

# Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis

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## Scientific summary

### Diagnosis, management and monitoring of haemostasis

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# Scientific summary

## Background

This assessment focuses on three patient groups at high risk of bleeding, identified by National Institute for Health and Care Excellence as clinical priority areas: those undergoing cardiac surgery, those who have experienced trauma, and women with post-partum haemorrhage (PPH). Patients with substantial bleeding usually require transfusion and/or (re)-operation. Red blood cell (RBC) transfusion is independently associated with a greater risk of infection and ischaemic post-operative morbidity, and increased hospital stay, hospital costs and mortality.

ROTEM (ROTEM® Delta, TEM International GmbH, Munich, Germany; [www.rotem.de](http://www.rotem.de)) is a point-of-care (POC) analyser that uses thromboelastometry, a viscoelastic (VE) method, to test for haemostasis in whole blood. Other similar VE techniques include thromboelastography (TEG® 5000 analyser, Haemonetics Corporation, Niles, IL, USA; [www.haemonetics.com](http://www.haemonetics.com)) and the Sonoclot (Sonoclot® coagulation and platelet function analyser, Sienco Inc., Arvada, CO, USA). This report refers to the three technologies as 'viscoelastic testing POC coagulation testing devices' or 'VE devices'. All are used near the patient, during surgery or when admitted following trauma or PPH. VE devices have a number of proposed advantages over standard laboratory tests (SLTs): they provide a result much quicker, are able to identify what part of the clotting process is disrupted, and provide information on clot formation over time and fibrinolysis. This assessment aims to investigate the impact of these potential advantages on patient outcomes.

## Objectives

The overall objective of this project was to summarise the evidence on the clinical effectiveness and cost-effectiveness of VE devices to assist with the diagnosis, management and monitoring of haemostasis disorders during and after cardiac surgery, trauma-induced coagulopathy or PPH. We defined the following research questions to address the review objective:

1. How do clinical outcomes differ among patients who are tested with VE devices during or after cardiac surgery compared with those who are not tested?
2. How do clinical outcomes differ among patients with coagulopathy induced by trauma who are tested with VE devices compared with those who are not tested?
3. How do clinical outcomes differ among patients with PPH who are tested with VE devices compared with those who are not tested?
4. What is the cost-effectiveness of VE devices during or after cardiac surgery?
5. What is the cost-effectiveness of VE devices in patients with trauma-induced coagulopathy?
6. What is the cost-effectiveness of VE devices in patients with PPH?

## Methods

### *Assessment of clinical effectiveness*

Sixteen databases, including MEDLINE and EMBASE, research registers and conference proceedings, were searched to December 2013: MEDLINE (OvidSP), MEDLINE In-Process and Other Non-Indexed Citations and Daily Update (OvidSP), EMBASE (OvidSP), BIOSIS Previews (Web of Knowledge), Science Citation Index (SCI) (Web of Science), Conference Proceedings Citation Index (CPCI-S) (Web of Science), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, Latin American and

Caribbean Health Sciences Literature (LILACS), International Network of Agencies for Health Technology Assessment (INAHTA), NIHR HTA programme, Aggressive Research Intelligence Facility (ARIF), Medion, and the International Prospective Register of Systematic Reviews (PROSPERO). Search results were screened for relevance independently by two reviewers. Full-text inclusion assessment, data extraction and quality assessment were conducted by one reviewer and checked by a second. Randomised controlled trials (RCTs) were assessed for quality using the Cochrane Risk of Bias Tool. Prediction studies were assessed using QUADAS-2. For RCTs, summary relative risks (RRs) were estimated using random-effects models. Heterogeneity was investigated visually using forest plots and statistically using the  $I^2$ - and Q-statistics. Continuous data were not reported in a suitable format for meta-analysis and so data were summarised narratively and in tables. For prediction studies, the odds ratio was selected as the primary effect estimate. This was extracted or calculated from available data and displayed on forest plots. There were insufficient data on the same VE parameters and outcomes to permit pooling for these studies.

### **Assessment of cost-effectiveness**

We assessed the cost-effectiveness of VE devices in two different populations: patients undergoing cardiac surgery and trauma patients. There was insufficient evidence to assess the cost-effectiveness of VE devices in women with PPH. For both populations the cost-effectiveness of ROTEM, TEG and Sonoclot were compared with SLTs. A decision tree was used to take into account all short-term complications and longer-term side effects from transfusion. The model assumed a 1-year time horizon, as relevant costs and effects from transfusion-related complications and infections were assumed to occur within the first year.

A previously published decision tree, used for the assessment of cell-saving strategies compared with allogeneic blood transfusion, formed the basis of our model. The same published decision tree was also used in an assessment of the cost-effectiveness of VE testing in patients undergoing cardiac surgery or liver transplantation, conducted for NHS Scotland.

For the cardiac surgery population, data from the clinical effectiveness review were used to estimate various parameters, such as transfusion rates and volumes transfused. For the trauma population, no data were available on the relative effectiveness of VE testing compared with SLTs. Studies included in the clinical effectiveness review therefore only served to estimate parameters for the SLTs strategy. VE device-specific estimates were then derived using RRs observed in the cardiac population.

The impact of uncertainty about the various input parameters on the outcomes was explored through probabilistic sensitivity analyses and scenario analyses.

## **Results**

Thirty-nine publications of 31 studies were included in the clinical effectiveness review for objectives 1–3.

### **How do clinical outcomes differ among patients who are tested with viscoelastic devices during or after cardiac surgery compared with those who are not tested?**

Eleven RCTs ( $n = 1089$ , range 22–228; 14 publications) assessed VE devices in patients undergoing cardiac surgery; six assessed TEG and five assessed ROTEM. There was a significant reduction in RBC transfusion [RR 0.88, 95% confidence interval (CI) 0.80 to 0.96; six studies], platelet transfusion (RR 0.72, 95% CI 0.58 to 0.89; six studies) and fresh frozen plasma (FFP) transfusion (RR 0.47, 95% CI 0.35 to 0.65; five studies) in VE testing groups compared with control. There were no significant differences between groups in terms of any blood component transfusion, factor VIIa transfusion or prothrombin complex concentrate transfusion, although data suggested a beneficial effect of the VE testing algorithm. These outcomes were evaluated in only two studies. There was no difference between groups in terms of fibrinogen (FIB) transfusion. Continuous data on blood component/product use supported these findings; the only blood component/product that was not associated with a reduced volume of use in the

VE testing group was FIB. There was a suggestion that bleeding was reduced in the VE testing groups but this was statistically significant in only two of the nine RCTs that evaluated this outcome. Clinical outcomes (re-operation, surgical cause of bleed on re-operation and mortality) did not differ between groups. There was some evidence of reduced bleeding and intensive care unit stay in the VE testing groups compared with control but this was not consistently reported across studies. There was no difference in length of hospital stay between groups. There were no apparent differences between ROTEM or TEG for any of the outcomes evaluated.

As none of the RCTs evaluated the Sonoclot VE test, we also included three prediction studies that evaluated Sonoclot in the review. Positive results on conventional tests, TEG and Sonoclot were all associated with an increased risk of bleeding, with no clear differences according to test.

### ***How do clinical outcomes differ among patients with coagulopathy induced by trauma who are tested with viscoelastic devices compared with those who are not tested?***

We identified one ongoing RCT that is comparing TEG (rapid assay) with conventional coagulation testing (international normalised ratio, partial thromboplastin time, FIB, D-dimer) in adults with blunt or penetrating trauma who are likely to require transfusion of RBC within 6 hours from admission, as indicated by clinical assessment. Results from this study are not yet available. One controlled clinical trial, reported only as an abstract, was included. This study did not report numerical results and was restricted to patients requiring massive transfusion.

As there were insufficient data from studies that evaluated differences in clinical outcomes between VE tested and untested populations, we included lower levels of evidence for this objective. Fifteen studies (18 publications;  $n = 4217$ ) provided data on the ability of TEG or ROTEM to predict transfusion-related outcomes and death in trauma patients; eight studies also provided these data for SLTs. No studies of Sonoclot were identified. The studies generally found that a positive result on each of the TEG or ROTEM parameters or on SLTs was associated with an increased risk of transfusion (RBC, any blood component and massive transfusion) and death. There were no clear differences between ROTEM, TEG or SLTs; however, none of the studies provided a direct comparison between TEG and ROTEM. An overall TEG result suggesting that a patient was hypocoagulable was the strongest predictor of any blood component transfusion. The presence of hyperfibrinolysis was the strongest predictor of mortality.

### ***How do clinical outcomes differ among patients with post-partum haemorrhage who are tested with viscoelastic devices compared with those who are not tested?***

Two studies evaluated VE devices in patients with PPH. Both provided data on the ability of ROTEM to predict outcomes; one also evaluated a SLT (Clauss fibrinogen). Both studies showed that ROTEM results were associated with the outcomes evaluated (RBC transfusion, invasive procedures, coagulopathy requiring treatment, FFP transfusion and platelet transfusion). The study that evaluated both ROTEM and Clauss fibrinogen reported similar results for both tests.

### ***What is the cost-effectiveness of VE devices during or after cardiac surgery?***

The cost-effectiveness study indicated that VE testing is cost-saving and more effective than standard laboratory testing. The per-patient cost-saving was slightly smaller for ROTEM (£43) than for TEG (£79) or Sonoclot (£132). This finding was entirely dependent on material costs, which are slightly higher for ROTEM in the base-case analysis. When alternative assay combinations were modelled then TEG could be more costly than ROTEM. When all uncertainties included in the model were taken into account, at a cost-effectiveness threshold of £30,000 per quality-adjusted life-year (QALY), the probability of cost-effectiveness for each of the three VE technologies was 0.79 for ROTEM (the most expensive device), 0.84 for TEG and 0.87 for Sonoclot (the cheapest device). In the absence of data on the clinical effectiveness of Sonoclot, we assumed that the TEG- and ROTEM-based estimates used in the model would also be applicable to Sonoclot. Thus, given that all three devices were assumed to be equally

effective, the same health-effect outcomes were obtained for all three VE devices. These results remained largely unchanged in scenario analyses, used to assess the potential impact of various input parameters on the model outcomes. VE testing was no longer cost-saving when the number of tests performed per machine per year was < 326. When the number of tests performed per machine per year was reduced to 152, the incremental cost-effectiveness ratio was around £30,000.

### ***What is the cost-effectiveness of viscoelastic devices in patients with trauma-induced coagulopathy?***

For the trauma population, the cost-savings because of VE testing were more substantial, amounting to per-patient savings of £688 for ROTEM compared with SLTs, £721 for TEG and £818 for Sonoclot. The probability that any of the VE technologies was cost-effective was higher for this population. The most expensive technology, ROTEM, had a cost-effectiveness probability equal to 0.96 at a threshold of £0 per QALY. As the ceiling ratio increased, this probability converged on 0.87.

The increased cost-savings observed for the trauma population were primarily due to the much higher blood volumes that are typically transfused in trauma patients. Results were similar for the scenario analyses constructed to assess the impact of various parameters. These results were quite robust, and indicated that, where the clinical effectiveness of VE testing was slightly better than SLTs, VE testing would be cost-saving. However, given the present lack of effectiveness data in trauma patients, the current results should be regarded as indicative of only the potential cost-effectiveness of VE testing in trauma patients.

### ***What is the cost-effectiveness of viscoelastic devices in patients with post-partum haemorrhage?***

The cost-effectiveness of VE devices could not be assessed in this population because of the lack of evidence identified by the clinical effectiveness review.

## **Conclusions**

Viscoelastic testing, particularly using the ROTEM or TEG devices, may be effective in reducing the numbers of cardiac surgery patients receiving RBC transfusion, platelet transfusion and FFP transfusion, compared with a SLTs-based management strategy. The available data do not currently support an improvement in clinical outcomes (re-operation, surgical cause of bleed on re-operation and mortality), or length of hospital stay, for cardiac surgery patients managed using VE testing compared with those managed using SLTs. There is no evidence to indicate a difference in clinical effectiveness between the TEG and ROTEM devices. There were no data on the clinical effectiveness of Sonoclot. There was no evidence on the clinical effectiveness of VE testing, using any device, in trauma patients or women with PPH. Available data generally indicated that a positive result on each of the TEG or ROTEM parameters or on SLTs was predictive of transfusion (RBC, any blood component and massive transfusion) and death. There were no clear differences between ROTEM, TEG or SLTs and no studies of Sonoclot were identified.

Cost-effectiveness analyses indicated that VE testing, using TEG, ROTEM or Sonoclot, is cost-saving and more effective than SLTs, in both patients undergoing cardiac surgery and trauma patients. However, this is based on the assumption that the effectiveness of Sonoclot is the same as that of TEG and ROTEM in the absence of data on the clinical effectiveness of this device. Scenario analyses, used to assess the potential impact of baseline prevalence of transfusion and annual number of tests per device, did not alter these conclusions. No cost-effectiveness modelling was conducted for women with PPH owing to lack of data.

Clinical trials, ideally comparing the effectiveness of different VE devices to SLTs, are required for trauma patients and women with PPH. If the adoption of Sonoclot is considered, trials of this technology are needed in all relevant populations. Future trials should include longer-term follow-up, beyond the initial hospital episode.



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