The use of viscoelastic haemostatic assays in non-cardiac surgical settings: a systematic review and meta-analysis

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Background. Thrombelastography (TEG) and rotational thromboelastometry (ROTEM) are viscoelastic haemostatic assays (VHA) which exploit the elastic properties of clotting blood. The aim of this systematic review and meta-analysis was to evaluate the usefulness of these tests in bleeding patients outside the cardiac surgical setting.

Materials and methods. We searched the Cochrane Library, MEDLINE, EMBASE and SCOPUS. We also searched clinical trial registries for ongoing and unpublished studies, and checked reference lists to identify additional studies.

Results. We found 4 randomised controlled trials (RCTs) that met our inclusion criteria with a total of 229 participants. The sample size was small (from 28 to 111 patients) and the follow-up periods very heterogenous (from 4 weeks to 3 years). Pooled data from the 3 trials reporting on mortality (199 participants) do not show any effect of the use of TEG on mortality as compared to standard monitoring (based on the average treatment effect from a fixed-effects model): Risk Ratio (RR) 0.71; 95% Confidence Interval (CI): 0.43 to 1.16. Likewise, the use of VHA does not reduce the need for red blood cells (mean difference –0.64; 95% CI: –1.51 to 0.23), platelet concentrates (mean difference –1.12; 95% CI: –3.25 to 1.02), and fresh frozen plasma (mean difference –0.91; 95% CI: –2.02 to 0.19) transfusion. The evidence on mortality and other outcomes was uncertain (very low-certainty evidence, down-graded due to risk of biases, imprecision, and inconsistency).

Conclusions. Overall, the certainty of the evidence provided by the trials was too low for us to be certain of the benefits and harms of viscoelastic haemostatic assay in non-cardiac surgical settings. More, larger, and better-designed RCTs should be carried out in this area.

Keywords: viscoelastic assay, TEG, ROTEM, bleeding, allogeneic blood transfusion.

Introduction

Viscoelastic testing was initially developed 70 years ago by Hartert to detect real-time changes in viscosity of blood during the clotting process[1]. More recently, with the aim of implementing the original technique, two computerized, commercially-available, automated systems have been developed: thromboelastography (TEG, Haemonetics, Braintree, MA, Unites States of America) and rotational thromboelastometry (ROTEM, Penthapharm, Basel, Switzerland)[2-4]. Both these viscoelastic haemostatic assays tests dynamically evaluate clot formation and fibrinolysis, by continuously measuring and graphically displaying the kinetics of all stages of clot formation (initiation, propagation, strength and dissolution). Technically, a pin suspended by a torsion wire is lowered into a cup filled with whole blood. Either the cup (TEG) or the pin (ROTEM) is alternately rotated clockwise or anti-clockwise. As the blood clots, strands of fibrin form between the cup and the pin transmitting the torque of the cup to the torsion wire. The torque is continuously recorded electronically and displayed as a graph[2,3].

In recent years, TEG and ROTEM have been used to evaluate global clotting function, and to monitor and guide haemostatic treatment and allogeneic blood transfusion requirements in a variety of conditions characterised by excessive bleeding, including major surgery, liver transplantation, obstetric haemorrhage and trauma[5-16]. Interestingly, the beneficial effect of fibrinogen itself, the use of which can be guided and monitored by these techniques, is still debated in some of the aforementioned clinical settings[17,18]. While the use

of these point-of-care systems in patients undergoing cardiovascular surgery has been extensively studied by several randomised controlled trials (RCTs) and their results summarised by many systematic reviews and meta-analyses[5,8,12,19,20], there has been less experience in other clinical settings where the use of this patient blood management technique is not supported by high strength recommendations[21-24].

Thus, the aim of this paper is to review, through a systematic analysis of the existing literature, the published RCTs on the use of TEG and ROTEM viscoelastic haemostatic assay (VHA) technologies in bleeding clinical situations outside the cardiac surgical setting.

Materials and methods

This systematic review was conducted according to the recommended Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guidelines[25].

Search methods

A computer-assisted literature search of the MEDLINE (through PUBMED), EMBASE, SCOPUS and Cochrane Library electronic databases was performed to identify RCTs on the use of TEG and ROTEM in bleeding conditions. The following search strategy was used to maximise search specificity and sensitivity: "viscoelastic assays" AND "thromboelastography" AND "TEG" AND "rotational thromboelastometry" AND "ROTEM" AND "trauma" AND "bleeding" AND "surgery" AND "obstetric hemorrhage" AND "liver transplantation" AND "allogeneic blood transfusion". In addition, we hand-searched the reference lists of the most relevant items (original studies and reviews) in order to identify potentially eligible studies not captured by the initial literature search.

Study selection

Study selection was performed independently by two reviewers (MF and MC), with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (CM). Eligibility assessment was based on the title or abstract and on the full text if required. Articles were eligible if they reported either in the title or in in the abstract the use of TEG and/or ROTEM in patients with bleeding conditions. Only RCTs published in full in English between January 1970 and November 2017 were included in this systematic review and meta-analysis. RCTs evaluating the use of TEG/ROTEM in cardiovascular surgery were excluded from this analysis since they have been extensively reviewed elsewhere[12,19,20].

Data extraction

For each study included in the systematic review, the following data were extracted by two reviewers (MF and MC) independently: sample size (TEG/ROTEM and control groups), inclusion criteria, type of intervention, follow up, blood loss, need for blood transfusion and amount of blood products transfused, mortality, complications and adverse events. The longest follow-up period for each trial was also recorded when available. Disagreement was resolved by consensus and by the opinion of a third reviewer (CM) if necessary.

Outcome measures

The monitoring by VHA during surgical or other invasive procedures was evaluated as a therapeutic treatment possibly producing beneficial effects in haemorrhage-prone patients. The efficacy was evaluated as all-causes mortality reduction (primary outcome). Moreover, the sparing effect regarding the administration of blood products (red blood cells, platelet concentrates and fresh frozen plasma) was also accounted for (secondary outcome).

Assessment of risk of bias in included studies

Two review authors (MF, MC) independently assessed the risk of bias of each included study following the domain-based evaluation described in the Cochrane Handbook for Systematic Reviews of Interventions[26]. They discussed any discrepancies and achieved consensus on the final assessment. The Cochrane "Risk of bias" tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, and other issues relating to bias. We have presented our assessment of risk of bias using two "Risk of bias" summary figures: 1) a summary of bias for each item across all studies; and 2) a cross-tabulation of each trial according to all the "Risk of bias" items.

"Summary of findings" tables

We used the principles of the GRADE system to assess the quality of the body of evidence associated with specific outcomes, and constructed a "Summary of findings" table using REVMAN 5[27]. These tables present key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of available data for the main outcomes[28]. The "Summary of findings" tables also includes an overall grading of the evidence related to each of the main outcomes using the GRADE approach, which defines the certainty of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest (Online Supplementary Table SI). The

certainty of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias[29]. We have presented the following outcomes in the "Summary of findings" tables: i) mortality; ii) transfusion of red blood cells; iii) transfusion of platelet concentrates; and iv) transfusion of fresh frozen plasma.

When evaluating the "Risk of bias" domain, we down-graded the GRADE assessment only when we classified a study as being at high risk of bias for one or more of the following domains: selection, attrition, reporting, and other bias; or when the "Risk of bias" assessment for selection bias was unclear (this was classified as unclear for either the generation of the randomisation sequence or the allocation concealment domain). We did not down-grade for high risk of bias in performance and detection domains, since we judged that the outcomes considered are not likely to be influenced by lack of blinding, and for unclear "Risk of bias" assessments in other domains.

Statistical evaluation and meta-analysis

The primary outcome was mortality, evaluated through meta-analytical pooling as the Risk Ratio (RR) between VHA monitoring (treatment group) *vs* standard of care (control group). Secondary outcomes were related to blood product use, including red blood cells (RBC), platelet concentrates (PC), and fresh frozen plasma (FFP) transfusion. For the secondary outcomes, the main index under evaluation through meta-analytical pooling was the unstandardised weighted mean difference (WMD) between VHA monitoring (treatment group) *vs* standard of care (control group).

In meta-analysis of continuous outcomes, the sample size, mean, and standard deviation are required from included studies. Some trial studies only report the median, the minimum and maximum values (range), and/or the first and third quartiles (interquartile range). When results concerning quantitative outcomes are provided as medians and range, or interquartile interval, pooling them with studies reporting means and standard deviations is problematic. Methods are available in the literature to convert medians and ranges to means and standard deviations. The best known are those by Hozo and Colleagues[30] and by Wan and Colleagues[31]. In the present meta-analysis, we used the method of Hozo and Colleagues, which is more reliable for small size studies.

We used a random-effects model as default approach for undertaking a meta-analysis. A fixed-effect approach was used only when clinical heterogeneity was considered minimal and statistical heterogeneity was not statistically significant for the χ^2 value and 0% for the I^2 measure[32].

In addition, the power for a prospective extension of the meta-analytic accumulation of evidence was investigated for the mortality outcome by the conventional approach, assuming a hypothetical, provisional guess (based on the actual data) of risk as 21% for TEG-monitored patients, and as 30% for control patients.

For statistical calculations and bias assessment, we used Cochrane Review Manager 5 software and Stata 15.1. Moreover, the same task was also viewed as an evolving prospective meta-analysis and graphically depicted by trial sequential analysis (TSA) with the use of TSA software[33,34].

Results

In total, 4,524 articles were initially identified after the initial electronic and manual search, which was concluded on 30th November 2017 (Figure 1). Of these, 4,472 were excluded because they focused on other topics. Thus, 52 potentially relevant articles were selected and the next screening led to the exclusion of 48 additional studies (reviews, protocols of RCTs, cohort studies, duplicates, studies containing no informative data). The remaining four randomised studies[35-38] were included in the systematic review and meta-analysis (see Table I for main characteristics and results of the included studies). Overall, 229 patients (114 undergoing viscoelastic tests and 115 controls) were enrolled in the four RCTs selected for the meta-analysis. Of these, three trials reported mortality as outcome, with different follow-up times (28 days, 90 days and 3 years).

Risk of bias in included studies

We assessed no study as being at low risk of bias. All the four included studies were at high risk of bias for one or more domains, and three studies were at unclear risk of bias for three domains (Figures 2 and 3).

Allocation

We assessed one study as being at high risk of selection bias, as randomisation was by weekly alternation of the two treatments, so the intervention allocations could have been foreseen in advance[37]. The reports on random sequence generation and allocation concealment in the remaining studies were unclear.

Blinding

All the studies were open label, and were graded as high risk of performance bias (blinding of participants and personnel). The study by Gonzalez *et al*.[37] was graded at low risk of detection bias, since outcome assessors had access to the text assigned to the study group and were blinded to the other tests, and because an independent data and safety

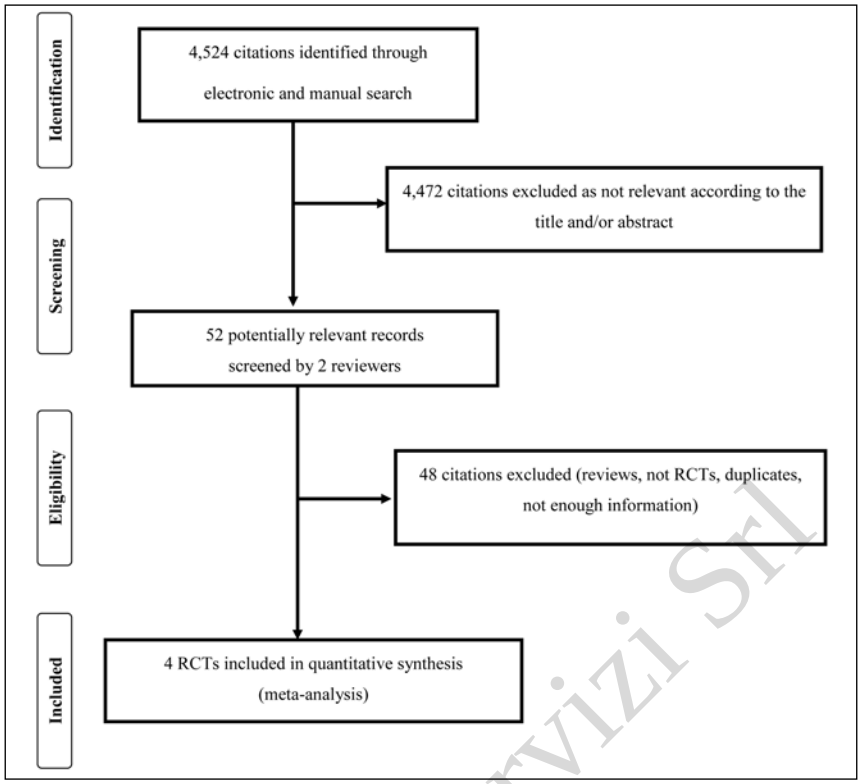

Figure 1 - Flow chart of the inclusion of the studies.

Table I - Characteristics and main results of the 4 RCTs on the use of TEG/ROTEM in bleeding patients included in the meta-analysis.

First author, year[ref.]	VHA group/ control group	Inclusion criteria	Interventions	Follow-up	Outcomes			
					Mortality[1]	*Blood loss mL*[2]	*Transfusions units*[2]	*Complications/ AEs*
Wang, 2010[35]	14/14	Patients undergoing OLT	IG: monitoring during surgery using TEG assay CG: monitoring using conventional coagulation assays	3 years	IG: 2/14 (14.3) CG: 3/14 (21.4)	IG: 4775.7 (4264.7) CG: 6348.0 (3704.1)	IG: RBC 14.2 (7.1) PC 27.3 (13.9) FFP 12.8 (7.0) CG: RBC 16.7 (12.8) PC 30.1 (18.5) FFP 21.5 (12.7)	NR
Schaden, 2012[36]	14/16	Surgical excision of burn wounds performed on the third day after burn trauma	IG: monitoring using ROTEM assay CG: coagulation management according to clinician's judgment	Until discharge from ICU	NR	NR	IG: RBC 3.1 (2.1) PC 0 FFP 0 CG: RBC 4.8 (3.0) PC 0.2 (0-2)[3] FFP 5.0 (1.5-7.5)[3]	NR
Gonzalez, 2016[37]	56/55	Injured adult patients	IG: monitoring using TEG assay CG: monitoring using conventional coagulation assays	28 days	IG: 11/56 (19.6) CG: 20/55 (36.4)	NR	IG: RBC 9.5 (5-16)[3] PC 1.0 (0-2)[3] FFP 5.0 (3-9)[3] CG: RBC 11.0 (6-16)[3] PC 1.0 (0-2)[3] FFP 6.0 (4-9)[3]	NR
De Pietri, 2016[38]	30/30	Patients with cirrhosis and severe coagulopathy undergoing invasive procedures	IG: monitoring using TEG assay CG: standard of care	90 days	IG: 8/30 (26.6) CG: 7/30 (23.3)	NR	IG: RBC 0.2 (0-2)[3] PC 0.9 (0-6)[3] FFP 0.7 (0-10)[3] CG: RBC 0.3 (0-2)[3] PC 3.5 (0-10)[3] FFP 4.4 (0-6)[3]	1 post-procedure bleeding event in CG

VHA: viscoelastic hemostatic assay; AEs: adverse events; OLT: orthotopic liver transplantation; IG: intervention group; CG: control group; TEG: thromboelastography; ROTEM: rotational thromboelastometry; ICU: intensive care unit; RBC: red blood cells; PC: platelet concentrates; FFP: fresh frozen plasma; NR: not reported. [1]Number (%); [2]Mean (standard deviation); [3]Median (range).

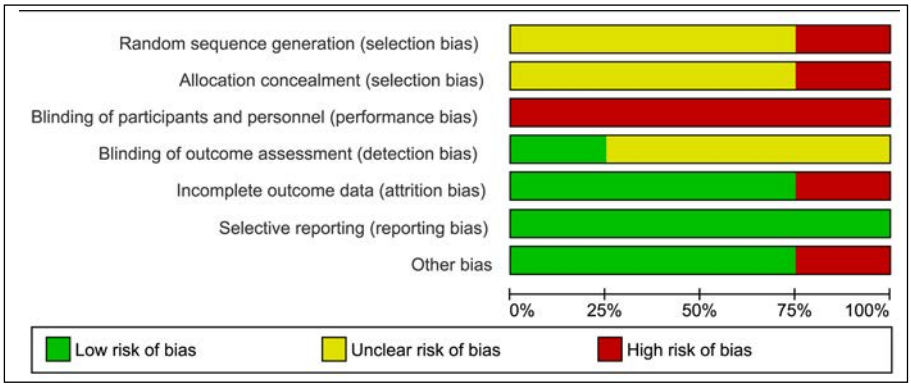

Figure 2 - Risk of bias. A review of Authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3 - Risk of bias summary. A review Authors' judgements about each risk of bias item for each included study.

monitoring board oversaw the conduct of the trial and reviewed any suspected adverse events; the remaining three studies were graded at unclear risk of detection bias due to the fact that they did not provide information to permit judgement about "high" or "low" risk of bias[35,36,38].

Incomplete outcome data

One study was judged at high risk of attrition bias because three patients randomised in the experimental group could not receive the assigned treatment, and were switched and treated as controls[30]. The remaining studies were judged at low risk of bias.

Selective reporting

Selective reporting was low in all included studies.

Other potential sources of bias

We judged at high risk of other source of bias one study performed in cirrhotic patients with coagulopathy, which excluded subjects most likely to suffer from alterations of coagulation (e.g., with suspected infections or sepsis), making the sample obtained not representative of the entire population intended to be analysed[38].

Effects of interventions

The effect of the intervention (VHA monitoring) on mortality (primary outcome) was assessed on three trials, all using TEG monitoring, reporting on this outcome. The overall mortality was 21% on treated patients (21 out of 100) and 30.3% in the control group (30 out of 99).

Using the average treatment effect from a fixed-effects model, the use of TEG does not reduce mortality when compared to the control group: three trials, 199 patients; RR 0.71, 95% CI: 0.44 to 1.15; p for overall effect=0.16; I^2=0% (Figure 4).

As far as the secondary outcomes is concerned, the use of VHA does not reduce the need for red blood cells (4 trials, 229 patients; mean difference –0.64, 95% CI: –1.51 to 0.23; p for overall effect=0.15; I^2=52%), for platelet concentrates (3 trials, 199 patients; mean difference –1.12, 95% CI: –3.25 to 1.02; p for overall effect=0.31; I^2=87%), as well as for fresh frozen plasma transfusions (3 trials, 199 patients; mean difference –0.91, 95% CI: –2.02 to 0.19; p for overall effect=0.11; I^2=52%) (Figure 5). Based on GRADE assessment, all these comparisons were graded as very low certainty evidence, and down-graded once because of imprecision

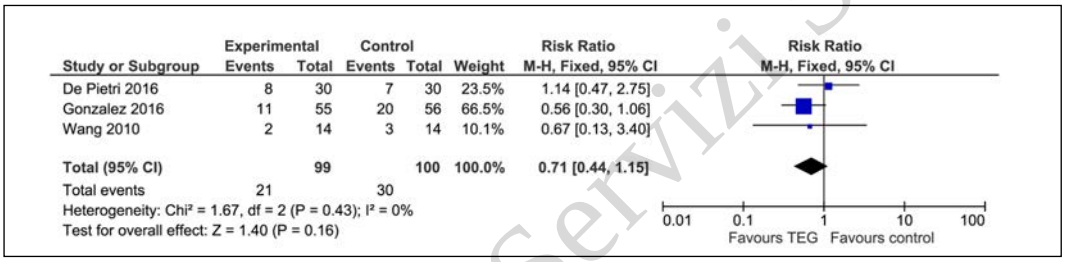

Figure 4 - Forest plot of comparison. Thromboelastography *vs* standard laboratory measures, outcome and mortality.

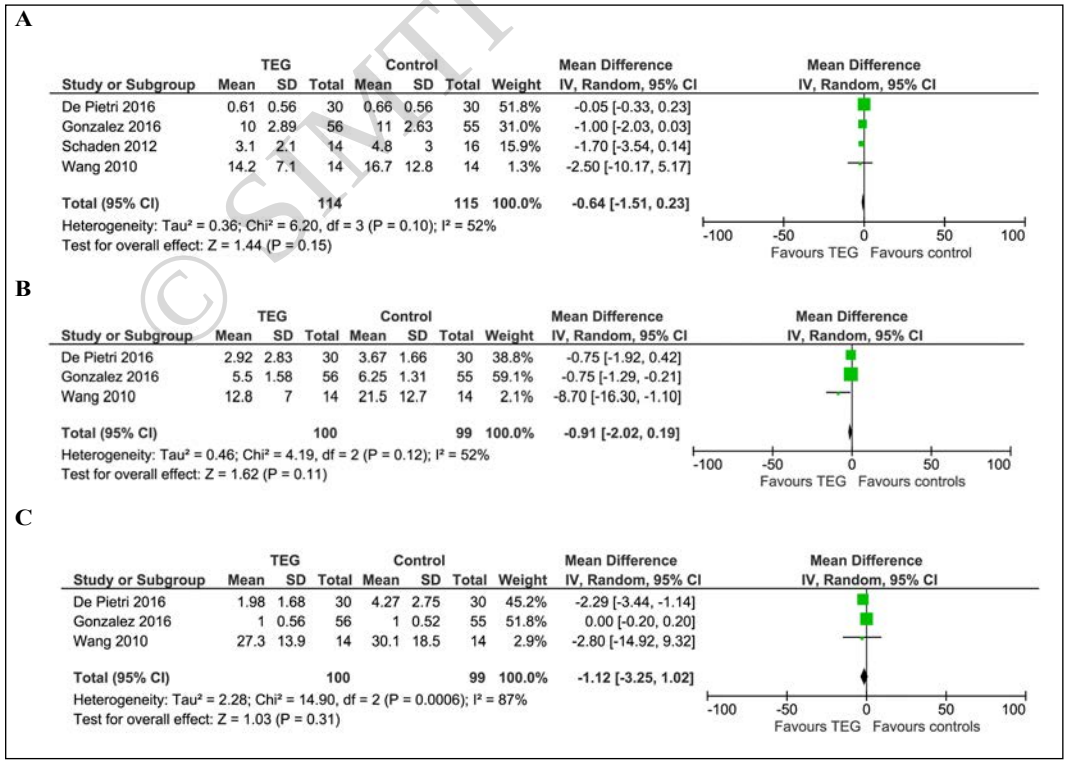

Figure 5 - Forest plots of comparison. Thromboelastography *vs* standard laboratory measures, secondary outcomes: (A) red blood cell transfusion, (B) platelet concentrate transfusion, and (C) fresh frozen plasma transfusion.

(due to small sample size), once because of inconsistency (I^2=52-87 %), and twice because of the risk of biases (see summary of findings in Table II, and funnel plots in Figures 2 and 3). Online Supplementary Content Figure S1 reports the TSA, i.e., the additional observations to reach a 50% power (n=362) and an 80% power (n=734). Actually, the available number is much lower, 199 (55% and 27%, respectively).

Discussion

Thrombelastography and ROTEM are point-of-care systems able to capture the dynamic nature of clotting. The information provided by these VHA has been used in recent years to create targeted, individualised treatment algorithms with the aim of improving outcome of patients with excessive bleeding[4]. A number of clinical trials have been performed in this field, mostly in the cardiac surgical setting, and an up-dated systematic review and meta-analysis of these was recently published by Serraino and Murphy[12]. After the analysis of 15 RCTs involving 8,737 participants, the Authors concluded that, although the use of TEG or ROTEM resulted in a reduction in the frequency of RBC and platelet transfusions, this did not have any

Table II - Thromboelastography (TEG) compared with standard laboratory measures for patients with coagulopathy in non-cardiac surgical settings. Summary of findings table.

Outcomes	Illustrative comparative risks* (95%CI)		Relative effect (95%CI)	N. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	*Corresponding risk*				
	Standard lab measures	*TEG*				
Mortality	30 per 100	21 per 100 (12.9 to 34.8)	RR 0.71 (0.43 to 1.16)	199 (3 studies)	⊕⊖⊖⊖ very low[1]	On average, it is unclear whether or not use of TEG compared with standard laboratory measures reduces mortality over a follow-up period ranging from 28 days to 3 years.
Red blood cell transfusion	804 units per 100 pts	740 units per 100 pts (653 to 827)	Mean difference : –0.64 (–1.51 to 0.23)	4 studies (229 patients)	⊕⊖⊖⊖ very low[2]	On average, it is unclear whether or not use of TEG compared with standard laboratory measures reduces the need for red blood cell transfusion
Platelet concentrate transfusion	587 units per 100 pts	475 Units per 100 pts (262 to 689)	Mean difference : –1.12 (–3.25 to 1.02)	3 studies (199 pts)	⊕⊖⊖⊖ very low[2]	On average, it is unclear whether or not use of TEG compared with standard laboratory measures reduces the need for platelet concentrate transfusion
Fresh frozen plasma	771 units per 100 patients	680 Units per 100 pts (569 to 790)	Mean difference: –0.91 (–2.02 to 0.19)	3 studies (199 pts)	⊕⊖⊖⊖ very low[2]	On average, it is unclear whether or not use of TEG compared with standard laboratory measures reduces the need for fresh frozen plasma transfusion

Patient population: patients with coagulopathy; **Settings:** inpatients; **Intervention:** thromboelastography; **Comparison:** standard laboratory measures of blood coagulation.

*The assumed risk is the mean control group risk across studies. The corresponding risk (and its 95% confidence interval [CI]) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). RR: Risk Ratio; pts: patients.

GRADE Working Group grades of evidence. **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Down-graded once for risk of bias due to 1 study (with the highest weighting in the meta-analysis) being at high risk of selection bias, and 3 studies being at unclear risk of selection bias. Down-graded once due to the design of one study in cirrhotic patients with coagulopathy, which excluded subjects most likely suffering from alterations of coagulation (e.g., with suspected infections or sepsis), making the sample obtained not representative of the population intended to be analysed. Down-graded once for imprecision due to small sample size. [2]Down-graded twice for risk of biases; down-graded once for imprecision; down-graded once for inconsistency due to the heterogeneity (I^2 52-87 %).

effect on mortality when compared with standard care. In order to assess the impact of viscoelastic blood tests in other bleeding settings, we performed a systematic review and meta-analysis of the existing literature. Only 4 RCTs were identified after a systematic search, covering various clinical areas (1 liver transplantation, 1 surgery in bleeding burn patients, 1 trauma-induced coagulopathy, and 1 invasive procedures in patients with severe coagulopathy associated with liver cirrhosis)[35-38].

After a pooled analysis of the results from the studies, we found that the use of TEG does not reduce mortality when compared with the control group: RR 0.71, 95% CI: 0.44 to 1.15.

The level of evidence according to the GRADE method was of very low quality, since the trials were at high risk of selection biases and imprecision due to the small sample size.

Likewise, the use of VHA as compared with standard laboratory measures does not reduce the need for RBC (mean difference, –0.64; 95% CI: –1.51 to 0.23), platelet concentrate (mean difference, –1.12; 95% CI: –3.25 to 1.02), and fresh frozen plasma transfusion (mean difference, –0.91; 95 % CI: –2.02 to 0.19). For all these outcomes, the level of the evidence was graded at very low quality due to risk of bias, imprecision and inconsistency, with a substantial degree of heterogeneity (Table II). One of the limits of our analysis relates to the approximate methods employed to obtain means and standard deviations from medians and ranges that add uncertainty to these evaluations. These methods are approximate, and give the best results when the true data distribution is normal or near normal. In our meta-analysis, the accuracy of the evaluation was necessarily indeterminate, since we have no indication of the real distribution of the continuous variables.

In conclusion, the available evidence does not allow any conclusions to be drawn as to whether the use of VHA offers a significant benefit regarding important clinical end points (mortality and transfusion needs) as compared to standard monitoring in bleeding patients outside the cardiac surgical setting. More, larger, and better designed randomised controlled trials should be carried out in this area in order to better clarify the exact role of VHA in the management of acquired bleeding conditions.

Disclosure of conflicts of interest

GML is the Editor-in-Chief of Blood Transfusion and this manuscript has undergone additional external review as a result. The other Authors declare no conflicts of interest.

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Arrived: 8 January 2018 - Revision accepted: 31 January 2015
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Online Supplementary Content

Table SI - GRADE ratings and their interpretation symbol.

GRADE symbols	Quality	Interpretation
⊕⊕⊕⊕	**High**	We are very confident that the true effect lies close to that of the estimate of the effect.
⊕⊕⊕O	**Moderate**	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.
⊕⊕OO	**Low**	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
⊕OOO	**Very low**	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table taken from the GRADE Handbook, available from: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html#h.9rdbelsnu4iy.

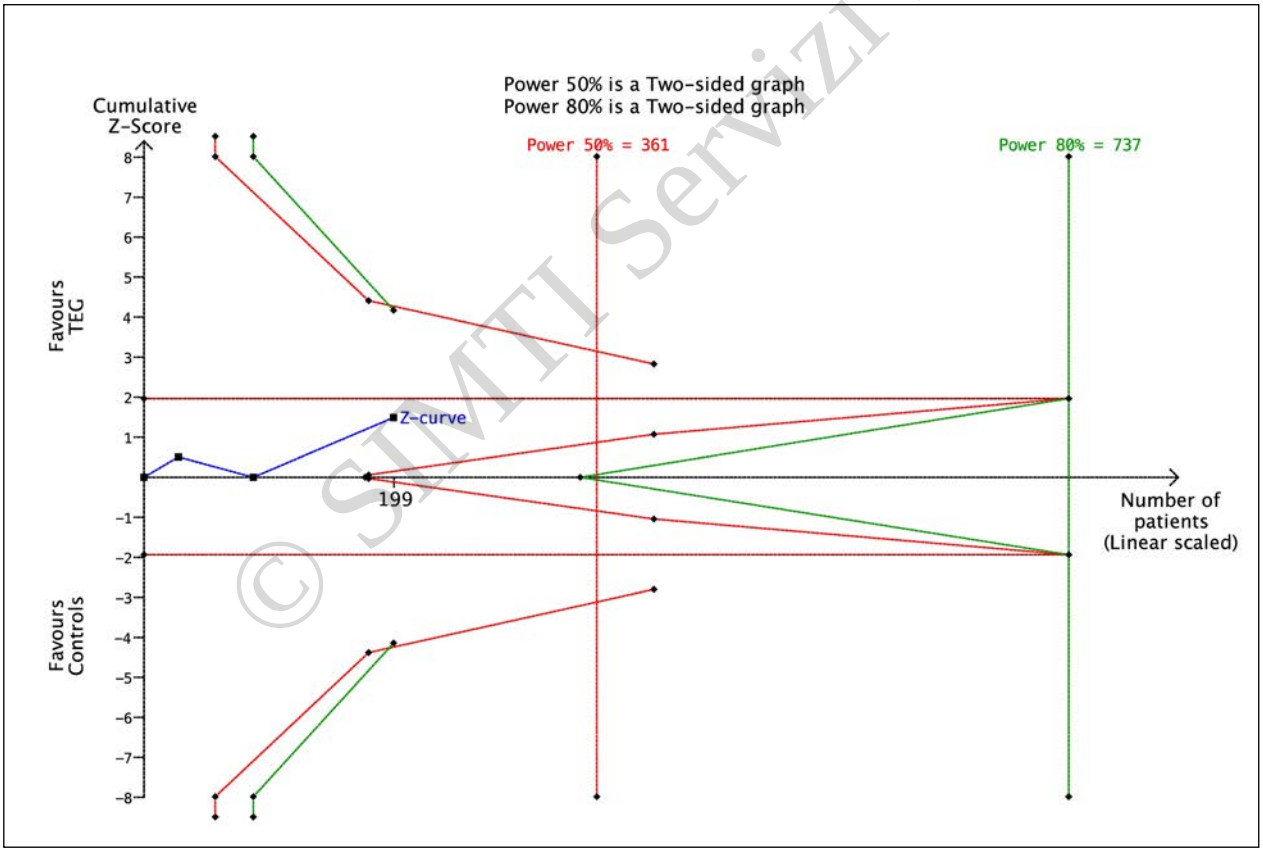

Figure S1 - Trial sequential analysis. The process of evidence accumulation is quantified as cumulative z-score (blue line). The x-axis reports the number of enrolled patients (sample axis). The y-axis spans the evidence against the null hypothesis, as Z-score. The horizontal brown lines indicate the limits of 5% significance according to the conventional method (without any penalisation). Bent lines of alpha error and beta error depict funnels, establishing a penalty for the initial, underpowered meta-analysis. (The alpha curves are actually over the horizontal brown line; the beta curves are underneath). Vertical lines indicate the number of enrolled patients for a power of 50% and 80%. The final objective is to assess the development of the investigation, which eventually could cross the alpha boundaries, thus endorsing the alternative hypothesis, or persisting in a low level, thus ending crossing the beta boundaries of futility; the latter possibility would suggest the practical failure to demonstrate the experimental hypothesis.