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

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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% to 17%, 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

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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. This makes management of coagulopathy complex in this setting. Although patient blood management has greatly improved over the last decades, there still remains wide variation in transfusion rates among different centres. 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. 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. 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.

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 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?’

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, 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.

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

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.
In total, 8555 patients were included in this systematic review. The study populations included mixed cardiac surgery, isolated coronary artery bypass graft (CABG) surgery, pulmonary endarterectomy, and cardiac surgery patients with excessive blood loss. 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. 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                                                                 | Control group                                                                                      | Intervention group                                                                                     |
|------------------|--------|-------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Bilecen et al.22 | RC     | 5219  | Mixed cardiac surgery                                                       | Conventional coagulation test: thrombocyte count                                                    | Conventional coagulation tests: thrombocyte count, aPTT, PT, fibrinogen, ACT, Ca<sup>2+</sup>            |
|                  |        |       |                                                                             | Transfusion based on the discretion of the anesthesiologist                                       | Implementing cell saver blood in the decision to transfuse blood products                             |
|                  |        |       |                                                                             | Transfusion triggers reported:                                                                      | Transfusion according to an algorithm with sequential order of treatment modalities:                   |
|                  |        |       |                                                                             | • RBC transfusion:                                                                                    | Step 1: Start surgery: Heparin initial dose (4 mg/kg) and tranexamic acid 2 g                          |
|                  |        |       |                                                                             | Hb < 4.0 mmol/L in healthy normovolemic patients,                                                   | Step 2: Pre-end CPB:                                                                                    |
|                  |        |       |                                                                             | blood loss from one locus (age 60 year)                                                            | • Hb < 5.0 mmol/L, Hct < 0.23: 1 unit of RBC                                                        |
|                  |        |       |                                                                             | Hb < 5.0 mmol/L in healthy normovolemic patients,                                                   | • Thrombo <80 x 10<sup>9</sup>/L: 1 unit of PLT                                                      |
|                  |        |       |                                                                             | blood loss form one locus (age > 60 years) or multiple loci (age < 60 years)                        | • Plasma loss >1 L: 2 units of FFP                                                                   |
|                  |        |       |                                                                             | Hb < 6.0 mmol/L patients with severe heart or lung disease (age not relevant)                        | • Plasma loss >2 L: 4 units of FFP                                                                   |
|                  |        |       |                                                                             | • PLT transfusion:                                                                                    | • Loss >50% circ. vol.: 4 units of FFP                                                               |
|                  |        |       |                                                                             | thrombocyte count <100 x 10<sup>9</sup>                                                              | • Fibrinogen <1.2 g/L: 4 units of FFP                                                               |
|                  |        |       |                                                                             | FFP transfusion trigger was not clear                                                                | • DDAVP 0.3 µg/kg, if ≥1 factor present: anti-PLT therapy, Ao stenosis surgery, CPB time >180 min or |
|                  |        |       |                                                                             |                                                                                                     | • urgent/emergent procedure                                                                         |
| Ereth et al.23   | RC     | 975   | Mixed cardiac surgery                                                       | Coagulation and haemostatic test: details not mentioned (abstract information)                      |                                                                                                     |
|                  |        |       |                                                                             | Transfusion timing based on clinical discretion                                                     | Transfusion according to an algorithm with pre-set coagulation and haemostatic test values guide transfusion |
|                  |        |       |                                                                             | No transfusion triggers reported                                                                    | (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                                                        | Conventional coagulation tests: thrombocyte count, aPTT/PT, fibrinogen, ACT, ionised calcium         |
|                  |        |       |                                                                             | Transfusion timing based on informal clinical guidelines                                             | Transfusion according to an algorithm with sequential order of treatment modalities:                  |
|                  |        |       |                                                                             | No transfusion triggers reported                                                                    | Step 1:                                                                                               |
|                  |        |       |                                                                             |                                                                                                     | • Top-up antifibrinolytics/protamine: If early bleed and aprotinin used, continue at 50 000 KIU/hr; 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<sup>2+</sup>, complete blood count (haemoglobin, platelet count), aPTT/PT, fibrinogen |

**Notes:**
- RBC: Red Blood Cell
- PLT: Platelet
- FFP: Fresh Frozen Plasma
- Hb: Haemoglobin
- Hct: Haematocrit
- aPTT: Activated Partial Thromboplastin Time
- PT: Prothrombin Time
- ACT: Activated Clotting Time
- Ca<sup>2+</sup>: Ionised Calcium
- DDAVP: Desmopressin
- Ao: Aortic
- CPB: Cardiopulmonary Bypass
- RBC transfusion: Red Blood Cell transfusion
- PLT transfusion: Platelet transfusion
- FFP transfusion trigger: Fresh Frozen Plasma transfusion trigger
- Microvascular bleeding: Microvascular bleeding
- ACT: Activated Clotting Time
- aPTT/PT: Activated Partial Thromboplastin Time/Prothrombin Time
- fibrinogen: Fibrinogen
### TABLE 2 (Continued)

| Study                        | Design n | Population               | Control group | Intervention group |
|------------------------------|----------|--------------------------|---------------|--------------------|
| McRae et al.25               | RC 25    | Elective PEA for CTEPH   | Conventional coagulation tests: thrombocyte count, INR, ACT, and fibrinogen | 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: |
|                              |          |                          |               | o FFP transfusion (10–15 ml/kg) |
|                              |          |                          |               | o PLT transfusion, if: persistent bleeding despite administration of FFP or patient had known underlying platelet disorder |
|                              |          |                          |               | o 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 (abstract information) | 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 | Epsilon-aminocaproic acid use was standardised Protocol with criteria to perform transfusion for: |
|                              |          |                          |               | • RBC transfusion: |
|                              |          |                          |               | o Hb <11 g/dl in patients with unstable coronary disease |
|                              |          |                          |               | o 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. |

(Continues)
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/mm³ |
|       |        |    |            | - 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 preoperative period. |

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; Ca²⁺, 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, haematocrit; 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                                     | 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            | No information     | Low risk           | Low risk           |
| Other bias                                                   | Unclear                                                | 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% to 19.5%, 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 inhospital 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.5 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
| Study                        | Study design | Effect measure     | Subanalysis | Control | Intervention | OR (95% CI), p-value | Risk of bias |
|-----------------------------|--------------|--------------------|-------------|---------|--------------|----------------------|--------------|
|                             |              |                   |             |         |              | p-value              |              |
|                             |              |                   |             |         |              |                     |              |
| **All blood component transfusion** |              |                   |             |         |              |                     |              |
| Bilecen et al. RC           | Mean         | Units transfused per patient | 1.46 | 1.29 | NS | 0.74 (0.60–0.92) | Serious |
| 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 | 0.69 (0.55–0.86) | Serious |
| Capraro et al. RCT          | Mean (SD)    | Units transfused during total hospitalisation | 5.7 (5.6) | 6.5 (5.6) | NS | <0.0001 | High |
| Ereth et al. RC             | %            | Patients transfused | 65.6 | 49.4 | <0.0001 |                      | Critical |
| Karkouti et al. RC          | %            | Patients transfused 4–6 units | 69 | 69 | NS |                      | Critical |
| McRae et al. RC             | %            | Patients transfused | 67 | 37 | NS | 0.63 (0.46–0.86) | 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 | 0.63 (0.46–0.86) | Serious |
| Capraro et al. RCT          | %            | Patients transfused | 23.3 | 10.7 | NS | 0.69 (0.55–0.86) | Serious |
| Ereth et al. RC             | Mean (SD)    | Units transfused during total hospitalisation | 2.3 (2.3) | 2.0 (2.6) | NS |                      | Critical |
| Karkouti et al. RC          | %            | Patients transfused | 46.8 | 27.3 | <0.0001 |                      | Critical |
| McRae et al. RC             | %            | Patients transfused | 17 | 23 | <0.05 |                      | Critical |
| Silva et al. RC             | %            | Patients transfused | 56 | 12 | NS | 0.63 (0.46–0.86) | Serious |
| **Platelets**               |              |                   |             |         |              |                     |              |
| Bilecen et al. RC           | Mean         | Units transfused per patient | 0.12 | 0.13 | NS | 0.63 (0.46–0.86) | Serious |
| Capraro et al. RCT          | %            | Patients transfused | 10 | 50 | 0.001 |                      | High |
| Ereth et al. RC             | %            | Patients transfused | 43.4 | 26.4 | <0.0001 |                      | Critical |
| Karkouti et al. RC          | %            | Patients transfused | 29 | 36 | <0.05 |                      | Critical |
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. 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.23 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 All of the above-mentioned

| 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. | RC | % | 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.

aRisk of bias in non-randomised Studies of Interventions and Cochrane Collaborations Risk of Bias Tool for Randomised Trials.

| Study | Study design | Effect measure | Control | Intervention | p-Value | Risk of bias a |
|-------|--------------|----------------|---------|--------------|---------|---------------|
|       |              |                |         |              |         |               |
|       |              |                |         |              |         |               |
| 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 |
| 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 |
| 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.

aRisk of Bias in Non-randomised Studies of Interventions and Cochrane Collaborations Risk of Bias Tool for Randomised Trials.
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.

ACKNOWLEDGEMENTS
We are grateful to Johannes C. F. Ket, literature researcher of the medical library, for his assistance with the literature search.

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.

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

How to cite this article: Boxma RPJ, Garnier RP, Bulte CSE, Meesters MI. The effect of non-point-of-care haemostasis management protocol implementation in cardiac surgery: A systematic review. Transfusion Medicine. 2021;1–11. https://doi.org/10.1111/tme.12790