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Review Article

REVIEW ARTICLE

Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis

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Abstract

Viscoelastic point-of-care tests are commonly used to provide prompt diagnosis of coagulopathy and allow targeted treatments in bleeding patients. We updated existing meta-analyses that have evaluated the clinical effectiveness of viscoelastic point-of-care tests *vs* the current standard of care for the management of cardiac surgery patients at risk of coagulopathic bleeding. Randomized controlled trials comparing viscoelastic point-of-care diagnostic testing with standard care in cardiac surgery patients were sought. All-cause mortality, blood loss, reoperation, blood transfusion, major morbidity, and intensive care unit and hospital length of stay were analysed using random-effects modelling. Fifteen trials that randomized a total of 8737 participants were included for the analysis. None of the trials was classified as low risk of bias. The use of thromboelastography- (TEG®) or thromboelastometry (ROTEM®)-guided algorithms did not reduce mortality [risk ratio (RR) 0.55, 95% confidence interval (CI) 0.28–1.10] without heterogeneity (I^2=1%), reoperation for bleeding, stroke, ventilation time, or hospital length of stay compared with standard care. Use of TEG® or ROTEM® resulted in reductions in the frequency of red blood cell (Risk Ratio 0.88, 95% Confidence Interval 0.79-0.97; I^2=43%) and platelet transfusion (Risk Ratio 0.78, 95% Confidence Interval 0.66-0.93; I^2=0%). Group Reading Assessment and Diagnostic Evaluation (GRADE) assessment demonstrated that the quality of the evidence was low or very low for all estimated outcomes. Routine use of viscoelastic point-of-care tests did not improve important clinical outcomes beyond transfusion in adults undergoing cardiac surgery.

Key words: cardiac surgical procedures; haemorrhage; review, systematic

Coagulopathic bleeding is a common and severe complication of cardiac surgery. Up to 5% of all cardiac surgery patients require emergency re-exploration for bleeding in the immediate postoperative period.[1] This is associated with a four-fold increase in mortality and resource use.[2–4] Viscoelastic point-of-care whole blood tests provide rapid quantitative assessments of global clotting and are commonly used to provide prompt diagnosis of coagulopathy and allow targeted treatment in bleeding patients. Existing National Institute for Health and Care Excellence (NICE) guidance recommends their routine use

Editor's key points

- Viscoelastic testing of whole blood coagulation is widely used to diagnose coagulopathic bleeding and guide treatment in cardiac surgery patients.
- In a systematic review and meta-analysis of randomized controlled trials, use of viscoelastic testing reduced red blood cell and platelet transfusion, but had no effect on mortality or major morbidity, except acute kidney injury.
- Viscoelastic testing is not effective in reducing mortality in cardiac surgery, and further large trials are unlikely to show such a benefit.

in the management of bleeding cardiac surgery patients.[5] A recent Cochrane review concluded that the existing trial evidence was insufficient to demonstrate that use of Viscoelastic testing improved clinical outcomes.[6] They recommended that a pragmatic multicentre randomized controlled trial (RCT) at low risk of bias be performed to address this knowledge gap. Karkouti and colleagues[7] have recently published such a trial, enrolling 7402 patients in 12 Canadian hospitals. The aim of the present study was to update existing meta-analyses that have evaluated viscoelastic tests to include this new evidence, and assess whether this will allow clearer conclusions with respect to the clinical benefits of these devices in cardiac surgery.

Methods

Protocol and registration

Search methods, data extraction, assessment, and presentation were performed as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1).[8] The analysis was specified in advance and documented on PROSPERO International prospective register of systematic reviews (CRD:42016033831) on January 31, 2016; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016033831 (accessed on January 1, 2017).

Eligibility criteria

Randomized controlled trials irrespective of blinding, language, publication status, date of publication, and sample size were considered eligible for this study. Participants of any age undergoing cardiac surgery for acquired or congenital disease or aortovascular disease with or without cardiopulmonary bypass were considered. No age restriction was applied. There were no exclusion criteria.

Type of intervention

We assessed trials evaluating the risks and benefits of the following viscoelastic point-of-care testing devices for coagulopathy: ROTEM (ROTEM® Delta; TEM International GmbH, Munich, Germany; www.rotem.de (accessed on January 18, 2017)), thromboelastography (TEG; TEG® 5000 analyser; Haemonetics Corporation, Niles, IL, USA; www.haemonetics.com (accessed on January 15, 2017)), or Sonoclot® Coagulation and Platelet Function Analyzer (Sienco Inc., CO, USA), alone or combined with platelet function testing.

Comparator

The comparator is represented by a combination of clinical judgement and standard laboratory tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT), activated clotting time, and plasma fibrinogen concentrations. We did not distinguish between these comparators for the purpose of this review.

Outcome measures

The primary outcome was 30 day or hospital all-cause mortality. The secondary outcomes were adverse events, including the following: reoperation for bleeding; red blood cell (RBC), platelet, fresh frozen plasma, fibrinogen, and prothrombin complex concentrate transfusion; acute kidney injury; cerebrovascular accident (stroke); myocardial infarction; ventilation time; and intensive care unit (ICU) and hospital length of stay (LoS).

Information sources

Potentially eligible trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL; Internet), Clinical Trials.gov, MEDLINE (PubMed 1946 to present), EMBASE (Ovid 1975 to present), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus (1979 to present), using a combination of subject headings and text words to identify relevant trials (see Supplementary material for detailed PubMed search criteria). The last search was run on December 3, 2016. In addition to searching databases, we searched in trials registries and we checked reference lists.

Study selection and data items

Two reviewers (G.J.M., G.F.S.) identified trials for inclusion independently of each other. Excluded studies and reasons for exclusion were recorded. Two authors independently screened search output to identify records of potentially eligible trials examining outcomes, the full texts of which were retrieved and assessed for inclusion. A standardized form was used to extract data from included studies for assessment of study quality and evidence synthesis. Extracted information included the following: year and language of publication; country of participant recruitment; year of conduct of the trial; study setting (university teaching hospital, non-university teaching hospital); study population, with inclusion and exclusion criteria; sample size; participant characteristics; baseline characteristics; type of surgery; outcomes and times of measurement; and information for assessment of the risk of bias.

Data extraction forms were completed by one author and checked by a second author. Likewise, quality assessment was done by one author and checked by a second.

Risk of bias in individual studies

The methodological quality of randomized trials was assessed using the Cochrane Collaboration's tools for assessing risk of bias in parallel group[9] and cluster[10] randomized trials. The items assessed for parallel group trials were as follows: (i) sequence generation; (ii) allocation concealment; (iii) blinding of outcome assessor; (iv) incomplete outcome data; (v) selective outcome reporting; and (vi) other sources of bias, including funder bias. Risk of bias was graded as unclear, high, or low. We graded sealed opaque envelopes as unclear evidence of allocation concealment. We also considered the absence of a prespecified protocol or trial registration of trial design as unclear evidence of reporting bias. Risk of bias in cluster-randomized trials was assessed as follows: (i) recruitment bias;

(ii) baseline imbalance; (iii) loss of clusters, incorrect analysis; and (iv) comparability with individually randomized trials.

Reporting bias

Where 10 or more studies are identified for each outcome, publication was assessed by the visual assessment of funnel plots and Egger's test.[11]

Missing data

We performed an intention-to-treat analysis where possible. For dichotomous data presented only as percentages, we estimated frequencies using reported sample sizes for this outcome. For continuous outcomes, if the mean and SD were not available from the trial report, we sought this information from the trial authors. When this information was still not available, we calculated the mean and SD from the median (interquartile range) using the software available in Review Manager Version 5.2.

Heterogeneity

We anticipated that major sources of clinical heterogeneity would be associated with different patient groups, use of different goal directed algorithms, use of co-interventions such as restrictive transfusion thresholds, and differences in methodology used to assess coagulative dysfunction. We explored heterogeneity within each meta-analysis using a χ^2 test with significance set at a $P<0.10$. We expressed the percentage of heterogeneity attributable to variation rather than to chance as I^2.[12] We defined heterogeneity as follows: I^2=0–40%, no or mild heterogeneity; I^2=40–80%, moderate heterogeneity; and I^2>80%, severe heterogeneity. In the presence of severe heterogeneity, meta-analysis was not performed.

Data synthesis

Meta-analysis was performed using the software package Review Manager version 5.2 and in accordance with recommendations of the Cochrane Handbook for Systematic Reviews of Intervention.[8] As a result of the inclusion of multiple small studies with significant heterogeneity, we presented the results of our random-effects models for the primary analyses. We also compared results of a random-effects model with a fixed-effects model to assess effects of small studies. Pooled effect estimates were expressed as risk ratios (RR) with the 95% confidence interval (CI). For continuous outcomes, we pooled mean differences (MD) or standardized mean differences (SMD) with 95% CI by using the inverse variance method.

Subgroup analyses were performed for different viscoelastic point-of-care testing devices and by participant group; coronary artery bypass graft (CABG) *vs* non-CABG. The test for subgroup differences with Review Manager was used, with a value of $P<0.05$ considered statistically significant.

Sensitivity analysis excluded trials with high risk of bias for any of the following: random sequence generation; allocation concealment; blinding of participants; health-care providers or outcome assessors; incomplete outcome data; attrition; and other sources of bias, including source of funder.

We presented the main results of the review in a 'summary of findings' table. We included the following outcomes: risk of mortality; risk of reoperation and bleeding; risk of RBC, FFB, and platelet transfusion; and resource use (ICU and hospital LoS).

We used GRADEpro software to prepare the 'summary of findings' table. We judged the overall quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' according to the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach. We considered the following: impact of risk of bias of individual trials; precision of pooled estimate; inconsistency or heterogeneity (clinical, methodological, and statistical); indirectness of evidence; and impact of selective reporting and publication bias on effect estimate.

Results

A total of 5125 abstracts were retrieved from the searches (Supplementary Fig. S1). There were 4570 articles excluded for duplicate publication, animal study, and reviews, and there were 533 articles excluded on the basis of title and abstracts. A total of 22 relevant publications were retrieved for further assessment. Fifteen trials that randomized a total of 8737 participants met the inclusion criteria and were included in the analysis.[7 13–26] Two of the included studies were published in abstract form.[17 22] The two review authors (G.J.M., G.F.S.) agreed on the selection of included studies. Key characteristics of individual studies are described in Table 1.

Included studies

Of the 15 trials identified, 13 enrolled adults undergoing CABG (n=2),[15 19] mixed cardiac surgery (n=10),[7 17 18 20–26] or surgery on the thoracic aorta (n=1),[16] and two enrolled children undergoing surgery for congenital disease.[15 19] The sample size ranged from 22 to 7402. The largest trial, which enrolled more patients (7402) than all previous trials, was a multicentre stepped wedge cluster RCT.[7] To adjust for the stepped wedge cluster design, we recalculated the effective sample size for this trial according to the recommendations in the Cochrane Handbook,[10] using the intracluster coefficient calculation of 0.095 stated in the trial methods.[7]

All trials evaluated the efficacy of blood management algorithms based on viscoelastic test results. One trial[18] evaluated ROTEG®, seven trials evaluated ROTEM®,[7 16 17 19 21 22 25] and seven trials evaluated TEG®.[13–15 20 23 24 26] Blood management in controls was at the clinicians' discretion in combination with standard laboratory tests in eight trials,[13 16 18 20 22–24 26] standard laboratory tests alone in six trials,[7 14 17 19 21 25] and clinical judgement alone in one trial.[15] Ten trials provided data on length of follow-up [7 14 16 18 19 21 22 24–26] that ranged from 24 h to 3 yr.

Excluded studies

Seven trials that met our inclusion criteria were excluded after review of the full manuscript (Supplementary Table S1). Four studies were excluded because of insufficient data to judge the study design.[27–30] One trial[31] used viscoelastic testing algorithms in the control group, and one[32] randomized abdominal aortic aneurysm surgeries. Two trials (NCT00772239; NCT01218074) were published only as protocols without any data available.

Risk of bias

The trial by Karkouti and colleagues[7] was judged to be at low risk of bias for the domains recruitment bias, baseline imbalance, loss of clusters, and incorrect analysis. No trial was judged to be at low risk of bias. Bias domains are presented in the 'risk of bias' graph and a 'risk of bias' summary figure (Fig. 1) and online Supplementary material.

Table 1 Characteristics of included studies. ACT, activated clotting/coagulation time; aPTT, activated partial thromboplastin time; CABG, coronary artery bypass graft; FIB, fibrinogen; ICU, intensive care unit; IQR, interquartile range; MEA, multiple-electrode aggregometer; PLT, platelets; PM, TEG platelet mapping; SLCT, standard laboratory coagulation tests; TEG, thromboelastography; NR, not reported

Reference	No. of patients	Age [yr; mean (SD)]	Inclusion criteria	Intervention test	Control test	Outcomes
Karkouti and colleagues (2016)[7]	7402	67 (59–75) median (IQR)	Mixed cardiac surgery	ROTEM, Plateletworks	SLCT	Blood products transfusion, major bleeding, major complications
Nakayama and colleagues (2015)[19]	100	12 (4–24) months median (IQR)	Cardiac surgery for paediatric disease	ROTEM	SLCT	Blood products transfusion
Weber and colleagues (2012)[25]	100	71 (8)	Mixed cardiac surgery	ROTEM, platelet function tests	SLCT	Transfusion, bleeding, reoperation, AKI, sepsis, death, ICU LoS, hospital LoS
Kempfert (2011)[17]	104	–	Patient with excessive bleeding after cardiac surgery	ROTEM	SLCT	Blood transfusion, drainage loss
Paniagua and colleagues (2011)[21]	22	NR, not reported	Mixed cardiac surgery	ROTEM	SLCT	Transfusion
Cui and colleagues (2010)[15]	100	30.9 (25.8) months	Cardiac surgery for cyanotic disease	TEG	Clinician decision	Blood products transfusion, drainage, ICU LoS, hospital LoS, ventilation time
Girdauskas and colleagues (2010)[16]	56	62 (16)	Aortic surgery	ROTEM	Clinician decision and SLCT	Transfusion, bleeding, reoperation, death, AKI, stroke, re-intubation, ICU LoS, hospital LoS
Westbrook and colleagues (2009)[26]	60	64 (20)	Mixed cardiac surgery	TEG	Clinician decision and SLCT	Transfusion, bleeding, reoperation, ICU LoS, hospital LoS
Ak and colleagues (2009)[13]	228	64 (20)	CABG	TEG	Clinician decision and SLCT	Transfusion, bleeding, reoperation, death, ICU LoS, hospital LoS
Rauter and colleagues (2007)[22]	213	NR, not reported	Mixed cardiac surgery	ROTEM, clinical signs	Clinician decision and SLCT	Transfusion
Kultufan Turan and colleagues (2006)[18]	40	53	Mixed cardiac surgery	ROTEG	Clinician decision and SLCT	Transfusion
Avidan and colleagues (2004)[14]	102	64	CABG	TEG, platelet function test, and ACT	SLCT	Transfusion, bleeding, and reoperation
Nuttall and colleagues (2001)[20]	92	63	Mixed cardiac surgery	TEG, PT, aPTT, platelets, and FIB	Clinician decision and SLCT	Transfusion
Royston and colleagues (2001)[23]	60	NR, not reported	Mixed cardiac surgery	TEG	Clinician decision and SLCT	Transfusion, bleeding, reoperation, and death
Shore-Lesserson and colleagues (1999)[24]	107	66 (15)	Mixed cardiac surgery	TEG, platelets, and FIB	Clinician decision and SLCT	Transfusion, bleeding, reoperation, and death

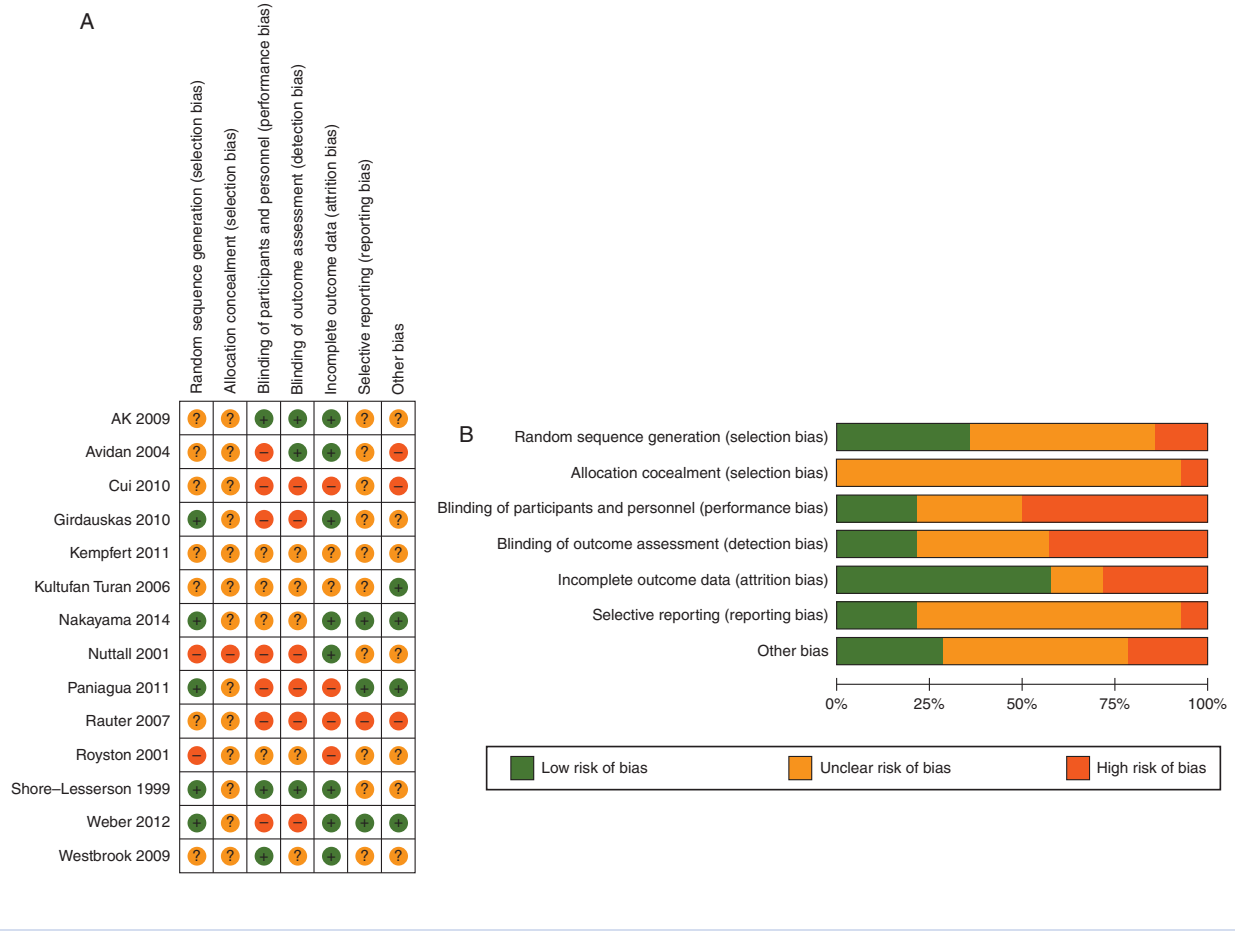

Fig 1 Risk of bias summary for individual studies (A) and all studies (B).

Sequence generation

Random sequence generation was adequate in four trials,[16 19 24 25] unclear in eight trials,[13–15 17 18 21 22 26] and with high risk of bias in two trials.[20 23]

Allocation concealment

Allocation concealment was unclear in 13 trials[13–19 21–26] and with high risk in one trial.[20]

Blinding

There was evidence of blinding of patients and clinical staff caring for patients in two trials,[13 24] unclear evidence in five trials,[17–19 21 23] and evidence of lack of blinding in seven trials.[14–16 20 22 25 26] There was evidence of blinding of outcome assessors in two trials,[14 24] unclear evidence of blinding of outcome assessors in seven trials,[13 17–19 21 23 26] and high risk of detection bias in five trials.[15 16 20 22 25]

Incomplete outcome data

Nine trials reported completeness of follow-up for the primary outcome.[13 14 16 19–21 24 26] All reported <10% loss to follow-up. Three trials that failed to report completeness of follow-up were considered to be at high risk of attrition bias.[15 22 23] Insufficient reporting of attrition or exclusion to permit a judgement was detected in two trials.[17 18]

Selective reporting

Three trials were published only as an abstract; in these trials, some outcomes were not reported, or treatment effects were not reported,[17 21 22] and thus were considered to be at high risk. All others trials but one[7] were considered at unclear risk because we were unable to retrieve the original protocols or evidence of publication in a trial registry.

Other potential sources of bias

Nine trials disclosed funding source.[7 14 15 18 19 21 22 24 25] Of these, three trials were at risk of funder bias.[7 19 25] For the remaining

studies, funding was defined as unknown. Sample size calculation was reported in eight trials.[7 13 14 16 20 23–25]

Effects of interventions

A summary of findings for the main comparison TEG® or ROTEM® *vs* usual care for patients undergoing cardiac surgery is reported in Supplementary Table S2.

Primary outcome

Hospital mortality was reported in seven trials.[13 16 19 21 23–25] Mortality was lower in patients treated with TEG®- or ROTEM®-guided algorithms (12/350) *vs* controls (23/339); however, this was not statistically significant (RR 0.55, 95% CI 0.28–1.10, I^2=1%; χ^2 test for heterogeneity, *P*=0.40; Fig. 2A).

Secondary outcomes

Bleeding and transfusion

Eleven RCTs reported data on the number of patients transfused with allogenic RBCs.[7 13–16 18 19 21 24–26] Red blood cell transfusion was reduced in patients treated with VE testing algorithms with some heterogeneity (RR 0.88, 95% CI 0.79–0.97; I^2=43%; χ^2 test for heterogeneity, *P*=0.06; Fig. 2B). Exclusion of the trial by Karkouti and colleagues[7] did not alter the summary effect estimate or heterogeneity (RR 0.86, 95% CI 0.76–0.96; I^2=52%; χ^2 test for heterogeneity, *P*=0.03).

Eight RCTs reported data on the number of patients receiving fresh frozen plasma.[7 13 14 16 19 21 24 25] The summary effects estimate for VE testing *vs* controls was RR 0.68, 95% CI 0.46–1, with significant heterogeneity (I^2=79%; χ^2 test for heterogeneity, *P*=0.0001; Fig. 2C). Exclusion of the trial by Karkouti and colleagues[7] did not significantly alter the summary effect estimate or reduce heterogeneity (RR 0.62, 95% CI 0.38–0.99; I^2=84%; χ^2 test for heterogeneity, *P*=0.05).

Ten RCTs reported data on the number of patients receiving platelet transfusion.[7 13–16 18 19 21 24 25] Use of VE tests resulted in a significant reduction in the number of patients receiving platelet transfusions (RR 0.78, 95% CI 0.66–0.93; I^2=0%; χ^2 test for heterogeneity, *P*=0.06; Fig. 2D). Exclusion of the trial by Karkouti and colleagues[7] did not alter these findings (RR 0.76, 95% CI 0.63–0.91; I^2=0%; χ^2 test for heterogeneity, *P*=0.003).

Four trials evaluated fibrinogen administration.[7 16 22 25] All four reported no difference between the VE algorithm group compared with the control group in the volume of fibrinogen transfused. Two of these trials provided dichotomous data on the number of patients who received fibrinogen in each intervention group.[16 25] The summary effects estimate for VE testing *vs* controls was RR 0.94, 95% CI 0.76–1.17; I^2=22%; χ^2 test for heterogeneity, *P*=0.59, suggesting no difference between groups (Supplementary Fig. S2A).

Four trials evaluated prothrombin complex concentrate administration.[7 16 22 25] Two of these trials provided dichotomous data on the number of patients who received prothrombin complex concentrate in each intervention group.[16 25] The summary effects estimate for VE testing *vs* controls was RR 0.39, 95% CI 0.07–2.16; I^2=91%; χ^2 test for heterogeneity, *P*=0.28, suggesting no difference between treatment groups (Supplementary Fig. S2B).

Nine trials reported the number of patients who required reoperation for bleeding.[13 14 16 17 20 21 23–25] Use of VE testing resulted in reductions in the number of reoperations for bleeding, but this effect did not reach statistical significance (RR 0.82, 95% CI 0.55–1.23; I^2=0%; χ^2 test for heterogeneity, *P*=0.63; Fig. 2E).

Major morbidity

Four trials[13 16 21 25] reported the number of patients with severe AKI. The use of VE testing reduced the frequency of severe AKI *vs* controls with moderate heterogeneity (RR 0.42, 95% CI 0.20–0.86; I^2=26%; *P*=0.02; Supplementary Fig. S2C).

Two trials[16 24] evaluated the number of patients with cerebrovascular accident. There was no difference between VE testing and controls with respect to the frequency of stroke (RR 1.73, 95% CI 0.41–7.23; I^2=0%; *P*=0.45; Supplementary Fig. S2D).

Three trials[13 16 21] provided continuous data (mean, SD) on ventilation time. Meta-analysis demonstrated shorter ventilation times in the VE testing group, but this was not statistically significant (MD 0.28, 95% CI −0.66 to 1.23; I^2=0%; *P*=0.56; Supplementary Fig. S2E).

Resource use

Intensive care unit length of stay

The ICU LoS was reported in three studies.[13 16 21] The ICU LoS was shorter in patients randomized to TEG®- or ROTEM®-guided algorithms *vs* controls, but this was not statistically significant (MD −31.76 h, 95% CI −94.68 to 31.17; I^2=59%; *P*=0.32; Supplementary Fig. S2F).

Hospital length of stay

Hospital LoS was reported in three studies.[13 16 21] Hospital LoS was shorter in patients randomized to TEG®- or ROTEM®-guided algorithms *vs* controls, but this was not statistically significant, with moderate heterogeneity (MD −3.11 days, 95% CI −9.57 to 3.34; I^2=69%; *P*=0.34; Supplementary Fig. S2G).

Publication bias

For two outcomes (RBC and fresh frozen plasma transfusion) there were sufficient numbers of trials providing data (10 or more studies identified for each outcome) for evaluation of publication bias. The funnel plot of standard error *vs* risk ratio for RBC transfusion showed an asymmetrical distribution and a regression test for funnel plot asymmetry model: z=−2.21, *P*<0.026 (random-effects version of Egger's test) indicating likely publication bias (Supplementary Fig. S3A). The funnel plot of standard error *vs* risk ratio for platelet transfusion showed a symmetrical distribution and a regression test for funnel plot asymmetry model: z=0.22, *P*=0.818 (random-effects version of Egger's test) that indicated no publication bias (Supplementary Fig. S3B). Exclusion of the trial by Karkouti and colleagues[7] did not alter these findings (*P*=0.015 for RBC transfusion and 0.724 for platelet transfusion).

Sensitivity analyses

Sensitivity analysis were not conducted because none of the included trials was considered at low risk of bias. Summary effect estimates from fixed-effects models did not materially alter our results.

Subgroup analyses

Results of subgroup analyses for TEG® algorithms *vs* ROTEM® algorithms, TEG® algorithm *vs* other algorithm, CABG *vs* non-CABG surgery or combined are shown in Supplementary Table S3. There was no significant interaction between prespecified subgroups and overall effect estimates for our primary and secondary end points.

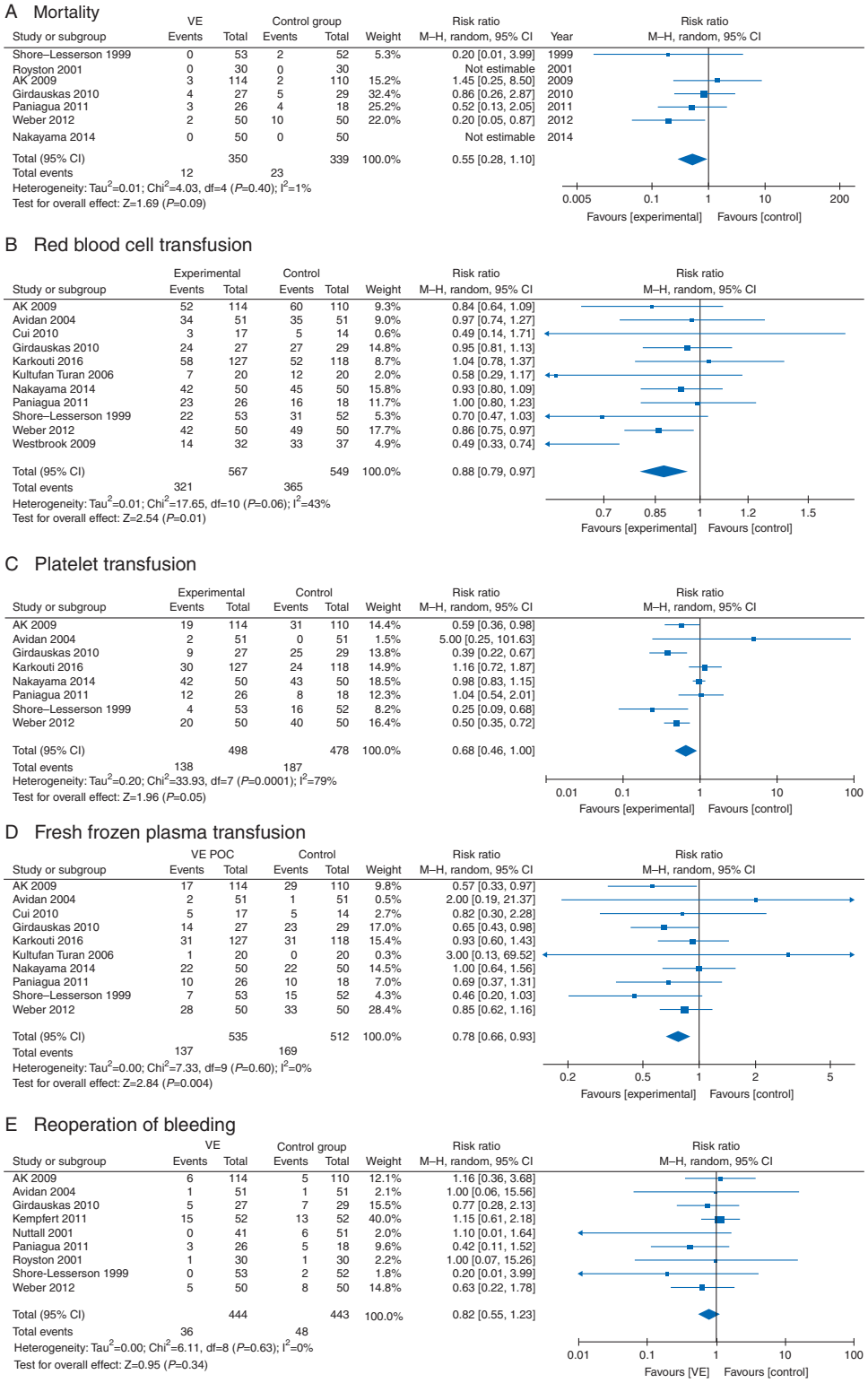

Fig 2 Forrest plots showing pooled effect estimated from random-effects models for mortality (A), red blood cell transfusion (B), platelet transfusion (C), fresh frozen plasma transfusion (D), and reoperation for bleeding (E).

GRADE summary

Results of the GRADE Summary of the evidence are listed in Table 2. There was no difference between viscoelastic testing and control groups for mortality, RBC transfusion, bleeding, major morbidity (with the exception of severe AKI), or resource use. The quality of evidence was 'low' or 'very low' for all outcomes assessed, implying a high level of uncertainty with respect to these results.

Discussion

Summary of evidence

A systematic review of trials of viscoelastic point-of-care testing in cardiac surgery identified 15 RCTs, of which we judged none was free from potential bias. Pooled effect estimates showed that TEG®- or ROTEM®-guided algorithms for management of coagulopathic haemorrhage reduced the number of patients requiring transfusion, but had no effect on mortality, stroke, prolonged intubation, emergency reoperation for bleeding, or in ICU and hospital length of stay. There was a significant reduction in the frequency of severe AKI in four trials where this was reported. GRADE assessment concluded that the quality of evidence was 'low' or 'very low' for all outcomes.

Strengths and limitations

The principal limitation of this sytematic review is that the findings and interpretations are limited by the quality and quantity of available evidence. We judged all of the 14 parallel group trials as having significant limitations in terms of methodological quality. The risk of procedural bias was high in these trials as there was little or no allocation concealment or blinding of clinical personnel. The potential to produce summary effect estimates was limited by the wide variety of outcomes reported and a lack of standardization of the way in which these were measured. The assessment of heterogeneity was limited by the relatively small number of studies that contributed to each meta-analysis. Our assessment of likely bias differed from that in a recent Cochrane review.[6] For example, in that analysis use of sealed envelopes was considered at low risk of bias for allocation concealment. However, Cochrane guidance states that only sealed opaque envelopes can be considered as evidence of allocation concelament.[9] Where the term opaque was omitted we therefore classified this as unclear and not low. Likewise, the Cochrane reviewers assessed several studies as having a low risk of reporting bias, despite the absence of prospective trial registration or availability of trial protocols for reference.[6] We judged that these trials should be categorized as having unclear evidence of reporting bias; hence, we found no trial at low risk of bias.

These limitations notwithstanding, the present meta-analysis provides the most comprehensive evaluation of viscoelastic point-of-care tests in cardiac surgery to date. It considered all trials identified in two recent meta-analyses,[6 33] along with the results of a recent large cluster randomized trial not included in these previous analyses.[7] The trial by Karkouti and colleagues[7] enrolled 7402 patients; almost five times the number patients enrolled in the previous RCTs identified in our search. We evaluated the effects of including or excluding this study from our primary analysis to assess how the results from this trial influenced the effect estimates. The analysis demonstrated that the inclusion of this trial did not substantially alter summary effect estimates for those outcomes where data were available; specifically, that viscoelastic tests reduced numbers of patients receiving RBC and platelet transfusions.

Transfusion decisions are subject to local and individual prejudices,[34] and these outcomes are particularly susceptible to the absence of random sequence generation, allocation concealment, blinding, or standardized transfusion and bleeding protocols in control groups, in almost all of the parallel group trials identified. Funnel plot analysis also indicated a high likelihood of publication bias for this outcome. The effect of viscoelastic testing on transfusion frequency in the trials is also at odds with the wide interinstitutional variability commonly observed for RBC transfusion, which suggests that this treatment is largely influenced by factors independent from the patient.[34] It is important to consider that RBC transfusion has a financial and societal cost; however, the low quality of the evidence for an effect on transfusion does not resolve uncertainty as to the effect of VE testing on this outcome. In contrast, objective outcomes, less dependent on subjective decision-making or bias, including mortality, emergency resternotomy, stroke, ventilation time, and intensive care and hospital stay, were not different between groups. There was a reduction in severe AKI associated with viscoelastic tests in the meta-analysis based on an analysis of 62 events in four trials, all of which were at high risk of bias. There was a reduction in major bleeding attributable to viscoelastic testing in the trial by Karkouti and colleagues,[7] and this potentially has clinical importance. However, this was a composite end point, and the frequencies of individual components of the end point were not published, despite a direct request to the authors, limiting our ability to evaluate these results. The trial by Karkouti and colleagues[7] also failed to demonstrate any difference in overall complication rates; although again the exact complications and their frequencies were not specified. Overall, the results of this trial mirrored the findings of the 2016 Cochrane review;[33] notably, that the use of viscoelastic testing reduced transfusion, but had no benefit with respect to objective clinically important end points. This is at odds with the findings of the systematic review conducted by Whiting and colleagues,[33] who concluded that viscoelastic testing was likely to be cost-effective. Their analysis directly informed current National Health Service NICE Guidelines, which recommend routine use of viscoelastic testing in cardiac surgery.[5] Whiting and colleagues demonstrated a reduction in RBC transfusion attributable to the use of viscoelastic testing.[33] Using assumptions based on historical data showing strong associations between RBC transfusion and adverse clinical outcomes,[35] they estimated that this reduction in RBC transfusion would be cost-effective.[33] However, cause and effect between RBC transfusion and adverse outcome has been questioned by recent studies,[36] including the Transfusion Indicating Threshold Reduction 2 (TITRE2) trial, where reductions in RBC transfusion attributable to application of a restrictive transfusion threshold increased mortality.[37] Combined with the uncertain effects of bias on subjective transfusion decisions, these results question the accuracy of existing NICE guidance. The absence of a causal relationship between RBC transfusion and adverse outcome could explain, in part, the apparent discordance between the assessment of efficacy (transfusion) and effectiveness (clinical outcomes) in the analyses.

Conclusions

Evidence to support routine use of viscoelastic testing in cardiac surgery is weak. Authors of the recent Cochrane review stated that further large pragmatic trials at low risk of bias were required to resolve this knowledge gap.[6] However, inclusion of

Table 2 Summary of main findings of systematic review and GRADE assessment of trial results. GRADE Working Group grades of evidence are as follows: high quality, we are very confident that the true effect lies close to that of the estimate of the effect; moderate quality, we are moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); low quality, our confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of the effect); and very low quality, we have very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect). *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). †Only two trials with low risks of bias. Two trials were 0 event trials. ‡Only one trial with low risk of bias. ¶Bleeding and coagulopathy as inclusion criteria might change the effect estimate. §All the included trials were at high risk of bias. ‖High risk of publication bias detected. CI, confidence interval; ICU, intensive care unit; LoS, length of stay; MD, mean difference; RCT, randomized controlled trial; RR, risk ratio

Viscoelastic point-of-care tests *vs* standard care in cardiac surgery patients at risk of coagulopathic bleeding					
Patient population, adult cardiac surgery; setting, tertiary cardiac centres					
Intervention: viscoelastic point-of-care test-based algorithms					
Control: standard care					
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**No. of Participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with Control	**Risk with NIRS**			
Mortality	68 per 1000	37 per 1000 (19–75)	RR 0.55 (0.28–1.10)	689 (7 RCTs)	⨁⨁◯◯ Low†
Red blood cell transfusion	391 per 1000	585 per 1000 (388–564)	RR 0.88 (0.79–0.97)	1116 (11 RCTs)	⨁◯◯◯ Very low†‖
Platelet transfusion	330 per 1000	257 per 1000 (218–307)	RR 0.78 (0.66–0.93)	1116 (11 RCTs)	⨁⨁◯◯ Low†
Severe acute kidney injury	188 per 1000	89 per 1000 (44–166)	RR 0.42 (0.20–0.86)	1047 (10 RCTs)	⨁◯◯◯ Very low†¶
Reoperation for bleeding	108 per 1000	89 per 1000 (60–133)	RR 0.82 (0.55–1.23)	744 (4 RCTs)	⨁◯◯◯ Very low‡¶
Intensive Care Unit Length of stay		The mean ICU LoS in the intervention group was 31.8 lower (94.7 lower to 31.1 higher)			⨁◯◯◯ Very low§
Hospital Length of stay		The mean hospital LoS was 3.1 lower (9.6 lower to 3.3 higher)			⨁⨁◯◯ Low†

the large pragmatic trial of viscoelastic testing by Karkouti and colleagues[7] did not alter the precision of the estimates from existing parallel group trials. Moreover, the trial by Karkouti and colleagues[7] was at low risk of bias for all of the conventional bias domains for cluster randomized trials, with the exception of potential funding bias, and also did not demonstrate benefits for important clinical end points. These findings lead us to hypothesize that viscoelastic testing lacks clinical effectiveness. This hypothesis is supported by weak evidence of predictive accuracy of viscoelastic testing for coagulopathic bleeding.[38] On the basis of the weight of the available evidence, further large trials are unlikely to demonstrate clinical benefits for current viscoelastic point-of-care tests. Research should now focus on development of new techniques to identify important and treatable causes of coagulopathy in cardiac surgery.

Authors' contributions

The authors had full access to all data and take responsibility for the integrity of the data and accuracy of the analysis.
Literature searches, data extraction, analysis, and writing the manuscript: G.F.S., G.J.M.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

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