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Viscoelastic haemostatic assays in the perioperative period of surgical procedures: Systematic review and meta-analysis

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ABSTRACT

Objective: The aim of this study is to evaluate the safety and efficacy of Viscoelastic Haemostatic Assays (VHA) to guide transfusions in patients undergoing surgical procedures.
Design: Systematic review with meta-analysis of randomized controlled trials up until June 5, 2019.
Setting: Hospitalized patients.
Interventions: VHAs compared to the Standard-Of-Care (SOC), which are represented by standard laboratory tests and/or clinical decisions.
Measurements: Primary - Risk of death, acute kidney injury, thrombotic events and reoperation for bleeding; Secondary – Risk of use of red blood cells (RBC), platelets, fresh frozen plasma (FFP), fibrinogen, factor VIIa, prothrombin complex, volume of RBC, platelets and FFP, length of hospital stay, and length of ICU stay.
Results: VHAs were associated to a statistically significant reduction in mortality (7.3% vs. 12.1%; RR = 0.64, *p*-value = 0.03), risk of acute kidney injury (10.5% vs. 17.6%; RR = 0.53, *p*-value = 0.005), volume of red blood cells (RBCs) transfused (MD = -1.63 U, *p*-value = 0.02), risk of platelet transfusion (23.9% vs. 27.3%; RR = 0.74, *p*-value = 0.006), risk of fresh frozen plasma (FFP) transfusion (RR = 0.57, *p*-value = 0.001), and volume of FFP transfused (MD = -0.90, p-value = 0.0003). No significant differences were observed in terms of thrombotic events, reexploration for bleeding, RBC transfusion, volume of platelets transfused, use of fibrinogen, prothrombin complex, or factor VIIa, length of hospitalization and length of ICU stay.
Conclusion: Viscoelastic haemostatic assays are safe and efficacious for coagulation control in patients undergoing surgical procedures, therefore it should be considered for use in practice.

1. Introduction

Massive bleeding is a major concern in patients undergoing surgery that, if not treated appropriately, may contribute to morbidity and mortality [1,2]. Bleeding control is achieved through surgical hemostasis and transfusion of blood products and blood components. Allogeneic blood product transfusion, however, has already been shown to be associated with adverse outcomes such as increased chance of infections, thrombotic events, acute renal failure, pulmonary complications, sepsis, and mortality in patients undergoing surgical procedures [3–7]. Authors estimate > 25% of all allogeneic blood transfusions are inappropriate [8] and this estimate might even be worse for fresh frozen plasma transfusions [9]. There is also a suggestion that all possible measures to reduce unnecessary or inappropriate use of allogeneic products should be taken [8].

The transfusion of blood components and products can be driven by algorithms based on clinical decisions associated or not to standard laboratory tests (SLTs) or viscoelastic haemostatic assays (VHAs) [1,10]. The most common SLTs are activated partial thromboplastin time (aPTT), prothrombin time (PT), platelet count (PC), plasma

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fibrinogen concentration (PFC) and activated clotting time (ACT) [11]. Although these laboratory tests are widely available, the turn-around time with the use of these tests can be as long as 45 to 60 min and this delay in the management of coagulopathies diminishes their usefulness in urgent settings [1,2,12–17]. It is also argued that PT and aPTT are poor predictors of bleeding in critically ill patients [18,19].

The fast and comprehensive results made the VHAs popular for monitoring the coagulation in patients undergoing cardiac surgery, liver transplantation and obstetric procedures [20]. They can distinguish between major coagulopathies, such as thrombocytopenia, deficiency of coagulation factors, heparin effect, hypofibrinogenemia, and hyperfibrinolysis, and guide a targeted, individualized and timely intervention [13,14]. Using VHAs near the patient, a response of 15 to 20 min could be achieved [2,8]. In addition, these tests are associated with a reduction in the number and amount of allogeneic products used in patients with potential clinical benefit [1,2,12,21,22]. Some very recent reviews, however, showed divergent results for the technology and raised questions about the efficacy of the VHAs in terms of final outcomes [1,2,21,22]. The objective of this study is, therefore, to evaluate the clinical benefits of VHAs in patients undergoing surgical procedures.

2. Methods

A systematic review with meta-analysis was conducted to assess the efficacy and safety of the VHAs compared to SLTs and/or clinical decision [which will be called Standard-of-Care (SOC) hereon] to monitor coagulation and to define the therapeutic approach for the treatment of postoperative coagulopathies in patients undergoing surgical procedures. This report followed the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [23–25]. The research question in PICO format is available at Supplemental Materials - Appendix 1.

2.1. Intervention

Two devices are most commonly recommended to perform the VHAs: (i) thromboelastography (TEG®; Haemoscope Corporation, Niles, IL, USA), which was described primarily in 1948 [26]; and (ii) rotational thromboelastometry (ROTEM®; Tem Innovations, GmbH, Munich, Germany), which emerged in the 1990s as an modification of the thromboelastography method. The principle of these tests is the change in blood viscoelastic properties during clot formation. The firmer the clot, the greater the force opposing the rotation or vibration movement of the device [14].

2.2. Literature search

An electronic search was performed on Medline (via PubMed), The Cochrane Library (in Trials), Lilacs/Ibecs (via BVS), and Center for Reviews and Dissemination (CRD) databases using various descriptors such as “Surgical Procedures, Operative”, “General Surgery”, “Surgery”, “Transplants”, “thromboelast*”, “Viscoelastic blood tests” and “rotem”. An additional search was performed on references from included studies, area-specific journals, conference abstracts, and Google Scholar. The searches were conducted on May 7, 2019, and updated on June 5, 2019. References were imported into EndNote® 7.5 for the removal of duplicates and later transported into Microsoft Excel® 2013 for the selection process. The search strategies and results are available at Supplemental Materials - Appendix 2.

2.3. Selection of studies

Randomized controlled trials that directly compared VHAs with SOC to guide transfusion in patients undergoing surgical procedures were included. Although not included in the analysis, some identified systematic reviews served as a source of unpublished data. Data taken indirectly from these reviews were explicit in the text. No date, language or place restrictions were made. In phase 1, references were selected by review of titles and abstracts. In phase 2, the full-texts of the remaining references were retrieved and evaluated for inclusion. In phase 3, data were collected regarding the outcomes of interest. Phases 1, 2 and 3 were performed by two researchers (AS and AO) independently and the differences resolved by consensus, as instructed by the Cochrane Collaboration method [27].

2.4. Outcomes

The primary outcomes evaluated were: mortality at the longest follow-up, acute kidney injury, thrombotic events, and reoperation for bleeding. Secondary outcomes were the risk of RBC, FFP, platelet, prothrombin complex, factor VIIa, and fibrinogen transfusion, the volume of RBC, FFP and platelet transfused, length of Intensive Care Unit (ICU) stay, and length of hospital stay.

2.5. Data analysis

Data was collected in pre-defined forms. The quantitative synthesis was performed in Review Manager® 5.3 using the DerSimonian and Laird random effects model [27,28]. Risk ratio (RR) or mean difference (MD) data were presented with 95% confidence intervals (95% CI). Results with p-value < 0.05 were considered statistically significant. Analyzes with $I^2 > 30\%$ were considered to have moderate heterogeneity, $I^2 > 50\%$ to have substantial heterogeneity, and $I^2 > 75\%$ to have high heterogeneity. Heterogeneity data with a p-value of the χ^2 test < 0.10 were considered statistically significant [27]. Volume data were included in the meta-analysis in units (U). When these data were presented in other units in the original references, the correction factors applied were: 250 mL/U for RBC; 270 mL/U for FFP; 340 mL/U for platelet concentrate [21]. Publication bias was accessed through funnel plots when there were at least ten studies included in the meta-analysis.

2.6. Quality assessment

To assess the methodological quality of the randomized controlled trials, the Cochrane Collaboration Risk of Bias scale was used [27]. Risk of Bias assessment of the primary studies was evaluated in duplicate (AS and AO) and divergences were solved by consensus. To evaluate the level of evidence, the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE) was used. The quality of evidence was classified into four levels: high, moderate, low and very low [27,29–34].

3. Results

3.1. Studies selection

The literature search identified 930 references (Supplementary Materials - Appendix 2). Of these, 157 duplicates were excluded, totaling 773 references included in the selection process. In phase 1, 729 references were excluded mainly by study type, population, intervention and comparator and some duplicates that remained after removal with EndNote® 7.5. Of the 44 references included in Phase 2, 3 could not be retrieved for full-text evaluation (Supplemental Materials - Appendix 3) and 20 were excluded. Reasons for exclusion are available at Supplemental Materials - Appendix 4. The final analysis encompassed 21 publications, referring to 21 studies (Fig. 1).

3.2. Characteristics of included studies

Of the 21 studies included, 16 were performed on patients undergoing cardiac surgery [35–50], two in the context of liver surgery

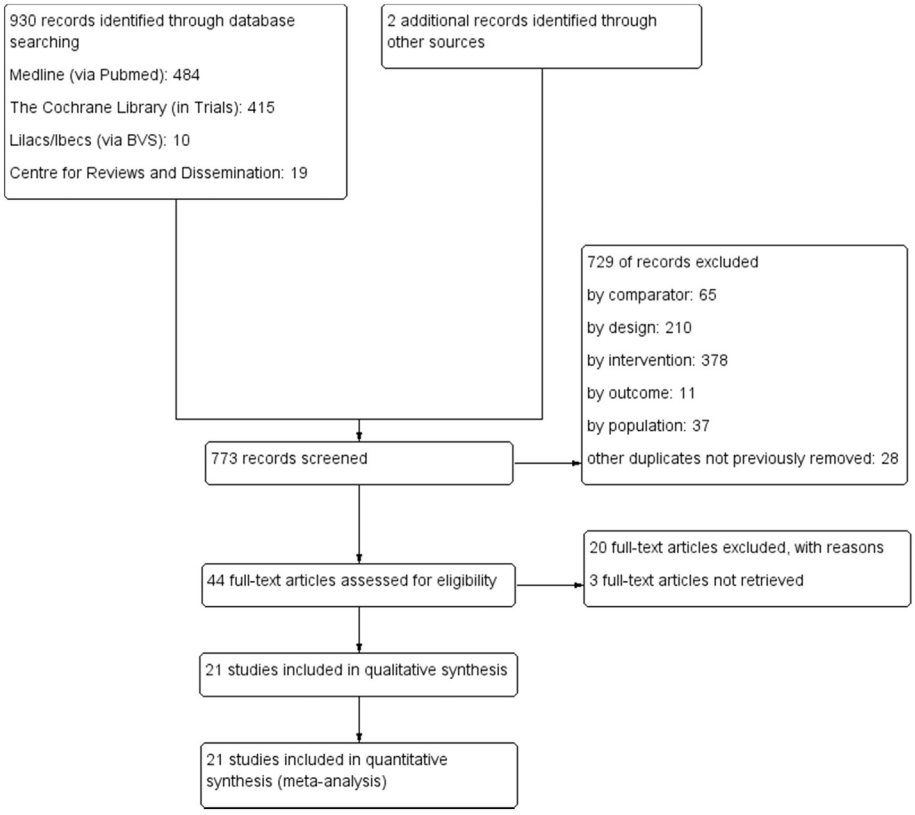

Fig. 1. Study flow diagram.

[20,51], one in orthopedic procedures [52], one in trauma [39] and one in burn victims [53]. Eleven studies used TEG® [20,35,36,39,41,42,44,45,51,52,54] and ten used ROTEM® [37,38,40,43,46–50,53] as the VHA device. Most studies included relatively small samples (100 patients or less: 15 studies; 100 to 200 patients: three studies; 200 to 300 patients: two studies). One study included 7406 patients [50], which is larger than the sum of all other studies. The studies were conducted in 12 countries: Turkey [43,44], United Kingdom [36,41], China [45,52], Italy [51], Germany [38,40,46,48], USA [35,39,54], Canada [50], Japan [49], Spain [47], Austria [53], Iran [37] and Australia [42]. Four studies are only available as a congress summary [37,40,47,52]. The general characteristics of the included studies are available in Supplemental Materials - Appendix 5.

3.3. Outcome analysis

3.3.1. Mortality at the longest follow-up

The VHAs significantly reduced patients' risk of death compared to the SOC (7.3% vs. 12.1%; RR = 0.64, 95%CI = 0.43–0.96, *p*-value = 0.03; I^2 = 0%, p-value = 0.52; 10 studies, 888 patients; Fig. 2). No significant difference of effect was identified at the subgroup analysis by type of technology or population (Fig. 2 and Supplemental Materials - Appendix 6). Heterogeneity between subgroups is null in both cases. However, it was observed that studies in liver patients showed results very close to the line of no effect. When these studies are removed from the meta-analysis, the result is even more favorable to the VHAs (5.7% vs. 10.9%; RR = 0.54, 95%CI = 0.34–0.87, p-value = 0.01; I^2 = 0%, p-value = 0.55; 8 studies, 800 patients). When considering only cardiac patients, the effect of the intervention on mortality is not significant at 5% in a random-effects model, but it is at a 10% significance level and in a fixed-effects model, since heterogeneity is very small (RR = 0.55, 95%CI = 0.28–1.10, p-value = 0.09 vs. RR = 0.50, 95%CI = 0.26–0.96, p-value = 0.04; I^2 = 1%, p-value = 0.40; 7 studies, 689 patients). When only cardiac patients with post-CPB coagulopathy are considered, the results are significant and more favorable to the technology even in a random-effects model (RR = 0.33, 95%CI = 0.12–0.91, p-value = 0.03; I^2 = 0%, p-value = 0.34; 2 studies, 144 patients).

The largest study published on the subject [50] did not directly report data on mortality. A subsequent systematic review [2] reported mortality data from the later, but only in the format of measure of association (log[RR] = −0.13, SE = 0.25, RR = 0.88, 95%CI = 0.54–1.43, 7402 patients). With log[RR], SE and the number of participants in the intervention and control group, the number of deaths was estimated using the calculator provided by the Cochrane Collaboration Review Manager® 5.3 software and the data was included in the meta-analysis. Even after including that data, a statistically significant advantage for VHAs over the SOC was demonstrated, but with a more discrete association (1.5% vs. 2.2%; RR = 0.73, 95%CI = 0.53–0.99, p-value = 0.04; I^2 = 0%, p-value = 0.54; 11 studies, 8290 patients; Supplemental Materials – Appendix 7). In addition to being statistically significant, the relative risk reduction (RRR) of 36%, or 27% when Karkouti et al. [50] is included, is clinically important. However, there is imprecision in the results and there are not enough studies to allow the evaluation of the funnel chart.

3.3.2. Acute kidney injury

VHAs significantly reduced the risk of acute kidney injury in patients compared to SOC (10.5% vs. 17.6%; RR = 0.53, 95%CI = 0.34–0.83, p-value = 0.005; I^2 = 0%, p-value = 0.43; five studies, 449 individuals; Fig. 3). In addition to being statistically significant, the 47% RRR is clinically important. However, there is imprecision in the results, as can be seen by the relatively long confidence interval. This is associated with the small sample size and number of events. Heterogeneity between subgroups is null for the technology type. All studies were conducted in cardiac patients. Acute kidney injury data from the study by Paniagua et al. [47] was extracted

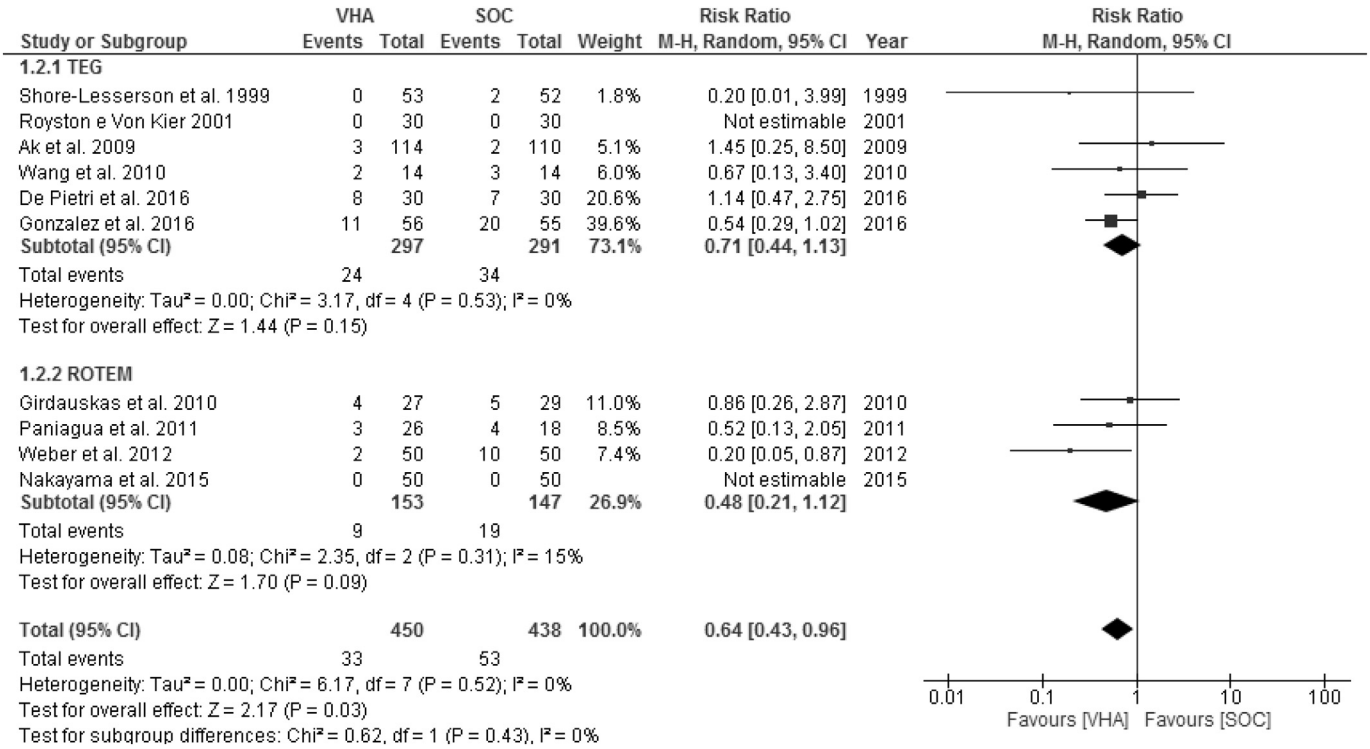

Fig. 2. Meta-analysis of mortality at the longest follow-up, stratified by technology.

indirectly from Wikkelsø et al. [1] and Serraino and Murphy [22]. There are not enough studies to allow the assessment of the funnel chart.

3.3.3. Thrombotic events

VHAs increased the risk of thrombotic events compared to SOC by 17% (RR = 1.17, 95%CI = 0.36–3.81, p-value = 0.80; I^2 = 0%, p-value = 0.41; four studies, 305 patients; Fig. 4). Heterogeneity between groups is null for the type of technology. The four studies were conducted in cardiac surgery patients. The thrombotic event data from the study by Paniagua et al. [47] was extracted indirectly from Wikkelsø et al. [1] and Serraino and Murphy [22]. There are not enough studies to allow evaluation of the funnel plot. There is a significant imprecision in the result. The number of events and the sample size included in the meta-analysis are not sufficient to allow any conclusion about the thrombotic event rate in each group.

3.3.4. Reoperation for bleeding

VHAs were associated to fewer cases of reoperation for excessive bleeding than SOC, but the difference was not statistically significant (8.1% vs. 10.8%; RR = 0.82, 95%CI = 0.55–1.23, p-value = 0.34; I^2 = 0%, p-value = 0.63; nine studies, 887 patients; Fig. 5).

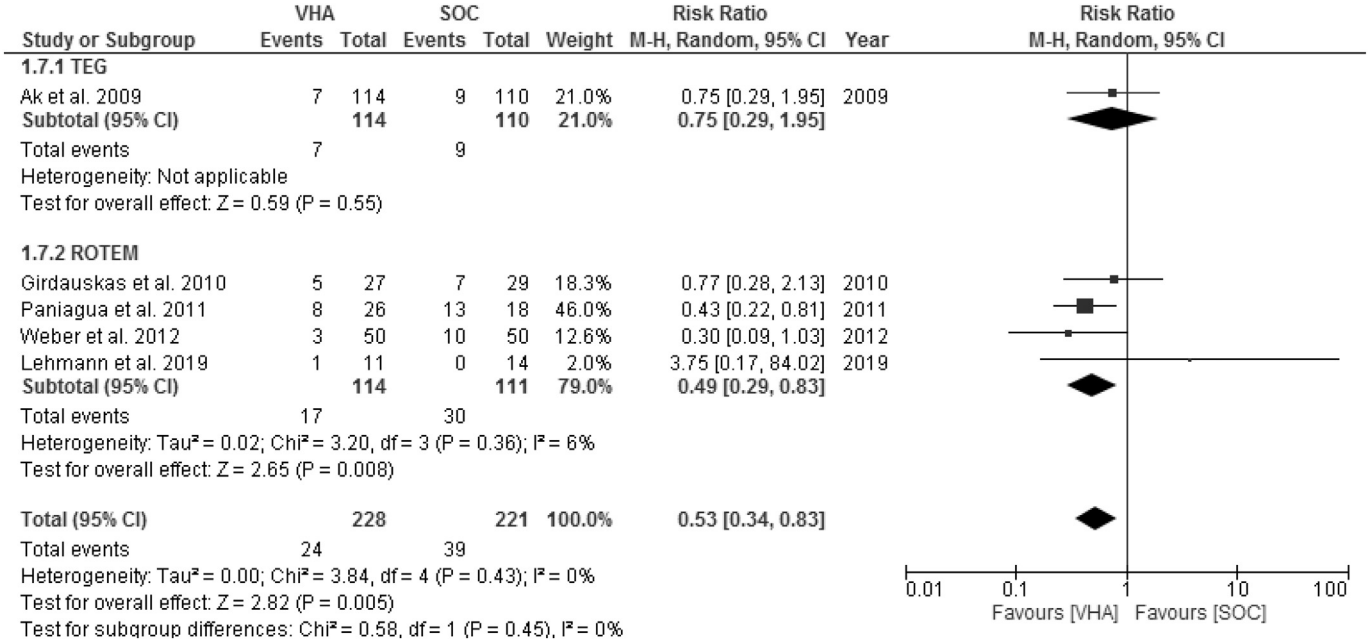

Fig. 3. Meta-analysis of risk of acute kidney injury, stratified by technology.

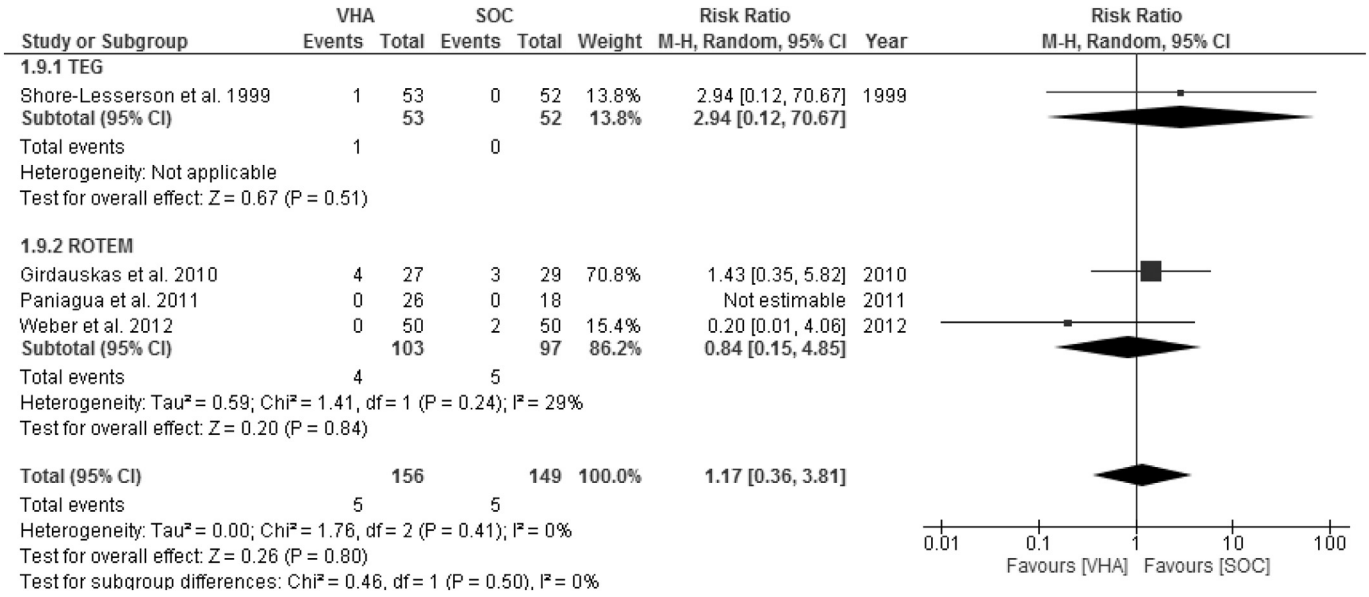

Fig. 4. Meta-analysis of risk of thromboembolic events, stratified by technology.

Heterogeneity between subgroups is null for the type of technology. All studies were conducted on patients undergoing cardiac surgery. Data from Paniagua et al. [47], Royston and von Kier [41] and Kempfert et al. [40] were extracted indirectly from Wikkelsø et al. [1] and Serraino and Murphy [22]. There are not enough studies to allow evaluation of the funnel plot and there is imprecision in the results.

3.3.5. RBC transfusion

VHAs were associated to lower risk of RBC transfusion than SOC, but the difference was not statistically significant (47.2% vs. 47.3%; RR = 0.93, 95%CI = 0.87–1,01, p-value = 0.07; I^2 = 37%, p-value = 0.09; 13 studies, 8339 patients; Supplemental Materials - Appendix 8). There is a moderate and statistically significant heterogeneity in the data. This heterogeneity is very dependent on Karkouti et al. [50]. The removal of this study from the meta-analysis changes the RR and the result becomes significantly in favor of VHA with low heterogeneity (60.9% vs. 69.4%; RR = 0.91, 95%CI = 0.85–0,97, p-value = 0.004; I^2 = 0%, p-value = 0.48; 12 studies, 937 patients). The clinical relevance of reducing the risk of RBC transfusion, however, is small in both cases. Heterogeneity between groups is null for populations, but moderate and not significant for the type of technology (I^2 = 32%, p-value = 0.23). This difference is also dependent on

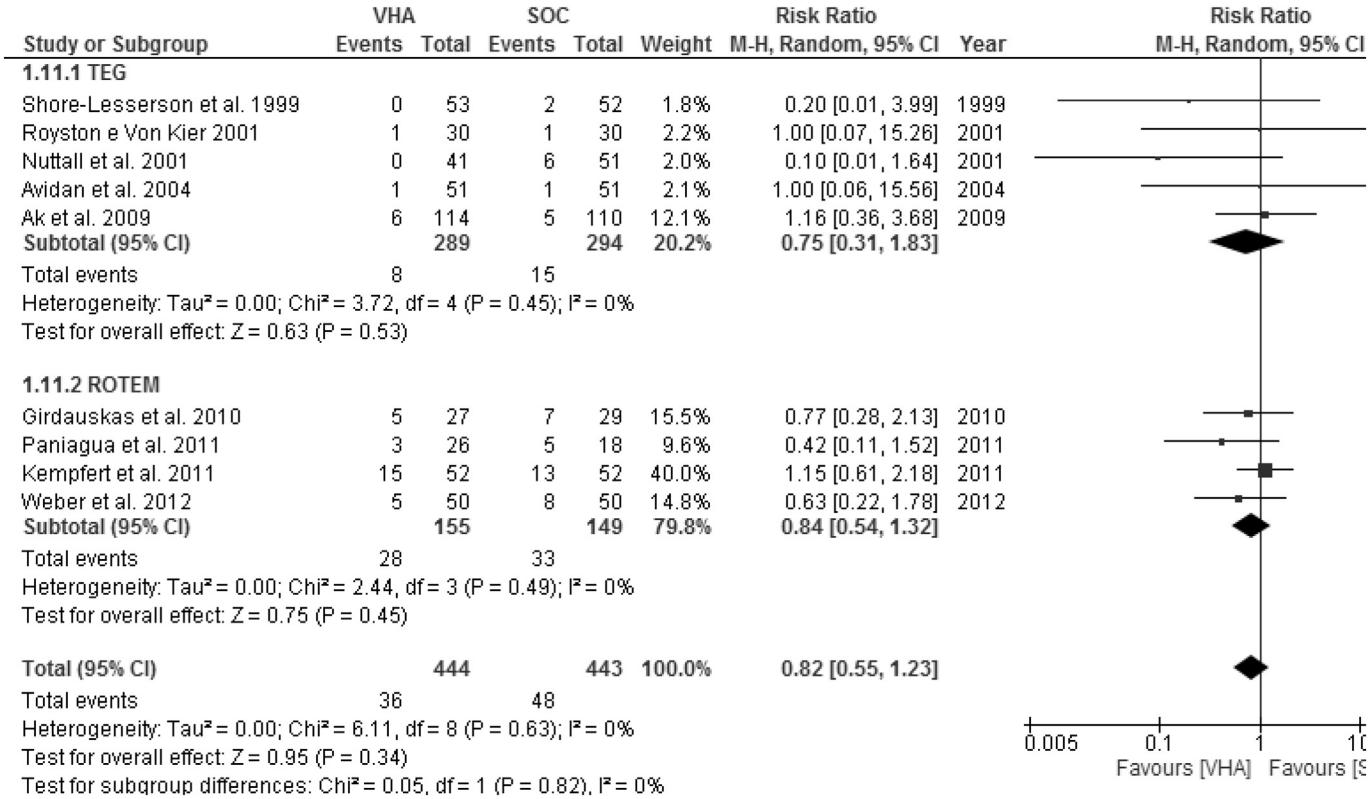

Fig. 5. Meta-analysis of risk of reoperation for bleeding, stratified by technology.

Karkouti et al. [50]. When this study is removed from the analysis, heterogeneity between groups by technology is also null. Visual inspection of the funnel chart indicates the presence of some publication bias (Supplemental Materials - Appendix 9). The confidence interval in the analysis is not very wide, which suggests that the result is not imprecise and that the effect of the technology for this outcome is not clinically very relevant. There is also inconsistency when the study by Karkouti et al. [50] is included in the analysis.

Considering the volume of RBC transfused, the meta-analysis result significantly favored the viscoelastic tests (MD = −1.63 U, 95%CI = −3.00 to −0.26, p-value = 0.02; I^2 = 73%, p-value = 0.005; five studies, 332 patients; Supplemental Materials - Appendix 10). Heterogeneity is substantial and significant in the overall analysis because of the heterogeneity between different populations (I^2 = 73.1%, p-value = 0.005), but not by technology type (I^2 = 0%, p-value = 0.95). The study by Girdauskas et al. [46] was not included in the meta-analysis because it did not provide mean and standard deviation data. The data from Gonzalez et al. [39] were collected indirectly from Fahrendorff et al. [21]. However, the exclusion of this study does not significantly modify the result (MD = −1.63, 95%CI = −3.10 to −0.15, p-value = 0.03; I^2 = 80%, p-value = 0.002; four studies, 223 patients).

3.3.6. Transfusion of platelets

VHAs were significantly associated to a lower risk of platelet transfusion than SOC (23.9% vs. 27.3%; RR = 0.74, 95%CI = 0.59–0.92, p-value = 0.006; I^2 = 47%, p-value = 0.03; 14 studies, 8399 patients; Supplemental Materials - Appendix 11). There is moderate and significant heterogeneity in the result. No single study has major influence on this heterogeneity. Heterogeneity between groups is substantial and significant for the type of technology (I^2 = 71.5%, p-value = 0.06). The result is more favorable to TEG® than to ROTEM® compared to SOC [(TEG: 13.6% vs. 24.9%; RR = 0.54, 95%CI = 0.37–0.78, p-value = 0.001; I^2 = 0%, p-value = 0.58; five studies, 522 patients) vs. (ROTEM: 24.6% vs. 27.5%; RR = 0.82, 95%CI = 0.65–1.03; p-value = 0.06, I^2 = 46%, p-value = 0.06; nine studies, 7877 patients); Supplemental Materials - Appendix 12]. Heterogeneity between subgroups is moderate but not significant for the population (I^2 = 48.7%, p-value = 0.14). The result for liver patients is significant and more favorable to the technology than for other subpopulations (RR = 0.36, 95%CI = 0.15–0.87, p-value = 0.02). Statistical significance was also achieved for cardiac patients as a subgroup (RR = 0.78, 95%CI = 0.63–0.96, p-value = 0.02). The removal of Karkouti et al. [50] did not significantly impact the overall assessment (23.0% vs. 34.2%; RR = 0.68, 95%CI = 0.52–0.90, p-value = 0.007; I^2 = 40%, p-value = 0.07; 13 studies, 997 patients). The clinical relevance of reducing the risk of platelet transfusion is uncertain, but may be important if associated with other outcomes (RRR = 26% to 32%). Visual inspection of the funnel plot slightly suggests publication bias (Supplemental Materials - Appendix 13). There is imprecision and inconsistency in the result, but not very important.

The result of the meta-analysis comparing the VHA to SOC for the volume of platelets transfused was not statistically significant (MD = −0.60, 95% CI = −1.66 to 0.45, p-value = 0.26; I^2 = 91%, p-value < 0.001; four studies, 302 patients; Supplemental Materials - Appendix 14). All studies included in the meta-analysis used TEG® as VHA. Heterogeneity between different populations is high and significant (I^2 = 91,4, p-value < 0,001). The studies by Girdauskas et al. [46] and Schaden et al. [53] favored the VHA but were not included in the meta-analysis because they did not provide data on mean and standard deviation. The data from Gonzalez et al. [39] indirectly was collected from Fahrendorff et al. [21].

3.3.7. Transfusion of FFP

VHAs were significantly associated to a lower risk of FFP transfusion than SOC (RR = 0.57, 95%CI = 0.41–0.81, p-value = 0.001; I^2 = 85%, p < 0.001; 12 studies, 8328 patients; Supplemental Materials - Appendix 15). There is high and significant heterogeneity in the result. No single study has a major influence on this heterogeneity. Heterogeneity between groups is low and not significant for the type of technology (I^2 = 29.5%, p-value = 0.23). The point estimate is more favorable to TEG® (RR = 0.38, 95%CI = 0.15–0.96, p-value = 0.04; I^2 = 66%, p-value = 0.03; four studies, 491 patients) than ROTEM® (RR = 0.69, 95%CI = 0.49–0.98, p-value = 0.04; I^2 = 85%, p-value < 0.001; eight studies, 7837 patients). Heterogeneity is substantial and significant in the evaluation within the TEG® subgroup and high and significant in the ROTEM® subgroup. Heterogeneity between subgroups is high and significant for different populations (I^2 = 80.5%, p-value = 0.006; Supplemental Materials - Appendix 16). The results for liver patients (RR = 0.15, 95%CI = 0.05–0.45, p-value = 0.0007; one study, 60 patients) and burn victims (RR = 0,04, 95%CI = 0.00–0.60, p-value = 0.02; one study, 30 patients) are significant and more favorable for the technology than for patients undergoing cardiac surgery. The removal of Karkouti et al. [50] does not impact significantly the overall result (RR = 0.44, 95%CI = 0.25–0.78, p-value = 0.005; I^2 = 87%, p-value < 0.001; 11 studies, 926 patients). The clinical relevance of reducing the risk of transfusion of FFP is uncertain but may be important if associated with other outcomes (RRR = 43%). Visual inspection of the funnel chart suggests publication bias (Supplemental Materials - Appendix 17). There are imprecision and inconsistency in the data, but not very important.

The result of the meta-analysis of volume of FFP transfused significantly favored VHAs (MD = −0.90,95%CI = −1.40 to −0.41, p-value = 0.0003; I^2 = 53%, p-value < 0.09; four studies, 302 patients; Supplemental Materials - Appendix 18). All studies included in the meta-analysis evaluated TEG® and the populations were different among them. The heterogeneity between studies is substantial and statistically significant. The studies by Girdauskas et al. [46] and Schaden et al. [53] reported data favoring the VHAs but were not included in the meta-analysis because they did not provide data on the mean and standard deviation. The data from Gonzalez et al. [39] was indirectly collected from Fahrendorff et al. [21].

3.3.8. Other outcomes

The outcomes of risk of use of fibrinogen, prothrombin complex, and factor VIIa, length of hospital stay and length of ICU stay are available at Supplementary Materials – Appendix 19 to 23.

3.4. Quality assessment

Many studies did not report the methods used for random sequence generation and allocation concealment. The studies by Karkouti et al. [50] and Gonzalez et al. [39] did not perform randomization at the individual level. Karkouti et al. [50] is Stepped-Wedge Clustered Trial. The authors randomized hospitals into one of six groups, consisting of two hospitals each. The intervention was sequentially implemented with a one-month separation between groups. The order of implementation was random. Thus, randomization and allocation concealment cannot be guaranteed. Gonzalez et al. [39] did a randomization process by the alternation of weeks. Therefore, it was considered at a high risk of bias for random sequence generation and allocation concealment. Almost all studies were not blinded, which is understandable given the nature of the intervention, but this choice may influence the decision of transfusion of blood components. Since there is a hypothesis that suggests that the transfusion of blood products may be associated with adverse clinical outcomes, they were considered to have a high risk of bias [3–7]. Most studies were considered to have a low risk of bias for incomplete outcome data. The relatively short follow-up times and the nature of the interventions contributed to this. Many studies did not include the research protocol for the assessment of selective reporting. Most studies for which the protocol number was

identified had a low risk of bias for this criterion. The Karkouti et al. [50] study was considered at a high risk of bias for not reporting absolute data and all outcomes of interest for a study of its size. Four studies were only available in abstract form [37,40,47,52], so they could not be assessed for the risk of bias (Supplementary Materials - Appendix 24). The quality of evidence was considered between low and very low (Supplementary Materials - Appendix 25). Many outcomes showed inconsistency and imprecision. All outcomes were considered to be at high risk of bias and the level of evidence was lowered at one point since the intervention influences the use of allogeneic blood products and there was no masking in the studies.

4. Discussion

VHAs were associated with a statistically significant reduction in mortality, risk of acute kidney injury, transfused red cell volume, risk of platelet transfusion, risk of FFP transfusion, and volume of FFP transfusion. No significant difference was observed in terms of risk of thrombotic events, risk of reexploration for bleeding, risk of RBC transfusion, the volume of platelets transfused, use of fibrinogen, use of prothrombin complex, use of factor VIIa, length of hospital stay or length of ICU stay.

Mortality is the most important outcome included in the analysis. Another six systematic reviews included mortality as an outcome for their assessment. In five of them, the statistically significant advantage with the use of VHA was not demonstrated [2,21,22,55,56] and one presented significant data favoring the technology [1,12] (Supplemental Materials - Appendix 26). The latter, however, used a fixed-effects model. Considering that populations are clearly different and this difference may affect the outcome, this study did not consider it appropriate to use a fixed-effects model [57]. Our review found statistically significant data in favor of the VHAs using a random-effects model. If a fixed-effects model were applied, as heterogeneity is null, the results would be even more favorable to the technology (RR = 0.61; 95%CI = 0.41–0.90; p-value = 0.01; ten studies, 888 patients). No significant difference was observed in the subgroup analysis by type of population, but there seems to be a trend in favor of the technology for cardiac surgery. Haensig et al. [58] confirm this advantage for the VHAs in terms of mortality at a 5-year follow-up time. Possibly the statistically significant difference was not observed in this subgroup meta-analysis because the optimal information size was not reached. Karkouti et al. [50] presented a less restrictive selection of patients and included patients undergoing cardiac surgery with cardiac bypass. This may be associated with the relatively low mortality observed in this study compared to others. In fact, a subgroup analysis dividing the studies by reporting inclusion of patients with massive bleeding or coagulopathy seems to indicate that the intervention is more useful in these patients [(14.8% vs. 26.8%; RR = 0,58, 95%CI = 0.32–1.07, p-value = 0.08; I^2 = 33%, p-value = 0.22; four studies, 315 patients) vs. (RR = 0.85, 95%CI = 0.56–1.30, p-value = 0.45; I^2 = 0%, p-value = 0.85; seven studies, 7975 patients); Supplementary Materials - Appendix 27].

Other important clinical outcomes were included in the analysis. In addition to this study, three other systematic reviews with meta-analysis found that VHAs are associated with a lower risk of acute kidney injury [1,12,22,55]. Sample sizes, however, are relatively small for meta-analyses of randomized controlled trials, which yielded more VHA-favorable results (Supplemental Materials - Appendix 28). Like our study, another systematic review of randomized controlled trials observed a RR higher than 1 for the risk of thrombotic events [1,12], also not statistically significant. Another review [55], which included observational and experimental studies, found a significant advantage for the technology in this outcome (Supplementary Materials - Appendix 29). Deppe et al. [55] observed that 1.3% of patients using VHAs and 2.9% of patients in the SOC had thrombotic events (OR = 0.44; 95%CI = 0.28 to 0.70, p-value = 0.0005; 3975 patients). In this study, there was no difference between the SOC and VHA groups regarding the occurrence of stroke (OR = 0.64; 95%CI = 0.31 to 1.30, p-value = 0.1345, 4054 patients). Serraino and Murphy [22] also found a non-significant advantage for the SOC regarding the occurrence of stroke (RR = 1.73, 95%CI = 0.41–7.23; I^2 = 0%; p-value = 0.45; two studies). The number of events and sample size are too small for any kind of conclusion. There is a reasonable likelihood that this result against the technology happened at random. Two meta-analyses that included only randomized controlled trials, such as ours, also found no significant difference between groups in terms of risk of reexploration for bleeding [1,12,22]. The observed RRR was consistent with the one found in this study (0.18 vs. 0.18 and 0.25). Our study and that of Serraino and Murphy [22] used exactly the same data as Wikkelso et al. [1,12] for this outcome and found different results due to the latter's use of a fixed-effects model. Three other meta-analyses evaluating this outcome found values significantly favorable to technology including observational studies (Supplemental Materials - Appendix 30).

Contrary to our meta-analysis, the results of six other meta-analyses significantly favor the VHAs in terms of the reduction of the risk of RBC transfusion (RR or OR = 0.62 to 0.91; Supplementary Materials - Appendix 31). The result observed here, however, is very dependent on data from Karkouti et al. [50]. Removing it, our study also found data significantly in favor of technology. The RR found is very close to that observed by Lodewyks et al. [2], Serraino and Murphy [22], Li et al. [56] and Wikkelsø et al. [1,12] (0.93 vs. 0.86 to 0.91) and also leaves doubts about the clinical relevance of this finding. The meta-analyses that included observational studies tend to demonstrate results more favorable to the VHAs (RR = 0.62–0.87; [10,55,56]). Another five meta-analyses found data suggesting a significant reduction in platelet transfusion risk(RR or OR = 0.55 to 0.78; Supplemental Materials - Appendix 32) and one study found no significant data favoring VHAs (RR = 0.86, 95%CI = 0.73–1.02; p-value = 0.08; [56]). The greatest effect, however, was observed in the risk of transfusion of FFP (RR or OR = 0.28 to 0.68; Supplementary Materials - Appendix 33). Meta-analyzes that included observational studies tend to present more favorable data.

There is no consensus in the literature on the superiority between ROTEM® and TEG®, so this review included both within the VHA category. Other previous systematic reviews have evaluated TEG® and ROTEM® jointly due to their technical similarity [1,2,12,21,22,56], and with populations undergoing various types of procedure [1,12,21]. In any case, subgroup analyzes considering population and technology were performed and reported. Unlike other studies [10,21,55,56], this systematic review only included studies that contained some form of randomization. Data provided by the study by Karkouti et al. [50] are different from the data considered in the meta-analysis of Serraino and Murphy [22]. We took the data directly from the unadjusted tables of Karkouti et al. [50]. The meta-analysis by Lodewyks et al. [2], co-authored by Karkouti, included the RR for death, but also did not provide absolute data. These data were used to include the study in the meta-analysis, but should be evaluated with some discretion. The lack of standardization of the parameters used to guide transfusion between studies is a limitation worth mentioning. The studies used different protocols and, therefore, some of the differences observed in their results might be due to this. It is worth mentioning that the protocol that guides practice using the SOC and VHA technologies are the real drivers of improvement of clinical outcomes. Our conclusion here is that the protocols guided by VHAs provide better outcomes than protocols guided by SOC. A sensitivity analysis was conducted removing this study when relevant. Some data had to be collected indirectly from other meta-analyses [1,2,12,21,22] because they were not available in the original reports. The data from Khalaf Adeli et al. [37] were obtained from contact with the author. The result of some meta-analyzes, in addition to not being statistically significant, are not clinically significant either; e. g. risk of RBC transfusion, risk of fibrinogen transfusion and length of hospital stay. Even if the sample was bigger, they

might not matter very much. Other analyses, although not statistically significant, are clinically relevant, and if larger individual randomized studies were included, they could also have shown statistical significance; e. g. mortality in cardiac surgery patients, mortality in trauma patients, risk of reoperation for bleeding, risk of use of prothrombin complex and risk of use of factor VIIa. Of course, there is always the chance that these results could have been achieved at random but, particularly for the outcome risk of death in cardiac surgery patients, there seems to be a tendency in favor of the VHAs. Some studies used more than one intervention in the VHA group like Hepcon® and PFA-100 [36], PlateletWorks® [50], Multiplate® Analyzer [38,48], and CoaguChek Plus and Coulter MD II [54] that might have improve results in the intervention group as well. Most studies, with the exception of Weber et al. [48] and Haensig et al. [58] have relatively short follow-up times. More studies with longer follow-up are necessary to advance this discussion.

The VHAs have been recommended in England [11] and Scotland [13] for patients undergoing cardiac surgery with postoperative coagulation disorders and patients undergoing liver transplantation. The recommendation made in England has been criticized by other authors who consider that this approval was based on intermediate outcomes and that there is reasonable doubt about the clinical benefits of the technology [22]. There is also doubt about the relationship between RBC transfusions and adverse results in final outcomes. Serraino and Murphy [22] even stated that the absence of a causal relationship between RBC transfusion and adverse clinical outcomes could partly explain the apparent disagreement between efficacy in reducing transfusion and the observed lack of clinical benefits in several studies [2,21,22,50]. Our assessment, however, is based on final outcomes.

The results of this study should be viewed with discretion. A non-significant p-value does not necessarily mean that the effect was not observed, much less that "there is no difference between the alternatives". It just means that the result was not precise enough to demonstrate with 95% confidence that the difference between the two alternatives is not due to random variation. This may be due to insufficient sample sizes or great variance, which diminishes our confidence that this result will be maintained if the study is repeated in similar conditions. Anyway, it is important to understand that there is some arbitrariness at this 5% threshold [59]. Other than the statistical significance, it is also important to assess the clinical relevance of the findings. The relative risks of death (RR = 0.64 or 0.73) and acute kidney injury (RR = 0.53), in addition to being statistically significant, are also clinically important. In conclusion, VHAs were considered efficacious and safe to guide transfusion in patients undergoing surgery based on final outcomes. This result seems particularly relevant for patients at high-risk of bleeding, coagulopathy or post-CPB bleeding.

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Appendix A. Supplementary data

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