeal bleeding i.e. >30 minutes in continuous duration; symptomatic oral blood blisters i.e. bleeding or causing major discomfort; multiple bruises, each >2cm or any one >10cm; petechiae/purpura that is diffuse or numerous, or >5 distinct purpuric lesions; visible blood in urine; abnormal bleeding from invasive or procedure sites; unexpected vaginal bleeding saturating more than 2 pads with blood in a 24hr period; bleeding in cavity fluids evident macroscopically; retinal hemorrhage with/without visual impairment.

	WHO Grade 3: Melena, hematemesis, hemoptysis, hematuria - including intermittent gross bleeding without clots, abnormal vaginal bleeding, fresh blood in stool, epistaxis and oropharyngeal bleeding, bleeding from invasive sites, musculoskeletal bleeding, or soft tissue bleeding requiring red cell transfusion specifically for support of bleeding within 24 hours of onset and without hemodynamic instability; bleeding in body cavity fluids grossly visible; cerebral bleeding noted on CT(computerized tomography) without neurological signs and symptoms. **WHO Grade 4**: Debilitating bleeding including retinal bleeding and visual impairment (visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmologic consultation); non-fatal cerebral bleeding with neurological signs and symptoms; bleeding associated with hemodynamic instability (hypotension, >30mmHg change in systolic or diastolic BP); fatal bleeding from any source. **Definition of clinically important bleeding:** Clinical bleeding was defined as bleeding of a modified WHO grade 2 or higher. **Definition of any bleeding:** No definition.
Bleeding assessment:	**Assessors:** A **l**ocal research nurse trained by a small core of research staff and separate from the treating unit nursing and medical staff, performed the bleeding assessment (unblinded). Patients who were discharged before study completion performed self-assessed daily bleeding diary. **Assessment:** Daily standardized bleeding-assessment forms were completed each day that the patient was in the hospital. Patients who were discharged home during the follow-up period completed bleeding diaries; if patients reported bleeding, clinical bleeding-assessment forms were completed at the next hospital visit or by telephone. Grading of bleeding (based on completed bleeding assessment forms) was performed by a computer algorithm at the time of data entry. The algorithm was validated after the first 100 patients had been enrolled. **Notes**: There were pre-agreed definitions and guide notes to help complete the bleeding assessment in a standardized fashion. Every six-month, educational meetings were held centrally including scenarios for assessing bleeding. During monitoring site visits, conducted by the central coordinating staff, duplicate assessments of bleeding scores were undertaken.
Co-interventions	The threshold for red-cell transfusion (in the absence of blood loss due to bleeding) was a hemoglobin level of less than 90 g per liter.
Follow-up	30 days
Author contact	Corresponding author contacted but could not provide further data.

Abbreviations: acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), chronic myeloid leukemia (CML), World Health Organization (WHO).

Wandt et al 2012[10] (published data only) Title: Therapeutic platelet transfusion versus Routine prophylactic transfusion in patients with haematological malignancies: An open-label, multicentre, randomised study.	
Information sources	Published paper, supplement to published paper.
Methods	Multicenter (5), randomized, parallel-group, open-label trial. **Enrolment period:** February 1st, 2005 to May 31st, 2010
Setting	Germany. Hospital ward.
Participants	**Inclusion criteria:** Two groups of hospital inpatients were eligible:

	Group A: Patients aged 16-80 years with all subtypes of acute myeloid leukemia (patients with promyelytic leukemia could only be included after reaching complete remission) receiving induction and consolidation chemotherapy of standard dose intensity. Group B: Patients aged 16-68 years of age with hematological cancers, who had undergone autologous peripheral blood stem-cell trans plantation receiving standard intensity of a high-dose chemotherapy regimen. **Exclusion criteria:** For both groups: Patients who were refractory to platelet transfusions or who had previous major bleeding or plasmatic coagulopathy were excluded. For group B: patients with pulmonary or cerebral lesions were excluded. N = 396 patients randomized. Women 45%. Prophylaxis group: N=197, AML=96, autologous HSCT=98. Median (range) age 55.5 (46-63) years. No-prophylaxis group: N=199, AML=94, autologous HSCT=103. Median (range) age 55.0 (46-62) years
Interventions	**Comparison**: Comparison between routine prophylactic platelet transfusion and therapeutic-only platelet transfusion. **Prophylaxis group**: Platelet transfusion (1 unit) was given prophylactically (with no signs of clinically relevant bleeding) when the morning platelet count was ≤ $10x10^9$/L. Platelet transfusion according to protocol started at day 1 after the end of induction chemotherapy, or at day 1 of each consolidation cycle in group A and at the day of stem-cell transplant in group B. **No-prophylaxis group:** Stable patients were only given platelet transfusion when clinically relevant bleeding occurred. If bleeding continued despite one platelet transfusion, further transfusions were given according to the decision of the treating physician. A prophylactic platelet transfusion was recommended at platelet counts of $10x10^9$/L when sepsis or infections with increased bleeding risk, such as invasive fungal infection or plasmatic coagulopathy (e.g. disseminated intravascular coagulation or hyperfibrinolysis) were present. **Platelet type:** Leuko-reduced single donor apheresis platelets and pooled platelet concentrates were used. **Platelet dose**: One platelet unit was transfused. If bleeding continued despite the platelet transfusion, further transfusions were giving at the discretion of the treating hematologist. Apheresis units: 200-400$x10^9$ platelets / unit. Pooled platelet concentrates: > 200$x10^9$ (range: 240-360$x10^9$) platelets / unit.
Outcomes	**Primary:** - Number of platelet transfusions given during a standardized observation time of 14 days per participant. **Secondary:** - Incidence of clinically relevant bleeding per treatment cycle. - Time to onset of first clinically relevant bleeding. - Percentage of days in which participants had bleeds of Grade 2 or higher, dependent on morning platelet count. - Days with platelet counts less than 20 x 109/L. - Side effects of transfusions. - Duration of hospitalization. - Survival. - Numbers of red blood cell transfusion.
Missing data	Prophylaxis group: 0/197 No prophylaxis group: 1/198 (1 withdrew consent and was not regarded as missing)
Bleeding scale and definitions	**Bleeding scale:** Modified WHO Bleeding scale.

	Petechiae and purpura of skin of any size were not regarded as clinically relevant and not registered. **WHO Grade 2**: Any oral or nasal bleeding that could not be treated at the bedside by a nurse, or that was unpleasant for the patient; spontaneous hematoma in deep tissues, joint bleeding; hematochezia, melanotic stool (proven by fecal blood test), hematemesis; visible hematuria; abnormal vaginal bleeding more than spotting; hemoptysis and bloody sputum with no nasal or oropharyngeal bleeding; bleeding at venipuncture sites, intravenous lines; other bleeding as described in the clinical report form. **WHO Grade** 3: Any bleeding necessitating transfusion of red blood cells over routine needs within 24 hours. **WHO Grade 4**: Any bleeding necessitating transfusion of red blood cells and associated with severe hemodynamic instability necessitating intensive care; any fatal bleeding; bleeding with visual impairment proven by fundoscopy; CNS symptoms and sudden headache showing CNS bleeding on CT, any fatal CNS bleeding. **Definition of clinically important bleeding:** Clinically relevant bleeding was defined as a modified WHO grade ≥2. **Definition of any bleeding:** No definition.
Bleeding assessment	**Assessor:** A physician or experienced nurse examined patients twice daily. The treating hematologist was responsible for documentation and reporting in each center. Two investigators masked to treatment strategy later transformed the bedside bleeding report into modified WHO categories. Consensus was needed in cases of disagreement. An independent central monitor reviewed and checked all clinical report forms with patients' charts; clinical data were then entered into the central data bank. **Assessment:** Clinical bleeding assessments was performed twice daily.
Co-interventions	Transfusion of packed red blood cells was given to maintain hemoglobin concentrations at 80 g/L or higher.
Follow-up	The study was completed when the platelet count was self-sustaining at more than 20×10^9 per L for 2 days or a maximum of 30 days, at hospital discharge, when treatment failure was diagnosed, at death, or at study withdrawal, which ever occurred first.
Author contact	Corresponding author contacted but did not respond.

Abbreviations: acute myeloid leukemia (AML), hematogenic stem cell transplantation (HSCT), World Health Organization (WHO).

van de Weerdt et al[11] (ongoing) Title: Prophylactic platelet transfusion prior to central venous catheter placement in patients with thrombocytopenia: study protocol for a randomised controlled trial.	
Information sources	Published protocol and trial registration (NTR5653).
Methods	Multi center (11), randomized controlled, non-inferiority trial. **Enrolment period:** February 2016 – ongoing.
Setting	Netherlands, hospital ward / ICU.
Participants	**Inclusion criteria:** Adult hematologic or ICU patients with thrombocytopenia (10-50 x 10^9/L) scheduled for emergency or elective insertion or replacement of a central line (both tunneled, non-tunneled or lines inserted for hemodiafiltration) and an expectation of the inserted line to be in situ for at least 24 hours.

	Exclusion criteria: Patients with an INR < 1.5 (if corrected by fresh frozen plasma or prothrombin concentrate, the patient will be eligible), history of congenital or acquired coagulation factor deficiency or bleeding diathesis, treatment with anticoagulant therapy (patients with a single platelet aggregation inhibitor and/or therapeutic unfractionated heparin that is discontinued at least 1 h prior to insertion will be considered eligible). **Planned sample size**: 392 patients (with a potential limit of 462 patients to accommodate loss to follow-up) Prophylaxis group: N=196 No-prophylaxis group: N=196
Interventions	**Comparison**: Comparison between prophylactic platelet transfusion and no platelet transfusion. **Prophylaxis group**: Patients will be transfused with 1 unit of platelet concentrate prior to placement of the catheter. **No prophylaxis group**: Patients will not receive platelet transfusions. **Note**: The proceduralist can administer rescue platelets at clinical indication in both arms. **Platelet type:** Leuko-reduced pooled random donor platelets. **Platelet dose**: Unclear. **Notes:**
Outcomes	**Primary:** - Procedure-related relevant bleeding, occurring within 24 h after the procedure. **Secondary:** - Platelet transfusion requirements within 24 h of CVC placement. - Number of RBC transfusions within 24 h of CVC placement. - WHO grade-1 bleeding within 24 h of CVC placement. - Hematoma size. - Hemoglobin level at 1 h and 24 h after CVC placement. - Platelet transfusion increment. - HEME bleeding score. - Allergic transfusion reaction within 24 h. - Onset of acute lung injury within 48 h. - Length of hospital stay. - Mortality. - Costs.
Missing data	
Bleeding scale and definitions	**Bleeding scale:** Modified WHO bleeding scale. **Grade 1**: Mild symptoms not requiring any intervention; for example, local hematoma formation or wound oozing. **Grade 2:** Mild symptoms requiring interventions, without hemodynamic instability or red blood cell (RBC) transfusion including procedure-related bleeding that requires more than 20 min of manual compression to stop. **Grade 3:** Procedure-related bleeding requiring red cell transfusion. **Grade 4**: Bleeding associated with hemodynamic instability or death, defined as CVC-related bleeding associated with severe hemodynamic instability (hypotension; > 50 mmHg fall or > 50%

	decrease in either systolic or diastolic blood pressure, with associated tachycardia (heart rate increase of > 20% for 20 min) and requiring RBC transfusion over routine transfusion needs or fatal bleeding **Definition of clinically important bleeding:** Modified WHO grade 2-4. **Definition of any bleeding:** None
Bleeding assessment	**Assessor:** Unclear. **Assessment:** Clinical bleeding will be assessed at 1h and 24h post-procedural. Clinical photos taken at 1h and 24h will be used to evaluate size of hematoma in a blinded fashion.
Co-interventions	None reported.
Follow-up	28 days.
Author contact	Corresponding author was contacted for unpublished data however the study was still ongoing.

Abbreviations: central venous catheter (CVC), World Health Organization (WHO).

NCT03713489 (awaiting classification - ongoing)[12] Title: Platelet Transfusion in HBV-related acute-on Chronic Liver Failure.	
Information sources	Trial registration only.
Methods	Single center, randomized, open-label trial. **Enrolment period:** October 2018 – ongoing.
Setting	China. Treating ward unclear.
Participants	**Inclusion criteria:** Patients 18-60 years, diagnosed with acute-on-chronic liver failure (grade 2) according to EASL-CLIF criteria and grading system and chronic hepatitis B infection and ADP inhibition rate ≥70%. **Exclusion criteria:** Chronic liver disease other than chronic HBV infection, previous decompensation, intracranial hemorrhage proved by radiological methods, symptoms and physical signs, use of anti-platelet or anticoagulants therapy within 4 weeks, esophageal variceal bleeding within 1 week, platelets transfusion within 1 week, hepatocellular carcinoma or other types of malignancies, pregnancy or breastfeeding, severe chronic extra-hepatic disease, situations that researchers considered not suitable for inclusion. **Estimated enrolment**: 20
Interventions	**Comparison**: Comparison between platelet transfusion in addition to standard care and standard care alone. **Prophylaxis group**: Participants in platelet transfusion group will receive one unit of apheresis platelets transfusion 3 times for the first week after enrolment, then 2 times a week in the following three weeks. **No prophylaxis group**: Standard care. **Platelet type:** Apheresis **Platelet dose**: Unclear **Notes:**
Outcomes	**Primary:**

	- 28-day transplant-free mortality. **Secondary:** - Transplant free survival time.
Missing data	
Bleeding scales and definitions	**Bleeding scale:** None. **Definition of clinically important bleeding:** None. **Definition of any bleeding:** None.
Bleeding assessment	None.
Co-interventions	None reported.
Follow-up	28 days for the primary outcome. Unclear for secondary outcomes.
Author contact	Corresponding author was contacted but did not respond.

Supplement 8 (S8) – Detailed Risk of Bias Adjudications

	Risk of bias domain (assessment for the effect of assignment to intervention)					Overall risk of bias
Outcome and study	1. Randomization process	2. Deviations from intended interventions	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported result	
All-cause mortality						
Lye et al., 2017	Low	Low	Some concerns	Low	Low	**Some concerns**
	Missing outcome data: missing outcome data for 38 patients (9.4%) lost to follow-up. No. of lost to follow-up substantially larger than number of events (zero). No sensitivity analyses made. Lost to follow-up was rather evenly distributed between groups (16 in the prophylaxis group, 22 in the no prophylaxis group).					
Murphy et al., 1982	Some concerns	Some concerns	Low	Low	Some concerns	**Some concerns**
	Randomization process: no description of randomization method or attempts to conceal allocation and almost no baseline data presented. *Deviations from intended interventions: no information on deviations from protocol.* *Selection of the reported results: no protocol, statistical analysis plan or study registration available.*					
Solomon et al., 1978	Some concerns	Some concerns	Low	Low	Some concerns	**Some concerns**
	Randomization process: no description of randomization method or attempts to conceal allocation and almost no baseline data presented. *Deviations from intended interventions: no information on deviations from protocol.* *Selection of the reported results: no protocol, statistical analysis plan or study registration available.*					
Stanworth et al., 2013	Low	Low	Low	Low	Low	**Low**
Wandt et al., 2012	Low	Some concerns	Low	Low	Some concerns	**Some concerns**
	Deviations from intended interventions: (i) in the prophylaxis group, routine prophylactic platelet transfusions were not given 148 times (11%) despite a morning platelet count of less than 10×10^9 per liter. In the no prophylaxis group, clinically relevant bleeds judged by the treating physician, such as extended petechial bleeding or purpura of the skin, were the main reason for patients in the therapeutic group receiving transfusions not in accordance with the protocol (22%). (ii) Post-randomization-exclusion of 3 participants in the prophylactic group (1 died before start of treatment and 2 were ineligible). *Selection of the reported result: no protocol or statistical analysis plan available. Study registration does include mortality as an outcome.*					
Clinically important bleeding						
Grossman et al., 1980	High	Low	Low	High	Some concerns	**High**
	Randomization process: the study author reported that randomization was performed using 25 envelopes, each with four cards inside, one for each treatment group: As participants were enrolled, their allocation was drawn from the envelope. Once all four cards in each envelope were					

	used, a new envelope was opened. Hence, when three patients were allocated the next allocation would be known before assignment. *Measurement of the outcome: the clinical team performed the assessment unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.* *Selection of the reported results: No protocol, statistical analysis plan or study registration available.*					
Lye et al., 2017	Low	Low	Some concerns	High	Low	**Some concerns**
	Missing outcome data: missing outcome data for 38 patients (9.4%) lost to follow-up. No. of lost to follow-up is large enough to have a substantial impact on the results (bleeding episodes; 91) but the lost to follow-up was rather evenly distributed between groups (16 in the prophylaxis group, 22 in the no prophylaxis group). *Measurement of the outcome: outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.*					
Murphy et al., 1982	Some concerns	Some concerns	Low	High	Some concerns	**High**
	Randomization process: no description of randomization method or attempts to conceal allocation and almost no baseline data presented. *Deviations from intended interventions: no information on deviations from protocol.* *Measurement of the outcome: unclear who assessed the outcome. Outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.* *Selection of the reported results: no protocol, statistical analysis plan or study registration available.*					
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	**Some concerns**
	Measurement of the outcome: outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. For in-patients the bleeding assessment were performed by a trained research nurse, separate from the treating clinical unit nursing and medical staff. All research staff that completed daily bleeding assessments received standardized training from a small core of research staff. There were pre-agreed definitions and guide notes to help complete the bleeding assessment in a standardized fashion. Every six months, educational meetings were held centrally including scenarios for assessing bleeding. During monitoring site visits, conducted by the central coordinating staff, duplicate assessments of bleeding scores were undertaken. Outpatients completed daily bleeding diaries. If they had bleeding, they completed a self-assessed bleeding form. Medical bleeding assessment forms would be completed following review of the self-assessed bleeding forms either at the next hospital attendance or by telephone. Grading of the bleeding was performed by a computer algorithm at the time of data entry. The algorithm was validated after the first 100 patients had been enrolled. Even though measurements were taken to standardize bleeding assessments, outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.					
Wandt et al., 2012	Low	Some concerns	Low	Some concerns	Some concerns	**Some concerns**
	Deviations from intended interventions: (i) in the prophylaxis group, routine prophylactic platelet transfusions were not given 148 times (11%) despite a morning platelet count of less than 10×10^9 per liter. In the no prophylaxis group, clinically relevant bleeds judged by the treating physician, such as extended petechial bleeding or purpura of the skin were the main reason for patients in					

	the therapeutic group receiving transfusions not in accordance with the protocol (22%). These deviations would probably result in an increased effect in the same direction as observed in the study. (ii) Post-randomization-exclusion of 3 participants in the prophylactic group (1 died before start of treatment and 2 were ineligible) *Measurement of the outcome: assessment of bleeding will inevitably involve some degree of subjective judgement. A physician or experienced nurse examined patients twice a day for new signs of bleeding. The treating hematologist was responsible for documentation and reporting in each center and was not blinded; knowledge of the intervention assignment could have affected the bleeding assessment.* *Selection of the reported result: no protocol or statistical analysis plan available.*					
Days with clinically important bleeding						
Murphy et al., 1980	Some concerns	Some concerns	Low	High	Some concerns	**High**
	Randomization process: no description of randomization method or attempts to conceal allocation and almost no baseline data presented. *Deviations from intended interventions: no information on deviations from protocol.* *Measurement of the outcome: Unclear who assessed the outcome. Outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.* *Selection of the reported results: no protocol, statistical analysis plan or study registration available.*					
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	**Some concerns**
	Measurement of the outcome: outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. For in-patients the bleeding assessment were performed separately from the treating clinical unit nursing and medical staff. All research staff that completed daily bleeding assessments received standardized training from a small core of research staff. There were pre-agreed definitions and guide notes to help complete the bleeding assessment in a standardized fashion. Every six months, educational meetings were held centrally including scenarios for assessing bleeding. During monitoring site visits, conducted by the central coordinating staff, duplicate assessments of bleeding scores were undertaken. Outpatients completed daily bleeding diaries. If they had bleeding, they completed a self-assessed bleeding form. Medical bleeding assessment forms would be completed following review of the self-assessed bleeding forms either at the next hospital attendance or by telephone. Grading of the bleeding was performed by a computer algorithm at the time of data entry. The algorithm was validated after the first 100 patients had been enrolled. Even though measurements were taken to standardize bleeding assessments, outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.					
Nosocomial infection						
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	**Some concerns**
	Measurement of the outcome: outcome assessors were not blinded. 'Infection' was reported as an SAE during the study assessed by the local study investigator. Assessment of infection will usually involve clinical evaluation and subjective judgment. 'Infection' was equally distributed on the two groups.					
Transfusion related adverse events						
Lye et al., 2017	Low	Some concerns	Some concerns	Some concerns	Low	**Some concerns**

	Deviations from intended protocol: secondary safety endpoints including 'adverse events from platelet transfusion' were analyzed in the as-treated cohort in which subjects were grouped as per actual treatment received regardless or randomized group. Five patients in the prophylaxis group received supportive care only and six patients in the no prophylaxis group received prophylactic platelet transfusion. *Missing outcome data: missing outcome data for 38 patients (9.4%) lost to follow-up. No. of lost to follow-up is substantially larger than number of events (adverse events from platelet transfusion; 9) but the lost to follow-up was rather evenly distributed between groups (16 in the prophylaxis group, 22 in the no prophylaxis group).* *Measurement of the outcome: outcome assessors were unblinded. Assessment of adverse events involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.*					
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	**Some concerns**
	Measurement of the outcome: outcome assessors were not blinded. Assessment of transfusion related adverse reactions usually involves clinical exam and subjective judgement which could be influenced by the knowledge of the intervention assignment. Only one transfusion related adverse event are reported in the prophylaxis group					
Wandt et al., 2012	Low	Some concerns	Low	Some concerns	Some concerns	**Some concerns**
	Deviations from intended protocol: (i) in the prophylaxis group, routine prophylactic platelet transfusions were not given 148 times (11%) despite a morning platelet count of less than 10×10^9 per liter. In the no prophylaxis group, clinically relevant bleeds judged by the treating physician, such as extended petechial bleeding or purpura of the skin, were the main reason for patients in the therapeutic group receiving transfusions not in accordance with the protocol (22%). These deviations would probably result in an increased rate of side effects in the no prophylaxis group, but this was not the case. (ii) Post-randomization-exclusion of 3 participants in the prophylactic group (1 died before start of treatment and 2 were ineligible). *Measurement of the outcome: no definition of 'transfusion side effects'. Outcome assessors not blinded. Assessment of side effects usually involves clinical exam and subjective judgement which could be influenced by the knowledge of intervention assignment.* *Selection of the reported result: no protocol or statistical analysis plan available. Study registration include 'side effects of transfusion' as an outcome but not specified further.*					
Length of hospital stay						
Lye et al., 2017	Low	Some concerns	Some concerns	Some concerns	Low	**Some concerns**
	Deviations from intended intervention: secondary safety endpoints including 'median length of hospital stay' were analyzed in the 'as-treated cohort' in which subjects were grouped as per actual treatment received regardless or randomized group. Five patients in the prophylaxis group received supportive care only, 6 patients in the no prophylaxis group received prophylactic platelet transfusions. Probably too few patients to markedly change results. *Missing outcome data: missing outcome data for 38 patients (9.4%) lost to follow-up. No. of lost to follow-up is substantial. There is no information on why these patients were lost to follow-up or how this was handled. The statistical analysis plan states that 'missing values will not be imputed'. The lost to follow-up was rather evenly distributed between groups (16 in the prophylaxis group, 22 in the no prophylaxis group).* *Measurement of the outcome: the caregivers responsible for giving the intervention are also responsible for patient discharge which involves judgment. Knowledge of the intervention assignment could affect the outcome.*					

Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	**Some concerns**
	Measurement of the outcome: the caregivers responsible for giving the intervention are also responsible for patient discharge which involves subjective judgment. Knowledge of the intervention assignment could affect the outcome.					
Wandt et al., 2012	Low	Some concerns	Low	Some concerns	Some concerns	**Some concerns**
	Deviations from intended protocol: (i) in the prophylaxis group, routine prophylactic platelet transfusions were not given 148 times (11%) despite a morning platelet count of less than 10×10^9 per L. In the no prophylaxis group, clinically relevant bleeds judged by the treating physician, such as extended petechial bleeding or purpura of the skin, were the main reason for patients in the therapeutic group receiving transfusions not in accordance with the protocol (22%). These deviations would probably result in an increased rate of side effects in the no prophylaxis group, but this was not the case. (ii) Post-randomization-exclusion of 3 participants in the prophylactic group (1 died before start of treatment and 2 were ineligible) *Measurement of the outcome: the caregivers responsible for giving the intervention are also responsible for patient discharge which involves judgment. Knowledge of the intervention assignment could affect the outcome.* *Selection of the reported result: no protocol or statistical analysis plan available. Study registration include 'duration of hospitalization' as an outcome but not specified further.*					
Any bleeding (sensitivity analysis)						
Assir et al. 2013	Some concerns	Some concerns	Low	High	Some concerns	**High**
	Randomization process: only reports that the study was 'randomized'. No further description *Deviations from intended protocol: Post-randomization exclusion of an ineligible patient, who received the intervention in an unblinded trial.* *Measurement of the outcome: no mention on who assessed the outcome. Outcome assessors were not blinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.* *Selection of the reported results: no protocol, statistical analysis plan or study registration available.*					
Grossman et al., 1980	High	Low	Low	High	Some concerns	**High**
	Randomization process: the study author reported that randomization was performed using 25 envelopes, each with four cards inside, one for each treatment group: As participants were enrolled, their allocation was drawn from the envelope. Once all four cards in each envelope were used, a new envelope was opened. Hence, when three patients were allocated the next allocation would be known before assignment. *Measurement of the outcome: the clinical team performed the assessment unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.* *Selection of the reported results: No protocol, statistical analysis plan or study registration available.*					
Lye et al., 2017	Low	Low	Some concerns	Some concerns	Low	**Some concerns**
	Missing outcome data: missing outcome data for 38 patients (9.4%) lost to follow-up. No. of lost to follow-up is large enough to have a substantial impact on the results (bleeding episodes; 91) but the lost to follow-up was rather evenly distributed between groups (16 in the prophylaxis group, 22 in the no prophylaxis group).					

	Measurement of the outcome: outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.					
Murphy et al., 1982	Some concerns	Some concerns	Low	High	Some concerns	**High**
	Randomization process: no description of randomization method or attempts to conceal allocation and almost no baseline data presented. *Deviations from intended interventions: no information on deviations from protocol.* *Measurement of the outcome: unclear who assessed the outcome. Outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.* *Selection of the reported results: no protocol, statistical analysis plan or study registration available.*					
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	**Some concerns**
	Measurement of the outcome: outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. For in-patients the bleeding assessment were performed separately from the treating clinical unit nursing and medical staff. All research staff that completed daily bleeding assessments received standardized training from a small core of research staff. There were pre-agreed definitions and guide notes to help complete the bleeding assessment in a standardized fashion. Every six months, educational meetings were held centrally including scenarios for assessing bleeding. During monitoring site visits, conducted by the central coordinating staff, duplicate assessments of bleeding scores were undertaken. Outpatients completed daily bleeding diaries. If they had bleeding, they completed a self-assessed bleeding form. Medical bleeding assessment forms would be completed following review of the self-assessed bleeding forms either at the next hospital attendance or by telephone. Grading of the bleeding was performed by a computer algorithm at the time of data entry. The algorithm was validated after the first 100 patients had been enrolled. Even though measurements were taken to standardize bleeding assessments, outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.					
Wandt et al., 2012	Low	Some concerns	Low	Some concerns	Some concerns	**Some concerns**
	Deviations from intended interventions: (i) in the prophylaxis group, routine prophylactic platelet transfusions were not given 148 times (11%) despite a morning platelet count of less than 10×10^9 per L. In the no prophylaxis group, clinically relevant bleeds judged by the treating physician, such as extended petechial bleeding or purpura of the skin, were the main reason for patients in the therapeutic group receiving transfusions not in accordance with the protocol (22%). These deviations would probably result in an increased effect in the same direction as observed in the study. (ii) Post-randomization-exclusion of 3 participants in the prophylactic group (1 died before start of treatment and 2 were ineligible) *Measurement of the outcome: assessment of bleeding will inevitably involve some degree of subjective judgement. A physician or experienced nurse examined patients twice a day for new signs of bleeding. The treating hematologist was responsible for documentation and reporting in each center and was not blinded; knowledge of the intervention assignment could have affected the bleeding assessment.* *Selection of the reported result: no protocol or statistical analysis plan available.*					
Days with any bleeding (sensitivity analysis)						
Murphy et al., 1980	Some concerns	Some concerns	Low	High	Some concerns	**High**

	Randomization process: no description of randomization method or attempts to conceal allocation and almost no baseline data presented. *Deviations from intended interventions: no information on deviations from protocol.* *Measurement of the outcome: Unclear who assessed the outcome. Outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.* *Selection of the reported results: no protocol, statistical analysis plan or study registration available.*					
Stanworth et al., 2013	Low	Low	Low	Some concerns	Low	**Some concerns**
	Measurement of the outcome: outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. For in-patients the bleeding assessment were performed separately from the treating clinical unit nursing and medical staff. All research staff that completed daily bleeding assessments received standardized training from a small core of research staff. There were pre-agreed definitions and guide notes to help complete the bleeding assessment in a standardized fashion. Every six months, educational meetings were held centrally including scenarios for assessing bleeding. During monitoring site visits, conducted by the central coordinating staff, duplicate assessments of bleeding scores were undertaken. Outpatients completed daily bleeding diaries. If they had bleeding, they completed a self-assessed bleeding form. Medical bleeding assessment forms would be completed following review of the self-assessed bleeding forms either at the next hospital attendance or by telephone. Grading of the bleeding was performed by a computer algorithm at the time of data entry. The algorithm was validated after the first 100 patients had been enrolled. Even though measurements were taken to standardize bleeding assessments, outcome assessors were unblinded. Assessment of bleeding involves clinical exam and subjective judgement. Outcome assessment could be influenced by the knowledge of intervention assignment.					
Long term all-cause mortality (>90 days) (Sensitivity analysis)						
Murphy et al., 1982	Some concerns	Some concerns	Low	Low	Some concerns	**Some concerns**
	Randomization process: no description of randomization method or attempts to conceal allocation and almost no baseline data presented. *Deviations from intended interventions: no information on deviations from protocol.* *Selection of the reported results: no protocol, statistical analysis plan or study registration available.*					

Supplement 9 (S9) – Fixed and random effects models for the primary analyses

In the main text we report results from fixed effect models if the I^2=0% and if I^2>0% we report both fixed effect models (FEM) and random effects models (REM) and conclusions are based on the most conservative estimate (highest P-value)[1,13]. Here, we present results from both fixed and random effects models for the primary analyses.

Additionally, forest plot for the secondary outcomes 'Transfusion related adverse events' and 'Length of hospital stay' are presented below in figure 6.1 and 62 respectively.

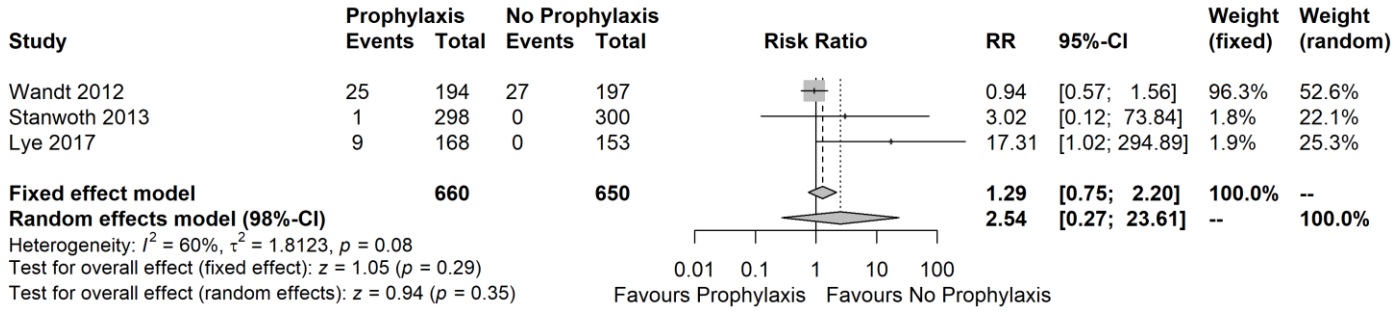
Table 9.1: Overview of fixed- (FEM) and random effects models (REM) for the primary analysis

Primary Outcome	**Trials**	**Statistical model**	**RR (95% CI) prophylaxis group vs. no prophylaxis group, I^2, P-value**
All-cause mortality at longest follow-up (low risk of bias)	1[9]	Single trial	0.81 (0.22 – 2.97), P=0.75
All-cause mortality at longest follow-up (all trials)	5[5,6,8–10]	FEM	0.99 (0.58 – 1.68), P=0.97; I^2=0%
		REM	1.00 (0.59 – 1.69), P=0.99; I^2=0%
Secondary outcomes	**Trials**	**Statistical model**	**RR/MD (97,5% CI) prophylaxis group vs. no prophylaxis group**
Clinically important bleeding	5[3,5,6,9,10]	FEM	0.75 (0.64-0.87), P<0.01; I^2=59%
		REM	0.70 (0.53-0.92), P<0.01; I^2=59%
Days with clinically important bleeding	1[9]	Single trial	-0.5 (-0.9 - -0.1), P=0.01[a]
Nosocomial infection	1[9]	Single trial	0.94 (0.45 – 1.91), P=0.86[a]
Venous or arterial thromboembolism	0	-	-
Transfusion related adverse events (Figure 9.1)	3[5,9,10]	FEM	1.29 (0.75 – 2.20), P=0.29; I^2=60%
		REM	2.54 (0.27 – 23.61), P=0.35; I^2=60%
Days alive without the use of life support	0	-	-
Length of hospital stay[b] (Figure 9.2)	2[5,10]	FEM	-0.23 (-0.60 – 0.13), P=0.16; I^2=0%
		REM	-0.23 (-0.60 – 0.13), P=0.16; I^2=0%
Quality of life	0	-	-

[a] We used a 95% CI as no meta-analysis was performed. These results were calculated from the available summary data from the single trial providing data for this outcome.

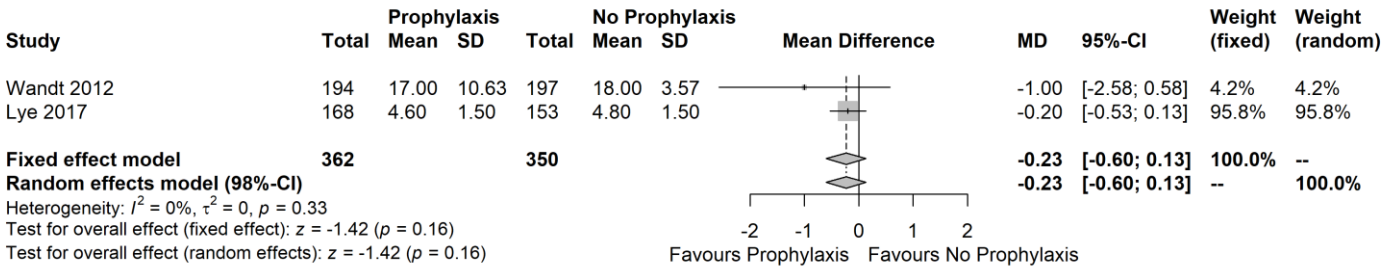
[b]Stanworth 2013 reported length of stay as median and IQR and were not included in the meta-analysis.

Figure 9.1 – Secondary outcome: transfusion related adverse events



Legend: Forest plot of the conventional meta-analysis of transfusion related adverse events. Lye 2017 reported adverse events from platelet transfusions in an 'as treated' cohort.

Figure 9.2 – Secondary outcome: length of hospital stay



Legend: Forest plot of the conventional meta-analysis of length of hospital stay. Lye 2017 reported length of hospital stay in an 'as treated' cohort.

Supplement 10 (S10) – Clinical diversity in Meta-analysis (CDIM)

We used the CDIM-tool where relevant and the scores are presented in the tables below.[14] We included all studies that reported data on the specified outcomes, even if they did not contribute to the meta-analysis because they reported a different summary statistic in the CDIM assessments. This was the case for two outcomes: days with clinically important bleeding and length of hospital stay. Importantly, data on days with clinically important bleeding from Wandt et al., 2012[10] were not reported with individual patients as the unit of analysis and hence the study were not included in the CDIM assessment for that outcome.

In short, the CDIM tool assess clinical diversity in four overall domains with individual items within each domain.[14] The first domain, population diversity, includes four items and assess diversity between the trial populations with respect to age, gender, disease severity and comorbidities. The second domain, setting diversity, includes one item and assess diversity between trials with respect to the time periods, developments status of the countries and treating unit in which the trials were conducted. The third domain, intervention diversity, includes four items and assess diversity in intervention intensity (dose, frequency, duration, cut off-values), timing of intervention, control interventions and co-interventions between the trials. The fourth domain, outcome diversity, assess diversity in definition of outcome and the timing of outcome assessment between the trials. Each item within each domain are scored using specific criteria (e.g. if there is more than 30% relative difference between trials in the dose of a drug intervention, that corresponds to a score of 2) either 0, 1 or 2 corresponding to low, moderate or unclear, and high clinical diversity. The total CDIM score is comprised from an unweighted addition of the individual scores for each item and ranges from 0 to 22. CDIM scores of 0 to 11, 12 to 18 and 19 to 22 corresponds to ‘low’, ‘moderate’ and ‘high’ clinical diversity, respectively.

Table 10.1 Outcome: all-cause mortality at longest follow-up (all trials).		
Domains of diversity	**Item**	**Score (0-2)**
Setting	1. Years reported (A), performed in developed vs developing country (B), unit type (C)	1
Population	2. Age	2
	3. Sex	0
	4. Participant inclusion criteria and baseline disease severity	1
	5. Comorbidities	1
Intervention	6. Intensity, strengths, or duration of intervention	2
	7. Timing	1
	8. Control intervention	1
	9. Cointerventions	0
	10. Definition of the outcome in the meta-analysis	0
	11. Timing of outcome measurement	2
Total CDIM score: low clinical diversity		**11**

Table 10.2 Outcome: clinically important bleeding.		
Domains of diversity	**Item**	**Score (0-2)**
Setting	1. Years reported (A), performed in developed vs developing country (B), unit type (C)	2
Population	2. Age	2
	3. Sex	1
	4. Participant inclusion criteria and baseline disease severity	2
	5. Comorbidities	1
Intervention	6. Intensity, strengths, or duration of intervention	2
	7. Timing	1
	8. Control intervention	1
	9. Cointerventions	1
	10. Definition of the outcome in the meta-analysis	2
	11. Timing of outcome measurement	2
Total CDIM score: moderate clinical diversity		**17**

Table 10.3 Outcome: days with clinically important bleeding.		
Domains of diversity	**Item**	**Score (0-2)**
Setting	1. Years reported (A), performed in developed vs developing country (B), unit type (C)	1
Population	2. Age	2
	3. Sex	1
	4. Participant inclusion criteria and baseline disease severity	1
	5. Comorbidities	1
Intervention	6. Intensity, strengths, or duration of intervention	2
	7. Timing	1
	8. Control intervention	1
	9. Cointerventions	1
	10. Definition of the outcome in the meta-analysis	2
	11. Timing of outcome measurement	2
Total CDIM score: moderate clinical diversity		**15**

Table 10.4 Outcome: transfusion related adverse effects.		
Domains of diversity	**Item**	**Score (0-2)**
Setting	1. Years reported (A), performed in developed vs developing country (B), unit type (C)	1
Population	2. Age	1
	3. Sex	1
	4. Participant inclusion criteria and baseline disease severity	2
	5. Comorbidities	1
Intervention	6. Intensity, strengths, or duration of intervention	2
	7. Timing	1
	8. Control intervention	1
	9. Cointerventions	1
	10. Definition of the outcome in the meta-analysis	2
	11. Timing of outcome measurement	0
Total CDIM score: moderate clinical diversity		**13**

Table 10.5 Outcome: length of hospital stay		
Domains of diversity	**Item**	**Score (0-2)**
Setting	1. Years reported (A), performed in developed vs developing country (B), unit type (C)	1
Population	2. Age	1
	3. Sex	1
	4. Participant inclusion criteria and baseline disease severity	2
	5. Comorbidities	1
Intervention	6. Intensity, strengths, or duration of intervention	2
	7. Timing	1
	8. Control intervention	1
	9. Cointerventions	1
	10. Definition of the outcome in the meta-analysis	1
	11. Timing of outcome measurement	0
Total CDIM score: moderate clinical diversity		**12**

Supplement 11 (S11) – Subgroup analyses

Table 11.1 Overview of subgroup analyses

Subgroup analysis	Comment	Analysis
Overall low risk of bias vs some concerns vs high risk of bias.	As less than 10 trial trials were included in any category, we analyzed overall low risk of bias vs some concerns or high risk of bias.[1]	Table 11.2 and Figure 11.1.
Patients with hematological malignancy vs patients with non-hematological cancer vs patients without cancer or hematological malignancy.	Not performed as no trials included patient with non-hematological cancer, and the trial conducted in patients without cancer or hematological malignancy had no events.	NA.
Medical vs surgical vs mixed patients.	Not performed as no data from trials in surgical or mixed patients were available.	NA.
Invasive procedures vs no invasive procedures.	Not performed as no data from trials in patients undergoing invasive procedures were available.	NA.
Neonates (including preterm) vs pediatric patients vs adult patients.	As no data was available for neonates (including preterm), we analyzed pediatric vs adults.	Table 11.2 and Figure 11.2.
Intensive care unit patients (including high-dependency units) vs non-ICU patients.	Not performed as no data mortality data from trials in the intensive care unit or high dependency patients were available.	NA.

Table 11.2 Results of subgroup analyses

Outcome: all-cause mortality at longest follow-up

Subgroup	Studies	Statistical model	RR (95% CI) prophylaxis group vs. no prophylaxis group
Overall low risk of bias vs. some concerns or high risk of bias		Test of interaction (P=0.72), I^2=0%	
Low risk of bias	1[9]	FEM	0.81 (22 to 2.97)
Some concerns or high risk of bias	4[5,6,8,10]	FEM	1.04 (0.58 to 1.85)
Pediatric patients vs. adults		Test of interaction (P=0.91), I^2=0%	
Adults	4[5,8–10]	FEM	0.97 (0.47 to 1.98)
Pediatrics	1[6]	FEM	1.03 (0.48 to 2.20)

Figure 11.1 Outcome: all-cause mortality at longest follow-up. Subgroup: overall low risk of bias vs. some concerns or high risk of bias.

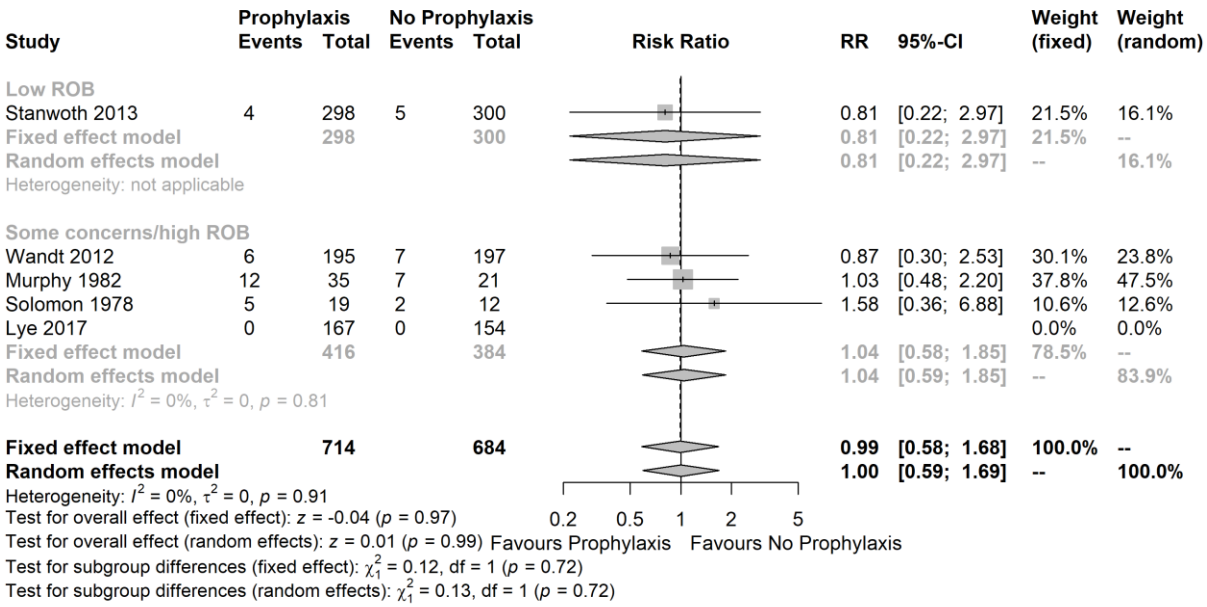
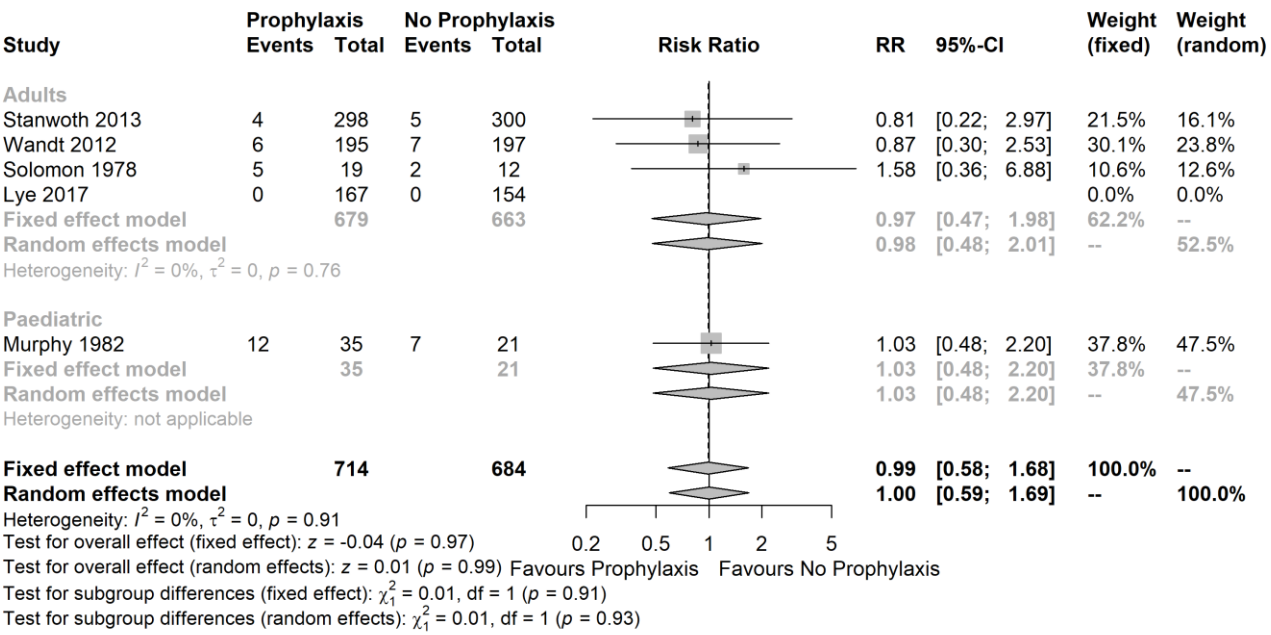


Figure 11.2 Outcome: all-cause mortality at longest follow-up. Subgroup: pediatric patients vs. adults.



Supplement 12 (S12) – Subgroup credibility (ICEMAN)

The completed assessment sheets for each conducted subgroup analysis are presented below. Our responses to the individual components are marked with red text.

Subgroup analysis: low vs. some concerns or high risk of bias

Preliminary considerations

Study reference(s): Prophylactic platelet transfusion in hospitalized patients with thrombocytopenia – a meta-analysis with trial sequential analysis.

If available, protocol reference(s): Anthon CT, Sivapalan P, Granholm A, Pène F, Puxty K, Perner A, Møller MH, Russell L. Prophylactic platelet transfusions in hospitalised patients with thrombocytopenia – protocol for a systematic review with meta-analysis. Acta Anaesthesiol Scand 2021 Apr 26. doi: 10.1111/aas.13826

State a single outcome and, if applicable, time-point of interest (e.g., mortality at 1 year follow-up): all-cause mortality at longest follow-up

State a single effect measure of interest (e.g., relative or absolute risk difference): relative risk

State a single potential effect modifier of interest (e.g., age or comorbidity): risk of bias (low vs. some concerns or high risk of bias)

Was the potential effect modifier measured before or at randomization? [ ] yes, continue [**X**] no, stop here and refer to manual for further instructions

Credibility assessment

1: Is the analysis of effect modification based on comparison within rather than between trials?

[**X**] Completely between	[ ] Mostly between or unclear	[ ] Mostly within	[ ] Completely within
Subgroup analysis or meta-regression comparing overall effects of each individual trial. This is typical for aggregate data meta-analysis.	*Subgroup analysis or meta-regression with most information coming from overall effects, but some trials providing within-trial subgroup information*	*Most trials providing within-trial subgroup information; or individual participant data analysis that combines within and between trial information*	*All trials providing within-trial subgroup information or individual participant data; and the analysis separates within from between trial information, e.g., meta-analysis of interactions*

Comment: subgroup analysis.

2: For within-trial comparisons, is the effect modification similar from trial to trial? [**X**] Not applicable: no or one within-RCT comparison

[ ] Definitely not similar	[ ] Probably not similar or unclear	[ ] Mostly similar	[ ] Definitely similar
Effect modification reported for two or more trials and clearly different directions	*Effect modification not reported for individual trials or too imprecise to tell*	*Effect modification reported for two or more trials, mostly similar in direction, but considerable differences in magnitude*	*Effect modification reported for two or more trials, similar in direction, only some differences in magnitude*

Comment:

3: For between-trial comparisons, is the number of trials large? [ ] Not applicable: no between RCT comparison

[**X**] Very small	[ ] Rather small or unclear	[ ] Rather large	[ ] Large
1 or 2 or in smallest subgroup; 5 or less in continuous meta-regression	*3-4 in smallest subgroup; 6-10 in continuous meta-regression*	*5-9 in smallest subgroup; 11 to 15 in continuous meta-regression*	*10 or more in smallest subgroup; more than 15 in continuous meta-regression*

Comment: very small number of trials; only one trial had overall low risk of bias; four had some concerns or high risk of bias.

4: Was the direction of effect modification correctly hypothesized a priori?

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[**X**] Definitely yes

Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible	*Vague hypothesis or hypothesized direction unclear*	*No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification*	*Prior protocol available and includes correct specification of direction of effect modification, e.g., based on a biologic rationale*

Comment: protocol available with six prespecified subgroup analyses for the primary outcome. Data only allowed two subgroup analysis to be performed. The authors hypothesized a direction of effect towards increased beneficial effects on trials with overall high risk of bias.

5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)

[**X**] Chance a very likely explanation	[ ] Chance a likely explanation or unclear	[ ] Chance may not explain	[ ] Chance an unlikely explanation
Interaction or meta-regression p-value >0.05	*Interaction or meta-regression p-value ≤0.05 and >0.01, or no test of interaction reported and not computable*	*Interaction or meta-regression p-value ≤0.01 and >0.005*	*Interaction or meta-regression p-value ≤0.005*

Comment: p-value = 0.72.

6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[**X**] Definitely yes
Explicitly exploratory analysis or large number of effect modifiers tested (e.g., greater than 10) and multiplicity not considered in analysis	*No mention of number or 4-10 effect modifiers tested and number not considered in analysis*	*No protocol available but unequivocal statement of 3 or fewer effect modifiers tested*	*Protocol available and 3 or fewer effect modifiers tested or number considered in analysis*

Comment: a total of two subgroup analyses was conducted.

7: Did the authors use a random effects model?

[**X**] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[ ] Definitely yes
Fixed (or common) effect or fixed effects model explicitly stated	*Probably fixed effect(s) model*	*Probably random (or mixed) effects*	*Random (or mixed) effects explicitly stated*

Comment: primary analysis used fixed effect models as I^2 =0% according to the protocol. In the subgroup analysis, I^2 was 0% and fixed effect model was used. Results from a random effects model would be comparable.

8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [**X**] not applicable: not continuous

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[ ] Definitely yes
Analysis based on exploratory cut point(s), e.g., picking cut point associated with highest interaction p-value	*Analysis based on cut point(s) of unclear origin*	*Analysis based on pre-specified cut point(s), e.g., suggested by prior RCT*	*Analysis based on the full continuum, e.g., assuming a linear or logarithmic relationship*

Comment:

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9 Optional: Are there any additional considerations that may increase or decrease credibility? (manual section 3.9) [**X**] not applicable

[ ] Yes, probably decrease	[ ] Yes, probably increase

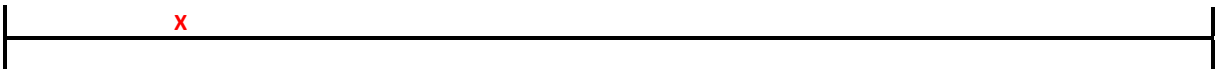
Comment:

10: How would you rate the overall credibility of the proposed effect modification?

The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:

- All responses definitely or probably decrease credibility or unclear → very low
- Two or more responses definitely decrease credibility → maximum usually low even if all other responses satisfy credibility criteria
- One response definitely decreases credibility → maximum usually moderate even if all other responses satisfy credibility criteria
- Two responses probably decrease credibility → maximum usually moderate even if all other responses satisfy credibility criteria
- No response options definitely or probably decrease credibility → high very likely

Place a mark on the continuous line (or type "x" in editable version)



Very low credibility	Low credibility	Moderate credibility	High credibility
Very likely no effect modification Use overall effect for each subgroup	Likely no effect modification Use overall effect for each subgroup but note remaining uncertainty	Likely effect modification Use separate effects for each subgroup but note remaining uncertainty	Very likely effect modification Use separate effects for each subgroup

Comment: no subgroup effect was observed. Very few studies contributed to the analysis. Information size probably too small to detect any differences (if any). Risk of type 2 error present.

Subgroup analysis: pediatric vs. adult patients.

Preliminary considerations

Study reference(s): Prophylactic platelet transfusion in hospitalized patients with thrombocytopenia – a meta-analysis with trial sequential analysis.

If available, protocol reference(s): Anthon CT, Sivapalan P, Granholm A, Pène F, Puxty K, Perner A, Møller MH, Russell L. Prophylactic platelet transfusions in hospitalised patients with thrombocytopenia – protocol for a systematic review with meta-analysis. Acta Anaesthesiol Scand 2021 Apr 26. doi: 10.1111/aas.13826

State a single outcome and, if applicable, time-point of interest (e.g., mortality at 1 year follow-up): all-cause mortality at longest follow-up

State a single effect measure of interest (e.g., relative or absolute risk difference): relative risk

State a single potential effect modifier of interest (e.g., age or comorbidity): age (adults vs. children)

Was the potential effect modifier measured before or at randomization? [**X**] yes, continue [ ] no, stop here and refer to manual for further instructions

Credibility assessment

1: Is the analysis of effect modification based on comparison within rather than between trials?

[**X**] Completely between	[ ] Mostly between or unclear	[ ] Mostly within	[ ] Completely within
Subgroup analysis or meta-regression comparing overall effects of each individual trial. This is typical for aggregate data meta-analysis.	*Subgroup analysis or meta-regression with most information coming from overall effects, but some trials providing within-trial subgroup information*	*Most trials providing within-trial subgroup information; or individual participant data analysis that combines within and between trial information*	*All trials providing within-trial subgroup information or individual participant data; and the analysis separates within from between trial information, e.g., meta-analysis of interactions*

Comment: subgroup analysis.

2: For within-trial comparisons, is the effect modification similar from trial to trial? [**X**] Not applicable: no or one within-RCT comparison

[ ] Definitely not similar	[ ] Probably not similar or unclear	[ ] Mostly similar	[ ] Definitely similar
Effect modification reported for two or more trials and clearly different directions	*Effect modification not reported for individual trials or too imprecise to tell*	*Effect modification reported for two or more trials, mostly similar in direction, but considerable differences in magnitude*	*Effect modification reported for two or more trials, similar in direction, only some differences in magnitude*

Comment:

3: For between-trial comparisons, is the number of trials large? [ ] Not applicable: no between RCT comparison

[**X**] Very small	[ ] Rather small or unclear	[ ] Rather large	[ ] Large
1 or 2 or in smallest subgroup; 5 or less in continuous meta-regression	*3-4 in smallest subgroup; 6-10 in continuous meta-regression*	*5-9 in smallest subgroup; 11 to 15 in continuous meta-regression*	*10 or more in smallest subgroup; more than 15 in continuous meta-regression*

Comment: very small number of trials; one trial was conducted in children; four trials were conducted in adults.

4: Was the direction of effect modification correctly hypothesized a priori?

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[**X**] Definitely yes
Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible	*Vague hypothesis or hypothesized direction unclear*	*No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification*	*Prior protocol available and includes correct specification of direction of effect modification, e.g., based on a biologic rationale*

Comment: protocol available with six prespecified subgroup analyses for the primary outcome. Data only allowed two subgroup analysis to be performed. The authors hypothesized a direction of effect towards increased harm in neonates. The subgroup had a statistically insignificant test of interaction, but numbers are likely to small to detect any difference (if present).

5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)

[**X**] Chance a very likely explanation	[ ] Chance a likely explanation or unclear	[ ] Chance may not explain	[ ] Chance an unlikely explanation
Interaction or meta-regression p-value >0.05	*Interaction or meta-regression p-value ≤0.05 and >0.01, or no test of interaction reported and not computable*	*Interaction or meta-regression p-value ≤0.01 and >0.005*	*Interaction or meta-regression p-value ≤0.005*

Comment: p-value for chi-squared test for interaction = 0.93.

6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[**X**] Definitely yes
Explicitly exploratory analysis or large number of effect modifiers tested (e.g., greater than 10) and multiplicity not considered in analysis	*No mention of number or 4-10 effect modifiers tested and number not considered in analysis*	*No protocol available but unequivocal statement of 3 or fewer effect modifiers tested*	*Protocol available and 3 or fewer effect modifiers tested or number considered in analysis*

Comment: two subgroup analyses was performed.

7: Did the authors use a random effects model?

[**X**] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[ ] Definitely yes
Fixed (or common) effect or fixed effects model explicitly stated	*Probably fixed effect(s) model*	*Probably random (or mixed) effects*	*Random (or mixed) effects explicitly stated*

Comment: the primary analysis used fixed effect models as I^2 =0% according to the protocol. In the subgroup analysis, I^2 was 0% and fixed effect model was used. Results from a random effects model would be comparable.

8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [ ] not applicable: not continuous

[ ] Definitely no	[ ] Probably no or unclear	[**X**] Probably yes	[ ] Definitely yes
Analysis based on exploratory cut point(s), e.g., picking cut point associated with highest interaction p-value	*Analysis based on cut point(s) of unclear origin*	*Analysis based on pre-specified cut point(s), e.g., suggested by prior RCT*	*Analysis based on the full continuum, e.g., assuming a linear or logarithmic relationship*

Comment: prespecified subgroup analysis of pediatric patients vs. adults (as specified in the included trials).

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9 Optional: Are there any additional considerations that may increase or decrease credibility? (manual section 3.9) [**X**] not applicable

[ ] Yes, probably decrease	[ ] Yes, probably increase

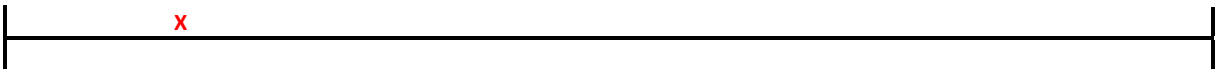
Comment:

10: How would you rate the overall credibility of the proposed effect modification?

The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:

- All responses definitely or probably decrease credibility or unclear → very low
- Two or more responses definitely decrease credibility → maximum usually low even if all other responses satisfy credibility criteria
- One response definitely decreases credibility → maximum usually moderate even if all other responses satisfy credibility criteria
- Two responses probably decrease credibility → maximum usually moderate even if all other responses satisfy credibility criteria
- No response options definitely or probably decrease credibility → high very likely

Place a mark on the continuous line (or type "x" in editable version)



Very low credibility	Low credibility	Moderate credibility	High credibility
Very likely no effect modification Use overall effect for each subgroup	Likely no effect modification Use overall effect for each subgroup but note remaining uncertainty	Likely effect modification Use separate effects for each subgroup but note remaining uncertainty	Very likely effect modification Use separate effects for each subgroup

Comment: no subgroup effect was observed. Very few, and rather small studies contributed to the analysis. Information size probably too small to detect any differences (if any). Risk of type 2 error present.

Supplement 13 (S13) – Sensitivity analyses

Table 13.1 Sensitivity analysis for the primary outcome: all-cause mortality at longest follow-up (low risk of bias trials)

Sensitivity analysis	Trials	Statistical model	RR (95% CI) prophylaxis group vs. no prophylaxis group
Long term all-cause mortality[a]	-	-	-
Empirical continuity correction[b]	-	-	-
Best-worst scenario[c]	1[9]	Single trial	0.67 (0.19 to 2.35), P=0.53
Worst-best scenario[d]	1[9]	Single trial	1.01 (0.29 to 3,44), P=0.99

[a]Not performed as no low risk of bias trials reported on this outcome.

[b]Not performed as no low risk of bias trials had zero events.

[c]Best-worst scenario is assuming that all patients lost to follow-up in the prophylaxis group survived, while all patients lost to follow-up in the no prophylaxis group did not.

[d]Worst-best scenario is assuming that all patients lost to follow-up in the prophylaxis group died, while all patients lost to follow-up in the no prophylaxis group did not.

Table 13.2 Sensitivity analysis for the primary outcome: all-cause mortality at longest follow-up (all trials)

Sensitivity analysis	Trials	Statistical model	RR (95% CI) prophylaxis group vs. no prophylaxis group
Long term all-cause mortality	1[6]	NA	1.03 (0.48 to 2.20), P=0.94
Empirical continuity correction	5[5,6,8–10]	FEM	0.99 (0.59 to 1.67), P=0.97; I^2=0%,
Best-worst scenario[a]	5[5,6,8–10]	FEM[b]	0.46 (0.29 to 0.73), P=<0.01; I^2=70%
		REM[b]	0.65 (0.23 to 1.82), P=0.41; I^2=70%
Worst-best scenario[c]	5[5,6,8–10]	FEM[b]	1.78 (1.11 to 2.87), P=0.02; I^2=56%
		REM[b]	1.38 (0.59 to 3.22), P=0.46; I^2=56%

[a]Best-worst scenario is assuming that all patients lost to follow-up in the prophylaxis group survived, while all patients lost to follow-up in the no prophylaxis group did not.

[b]We report both fixed- (FEM) and random effects model (REM) if $I^2 > 0\%$ in the sensitivity analysis and the primary analysis used FEM.

[c]Worst-best scenario is assuming that all patients lost to follow-up in the prophylaxis group died, while all patients lost to follow-up in the no prophylaxis group did not.

Table 13.3 Sensitivity analysis for the secondary outcomes			
Sensitivity analysis	**Trials**	**Statistical model**	**RR/MD (97.5% CI) prophylaxis group vs. no prophylaxis group**
Outcome: clinically important bleeding			
Any bleeding	6[2,3,5,6,9,10]	REM	0.75 (0.54 to 1.03), P=0.04; I^2=76%
Empirical continuity correction[a]	-	-	-
Best-worst scenario[b]	5[3,5,6,9,10]	REM	0.63 (0.46 to 0.86), P<0.01; I^2=70%
Worst-best scenario[c]	5[3,5,6,9,10]	REM	0.74 (0.52 to 1.04), P=0.05; I^2=75%
Outcome: days with clinically important bleeding			
Any bleeding[d]	-	-	-
Empirical continuity correction[a]	-	-	-
Best-worst scenario[e]	1[9]	-	-0.53 (-0.93 to -0.13)[g], P=0.01
Worst-best scenario[f]	1[9]	-	-0.47 (-0.87 to - 0.07)[g], P=0.02
Outcome: nosocomial infection			
Empirical continuity correction[a]	-	-	-
Best-worst scenario[b]	1[9]	-	0.88 (0.44 to 1.77)[g], P=0.72
Worst-best scenario[c]	1[9]	-	1.01 (0.50 to 2.02)[g], P=0.98
Outcome: transfusion related adverse events			
Empirical continuity correction	3[5,9,10]	REM	2.55 (0.27 to 24.19), P=0.35; I^2=60%
Best-worst scenario[b]	3[5,9,10]	REM	0.61 (0.25 to 1.53), P=0.23; I^2=58%
Worst-best scenario[c]	3[5,9,10]	REM	5.34 (0.13 to 213.03), P=0.31; I^2=85%
Outcome: length of hospital stay			
Empirical continuity correction[a]	-	-	-
Best-worst scenario[e]	2[5,10]	FEM	-0.93 (-1.32 to -0.53), P=<0.01; I^2=0%
Worst-best scenario[f]	2[5,10]	FEM[h]	0.44 (0.05 to 0.83), P=0.01; I^2=69%
		REM[h]	-0.02 (-1.61 to 1.57), P=0.98; I^2=69%

[a]Not performed as no trials had zero events.

[b]Best-worst scenario is assuming that all patients lost to follow-up in the prophylaxis group did not experience the outcome, while all patients lost to follow-up in the no prophylaxis group did.

[c]Worst-best scenario is assuming that all patients lost to follow-up in the prophylaxis group did experience the outcome, while all patients lost to follow-up in the no prophylaxis group did not.

[d]Not performed as not trials reported on that outcome.

[e]Best-worst scenario is assuming that all patients lost to follow-up in the prophylaxis group had a mean minus 2 standard deviations (SDs) of the group mean, while all patients lost to follow-up in the no prophylaxis group had a mean plus 2 SDs of the group mean.

[f]Worst-best scenario is assuming that all patients lost to follow-up in the prophylaxis group had a mean plus

2 SDs of the group mean, while all patients lost to follow-up in the no prophylaxis group had a mean minus 2 SDs of the group mean.

[g]As no meta-analysis was performed, we used 95% CI as reported in the trial.

[h]We report both fixed- (FEM) and random effects model (REM) if $I^2 > 0\%$ in the sensitivity analysis and the primary analysis used FEM.

Supplement 14 (S14) – Process variables

The forest plots for the process variables are available below. No studies reported on units of fresh frozen plasma transfused per participant.

Fig. 14.1 Mean number of platelet transfusions per participant

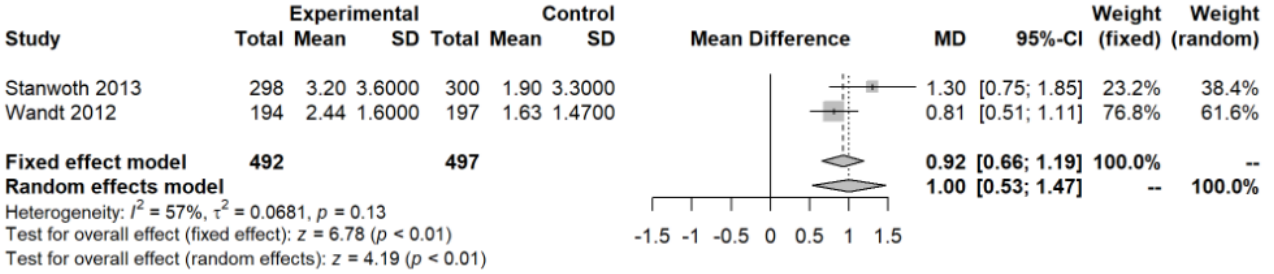
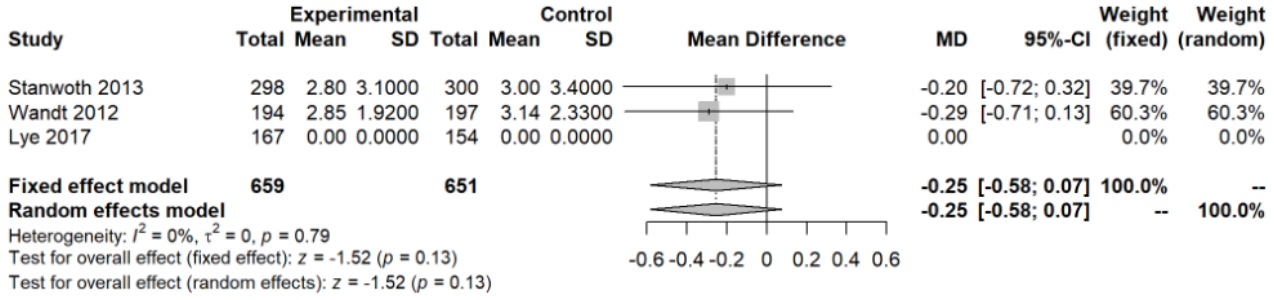


Fig. 14.2 Mean number of red blood cell transfusions per participant



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