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REVIEW ARTICLE/BRIEF REVIEW

Point-of-care viscoelastic hemostatic testing in cardiac surgery patients: a systematic review and meta-analysis

Tests hémostatiques viscoélastiques au point de service des patients subissant une chirurgie cardiaque : revue systématique de la littérature et méta-analyse

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Abstract

Purpose *Thromboelastography and rotational thromboelastometry are point-of-care (POC) viscoelastic tests used to help guide blood product administration. It is unclear whether these tests improve clinical or transfusion-related outcomes. The objective of this study was to appraise data from randomized trials evaluating the benefit of POC testing in cardiac surgery patients. Primary outcomes were the proportion of patients transfused with blood products and all-cause mortality.*

Source *Medline (Ovid), EMBASE (Ovid), CENTRAL (the Cochrane Library-Wiley), Web of Science, Biosis, Scopus, and CINAHL databases, as well as clinical trial registries and conference proceedings were queried from inception to February 2018.*

Principal findings *We identified 1,917 records, 11 of which were included in our analysis (8,294 patients). Point-of-care testing was not associated with a difference in the proportion of patients transfused with any blood product (risk ratio [RR], 0.90; 95% confidence interval [CI], 0.79 to 1.02; I^2 = 51%; four trials, 7,623 patients), or all-cause mortality (RR, 0.73; 95% CI, 0.47 to 1.13; I^2 =*

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5%; six trials, 7,931 patients). Nevertheless, POC testing was weakly associated with a decrease in the proportion of patients receiving red blood cells (RBC) (RR, 0.91; 95% CI, 0.85 to 0.96; I^2 = 0%; seven trials, 8,029 patients), and heterogeneous reductions in frozen plasma (FP) (RR, 0.58; 95% CI, 0.34 to 0.99; I^2 = 87%; six trials, 7,989 patients) and platelets (RR, 0.66; 95% CI, 0.49 to 0.90; I^2 = 65%; seven trials, 8,029 patients). Meta-analysis of the number of units of RBCs and FP was not possible due to heterogeneity in reporting, however POC testing significantly reduced the units of platelets transfused (standard mean difference, -0.09; 95% CI, -0.18 to 0.00; four trials, 7,643 patients).

Conclusion *Our review indicates that in cardiac surgery patients, POC viscoelastic hemostatic testing is not associated with a reduction in the proportion of patients receiving any blood product or all-cause mortality. However, viscoelastic testing is weakly associated with a reduction in proportion of patients transfused with specific blood products. Presently, the benefits associated with viscoelastic testing in cardiac surgery patients are insufficiently robust to recommend routine implementation of this technology.*

Trial registration *PROSPERO (CRD4201706577). Registered 11 May 2017.*

Résumé

Objectif *La thromboélastographie et la thromboélastométrie rotative sont des tests de la viscosité sanguine au point de service du patient et qui peuvent servir de guide à l'administration de produits sanguins. On ne sait pas avec certitude si ces tests améliorent l'évolution clinique ou les résultats liés à la transfusion. L'objectif de cette étude était d'évaluer les données provenant d'essais randomisés ayant étudié les bénéfices des tests de viscosité sanguine au point de service des patients subissant une chirurgie cardiaque. Les critères d'évaluation principaux ont été le pourcentage de patients recevant des transfusions de produits sanguins et la mortalité toutes causes confondues.*

Sources *les bases de données MEDLINE (Ovid), EMBASE (Ovid), CENTRAL (la Cochrane Library-Wiley), Web of Science, Biosis, Scopus et CINAHL, ainsi que les registres d'essais cliniques et les comptes rendus de congrès ont été passés au crible depuis leur création jusqu'en février 2018.*

Constatations principales *Nous avons identifié 1 917 rapports, dont 11 qui ont été inclus dans notre analyse (8 294 patients). Les tests de viscosité au point de service n'ont été associés à aucune différence en termes de pourcentages de patients recevant des transfusions de différents produits sanguins (rapport de risque [RR], 0,90; intervalle de confiance [IC] à 95 % : 0,79 à 1,02; I^2 = 51 %; quatre essais, 7 623 patients) ou la mortalité toutes causes (RR, 0,73; IC à 95 % : 0,47 à 1,13; I^2 = 5 %; six essais, 7 931 patients). Néanmoins, les tests de viscosité au point de service du patient ont été faiblement associés à une diminution du pourcentage de patients recevant des globules rouges (RR, 0,91; IC à 95 % : 0,85 à 0,96; I^2 = 0 %; sept essais, 8 029 patients) et à des réductions hétérogènes de plasma congelé (RR, 0,58; IC à 95 % : 0,34 à 0,99; I^2 = 87 %; six essais, 7 989 patients) et de plaquettes (RR, 0,66; IC à 95 % : 0,49 à 0,90; I^2 = 65 %; sept essais, 8 029 patients). Une méta-analyse du nombre d'unités de globules rouges et de plasma congelé n'a pas été possible en raison de l'hétérogénéité des rapports; cependant, les tests de viscosité au point de service du patient ont significativement réduit le nombre d'unités de plaquettes transfusées (différence des moyennes standard, -0,09; IC à 95 % : -0,18 à 0,00; quatre essais, 7 643 patients).*

Conclusion *Notre analyse indique que chez les patients subissant une chirurgie cardiaque, les tests de viscosité sanguine au point de service du patient ne sont pas associés à une réduction du pourcentage de patients recevant un produit sanguin ou à une réduction de la mortalité toutes causes confondues. Cependant, les tests de viscosité sont faiblement associés à une réduction du pourcentage de patients transfusés avec des produits sanguins spécifiques. Actuellement, les avantages associés aux tests de la viscosité sanguine chez les patients de chirurgie cardiaque ne sont pas suffisamment robustes pour recommander la mise en œuvre systématique de cette technologie.*

Enregistrement de l'essai clinique *PROSPERO (CRD4201706577). Enregistré le 11 mai 2017.*

The incidence of major bleeding in patients undergoing cardiac surgery requiring cardiopulmonary bypass (CPB) is between 3 and 11%.[1-3] The transfusion rates in cardiac surgery are variable, with up to 95% of patients receiving blood products in some centres.[4] In observational studies, transfusion of blood products has been associated with increased morbidity and mortality,[5] as well as healthcare costs.[6]

Options for monitoring hemostasis in patients undergoing cardiac surgery include standard laboratory tests of hematocrit, hemoglobin, platelet count, activated partial thromboplastin time, international normalized ratio, and fibrinogen levels. While these tests are readily available, there may be substantial delays in obtaining the results, which decreases their utility in the setting of urgent and immediate management of coagulopathy.[7]

Point-of-care (POC) viscoelastic tests, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) provide timely, comprehensive information regarding the coagulation status of a patient (usually within 15 min), making them attractive for monitoring hemostasis in acutely bleeding trauma and surgical patients. Unlike standard laboratory tests, TEG/ROTEM utilizes whole blood samples to assess detailed information on clot formation, strength, and lysis allowing rapid identification of the specific coagulation defect[7] (Appendix 1). Point-of-care viscoelastic tests can potentially be used to more effectively tailor blood product administration, avoid transfusion of unnecessary products, and reduce morbidity and mortality.[8,9]

Until recently, evidence to support the routine use of TEG and ROTEM has been limited to non-randomized studies[10-12] or small single-centre randomized controlled trials (RCTs).[8,13,14] In 2016, the first large multi-centre RCT evaluating POC viscoelastic testing in cardiac surgery was published. Data from this trial pertaining to the proportion of patients transfused with blood products and mortality have yet to be considered in the context of a meta-analysis of the existing literature.[9] To provide additional clarity on the utility of viscoelastic testing in adult cardiac surgery patients, we conducted a systematic review and meta-analysis that focuses on patient-centred outcomes.

Methods

To conduct this systematic review, we used the Methodological Expectations of Cochrane Intervention Reviews guidelines.[15] The protocol was developed *a priori* and registered on PROSPERO (CRD42017065777). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to report our results.[16] A completed PRISMA checklist is provided in the supplementary materials.

Research question

Our research question was "In adult cardiac surgery patients, compared with standard laboratory testing and/or physician discretion, does the use of POC viscoelastic hemostatic testing impact blood product transfusion, mortality, intensive care unit (ICU), or hospital length of stay?" We included RCTs involving patients > 18 yr of age, where at least 80% of the patients underwent cardiac surgery utilizing CPB. Either TEG or ROTEM had to be used as the intervention in the trial.

Our primary outcomes were the proportion of patients receiving anyblood product and all-cause mortality at the longest follow-up interval. Our secondary outcomes included the proportion of patients transfused with specific blood components (red blood cells [RBC], platelets, frozen plasma [FP], and cryoprecipitate), the volume of blood products transfused, the number of patients requiring reoperation for bleeding, and ICU and hospital length of stay. We included the incidence of transfusion-associated infection, allergic reactions, and anaphylaxis as transfusion-related safety outcomes.

Search strategy and study selection

We searched Medline (Ovid), EMBASE (Ovid), CENTRAL (the Cochrane Library-Wiley), Web of Science, Biosis, Scopus, and CINAHL databases from inception to February 14, 2018. We used the Cochrane Highly Sensitive Search Strategy to create individual search strategies for each database. The strategy from the Medline search is presented in Appendix 2. We conducted a query of the World Health Organization's International Clinical trials registry, clinicaltrials.gov, and ISRCTN to identify ongoing or planned clinical trials.

In addition to electronic database searching, to identify eligible trials, we searched abstracts and conference proceedings of the following societies from 2014 to 2017: *American Society of Anesthesiology, Canadian Anesthesiologist's Society, Society of Thoracic Surgeons, American Association for Thoracic Surgery, European Association for Cardio-Thoracic Surgery, Society of Critical Care Medicine,* and *Canadian Cardiovascular Society*. Hand searching of reference lists from relevant citations and previously published systematic reviews was also conducted. References were managed using Endnote™ (ver. X7 Thomson Reuters, Carlsbad, CA, USA).

Two reviewers (C.L. and J.H.) independently screened titles and abstracts to determine if the study met the inclusion criteria. Each report was classified as: "include", "exclude", "unclear", or "duplicate of another citation". All full-text reports classified as "include" or "unclear" by either reviewer were retrieved for formal review. Any full-text report that was not available from library services was excluded. Next, the reviewers independently assessed each full-text report using a pilot-tested standardized form. Disagreements were resolved by discussion between the two reviewers; third-party adjudication was not necessary.

Data abstraction and management

Data were independently extracted by two reviewers (C.L. and J.H.) from all included trials using a standardized pilot-tested form. All disagreements were resolved through consensus; third-party assistance was not required. The following data were extracted: author identification, year

and language of publication, source of funding, study design, population (including study inclusion and exclusion criteria), patient characteristics (age, sex, body mass index), and procedural characteristics (type and urgency of surgical procedure, CPB duration, preoperative anticoagulant use, and anti-fibrinolytic use), intervention (TEG or ROTEM, plus any other POC coagulation tests), details pertaining to comparator interventions, as well as primary, secondary, and safety outcomes.

Risk of bias assessment

To evaluate the internal validity of included trials, we used the Cochrane Collaboration Risk of Bias tool.[17,18] The overall risk of bias assessment for each trial was based on the adjudication of six individual domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other" sources of bias). Each domain was rated "low risk", "unclear risk", or "high risk". If one or more individual domains were assessed as being "high risk", our overall assessment of the trial's risk of bias was rated as such. For a trial to be considered "low risk", all individual domains must have received a "low risk" rating. The risk of bias for all other studies was adjudicated as "unclear". Publication bias assessment[19,20] using funnel plot techniques was not possible given the small number of included trials.

Measures of treatment effect

We analyzed data from the included studies using RevMan (version 5.3.5, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Data from a single cluster RCT were adjusted for cluster and time and presented as relative risk with the 95% confidence interval (CI). Continuous data for the parallel trials were pooled using the generic inverse variance method and expressed as a mean difference (MD) with the 95% CI. For continuous outcomes including cluster randomized data, pooling was done using the generic inverse variance method with effect measures expressed as a standard MD with 95% CI. Dichotomous outcomes, including cluster randomized data, were pooled using the generic inverse variance method and expressed as a log (risk ratio [RR]) with standard error. All data were analyzed using the random effects method. Statistical heterogeneity was explored using the I^2 test.[18] If significant heterogeneity was encountered with an I^2 value greater than 50%, further subgroup analyses were conducted.

Subgroup and sensitivity analysis

A priori subgroups related to our primary outcomes included: risk of bias, source of funding, surgical urgency, and procedural complexity.

Results

From 1,917 identified records, we included 11 trials that enrolled 8,294 patients (Fig. 1).[2,8,9,13,14,21-26] Between 1999 and 2016, ten trials were published in English and one in Turkish. Ten of the trials were single-centre trials,[2,8,13,14,21-26] and one was multi-centre involving 12 hospitals.[9] Four trials were conducted in North America,[2,9,24,25] six in Europe,[8,14,21-23,26] and one in Australia.[13] One trial published preliminary data as an electronic abstract[22] with the final data included in a recently published systematic review and meta-analysis.[27] Three trials were adjudicated to be at high risk of bias[8,9,25] because of lack of participant and personnel blinding; the remaining eight trials were classified as "unclear" primarily because of poor reporting (Fig. 2).

The baseline characteristics of the included trials are presented in Table 1. The mean age range of enrolled patients was 51-72 yr old. Five trials provided adequate operative details to determine the exact number of patients who had undergone "simple" *vs* "complex" procedures.[8,9,14,21,25] Two of these trials enrolled only patients undergoing elective cardiopulmonary bypass,[21,25] which was classified as a "simple" procedure. All patients in the third trial underwent complex aortic surgery,[14] and the patients in the fourth and fifth trials underwent a variety of "simple" and "complex" procedures.[8,9] Seven trials used TEG as the primary intervention,[2,13,21,23-26] and four trials used ROTEM.[8,9,14,22] The comparator group involved a transfusion algorithm based on standard laboratory tests in four trials,[8,22,24-26] and a combination of standard laboratory tests and clinician discretion in five trials.[2,13,14,21,23] The intervention (TEG or ROTEM) was implemented during re-warming on CPB and/or post protamine in all trials; three trials reported pre-CPB baseline values,[23,24,26] and eight trials also utilized POC tests under various conditions in the ICU.[2,8,13,14,21,22,25,26] Nine trials reported administration of blood products in both the intraoperative and postoperative period,[2,8,9,13,14,21,23-25] while two trials examined only postoperative product use.[22,26] The only multi-centre study was a pragmatic stepped-wedge cluster RCT where each centre was instructed to continue their usual institutional practice prior to implementation of the transfusion

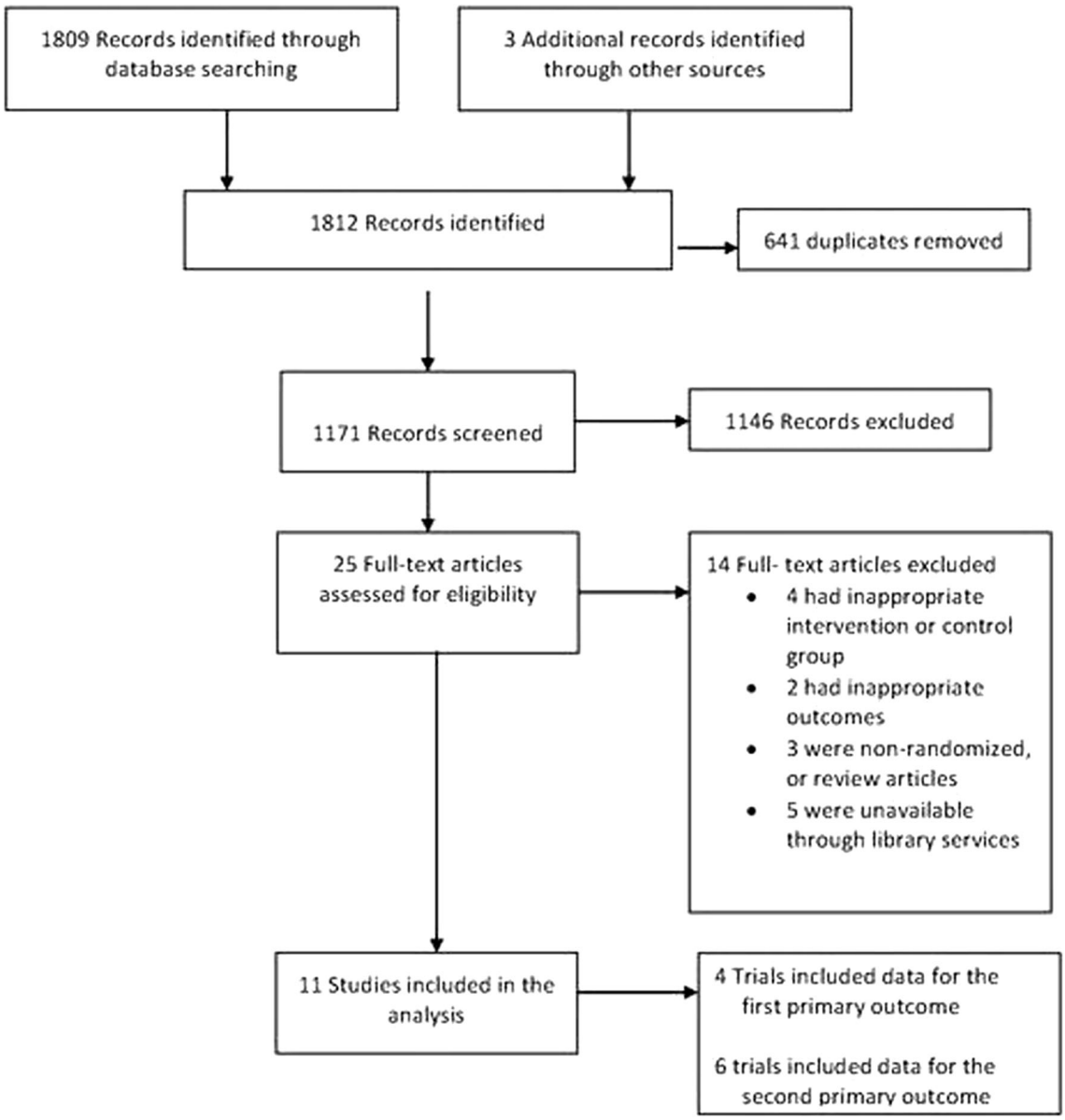

Fig. 1 Literature review process. Flow diagram illustrating the citation and manuscript review process utilizing the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines

algorithm.[9] Point-of-care platelet function tests were also used in addition to TEG/ROTEM in five studies.[8,9,13,21,25] Postoperative follow-up duration varied among all included studies, ranging from 24 hr to six months.

Primary outcomes

The use of POC viscoelastic testing was not associated with a difference in the proportion of patients transfused with any blood product (RR, 0.90; 95% CI, 0.79 to 1.02; I^2 = 51%; four trials, 7,623 patients)[9,14,23,24] (Fig. 3) or mortality at the longest follow up (RR, 0.73; 95% CI, 0.47 to 1.13; I^2 = 5%; six trials, 7,931 patients)[8,9,14,21,22,24,27] (Fig. 4). We found no difference in proportion of patients transfused with any blood product or all-cause mortality across all subgroups examined, including risk of bias, funding source, procedure urgency, and complexity (Appendices 4 and 5).

Secondary outcomes

Transfusion-related variables

Compared with standard laboratory testing, the use of POC viscoelastic testing was weakly associated with a reduction in the proportion of patients receiving RBCs (RR, 0.91; 95% CI, 0.85 to 0.96; I^2 = 0%; seven trials, 8,029 patients),

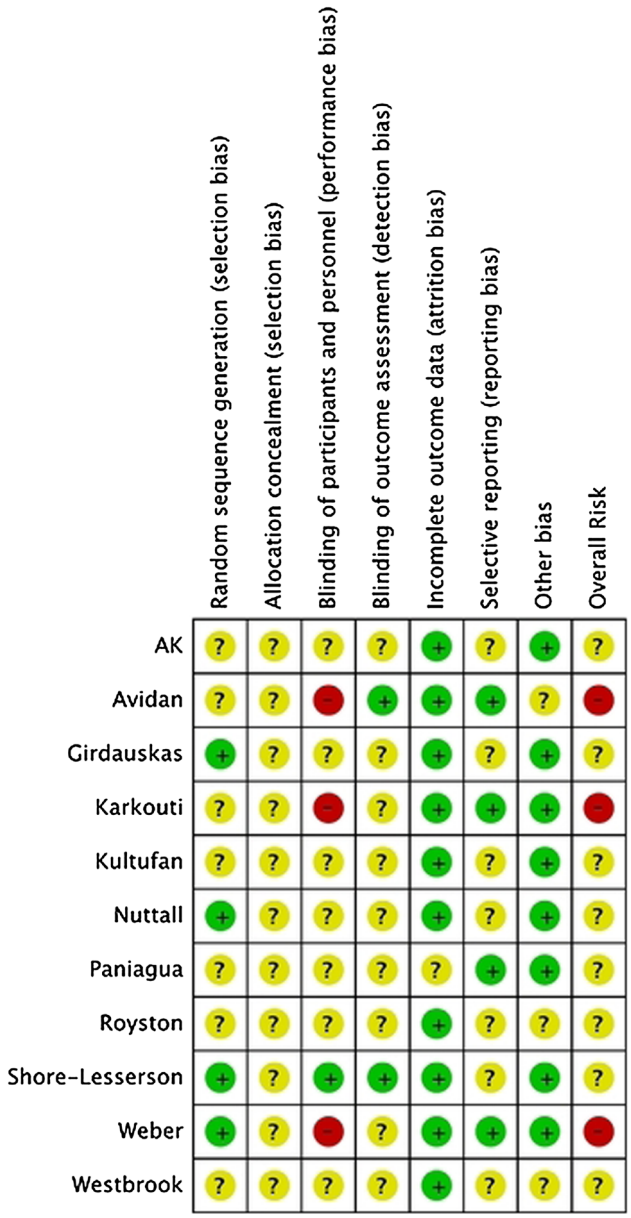

Fig. 2 Risk of bias summary. Each trial was assessed on six different domains with the decision illustrated by circles representing "low", "high", and "unclear" risks of bias. The final column displays the overall judgement of the trial

platelets (RR, 0.66; 95% CI, 0.49 to 0.90; I^2 = 65%; seven trials, 8,029 patients),[8,9,14,21,24-26] and FP (RR, 0.58; 95% CI, 0.34 to 0.99; I^2 = 87%; six trials, 7,989 patients) (Appendices 6-8). The proportion of patients transfused with cryoprecipitate was not reported directly in any trial except in the cluster RCT, where POC testing was weakly associated with an increase in the relative risk of receiving cryoprecipitate or fibrinogen concentrate (RR, 1.77; 95% CI, 1.01 to 1.86; 7,402 patients).[9] To explore statistical heterogeneity in the proportion receiving FP, we performed a subgroup analysis based on trial design. In the five parallel-group RCTs, viscoelastic testing was associated with a lower proportion of patients transfused with FP (RR, 0.48; 95% CI, 0.35 to 0.65; I^2 = 22%; five trials; 587 patients)[8,14,21,24,25] while in the multi-centre cluster RCT, no difference in plasma use was observed (RR, 0.95; 95% CI, 0.89 to 1.03; 7,402 patients)[9] (Appendix 7).

The volume of RBCs, FP, and platelets transfused was reported heterogeneously, with three trials presenting data as median and interquartile range,[8,14,21] two as mean volume transfused (in mL),[22,24,27] two as a median and range,[2,26] one as the total number of units transfused,[13] and the cluster data as relative risk with 95% CI accounting for cluster and time.[9] Of the eight trials reporting the number of transfused units of RBCs and FP,[2,8,9,14,21,22,24,26] only two showed a reduction in the number of units of RBCs administered[2,8] (Table 2). Conversely, the majority (5/8) of trials showed a reduction in the number of transfused units of FP[2,8,14,21,24] (Table 2). Viscoelastic testing was associated with a decrease in the units of platelets transfused (standard MD, −0.09; 95% CI, −0.18 to 0.00; four trials, 7,643 patients). Only one trial reported the units of cryoprecipitate used, with zero units in the TEG group and 20 units in the control group; no measures of significance were provided.[13]

Clinical and safety outcomes

Point-of-care testing was not associated with a decrease in hospital or ICU length of stay[8,13,14,21,22,27] (Table 3). The rate of reoperation was not different between the ROTEM/TEG and control groups (Table 3). Transfusion-related adverse events including infection, allergic reaction, and anaphylaxis were not reported in any of the trials included in this study.

Discussion

In this systematic review and meta-analysis, there was insufficient evidence to determine whether POC viscoelastic testing reduced the proportion of patients transfused with any blood product or all-cause mortality. When analyzed separately, POC testing was weakly associated with a reduction in the proportion of patients transfused with RBC, FP, and platelets. The volume of RBCs and FP transfused could not be pooled as the data were presented heterogeneously. Nevertheless, across individual studies, POC viscoelastic testing was associated with a trend towards decreased FP transfusion as reported in previous reviews.[27,28] Pooled data concerning the volume of platelets transfused showed a reduction associated with viscoelastic testing.

Table 1 Baseline characteristics of included studies

Study	N (V/Ctl)	Age (V/Ctl)	Population	Intervention	Control	CPB time (min) (V/Ctl)	Preoperative anticoagulation (n - V/Ctl)	Intraoperative antifibrinolytics (n-V/Ctl)	Adjunctive POC tests
Ak *et al.*	114/110	63/66 (mean)	Elective CABG	TEG	Clinician discretion and standard labs	60/59 (mean)	67/71 Acetylsalicylic acid	10/21 Tranexamic acid	ADP platelet aggregation analysis
Avidan *et al.*	51/51	66/62 (mean)	Elective CABG	TEG	Standard labs	81/76 (median)	None	51/51- Tranexamic acid 2/10- Aprotinin	PFA-100
Girdauskas *et al.*	27/29	64/6 (mean)	Complex aortic surgery	ROTEM	Clinician discretion and standard labs	197/208 (mean)	1/1- Warfarin 9/8- Acetylsalicylic acid	27/29- Tranexamic acid	None
Karkouti *et al.*	3,847/3,555	67/67 (median)	All cardiac surgery patients undergoing CPB	ROTEM	Standard institutional practice	100/98 (median)	Not specified	3660/3357- Tranexamic acid	TEM, platelet works
Kultufan Turan *et al.*	20/20	51/55 (mean)	Patients undergoing cardiac surgery- valve + other	ROTEG	Standard labs	Not specified	Not specified	Not specified	None
Nuttall *et al.*	41/51	69/68 (median)	Elective cardiac surgery with CPB- CABG, valve, CABG+ valve, other	TEG	Clinician discretion and standard labs	110/112 (median)	14/8- Warfarin 10/9- Heparin IV 17/23- Acetylsalicylic acid	26/27- Tranexamic acid 8/15- Aprotinin	Whole blood PT and aPTT, platelet counts by Coulter
Paniagua *et al.**	26/18	Not specified	All cardiac surgery patients undergoing CPB and major postoperative bleeding (> 300 mL in first hour)	ROTEM	Standard labs	Not specified	Not specified	Not specified	None
Royston *et al.*	30/30	Not specified	Cardiac surgery with CPB- transplant, CABG, valve, other	TEG	Clinician discretion and standard labs	Not specified	3/3- Acetylsalicylic acid or warfarin	None	None
Shore-Lesserson *et al.*	53/52	64/67 (mean)	Single or multi valve, CABG + valve, reoperation, aortic replacement	TEG	Standard labs	163/167 (mean)	None	53/52- Amicar	None
Weber *et al.*	50/50	72/70 (mean)	CABG+valve, double or triple valve, aortic surgery or redo	ROTEM	Standard labs	148/166 (mean)	Not specified	Not specified	Platelet function aggregometry

Table 1 continued

Study	N (V/Ctl)	Age (V/Ctl)	Population	Intervention	Control	CPB time (min) (V/Ctl)	Preoperative anticoagulation (n - V/Ctl)	Intraoperative antifibrinolytics (n-V/Ctl)	Adjunctive POC tests
Westbrook *et al.*	32/37	66/61 (mean)	All patients presenting for cardiac surgery	TEG	Clinician discretion and standard labs	Not specified	5/4- Warfarin 3/2- Heparin IV 8/9- Acetylsalicylic acid 2/1- Plavix	13/13- Aprotinin	TEG platelet mapping

aPTT = activated partial thromboplastin time; CAB = coronary artery bypass grafting; CPB = cardiopulmonary bypass; Ctl = control; PFA = platelet function analyzer; POC = point-of-care; PT = prothrombin; ROTEM = rotational thromboelastometry; TEG = thromboelastography; V = viscoelastic tests. *Preliminary data presented in abstract, complete data presented in review paper[23]

The effect estimate of the proportion of patients transfused with FP was heterogeneous with an I^2 value of 87%. To further explore this result, a *post hoc* sensitivity analysis was performed based on trial design (Appendix 7). This illustrated that the data from the cluster RCT[9] showed no significant benefit associated with viscoelastic testing and was likely an outlier. In our analysis, the loss of significance when combining the individual products into one outcome is likely driven by the FP data from the cluster RCT, given its large size and weight within the analysis. We were unable to meta-analyze the data for the volume of RBCs and FP transfused. While there may be a trend of decreased FP transfusion across individual trials, it was not possible to arrive at a definitive conclusion regarding the influence of viscoelastic testing on the number of units transfused. Overall, the transfusion-related data were substantially heterogeneous, highlighting the variability in transfusion practice across centres that can be influenced by product availability, centre-specific transfusion culture, clinician preference, use of local transfusion protocols, and secular trends over time. Adherence to transfusion protocols may be limited by the multiple environmental factors that influence transfusion practice. Some of these factors (i.e., product availability) may be modifiable, while changes in culture and institutional tradition can be much harder to achieve.

There have been several recent systematic reviews concerning the use of POC viscoelastic testing in bleeding patients.[27-31] Four of these reviews showed no significant difference in all-cause mortality in the ROTEM/TEG compared with the control groups.[27-30] None of the reviews included data from the large cluster RCT for the pooled mortality estimate.[9] POC testing primarily reduces the delay in identifying the specific mediators of an underlying medical coagulopathy, and is typically implemented as part of a transfusion algorithm. In patients undergoing complex surgery, transfusion is only one of many potential variables affecting mortality, and so it is acknowledged that it may be exceedingly difficult to establish a robust association.

Our systematic review and meta-analysis has several strengths. It is the only study focused on RCTs that are specifically concerned with adult cardiac surgery patients and it is the first analysis to include the proportion of patients receiving any blood product and all-cause mortality data from the recent multi-centre cluster RCT.[9] Our review's thoroughness is evidenced by our extensive database and grey literature search using librarian supported search strategies. All of the screening and data extraction were done in duplicate and we evaluated the internal validity of included trials using the Cochrane Risk of Bias tool.

Table 2 Units of packed red blood cells and frozen plasma transfused

Study	Effect measure	POC test	Control	*P* value
RED BLOOD CELLS				
Ak *et al.*	Median [IQR]	1 [0-1]	1 [1-2]	0.60
Girdauskas *et al.*	Median [IQR]	6 [2-13]	9 [4-14]	0.20
Karkouti *et al.*	RR (95% CI)	-	-	0.06
Nuttall *et al.*	Median (range)	0 (0-6)	1 (0-6)	0.01*
Paniagua *et al.*	Mean (SD), mL	1774 (1394)	1604 (1366)	Not reported
Shore-Lesserson *et al.*	Mean (SD), mL	354 (487)	475 (593)	0.12
Weber *et al.*	Median [IQR]	3 [2-6]	5 [4-9]	< 0.001*
Westbrook *et al.*	Total units	14	33	Reported "not significant"
FROZEN PLASMA				
Ak *et al.*	Median [IQR]	1 [1-1]	1 [1-2]	0.001*
Girdauskas *et al.*	Median [IQR]	3 [0-12]	8 [4-18]	0.01*
Karkouti *et al.*	RR (95% CI)	-	-	0.26
Kultufan Turan *et al.*	Mean (range)	2.8 (2-6)	2.7 (1-6)	0.40
Nuttall *et al.*	Median (range)	2 (0-8)	3 (0-10)	0.002*
Paniagua *et al.*	Mean (SD), mL	36 (142)	217 (463)	Not reported
Shore-Lesserson *et al.*	Mean (SD), mL	36 (142)	217 (463)	< 0.04*
Weber *et al.*	Median [IQR]	0 [0-3]	5 [3-8]	< 0.001*
Westbrook *et al.*	Total units	18	22	Reported "not significant"

CI = confidence interval; IQR = interquartile range; POC = point-of-care; SD = standard deviation; *denotes significant at $P < 0.05$ level

Table 3 Summary of the meta-analysis of secondary outcomes

Outcome	Trials	Number of patients (*n*)	Effect estimate (95% CI)	I^2
RBC: proportion transfused	7	8,029	RR, 0.91 (0.85 to 0.96)	0%
FP: proportion transfused	6	7,989	RR, 0.58 (0.34 to 0.99)	87%
Platelets: proportion transfused	7	8,029	RR, 0.66 (0.49 to 0.90)	65%
Platelets: number of units	4	7,643	SMD, −0.09 (−0.18 to 0.00)	0%
Reoperation for bleeding	7	739	RR, 0.74 (0.42 to 1.31)	0%
ICU length of stay	5	493	MD, −1.85 (−5.16 to 1.47)	23%
Hospital length of stay	5	493	MD, −0.14 (−1.81 to 1.54)	48%

CI = confidence interval; FP = frozen plasma; ICU = intensive care unit; I^2 = I squared; MD = mean difference; RBC = red blood cells; RR = risk ratio; SMD = standard mean difference

Our review also has limitations. The reporting of primary and secondary outcomes in the literature we assessed was variable and often incomplete. Of the eleven included trials, four included data on the proportion of patients transfused with any blood product and six reviewed all-cause mortality. Safety data were especially lacking. For some transfusion outcomes, we detected substantial statistical heterogeneity necessitating exploratory subgroup analyses. It is possible that some of this heterogeneity may be related to variability in test interpretation and equipment calibration that were not accounted for in our analysis. None of the included trials were adjudicated to be at "low risk" of bias primarily because of lack of reporting consistent with the PRISMA checklist. We acknowledge that, while blood conservation can reduce cost, viscoelastic testing is also an expense. We did not examine whether the reduction in blood product use with viscoelastic testing was cost effective, but this is an outcome worthy of future consideration.

Conclusion

In cardiac surgery patients, POC viscoelastic hemostatic testing was not associated with a reduction in the proportion of patients receiving any blood product or all-cause mortality. However, viscoelastic testing was weakly associated with a reduction in proportion of patients

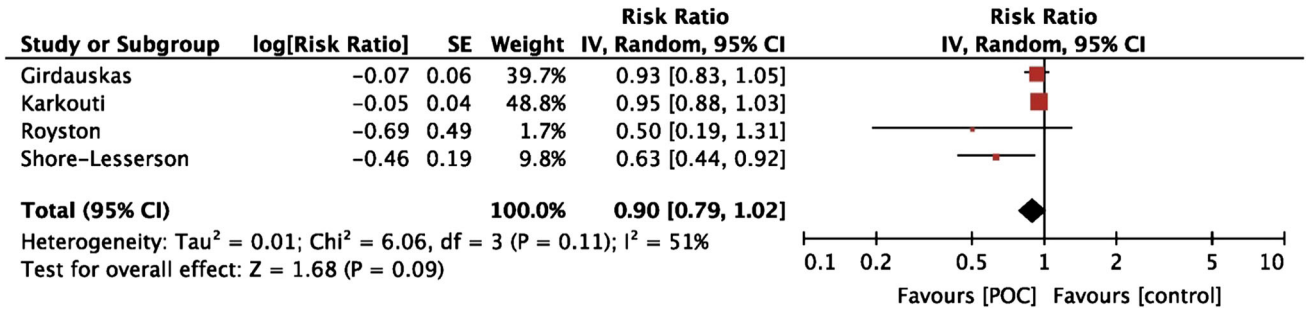

Fig. 3 Forest plot of proportion of patients receiving any blood product. The point estimates and 95% confidence intervals of each trial are displayed in the forest plot with the summary estimate provided below. Chi^2 = Chi-squared, df = degrees of freedom, I^2 = I squared, P = *P* value, Tau^2 = Tau-squared, Z= Z score

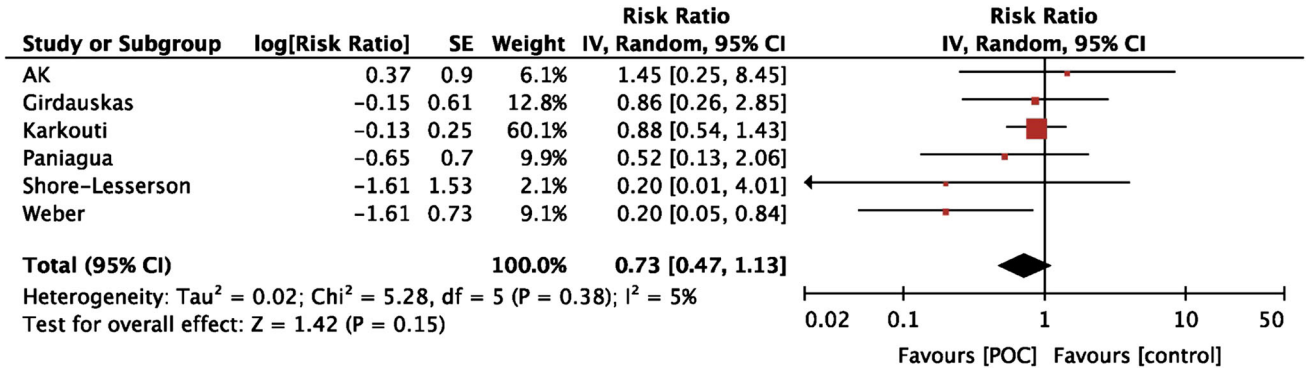

Fig. 4 Forest plot of all-cause mortality at longest follow-up interval. The point estimates and 95% confidence intervals of each trial are displayed in the forest plot with the summary estimate provided below. Chi^2= Chi-squared, df = degrees of freedom, I^2= I squared, P = *P* value, Tau^2 = Tau-squared, Z = Z score

transfused with specific blood products. At present, benefits conferred by viscoelastic testing are not sufficiently robust to recommend the universal implementation of this technology in adult patients undergoing cardiac surgical procedures.

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Conflicts of interest None declared.

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Author contributions *Carly Lodewyks* coordinated all aspects of the review, assisted with the literature search, screened relevant material, extracted and analyzed data, and prepared the final manuscript; *Jeffrey Heinrichs* assisted with screening relevant material, and extracting data in duplicate; two cardiac anesthesiologists (*Hilary P. Grocott* and *Keyvan Karkouti*) and one hematologist/critical care physician (*Ryan Zarychanski*) provided content expertise and methodological advice; one librarian with expertise in systematic review search methodology designed and executed the literature search strategies (*Grace Romund*); one clinician/researcher with expertise in conducting systematic reviews provided technical and methodological advice (*Ahmed Abou-Setta*); one senior biostatistician (*Rasheda Rabbani*) provided methodological expertise on statistical analysis; two clinician/researchers assisted with project planning and manuscript preparation (*Rakesh C. Arora* and *Navdeep Tangri*).

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Appendix 1 Interpretation of thromboelastography (TEG) and rotational thromboelastometry (ROTEM) test results

While the overall results from both TEG and ROTEM testing convey similar messages, their design and output formats are different. With TEG, clotting parameters are shown on a single graph. If the time to initiation of clot formation (R value) is prolonged, a deficiency in coagulation factors or presence of an anticoagulant is presumed and replacement with frozen plasma (FP) or reversal of the anticoagulant should be initiated. If the time to achieve a fixed clot strength (K time) or the rate of clot formation (alpha angle) is increased, fibrinogen is likely deficient and may be replaced with cryoprecipitate or fibrinogen concentrate. The maximum amplitude (MA)

indicates fibrin clot strength and stability. If it is decreased, platelet count and/or function may be abnormal and platelet administration should be considered. Finally, fibrinolysis is evaluated by assessing the amplitude at 30 min (LY30) following the MA measurement. If fibrinolysis is increased, tranexamic acid may be administered.

Rotational thromboelastometry provides four separate tracings to evaluate analogous components of clotting and include the clotting time (similar to the R value), alpha angle/clot formation time (similar to the K value/alpha angle), maximum clot firmness (similar to the MA), and clot lysis (similar to the LY30). Depending on the configuration, ROTEM tracings evaluate specific aspects of the clotting cascade, including the intrinsic and extrinsic clotting pathways, in addition to assessing measures of fibrinolysis and heparinization. Thromboelastography and ROTEM testing can be combined to more comprehensively evaluate platelet function. Blood product transfusion administration should be guided by abnormal test results combined with evidence of ongoing medical bleed

Appendix 2 Medline search strategy

#	Searches	Results
1	thoracic surgery/	11927
2	exp cardiovascular surgical procedures/	333550
3	(heart adj3 (surger* or surgic*).ti,ab.	18878
4	(cardiothoracic adj3 (surger* or surgic*)).ti,ab.	265
5	(cardiothoracic adj3 (surger* or surgic*)).ti,ab.	2315
6	(thoracic adj3 (surger* or surgic*)).ti,ab.	13074
7	(cardiovascular adj3 (surger* or surgic*)).ti,ab.	48
8	(cardiovascular adj3 (surger* or surgic*)).ti,ab.	5029
9	(cardiac adj3 (surger* or surgic*)).ti,ab. [1-9 cardiac surgery]	38770
10	exp extracorporeal circulation/	62323
11	exp heart-lung machine/	2059
12	(cardiopulmonary adj3 bypass).ti,ab.	401
13	(cardiopulmonary adj3 bypass).ti,ab.	28041
14	CPB.ti,ab.	9095
15	(on adj3 pump adj3 (surger* or surgic*)).ti,ab.	656
16	"heart-lung machine".ti,ab.	728
17	(heart adj3 bypass).ti,ab.	1726
18	(cardiac adj3 bypass).ti,ab.	1456
19	extracorporeal circulation.ti,ab.	291
20	"extracorporeal circulation".ti,ab. [10-20 bypass]	7251
21	or/1-20 [cardiac OR bypass surgery]	424361
22	exp thrombelastography/	4294
23	blood coagulation tests/	18043
24	whole blood coagulation time/	1255
25	thromb?elastograph*.ti,ab.	3081
26	thromb?elastogram*.ti,ab.	468
27	thromb?elastometr*.ti,ab.	876
28	(visco-elastic adj3 (test* or assay? or analy*)).ti,ab.	26
29	(viscoelastic adj3 (test* or assay? or analy*)).ti,ab.	483
30	"TEG".ti,ab.	1555
31	"ROTEM".ti,ab.	609
32	"ROTEG".ti,ab.	16
33	(("point-of-care" or "POC") adj3 h?emostatic adj3 (test* or assay? or analy*)).ti,ab.	17
34	or/22-33 [TEG/ROTEM]	24450
35	21 and 34	2013
36	exp randomized controlled trials as topic/	111809
37	exp randomized controlled trial/	449033
38	random allocation/	89907
39	double blind method/	143395
40	single blind method/	23793
41	clinical trial/	508394
42	clinical trial, phase i.pt.	18008
43	clinical trial, phase ii.pt.	29027
44	clinical trial, phase iii.pt.	13154
45	clinical trial, phase iv.pt.	1407
46	controlled clinical trial.pt.	91965
47	randomized controlled trial.pt.	448874
48	multicentre study.pt.	219457
49	trial.ti.	174706
50	RCT.ti.	992
51	RCTs.ti.	339
52	exp clinical trials as topic/	304776
53	(clinical adj trial$).tw.	288260
54	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	153084
55	PLACEBOS/	34202
56	placebo$.tw.	189981
57	randomly allocated.tw.	22494
58	(allocated adj2 random$).tw.	25427
59	or/36-58	1426845
60	(letter not (letter and randomized controlled trial)).pt.	950119
61	editorial/	426986
62	comment/	679573
63	interview/	27409
64	news/	181035
65	historical article/	339268
66	or/60-65	2056207
67	59 not 66 [RCT filter - modified SIGN filter]	1366513
68	animals/ not (animals/ and humans/)	4292692
69	67 not 68 [animals filter]	1286595
70	35 and 69	441

Appendix 3 Mortality: subgroup analysis of trials comparing viscoelastic testing *vs* control

Subgroup	Studies	Effect estimate (95% CI)	I^2	Across subgroups
CLINICAL CONSIDERATIONS				
Procedure urgency				
Elective	2	RR, 0.50 (0.07 to 3.47)	66%	*P* 0.64
Urgent/emergent	0	NE	NE	I^2 0%
Not specified/all comers	4	RR, 0.81 (0.53 to 1.24)	0%	
Procedure complexity				
Simple	1	RR, 1.45 (0.25 to 8.45)	NE	*P* 0.57
Complex	2	RR, 0.44 (0.11 to 1.83)	58%	I^2 0%
Multiple types/all comers/not specified	3	RR, 0.80 (0.51 to 1.26)	0%	
METHODOLOGICAL CONSIDERATIONS				
Risk of bias				
Low risk	0	NE	NE	NE
Unclear/high risk	6	RR, 0.73 (0.47 to 1.13)	5%	
Funding source				
No industry sponsorship	1	RR, 0.2 (0.05 to 0.85)	NE	*P* 0.15
Industry sponsored	1	RR, 0.88 (0.54 to 1.43)	NE	I^2 5%
Not specified	4	RR, 0.74 (0.34 to 1.60)	0%	

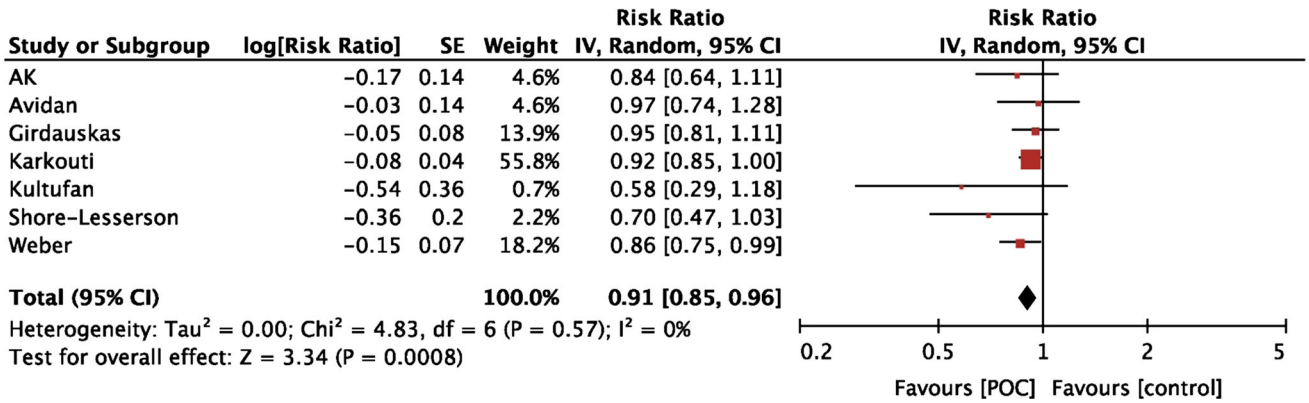
CI = confidence interval; I^2 = I squared; NE = not estimable; RR= risk ratio

Appendix 4 Proportion of patients receiving any blood product: subgroup analysis of trials comparing viscoelastic testing *vs* control

Subgroup	Studies	Effect estimate (95% CI)	I^2	Across subgroups
CLINICAL CONSIDERATIONS				
Procedure urgency				
Elective	0	NE	NE	NE
Urgent/emergent	0	NE	NE	
Not specified/all comers	4	RR, 0.90 (0.79 to 1.02)	51%	
Procedure complexity				
Simple	0	NE	NE	NE
Complex	1	RR, 0.93 (0.83 to 1.05)	NE	
Multiple types/all comers/not specified	3	RR, 0.76 (0.53 to 1.11)	67%	
METHODOLOGICAL CONSIDERATIONS				
Risk of bias				
Low risk	0	NE	NE	NE
Unclear/high risk	4	RR, 0.90 (0.79 to 1.02)	51%	
Funding source				
No industry sponsorship	0	NE	NE	NE
Industry sponsored	1	RR, 0.95 (0.88 to 1.03)	NE	
Not specified	3	RR, 0.76 (0.53 to1.08)	62%	

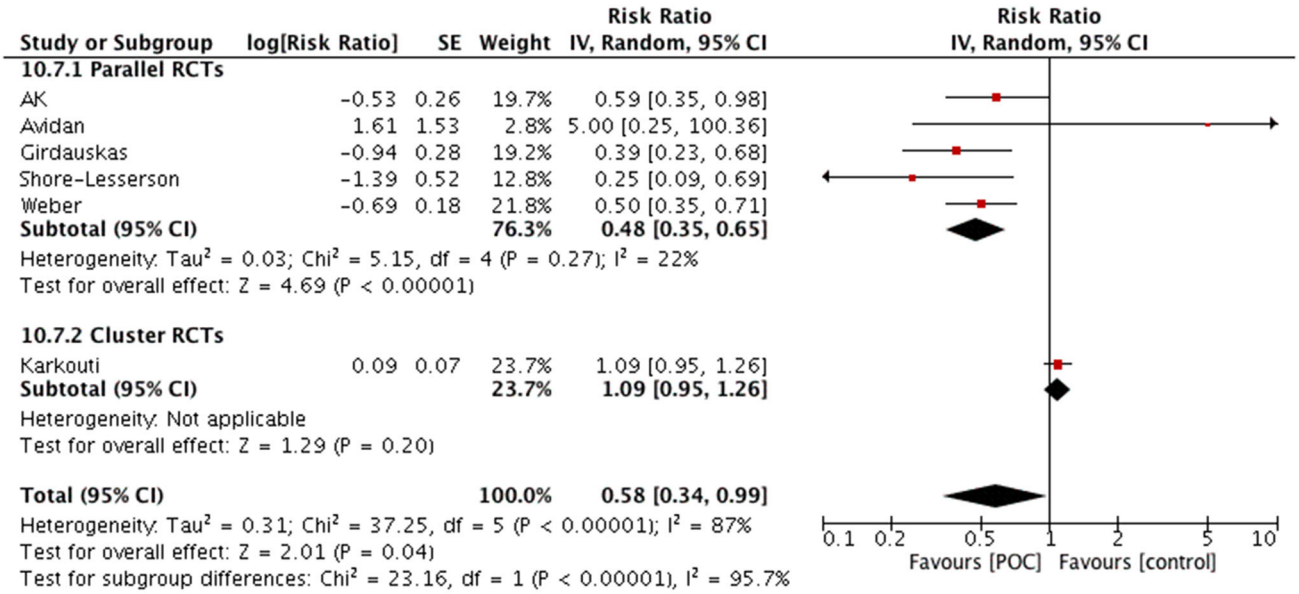
CI = confidence interval; I^2= I squared; NE = not estimable; RR = risk ratio

Appendix 5 Forest plot for the proportion of patients receiving red blood cell transfusion



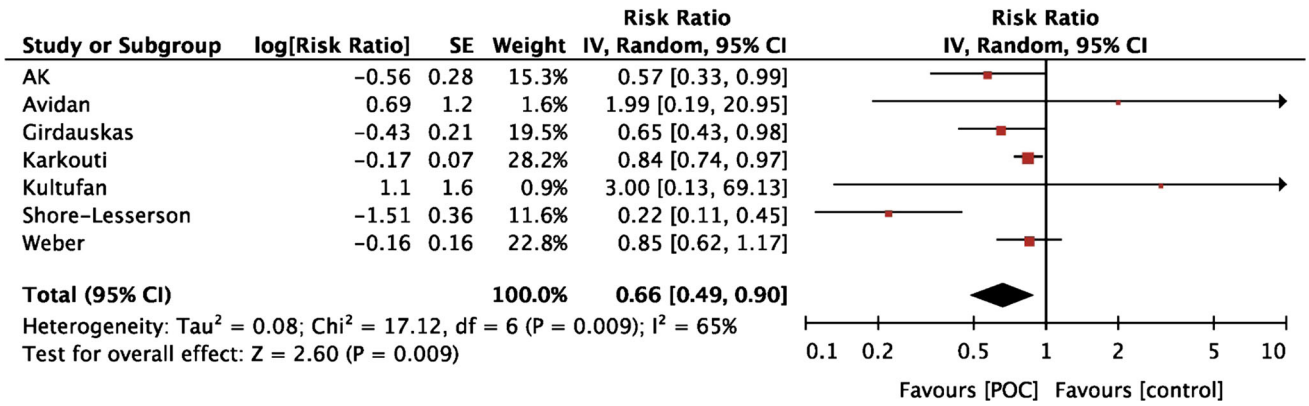
CI = confidence interval; IV = **inverse variance;** POC = point-of-care; SE = standard error.

Appendix 6 Forest plots for the proportion of patients receiving frozen plasma including sensitivity analysis by trial design



CI = confidence interval; IV = **inverse variance**; POC = point-of-care; RCT = randomized controlled trial; SE = standard error.

Appendix 7 Forest plot for the proportion of patients receiving platelet transfusion



CI = confidence interval; IV = **inverse variance;** POC = point-of-care; RCT = randomized controlled trial; SE = standard error.

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