Viscoelastic Blood Tests Use in Adult Cardiac Surgery: Meta-Analysis, Meta-Regression, and Trial Sequential Analysis

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Objectives: Postoperative hemorrhage in cardiac surgery is a significant cause of morbidity and mortality. Standard laboratory tests fail as predictors for bleeding in the surgical setting. The use of viscoelastic (VE) hemostatic assays thromboelastography (TEG) and rotational thromboelastometry (ROTEM) could be an advantage in patients undergoing cardiac surgery. The objective of this meta-analysis was to analyze the effects (benefits and harms) of VE-guided transfusion practice in cardiac surgery patients.

Design: A meta-analysis of randomized trials.

Setting: For this study, PubMed, EMBASE, Scopus, and the Cochrane Collaboration database were searched, and only randomized controlled trials were included. A systematic review and meta-analysis were performed in accordance with the standards set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, using a random-effects model.

Participants: The study comprised adult cardiac surgery patients.

Interventions: VE-hemostatic assays transfusion algorithm compared with transfusion algorithms based on clinicians’ discretion.

Measurements and Main Results: Seven comparative randomized controlled trials were considered, including a total of 1,035 patients (522 patients in whom a TEG- or ROTEM-based transfusion algorithm was used). In patients treated according to VE-guided algorithms, red blood cell (odds ratio 0.61; 95% confidence interval [CI]: 0.37–0.99; p: 0.04; I²: 66%) and fresh frozen plasma transfusions (risk difference 0.22; 95% CI: 0.11–0.33; p < 0.0001; I²: 79%) use was reduced; platelets transfusion was not reduced (odds ratio 0.61; 95% CI: 0.32–1.15; p: 0.12; I²: 74%).

Conclusions: This study demonstrated that the use of VE assays in cardiac surgical patients is effective in reducing allogenic blood products exposure, postoperative bleeding at 12 and 24 hours after surgery, and the need for redo surgery unrelated to surgical bleeding.

Key Words: viscoelastic blood test; rotational thromboelastography; adult cardiac surgery; hemorrhage; meta-analysis

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CARDIAC SURGERY with cardiopulmonary bypass causes severe derangements in the hemostatic system, which contributes to intraoperative and postoperative bleeding and is associated with increased morbidity and mortality.\textsuperscript{1,4} Transfusion of hemostatic blood products may be guided by clinical judgment, standard laboratory tests, thromboelastography (TEG) or rotational thromboelastometry (ROTEM), or a combination of these in a treatment algorithm. None of the standard laboratory tests (activated partial thromboplastin time, prothrombin time, international normalized ratio, platelet count, and plasma fibrinogen) was developed to predict bleeding or to guide coagulation management in the surgical setting.\textsuperscript{5,6} TEG and ROTEM are viscoelastic (VE) hemostatic assays\textsuperscript{7} that provide a graphical evaluation of the kinetics of almost all stages of clot formation in the whole blood.

The monitoring of the dynamic changes of hemostasis with TEG or ROTEM has a pathophysiologic rationale, allowing for the diagnosis of a specific type of coagulopathy and possibly guiding a cause-oriented hemostatic treatment.\textsuperscript{8} VE tests are not without limitations, which should be considered carefully as they measure coagulation parameters under static rather than dynamic conditions\textsuperscript{9}. Moreover, not all stages of coagulation can be monitored\textsuperscript{10} and the assays have a reduced standardization and validation of reference ranges compared with standard laboratory tests.\textsuperscript{11,12}

Moreover, both in cardiac and noncardiac surgical settings, there is no strong evidence about the efficacy of VE tests in reducing the incidence of strong negative outcomes in patients receiving VE-guided bleeding management. A recent meta-analysis of the use of VE hemostatic assays in noncardiac surgical settings showed that no definitive evidence can be drawn about the efficacy of these tests due to the high heterogeneity of the studies considered.\textsuperscript{13} Similar results in terms of lack of effect on outcomes have been demonstrated by Serraino et al.\textsuperscript{14} In the light of this persistent uncertainty, the authors conducted the present study to assess the effects of VE-guided management of bleeding/coagulopathy in cardiac surgery.

**Material and Methods**

**Data Sources and Search Strategy**

A systematic review and meta-analysis were performed in accordance with the standards set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.\textsuperscript{15} PubMed, EMBASE, Web of Science, and the Cochrane Collaboration were searched (see Appendix 1 for the research strategy used in the study). In addition, references of retrieved articles were hand-searched, and PubMed’s related articles feature was used to identify studies not captured by the present study’s primary search strategy. Parallel group, randomized controlled trials were included. If necessary, the investigators and authors were contacted in order to retrieve the relevant data. Studies with nonstandard designs, such as crossover trials, were not included. No subgroup of the patient population was excluded. The final search was run on April 22, 2019.

**Study Selection**

Once full articles were retrieved, studies were further excluded if there was an overlap in patients with another study within the same analysis (in this case, the larger sample size of the 2 studies was selected).

Two reviewers (MM and AM) evaluated each article separately. Disagreements were resolved by discussion with a third party (GA).

The quality of studies was examined using the method recommended by a Cochrane Collaboration tool for assessing risk of bias in the included studies. Factors that were assessed are as follows: (1) random sequence generation (selection bias), (2) allocation concealment, (3) blinding of involved personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, and (6) selective reporting. In the studies reporting only median and interquartile range, we interpreted the value of median as a mean, and standard deviation as interquartile range/1.35\textsuperscript{16} as described by Wan (10). Two authors (MM and GA) independently extracted the relevant data from articles, and their results were compared to assure accuracy. Any disagreement was solved by consensus.

**Outcomes**

The primary endpoint was the number of patients transfused with packed red blood cells, fresh frozen plasma, and platelets. Secondary endpoints were as follows: (1) total blood loss, (2) intensive care unit (ICU) stay, (3) ventilation time, (4) re-sternotomy for bleeding, and (5) mortality.

**Selection Criteria**

Two authors (MM and AM) screened the literature and selected potential relevant articles. Inclusion criteria were established a priori. Inclusion criteria were randomized controlled trials that studied the effect of VE testing on allogenic blood products exposure in adult cardiac surgery.

**Moderators (Covariates) Analysis**

The following covariates (moderators) were considered as factors that potentially could affect the efficacy of viscoelastic (VE) tests in reducing patients’ exposure to allogenic blood products: (1) intraoperative routine use of antifibrinolytics, (2) percentage of high-risk interventions in each study, (3) preoperative percentage of patients in antiaggregant therapy, (4) quality of transfusion algorithm, (5) type of VE test used (TEG or ROTEM), and (6) preoperative anemia. The present study tested whether any of these factors explained the heterogeneity identified in the results. A detailed moderators analysis is reported in Appendix 3.

**Data Analysis**

Random-effects models were used to determine the effect of VE tests a priori because random-effects models handle
heterogeneity more precisely. For dichotomous outcomes, the relative effect sizes were calculated as an odds ratio (OR) with 95% confidence interval (CI). For continuous outcomes, estimates reported as mean difference with 95% CI were pooled.

Heterogeneity was assessed using the I² statistic. Values from 50% to 75% were considered to represent substantial heterogeneity and from 75% to 100% considerable heterogeneity. Meta-regression analysis was used to explore whether the aforementioned covariates affect the relative effectiveness of VE tests and whether these variables account for part of the heterogeneity observed. The authors expected the inclusion of covariates to explain some of the between-study heterogeneity. A negative value suggests that covariates predict less heterogeneity than what would be expected by chance.

**Publication Bias**

Small-study effects were explored for both visually by drawing a funnel plot and statistically by applying Egger’s regression test. An asymmetric funnel plot is expected in the presence of publication bias.

Normal quantile plots often are used to assess data normality. The normal quantile plot for meta-analysis has each individual study’s z score on the y-axis and the normalized quantile of its rank on the x-axis. The plot can be used in meta-analysis to check the normality of the data (dots expected on a straight line), to investigate heterogeneity (clustering of dots), and to assess for the presence of publication bias (deviation of the tails from the regression line).

The Galbraith plot was used to identify potential outlier studies after which their influence on pooled effects and/or heterogeneity was examined graphically. Outlier analysis was directed at studies in the overall findings and in the power groups. The L’Abbé plot plots the risks (or odds) in the exposed, or index, group (y-axis) against those of the control group (x-axis) and contains a regression line and a central diagonal line indicating identical risks in each group. The sizes of the dots are proportional to the study weights. This plot was used to view the range of event rates among the trials to highlight excessive heterogeneity.

**Sensitivity Analysis**

A random-effects model was used for primary analysis and a fixed-effects model for sensitivity analysis. The results from the 2 models were compared. If the results between the 2 models were similar, the results from the random-effects analysis were reported, and if the results differed substantially, the authors evaluated for small-study effects.

**Trial Sequential Analyses**

In a single trial, interim analyses increase the risk of type I error. To avoid an increase in the overall type I error, monitoring boundaries can be applied to decide whether a single randomized trial could be terminated early because of the p value being sufficiently small. Because no reason exists why the standards for a meta-analysis should be less rigorous then those for a single trial, analogous trial sequential monitoring boundaries can be applied to a meta-analysis as a trial sequential analysis (TSA). Cumulative meta-analyses of trials are at risk of producing random errors because of few data and repetitive testing of accumulating data and because the requirement for the amount of information analogous to the simple size of a single optimally powered clinical trial might not be met.

The underlying assumption for TSA is that significance testing and CI calculation are performed each time a new trial is published. TSA depends on the quantification of the required amount of information. TSA-adjusted CIs are derived considering the adjusted levels of statistical significance calculated by sequential monitoring boundaries, thereby taking into account how much information actually has been accrued considering the effect size originally anticipated. For the present study, TSA was used to infer whether the cumulative existing evidence is sufficient to draw firm conclusions using 2-sided tests with type I error set at 5% and power set at 80%, and TSAs were performed on only blood product exposure.

Other data were derived from the meta-analyses results as a measure of diversity (D²), which is a measure of heterogeneity measuring the proportion of between-trial variance to the sum of the between-trial variance and the arithmetic mean of the within-trial variances from the included trials. For the present study, the authors used as quantification of D² between included trials in a meta-analysis the relative model variance reduction when the model of pooling was changed from a random-effects model into a fixed-effect model. The required information size for each meta-analysis was adjusted for D².

### Software Used

The following software were used for the present study: Review Manager, version 5.3 (Cochrane, London, United Kingdom) for the meta-analyses; (2) R (R Project for Statistical Computing) for the meta-regression and publication bias; (3) GRADEpro Guideline Development Tool (McMaster University [developed by Evidence Prime, Inc.], Canada) for developing the group reading assessment and diagnostic evaluation; and (4) TSA software, version 0.9 beta (Copenhagen Trial Unit, Denmark), for TSAs.

### Results

**Characteristics of Included Studies**

The study selection process is shown in Figure 1. After exclusion of duplicate or irrelevant references, 37 potentially relevant articles were retrieved. After detailed evaluation, 8 comparative randomized controlled trials met the inclusion criteria and were considered in the present meta-analysis, including a total of 1,035 patients, 522 patients in whom a TEG- or ROTEM-based transfusion algorithm was used and 513 patients with a transfusion algorithm based solely on clinicians’ discretion. The list of included studies and the quality assessment for each study are presented in Table 1. A complete list of excluded studies is reported in Appendix 4.
Meta-Analyses Results

Of the 8 trials identified, 3 enrolled adults patients undergoing coronary artery bypass grafting,\textsuperscript{21-23} and 5 enrolled adult patients undergoing mixed cardiac surgery.\textsuperscript{24-28} The sample size ranged from 26 to 7,402. The trial that enrolled 7,402 patients\textsuperscript{24} was a multicenter, stepped wedge cluster, randomized control trial. To adjust for the stepped wedge cluster design, the effective sample size was recalculated according to the recommendation in the Cochrane Handbook, using the intracluster coefficient calculation of 0.095.

Five trials evaluated the efficacy of bleeding management algorithms based on TEG results,\textsuperscript{21,22,23,25,27} and 3 trials evaluated the efficacy of bleeding management algorithms based on ROTEM.\textsuperscript{24,26,28} Bleeding management in control patients was based on standard laboratory tests in combination with clinicians’ discretion in all included trials. One trial\textsuperscript{21} randomly assigned patients in the following different groups: in the first group, a multiple electronic aggregometry-based algorithm was used; in the second group, a TEG-based algorithm was used; and in the third group, only clinical judgment was used. For that trial, the authors of the present study analyzed the results by comparing the TEG-based group and patients in whom clinical judgment was used.

Risk of Bias

One trial\textsuperscript{26} was judged to be at low risk of bias for the recruitment bias, loss of clusters, and incorrect analysis. Random sequence generation was adequate in 5 trials\textsuperscript{21-25} and was unclear in 3 trials.\textsuperscript{26-28} Allocation concealment was unclear in all trials. In all included trials there was unclear evidence of blinding of patients and clinical staff caring for patients. The complete analysis of bias risk is reported in Appendix 3.

Primary Outcomes

Seven RCTs \textsuperscript{21-27} reported data on the blood exposition, RBCs transfusion, platelets transfusions.

Blood exposition was significantly lower in patients treated with VE tests-guided algorithms (288/511) versus controls (330/499), (OR: 0.85, 95\% CI: 0.74-0.97, p: 0.002), but there was a substantial heterogeneity ($I^2$: 58\%) (Fig 2, A). RBCs transfusion was reduced in patients treated with VE testing algorithms (OR: 0.55, 95\% CI: 0.34-0.88, p: 0.01, $I^2$: 64\%) (Fig 2, B). Platelet transfusion was reduced in patients treated with VE testing algorithms (OR: 0.54, 95\% CI: 0.30-1, p: 0.05, $I^2$: 73\%) (Fig 2, C). The summary effects estimate for VE testing versus control for fresh frozen plasma transfusion was a risk difference of 0.24 (95\% CI: 0.12-0.36, p<0.0001, $I^2$: 81\%) (Fig 2, D).

Three trials\textsuperscript{21,26,27} reported data on the number of patients receiving cryoprecipitate. The summary effects estimate for VE testing versus controls was OR 0.31 (95\% CI: 0.04-2.32, p=0.26, $I^2$: 78\%) (Fig 3, A).

Secondary Outcomes

Bleeding and Redo Surgery

Three studies\textsuperscript{25,27} reported the effects of VE testing algorithms on bleeding after 12 hours of intervention. The summary effects estimate for VE testing versus control patients was mean
difference (MD) −178.7 (95% CI: −308.9 to −48.4); p = 0.007; I² 84%, showing that 12-hour bleeding was reduced significantly in VE testing patients (Fig 3, B). Four studies23,25-27 reported the effects of VE testing algorithms on bleeding after 24 hours from surgery. The summary effects estimate for VE testing versus control patients was MD −175.4 (95% CI: −305.7 to −40.9; p = 0.01; I²: 6%), showing that 24-hour bleeding also was reduced significantly in VE testing patients (Fig 3, C). Use of VE testing resulted in a significant reduction in the number of redo surgeries for bleeding (OR: 0.51; 95% CI: 0.28-0.94; p = 0.03; I²: 0%) (Fig 4, A).

Use of VE testing resulted in a significant reduction in ICU stay (OR: −4.03; 95% CI: −6.28 to −1.78; p = 0.005; I²: 91%) (Fig 4, C), whereas the summary effects estimate for VE testing versus control patients showed no difference in mortality between the 2 groups (OR: 0.57; 95% CI: 0.18-1.74; p = 0.38; I²: 42%) (Fig 4, D).

Publication Bias

A visual inspection of the funnel plot showed asymmetry (Fig 5, A). This finding was further evaluated by conducting Egger’s test for small-study effects (regression line showing the association between standard error (SE) and effect size embedded in the funnel plot), which gave a p value of 0.099 when all studies were considered, clearly suggesting the presence of small-study effects.

Small-study effects may be caused by publication bias or true differences between small and large studies. By drawing a trim and fill analysis, the authors found that there were no missing studies, suggesting that the omission of small negative studies may be not the cause for the asymmetry in the funnel plot (Fig 5, E).

In order to investigate the asymmetry of the funnel plot further, several regression tests for publication bias were used. None of the regression tests showed important publication bias.

Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Patients</th>
<th>Type of Study</th>
<th>Inclusion Criteria</th>
<th>Intervention Test</th>
<th>Control Test</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karkouti (2016)²⁴</td>
<td>7,402</td>
<td>Mixed cardiac surgery</td>
<td>ROTEM</td>
<td>Standard laboratory tests</td>
<td>Blood products transfusion, bleeding, complications</td>
<td></td>
</tr>
<tr>
<td>Weber (2012)²⁶</td>
<td>100</td>
<td>RCT</td>
<td>Mixed cardiac surgery</td>
<td>ROTEM</td>
<td>Standard laboratory tests</td>
<td>Transfusion, bleeding, complications, mortality</td>
</tr>
<tr>
<td>Westbrook (2009)²⁷</td>
<td>60</td>
<td>RCT</td>
<td>Mixed cardiac surgery</td>
<td>TEG</td>
<td>Standard laboratory tests</td>
<td>Transfusion, bleeding, complications, mortality</td>
</tr>
<tr>
<td>Ak (2009)²²</td>
<td>224</td>
<td>RCT</td>
<td>CABG</td>
<td>TEG</td>
<td>Standard laboratory tests</td>
<td>Transfusion, bleeding, complications, mortality</td>
</tr>
<tr>
<td>Avidan (2004)²³</td>
<td>102</td>
<td>RCT</td>
<td>CABG</td>
<td>TEG</td>
<td>Standard laboratory tests</td>
<td>Transfusions, bleeding, redo surgeries, intensive care unit stay</td>
</tr>
<tr>
<td>Agarwal (2015)²¹</td>
<td>165</td>
<td>RCT</td>
<td>CABG</td>
<td>TEG</td>
<td>Standard laboratory tests</td>
<td>Transfusions, bleeding</td>
</tr>
<tr>
<td>Shore-Lesserson (1999)²⁵</td>
<td>105</td>
<td>RCT</td>
<td>Mixed cardiac surgery</td>
<td>TEG</td>
<td>Standard laboratory tests</td>
<td>Transfusions, bleeding</td>
</tr>
<tr>
<td>Lehmann (2019)²⁸</td>
<td>26</td>
<td>RCT</td>
<td>Mixed cardiac surgery</td>
<td>ROTEM</td>
<td>Standard laboratory tests</td>
<td>Transfusions, bleeding</td>
</tr>
</tbody>
</table>

Abbreviations: CABG, coronary artery bypass grafting; ICU, intensive care unit; RCT, randomized controlled trials; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

Fig 2. Meta-analysis of studies assessing the effect of viscoelastic testing on (A) allogenic blood products transfusions, (B) red blood cell exposition, (C) platelet exposition, (D) fresh frozen plasma transfusion.
in the present study, leading the authors to believe that publication bias was not a significant problem in the present study.

**Meta-Regression Results**

Meta-regression analyses were performed to explore whether differences in true effect sizes were explained by the following: (1) intraoperative routine use of antifibrinolytics, (2) percentage of high-risk surgery (defined according to the definition of “high-risk surgery” or “complex surgery” in each study), (3) preoperative percentage of patients in antiaggregant therapy, (4) quality of transfusion algorithm used, and (5) VE test type used (TEG or ROTEM). The logarithm of the observed OR with these covariates was regressed, and the effect size was significantly related to the quality of transfusion algorithm used. The results are presented in Appendix 5. The authors believe that this evidence is able to justify the presence of significant heterogeneity among the trials inserted in this meta-analysis.

It should be noted that in applying multiple univariate meta-regression, the present study ran a high risk of spurious findings due to an inflated type I error rate, and the possibility of confounders cannot be excluded.

**Trial Sequential Analysis**

TSA for blood product exposure was conducted with the following conditions: boundary type was 2-sided, type I error of...
5%, and type II error of 20% (80% power). The TSA was performed using an a priori anticipated intervention effect of 20% relative risk reduction (RRR), diversity of 30% in the included trials, and a control event proportion derived from the accumulated control group of the included trial.

By using these assumptions, the required information size was 621, being considerably lower under these data-driven assumptions. The trial sequential monitoring boundaries for benefit were surpassed, the required information size to detect or reject an RRR of 20% was reached, and the TSA-adjusted CI was similar to the conventional 95% CI (0.72-0.86) (Fig 6).

Sensitivity Analysis

Sensitivity analyses for the primary outcomes was performed by evaluating the difference in the outcome direction, magnitude, and significance when fixed-effect and random-effects models were used for the meta-analysis or if studies that scored “unclear” in more than 3 of the Cochrane risk of bias assessment were removed. No difference in the direction of any outcome variable was found.

Discussion

By using conventional meta-analysis, the present study demonstrated that the routine use of VE blood tests in adult cardiac surgery patients decreases the number of patients who underwent transfusions with fresh frozen plasma, platelets, and red blood cells. In addition, a significant reduction in postoperative bleeding at both 12 hours and 24 hours was observed. The meta-analysis also demonstrated a significant decrease in the incidence of redo sternotomies that were not due to surgical causes in patients treated with VE tests. Furthermore, the use of TSA confirmed the evidence on the effects of VE tests in reducing the exposure to blood products in general.

Upon analysis of publication bias, asymmetry of the funnel plot was observed, indicating the presence of publication bias, but none of the regression tests showed important publication bias in the present study. The meta-regression analyses identified 2 significant associations—the intraoperative use of antifibrinolytics and the proportion of high-risk interventions in each study. These modifiers are associated with different degrees of efficacy of VE tests in reducing patients’ exposure to blood products. This evidence led the authors to conclude that probably the asymmetry highlighted in the funnel plot, although minimal, still was justifiable by the presence of a “clinical” heterogeneity within the studies.

The TSA, as described by Kulynskaja, was performed with the sole purpose of clarifying whether this meta-analysis could provide firm evidence for what concerned the exposure of patients to allogeneic blood products. We have not analyzed other outcomes as VE tests in cardiac surgery are not intended to reduce the mortality, but to manage in the best possible way the administration of allogeneic blood products.

A TSA using an anticipated intervention effect derived from the point estimate of the RRR was evaluated.

The blood product exposition meta-analysis with an anticipated intervention effect of 20% RRR provided TSA analysis
with breakthrough of the trial sequential monitoring boundaries, confirming the positive results of the primary meta-analysis.

In a recent meta-analysis, Serraino et al.\textsuperscript{29} identified 15 randomized controlled trials, of which none was judged to be free from potential bias. They showed that TEG- or ROTEM-guided algorithms for management of coagulopathic hemorrhage reduced the number of patients requiring transfusions but had no effect on mortality, stroke, prolonged intubation, emergency redo surgery for bleeding, and ICU and hospital length of stay. The group reading assessment and diagnostic evaluation assessment concluded that the quality of evidence was “low” or “very low” for all outcomes. It also determined that trials without prospective trial registration or availability of trial protocols for reference should be categorized as having unclear evidence of reporting bias. These findings led Serraino et al.\textsuperscript{29} to hypothesize that VE tests lack clinical effectiveness and to conclude that additional larger trials are unlikely to demonstrate clinical benefits for current VE point-of-care tests and that research should focus on development of new techniques. In the opinion of the authors of the present study, choosing postoperative mortality as a primary outcome is misleading; the main effect of VE tests is to reduce postoperative bleeding and blood product consumption and possibly reduce mortality as a consequence of minor exposure to allogenic blood products. Choosing an indirect effect as a primary outcome is a methodological mistake potentially compromising all the results of the study. Similarly, to include in the meta-analysis unpublished conference abstracts increases the risk of bias and altering meta-analysis data. Moreover, Serraino et al. included in their meta-analysis studies on the pediatric population with cyanogenic heart disease, which is notoriously accompanied by major specific clotting abnormalities.

Whiting et al.\textsuperscript{7} in a systematic review concluded that VE tests were likely to be cost-effective. Their analysis, based on historical data showing strong associations between red blood cell transfusion and adverse clinical outcomes, directly informed current National Health Service NICE guidelines, which recommend routine use of VE testing in cardiac surgery.

The strength of this meta-analysis is the construction of a sound study aimed at obtaining reliable clinical data on the use of VE tests in adult cardiac surgical patients, who represent the real world of the authors’ clinical activity.

The authors of the present study tried to omit from their meta-analysis any study that could represent a “confounder” (eg, surgery of cyanogenic defects or surgery in hypothermic circulatory arrest). Moreover, by using TSA, VE tests were observed to decrease the exposure of patients to allogenic blood products. This study appears to demonstrate that the use

![Fig 6. Trial sequential analysis shows that there was enough information to confirm an relative risk reduction (RRR) of 20% (trial sequential analysis adjusted 95% confidence interval 0.72-0.86). The z curve crosses the boundaries for benefit.](image)
of VE tests in cardiac surgery to guide transfusion strategy is effective in reducing allogenic blood products exposure and postoperative bleeding at 12 and 24 hours after surgery.

Limitations

The main limitation was the important heterogeneity present in the conventional meta-analysis. In the authors’ opinion, the meta-regression provided valid indications that the majority of the observed heterogeneity was not a result of selection bias but rather clinical reasons.

Conclusions

This study demonstrates that the use of VE-guided management of bleeding/coagulopathy in cardiac surgery is effective in reducing allogenic blood products exposure and postoperative bleeding at 12 and 24 hours after surgery.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2019.06.030.

References