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The effect of non-point-of-care haemostasis management protocol implementation in cardiac surgery: A systematic review

Reinier P. J. Boxma[1] | Robert P. Garnier[1] | Carolien S. E. Bulte[1] | Michael I. Meesters[2]

[1]Department of Anesthesiology, Amsterdam University Medical Center, Location VU Medical Center, Amsterdam, The Netherlands

[2]Department of Anesthesiology, Catharina Hospital Eindhoven, Eindhoven, The Netherlands

Correspondence
Reinier P. J. Boxma, Department of Anesthesiology, Amsterdam University Medical Centers, Location VU Medical Center, De Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands.
Email: r.boxma@amsterdamumc.nl

Abstract

Objectives: This systematic review aims to outline the evidence on the implementation of a non-point-of-care (non-point-of-care [POC]) haemostasis management protocol compared to experience-based practice in adult cardiac surgery.

Background: Management of coagulopathy in cardiac surgery is complex and remains highly variable among centres and physicians. Although various guidelines recommend the implementation of a transfusion protocol, the literature on this topic has never been systematically reviewed.

Methods: PubMed, Embase, Cochrane Library, and Web of Science were searched from January 2000 till May 2020.

Results: A total of seven studies (one randomised controlled trial [RCT], one prospective cohort study, and five retrospective studies) met the inclusion criteria. Among the six non-randomised, controlled studies, the risk of bias was determined to be serious to critical, and the one RCT was determined to have a high risk of bias. Five studies showed a significant reduction in red blood cells, fresh frozen plasma, and/or platelet transfusion after the implementation of a structural non-POC algorithm, ranging from 2% to 28%, 2% to 19.5%, and 7% to17%, respectively. One study found that fewer patients required transfusion of any blood component in the protocol group. Another study had reported a significantly increased transfusion rate of platelet concentrate in the haemostasis algorithm group.

Conclusion: Owing to the high heterogeneity and a substantial risk of bias of the included studies, no conclusion can be drawn on the additive value of the implementation of a cardiac-surgery-specific non-POC transfusion and haemostasis management algorithm compared to experience-based practice. To define the exact impact of a transfusion protocol on blood product transfusion, bleeding, and adverse events, well-designed prospective clinical trials are required.

KEYWORDS
cardiac surgery, haemostasis, protocol, transfusion

1 | INTRODUCTION

Cardiac surgery is associated with major blood loss and the subsequent need for allogeneic blood transfusion. The origin of coagulopathy is multifactorial, owing to the invasiveness of the procedure, use of anticoagulants, and exposure to the extracorporeal bypass circuit.[1] This makes management of coagulopathy complex in this setting. Although patient blood management has greatly improved over the last decades,[2] there still remains wide variation in transfusion rates among different centres.[3–5] An explanation might be the differences in transfusion practices among institutions and physicians.

To overcome this heterogeneity in practice, various guidelines support the use of a haemostasis algorithm for the management of non-surgical (i.e., coagulopathic) bleeding, aiming to improve outcome.[6–8] This algorithmic approach can be guided by point-of-care (POC) haemostasis monitoring (e.g., TEG®, ROTEM®, Multiplate®, or VerifyNow®) to identify the underlying cause of bleeding. In the last decades, much emphasis has been placed on the use of these devices in cardiac surgery. While the first studies showed impressive results, more recent data indicate reduced benefit from the implementation of POC coagulation management.[9–11] In many studies, these devices were implemented in combination with a structural haemostasis management protocol, leading to the investigation of two interventions in the study group, which might bias the results.[12–16]

We hypothesised that the implementation of a structural non-POC haemostasis management protocol by itself would reduce bleeding and transfusion compared to experience-based practice. Therefore, we performed a systematic review of the literature to investigate the effect of the implementation of a non-POC-based haemostasis management protocol on blood components transfusion in adult cardiac surgery.

2 | METHOD

The systematic review was performed in accordance with the recommendation for systematic reviews[17] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. PubMed, Embase, Wiley/Cochrane Library, and Clarivate Analytics/Web of Science Core Collection were searched from inception until 6 May 2020 (R. B., J. C. F. K., and M. M.). Search strategies were developed specifically for each database. The following question was the fundamental for the literature search: 'Does the implementation of a non-POC guided haemostasis management protocol lead to a reduction in transfusion in cardiac surgery?'[18]

Participants undergoing cardiothoracic surgical procedures with or without cardiopulmonary bypass were considered eligible. Randomised controlled trials (RCTs), retrospective cohort studies, and matched case–control studies were included when evaluating the effect of transfusion requirements after the implementation of a non-POC guided haemostasis management protocol compared to the clinician's judgement with or without the guidance of conventional coagulation tests. Conventional coagulation tests included the following: prothrombin time (PT), activated partial thromboplastin time, activated clotting time, fibrinogen, and thrombocyte count. In line with the current European guideline on haemostasis and transfusion in cardiac surgery,[7] only studies published from 2000 onwards were considered eligible, as patient blood management strategies, surgical techniques, and cardiopulmonary bypass practice before 2000 differ greatly from current practice. We excluded case reports, non-English language, animal studies, use of (POC) haemostasis monitoring (e.g., TEG®, ROTEM®, Multiplate®, or VerifyNow®), and studies including patients below 18 years of age. PubMed, Embase, Wiley/Cochrane Library, and Clarivate Analytics/Web of Science Core Collection were searched from inception until 6 May 2020 (R. B., J. C. F. K., and M. M.), using thesaurus for cardiothoracic surgery, algorithm/protocol, and bleeding/transfusion. Data S1 shows the full search strategy per database.

Two reviewers (R. B. and R. G.) independently screened the titles retrieved from the search for potential eligibility. The selected titles were merged, duplicates were removed, and the subsequent results were further screened by abstract. This was repeated after the abstract selection, leading to the full text selection. The subsequent papers were read and, when relevant, included in the final selection. The references of all included papers were also screened for possible eligibility.

Two authors (R. B. and C. B.) independently assessed the risk of bias using the Cochrane Collaborations Risk of Bias Tool for Randomised Trials[19] and Risk of Bias in Non-randomised Studies of Interventions for prospective and retrospective studies.[20] If additional information was required for the systematic review, the authors of the included studies were requested to provide this information. A standardised form was used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information included the following variables: year of publication, study design, sample size, type of surgery, blood component transfusion rate, in-hospital mortality, chest tube drainage, rethoracotomy, and information for assessment of the risk of bias. Data extraction forms were completed by one author (R. B.) and checked by another (M. M.).

The primary outcome included the proportion of patients transfused with allogeneic blood, including red blood cell (RBC), fresh frozen plasma (FFP), and platelet (PLT) concentrates. The secondary outcomes were adverse events, including in-hospital mortality, chest tube drainage, and rethoracotomy. Data collection included author, publication date, study design, participants, type of operation, blood product transfusion rate, in-hospital mortality, chest tube drainage, and rethoracotomy.

3 | RESULTS

3.1 | Patient characteristics

After the selection process, seven publications were identified investigating a non-POC-guided haemostasis management protocol in cardiac surgery compared to experience-based practice

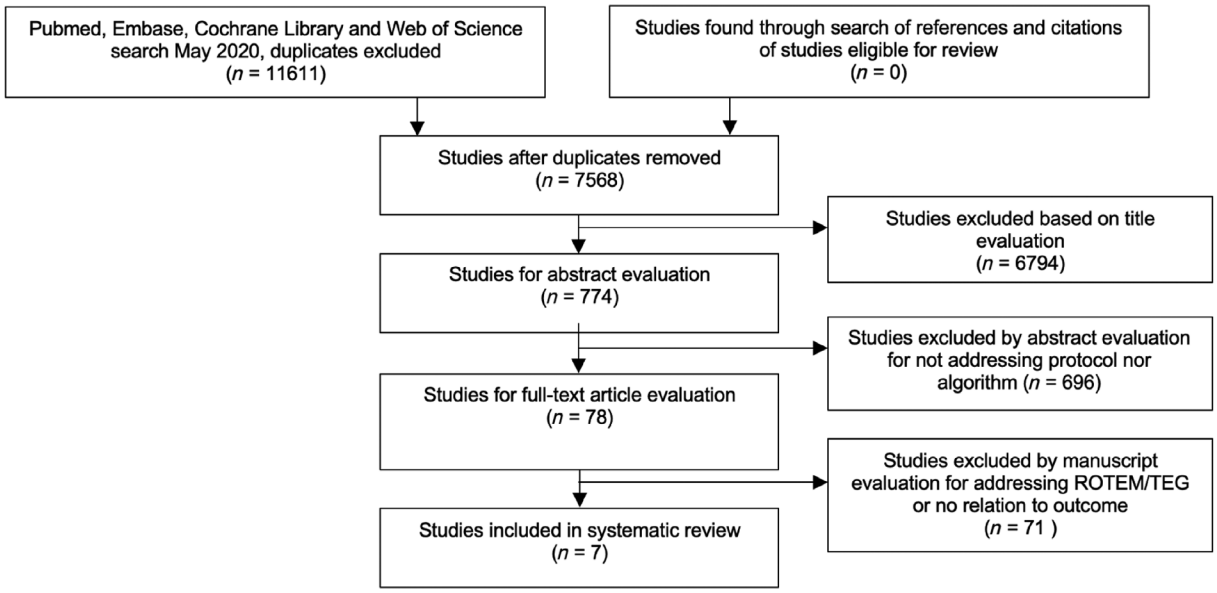

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

TABLE 1 Details of the randomised studies

				Transfusion and haemostasis management	
Study	**Design**	***n***	**Population**	**Control group**	**Intervention group**
Capraro et al.[21]	RCT	58	Mixed elective cardiac surgery, bleeding >1.5 ml/kg 15 min after first mediastinal drains emptying	Conventional coagulation tests were prohibited and only ACT after heparin neutralisation was performed	Conventional coagulation tests: thrombocyte count, PT, aPTT, ACT
				Transfusion based on clinical discretion No transfusion triggers reported	Transfusion according to an algorithm with sequential order of treatment modalities during the immediate recovery period (1 h after surgery): Step 1: Hb <90 g/L: 1 unit of RBC and new haemoglobin measurement before each RBC unit Step 2: Thrombo <100 × 10^9/L: 1 unit of PLT/10 kg, round up to the nearest full 4 units Step 3: aPTT or PT 1.5× normal value: FFP 10 ml/kg Step 4: ACT >10 s than preoperative ACT: protamine 0.5 mg/kg Step 5: Bleeding time > 12 min: DDAVP 0.3 μg/kg Step 6: Normal values in all previous tests: tranexamic acid 10 mg/kg

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; DDAVP, desmopressin; FFP, fresh frozen plasma; Hb, haemoglobin; PLT, platelet; PT, prothrombin time; RBC, red blood cells; RCT, randomised controlled trial.

(Figure 1).[21–27] In total, 8555 patients were included in this systematic review. The study populations included mixed cardiac surgery,[22,23,26] isolated coronary artery bypass graft (CABG) surgery,[27] pulmonary endarterectomy,[25] and cardiac surgery patients with excessive blood loss.[21,24] Details concerning the transfusion and haemostasis management practice in the control group and intervention group of the included studies are reported in Tables 1 and 2.

3.2 | Study characteristics

The final selection included one RCT, one prospective cohort study, and five retrospective cohort studies.[21–27] The one RCT was determined to have a high risk of bias. Among the six non-randomised controlled studies, the risk of bias was determined to be serious to critical, as shown in Table 3. A detailed assessment of the risk of bias is available in Data S2.

TABLE 2 Details of the non-randomised studies included in the systematic review

Study	Design	*n*	Population	Transfusion and haemostasis management	
				Control group	**Intervention group**
Bilecen et al.[22]	RC	5219	Mixed cardiac surgery	Conventional coagulation test: thrombocyte count Transfusion based on the discretion of the anesthesiologist Transfusion triggers reported: • RBC transfusion: Hb < 4.0 mmol/L in healthy normovolemic patients, blood loss from one locus (age 60 year) Hb < 5.0 mmol/L in healthy normovolemic patients, blood loss form one locus (age > 60 years) or multiple loci (age < 60 years) Hb < 6.0 mmol/L patients with severe heart or lung disease (age not relevant) • PLT transfusion: thrombocyte count <100 × 10^9 • FFP transfusion trigger was not clear	Conventional coagulation tests: thrombocyte count, aPTT, PT, fibrinogen, ACT, Ca^{2+} Implementing cell saver blood in the decision to transfuse blood products Transfusion according to an algorithm with sequential order of treatment modalities: Step 1: Start surgery: Heparin initial dose (4 mg/kg) and tranexamic acid 2 g Step 2: Pre-end CPB: • Hb < 5.0 mmoL/L, Hct < 0.23: 1 unit of RBC • Thrombo <80 × 10^9/L: 1 unit of PLT • Plasma loss >1 L: 2 units of FFP • Plasma loss >2 L: 4 units of FFP • Loss >50% circ. vol.: 4 units of FFP • Fibrinogen <1.2 g/L: 4 units of FFP • DDAVP 0.3 μg/kg, if ≥1 factor present: anti-PLT therapy, Ao stenosis surgery, CPB time >180 min or • urgent/emergent procedure Step 3: Post-CPB • Tranexamic acid 1 g • Microvascular bleeding and ACT >140 s: protamine antagonise 1:1 • Microvacsulair bleeding, if yes: Hb <5.3 mmol/L or Hct < 0.25: 1× unit of RBC; Thrombo <80 × 10^9/L: 1× unit of PLT; Plasma loss >1 L: 2 units of FFP; Plasma loss >2 L, >50% circ. vol. or fibrinogen <1.2 g/L: 4 units of FFP Step 4: Post-CPB • Microvascular bleeding: 1 unit PLT or 2 units of FFP; if not given previously • ACT >140 s: protamine antagonise • Laboratory: Ca^{2+}, blood gas analysis, thrombocyten count, fibrinogen, aPTT/PT Step 5: Post-CPB: Microvacsulair bleeding and ACT <140 s, if yes: Thrombo <80 × 10^9/L: 1× unit of PLT; Plasma loss >1 L and thrombo >80 × 10^9/L: 2 units of FFP; Plasma loss >2 L, >50% circ. vol. or fibrinogen <1.2 g/L: 4 units of FFP Step 6: Microvascular bleeding persists: all patients 2 g fibrinogen. If fibrinogen <1 g/L: 2 g extra fibrinogen
Ereth et al.[23]	RC	975	Mixed cardiac surgery	Conventional coagulation tests not mentioned Transfusion timing based on clinical discretion No transfusion triggers reported	Coagulation and haemostatic test: details not mentioned (abstract information) Transfusion according to an algorithm with pre-set coagulation and haemostatic test values guide transfusion (no further information available)
Karkouti et al.[24]	RC	1875	Mixed cardiac surgery with excessive blood loss and received ≥4 RBC within the first day of surgery	Conventional coagulation tests not mentioned Transfusion timing based on informal clinical guidelines No transfusion triggers reported	Conventional coagulation tests: thrombocyte count, aPTT/PT, fibrinogen, ACT, ionised calcium Transfusion according to an algorithm with sequential order of treatment modalities: Step 1: • Top-up antifibrinolytics/protamine: If early bleed and aprotinin used, continue at 50 000 KIU/h; if tranexamic acid used or late bleed, consider tranexamic acid bolus 50 mg/kg. Protamine: Target ACT within 10% of baseline or until there is no response to additional protamine administration. • Consider DDAVP (16–20 mcg) • Laboratory: blood gas analysis, Hct, Lytes, Ca^{2+}, complete blood count (heamoglobin, platelet count), aPTT/PT, fibrinogen

(Continues)

TABLE 2 (Continued)

Study	Design	*n*	Population	Transfusion and haemostasis management	
				Control group	**Intervention group**
					Step 2: • Rule out surgical source: prolonged (>2 h) exploration post-CPB during original surgery or return to operation room for re-exploration • Avoid/correct anaemia: RBC transfusion to keep Hct > 24% • Correct (potential) coagulopathy: Thrombo <80× 10^9/L: 5 units of platelets; INR > 1.5: 2–4 units of FFP; Fib <1.0 g/L: 8 units of cryoprecipitate Step 3: Consider rFVIIa (2.4–4.8 mg up to two doses) if: • ≥2 L blood loss • ≥4 units of RBC/≥5 units of platelets/≥4 units of FFP • Hct >24%/thrombo >80 × 10^9/L/INR < 1.5/Fibrinogen >1 g/L
McRae et al.[25]	RC	25	Elective PEA for CTEPH	Conventional coagulation tests: thrombocyte count, INR, ACT, and fibrinogen	Conventional coagulation tests: thrombocyte count, INR, ACT, and fibrinogen
				Transfusion based on the discretion of the anesthesiologist Transfusion triggers reported: • RBC transfusion: Hb < 80–90 g/L • PLT transfusion: thrombocyte count 50-100 × 10^9 • FFP transfusion: INR > 2	Transfusion according to an algorithm with sequential order of treatment modalities: Step 1: Start surgery • Autologous blood predonation in patients with a preoperative Hb >130 g/L • Standardised use of cell-saver technique • Use antifibrinolytics (aprotinin [08/2005–10/2007] and tranexamic acid [10/2007–03/2009] was standardised) Step 2: Pre-end CPB: Autologous blood reinfused before heparin reversal with protamine. Step 3: Post-CPB • Ongoing bleeding associated with an abnormal INR: ○ FFP transfusion (10–15 ml/kg) ○ PLT transfusion, if: persistent bleeding despite administration of FFP or patient had known underlying platelet disorder ○ RBC transfusion, if: Hb < 80 g/L or Hct <25% • INR >2 and absence of ongoing clinical bleeding: no treatment, allowed to drift down spontaneously and intravenous infusion of unfractioned heparin was started 4–6 h post-operatively or INR <2
Rosenthal et al.[26]	PC	152	Mixed elective cardiac surgery	Conventional coagulation tests: not mentioned	Conventional coagulation tests not mentioned (abstract information)
				Transfusion based on clinical discretion No transfusion triggers reported	Transfusion according to a guideline-based standard operating procedure for transfusion triggers (no further information available)
Silva et al.[27]	RC	251	Elective and emergency CABG. No use of CPB: control group 94% vs. intervention group 91%	Conventional coagulation tests: not mentioned	Conventional coagulation tests: thrombocyte count, INR
				Transfusion based on clinical discretion No transfusion triggers reported	Epsilon-aminocaproic acid use was standardised Protocol with criteria to perform transfusion for: • RBC transfusion: ○ Hb <11 g/dl in patients with unstable coronary disease ○ Hb <10 g/dl for patients in clinical situations with risk more elevated for bleeding or low intraoperative tissue perfusion, falciform anaemia, thalassemia, age over 65 years old, etc.

TABLE 2 (Continued)

Study	Design	*n*	Population	Transfusion and haemostasis management	
				Control group	Intervention group
					○ Hb < 10 g/dl and symptomatic anaemia without specific treatment ○ Hb 7–10 g/dl in patients with risk to cardiac ischemia in preoperative period ○ Hb <7 g/dl in asymptomatic patient in the perioperative period; ○ Acute anaemia caused by bleeding with clinical criteria of low tissue perfusion such as tachycardia, hypotension, late capillary refill, tachypnea, low urinary output, altered mental status. • PLT transfusion: ○ Active bleeding with thrombo <50 ml/mm^3 ○ Platelet dysfunction with active bleeding ○ Thrombo <20 000 associated with chemotherapy, tumour invasion, leukaemia or bone marrow aplasia. • FFP transfusion: ○ Active bleeding followed by multiple coagulation factor deficiency; ○ Hepatopathy patients with ISI >1.5 and with signals of active bleeding or in preoperatory period.

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; Ca^{2+}, ionised calcium; CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; CTEPH, chronic thromboembolic pulmonary hypertension; DDAVP, desmopressin; FFP, fresh frozen plasma; Hb, haemoglobin; Hct, haemotocrit; INR, International Normalised Ratio; ISI, International Standard Index; PC, prospective cohort; PEA, pulmonary endarterectomy; PLT, platelet; PT, prothrombin time; RBC, red blood cells; RC, retrospective cohort; rFVIIa, Recombinant factor VIIa.

TABLE 3 Risk of bias of the included studies

Cochrane Collaborations Risk of Bias Tool for Randomised Trials		Risk of bias in non-randomised studies of interventions						
Bias domain	Capraro et al. 2001	Bias domain	Bilecen et al. 2014	Ereth et al. 2012	Karkouti et al. 2006	McRae et al. 2011	Rosenthal et al. 2013	Silva et al. 2013
Random sequence generation (selection bias)	High risk	Due to confounding	Serious risk	Critical risk	Critical risk	Serious risk	Critical risk	Critical risk
Allocation concealment (selection bias)	High risk	Selection of participants	Low risk	No information	Moderate risk	Low risk	Low risk	Low risk
Blinding of participants and personnel (performance bias)	High risk	Classification of intervention	Low risk	No information	Low risk	Low risk	No information	Low risk
Blinding of outcome assessment (detection bias)	High risk	Deviations from intended interventions	Moderate risk	No information	Serious risk	No information	No information	Low risk
Incomplete outcome data (attrition bias)	Low risk	Missing data	Low risk	No information	No information	Low risk	No information	No information
Selective reporting (reporting bias)	Unclear	Measurement of outcomes	Low risk	No information	Low risk	Low risk	No information	Low risk
Other bias	Unclear risk	Selection of reported results	Low risk	No information	Low risk	Low risk	No information	Low risk
Overall bias	High risk	Overall bias	Serious risk	Critical risk	Critical risk	Serious risk	Critical risk	Critical risk

3.3 | Primary outcome

Five studies showed a significant reduction of transfused RBC, FFP, and/or PLT after the implementation of a structural non-POC transfusion and haemostasis protocol in mixed cardiac surgery and CABG surgery. These five studies combined form the vast majority of the included patients (8472 out of the total 8555 patients). In these studies, the reduction in RBC, FFP, and PLT transfusion ranged from 2% to 28%, 2% to19.5%, and 7% to 17%, respectively (Table 4).[22–24,26,27]

In the study of Bilecen et al., patients undergoing mixed cardiac surgery accounted for more than 60% of the patients included in this systematic review. The study showed no difference between the control and intervention group regarding the mean amount of transfusion of RBC, FFP, and PLTs. Regarding the proportion of patients transfused, significantly fewer patients were transfused with RBC (29% vs. 27%; $p < 0.05$) and FFP (11% vs. 9%; $p < 0.05$) after the implementation of a non-POC transfusion algorithm.[22]

Karkouti et al. implemented a haemostasis protocol among patients with excessive blood loss, defined as transfusion of ≥4 RBC units within the first day of surgery. The number of RBC transfusions remained unchanged despite the higher transfusion trigger for RBC transfusion after the implementation of a haemostasis algorithm (haematocrit trigger increase from 18% to 20%). Still, the percentage of patients requiring FFP and PLT transfusion decreased. Interestingly, in categorical analysis, an increase in massive FFP transfusion (>11 units) was found in the haemostasis protocol group (9% vs. 14%), which might be explained by an increased incidence of complex surgery in the haemostasis algorithm group.[24]

Silva et al. implemented a transfusion protocol in patients undergoing isolated CABG surgery of which the majority used cardiopulmonary bypass (94% vs. 91%, *p*-value: not significant). This resulted in a decreased amount of RBC, FFP, and PLT transfusion of 28%, 13%, and 11%, respectively.[27]

The study of Ereth et al. successfully implemented a transfusion protocol in mixed cardiac surgery. The study showed a reduction in blood component exposure of RBC, FFP, and also PLT (16.2%, 19.5%, and 17%, respectively).[23] The study of Rosenthal et al. showed a decrease in the number of transfused patients (40.5% vs. 18.2%) and RBC transfusion requirements (26.2% vs. 10.9%) in elective cardiac surgery patients.[26]

The small retrospective study of McRae et al. introduced a transfusion algorithm in patients with chronic thromboembolic pulmonary hypertension undergoing elective pulmonary endarterectomy. The percentage of patients requiring transfusion of any blood components reduced significantly after the implementation of a transfusion algorithm (89% vs. 44%).[25]

Capraro et al. conducted a randomised controlled trial, with a small sample size, in patients undergoing elective mixed cardiac surgery with an increased bleeding tendency after heparin neutralisation (i.e., bleeding >1.5 ml/kg in 15 min after the mediastinal drains were emptied for the first time). This was the only study reporting an increased rate of PLT transfusion (10% vs. 50%; $p = 0.001$) after the implementation of a haemostasis management algorithm during the first post-operative hour. The other rates of blood component transfusion were similar among the groups.[21]

3.4 | Secondary outcome

None of the studies found a difference in rethoracotomies or in-hospital mortality among the groups (Table 5).[21–24,27] Three studies reported on post-operative blood loss, of which one study found a significant difference in post-operative chest tube drainage in favour of the introduction of a non-POC haemostasis protocol compared to standard therapy.[21,23,25]

4 | DISCUSSION

Bleeding after cardiac surgery is common and frequently due to haemostatic disturbances with a multifactorial origin.[1] To date, treatment of post-operative coagulopathy remains highly variable among centres and physicians.[3–5] In order to guide and make uniform haemostasis treatment, many institutions have developed haemostasis treatment protocols. Although several guidelines recommend the use of these transfusion algorithms, its evidence has not been well outlined.[6,7,28] This systematic review included several studies which concluded that the implementation of a cardiac surgery-specific haemostasis management protocol (not based on POC monitoring) might contribute to a reduction in blood component transfusion compared to experience-based transfusion practice. However, all studies had a serious to critical risk of bias, which hampered the deduction of the additive value of these transfusion protocols. Therefore, the principal finding of this systematic review is that no conclusions can be drawn on the additive value of a non-POC haemostasis protocol compared to experience-based practice in cardiac surgery.

The quality of the evidence was low because of several factors. In terms of heterogeneity, in various included trials the intervention group differed in several important aspects from the control group. In some studies, only the intervention group routinely received tranexamic acid.[21,22,24] As tranexamic acid has been shown to reduce bleeding and transfusion, this might have influenced the results.[29] Moreover, some studies introduced the use of a cell saver technique to reduce RBC transfusion with the implementation of a structural transfusion algorithm.[22,25] A recently published meta-analysis showed that cell salvage tends to decrease the rate of RBC transfusion in cardiac surgery, possibly biasing the results.[30] Furthermore, McRae et al. implemented autologous blood predonation in patients with preoperative haemoglobin >130 g/L in the intervention group.[25] This technique has proven to reduce blood product transfusion, limiting the results.[31]

The randomised controlled trial of Capraro et al. was the only study that demonstrated a significant increase in the transfusion of platelet concentrate during the immediate recovery period (1 h after

TABLE 4 Blood component usage

Study	Study design	Effect measure	Subanalysis	Control	Intervention	OR (95% CI), *p*-value	Risk of bias[a]
All blood component transfusion							
Bilecen et al.	RC	Mean	Units transfused per patient	1.46	1.29	NS	Serious
		%	Patients transfused	33	31	0.74 (0.60–0.92)	
Capraro et al.	RCT	Mean (SD)	Units transfused during total hospitalisation	14.4 (14.0)	17.2 (17.2)	NS	High
Karkouti et al.	RC	Median (IQR)	Units transfused per patient	15 [9–24]	14 [7–25]	NS	Critical
McRae et al.	RC	%	Patients transfused	89	44	0.04	Serious
Rosenthal et al.	PC	%	Patients transfused	40.5	18.2	<0.05	Critical
Red blood cells							
Bilecen et al.	RC	Mean	Units transfused per patient	0.88	0.78	NS	Serious
		%	Patients transfused	29	27	0.69 (0.55–0.86)	
Capraro et al.	RCT	Mean (SD)	Units transfused during total hospitalisation	5.7 (5.6)	6.5 (5.6)	NS	High
Ereth et al.	RC	%	Patients transfused	65.6	49.4	<0.0001	Critical
		Mean (SD)	Units transfused per patient	2.6 (3.62)	1.5 (2.37)	<0.0001	
Karkouti et al.	RC	%	Patients transfused 4–6 units	69	69	NS	Critical
			Patients transfused 7–12 units	20	20		
			Patients transfused >12 units	12	11		
McRae et al.	RC	%	Patients transfused	67	37	NS	Serious
Rosenthal et al.	PC	%	Patients transfused	26.2	10.9	<0.05	Critical
Silva et al.	RC	%	Patients transfused	64	36	<0.001	Critical
Fresh frozen plasma							
Bilecen et al.	RC	Mean	Units transfused per patient	0.47	0.37	NS	Serious
		%	Patients transfused	11	9	0.63 (0.46–0.86)	
Capraro et al.	RCT	%	Patients transfused in recovery period (1 h after surgery)	23.3	10.7	NS	High
		Mean (SD)	Units transfused during total hospitalisation	2.3 (2.3)	2.0 (2.6)	NS	
Ereth et al.	RC	%	Patients transfused	46.8	27.3	<0.0001	Critical
		Mean (SD)	Units transfused per patient	1.7 (2.72)	0.8 (1.89)	<0.0001	
Karkouti et al.	RC	%	Patients transfused 0 units	17	23	<0.05	Critical
			Patients transfused 1–4 units	47	36		
			Patients transfused 5–11 units	27	28		
			Patients transfused >11 units	9	14		
McRae et al.	RC	%	Patients transfused	56	12	NS	Serious
Silva et al.	RC	%	Patients transfused	20	7	<0.001	Critical
Platelets							
Bilecen et al.	RC	Mean	Units transfused per patient	0.12	0.13	NS	Serious
		%	Patients transfused	9	10	NS	
Capraro et al.	RCT	%	Patients transfused in recovery period (1 h after surgery)	10	50	0.001	High
		Mean (SD)	Units transfused during total hospitalisation	6.5 (7.5)	8.7 (10.1)	NS	
Ereth et al.	RC	%	Patients transfused	43.4	26.4	<0.0001	Critical
		Mean (SD)	Units transfused per patient	0.8 (1.31)	0.4 (0.85)	<0.0001	
Karkouti et al.	RC	%	Patients transfused 0 units	29	36	<0.05	Critical
			Patients transfused 1–10 units	54	52		

(Continues)

TABLE 4 (Continued)

Study	Study design	Effect measure	Subanalysis	Control	Intervention	OR (95% CI), *p*-value	Risk of bias[a]
			Patients transfused 11–15 units	8	7		
			Patients transfused >15 units	10	6		
McRae et al.	RC	%	Patients transfused	44	19	NS	Serious
Silva et al.		%	Patients transfused	15	4	<0.001	Critical

Abbreviations: [], interquartile range; (), standard deviation; IQR, interquartile range; PC, prospective cohort; RC, retrospective cohort; RCT, randomised controlled trial; NS, non-significant result.
[a]Risk of bias in non-randomised Studies of Interventions and Cochrane Collaborations Risk of Bias Tool for Randomised Trials.

TABLE 5 Secondary outcomes

Study	Study design	Effect measure	Control	Intervention	*p*-Value	Risk of bias[a]
In-hospital mortality						
Bilicen et al.	RC	%	2.5	2.3	NS	Serious
Capraro et al.	RCT	%	3	0	NS	High
Karkouti et al.	RC	%	8.3	6.0	NS	Critical
Silva et al.	RC	%	3	3	NS	Critical
Rethoracotomy						
Bilicen et al.	RC	%	8.2	9.5	NS	Serious
Capraro et al.	RCT	%	23	21	NS	High
Ereth et al.	RC	%	3.2	3.1	NS	Critical
Karkouti et al.	RC	%	27	26	NS	Critical
Silva et al.	RC	%	18	15	NS	Critical
Chest tube drainage during post-operative period						
Capraro et al.	RCT		Exact number not reported	Exact number not reported	NS	High
Ereth et al.	RC	ml mean (SD)	498 (533)	335 (323)	<0.0001	Critical
McRae et al.	RC		Exact number not reported	Exact number not reported	NS	Serious

Abbreviations: (), standard deviation; NS, non-significant result; RC, retrospective cohort; RCT, randomised controlled trial.
[a]Risk of Bias in Non-randomised Studies of Interventions and Cochrane Collaborations Risk of Bias Tool for Randomised Trials.

surgery). However, the haemostasis management algorithm was solely implemented during the first post-operative hour. Additionally, the number of patients undergoing combined procedures was significantly higher in the intervention group, which likely contributed to increased thrombocyte transfusion.[21,32] Furthermore, with the exception of the studies of Bilecen et al., McRae et al., and Capraro et al. it was unclear which conventional coagulation tests were performed in the control group.[21,22,25]

Another limitation of our review is that most studies were limited by their retrospective sequential design and subsequent risk of bias. The implementation of a transfusion algorithm and conduct of a study raises awareness for patient blood management, which might bias the results in non-randomised studies (Hawthorn effect). This is a bias to be considered in all of the included observational studies. This hypothesis is substantiated by previous studies, which have shown that patient blood management education programmes by themselves lead to a reduction in blood component utilisation.[33] Notably, Silva et al. introduced such an educational campaign among their healthcare personnel (i.e., surgical, anaesthesia, and intensive therapy teams) in the intervention group.[27] This increase in awareness of the implemented transfusion protocol may have contributed to fewer patients requiring transfusion. Furthermore, the study of Silva et al. reported that several patients had undergone CABG without cardiopulmonary bypass. As procedures without cardiopulmonary bypass are associated with reduced transfusion requirements, this could have influenced the results.[34] However, off-pump coronary artery bypass patients were evenly distributed among the groups, reducing the risk of bias.[27] Still, a study solely including on- or off-pump surgery would have been of higher quality.

Additionally, protocol adherence was not assessed in the included studies. It has been shown that adherence to introduced haemostasis algorithms is frequently modest, which might result in a reduced effect of the intervention.[35] Finally, in two of the included studies, only the abstract information was available, leading to a lack of relevant information concerning the details of their transfusion algorithm and additional interventions.[23,26] All of the above-mentioned

limitations, in addition to evaluation of the risk on bias as shown in Table 3, lead to the fact that no conclusion can be drawn on the additive value of transfusion protocols not based on POC tests.

A recent survey did not show any wide-spread implementation of transfusion protocols in cardiac surgery. The survey was performed among Australian cardiac surgeons, cardiac anaesthesiologists, and perfusionists and reported that just over half of the respondents (54%) use a haemostasis management algorithm.[36] Frequently, POC haemostasis tests are used to guide haemostasis transfusion protocols. In the last decades, great emphasis has been placed on the use of these devices to provide rapid assessment of haemostasis and guidance of bleeding management. However, POC tests of coagulation are still not routinely available in many medical centres.[6]

Various meta-analyses on the use of these devices suggested a significant reduction in transfusion requirements. However, also these reviews are limited by the low quality of the available evidence.[9–11] Furthermore, whether the reduced transfusion rate is a result of the implementation of POC testing or due to simultaneous implementation of a structural transfusion and haemostasis management protocol remains unclear in various studies.[12–16]

In conclusion, due to the high heterogeneity and a substantial risk of bias of the included studies, no conclusion can be drawn on the additive value of the implementation of a cardiac surgery-specific non-POC transfusion and haemostasis management algorithm compared to experience-based practice. To define the exact impact of a transfusion protocol on blood product transfusion, bleeding, and adverse events, well-designed prospective clinical trials are required.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

Reinier P. J. Boxma: Data selection, drafting, data processing, assessment of included studies, and manuscript revision. **Robert P. Garnier**: Data selection, manuscript revision. **Carolien S. E. Bulte**: Assessment of included studies, manuscript revision. **Michael I. Meesters**: Coordination of data selection and drafting, reviewing, and editing of manuscript.

REFERENCES

1. Meesters MI, von Heymann C. Optimizing perioperative blood and coagulation management during cardiac surgery. *Anesthesiol Clin*. 2019;37:713-728.
2. Vonk AB, Meesters MI, van Dijk WB, et al. Ten-year paterns in blood product utilization during cardiothoracic surgery with cardiopulmonary bypass in a tertiary hospital. *Transfusion*. 2014;54:2608-2616.
3. Bennett-Guerrero E, Zhao Y, O'Brien SM, et al. Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA*. 2010;304:1568-1575.
4. Snyder-Ramos SA, Möhnle P, Weng YS, et al.; Investigators of the Multicenter Study of Perioperative Ischemia; MCSPI Research Group. The ongoing variability in blood transfusion practices in cardiac surgery. *Transfusion*. 2008;48:1284-1299.
5. Colson PH, Gaudard P, Fellahi JL, et al. Active bleeding after cardiac surgery: a prospective observational multicenter study. *PLoS One*. 2016;11:e0162396.
6. Raphael J, Mazer CD, Subramani S, et al. Society of Cardiovascular Anesthesiologists Clinical Practice Improvement Advisory for management of perioperative bleeding and hemostasis in cardiac surgery patients. *Anesth Analg*. 2019;129:1209-1221.
7. Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA), Boer C, Meesters MI, et al. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *J Cardiothorac Vasc Anesth*. 2018;32:88-120.
8. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg*. 2011;91:944-982.
9. Lodewyks C, Heinrichs J, Grocott HP, et al. Point-of-care viscoelastic hemostatic testing in cardiac surgery patients: a systematic review and meta-analysis. *Can J Anaesth*. 2018;65:1333-1347.
10. Li C, Zhao Q, Yang K, Jiang L, Yu J. Thromboelastography or rotational thromboelastometry for bleeding management in adults undergoing cardiac surgery: a systematic review with meta-analysis and trial sequential analysis. *J Thorac Dis*. 2019;11:1170-1181.
11. Serraino GF, Murphy GJ. Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis. *Br J Anaesth*. 2017;118:823-833.
12. Karkouti K, Callum J, Wijeysundera DN, et al. Point-of-care hemostatic testing in cardiac surgery: a stepped-wedge clustered randomized controlled trial. *Circulation*. 2016;134:1152-1162.
13. Westbrook AJ, Olsen J, Bailey M, Bates J, Scully M, Salamonsen RF. Protocol based on thromboelastograph (TEG) out-performs physician preference using laboratory coagulation tests to guide blood replacement during and after cardiac surgery: a pilot study. *Heart Lung Circ*. 2009;18:277-288.
14. Nuttall GA, Oliver WC, Santrach PJ, et al. Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after cardiopulmonary bypass. *Anesthesiology*. 2001;94:773-781.
15. Fassl J, Matt P, Eckstein F, et al. Transfusion of allogeneic blood products in proximal aortic surgery with hypothermic circulatory arrest: effect of thromboelastometry-guided transfusion management. *J Cardiothorac Vasc Anesth*. 2013;27:1181-1188.
16. Royston D, von Kier S. Reduced haemostatic factor transfusion using heparinase-modified thrombelastography during cardiopulmonary bypass. *Br J Anaesth*. 2001;86:575-578.
17. Møller AM, Myles PS. What makes a good systematic review and meta-analysis? *Br J Anaesth*. 2016;117:428-430.
18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62:e1-e34.
19. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
20. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.

21. Capraro L, Kuitunen A, Salmenperä M, Kekomäki R. On-site coagulation monitoring does not affect hemostatic outcome after cardiac surgery. *Acta Anaesthesiol Scand*. 2001;45:200-206.
22. Bilecen S, de Groot JA, Kalkman CJ, Spanjersberg AJ, Moons KG, Nierich AP. Effectiveness of a cardiac surgery-specific transfusion protocol. *Transfusion*. 2014;54:708-716.
23. Ereth MH, Kor DJ, Nuttall GA, et al. Transfusion algorithms reduce blood use and acute kidney injury in cardiac surgery. *Transfus Altern in Transfus Med*. 2012;12:2.
24. Karkouti K, Yau TM, Av R, et al. The effects of a treatment protocol for cardiac surgical patients with excessive blood loss on clinical outcomes. *Vox Sang*. 2006;91:148-156.
25. McRae K, Shargall Y, Ma M, et al. Feasibility of blood conservation strategies in pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *Interact Cardiovasc Thorac Surg*. 2011;13:35-38.
26. Rosenthal C, Wicht J, Sander M, Knipprath U, Von Heymann C. Implementation of Standard Operating Procedures (SOPs) for transfusion triggers reduces intraoperative transfusion requirements in elective cardiac-surgery. *Transfus Med Hemother*. 2013;40(suppl 1):63.
27. Silva PG, Ikeoka DT, Fernandes VA, et al. Implementation of an institutional protocol for rational use of blood products and its impact on postoperative of coronary artery bypass graft surgery. *Einstein (Sao Paulo)*. 2013;11:310-316.
28. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiology*. 2015;122:241-275.
29. Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. *N Engl J Med*. 2017;376:136-148.
30. Al Khabori M, Al Riyami A, Siddiqi MS, Sarfaraz ZK, Ziadinov E, Al SH. Impact of cell saver during cardiac surgery on blood transfusion requirements: a systematic review and meta-analysis. *Vox Sang*. 2019;114:553-565.
31. Zimmermann E, Zhu R, Ogami T, et al. Intraoperative autologous blood donation leads to fewer transfusions in cardiac surgery. *Ann Thorac Surg*. 2019;108:1738-1744.
32. Hardy JF, Perrault J, Tremblay N, Robitaille D, Blain R, Carrier M. The stratification of cardiac surgical procedures according to use of blood products: a retrospective analysis of 1480 cases. *Can J Anaesth*. 1991;38:511-517.
33. Beaty CA, Haggerty KA, Moser MG, et al. Disclosure of physician-specific behavior improves blood utilization protocol adherence in cardiac surgery. *Ann Thorac Surg*. 2013;96:2168-2174.
34. Zhang P, Wang L, Zhai K, et al. Off-pump versus on-pump redo coronary artery bypass grafting: a systematic review and meta-analysis. *Perfusion*. 2020;267659120960310.
35. Shehata N, Burns LA, Nathan H, et al. A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. *Transfusion*. 2012;52:91-99.
36. Pearse BL, Keogh S, Rickard C, et al. Bleeding Management Practices of Australian Cardiac Surgeons, Anesthesiologists and Perfusionists: a cross-sectional National Survey Incorporating the theoretical domains framework (TDF) and COM-B model. *J Multidiscip Healthc*. 2020;13:27-41.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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