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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Contributions of authors

Penny Whiting and Marie Westwood planned and performed the systematic review and interpretation of evidence. Maiwenn Al and Isaac Corro Ramos planned and performed the cost-effectiveness analyses and interpreted results. Steve Ryder and Nigel Armstrong contributed to planning and interpretation of cost-effectiveness analyses and acquisition of input data for modelling. Kate Misso and Janine Ross devised and performed the literature searches and provided

information support to the project. Jos Kleijnen and Johan Severens provided senior advice and support to the systematic review and cost-effectiveness analyses, respectively. All parties were involved in drafting and/or commenting on the report.

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LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

A10	amplitude ten minutes after clotting time
ACT	activated clotting/coagulation time
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
ARIF	Aggressive Research Intelligence Facility
ASA	American Society of Anaesthesiologists
AUC	area under the curve
CABG	coronary artery bypass graft
CADTH	Canadian Agency for Drugs and Technologies
CDSR	Cochrane Database of Systematic Reviews
CE	cost-effectiveness
CEACS	cost-effectiveness acceptability curve
CFT	clot formation time
CI	confidence interval
CL	clot lysis
CLT	clot lysis time
CPB	cardio-pulmonary bypass
CPCI-S	Conference Proceedings Citation Index
CRD	Centre for Reviews and Dissemination
CT	clotting time
DARE	Database of Abstracts of Reviews of Effects
DTA	diagnostic test accuracy
DVT	deep vein thrombosis
EACTA	European Association of Cardiothoracic Anaesthesiologists
ED	emergency department
FAST	focussed assessment of the sonography of trauma
FFP	fresh frozen plasma
FIB	fibrinogen
gb-ACT	glass bead-activated test
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HEED	Health Economics Evaluation Database
HES	Hospital Episode Statistics
HIV	human immunodeficiency virus
HRQoL	Health-Related Quality of Life
HTA	Health technology Assessment
HTLV	human T-cell lymphotropic virus
IC	incremental cost
ICER	Incremental Cost-Effectiveness Ratio
ICTRP	International Clinical Trials Registry Platform

ICU	intensive care unit
INR	international normalised ratio
IPA	impedance platelet aggregometry
ISI	international sensitivity index
ISS	injury severity score
IQR	interquartile range
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention-to-treat
LI30	lysis index 30 minutes after clotting time
LoS	length of stay
LY	life year
LY30	lysis at 30 minutes
LY45	lysis at 45 minutes
LY60	lysis at 60 minutes
MCF	maximum clot firmness
MI	myocardial infarction
ML	maximum lysis
MOF	multiple organ failure
MPV	maximum platelet volume
mRCT	metaRegister of Controlled Trials
NA	not applicable
NEQAS	National External Quality Assurance Scheme
NHS	National Health Service
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
NR	not reported
OR	odds ratio
PFA	platelet function analyser
POC	point-of-care
PPH	post-partum haemorrhage
PPV	positive predictive value
PR	prothrombin ratio
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PT	prothrombin time
PTP	post-transfusion purpura
QALY	Quality-Adjusted Life Year
RBC	red blood cell
RCT	randomised controlled trial
ROC	receiver operating characteristic
RR	relative risk
SCI	Science Citation Index
Sd	standard deviation
SE	standard error

SHOT	Serious Hazards of Transfusion
SIRS	systemic inflammatory response syndrome
SLT	standard laboratory test
TEG	thromboelastography
TRALI	transfusion-related acute lung injury
TTL	time to lysis
vCJD	variant Creutzfeldt Jakob disease
VE	viscoelastic
WHO	World Health Organisation

TECHNICAL GLOSSARY

Cost-effectiveness analysis	An economic analysis that converts effects into health terms and describes the costs for additional health gain.
Decision modelling	A theoretical construct that allows the comparison of the relationship between costs and outcomes of alternative healthcare interventions.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.
Index test	The test whose performance is being evaluated.
Markov model	An analytic method particularly suited to modelling repeated events, or the progression of a chronic disease over time.
Meta-analysis	Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.
Meta-regression	Statistical technique used to explore the relationship between study characteristics and study results.
Opportunity costs	The cost of forgone outcomes that could have been achieved through alternative investments.
Prediction study	Study that evaluates the ability of a variable to predict an outcome
Publication bias	Bias arising from the preferential publication of studies with statistically significant results.
Quality of life	An individual's emotional, social and physical well-being and their ability to perform the ordinary tasks of living.
Quality-adjusted life year (QALY)	A measure of health gain, used in economic evaluations, in which survival duration is weighted or adjusted by the patient's quality of life during the survival period.
Receiver Operating Characteristic (ROC) curve	A graph which illustrates the trade-offs between sensitivity and specificity which result from varying the diagnostic threshold.
Reference standard	The best currently available diagnostic test, against which the index test is compared.
Sensitivity	Proportion of people with the target disorder who have a positive test result.
Specificity	Proportion of people without the target disorder who have a negative test result.
Viscoelastic (VE) test	A test that uses a viscoelastic method, either thromboelastometry or thromboelastography, to test for haemostasis.

SCIENTIFIC SUMMARY (2193 WORDS)

Background

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

ROTEM is a point-of-care analyser that uses thromboelastometry, a viscoelastic method, to test for haemostasis in whole blood. Other similar viscoelastic techniques include TEG and the Sonoclot coagulation and platelet function analyser. This report refers to the three technologies as "viscoelastic testing point of care 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- and cost-effectiveness of viscoelastic (VE) devices to assist with the diagnosis, management and monitoring of haemostasis disorders during and after cardiac surgery, trauma induced coagulopathy or post-partum haemorrhage (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 to 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 to those who are not tested?
3. How do clinical outcomes differ among patients with PPH who are tested with VE devices compared to 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. 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 (RR) 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 (OR) 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 to 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 one year time horizon, since 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 to 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 to 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.

1. *How do clinical outcomes differ among patients who are tested with VE devices during or after cardiac surgery compared to those who are not tested?*

Eleven RCTs (n=1089, range 22 to 228) (14 publications) assessed VE devices in patients undergoing cardiac surgery; six assessed TEG and five assessed ROTEM. There was a significant reduction in red blood cell transfusion (RR 0.88, 95% CI 0.80, 0.96; six studies), platelet transfusion (RR 0.72, 95% CI 0.58, 0.89; six studies) and FFP transfusion (RR 0.47, 95% CI 0.35, 0.65; five studies) in VE testing groups compared to control. There were no significant differences between groups in terms of any blood product transfusion, factor VIIa transfusion or prothrombin transfusion, although data suggested a beneficial effect of the VE testing algorithm. These outcomes were only evaluated in two studies. There was no difference between groups in terms of fibrinogen transfusion. Continuous data on blood product use supported these findings; the only blood product which was not associated with a reduced volume of use in the VE testing group was fibrinogen. There was a suggestion that bleeding was reduced in the VE testing groups but this was only statistically significant in 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 ICU stay in the VE testing groups compared to 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 which 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.

2. *How do clinical outcomes differ among patients with coagulopathy induced by trauma who are tested with VE devices compared to those who are not tested?*

We identified one ongoing RCT that is comparing TEG (rapid assay) with conventional coagulation testing (INR, PTT, fibrinogen, D-dimer) in adults with blunt or penetrating trauma who are likely to require transfusion of RBC within six hours from admission as indicated by clinical assessment. Results from this study are not yet available. One controlled clinical trial (CCT) 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 product 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 hypocoaguable was the strongest predictor of any blood product transfusion. The presence of hyperfibrinolysis was the strongest predictor of mortality.

3. *How do clinical outcomes differ among patients with PPH who are tested with VE devices compared to 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 an 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.

4. *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. When all uncertainties included in the model were taken into account, at a cost-effectiveness threshold of £30,000 per 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 less than 326. When the number of tests performed per machine per year was reduced to 152, the ICER was around £30,000.

5. What is the cost-effectiveness of VE devices in patients with trauma induced coagulopathy?

For the trauma population, the cost savings due to VE testing were more substantial, amounting to per patient savings of £688 for ROTEM compared to 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 only be regarded as indicative of the potential cost-effectiveness of VE testing in trauma patients.

6. What is the cost-effectiveness of VE devices in patients with PPH?

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

Conclusions

VE testing, particularly using the ROTEM or TEG devices may be effective in reducing the numbers of cardiac surgery patients receiving red blood cell transfusion, platelet transfusion and FFP transfusion, compared with an 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 product 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. 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 due 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.

PLAIN ENGLISH SUMMARY (246 WORDS)

Bleeding can occur as a result of surgery or injury or due to problems with the blood's clotting process. Patients with bleeding usually require a blood transfusion and/or (re)-operation, both of which may lead to increased morbidity and mortality. It is important to appropriately treat the cause of the bleed and reduce the blood loss. ROTEM, TEG and Sonoclot are "viscoelastic" methods developed to monitor the clotting process. They are performed near the patient and can help differentiate between abnormal bleeding and a clotting disorder. VE testing methods offer two key potential benefits over standard laboratory (SLTs) tests: they provide results in a shorter timescale and provide the additional information on the clotting process. This means requirements for specific blood products can be targeted and so the patient is not subjected to risks associated with unnecessary transfusion.

This assessment aimed to determine the effectiveness of VE devices to assist with the assessment of clotting disorders during and after cardiac surgery or trauma; we also planned to include information on the management of excessive bleeding post-childbirth but there was insufficient evidence. We found that VE testing using ROTEM or TEG may be effective in reducing the numbers of cardiac surgery patients receiving blood product transfusion. We did not find any studies on the clinical effectiveness of Sonoclot or in the effectiveness in trauma patients. Cost-effectiveness analyses indicated that VE testing was cost saving and more effective than SLTs in both patients undergoing cardiac surgery and trauma patients.

1. OBJECTIVE

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

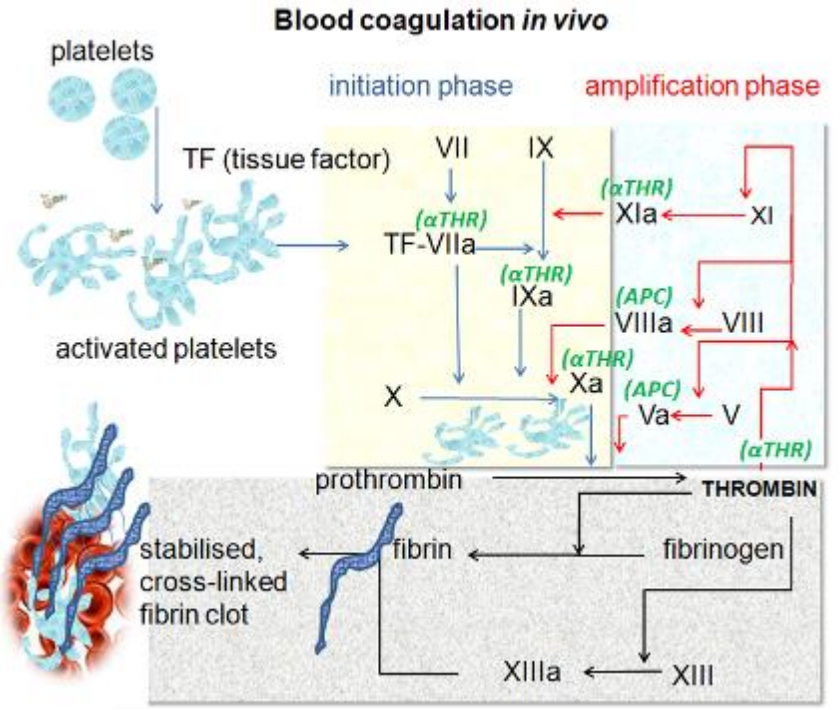
1. How do clinical outcomes differ among patients who are tested with VE devices during or after cardiac surgery compared to those who are not tested?
    a. Where there were no data on one of more of the VE devices we evaluated the accuracy of that or those VE device(s) for the prediction of relevant clinical outcomes (e.g. transfusion requirement) during or after cardiac surgery.
2. How do clinical outcomes differ among patients with coagulopathy induced by trauma who are tested with VE devices compared to those who are not tested?
    a. Where there were no data on one of more of the VE devices we evaluated the accuracy of that or those VE device(s) for the prediction of relevant clinical outcomes (e.g. transfusion requirement) in patients with trauma induced coagulopathy.
3. How do clinical outcomes differ among patients with PPH who are tested with VE devices compared to those who are not tested?
    a. Where there were no data on one of more of the VE devices we evaluated the accuracy of that or those VE device(s) for the prediction of relevant clinical outcomes (e.g. transfusion requirement) in patients with PPH.
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 trauma induced PPH?

2. BACKGROUND AND DEFINITION OF THE DECISION PROBLEM(S)

2.1 Population

This assessment focuses on three patient groups at high risk of bleeding identified by NICE as clinical priority areas: those undergoing cardiac surgery, those who have experienced trauma and women with post-partum haemorrhage (PPH). Patients undergoing cardiac surgery commonly present with bleeding complications which can have a negative impact on their clinical outcome in terms of increased peri-operative and post-operative morbidity and mortality. Bleeding can occur either as a result of the surgery/injury itself or due to acquired coagulation abnormalities as a result of the surgery, trauma or PPH. Coagulopathy occurs when the normal clotting mechanism (haemostasis) is interrupted impairing the blood's ability to clot. The normal clotting process starts with platelets which, combined with a number of clotting proteins, go through a series of steps to produce a solid fibrin clot (Figure 1). If any of these steps are interrupted this may result in prolonged or excessive bleeding. While coagulopathy can be caused by genetic disorders such as haemophilia it can also occur following injury, as occurs in peri-operative or trauma induced coagulopathy. The underlying mechanism of coagulopathy can include hyperfibrinolysis (markedly enhanced fibrinolytic activity), hypofibrinogenaemia (fibrinogen deficiency), thrombocytopenia (low levels of platelets), factor deficiency, and heparin effect.[1] There are several factors that increase the risk of coagulopathy during surgery. In cardiac surgery the use of heparin to prevent clotting whilst on cardiopulmonary bypass (CPB), pre-operative anticoagulation medication, the dilution, activation and consumption of coagulation factors, and the use of cardiopulmonary bypass machines which may result in acquired platelet dysfunction, hypothermia (body temperature $<35^{o}C$), and hyperfibrilation are all associated with an increased risk of coagulopathy.[2] In major trauma the following are associated with an increased risk of coagulopathy: consumption of coagulation factors and platelets during clot formation in an attempt to prevent loss of blood through damaged vessels; dilution of whole blood as a consequence of red cell transfusion; hormonal and cytokine induced changes; hypoxia, acidosis and hypothermia which predispose to further bleeding; and ongoing bleeding.[3] During pregnancy there are marked changes in haemostasis, with fibrinogen deficiency thought to be the major coagulation abnormality associated with bleeding in PPH.[4]

Figure 1: Blood coagulation *in vivo*[5]



The populations at risk of bleeding for the patient groups considered in this assessment present a significant burden to the NHS. There were 36,702 cardiac surgery cases (based on Specialised Services National Definitions Set),[6] based on Hospital Episode Statistics data.[5] There are approximately 20,000 major trauma cases in England every year[7] and injuries account for over 700,000 hospital admission each year.[8] The incidence of major obstetric haemorrhage is 3.7/1,000 births in the UK.[9]

Patients with substantive bleeding usually require transfusion and/or re-operation. Cardiothoracic surgery (i.e. cardiac and thoracic surgery) uses 5% of all donated blood in the UK,[10] and the proportion of patients requiring re-operation for bleeding is estimated at 2-8% of cardiac surgery patients.[11] Table 1 summarises the number of patients undergoing various cardiac surgeries in Scotland over a two year period and shows the proportion of these patients who received a blood transfusion and the number of red blood cell units per episode transfused.[12] The increased morbidity and mortality associated with bleeding following surgery has been shown to be related to both blood transfusion and re-operation for bleeding.[11] Patients with a diagnosis of trauma induced coagulopathy on admission to hospital have a 3 to 4 fold greater mortality risk and it is independently associated with increased transfusion requirements, organ injury, septic complications, and longer critical care stays.[3] Trauma is the leading cause of death and disability in adults aged under 36 years around the world,[13] and haemorrhage is the cause of 40% of all trauma deaths in the UK.[14] PPH is one of the major causes of maternal mortality. There were 14 direct

deaths from obstetric haemorrhage (nine from PPH) from 2006-2008, accounting for 9% of all maternal deaths in this period.[9]

Red blood cell transfusion is independently associated with a greater risk of both infection and ischemic postoperative morbidity, hospital stay, increased early (30 day post-operative) and late mortality (up to and >1 year post-operative), and hospital costs.[15] It is therefore important to appropriately treat the coagulopathy and reduce the blood loss thus reducing the requirement for blood transfusion and reducing the risks of transfusion-related adverse events and saving costs.[2] Knowledge of the exact cause of the bleed allows treatment to be tailored to the cause of the coagulopathy rather than replacing blood loss with transfusion. For example, if thrombocytopenia is identified as the cause of the bleed this can be treated by platelet transfusion.[16] Furthermore, the cost of donor blood and blood has increased and availability has reduced and there is also the risk of blood borne infection.[10]

Table 1: Surgical blood use in 2005-6

Procedure	Number of episodes	% Episodes transfused	RBC units/episode transfused
Coronary replacement operations (minus revisions)	2,359	47.9	1.6
Heart and lung transplant	8	75.0	11.3
Revision coronary replacement operations	29	44.8	2.1
Valves and adjacent structures	758	54.5	2.5

RBC: red blood cell

2.2 Intervention technologies

2.2.1 The ROTEM Delta point-of-care analyser

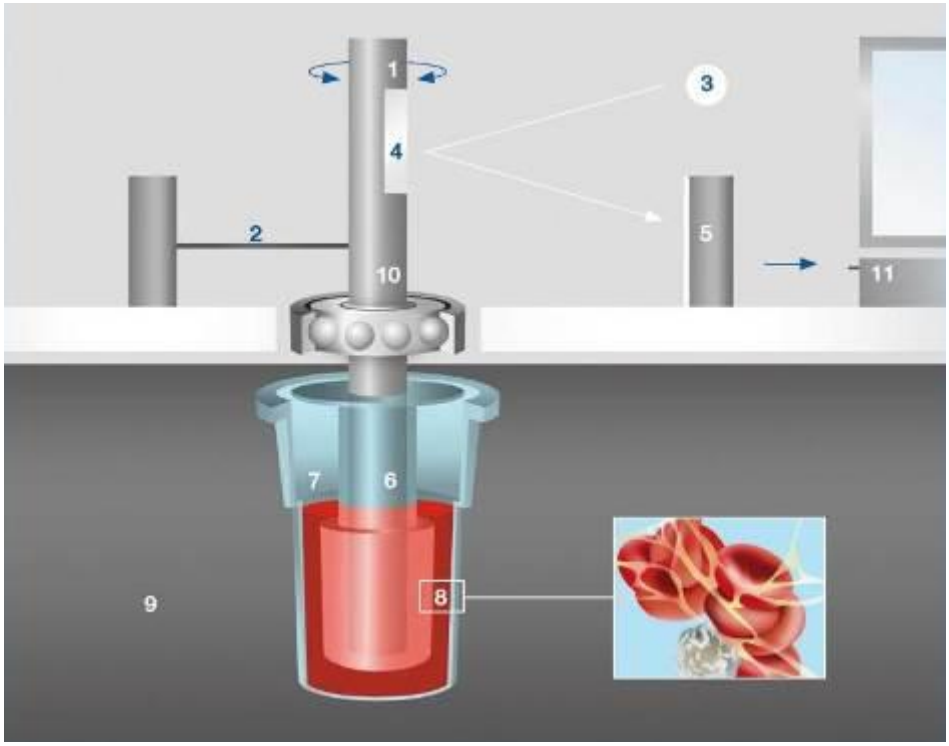
The ROTEM Delta (trademark of TEM International GmbH; www.rotem.de) is a point-of-care (POC) analyser which uses thromboelastometry, a viscoelastic method, to test for haemostasis in whole blood. It was previously known as rotational TEG or ROTEG.[5] It is performed near the patient during surgery or when admitted following trauma. It is used to assist with the diagnosis, management and monitoring of haemostasis disorders during and after surgery associated with high blood loss. It is an integrated all-in-one system and analyses the coagulation status of a blood sample to differentiate between surgical bleeding and a haemostasis disorder.[17] It uses a combination of five assays to characterise the coagulation profile of a citrated whole blood sample (Table 2). Initial screening is performed using the INTEM and EXTEM assays, if these are normal then it is an indication that surgical bleeding rather than coagulopathy is present. The use of different assays allows for rapid differential diagnosis between different haemostasis defects and anticoagulant drug effects.[17] Training in use of the technology is required but specialist laboratory staff are not needed.

Table 2: Summary of ROTEM Delta assays

Assay	Activator/Inhibitor	Role
INTEM	Ellagenic acid (contact activator)	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the intrinsic pathway.
EXTEM	Tissue factor	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the extrinsic pathway. Not influenced by heparin. EXTEM is also the base activator for FIBTEM and ABTEM.
HEPTEM	Ellagenic acid + heparinase	Assessment of clot formation in heparinised patients. INTEM assay performed in the presence of heparinise; the difference between HEPTEM and INTEM confirms the presence of heparin.
FIBTEM	Tissue factor + platelet antagonist	Assessment of fibrinogen status allows detection of fibrinogen deficiency or fibrin polymerisation disorders
APTEM	Tissue factor + fibrinolysis inhibitor (aprotonin)	In-vitro fibrinolysis inhibition: Fast detection of lysis when compared to EXTEM.
Na-TEM	None	Non-activated assay. Can be used to run custom haemostasis tests.

Figure 2 shows the ROTEM system. A 340 µl blood sample that has been anticoagulated with citrate is placed into the disposable cuvette (sample cup) (7) using an electronic pipette. A disposable sensor pin (6) is attached to the shaft which is connected with a thin spring (2) and slowly oscillates back and forth (1) suspended in the blood sample. The signal from the pin is transmitted via an optical detector system (3, 4, 5). The test is started by adding the reagents described above. Although the typical test temperature is 37°C, different temperatures can be selected, for example for patients with hypothermia. Whilst the blood remains liquid the movement is unrestricted, as the blood starts clotting, the clot restricts the rotation of the pin with increasing resistance as the firmness of the clot increases. This is measured by the ROTEM system and translated to the output, which consist of graphical displays and numerical parameters.

Figure 2: ROTEM system[18]



1 Oscillating axis
2 Counterforce spring
3 Light beam from LED
4 Mirror
5 Detector (electr. Camera)
6 Sensor Pin
7 cuvette with blood sample
8 Fibrin strands & platelet aggregates
9 Heated cuvette holder
10 Ball bearing
11 Data processing unit

The graphical output of results produced by the ROTEM system is shown in Figure 3. A separate graphical display is produced for each reagent by an integrated computer. Numerical values for each of the following are also calculated and presented below the graph. Initial results are available within 5-10 minutes and full qualitative results are available in 20 minutes:

CT: Clotting time – time from adding the start reagent until the blood starts to clot. A prolonged clotting time indicates abnormal clot formation.

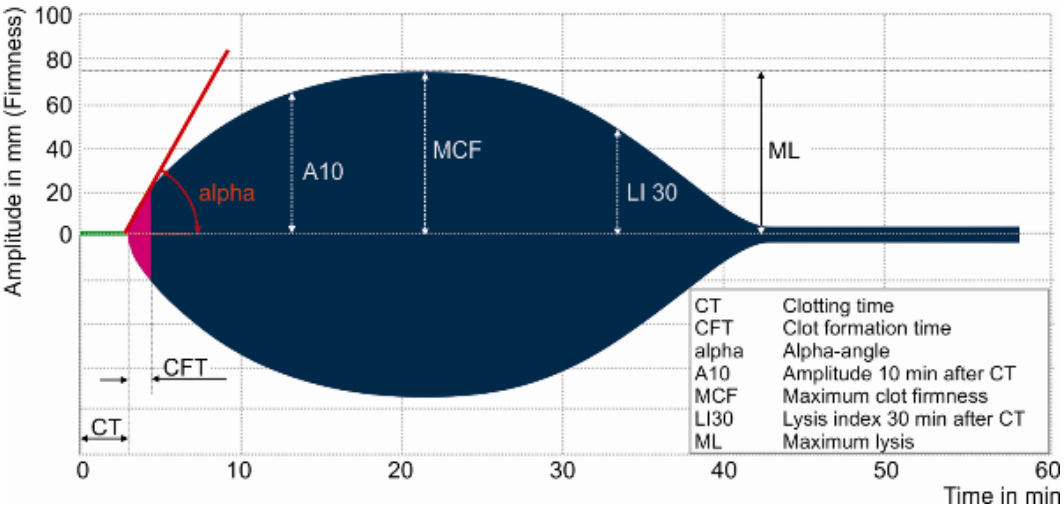
CFT: Clot formation time – time from CT until a clot firmness of 20 mm point has been reached and a: *Alpha angle* – angle of tangent between 2 and the curve. These measures indicate the speed at which the clot is forming and are mainly influenced by platelet function but are also affected by fibrinogen and coagulation factors.

A10: Amplitude 10 minutes after CT – used to predict MCF at an earlier stage and so allows earlier therapeutic decisions.

MCF: Maximum clot firmness – the greatest vertical amplitude of the trace. A low MCF value suggests decreased platelet numbers or function, decreased fibrinogen levels of fibrin polymerisation disorders, or low factor XIII activity.

ML: Maximum lysis. Fibrinolysis is detected by ML >15% or by better clot formation in APTEM compared to EXTEM.

Figure 3: ROTEM Analysis and interpretation of results[19]



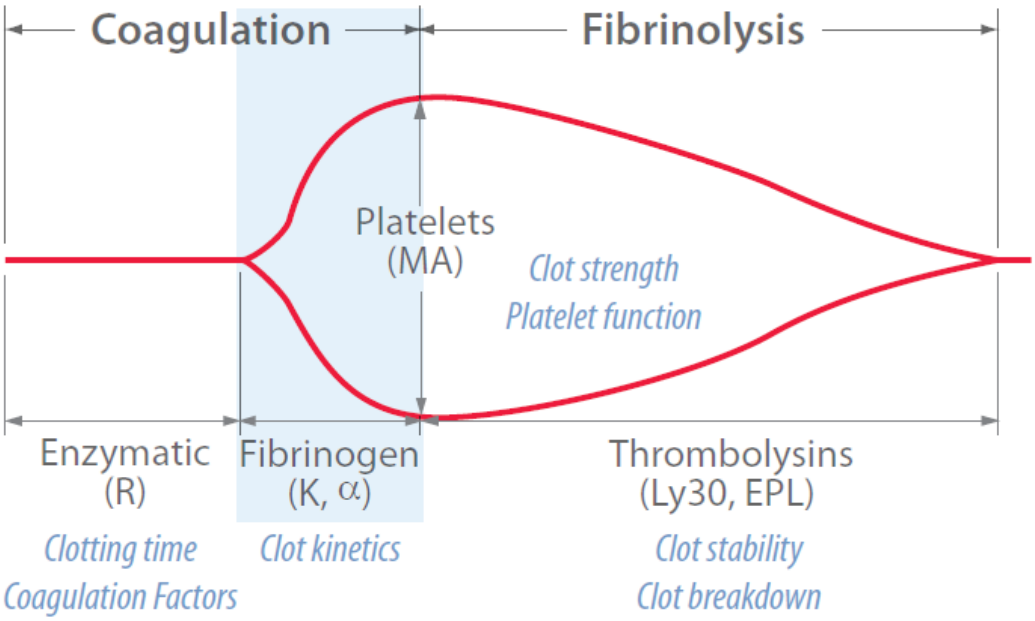
2.2.2 Thromboelastography

The ROTEM system is a variant of the traditional thromboelastography (TEG) method developed by Hartert in 1948.[20] The two techniques are very similar and other recent reviews have evaluated them as a single intervention class.[12,21,22] Like ROTEM, thromboelastography is a viscoelastic method and provides a graphical representation of the clotting process. Thromboelastography is used in the TEG 5000 analyser (trademark of Haemonetics Corporation, IL, USA; www.haemonetics.com). The rate of fibrin polymerisation and the overall clot strength is assessed.[1] Like ROTEM, TEG is able to provide an analysis of platelet function, coagulation proteases and inhibitors, and the fibrinolytic system within 30 minutes, or within 15 minutes if the rapid assay is used. The nomenclature used in TEG differs from that used in ROTEM; differences are summarised in Table 3. The practical differences between TEG and ROTEM are that TEG uses a torsion wire rather than the optical detector used in ROTEM to measure the clot formation, and while the movement in ROTEM is initiated with the pin, with TEG it is initiated from the cuvette.[1] The assays used in TEG also differ (Table 3).[23, 24] The platelet mapping function means that TEG is able to measure platelet function which cannot be assessed using ROTEM. Sample size requirements do not differ substantially between TEG and ROTEM; TEG uses a 360µl blood sample compared to the 340µl sample used in ROTEM.[24]

Table 3: Summary of TEG assays

Assay	Activator/Inhibitor	Role
Kaolin	Kaolin	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the intrinsic pathway.
Heparinase	Kaolin + heparinise	Assessment of clot formation in heparinised patients (both unfractionated and low molecular weight)
Platelet Mapping	ADP Arachidonic acid	To assess platelet function and monitor antiplatelet therapy (e.g. aspirin)
RapidTEG	Kaolin + tissue factor	Extrinsic pathway test. Provides more rapid results than standard kaolin assay (mean 20 minutes versus 30 minutes for standard TEG with initial results in less than one minute).
Functional fibrinogen assay	Lyophilized tissue factor + platelet inhibitor	Partitions clot strength (MA) into contributions from platelets and contribution from fibrin
Native	None	Non-activated assay. Can be used to run custom haemostasis tests.

Figure 4: TEG Analysis and interpretation of results[25]



2.2.3 Sonoclot Coagulation and Platelet Function Analyser

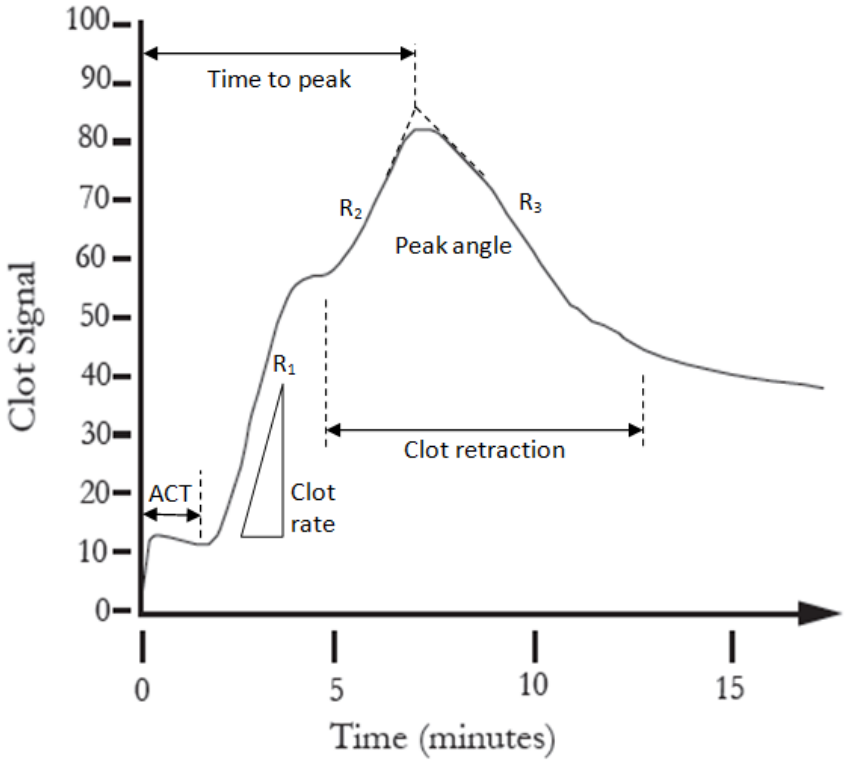
Another method that uses viscoelastometry to measure coagulation is the Sonoclot coagulation and platelet function analyser (Sienco Inc., Arvada, CO). This analyser was first introduced in 1975 by von Kualla et al.[26] It provides information on the haemostasis process including coagulation, fibrin gel formation, fibrinolysis, and, like TEG, is also able to assess platelet function. The Sonoclot process is similar to ROTEM and TEG, although Sonoclot is able to use either a whole blood or plasma sample, citrated blood samples can be used but are not required.[27] A hollow, open-ended disposable plastic probe is mounted on the transducer head. The test sample (blood or plasma) is added to the cuvette containing the reagents. A similar volume to ROTEM and TEG is used – 330 to

360 µl. As with ROTEM it is the probe that moves within the sample, however, rather than moving horizontally the probe moves up and down along the vertical axis. As the sample starts to clot changes in impedance to movement are measured. Like TEG and ROTEM, Sonoclot produces a qualitative graphical display of the clotting process and also produces quantitative results of activated clotting time, the clot rate and the platelet function (Figure 3, Table 4).[23] However, the measure of activated clotting time (ACT) produced by Sonoclot reflects initial fibrin formation whereas the equivalent measures produced by TEG and ROTEM reflects a more developed and later stage of initial clot formation.[23] Most information on clot formation is available after 15 minutes. If details on platelet function are required this may take up to 20-30 minutes.[27]

Table 4: Summary of Sonoclot assays

Assay	Activator/Inhibitor	Role
SonACT	Celite	Large-dose heparin management without aprotonin
kACT	Kaolin	Large-dose heparin management with/without aprotonin
aiACT	Celite + Clay	Large-dose heparin management with aprotonin
gbACT+	Glass beads	Overall coagulation and platelet function assessment for use on non-heparinised patients.
H-gbACT+	Glass beads + Heparinase	Overall coagulation and platelet function assessment in presence of heparin
Native	None	Non-activated assay. Can be used to run custom haemostasis tests.

Figure 3: Sonoclot Analysis and interpretation of results



2.2.4 Comparison of viscoelastic testing devices

This report refers to the three technologies, ROTEM, TEG and Sonoclot, as a class as "viscoelastic testing point of care coagulation testing devices" or "VE devices," however, data from each device are analysed separately. Table 5 provides an overview of the different terms used by each device to refer to the different test outputs. This table also summarises the factors affecting clot formation at each stage and the different therapeutic options.

Table 5: Stages of clot formation, factors affecting the clot, therapeutic options and terms used in TEG, ROTEM and Sonoclot[1, 23]

Development of clot	Factors affecting clot[28]	Therapeutic Options	ROTEM	TEG	Sonoclot
Measurement period	NA	NA	RT	-	-
Initial clot/fibrin formation	Factor XII and X1 activity; reflective of intrinsic pathway if activators not used	Administration of plasma, coagulation factors, fibrinogen or platelets.	Clotting time (CT)	R	ACT
Development of clot or rapidity of clot formation	Factor II and VIII activity; platelet count and function, thrombin, fibrinogen, HCT		Clot formation time (CFT) and α angle (α)	Kinetics (k) and α angle (α)	CR
Maximum clot strength	Fibrinogen, platelet count and function, thrombin, factor XIII activity, HCT		Maximum clot firmness (MCF)	Maximum amplitude (MA)	PEAK (Peak amplitude)
Time to maximum clot strength			Time to MCF (MCF-t)	Time to MA (TMA)	Time to shoulder (P1), time to peak (P2), time from shoulder to peak (P2-P1)
Amplitude (at set time)			A5, A10…	A (A5, A10..)	
Clot elasticity			Maximum clot elasticity (MCE)	G	-
Maximum lysis	Fibrinolysis	Antifibrinolytic drugs and additional measures such as administration of fibrinogen or platelets.	Maximum Lysis (ML)	-	R_1 ,R_2 ,R_3
Lysis at fixed time			Lysis in 30, 45, 60 minutes (LY30, LY45, LY60)	Clot lysis (CL)30, CL45, CL60	
Time to lysis			Clot lysis time (CLT) (10% from MCF)	Time to lysis (TTL) (2mm drop from MA)	
Maximum lysis			CLR	_	
Platelet function	Platelet function	Platelets	_	Platelet function	PF

2.3 Platelet function tests

VE tests are often performed in combination with platelet function tests in patients receiving antiplatelet drugs such as aspirin and clopidogrel. Whilst light transmission aggregometry in platelet rich plasma is the gold standard test for platelet function, a number of rapid near patient tests are available.[29] One of the most commonly used is the platelet function analyser (PFA) 100 (Dade-Behring, Marburg, Germany).[30] A more recently developed test which is commonly used in combination with ROTEM is the Multiplate analyzer (Roche), a near patient test designed to detect platelet dysfunction.[31] It uses whole blood and is based on the principle of impedance platelet aggregometry (IPA). It has a turnaround time of 10 minutes and can process up to 30 tests per hour. As mentioned above, both TEG and Sonoclot can run specific platelet mapping assays – the TEG platelet mapping assay and gbACT+ assay for Sonoclot. However, some centres prefer to use a separate platelet function test such as the Multiplate analyser instead of these assays. Tem International GmbH, the manufacturer of ROTEM, has recently introduced a new platelet module that is run in conjunction with the ROTEM delta. It measures platelet aggregation in whole blood samples using impedance aggregometry.

2.4 Comparator: Standard laboratory tests for coagulopathy

The comparator for this technology appraisal is a combination of clinical judgement and standard laboratory tests (SLTs). Standard laboratory coagulation analyses include the following:

Prothrombin time – also used to derive measures *prothrombin ratio (PR)* and *international normalised ratio (INR).* Measure of the extrinsic pathway of coagulation. It measures factors I (fibrinogen), II (prothrombin), V, VII, and X in blood plasma at 37^{o}C. The sample is added to a test tube containing liquid sodium citrate and centrifuged, tissue factor is then added and the time the sample takes to clot is measured. The prothrombin ratio is the prothrombin time for a patient, divided by the result for control plasma. The INR is the ratio of a patient's prothrombin time to a normal (control sample) raised to the power of the international sensitivity index (ISI) value for the analytical system used. The ISI value indicates how a particular batch of tissue factor compares to an international reference tissue factor.

Activated partial thromboplastin time (aPTT) – measures the "intrinsic" or contact activation pathway and the common coagulation pathway. An activated matrix (e.g. silica, celite, kaolin, ellagic acid) and calcium are mixed into the plasma sample and the time the sample takes to clot is measured.

Activated clotting/coagulation time (ACT) – based on ability of whole blood to form a visible fibrin monomer in a glass tube. Used to measure heparin anticoagulation.

Platelet count – In general a low platelet count is associated with an increased risk of bleeding. It is a purely quantitative measure and cannot detect pre-existing, drug-induced, or peri-operatively acquired platelet dysfunction.[2]

Plasma fibrinogen concentration – a number of assays are available to assess plasma fibrinogen levels, the Clauss fibrinogen assay is the most common and is based on the thrombin clotting time. Diluted plasma is clotted with a high concentration of thrombin at 37°C and the clotting time is measured. The result is compared with a calibration curve prepared by clotting a series of dilutions of a reference plasma sample of known fibrinogen concentration to give a result in g/L. Most laboratories use an automated method in which clot formation is considered to have occurred when the optical density of the mixture has exceeded a certain threshold.[32]

These tests have a number of limitations for prediction and detection of perioperative coagulopathy as they were not developed to predict bleeding or guide coagulation management in a surgical setting. In general, they are only able to identify that the blood is not clotting properly but are not able to identify what part of the clotting process is disrupted. They are performed at a standardised temperature of 37^{o}C which limits the detection of coagulopathies induced by hypothermia.[2] The aPTT and INR tests only affect the initial formation of thrombin in plasma without the presence of platelets or other blood cells. These tests are also not able to provide any information regarding clot formation over time or on fibrinolysis and so they cannot detect hyperfibrinolysis. They generally take between 40 and 90 minutes from taking the blood sample to give a result; this turnaround time may be so long that it does not reflect the current state of the coagulation system when the results are reported.[2]

2.5 Care pathway

2.5.1 Current care pathway

The exact care pathway and use of SLTs before, during, and after surgery, will vary according to the specific type of surgery. Some centres routinely screen all patients pre-operatively for coagulation disorders using SLTs such as the PT and aPTT tests.[33] However, UK guidelines published in 2008 do not recommend routine coagulation tests to predict perioperative bleeding risk in unselected patients before surgery.[34] Instead, pre-operative testing should only be considered in patients at risk of a bleeding disorder, for example those with liver disease, family history of inherited bleeding

disorder, sepsis, diffuse intravascular coagulation, pre-eclampsia, cholestasis and those at risk of vitamin k deficiency.[33]

It is generally recommended that patients stop taking anticoagulant medications (clopidogrel, warfarin, and aspirin) a number of days before surgery to reduce the risk of bleeding during surgery.[10, 35] In the event of emergency surgery this may not be possible in which case coagulation testing should be performed.[33] If the surgery involves cardiopulmonary bypass (CPB) then heparin may be administered prophylactically to reduce the risk of clotting whilst on CPB.[35] It is essential to monitor heparin anticoagulation if this has been administered. An initial ACT test should be performed after the first surgical incision and be repeated at regular intervals during surgery.[36] Standard coagulation tests (platelet count, fibrinogen concentration, INR, PT, aPTT) are most commonly used to assess the coagulation status of patients who are experiencing high blood loss during surgery. However, these generally take too long to give a result that can inform treatment decisions. Instead decisions on how to treat the bleed have to be based largely on clinical judgement. The same tests are used after surgery to monitor coagulation status.

If bleeding occurs surgical intervention may be needed or packed erythrocytes are transfused if required. This is generally to maintain a haemoglobin concentration above 6g/dL during CPB and 8g/dL after CPB or according to other requirements as indicated by national guidelines. Other therapeutic options depending on laboratory test results include fibrinogen concentrate (bleeding patients with abnormal fibrinogen), fresh frozen plasma (if after transfusion of packed erythrocytes new laboratory results were not available and/or bleeding did not stop after fibrinogen administration), prothrombin complex concentrate (abnormal INR or aPTT), antithrombin concentrate (when ACT analyses not controlled by heparin alone), desmopressin (suspected platelet dysfunction), platelet concentrates (low platelet count).[35] If bleeding continues despite these treatments then additional treatment options include factor XIII concentrate and activated recombinant factor VII or factor VIIa.[10, 35] Heparin does adjustments may be made to try and control the bleeding.

2.5.2 Role of VE testing in the care pathway

VE testing can be repeatedly performed during and after surgery and so can provide a dynamic picture of the coagulation process during and after surgery. The role of VE testing in the care pathway is unclear. It could be used either as an *add-on* test in which case it would be performed as well as standard laboratory tests, or it could be as *replacement* test in which case standard laboratory tests would no longer be needed.

If VE testing does not prevent the need for SLTs and provides complementary findings then it should be performed in addition to any laboratory coagulation tests already recommended for specific populations. However, if the standard laboratory tests do not offer any supplementary information to that provided by VE testing then there should no longer be a need for standard tests and VE testing should replace some or all of the standard laboratory tests. VE tests offer two key potential benefits over standard laboratory tests: the shorter timescale in which they are able to provide results and the additional information on the clotting process which they offer compared to standard tests. It is hypothesised that by providing additional information and quicker results requirements for blood products could be targeted and so the patient is not subjected to risks associated with unnecessary transfusion. Time in theatre, resource use, length of stay in a critical care unit, length of hospital stay, blood product usage, and the associated costs may therefore be reduced.

3. ASSESSMENT OF CLINICAL EFFECTIVENESS

A systematic review was conducted to summarise the evidence on the clinical effectiveness of VE point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis. Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[37] and NICE Diagnostic Assessment Programme manual.[38] We developed a protocol for the review (Appendix 7) and the protocol was registered on the PROSPERO database (CRD42013005623).

3.1 Systematic review methods

3.1.1 Search strategy

Search strategies were based on index test (ROTEM Delta, TEG and Sonoclot), as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[37] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[39]

Candidate search terms were identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase EMTREE), existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches were used to generate test sets of target references, which informed text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development involved an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases and aimed to reach a satisfactory balance of sensitivity and specificity.

Search strategies were developed specifically for each database and the keywords associated with ROTEM, thromboelastography, thromboelastometry and Sonoclot were adapted according to the configuration of each database.

3.1.1.1 Primary clinical effectiveness searches

Primary searches were undertaken for randomised controlled trials in thromboelastography, thromboelastometry, and Sonoclot, and these searches were limited with an objectively-derived study design filter, where appropriate.

The following databases were searched for relevant studies from inception to December 2013:

- MEDLINE (OvidSP): 1946-2013/09/wk 3
- MEDLINE In-Process Citations and Daily Update (OvidSP): up to 26.9.13
- EMBASE (OvidSP): 1974-2013/09/30
- BIOSIS Previews (Web of Knowledge): 1956-2013/09/26

- Science Citation Index (SCI) (Web of Science): 1970-2013/09/26
- Conference Proceedings Citation Index (CPCI-S) (Web of Science): 1990-2013/09/26
- Cochrane Database of Systematic Reviews (CDSR) (Internet): Issue 10. October/2013
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet): Issue 10. October/2013
- Database of Abstracts of Reviews of Effects (DARE) (Internet): Issue 4. October/2013
- Health Technology Assessment Database (HTA) (Internet): Issue 4. October/2013
- Latin American and Caribbean Health Sciences Literature (LILACS) (Internet): http://regional.bvsalud.org/php/index.php?lang=en
- International Network of Agencies for Health Technology Assessment (INAHTA): up to 2013/09/27 http://www.inahta.org/
- NIHR Health Technology Assessment Programme (Internet): up to 2013/9/27
- Aggressive Research Intelligence Facility (ARIF) (Internet): 1996-2013/09/27 http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/index.aspx
- MEDION (Internet): up to 2013/09/27 http://www.mediondatabase.nl/
- International Prospective Register of Systematic Reviews (PROSPERO) (Internet): up to 2013/09/27 http://www.crd.york.ac.uk/prospero/

Completed and ongoing trials were identified by searches of the following resources:

- NIH ClinicalTrials.gov (Internet): up to 2013/09/27 http://www.clinicaltrials.gov/
- metaRegister of Controlled Trials (mRCT) (Internet): up to 2013/09/27 http://www.controlled-trials.com/
- WHO International Clinical Trials Registry Platform (ICTRP) (Internet): up to 2013/09/26 http://www.who.int/ictrp/en/

Electronic searches were undertaken for the following conference abstracts:

- International Society on Thrombosis and Haemostasis (ISTH) (Internet): 2009, 2011 http://www.isth.org/?PastMeetings
- American Society of Anesthesiologists (ASA) (Internet): 2009-2013 http://www.asaabstracts.com/strands/asaabstracts/search.htm;jsessionid=FF1E2F6EA4FF34468F5594FA255F3423
- European Association of Cardiothoracic Anaesthetists (EACTA) (Internet): 2009-2013

  2013 - http://www.applied-cardiopulmonary-pathophysiology.com/acp-2-2013.html

  2012 – http://www.applied-cardiopulmonary-pathophysiology.com/acp-supp1-2012.html

  2011 – Searched via publisher's website

  2010 – http://www.applied-cardiopulmonary-pathophysiology.com/fileadmin/downloads/acp-2010-1/10_abstracts.pdf

2009 - http://www.applied-cardiopulmonary-pathophysiology.com/fileadmin/downloads/acp-2009-S1/EACTA-2009-abstracts.pdf

3.1.1.2 VE testing in post-partum haemorrhage and trauma

A second series of focussed searches were undertaken without a study design filter to identify relevant references reporting thromboelastography, thromboelastometry and Sonoclot in post-partum haemorrhage or trauma response.

The following databases were searched for relevant studies from inception to December 2013:

- MEDLINE (OvidSP): 1946-2013/09/wk 3
- MEDLINE In-Process Citations and Daily Update (OvidSP): up to 26.9.13
- EMBASE (OvidSP): 1974-2013/11/05

No restrictions on language or publication status were applied. All search strategies are presented in Appendix 1. The main Embase strategy for each search was independently peer reviewed by a second Information Specialist, using the Canadian Agency for Drugs and Technologies (CADTH) Peer Review checklist.[40] Identified references were downloaded in Endnote X4 software for further assessment and handling. References in retrieved articles and the websites set up by the manufacturers of ROTEM Delta and Sonoclot were also screened for additional references. The manufacturers of ROTEM and Sonoclot and clinical experts submitted references of relevant publications for consideration for inclusion in the review. The final list of included papers was checked on PubMed for retractions, errata and related citations.[41-43]

3.1.2 Inclusion and exclusion criteria

Inclusion criteria for each of the three clinical review questions are summarised in Table 6. Studies which fulfilled these criteria were eligible for inclusion in the review.

Table 6: Inclusion criteria

Question	1. Clinical outcomes in cardiac surgery	Prediction in cardiac surgery	2. Clinical outcomes in trauma-induced coagulopathy	2a. Prediction in trauma-induced coagulopathy	3. Clinical outcomes in PPH	3a. Prediction in PPH
Participants	Adult (age ≥18 years) patients undergoing cardiac surgery		Adult (age ≥18 years) with clinically suspected coagulopathy induced by trauma		Women with post-partum haemorrhage	
Index test	VE devices (ROTEM, TEG or Sonoclot) alone or combined with platelet testing (e.g. multiplate test) or SLTs	VE devices (ROTEM, TEG or Sonoclot)	VE devices (ROTEM, TEG or Sonoclot) or SLTs	VE devices (ROTEM, TEG or Sonoclot)	VE devices (ROTEM, TEG or Sonoclot) or SLTs	VE devices (ROTEM, TEG or Sonoclot)
Comparators	No testing, SLTs, or other VE device	Any other VE device or None	No testing, SLTs, or other VE device	Any other VE device or None	No testing, SLTs, or other VE device	Any other VE device or None
Reference standard	NA	Patient relevant outcomes e.g. transfusion, bleeding	NA	Patient relevant outcomes e.g. transfusion, bleeding	NA	Patient relevant outcomes e.g. transfusion, bleeding
Outcomes	Any reported outcomes. We anticipate that outcomes will include postoperative mortality, bleeding and transfusion outcomes, complications and re-intervention outcomes.	Sufficient data to construct a 2x2 table of test performance	Any reported outcomes. We anticipate that outcomes will include postoperative mortality, bleeding and transfusion outcomes, complications and re-intervention outcomes.	Sufficient data to construct a 2x2 table of test performance **or prediction model data**	Any reported outcomes. We anticipate that outcomes will include postoperative mortality, bleeding and transfusion outcomes, complications and re-intervention outcomes.	Sufficient data to construct a 2x2 table of test performance **or prediction model data**
Study design	RCTs*	Diagnostic cohort studies/prediction studies	RCTs*	Diagnostic cohort/**prediction studies**	RCTs*	Diagnostic cohort/**prediction studies**

* if insufficient RCTs are available then lower levels of evidence will be considered; NA: not applicable

Protocol modification: In addition to diagnostic cohort studies, our review identified a number of studies which used multi-variate regression modelling to assess the ability of VE tests to predict outcomes in trauma patients; data from studies of this type were considered to be useful and the inclusion criteria were expanded accordingly

3.1.3 Inclusion screening and data extraction

Two reviewers (MW and PW) independently screened the titles and abstracts of all reports identified by searches and any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant were obtained and the same two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus. Details of studies excluded at the full paper screening stage are presented in Appendix 4.

Studies cited in materials provided by the manufacturers of ROTEM, TEG or Sonoclot were first checked against the project reference database, in Endnote X4; any studies not already identified by our searches were screened for inclusion following the process described above.

Data were extracted on the following: participant characteristics; study design; inclusion and exclusion criteria; details of VE test and/or test parameters evaluated; details of SLTs, where applicable; details of outcomes assessed (main outcomes were bleeding outcomes, transfusion outcomes, hospital/ICU stay, re-operation and mortality); results. Data were extracted by one reviewer, using a piloted, standard data extraction form and checked by a second (MW and PW); any disagreements were resolved by consensus. Full data extraction tables are provided in Appendix 2.

3.1.4 Quality assessment

The methodological quality of included RCTs was assessed using the Cochrane Risk of Bias Tool.[44] Prediction studies were assessed for methodological quality using QUADAS-2.[45] Risk of bias assessments were undertaken by one reviewer and checked by a second reviewer (MW and PW), and any disagreements were resolved by consensus.

The results of the risk of bias assessments are summarised and presented in tables and graphs in the results of the systematic review and are presented in full, by study, in Appendix 3.

3.1.5 Methods of analysis/synthesis

We provided a narrative synthesis involving the use of text and tables to summarise data to show differences in study designs, population, VE device and potential sources of bias for each of the studies being reviewed. Studies were organised by research question addressed (study population), outcome and VE device.

3.1.5.1 RCTs comparing VE testing with no testing

Meta-analysis was used to estimate summary effect sizes for outcomes evaluated in multiple studies for which sufficient data were reported. Data were only reported in an appropriate format to permit pooling for dichotomous data. Summary relative risks (RR) together with 95% CIs were estimated using DerSimonian and Laird random effects models. Heterogeneity was investigated visually using forest plots and statistically using the I^2 and Q statistics. Data were pooled for all VE devices combined and stratified according to VE device; if no difference based on VE device was found a summary estimate was calculated comparing VE testing irrespective of VE device to no testing. Where multiple sets of data were reported for the same outcome for a single study, for example pre-operative, post-operative and total number of patients transfused, a single dataset was selected. The dataset relating to the largest number of participants or latest time point was selected.

For continuous outcomes, data were not reported in sufficiently similar format to permit pooling. Only a small number of studies reported data as means and standard deviations or CIs, which would have allowed calculations of mean differences, and there were insufficient studies reporting data in this format to pool data. Most studies reported data as medians (some with interquartile ranges) and some reported p-values for comparisons of the differences between medians, usually estimated using the Mann Whitney or Wilcoxon rank sum tests. Some studies only reported medians with no measure of distribution around the median or estimation of the significance of the difference between groups. We summarised the results for continuous outcomes in a table showing the measure of effect reported in the study (mean or median with associated standard deviation, CI, IQR or range), the effect estimate in the VE testing and in the control group and any reported p-value for the comparison between the two groups.

3.1.5.2 Prediction studies

Prediction studies provided data in a variety of formats:

- Logistic regression models for the association of the VE test parameter and the outcome (reference standard) under investigation, adjusted for a range of other variables. From these studies, we selected the adjusted OR and associated 95% CI as the measure to use in the analysis.
- Crude (unadjusted) ORs with associated 95% CIs for the association of the VE test parameter and the outcome (reference standard) under investigation. We selected these as the measure to use in the analysis.

- 2 x 2 data for the association of the VE test parameter (index test) with the outcome (reference standard) under investigation. We used these data to calculate crude ORs and associated 95% CIs.
- Sensitivity and specificity data for the VE test parameter for the prediction of the outcome (reference standard) under investigation. If these studies also reported data on the number of participants with and without the outcome these data were used to calculate a 2x2 table from which ORs were derived as described above. If this information was not provided sensitivity and specificity were used to calculate ORs; for these studies it was not possible to calculate associated CIs.
- Area under the receiver operating characteristic (ROC) curve (AUC) for the VE test parameter for the prediction of the outcome (reference standard) under investigation. Some studies reported crude (un-adjusted) AUCs others used regression models to adjust the AUC for various other variables. If both were reported the adjusted values were selected, otherwise crude (un-adjusted) AUCs together with 95% CIs were selected.

Data were not sufficiently similar to permit pooling for any of the outcomes for any of the population groups for the prediction studies; studies differed in the variables adjusted for in the regression models and the VE test parameters evaluated. For outcomes evaluated in more than two studies, forest plots were used to display adjusted and crude (un-adjusted) ORs or AUCs together with 95% CIs for individual studies. A narrative summary of the results was provided.

3.1.5.3 Investigation of heterogeneity

There was no evidence of statistical heterogeneity between studies included in the meta-analyses, therefore formal statistical investigation of heterogeneity for these analyses was not appropriate. The following variables were considered as possible explanations for differences between studies in the narrative synthesis: patient demographics (age, gender, surgery type), type of VE device (ROTEM, TEG, Sonoclot), time point of surgery (during surgery only, during and after surgery, and risk of bias domains.

3.2 Results of the assessment of clinical effectiveness

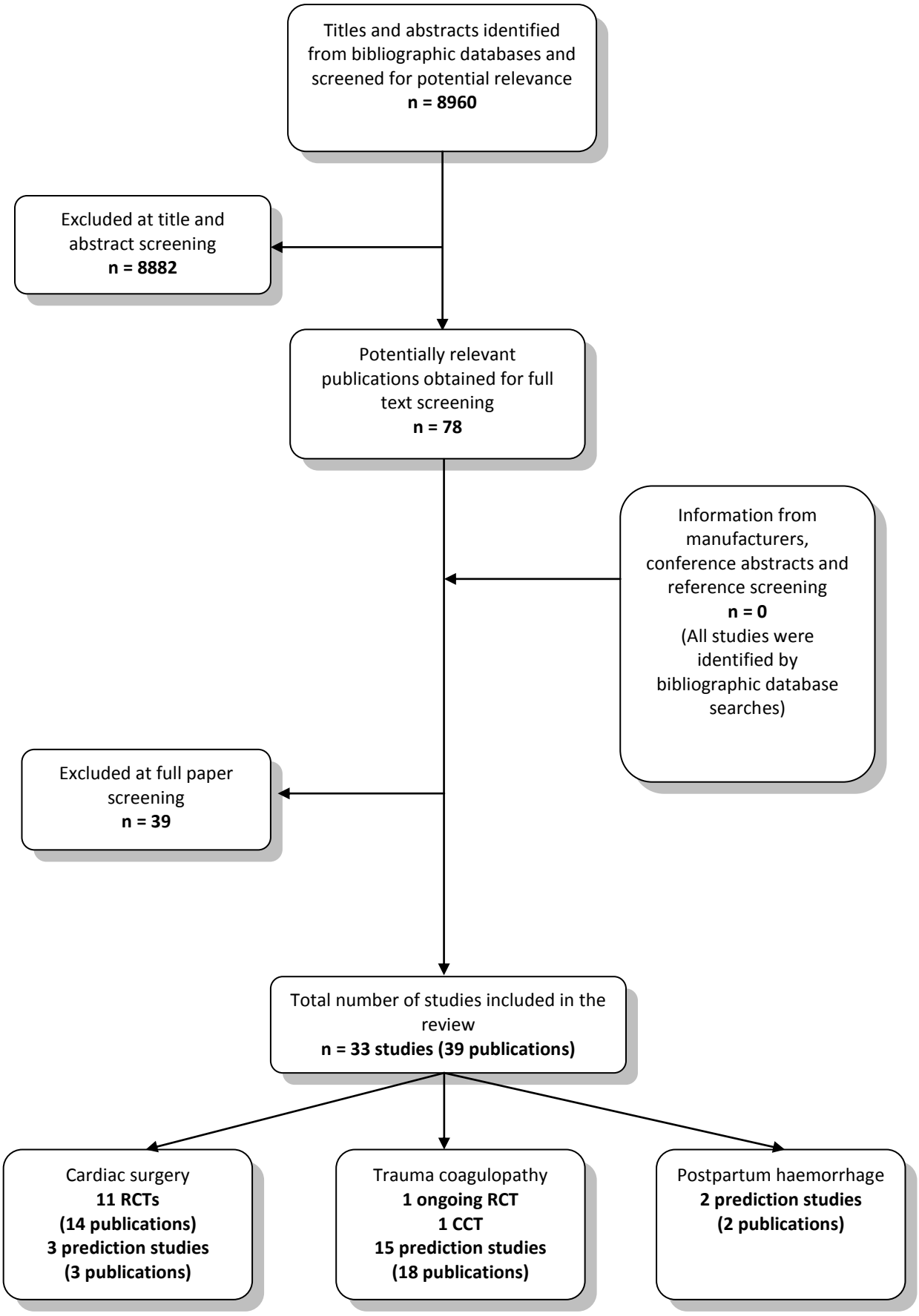
The literature searches of bibliographic databases identified 8,960 references. After initial screening of titles and abstracts, 78 were considered to be potentially relevant and ordered for full paper screening. No additional papers were ordered based on screening of papers provided by test manufacturers, conference abstract hand searching or screening references

of included studies; all studies cited in documents supplied by the test manufacturers, identified through reference screening or conference abstract screening had already been identified by bibliographic database searches. Figure 4 shows the flow of studies through the review process, and Appendix 4 provides details, with reasons for exclusions, of all publications excluded at the full paper screening stage.

Based on the searches and inclusion screening described above, 39 publications of 33 studies were included in the review. We included 11 RCTs (14 publications) evaluating ROTEM and TEG in cardiac surgery patients; as no RCTs evaluating Sonoclot were identified, we also included three prediction studies that evaluated Sonoclot. We included one ongoing RCT, one CCT and 15 prediction studies (18 publications) in trauma patients and two prediction studies in women with PPH.

Full details of the characteristics of study participants, study inclusion and exclusion criteria, VE test used and results are reported in the data the extraction tables presented in Appendix 2. The results of the risk of bias assessments are presented in Appendix 3.

Figure 4: Flow of studies through the review process



3.2.1 How do clinical outcomes differ among patients who are tested with VE devices during or after cardiac surgery compared to those who are not tested?

We included 11 RCTs (n=1089, range 22 to 228) (14 publications)[35, 46-55, 56, 57, 58] for the assessment of VE devices in patients undergoing cardiac surgery; six assessed TEG, four assessed ROTEM and one assessed ROTEG. ROTEG was an early name for ROTEM and so the study assessing ROTEG was grouped with the ROTEM studies in the analyses.[52] Two RCTs were only available as abstracts.[53, 55]

3.2.1.1 Study details

The RCTs were conducted in Australia, Austria, Germany, Spain, Turkey, UK and USA. Most included patients undergoing surgery irrespective of whether or not they had a bleeding event, however, two RCTs assessing ROTEM were restricted to patients who had experienced bleeding above a certain level (≥300 mL in first post-operative hour [53] or bleeding from capillary beds requiring haemostatic therapy or blood loss exceeding 250mL/h or 50mL/10 minutes[35]). A further RCT of TEG was restricted to patients at moderate to high risk for transfusion procedures.[51] One RCT was restricted to patients undergoing aortic surgery[54], two included patients undergoing coronary artery bypass graft (CABG)[46, 48] and the remainder included patients undergoing mixed cardiac surgery. One study excluded patients with abnormal pre-operative conventional coagulation tests,[48] another excluded patients with preoperative haemodynamic instability or a history of bleeding diathesis[46] and one excluded patients with known (inherited) coagulation disorders.[54] The majority of studies did not place any restriction on entry based on anti-coagulation use, but one study excluded patients who had used low molecular weight heparin up to the day of operation.[48] One study excluded patients with pre-existing hepatic or severe renal disease.[51] Mean or median age, where reported, ranged from 53 to 72 years. The proportion of men ranged from 56% to 90%.

The ROTEM/TEG algorithms varied across studies. Six studies used an algorithm based on TEG or ROTEM alone. Two studies combined TEG with SLTs,[50, 51] two combined ROTEM with platelet function testing (point of care in one),[35] one of these also used Hepcon to monitor heparin and protamine dosage,[48] and one combined ROTEM with clinical evaluation.[55] The timing of the VE test varied across studies. All except one study which performed TEG on arrival at the intensive care unit (ICU)[50] administered multiple VE tests. Timing included baseline/before bypass/before anaesthesia, after CPB, after protamine administration, on admission to ICU and up to 24 hours post CPB in one study.[46] Four studies only performed

VE testing post-surgery in patients who were continuing to bleed.[35, 47, 48, 54] Four studies used an algorithm based on SLTs in the control group;[35, 46, 48, 53] all other studies stated that control groups included combinations of clinical judgements and SLTs. Further details are summarised in Table 7.

Table 7: Baseline details of RCTs evaluating VE devices in patients undergoing cardiac surgery

Study details	n	Patient category	Entry restricted to excessive bleeding?	Entry restriction based on anti-coagulation?	VE testing algorithm	Control	Timing of VE test
Ak(2009)[46]	228	CABG	No	No	TEG	Clinician judgement including SLTs	Before anaesthesia, after CPB, 15 mins after protamine, admission to ICU, 6 & 24 hours post CPB
Avidan(2004)[48]	102	CABG	No	Yes – no coagulation medication <72 hours of surgery	TEG combined with Hepcon, platelet function testing and ACT	SLTs algorithm	5 mins & 1 hour post CPB, 20 mins post protamine, 2 hours post-surgery if bleeding
Girdauskas(2010)[54]	56	Aortic surgery	No	No	ROTEM	Clinician judgement including SLTs	Rewarming phase of CPB, before chest closure, on ICU in case of increased bleeding. Repeat ROTEM also performed 15 minutes after administration of coagulation products
Kultufan Turan(2006)[52]	40	CABG or valve surgery	No	Unclear	ROTEG	Routine transfusion therapy & SLTs	Pre-operation, 1 hour post operation
Nuttall(2001)[50]	92	Mixed cardiac surgery	No	No	TEG combined with PT, APTT, platelet counts and fibrinogen concentration	Clinician judgement with or without SLTs	On arrival in ICU
Paniagua(2011)[53]*	22	Mixed cardiac surgery	Yes (≥300mL in first post-operative hour)	NR	ROTEM	SLTs	NR
Rauter(2007)[55]*	213	Mixed cardiac surgery	No	NR	ROTEM + clinical signs	Routine management including SLTs	NR

Study details	n	Patient category	Entry restricted to excessive bleeding?	Entry restriction based on anti-coagulation?	VE testing algorithm	Control	Timing of VE test
Royston(2001)[49]	60	Mixed cardiac surgery	No	No	TEG	Clinician judgement including SLTs	Prior to surgery, at bypass 10-15 mins after protamine
Shore-Lesserson(1999)[51]	107	Mixed cardiac surgery	Moderate to high risk for transfusion procedures	No	TEG + platelet count + fibrinogen +	SLTs algorithm	Baseline, during rewarming on CPB, after protamine
Weber(2012)[35]	100	Mixed cardiac surgery	Yes – bleeding from capillary beds or blood loss >250mL/h or 50mL/10 min	Yes – pre-operative antiplatelet therapy stopped >6 days before surgery	ROTEM + POC testing for platelet function	SLTs algorithm	Unclear; appears to be before weaning off CPB, after protamine, for ongoing bleeding
Westbrook(2009)[47]	69	Mixed cardiac surgery	No	No	TEG	Clinician judgement including SLTs	Prior to surgery, at bypass, 10-15 minutes after protamine

SLTs=standard laboratory tests; *Studies reported only as abstracts

3.2.1.2 Risk of bias assessment

There were a number of methodological issues with the RCTs included in this assessment. Only three of the 11 RCTs were rated as 'low' risk of bias with respect to their randomisation procedures.[35, 51, 54] The trials were generally poorly reported; all were rated as 'unclear' or 'high' risk of bias on at least 50% of the assessed criteria. Allocation concealment and blinding were particularly poorly reported. Only one study reported sufficient information to assess risk of bias in relation to allocation concealment and this study was considered to have a 'high' risk of bias on this criterion.[50] This study moved four patients initially randomised to the algorithm group to the control group and so allocation was not concealed for these patients.

Five of the 11 RCTs reported details of blinding of study participants and personnel; [46-48, 52, 55] only three of these were rated as 'low' risk of bias.[46, 47] In one of these studies the anaesthesiologist who performed the transfusion was blinded to the patient's group assignments, in one the surgeons were blinded to the method of haemostasis assessment,[47] and in the third the physician in charge of ROTEG and ICU physician were blinded.[52] The other two studies explicitly stated that they were unblinded.[48, 55] Only three RCTs reported details on blinding of outcome assessors.[47, 48, 50, 55] Two were rated as 'low' risk of bias, [48, 50] one reported that outcomes were recorded by staff in the recovery unit who were unaware of group allocation,[48] the other stated that surgeons and anaesthesiologists were not aware of group allocation at the time the decision on whether to transfuse was made.[50] The third reported that it was unblinded.[55]

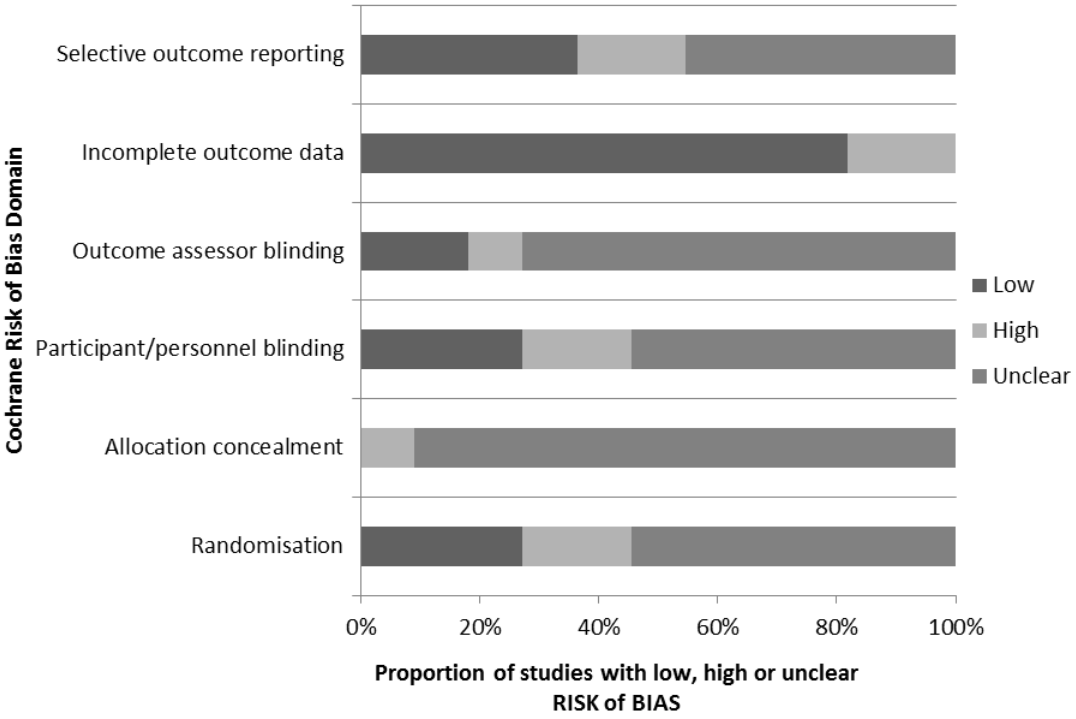
Inclusion of all study participants in analyses was the only notable area of methodological strength, with all but three trials rated as 'low' risk of bias for the completeness of outcome data criterion.[35, 46, 48, 50-54] The results of risk of bias assessments are summarised in Table 8 and Figure 5; full risk of bias assessments for each study are provided in Appendix 3.

Table 8: Risk of bias assessments for RCTs evaluating VE devices in patients undergoing cardiac surgery

Study	RISK OF BIAS					
	Randomisation	Allocation concealment	Participant and personnel blinding	Outcome assessor blinding	Incomplete outcome data	Selective outcome reporting
Ak(2009)[46]	?	?	☺	?	☺	☺
Avidan(2004)[48]	?	?	☹	☺	☺	?
Girdauskas(2010)[54]	☺	?	?	?	☺	☺
Kultufan Turan(2006)[52]	?	?	☺	?	☺	☺
Nuttall(2001)[50]	☹	☹	?	☺	☺	?
Paniagua(2011)[53]	?	?	?	?	☺	☹
Rauter(2007)[55]	?	?	☹	☹	☹	☹
Royston(2001)[49]	☹	?	?	?	☹	?
Shore-Lesserson(1999([51]	☺	?	?	?	☺	?
Weber(2012)[35]	☺	?	?	?	☺	☺
Westbrook(2009)[47]	?	?	☺	?	☹	?

☺Low Risk ☹High Risk ? Unclear Risk

Figure 5: Proportion of studies fulfilling each risk of bias criteria for RCTs evaluating VE devices in patients undergoing cardiac surgery



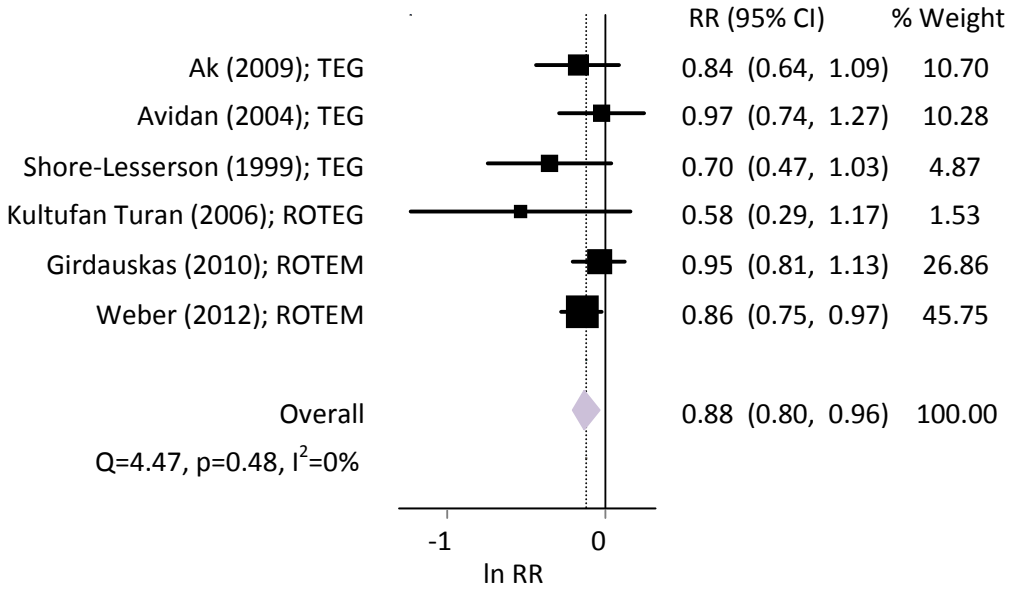
3.2.1.3 Results

RBC transfusion

All but one of the included RCTs evaluated RBC transfusion as either a continuous or dichotomous outcome.[49] Eight RCTs evaluated RBC transfusion within 24 to 48 hours as a continuous outcome (Table 9).[35, 46, 47, 50, 51, 53-55] All RCTs reported less volume of RBC transfusion in the VE algorithm group compared to the control group but this was only statistically significant in three (two of ROTEM and one of TEG);[35, 50, 55] one RCT did not report on the statistical significance of the difference.[53]

Six RCTs[35, 46, 48, 51, 52, 54] provided dichotomous data on the number of patients who received an RBC transfusion in each intervention group. The summary RR was 0.88 (95% CI 0.80, 0.96) suggesting a significant beneficial effect of the VE testing algorithm in reducing the number of patients who received an RBC transfusion (Figure 6). There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to VE device: RR 0.86 (95% CI 0.72, 1.02) for the three RCTs that evaluated TEG and 0.88 (95% CI 0.78, 1.00) for the three RCTs that evaluated ROTEM and ROTEG.

Figure 6: Forest Plot showing RRs (95% CI) for number of patients receiving RBC transfusion in VE groups compared to controls groups in cardiac patients



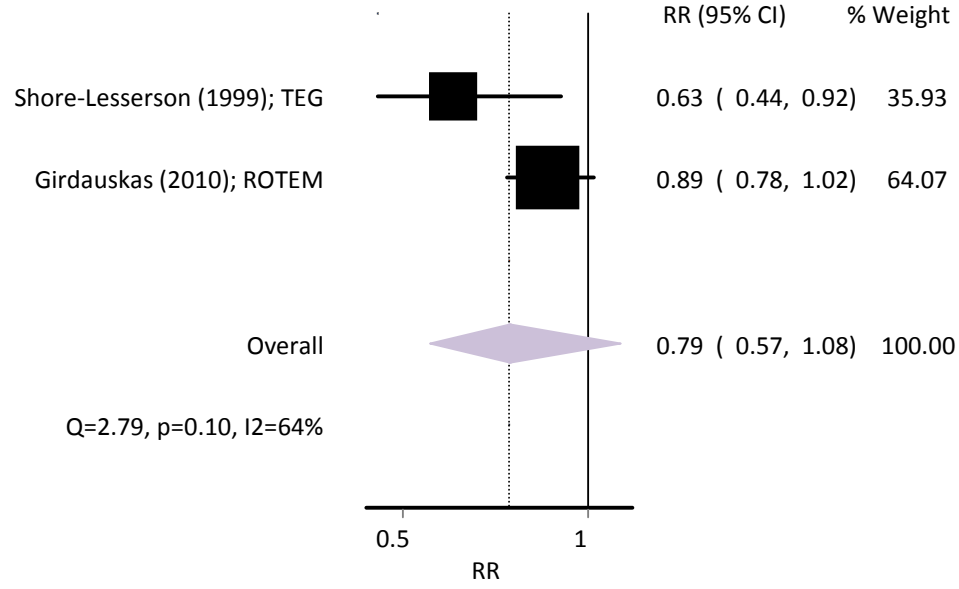
Any blood product transfusion

Three RCTs evaluated any blood product transfusion as a continuous outcome (Table 9).[46, 47, 54] All three reported less volume of any blood product transfusion in the VE algorithm group

compared to the control group. This was statistically significant in two (one ROTEM and one TEG);[46, 54] the third did not report on the statistical significance of the difference.[53]

Two RCTs[49, 51, 52, 54] provided dichotomous data on the number of patients who received any blood product (defined as any blood product in one and allogeneic blood product in the other) transfusion in each intervention group. One assessed ROTEM (RR 0.89, 95% CI 0.78, 1.02) and the other assessed TEG (RR 0.63, 95% CI 0.44, 0.92). The summary RR was 0.79 (95% CI 0.57, 1.08) suggesting a beneficial effect of the VE testing algorithm in reducing the number of patients who received any blood product transfusion, although this did not reach statistical significance (Figure 7). There was some evidence of heterogeneity across studies (I^2=64%).

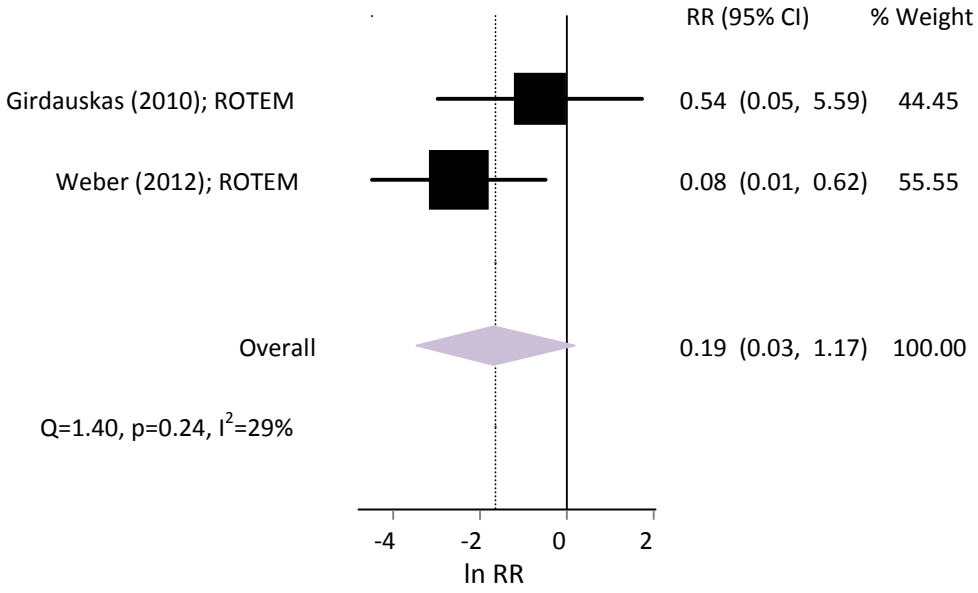
Figure 7: Forest Plot showing RRs (95% CI) for number of patients receiving any blood product transfusion in VE groups compared to controls groups in cardiac patients



Factor VIIa Transfusion

Two RCTs[35, 54] that assessed ROTEM provided dichotomous data on the number of patients who received a factor VIIa transfusion in each intervention group. The summary RR was 0.19 (95% CI 0.03, 1.17) suggesting a beneficial effect of the ROTEM testing algorithm, although this difference did not reach statistical significance (p>0.05) (Figure 8). There was no evidence of heterogeneity across studies (I^2=0%).

Figure 8: Forest Plot showing RRs (95% CI) for number of patients receiving any Factor VIIa Transfusion in VE groups compared to controls groups in cardiac patients

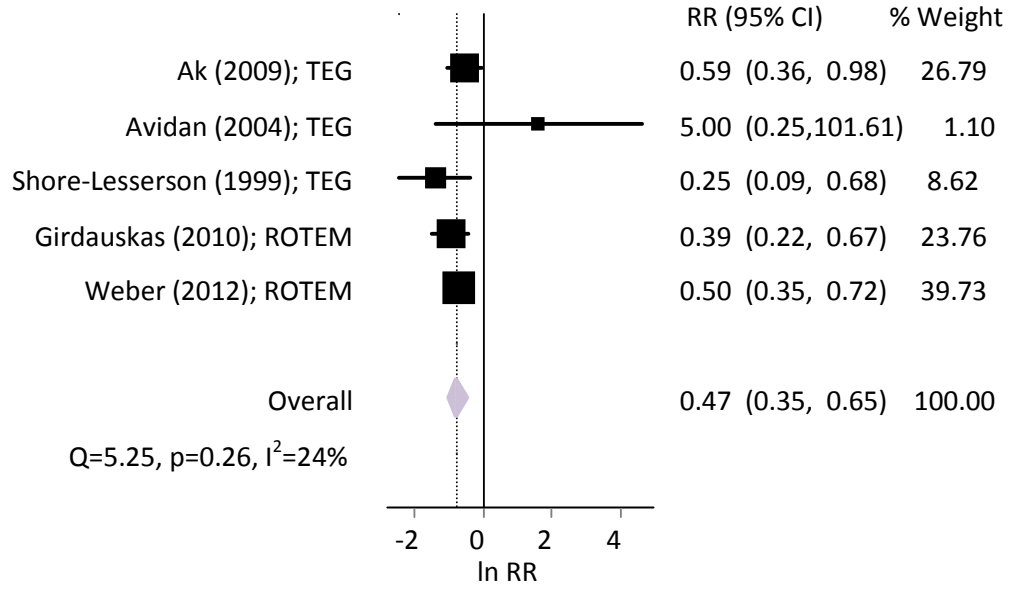


Fresh frozen plasmas (FFP) transfusion

All of the included RCTs evaluated FFP transfusion as either a continuous or dichotomous outcome. Ten RCTs evaluated RBC transfusion within 24 to 48 hours as a continuous outcome (Table 9).[35, 46, 47, 49-55] All but two RCTs reported less volume of FFP transfusion in the VE algorithm group compared to the control group, this was statistically significant in six (two of ROTEM and four of TEG);[35, 46, 49-51, 54] three RCTs did not report on the statistical significance of the difference.[47, 53, 55]

Five RCTs[35, 46, 48, 51, 54] provided dichotomous data on the number of patients who received an FFP transfusion in each intervention group, all but one of which also reported continuous data[48]. The summary RR was 0.47 (95% CI 0.35, 0.65) suggesting a significant beneficial effect of the VE testing algorithm in reducing the number of patients who received an FFP transfusion (Figure 9). There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to VE device: RR 0.52 (95% CI 0.20, 1.35) for the three RCTs that evaluated TEG and 0.46 (95% CI 0.34, 0.63) for the two RCTs that evaluated ROTEM.

Figure 9: Forest Plot showing RRs (95% CI) for number of patients receiving FFP transfusion in VE groups compared to controls groups in cardiac patients

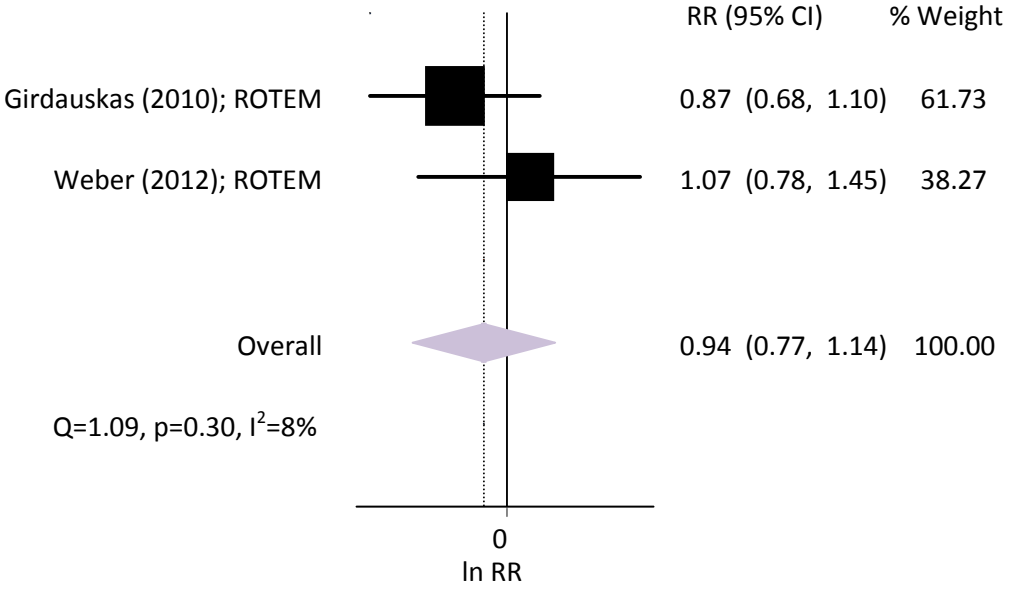


Fibrinogen transfusion

Three RCTs evaluated any fibrinogen transfusion as a continuous outcome (Table 9).[35, 54, 55] All three reported no difference between the VE algorithm group compared to the control group in the volume of fibrinogen transfused.

Two of these RCTs[35, 54] also provided dichotomous data on the number of patients who received a fibrinogen transfusion in each intervention group. The summary RR was 0.94 (95% CI 0.77, 1.14) suggesting no difference between the treatment groups (Figure 10).

Figure 10: Forest Plot showing RRs (95% CI) for number of patients receiving fibrinogen transfusion in VE groups compared to controls groups in cardiac patients

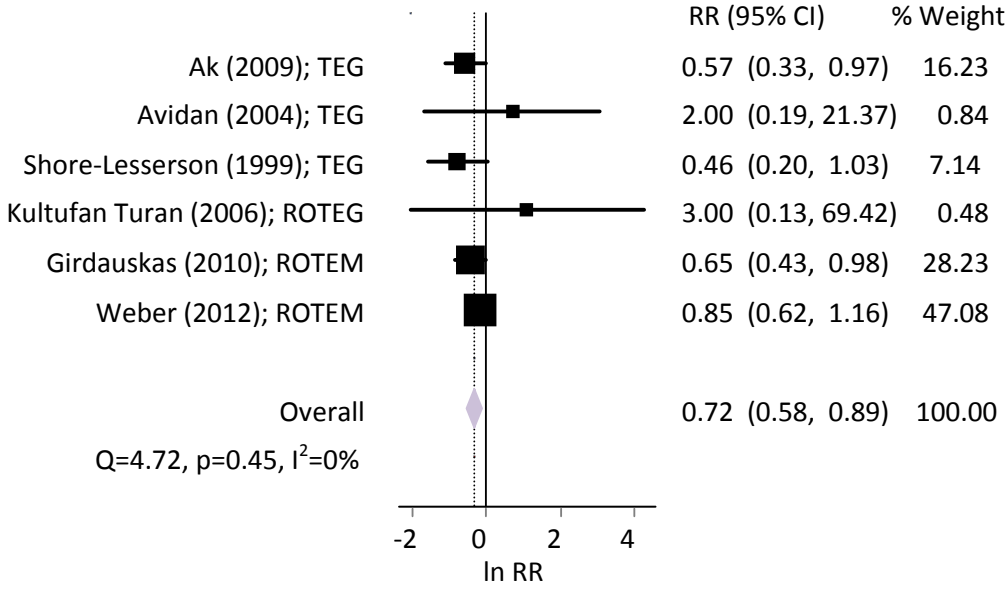


Platelet transfusion

All of the included RCTs evaluated platelet transfusion as either a continuous or dichotomous outcome. Eight RCTs evaluated platelet within 24 to 48 hours as a continuous outcome (Table 9).[35, 46, 47, 49-51, 53-55] All RCTs reported less volume of platelet transfusion in the VE algorithm group compared to the control group but this was only statistically significant in five (two of ROTEM and three of TEG);[35, 46, 49, 50, 53] two RCTs did not report on the statistical significance of the difference.[47, 55]

Six RCTs[35, 46, 48, 51, 52, 54] provided dichotomous data on the number of patients who received a platelet transfusion in each intervention group. The summary RR was 0.72 (95% CI 0.58, 0.89) suggesting a significant beneficial effect of the VE testing algorithm in reducing the number of patients who received a platelet transfusion (Figure 11). There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to VE device: RR 0.56 (95% CI 0.36, 0.86) for the three RCTs that evaluated TEG and 0.78 (95% CI 0.60, 1.00) for the three RCTs that evaluated ROTEM and ROTEG.

Figure 11: Forest Plot showing RRs (95% CI) for number of patients receiving platelet transfusion in VE groups compared to controls groups in cardiac patients



Prothrombin transfusion

Three RCTs evaluated any prothrombin transfusion as a continuous outcome (Table 9).[35, 54, 55] All three reported less volume of prothrombin transfusion in the VE algorithm group compared to the control group but this was only statistically significant in one (p<0.001);[54] one RCT did not report on the statistical significance of the difference.[55]

Two of these RCTs[35, 54] also provided dichotomous data on the number of patients who received a prothrombin transfusion in each intervention group. The summary RR was 0.39 (95% CI 0.08, 1.95) suggesting no difference between the treatment groups (Figure 12).

Figure 12: Forest Plot showing RRs (95% CI) for number of patients receiving prothrombin transfusion in VE groups compared to controls groups in cardiac patients

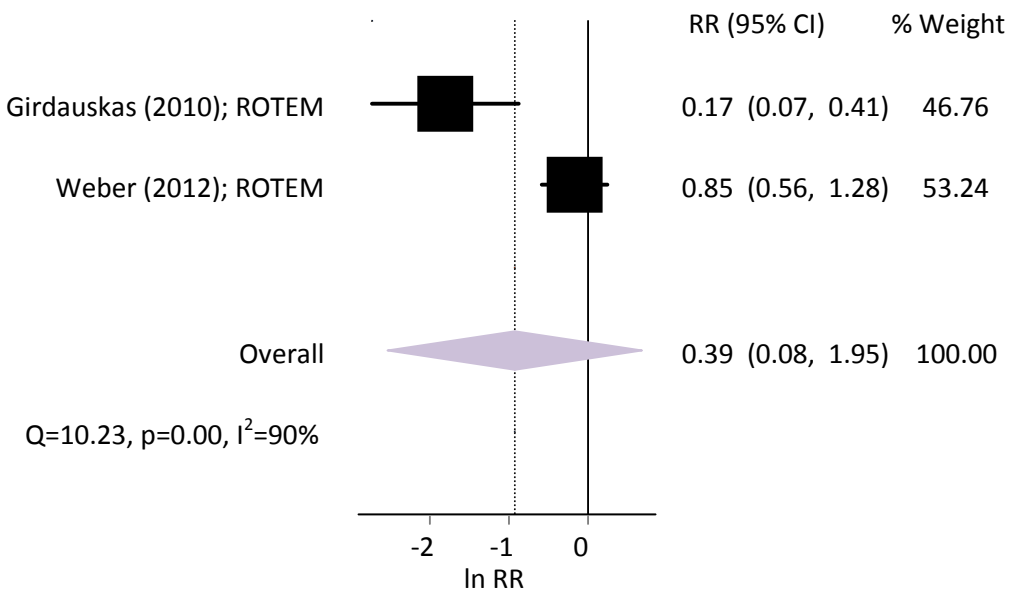


Table 9: Results from RCTs evaluating VE devices in patients undergoing cardiac surgery that reported continuous data for blood product use

Study	Data available	Intervention Results	Control Results	p-value for difference between groups*
RBC transfusion (units unless otherwise stated) within 24 to 48 hours				
Ak(2009)[46]; TEG	Median (IQR)	1 (0, 1)	1 (1, 2)	0.599
Nuttall(2001)[50]; TEG	Median (range)	**2 (0, 9)**	**3 (0, 70)**	**0.039**
Shore-Lesserson(1999)[51]; TEG	Mean (sd)	354 (487)mL	475 (593)mL	0.12
Westbrook(2009)[47]; TEG	Total	14	33	0.12
Girdauskas(2010)[54]; ROTEM	Median (IQR)	6(2, 13)	9(4, 14)	0.20
Paniagua(2011)[53]; ROTEM	Mean	3.8	6.4	NR
Rauter(2007)[55]; ROTEM	Mean	**0.8**	**1.3**	**p<0.05**
Weber(2012)[35]; ROTEM	Median (IQR)	**3 (2, 6)**	**5 (4, 9)**	**<0.001**
Any blood product transfusion (units)				
Ak(2009)[46]; TEG	Median (IQR)	**2 (1, 3)**	**3 (2, 4)**	**0.001**

Study	Data available	Intervention Results	Control Results	p-value for difference between groups*
Westbrook(2009)[47]; TEG	Total	37 (NR)	90 (NR)	NR
Girdauskas(2010)[54]; ROTEM	Median (IQR)	**9 (2, 30)**	**16 (9, 23)**	**0.02**
FFP transfusion (units unless stated) at 12-48 hours				
Ak(2009)[46]; TEG	Median (IQR)	**1 (1, 1)**	**1 (1, 2)**	**0.001**
Nuttall(2001)[50]; TEG	Median (range)	**2 (0, 10)**	**4 (0, 75)**	**0.005**
Royston(2001)[49]; TEG	Total	**5**	**16**	**<0.05**
Shore-Lesserson(1999)[51]; TEG	Mean	**36 (142) mL**	**217 (463) mL**	**<0.04**
Westbrook(2009)[47]; TEG	Total	22	18	NR
Kultufan Turan(2006)[52]; ROTEG	Mean(SD)	2.80 (0.95)	2.70 (1.46)	0.403
Girdauskas(2010)[54]; ROTEM	Median (IQR)	**3 (0, 12)**	**8 (4, 18)**	**0.01**
Paniagua(2011)[53]; ROTEM	Total	3.1	3.4	NR
Rauter(2007)[55]; ROTEM	Total	0	4	NR
Weber(2012)[35]; ROTEM	Median (IQR)	**0 (0, 3)**	**5 (3, 8)**	**<0.001**
Fibrinogen (g) transfusion at 24-48 hours				
Girdauskas(2010)[54]; ROTEM	Median (IQR)	2 (2, 3)	2 (2, 3)	0.70
Rauter(2007)[55]; ROTEM	Total	31	30	NR
Weber(2012)[35]; ROTEM	Median (IQR)	2 (0, 4)	2 (0, 6)	0.481
Platelet transfusion (units, unless otherwise stated) transfusion at 12-48 hours				
Ak(2009)[46]; TEG	Median (IQR)	**1 (1, 1)**	**1 (1, 2)**	**0.001**
Nuttall(2001)[50]; TEG	Median (range)	**6 (0, 18)**	**6 (0, 144)**	**0.0001**
Royston(2001)[49]; TEG	Total	**1**	**9**	**<0.05**
Shore-Lesserson(1999)[51]; TEG	Mean (sd)	34 (94)mL	83 (160)mL	0.16
Westbrook(2009)[47]; TEG	Total	5	15	NR
Girdauskas(2010)[54]; ROTEM	Median (IQR)	1 (0, 4)	2 (1, 3)	0.70
Paniagua(2011)[53]; ROTEM	Total	**0.50**	**1.57**	**<0.05**
Rauter(2007)[55]; ROTEM	Total	0	0	NR
Weber(2012)[35]; ROTEM	Median (IQR)	**2 (0, 2)**	**2 (0, 5)**	**0.010**
Prothrombin complex concentrate (international units) transfusion at 24 to 48 hours				
Girdauskas(2010)[54]; ROTEM	Median (IQR)	**0 (0, 2000)**	**3000 (2000, 3000)**	**<0.001**
Rauter(2007)[55]; ROTEM	Total	3000	13600	NR
Weber(2012)[35]; ROTEM	Median (IQR)	0(0, 1800)	1200 (0, 1800)	0.155

*Comparisons which showed a significant difference ($p<0.05$) between groups are shown in bold; NR: not reported; sd: standard deviation

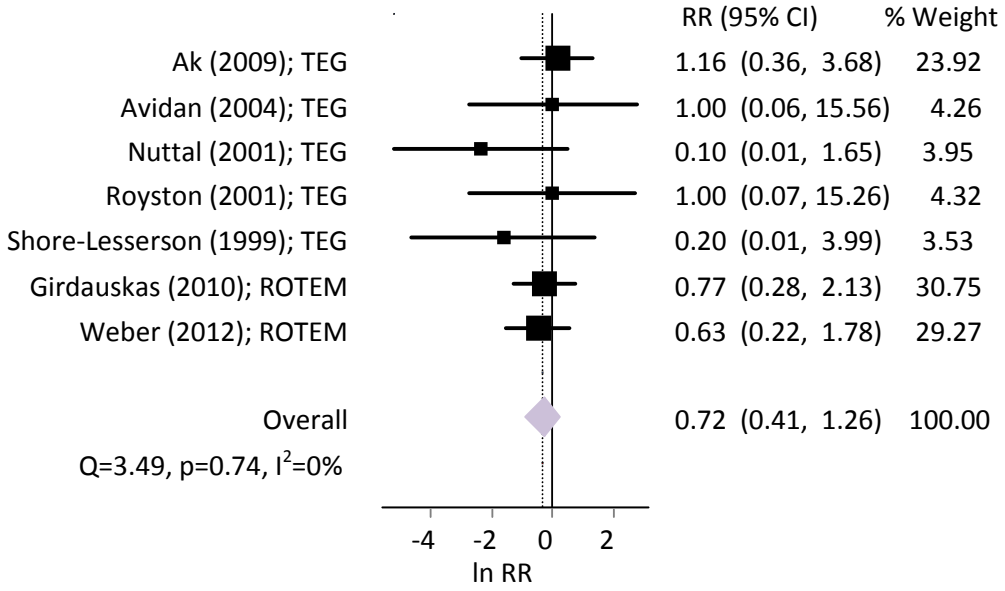
Bleeding

Nine RCTs evaluated bleeding, generally measured as mediastinal tube drainage, as a continuous outcome (Table 10). [35, 46-52, 54] The majority reported less bleeding in the VE intervention group, however, only two studies reported a statistically significant difference in bleeding between the two groups.[35, 50]

Re-operation

Seven RCTs[35, 46, 48-51, 54] provided dichotomous data on the number of patients who required re-operation to investigate bleeding in each intervention group. The summary RR was 0.72 (95% CI 0.41, 1.26) suggesting a significant beneficial effect of the VE testing algorithm in reducing the number of patients requiring re-operation, however, this difference was not statistically significant (Figure 13). There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to VE device: RR 0.75 (95% CI 0.31, 1.83) for the five RCTs that evaluated TEG and 0.69 (95% CI 0.33, 1.44) for the two RCTs that evaluated ROTEM.

Figure 13: Forest Plot showing RRs (95% CI) for number of patients requiring re-operation in VE groups compared to controls groups in cardiac patients

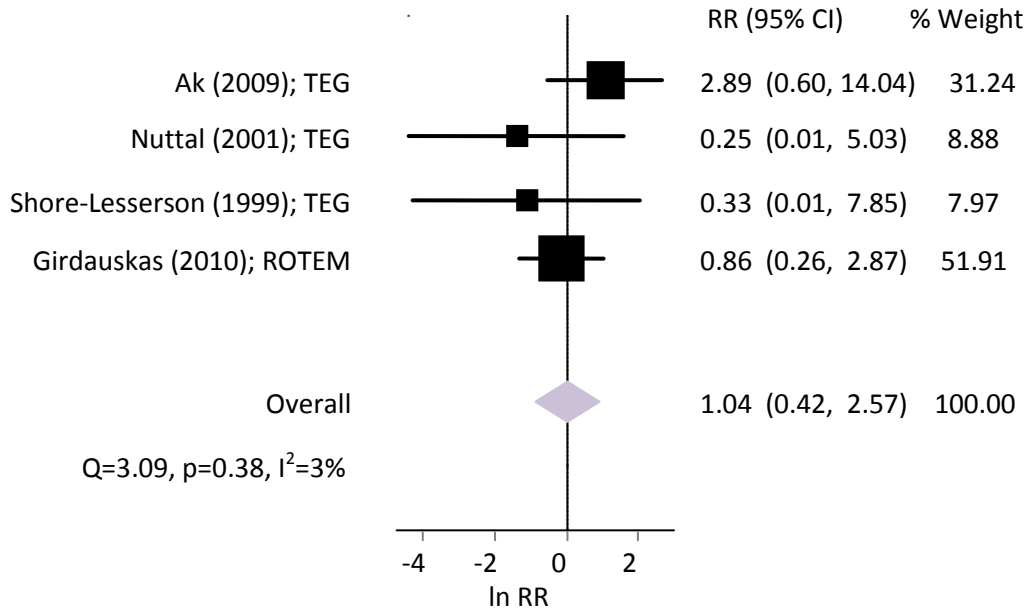


Surgical source of bleeding identified on re-operation

Four RCTs[46, 50, 51, 59] provided dichotomous data on the number of patients in whom a surgical source of bleeding was identified on re-operation in each intervention group. The summary RR was 1.04 (95% CI 0.42, 2.57) suggesting no difference between the intervention groups (Figure 14). There was very little evidence of heterogeneity across studies (I^2=3%). One RCT

assessed ROTEM and reported a RR of 0.86 (95% CI 0.26, 2.87), the summary estimate for the three RCTs assessing TEG was similar at 0.99 (95% CI 0.18, 5.36).

Figure 14: Forest Plot showing RRs (95% CI) for number of patients in whom a surgical source of bleeding was identified on re-operation in VE groups compared to controls groups in cardiac patients



Length of ICU stay

Four RCTs evaluated the length of ICU stay as a continuous outcome (Table 10). [35, 46, 47, 54] All reported shorted stays in the VE group compared to control but this difference was only statistically significant in one study.[35]

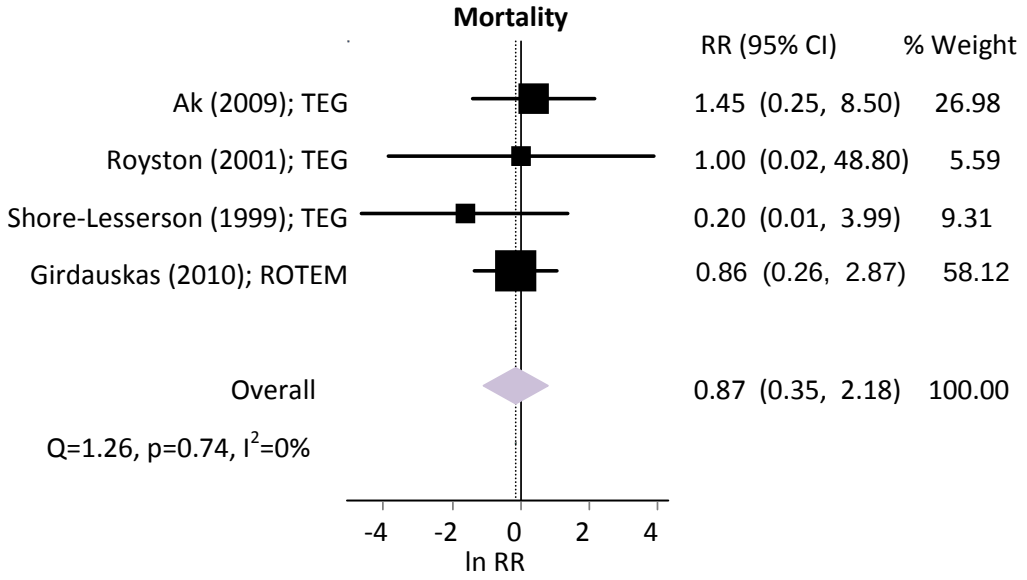
Length of hospital stay

Four RCTs evaluated the length of hospital stay as a continuous outcome (Table 10). [35, 46, 47, 54] All studies reported similar durations of stay in the two treatment groups; none reported a statistically significant difference between groups.

Mortality

Four RCTs[46, 49, 51, 54] provided dichotomous data on the number of deaths (within 24 hours,[51] 48 hours,[49] in hospital[54] or "early mortality"[46]) in each intervention group. The summary RR was 0.87 (95% CI 0.35, 2.18) suggesting no difference between the intervention groups (Figure 15). There was no evidence of heterogeneity across studies (I^2=0%). One RCT assessed ROTEM and reported a RR of 0.86 (95% CI 0.26, 2.87), the summary estimate for the three RCTs assessing TEG was similar at 0.88 (95% CI 0.21, 3.66).

Figure 15: Forest Plot showing RRs (95% CI) for number of deaths in VE groups compared to controls groups in cardiac patients



Other reported outcomes

Data were also reported on the following outcomes but each were only assessed in one or two studies and so are not discussed in detail here: cryoprecipitate use, desmopressin treatment, dialysis dependent renal failure, duration of ventilation, factor VIIa, fresh b intubation time, need for additional protamine, non-RBC balance, post-operative confusion, reinfusion, reintubation, stroke, time to stop bleeding, total heparin dose, total protamine dose, total ventilation time, time to extubation, and tranexamic acid use. Full results can be found in Appendix 2.

Table 10: Results from RCTs evaluating VE devices in patients undergoing cardiac surgery that reported continuous data for clinical outcomes

Study	Data available	Intervention Results	Control Results	p-value for difference between groups
Bleeding/Mediastinal tub drainage (mL) at 12/24h follow-up				
Ak(2009)[46]; TEG	Mean (sd)	480.5 (351.0)	591.4 (339.2)	0.087
Avidan(2004)[48]; TEG	Median (IQR)	755 (606, 975)	850 (688, 1095)	>0.05
Nuttall(2001)[50]; TEG	Median (range)	**590 (240, 2335)**	**850 (290, 10190)**	**0.019**
Royston(2001)[49]; TEG	Median (IQR)	470 (295, 820)	390 (240, 820)	NR
Shore-Lesserson(1999)[51]; TEG	Mean (sd)	702 (500)	901 (847)	0.27
Westbrook(2009)[47]; TEG	Median (IQR)	875 (755, 1130)	960 (820, 1200)	0.437
Kultufan Turan(2006)[52]; ROTEG	Mean (sd)	837.5 (494.1)	711.10 (489.2)	0.581
Girdauskas(2010)[54]; ROTEM	Median (IQR)	890 (600, 1250)	950 (650, 1400)	0.50
Weber(2012)[35]; ROTEM	Median (IQR)	**600 (263, 875)**	**900 (600, 1288)**	**0.021**
Length of ICU stay (hours)				
Ak(2009)[46]; TEG	Mean (sd)	23.3 (5.7)	25.3 (11.2)	0.099
Westbrook(2009)[47]; TEG	Median (IQR)	29.4 (14.3, 56.4)	32.5 (22.0, 74.5)	0.369
Girdauskas(2010)[54]; ROTEM	Mean (sd)	175.2 (218.4)	194.4 (201.6)	0.6
Weber(2012)[35]; ROTEM	Median (IQR)	**21 (18, 31)**	**24 (20, 87)**	**0.019**
Length of hospital stay (days)				
Ak(2009)[46]; TEG	Mean (sd)	6.2 (1.1)	6.3 (1.4)	0.552
Westbrook(2009)[47]; TEG	Median (IQR)	9 (7, 13)	8 (7, 12)	>0.05
Girdauskas(2010)[54]; ROTEM	Mean (sd)	16.6 (16.4)	17.0 (14.8)	0.80
Weber(2012)[35]; ROTEM	Median (IQR)	12 (9, 22)	12 (9, 23)	0.718

Summary

Pooled estimates from each of the meta-analyses are summarised in Table 11. Overall there was a significant reduction in red blood cell transfusion, platelet transfusion and FFP transfusion in VE testing groups compared to control. There was no significant difference between groups in terms of any blood product transfusion, Factor VIIa transfusion or prothrombin transfusion, although data suggested a beneficial effect of the VE testing algorithm but these outcomes were only evaluated in two studies. There was no difference between groups in terms of fibrinogen transfusion. Continuous data on blood product use, although inconsistently reported across studies, supported these findings; the only blood

product which was not associated with a reduced volume of use in the VE testing group was fibrinogen. There was a suggestion that bleeding was reduced in the VE testing groups but this was only statistically significant in 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 ICU stay in the VE testing groups compared to control but this was not consistently reported across studies. There was no difference in length of hospital stay between groups. There was no apparent difference between ROTEM or TEG for any of the outcomes evaluated.

Table 11: Pooled estimates for dichotomous outcomes from RCTs evaluating VE devices in patients undergoing cardiac surgery

Outcome	Summary RR (95% CI)	Number of studies	Heterogeneity
Blood product use			
Red blood cell transfusion	**0.88 (0.80, 0.96)**	6	Q=4.47, p=0.48, I^2=0%
Any blood product transfusion	0.79 (0.57, 1.08)	2	Q=2.79, p=0.10, I2=64%
Platelet transfusion	**0.72 (0.58, 0.89)**	6	Q=4.47, p=0.48, I^2=0%
FFP transfusion	**0.47 (0.35, 0.65)**	5	Q=4.72, p=0.45, I^2=0%
Factor VIIa transfusion	0.19 (0.03, 1.17)	2	Q=1.40, p=0.24, I^2=29%
Fibrinogen transfusion	0.94 (0.77, 1.14)	2	Q=1.09, p=0.30, I^2=8%
Prothrombin transfusion	0.39 (0.08, 1.95)	2	Q=10.23, p=0.00, I^2=90%
Clinical outcomes			
Re-operation	0.72 (0.41, 1.26)	7	Q=3.49, p=0.74, I^2=0%
Surgical cause of bleed on re-operation	1.04 (0.42, 2.57)	4	Q=3.09, p=0.38, I^2=3%
Mortality	0.87 (0.35, 2.18)	4	Q=1.26, p=0.74, I2=0%

3.2.2 How well do VE devices predict relevant clinical outcomes during or after cardiac surgery?

As none of the RCTs evaluated the Sonoclot VE test, we included lower levels of evidence for this device. Three prediction studies which evaluated Sonoclot were included in the review,[60-62] two of these also evaluated TEG and so provided a direct comparison between these two devices.[60-62] Baseline data from these studies are summarised in Table 12; full details of the studies are provided in Appendix 2.

3.2.2.1 Study details

The cardiac prediction studies were conducted in Switzerland and USA. All included patients undergoing mixed cardiac surgery irrespective of whether or not they had a bleeding event. One study excluded patients with a known coagulopathy[60] and another excluded patients with abnormal pre-operative coagulation studies;[62] both of these studies excluded patients receiving anti-coagulant medication and one also excluded patients on anti-platelet medications.[62] Mean or median age, where reported, ranged from 63 to 65 years. The proportion of men ranged from 61% to 69%.

One of the studies evaluated Sonoclot alone and provided data on the accuracy of various different parameters to predict bleeding within four hours of surgery.[60] One evaluated Sonoclot, TEG and conventional laboratory tests and also provided data on the accuracy of different parameters of each of these tests for predicting bleeding based on a subjective evaluation by the anaesthesiologist and surgeon 10 minutes after protamine administration. The third evaluated Sonoclot, TEG and standard laboratory testing and provided data on the accuracy of each test as a whole to predict bleeding in the first eight hours following surgery.[62]

Table 12: Baseline details of prediction studies evaluating VE devices in patients undergoing cardiac surgery

Study details	n	Patient category	Entry restricted to excessive bleeding?	Entry restriction based on anti-coagulation?	VE Test	Conventional tests	Outcome/Reference standard
Bischof(2009)[60]*	300	Mixed cardiac surgery	No	Yes - no anticoagulant medication	Sonoclot	None	Bleeding; >800mL 4 hours after surgery
Nuttall(1997)[61]	82	Mixed cardiac surgery	No	No	Sonoclot, TEG	Bleeding time, platelet maximum platelet volume (MPV), plasma fibrinogen concentration, platelet count, PT, aPTT, platelet haematocrit	Bleeding; subjective evaluation by anaesthesiologist and surgeon 10 minutes after protamine administration
Tuman(1989)[62]	42	Mixed cardiac patients	High risk for transfusion procedures	Yes – no anticoagulant or antiplatelet medications 7 days before surgery	Sonoclot, TEG	ACT, PT, PTT, PLT, and fibrinogen (FIB)	Bleeding; chest tube drainage greater than 150 mL/hr for 2 consecutive hr or greater than 300 mL/hr in 1 hr during the first 8 hr after surgery

*Studies reported only as abstracts

3.2.2.2 Risk of bias and applicability assessment

Three studies used a predictive accuracy approach to assess the ability of VE point-of-care testing devices to predict outcomes in patients undergoing cardiac surgery.[60-62] The main areas of concern with regard to these studies were the participant selection process, which was unclear in all cases, and the applicability to the objectives of this assessment of the way in which VE testing was applied. Two of the three studies were rated as having 'high' applicability concerns for the index test because they assessed the predictive ability of selected individual parameters of VE testing, rather than assessing the device as a whole, or reporting data for all assays and parameters measured by the device.[60, 61] The results of QUADAS-2 assessments are summarised in Table 13; full QUADAS-2 assessments for each study are provided in Appendix 3.

Table 13: QUADAS-2 assessments for prediction studies evaluating VE devices in patients undergoing cardiac surgery

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Nuttall(1997)[61]	?	☺	☺	☹	☺	☹	☺
Tuman(1989)[62]	?	☺	?	☺	☺	☺	☺
Bischof(2009)[60]	?	?	☺	☺	?	☹	☺

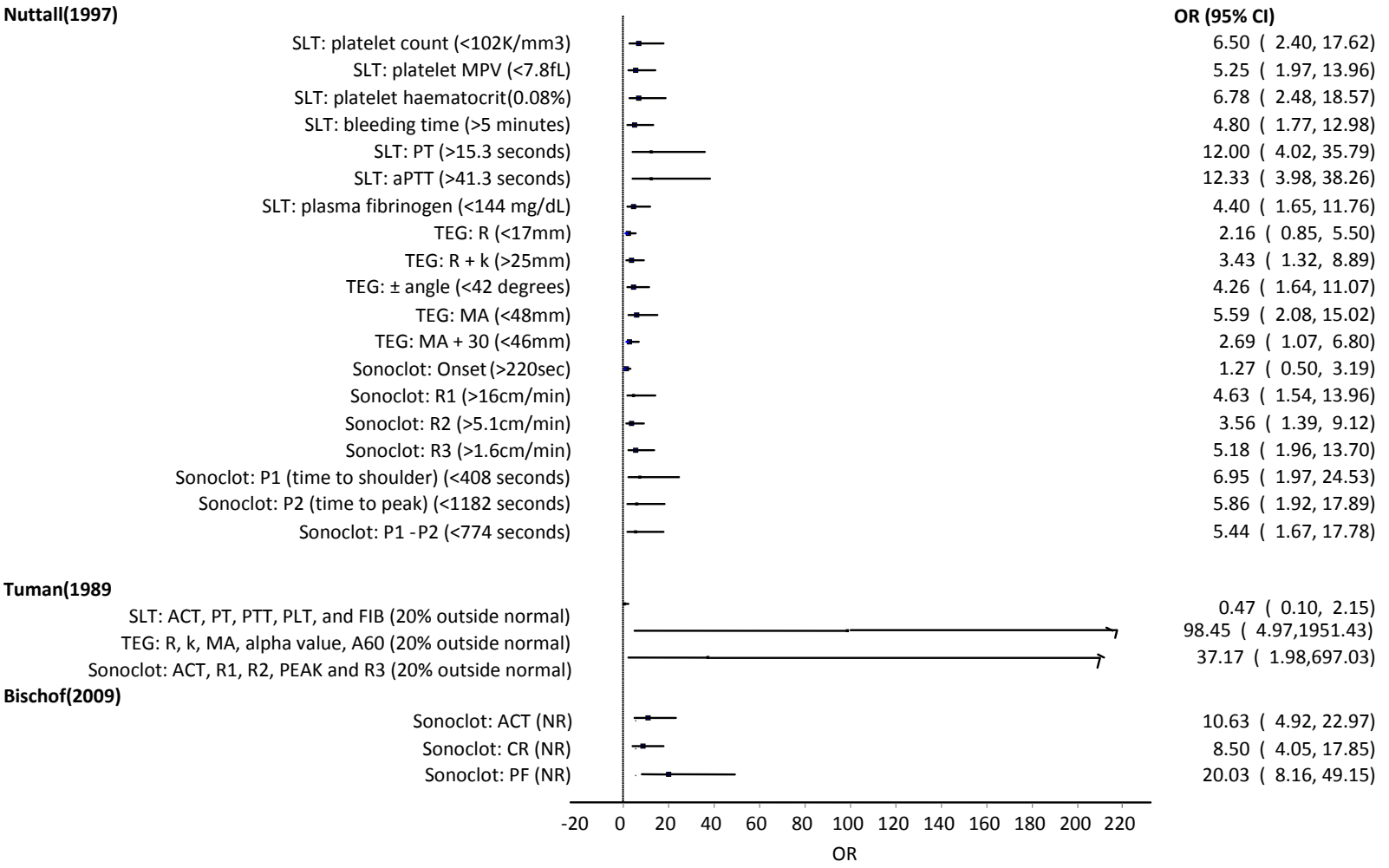
☺Low Risk ☹High Risk ? Unclear Risk

3.2.2.3 Results

All three studies provided data that allowed calculation of ORs for the prediction of bleeding in patients who tested positive on a particular test or test parameter (Sonoclot, TEG or SLTs) compared to those who tested negative (Figure 16). Positive results on conventional tests, TEG and Sonoclot were all associated with an increased risk of bleeding with no clear differences according to test. Nuttal[61] evaluated individual components of each of the tests separately and found that all of the parameters investigated with the exception of one TEG and one Sonoclot parameter, were associated with a significant ($p<0.05$) increased risk of bleeding. Two of the SLTs (PT and aPTT) showed higher ORs than other parameters, but CIs overlapped with other SLTs and TEG and Sonoclot parameters. Bischof[60] also evaluated individual test components but only evaluated the Sonoclot test; a direct comparison between Sonoclot and TEG or SLTs was therefore not possible from the results of this study. All three Sonoclot parameters showed a strong positive relationship with bleeding. Tuman[62] was potentially the most informative study as it evaluated each test class as a whole i.e. it evaluated a positive "TEG" result rather looking at individual components of the TEG,

similarly it evaluated SLTs as a class and Sonoclot as a whole. This study found that a positive TEG or Sonoclot result were both highly predictive of bleeding. However, the study was very small and confidence intervals were wide. The limited data suggested that TEG results were more predictive than Sonoclot, but confidence intervals overlapped. The SLTs performed less well and were not predictive of bleeding; this study was performed in 1989 and so may not be reflective of current practice.

Figure 16: Forest Plot showing ORs (95% CI) for prediction of bleeding by VE devices and standard laboratory tests in cardiac patients



3.2.3 How do clinical outcomes differ among patients with coagulopathy induced by trauma who are tested with VE devices compared to those who are not tested?

We identified one ongoing RCT that is comparing TEG (rapid assay) with conventional coagulation testing (INR, PTT, fibrinogen, D-dimer) in adults with blunt or penetrating trauma who are likely to require a transfusion of RBCs within six hours from admission as indicated by clinical assessment.[63, 64] Additional information on this trial was provided by the study authors in the form of the study protocol.[64] The following outcomes are being evaluated in this study: quality and quantity of blood products transfused (packed RBCs, FFP, cryoprecipitate and apheresis platelets), patterns of transfusion ratios of RBC: FFP, haemorrhage-related deaths specified as very early mortality (<2 hours post-injury) and early mortality; late mortality; cessation of coagulopathic bleeding; multiple organ failure (MOF). Results from this study are not yet available. As no other RCTs were identified we therefore considered lower levels of evidence for this objective. One CCT reported only as an abstract was included.[65] This study compared a rapid-TEG guided protocol with a standard transfusion protocol in adult trauma patients requiring massive transfusion (>12 RBC units in 24 hours or >4 units in four hours); both groups also included a near patient haematocrit assay. This study did not report numerical or statistical outcome data. It stated that there were no statistically significant differences between groups for death, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), multi-system organ failure, sepsis, DVT, stroke, acute coronary syndrome, or days to discharge. There was non-significant trend towards reduced pneumonia, days on the ventilator, and ICU days and a trend toward increasing platelet use in the TEG treated group. Baseline data from these studies are summarised in Table 14; full details of the studies are provided in Appendix 2. No other studies with a concurrent control group were identified for the trauma population.

3.2.4.3 Risk of bias and applicability assessment

As the RCT has not yet been published it was not possible to assess the risk of bias in this study.[63] Details on this risk of bias assessment for the CCT are reported in Appendix 3. This study was rated as high risk of bias for randomisation and concealment of treatment allocation as it was not a randomised study.[65] It was rated unclear for all other domains as insufficient information were reported to make a judgement on these.

Table 14: Baseline details of CCTs and RCTs evaluating VE devices in trauma patients

Study details	n	Patient category	Entry restricted to excessive bleeding?	Entry restriction based on anti-coagulation?	VE testing algorithm	Control	Timing of VE test	Outcomes assessed
Messenger (2011)[65]	50	Mixed trauma	Yes - patients requiring massive transfusion (>12 RBC units in 24 hours or >4 units in 4 hours)	NR	TEG-guided protocol and haematocrit assay	Treatment according to institutional massive transfusion protocol including haematocrit assay	NR	Death, ARDS, SIRS, multi-system organ failure, sepsis, DVT, stroke, acute coronary syndrome, days to discharge, pneumonia, days on ventilator, ICU days, platelet use.
Moore (ongoing)[63]	Ongoing	Mixed trauma	Yes - likely to require transfusion of RBC within 6 hours	No	TEG (r-TEG)	INR, PTT, fibrinogen, D-dimer	On hospital admission (usually within an hour), twice within first 6 hours post-injury, 12 and 24 hours post-injury.	Quality and quantity of blood products transfused (packed RBCs, FFP, cryoprecipitate and apheresis platelets), patterns of transfusion ratios of RBC: FFP, haemorrhage-related deaths specified as very early mortality (<2 hours post-injury) and early mortality; late mortality; cessation of coagulopathic bleeding; multiple organ failure (MOF)

3.2.4 How well do VE devices predict relevant clinical outcomes in patients with coagulopathy induced by trauma?

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 prediction studies (18 publications; n=4217) were included for this objective. Nine studies evaluated TEG, four of these also evaluated SLTs; the other six studies evaluated ROTEM with four also evaluating SLTs. No studies of Sonoclot were identified. None of the studies evaluated both TEG and ROTEM in the same patients. Baseline data from these studies are summarised in Table 15; full details of the studies are provided in Appendix 2.

3.2.4.1 Study details

The prediction studies in trauma patients were conducted in UK, USA, Switzerland, Netherlands, Denmark and Austria. The majority included mixed trauma patients but three were restricted to patients with blunt trauma[66-68] and two were restricted to patient with traumatic brain injury.[69, 70] One study excluded patients with traumatic brain injury,[71] and one excluded patients with isolated head injury.[67] None of the studies restricted inclusion based on bleeding. One study excluded patients who had previously taken anti-coagulant medication[72] and another excluded patients who had recently taken clopidogrel or warfarin.[69] Mean or median age, where reported, ranged from 33 to 49 years. The proportion of men ranged from 59% to 82%. Mean injury severity score (ISS), reported in 11 studies, ranged from 12 to 34. Mean Glasgow Coma Scale scores ranged from 11 to 14 but were only reported in six studies.

All studies performed VE testing on admission. Three studies evaluated TEG as a whole with a positive result based on a combination of different TEG parameters.[66, 73, 74] A further two studies assessed the presence of hyperfibrinolysis on TEG and ROTEM which appeared to be based on more than one test parameter however exact details on how hyperfibrinolysis was defined were not provided.[68, 71] All other studies assessed individual components of the TEG or ROTEM separately. SLTs (APTT, INR, plasma fibrinogen, platelet count and PT) were each evaluated separately. Outcomes assessed in the studies included any blood product transfusion, FFP transfusion, massive transfusion, massive transfusion of cryoprecipitate, massive transfusion of plasma, massive transfusion of platelets, plasma transfusion, platelet transfusion, RBC transfusion, bleeding, neurosurgical intervention, and death. Six studies used multiple logistic regression models to estimate ORs for the association of individual

TEG or ROTEM parameters or SLTs with the outcomes of interest controlled for various factors such as red blood cells transfusion, age, sex, mechanism of injury, trauma/injury severity, haemoglobin levels and race.[67, 73-77] Other studies reported 2x2 data on the number of patients with a positive and negative test results who did and did not have the outcome of interest,[66, 68, 69, 71, 72, 74] sensitivity and specificity but without sufficient data to populate 2x2 tables,[70, 73, 78, 79] and AUC for the ROC curve.[70, 73, 78]

Table 15: Baseline details of prediction studies evaluating VE devices in patients with coagulopathy induced by trauma

Study details	n	Patient category	Entry restriction based on anti-coagulation?	VE Test	Conventional test(s)	Outcome/Reference standard	Variables controlled for in multivariate analysis (if used)
Cotton(2011)[75]	272	Mixed trauma	NR	TEG	None	Massive transfusion (≥10 units PRBC in 6 hours) RBC transfusion (any within 6 hours)	Age (yrs), gender, blunt mechanism of injury, race, emergency department (ED) systolic blood pressure, ED heart rate, positive FAST (focussed assessment for the sonography of trauma) examination
Davenport(2011)[72, 80]	300	Mixed trauma	Yes – excluded patients taking anti-coagulation medication	ROTEM	PTr	FFP transfusion (any within 12 hours) Massive transfusion (>10 units RBC within 12 hours) RBC transfusion (any within 12 hours)	No multivariate analysis
Holcomb(2012)[76]	1974	Mixed trauma	No	TEG	Plasma fibrinogen, Platelet count, PT, aPTT, INR	Massive transfusion (>=10 units RBC within 6 hours) Massive transfusion of cryoprecipitate (>=20 units within 6 hours) Massive transfusion of plasma (>=6 units within 6 hours) Massive transfusion of platelets (>=2 apheresis units within 6 hours) Substantial bleeding (receiving first RBC unit within 2 hours of ED arrival and (2) at least 5 RBC transfusion or death from haemorrhage within 4 hours of ED arrival).	Age, sex, mechanism of injury, base deficit, weighted, revised trauma score, and injury severity score
Ives(2012)[74]	118	Mixed trauma	NR	TEG	None	Plasma transfusion Platelet transfusion RBC transfusion Death	Packed red blood cells in 24h >10U

Study details	n	Patient category	Entry restriction based on anti-coagulation?	VE Test	Conventional test(s)	Outcome/Reference standard	Variables controlled for in multivariate analysis (if used)
Jeger(2012)[79, 81]	76	Mixed trauma	NR	TEG	aPTT, INR, Plasma fibrinogen, Thrombin time	Any blood product transfusion within 24 hours	No multivariate analysis
Kaufmann(1997)[66]	69	Blunt trauma	No	TEG	None	Any blood product transfusion within 24 hours	No multivariate analysis
Korfage(2011)[77]*	142	Mixed trauma	No	ROTEM	None	Any blood product transfusion within 48 hours	Study reports that predictive values were determined using multinomial regression analyses, but it is not clear which variables were included in the final model.
Kunio(2012)[69]	69	Traumatic brain injury	Yes - patients taking clopidogrel or warfarin ≤days of admission excluded	TEG	None	Death Neurosurgical intervention	No multivariate analysis
Leemann(2010)[67]	53	Blunt trauma	NR	ROTEM	aPTT, INR, platelet count	Massive transfusion (≥10 units PRBC within 24 hours)	Haemoglobin ≤10 g/dL
Nystrup(2011)[73]	89	Mixed trauma	NR	TEG	aPTT, INR	Death within 30 days	Age and ISS
Pezold(2012)[82]	80	Mixed trauma	NR	TEG	aPTT, INR	Coagulation-related mortality (death after receiving a MT ≥10 PRBC units) within 6 hours Massive transfusion (≥10 units PRBC within 6 hours)	No multivariate analysis
Schochl(2011)[78, 83]	323	Mixed trauma	NR	ROTEM	Platelet count, aPTT, plasma fibrinogen	Massive transfusion (≥10 RBC units within 24 hours)	No multivariate analysis

Study details	n	Patient category	Entry restriction based on anti-coagulation?	VE Test	Conventional test(s)	Outcome/Reference standard	Variables controlled for in multivariate analysis (if used)
Schochl(2011)[70, 78]*	88	Traumatic brain injury	NR	ROTEM	aPTT	Death	No multivariate analysis
Tapia(2012)[71]*	230	Mixed trauma	NR	TEG	None	Death within 30 days	No multivariate analysis
Tauber(2011)[68]	334	Blunt trauma	NR	ROTEM	None	Death within 24 hours	No multivariate analysis

n: number enrolled; *Studies reported only as abstracts

3.2.4.2 Risk of bias and applicability assessment

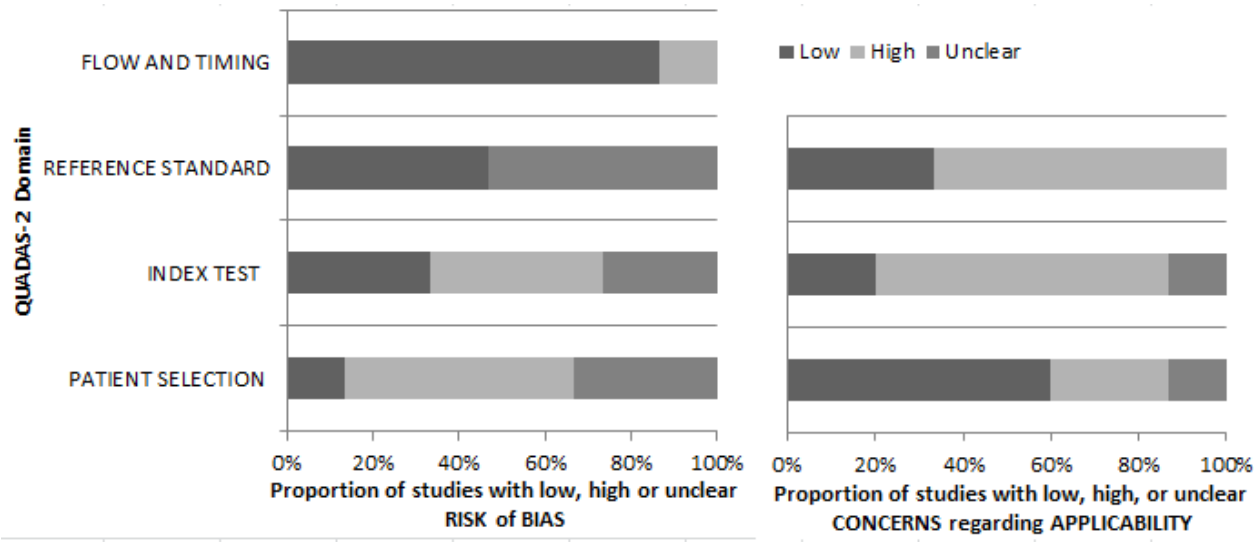
All the studies that assessed the ability of VE testing devices to predict outcomes in trauma patients used a predictive accuracy or prediction modelling approach. The main areas of concern with regard to these studies were the process of participant selection and the applicability to the objectives of this assessment of the way in which both VE testing and the reference standard were applied. With two exceptions,[75, 76] all studies were rated as 'high' or 'unclear' risk of bias in the participant selection process, usually because of poor reporting, or inappropriate exclusion of particular groups of patients. Ten of the 15 studies were rated as having 'high' applicability concerns for the index test because they assessed the predictive ability of selected individual components of VE testing, rather than assessing the device as a whole, or reporting data for all assays and parameters measured by the device;[67, 69, 70, 72, 75-79, 82] two further studies were rated as having 'unclear' applicability because, although the testing VE device was specified, no details of the assay(s) used or parameters measured were reported.[68, 71] Ten studies were rated as having 'high' applicability concerns with respect to the reference standard, where the reference standard was one or more measure(s) of transfusion requirements, because it was unclear whether or not the decision to transfuse was informed by VE testing results, this also resulted in an 'unclear' risk of bias rating with respect to the reference standard. [66, 67, 72, 74-79, 82] In practice the results of VE testing would inform the decision to transfuse, a situation which gives rise to the paradox that this type of study cannot have both 'low' risk of bias and 'low' applicability with respect to the reference standard; if the reference standard is applied as it would be in clinical practice, the study will necessarily be subject to incorporation bias. The remaining five studies were rated as 'low' applicability concerns because they reported objective reference standards (e.g. mortality).[68-71, 73] The results of QUADAS-2 assessments are summarised in Table 16 and Figure 17; full QUADAS-2 assessments for each study are provided in Appendix 3.

Table 16: QUADAS-2 assessments for prediction studies evaluating VE devices in patients with coagulopathy induced by trauma

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Cotton (2011)[75]	☺	☹	?	☺	☺	☹	☹
Davenport (2011)[72]	☹	☹	?	☺	☺	☹	☹
Holcomb (2012)[76]	☺	?	?	☺	☺	☹	☹
Ives (2012)[74]	☹	☺	☺/ ?	☹	☺	☺	☺/☹
Jeger (2012)[79]	☹	☹	☺	☺	☺	☹	☹
Kaufman (1997)[66]	?	☺	☺	☺	☺	☺	☹
Korfage (2011)[77]	?	?	?	☺	?	☹	☹
Kunio (2012)[69]	?	☺	☺	☺	☹	☹	☺
Leeman (2010)[67]	☹	☺	?	☺	☹	☹	☹
Nystrup (2011)[73]	☹	?	☺	☺	☺	☺	☺
Pezold (2012)[82]	☹	☹	?	☺	☺	☹	☹
Schochl (2011)[78]	☹	☹	?	☺	☺	☹	☹
Schochl (2011)[70]	?	☹	☺	☺	☹	☹	☺
Tapia (2012)[71]	☹	?	☺	☹	?	?	☺
Tauber (2011)[68]	?	☺	☺	☺	☹	?	☺

☺Low Risk ☹High Risk ? Unclear Risk

Figure 17: Proportion of studies fulfilling each QUADAS-2 criteria for prediction studies evaluating VE devices in patients with coagulopathy induced by trauma



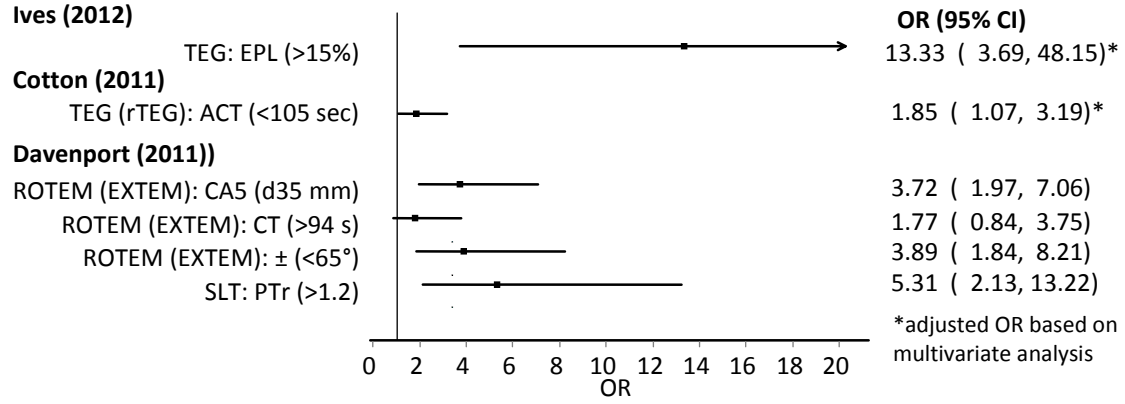
3.2.4.3 Results

RBC Transfusion

Three studies (two of TEG,[74, 75] one of ROTEM and SLTs[72]) evaluated the ability of VE devices to predict RBC transfusion (Figure 18). One used an endpoint of any RBC transfusion within

12 hours,[72] one within six hours[75] and one did not specify the time point.[74] A positive result on each of the parameters assessed, with the exception of CT on ROTEM, was associated with an increased risk of RBC transfusion. There were no clear differences between ROTEM parameters or ROTEM and SLTs in the one study that reported multiple evaluations.[72]

Figure 18: Forest Plot showing ORs (95% CI) for prediction of RBC transfusion by VE devices and SLTs in trauma patients



Any blood product transfusion

Three studies evaluated the ability of VE devices to predict any blood product transfusion (Figure 19).[66, 77, 79] Two evaluated TEG[66, 79] and one evaluated ROTEM;[77] one of the studies of TEG[79] also evaluated SLTs. The time frame for transfusion was within 24 hours in two studies[66, 79] and within 48 hours in the third.[77] A positive result on each of the parameters assessed was associated with an increased risk of any blood product transfusion; an overall TEG results suggesting the patient was hypercoaguable was associated with a decreased risk of transfusion (OR 0.14, 95% CI 0.03, 0.76). One of the studies did not provide sufficient data to calculate CIs and so the significance of the ORs from this study could not be assessed. The other two studies both reported statistically significant ($p<0.05$) associations for all parameters assessed. An overall TEG result indicating that the patient was hypocaoguable was found to be associated with the greatest increased risk of transfusion, but CIs were very wide (OR 180.00 , 95% CI 14.15,2289.13). ORs for individual TEG, ROTEM or SLTs were much smaller ranging from 2.50 to 15.26.

Massive transfusion

Six studies evaluated the ability of VE devices to predict massive RBC transfusion.[67, 72, 75, 76, 78, 82] Three evaluated TEG[75, 76, 82] and three evaluated ROTEM,[67, 72, 78] all but one[75] also evaluated SLTs. All used a threshold of ≥10 units of RBC transfused to define massive transfusion but the time frame within which this had to occur ranged from 6 to 24 hours.

Three studies provided data as adjusted ORs[67, 75, 76] for at least one of the VE test components; a further study provided data that permitted calculation of ORs (Figure 20).[72] The other two studies[78, 82] only provided data on AUC for the ROC curve together with 95% CIs (Figure 21). A positive result on each of the parameters assessed was associated with an increased risk of massive transfusion; however, this difference was not statistically significant for some of the ROTEM parameters and SLTs. There were no clear differences between ROTEM, TEG or SLTs, or individual test parameters, in terms of ability to predict massive transfusion. AUCs, where reported, were between 0.70 and 0.92 with no clear differences between ROTEM, TEG or SLTs.

Figure 19: Forest Plot showing ORs (95% CI) for prediction of any blood product transfusion by VE devices and SLTs in trauma patients

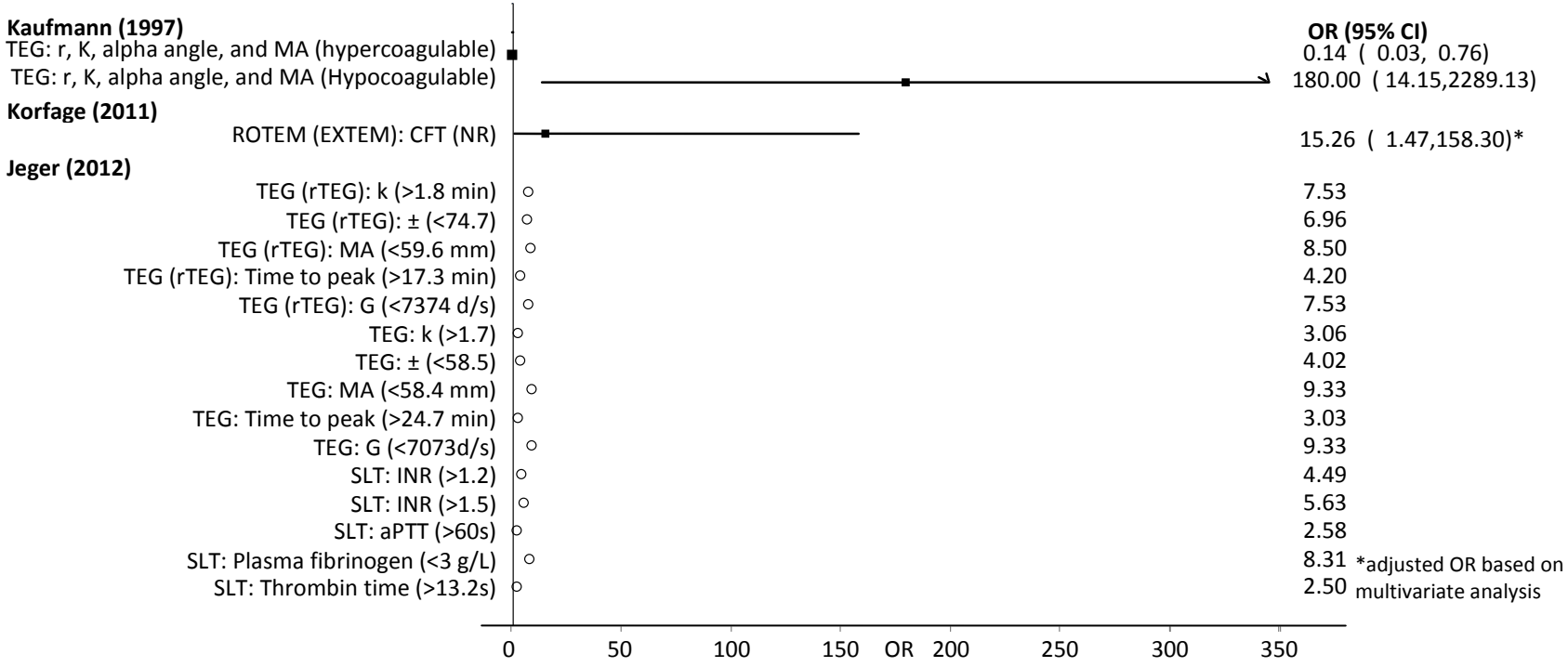


Figure 20: Forest Plot showing ORs (95% CI) for prediction of massive transfusion by VE devices and SLTs in trauma patients

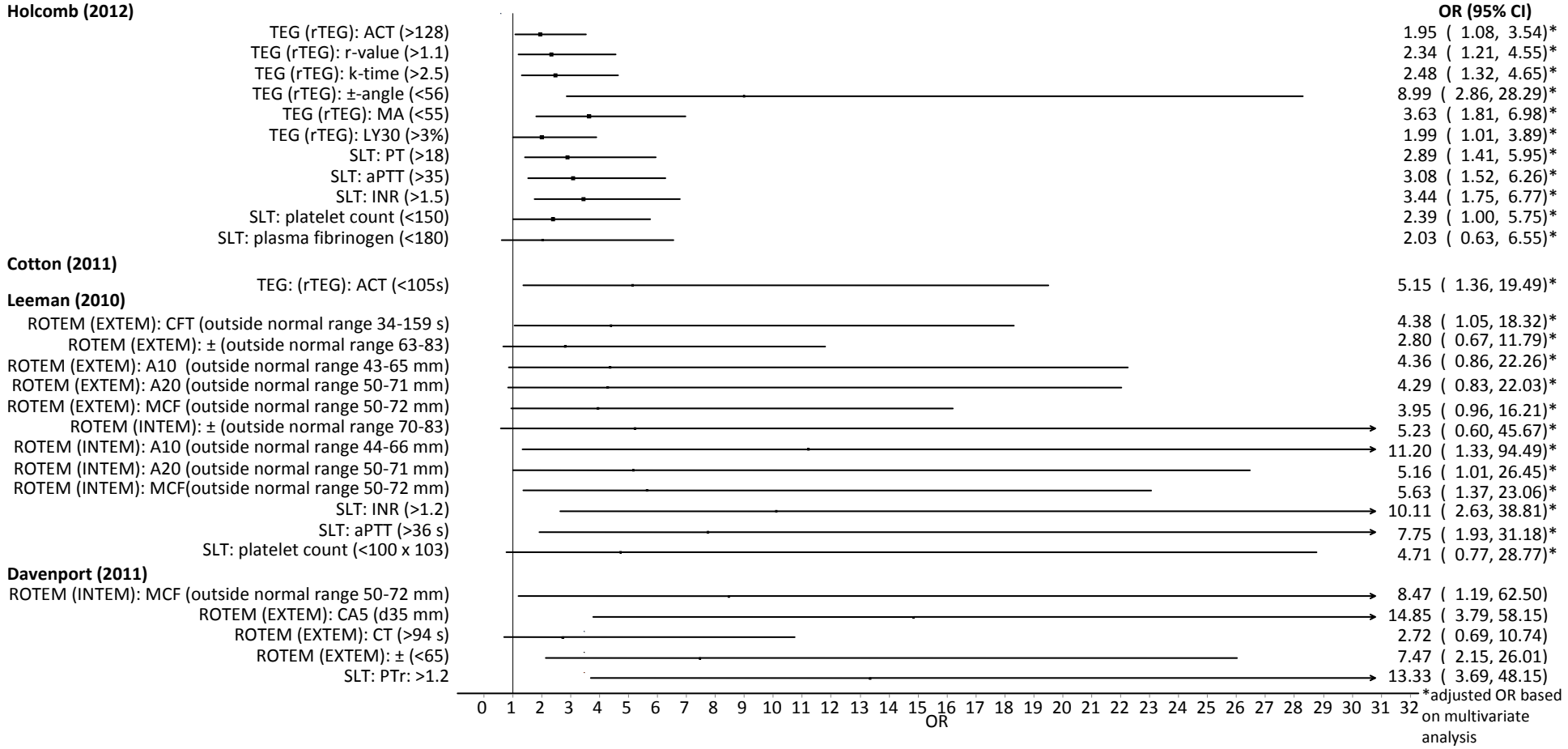
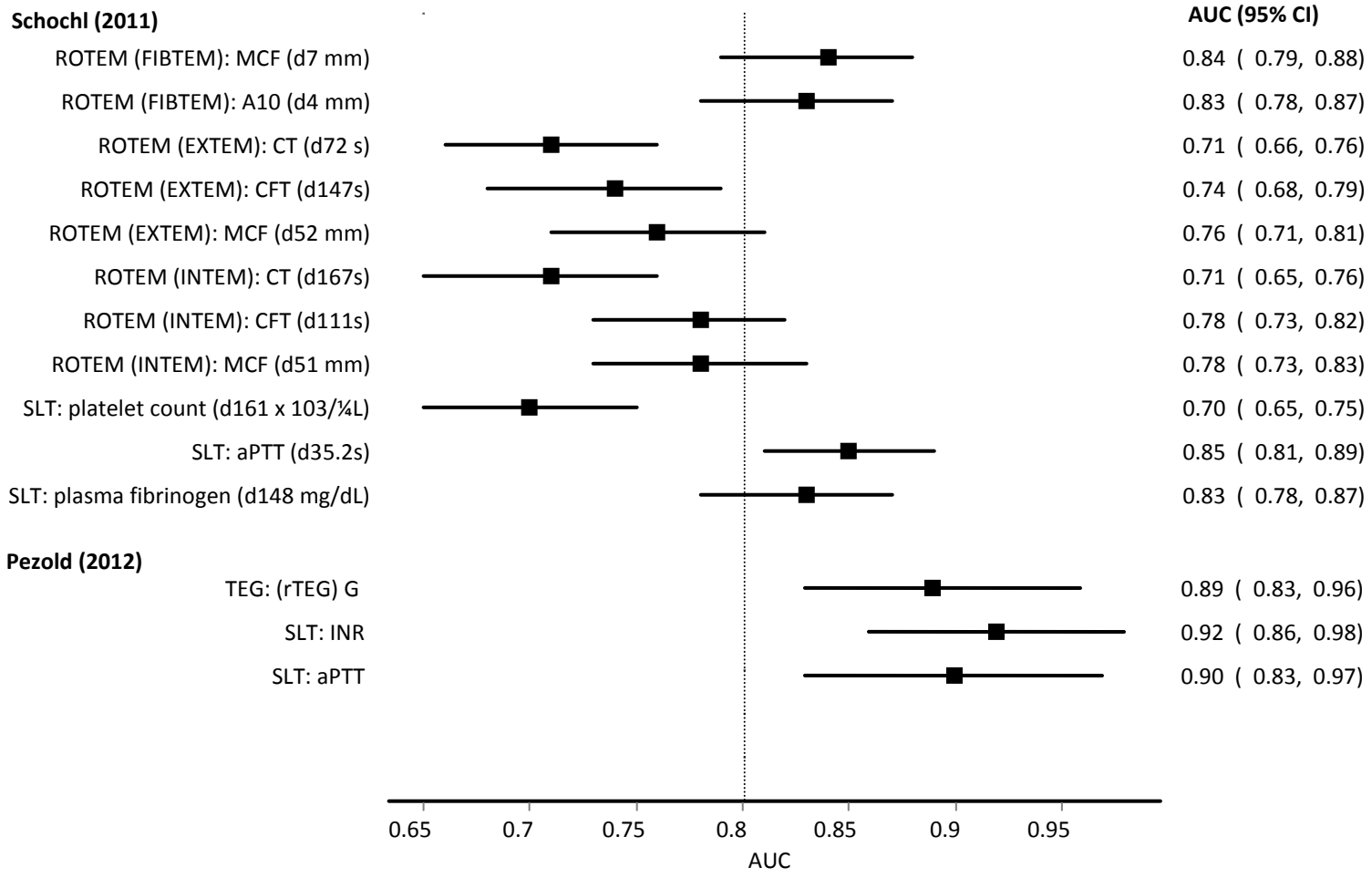


Figure 21: Forest Plot showing AUCs (95% CI) of ROC curves for prediction of massive transfusion by VE devices and SLTs in trauma patients



Mortality

Seven studies evaluated the association of VE devices with mortality.[68-71, 73, 74, 82] Five evaluated TEG[69, 71, 73, 74, 82] and two evaluated ROTEM,[68, 70] thee also evaluated SLTs.[70, 73, 82] Two defined mortality as death within 24 hours,[68, 74] one as death in hospital,[69] two as death within 30 days,[71, 73] one did not provide a definition,[70] and one restricted their definition of mortality to coagulation-related mortality (death after receiving a massive transfusion≥10 PRBC units).[82]

Two studies provided data as adjusted ORs[73, 74]; thee further studies provided data that permitted calculation of ORs and associated CIs (Figure 22).[72] The other two studies[70, 82] only provided data on AUC for the ROC curve together with 95% CIs; these data were also reported in one of the studies that reported adjusted ORs (Figure 23). A positive result assessed was associated a statistically significant increased risk of death for most parameters assessed. The only exceptions were two parameters that were associated with a decreased risk of death, although this difference was not statistically significant: the presence of moderate hyperfibrinolysis (0.76, 95% CI 0.09, 6.20)[68] and an overall TEG result suggesting that a patient was hypocaguable (OR 0.23, 95% CI 0.03, 1.91).[74] Three studies that evaluated a ROTEM or TEG result indicating the presence of hyperfibrinolysis showed the strongest association with death with ORs ranging from 25 to 147, although CIs were wide.[68, 71, 74] AUCs were between 0.63 and 0.93 with no clear differences between ROTEM, TEG or SLTs.

Other outcomes

Data were also reported on the following outcomes but each were only assessed in single studies and so are not discussed in detail here: FFP transfusion, massive transfusion of cryoprecipitate, massive transfusion of plasma, massive transfusion of platelets, plasma transfusion, platelet transfusion, substantial bleeding, and neurosurgical intervention. Full results can be found in Appendix 2.

Summary

Fifteen studies provided data on the accuracy of TEG or ROTEM for the prediction of transfusion related outcomes and death in trauma patients; eight studies also provided data on the accuracy of SLTs. 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 product and massive transfusion) and death. There was no clear difference 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 hypocoaguable was the strongest predictor of any blood product transfusion. The presence of hyperfibrinolysis was the strongest predictor of mortality.

Figure 22: Forest Plot showing ORs (95% CI) for prediction of death by VE devices and SLTs in trauma patients

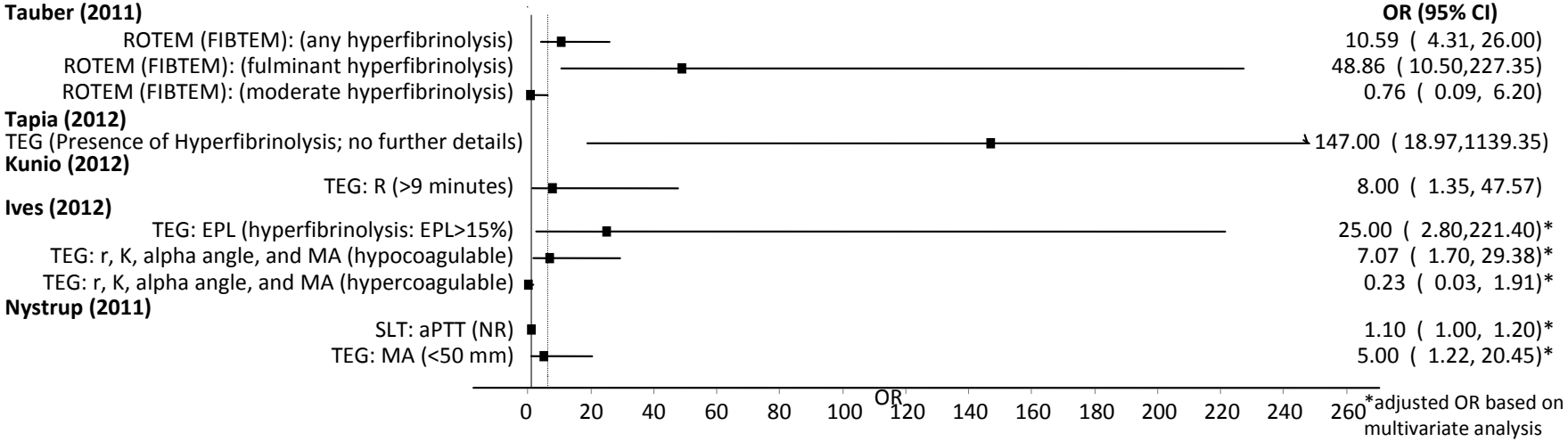
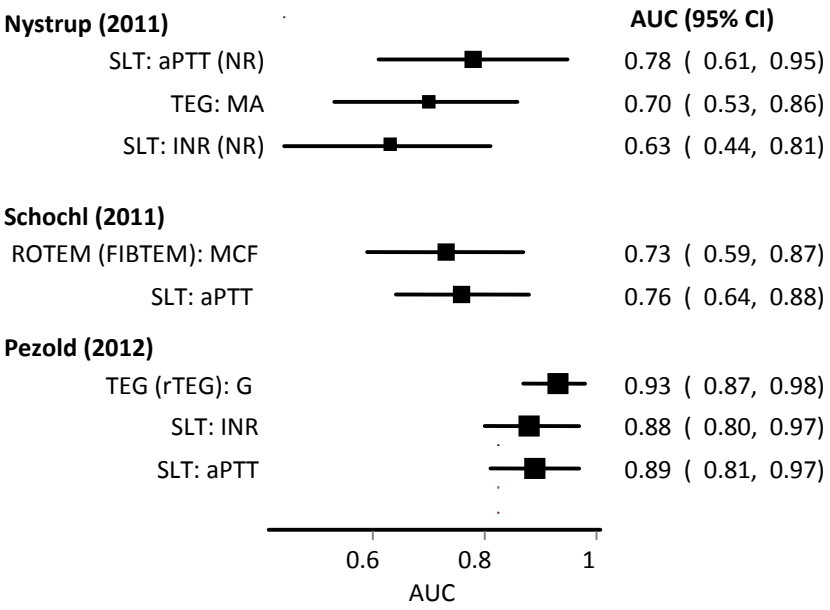


Figure 23: Forest Plot showing AUCs (95% CI) of ROC curves for prediction of death by VE devices and SLTs in trauma patients



3.2.5 How do clinical outcomes differ among patients with PPH who are tested with VE devices compared to those who are not tested?

No studies were identified that compared clinical outcomes among patients with PPH who were tested with VE devices compared to those who were not tested.

3.2.6 How well do VE devices predict relevant clinical outcomes in patients with PPH?

As no studies evaluated differences in clinical outcomes between VE tested and untested populations, we included lower levels of evidence for this objective. Two prediction studies were included in the review (n=245).[84, 85] Both studies were available only as abstracts. Baseline data from these studies are summarised in Table 17; full details of the studies are provided in Appendix 2.

3.2.6.1 Study details

The studies were both conducted in the UK. One included women with PPH defined as ≥1000mL blood loss, the other included women with major obstetric haemorrhage defined as ≥1500mL blood loss. Neither study provided data on restriction based on previous anti-coagulation therapy, or information on the mean age of study participants.

One study evaluated the MCF based on FIBTEM on ROTEM; this study also evaluated an SLTs (Clauss fibrinogen).[85] The other study only evaluated ROTEM but did not provide any further details on what aspects of the ROTEM test were evaluated or whether data related to

individual components or the test as a whole. The outcomes evaluated in the studies varied – one assessed the prediction of coagulopathy requiring treatment, FFP transfusion and platelet transfusion[84] the other assessed the prediction of RBC transfusion and invasive procedures.[85]

Table 17: Baseline details of prediction studies evaluating VE devices in women with PPH

Study details	n	Population	Entry restriction based on anti-coagulation?	VE Test	Conventional tests	Outcome/Reference standard
Bolton(2011)[84]	66	Major obstetric haemorrhage (≥1500 mL)	NR	ROTEM	None	Coagulopathy requiring treatment FFP transfusion; platelet transfusion (threshold and time point NR)
Lilley(2013)[85]	179	PPH (≥1000mL)	NR	ROTEM	Clauss fibrinogen	RBC transfusion (≥4 units or any transfusion) Invasive procedure

3.2.6.2 Risk of bias and applicability assessment

As with the trauma studies, the main areas of concern with regard to the two prediction studies conducted in patients with PPH[84, 85] were the applicability to the objectives of this assessment of the way in which both VE testing and the reference standard were applied. One study was rated as having 'high' applicability concerns for the index test because it assessed the predictive ability of selected individual parameters of the FIBTEM assay on the ROTEM device, rather than assessing the device as a whole, or reporting data for all assays and parameters measured by the device;[85] the other study was rated as having 'unclear' applicability because, although it assessed the ROTEM device, no details of the assay(s) used were reported.[84] Both studies were rated as having 'high' applicability concerns with respect to the reference standard because it was unclear whether or not the decision to transfuse was informed by ROTEM results, this also resulted in an 'unclear' risk of bias rating with respect to the reference standard.[84, 85] In practice the results of ROTEM testing would inform the decision to transfuse, a situation which gives rise to the paradox that this type of study cannot have both 'low' risk of bias and 'low' applicability with respect to the reference standard; if the reference standard is applied as it would be in clinical practice, the study will necessarily be subject to incorporation bias. The results of QUADAS-2 assessments are summarised in Table 18; full QUADAS-2 assessments for each study are provided in Appendix 3.

Table 18: QUADAS-2 assessments for prediction studies evaluating VE devices in patients with PPH

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Bolton (2011)[84]	?	?	?	☺	☹	?	☹
Lilley (2013)[85]	☺	?	?	☺	☺	☹	☹

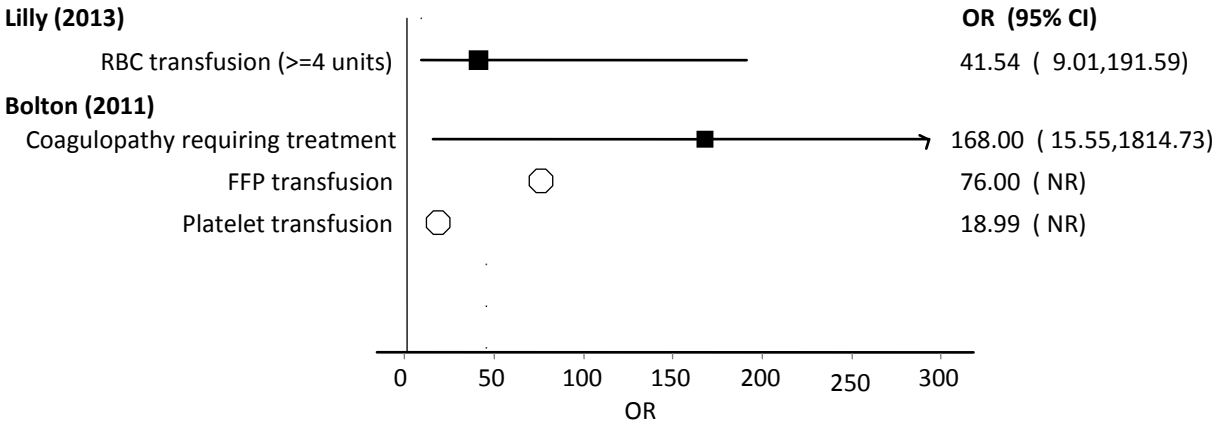
☺Low Risk ☹High Risk ? Unclear Risk

Results

Both studies provided data that allowed calculation of ORs for the prediction of outcomes in patients who tested positive on ROTEM compared to those who tested negative (Figure 24). The study which evaluated ROTEM and SLTs only reported data in a format that allowed calculation of ORs for the ROTEM parameter (MCF based on FIBTEM analysis) for the prediction of RBC transfusion of at least four units. There was a strong positive relationship between this parameter and RBC transfusion (OR 41.54, 95% CI 9.01, 191.59). Data for other outcomes and for the SLT (Clauss fibrinogen) were reported as AUC for the ROC curve; these were very similar for Clauss fibrinogen and for MCF based on ROTEM (FIBTEM).[85] CIs were not presented and so formal comparisons of AUCs was not possible.

The other reported that a positive ROTEM result was associated with coagulopathy requiring treatment (OR 168.0, 95% CI 15.6, 1814. 7).[84] This study also evaluated FFP transfusion and platelet transfusion; data were available to calculate ORs for these outcomes but not associated CIs. The ROTEM results were also predictive of both these outcomes but the significance of the association was unclear. The size of the OR was smaller than for the association with coagulopathy requiring treatment (OR 76 for FFP transfusion and 19 for platelet transfusion).[84]

Figure 24: Forest Plot showing ORs (95% CI) for prediction of specified outcomes by ROTEM in cardiac patients



Summary

Only two studies were identified that evaluated VE devices in patients with PPH. Both provided data on the accuracy of ROTEM for the prediction of outcomes; one also evaluated an 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 but did provide CIs to accompany effect estimates.

4. ASSESSMENT OF COST-EFFECTIVENESS

This chapter explores the cost-effectiveness of VE point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis.

4.1 Review of economic analyses of VE testing

4.1.1 Search methods

Searches were undertaken to identify cost-effectiveness studies of VE point-of-care testing. As with the clinical effectiveness searching, the main Embase strategy for each set of searches was independently peer reviewed by a second Information Specialist, using the CADTH Peer Review checklist.[40] Search strategies were developed specifically for each database and searches took into account generic and other product names for the intervention. All search strategies are reported in Appendix 1.

The following databases were searched for relevant studies from inception to November 2013:

- MEDLINE (OvidSP): 1946-2013/10/wk 4
- MEDLINE In-Process Citations and Daily Update (OvidSP): up to 2013/11/05
- EMBASE (OvidSP): 1974-2013/11/05
- NHS Economic Evaluation Database (NHS EED) (Wiley): Issue 4. October/2013
- EconLIT (EBSCO): 1990-2013/09/01
- Health Economic Evaluation Database (HEED) (Wiley): up to 2013/11/07 http://onlinelibrary.wiley.com/book/10.1002/9780470510933
- IDEAS via Research Papers in Economics (REPEC) (Internet): up to 2013/11/07 http://repec.org/

Identified references were downloaded in Endnote X4 software for further assessment and handling. References in retrieved articles were checked for additional studies.

4.1.2 Inclusion criteria

Cost minimisation and cost effectiveness studies that evaluated the use of TEG, ROTEM or Sonoclot compared to a control group (either concurrent or historical) consisting of no-testing, clinical judgement or SLTs were eligible for inclusion. Studies in children were excluded.

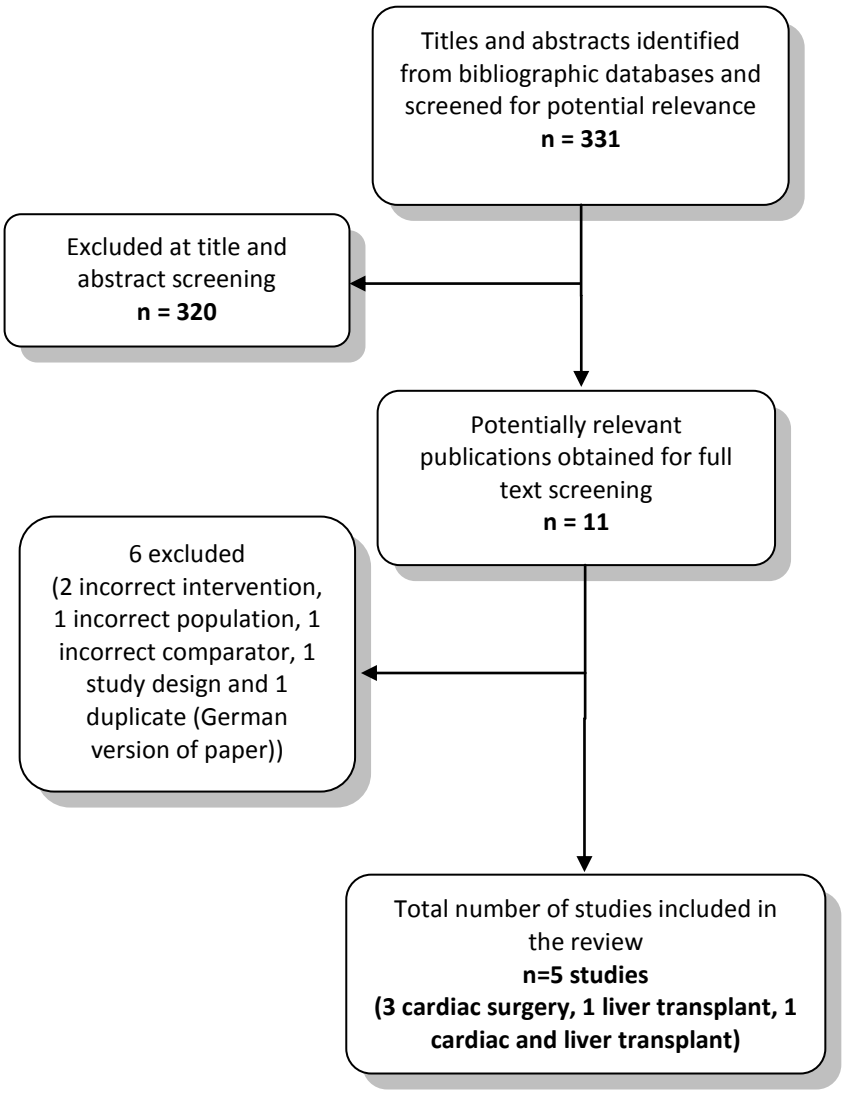
4.1.3 Quality assessment

Full cost-effectiveness studies were appraised using the Drummond checklist.[86]

4.1.4 Results

The searches identified 331 records of which five studies fulfilled the inclusion criteria,[12, 87-90] two were only available as conference abstracts (Figure 25).[87, 88] Three were conducted in cardiac patients,[88-90] one in patients undergoing liver transplant,[87] and one in both cardiac and liver transplant patients.[12] One study was a formal cost-effectiveness analysis of VE devices in cardiac and liver transplant patients.[12] The other four studies were cost-minimisation studies performed alongside a retrospective before/after study.

Figure 25: Flow of studies through the health economic review process



4.1.4.1 Cost-effectiveness analyses

The only formal cost-effectiveness analysis was conducted for the Scottish NHS.[12, 91] This report assessed the cost-effectiveness of VE in cardiac and liver transplant patients, and the model was based, to a large extent on an earlier study by Davies et al.[92] This latter study[92] did not fulfil the inclusion criteria (as it did not study one of the listed devices) but was, nevertheless, very informative for the current assessment. This study assessed the costs and effects of various methods of minimising peri-operative allogeneic blood transfusion, with cardiac patients as a subpopulation. The resulting model took into account the relationship between blood product use and related complications and adverse events.

A detailed summary of both of these studies and a quality check-list based on Drummond et al[86] are provided in Appendices 5 and 6. Both studies were in general of good quality. However, they did not completely address our research questions. The study by Davies et al[92] did not consider the use of viscoelastic testing, but did model the SLTs group. The Scottish report used most of the approach seen in Davies,[92] including most input parameters. The structure of our model was also largely based on these two studies and we used them as main source of input data. As the Scottish study did not include a PSA, we added this to the analysis. In addition, although the Scottish study considered both short term (up to one month) and long term (up to one year) effects of mortality, it failed to capture any difference between one month and one year mortality. However, recent data suggest that the effects of transfusion on mortality are not just short term with differences in mortality reported up to and beyond one year.[15]

The cost-effectiveness of VE testing in cardiac surgery patients was assessed in the Scottish NHS report,[12] but trauma patients with suspected coagulopathy were not included in the study. Furthermore, a probabilistic sensitivity analysis was not performed. Although the structure of our model was largely based on these two studies and we have used them as main source of input data, when possible, for the cardiac population, the values of the input parameters were updated using more recent literature and a PSA was added.

4.1.4.2 Cost-minimisation studies

The four cost-minimisation studies all measured and costed the volume of blood transfused before the introduction of a VE device and compared this with volumes and costs of blood transfused after the VE device was introduced. Three studies evaluated ROTEM[87, 89, 90] and one evaluated TEG.[88] All four studies found that costs were reduced as a result of the introduction of a VE device. As these were not full cost-effectiveness studies, a formal quality appraisal was not performed.

One study of ROTEM[89] showed that after the introduction of ROTEM the cumulative average monthly costs of all blood products decreased from €66.000 to €45.000 (-32%) and the average monthly costs for ROTEM were €1.580. Two other studies, one in liver transplant patients[87] and one in cardiac patients[90] also reported that an algorithm incorporating ROTEM reduced costs, but neither reported a detailed breakdown of cost savings of transfusion or of the costs of the ROTEM device.

The study that evaluated TEG concluded that its use in cardiac surgery reduced costs.[88] However, no numerical data were presented and data on the effect measure used were not provided.

4.2 Model structure and methodology

This section describes the de novo model used to evaluate the cost-effectiveness of ROTEM, TEG, and Sonoclot (VE devices) compared to standard laboratory tests (SLTs) (no VE devices) to assist with the diagnosis, management and monitoring of haemostasis in the patient populations of interest: cardiac surgery patients and trauma patients with suspected coagulopathy. There were insufficient data from the effectiveness review to construct a model for the assessment VE devices in women with post-partum haemorrhage (see Section 3.2.6). The models were constructed in Microsoft Excel.

4.2.1 Cardiac surgery

We adopted the model structure used by the HTA undertaken for NHS Scotland in 2008,[12] which was largely based on a cost-effectiveness study of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion by Davies et al. 2006.[92] As these studies were undertaken in 2008 and 2006, respectively, more recent data sources were used to update the input parameters of the model wherever possible.

Our model is based on a decision tree that starts with the choice of strategy to be followed, i.e. VE device (ROTEM, TEG, or Sonoclot) or SLTs. Within each strategy, patients then either do or do not receive a transfusion.

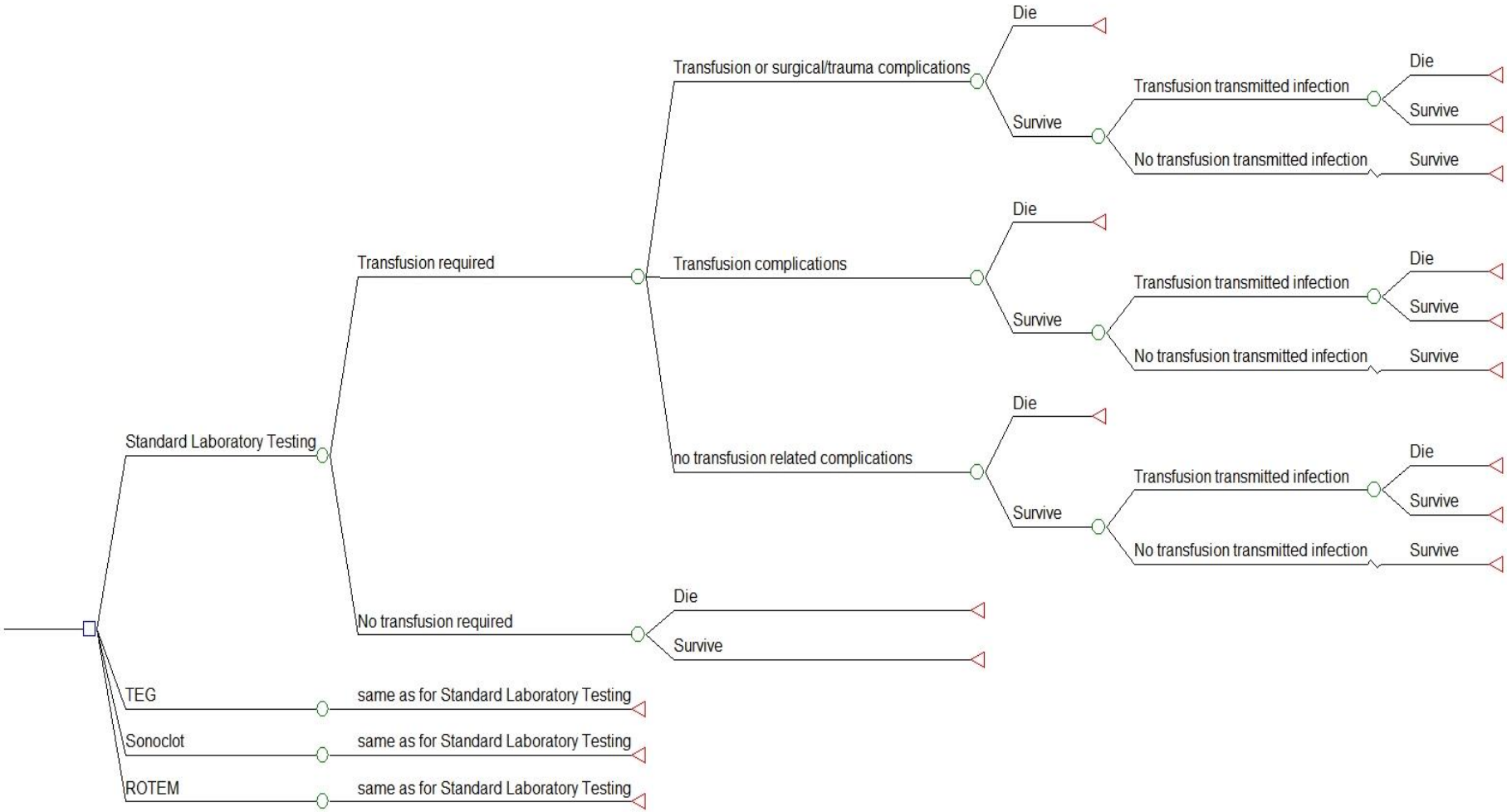
RBC transfusion, where it occurs, may be associated with adverse events or complications. The complications included in the model were those considered in Davies et al. 2006[92] and the Scottish HTA.[12] Most complications are a consequence of RBC transfusion, although some were modelled as a consequence of any transfusion.

Complications were categorised as (1) complications related to surgery and/or transfusion or (2) transfusion-related complications. Complications related to surgery and/or transfusion, included in the model were: renal dysfunction, myocardial infarction, stroke, thrombosis, excessive bleeding

requiring re-operation, wound complications and septicaemia. Transfusion-related complications included transfusion-associated graft versus host disease, complications related to the administration of an incorrect blood component, haemolytic transfusion reactions (acute or delayed), post-transfusion purpura (PTP), transfusion-related acute lung injury (TRALI) and febrile reaction. In addition, we assumed that patients may also experience transfusion-transmitted infections. Transfusion-transmitted infections include bacterial contamination, variant Creutzfeldt - Jakob disease (vCJD), hepatitis A virus (HAV), malaria, human T-cell lymphotropic virus (HTLV), Human Immunodeficiency Virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The model structure is shown in Figure 26.

The model's time horizons were set to one month and one year because the benefits of a reduction in RBC transfusion were considered to have occurred within this timeframe. At one month, the model reflects the period of hospitalisation and accordingly captures the impact of complications related to surgery and blood loss, transfusion-related complications and infection caused by bacterial contamination. It should be noted that, as in Davies et al. 2006[92], bacterial contamination is the only transfusion-transmitted infection that was assumed to occur during the hospitalisation period. For other transfusion-transmitted infections included in the model, a time horizon of one year was considered more appropriate, as these infections do not usually manifest themselves immediately. Discounting was not necessary since the longest time horizon was set at one year. Costs were estimated from the perspective of the NHS in England and Wales. Consequences were expressed in life years gained and quality adjusted life years (QALYs). QALY weights (utilities) were assigned to adverse events to express their consequences. Sensitivity analysis relating to extended time periods would have been undertaken had there been potential to impact on results and conclusions.

Figure 26: Cost-effectiveness model structure



4.2.2 Patients with coagulopathy induced by trauma

The model for trauma patients has largely the same structure as the model in cardiac surgery patients. The only difference relates to the "surgery and/or transfusion related complications", which were replaced with "trauma and/or transfusion related complications" - acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF).

4.3 Model input parameters

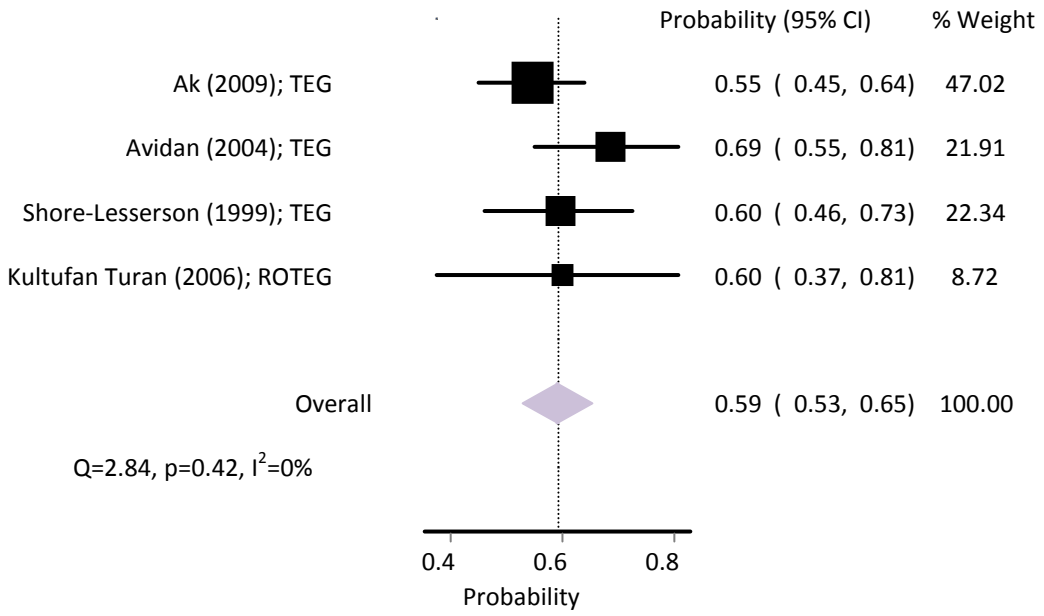
This section describes the input parameters used in the model for the cardiac and trauma populations and how we estimated their values. Whenever possible, parameters were estimated from our systematic review (Section 3). If systematic review data were not available, model input parameters were derived from various sources including Davies[92] and the Scottish HTA reports.[12] Where standard errors were not reported, estimates for the Probabilistic Sensitivity Analysis (PSA) assumed a 95% CI with limits deviating 20% from the mean, as we assumed that this would represent a reasonable range of variation.

4.3.1 Cardiac surgery

4.3.1.1 Probability of RBC transfusion

We estimated the baseline risk of having a transfusion based on the number of transfusions in the SLTs group in the cardiac surgery trials included in the effectiveness review (Figure 27). This analysis was based on the studies by Ak,[46] Avidan,[48] Shore-Lesserson[51] and Kultufan Turan[52]. We excluded two studies as we did not think that the patients included in these studies were representative of general cardiac surgery patients;[35, 54] one enrolled only high risk patients (aortic surgery requiring hypothermic circulatory arrest, including urgent and emergency surgery)[54] and the other was restricted to patients with excessive bleeding.[35] The summary estimate for the probability of RBC transfusion from these four studies was 0.592 (95% CI 0.528, 0.654). The RR of RBC transfusion in cardiac surgery patients whose blood was tested with VE devices compared to SLTs was reported in Section 3.2.1.3.

Figure 27: Forest Plot showing the probability of RBC transfusion (95% CI) in control groups in cardiac surgery trials



To estimate the probability of RBC transfusion for the three VE strategies a relative risk was applied to the baseline prevalence of RBC transfusion. The effectiveness review found no evidence of a difference in the RR of RBC transfusion between studies that assessed ROTEM and those that assessed TEG (section 3.2.1.3). We therefore applied the summary RR for RBC transfusion estimated for all studies for the ROTEM and TEG models. Limited data suggested that the accuracy of Sonoclot in predicting clinical outcomes may be similar to that of TEG. We therefore also assumed that this summary RR could be applied in the Sonoclot model. The baseline prevalence of RBC transfusion in patients who received SLTs and the RR for the three VE devices can be seen in Table 19. A Beta and a Normal distribution, respectively, were assigned for the PSA.

Table 19: Probability of RBC transfusion for patients undergoing cardiac surgery according to SLTs management and RR associated with VE technologies.

Technology	Mean value	Distribution	Distribution parameters	Source
Baseline risk of RBC transfusion in SLTs group	Base case: 0.592	Normal[1] (prob. of RBC transfusion)	μ =0.592; σ = 0.03	Section 3.2.1.3
RR: ROTEM, TEG and Sonoclot	Base case RR=0.88	Normal[2]	μ =0.88; σ =0.04	Section 3.2.1.3

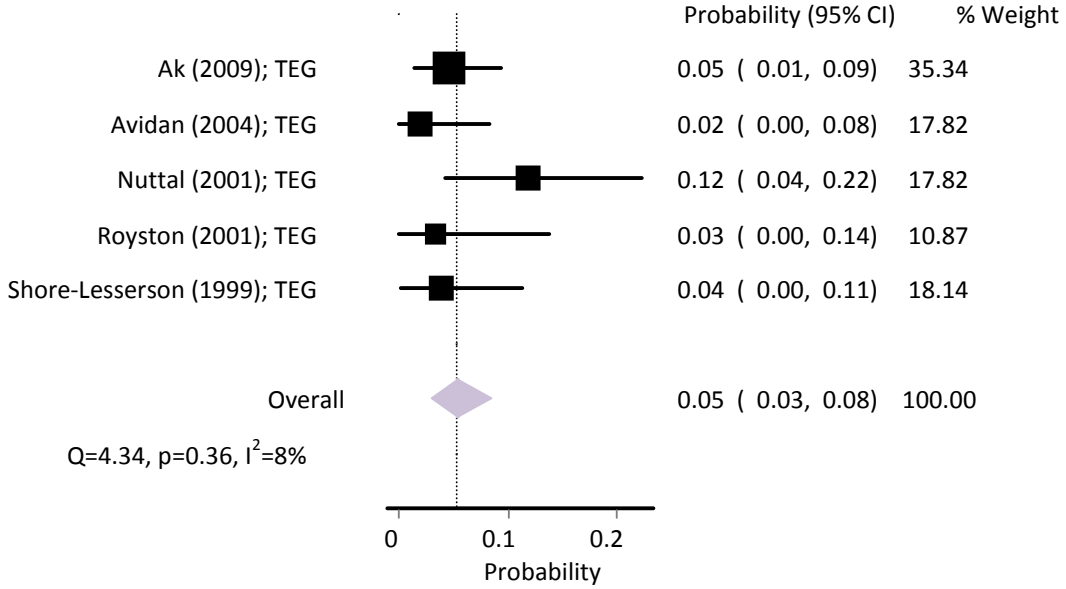
4.3.1.2 Complications related to surgery and transfusion

Complications included in the model relating to surgery and/or transfusion were: renal dysfunction, myocardial infarction, stroke, thrombosis (any type, such as DVT or peripheral vascular thrombosis), excessive bleeding requiring re-operation, wound complications and septicaemia. The only one of these complications evaluated by the RCTs included in the effectiveness review (section 3.2.1.3) was re-operation to investigate bleeding. As with the probability of transfusion, we excluded two studies from this analysis as the patients included in these studies were representative of general cardiac surgery patients.[35, 54] The summary estimate for the probability of re-operation from the remaining four studies was 0.053 (95% CI 0.029, 0.084). The summary RR for the difference in transfusion risk for patients who received VE testing compared to SLTs was also taken from the clinical effectiveness review (Table 11).

[1]The 95% CI reported for the mean probability of RBC transfusion suggests a Normal distribution.

[2] Although theoretically lognormal, the 95% CI reported for the RR suggests a Normal distribution.

Figure 28: Forest Plot showing the probability of re-operation for bleeding (95% CI) in control groups in cardiac surgery trials



Data on the other complications were limited and we therefore assumed that there was no difference in the direct risk of having a complication between those tested with VE devices and those tested with SLTs as in Davies et al.[92] However, the risk of complications in each testing strategy was influenced indirectly by the different RBC transfusion rates associated with each strategy. The probabilities of experiencing complications related to surgery and/or transfusion and the probability distributions for the PSA are shown in Table 20. The probability of experiencing septicaemia was sourced, as in the Scottish study, from Karkouti et al. 2006.[93] However, the population in this study was not representative of our population since it only included patients who received four or more units of RBC within one day of surgery (i.e. patients with massive bleed). As this estimate was judged to be too high, our model used the estimate in Karkouti et al. 2006[93] reduced by an arbitrary factor of 0.5.

Table 20: Probability of experiencing a complication related to surgery and blood loss in transfused patients undergoing cardiac surgery

Type of complication	Mean value	Distribution	Distribution parameters[3]	Source
Renal dysfunction	0.03	Normal	μ =0.03; σ =0.003	Davies et al. 2006[92]
Myocardial infarction	0.03	Normal	μ =0.03; σ =0.003	Davies et al. 2006[92]
Stroke	0.01	Normal	μ =0.01; σ =0.001	Davies et al. 2006[92]
Thrombosis	0.03	Normal	μ =0.03; σ =0.003	Davies et al. 2006[92]
Excessive bleeding re-operation Baseline risk SLTs Relative Risk VE devices	0.053 0.72	Normal Log-Normal	μ =0.053; σ =0.019 μ =0.72; σ =0.285	Section 3.2.1.2
Wound complications	0.07	Normal	μ =0.07; σ =0.007	Davies et al. 2006[92]
Septicaemia	0.0207 (0.0414 from Karkouti et al. 2006 [93])	Beta	α =38; β =917	Karkouti et al. 2006 [93] and assumption

4.3.1.3 Transfusion-related complications

The trials included in the clinical effectiveness review did not report data on transfusion-related complications, therefore data on the probabilities of experiencing transfusion-related complications were based on reports from the UK Serious Hazards of Transfusion (SHOT).[94] The SHOT observations were first corrected for the participation in the SHOT survey, as was done in Davies et al;[92] this was 96% in 2001 [95] and 99% in 2004 [96] . Since we used data dating back to 2000 (after the start of leucodepletion), we used an average of 98% participation. We assumed, as in the Davies report, that the total number of transfused patients per year is around 800,000.[97] Therefore, the probabilities shown in Table 21 are calculated in the following steps:

1) estimate the average number of complications per year over the available number of years (for some complications data was available from 2000 to 2012, for others only 2012 data was available);

[3] Davies et al. [92] Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C. Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model. *Health Technol Assess* 2006;10(44):iii-iv, ix-x, 1-210. only reports mean values. Standard deviations were derived assuming a 95% CI with limits deviating 20% from the mean.

2) divided by 800,000 to get number per transfused patient;
3) divided by 0.98 to correct for survey participation.

Probabilities of experiencing a transfusion-related complication were reported as the risk per patient transfused (Table 21).

Table 21: Probability of experiencing a transfusion-related complication in transfused patients undergoing cardiac surgery

Type of complication	Mean value	Distribution	Distribution parameters[4]	Source
Transfusion-associated graft versus host disease	0.00000021	Normal	μ=0.00000021; σ=0.000000022	UK Serious Hazards of Transfusion (SHOT).[94]
Incorrect blood component	0.0003	Normal	μ=0.00030; σ=0.00003086	
Haemolytic transfusion reactions – acute	0.000011	Normal	μ=0.000011; σ=0.00000112	
Haemolytic transfusion reactions – delayed	0.00004	Normal	μ=0.00004; σ=0.000004125	
PTP	0.0000015	Normal	μ=0.0000015; σ=0.000000156	
TRALI	0.000023	Normal	μ=0.000023; σ=0.0000024	
Febrile reaction	0.0003	Normal	μ=0.0003; σ=0.000030751	

4.3.1.4 Transfusion-transmitted infections

The probabilities of experiencing transfusion-transmitted infections were also taken from the UK SHOT report using the same method of calculation as for transfusion-related complications (Table 22).[94] These were also reported as the risk per patient transfused.

[4] Only mean values are reported in the SHOT report[94] Serious Hazards of Transfusion (SHOT) Steering Group. *Serious hazards of transfusion: annual SHOT report 2012 [Internet]*. Manchester: SHOT, 2012 [accessed 17.12.13]. 200p. Available from: http://www.shotuk.org/wp-content/uploads/2013/08/SHOT-Annual-Report-2012.pdf Standard deviations were derived assuming a 95% CI with limits deviating 20% from the mean.

Table 22: Probability of experiencing a transfusion-transmitted infection in transfused patients undergoing cardiac surgery

Type of infection	Mean value	Distribution	Distribution parameters	Source
Bacterial contamination	0.000002657	Normal	μ=0.000002657; σ=0.000000271	UK Serious Hazards of Transfusion (SHOT).[94]
vCJD	0.000000319	Normal	μ=0.000000319; σ=0.000000033	
HAV	0.000000213	Normal	μ =0.000000213; σ=0.000000022	
Malaria	0.000000106	Normal	μ=0.000000106; σ=0.000000011	
HTLV	0.000000213	Normal	μ =0.000000213; σ=0.000000022	
HIV	0.000000106	Normal	μ=0.000000109; σ=0.000000011	
HBV	0.000000531	Normal	μ=0.000000531; σ=0.000000054	
HCV	0	NA	NA	

4.3.1.5 Mortality

At one month, we estimated the risk of mortality in the SLTs group based on the number of deaths reported in Murphy et al[15] as this study was based on a large sample (n=8,598) of a population that matched our target population. Murphy et al[15] reported a one month mortality of 0.4% for non-transfused patients and 4.3% for transfused patients (note that these numbers were taken from the survival curves presented). Using the transfusion percentage applied in the current model (59.2%, Table 19), this would yield an overall (transfused or not) one month mortality of 2.7%.

Several different complications can occur with transfusion and one would expect the mortality to vary by complication. However, it was assumed that the mortality of all transfused patients (essentially the sum of mortalities due to each complication and no complication) was fixed at 4.3%. Therefore, in order to obtain a 4.3% mortality rate in the transfused group, we used a calibration procedure. What this meant is that where reliable estimates were available or some assumption necessary, a specific mortality estimate was applied to each complication. For the rest, and for no complications the mortality value was calculated so that the total mortality added up to 4.3%. This mortality value was calculated to be 4.28%, as can be seen in Table 23.

For the transfusion-transmitted infections (except bacterial contamination), the one month mortality was assumed to be zero since these infections were assumed to manifest

themselves after the hospitalisation period. Mortality rates for various transfusion-related complications and bacterial contamination were derived from the SHOT survey.[94] Exceptions were 'incorrect blood component', 'delayed haemolytic transfusion reactions' and 'febrile reaction'. For these the SHOT survey reported mortality rates of (close to) zero. Implementing this in the model would imply that having such a complication would actually prevent mortality; we therefore disregarded the SHOT mortality rates for these complications. Therefore, the calibration procedure was used to calculate the mortality for all surgery and/or transfusion complications, transfusion but without complications and 'incorrect blood component', 'delayed haemolytic transfusion reactions' and 'febrile reaction'.

In order to estimate the mortality for VE testing, we assumed that any mortality benefit from VE testing resulted from fewer patients receiving a transfusion. This meant that the one month mortality for each patient group (not transfused, transfused without complications, transfused with complications) in the VE group was assumed to be the same as in the SLTs group.

At one year the mortality in the SLTs group was also estimated using data from Murphy et al,[15] which reported a one year mortality of 1.2% for non-transfused patients and 7.8% for transfused patients. For the non-transfused patients, a 0.4% mortality at one month and a 1.2% mortality at one year yielded a mortality rate for between one and 12 months of (1.2% - 0.4%)/(1-0.4%) = 0.8%. Similarly, for the transfused patients a mortality rate for between one and 12 months was calculated as (7.8% - 4.3%)/(1-4.3%) = 3.66%.

As for one month mortality, the one year mortality for each sub-group of patients in the VE group was assumed to be the same as in the SLTs group. All the mortality rates used in the model for the cardiac surgery population are summarised in Table 23.

Table 23: Probability of patient dying per complication or infection (cardiac surgery population).

Type of complication or infection	1 month		1 year	
	Mean and SD[5] (SLTs and VE)	Source	Mean value and SD (SLTs and VE)	Source
No transfusion	μ=0.0040; σ=0.0004	Murphy et al.[15]	μ=0.0080; σ=0.0008	Murphy et al.[15]
Transfusion and no complications	μ=0.0428; σ=0.0043	Calibration	μ=0.0366; σ=0.0037	Calibration
Renal dysfunction	μ=0.0428; σ=0.0043		μ=0.0366; σ=0.0037	
Myocardial infarction	μ=0.0428; σ=0.0043		μ=0.0366; σ=0.0037	
Stroke	μ=0.0428; σ=0.0043		μ=0.0366; σ=0.0037	
Thrombosis	μ=0.0428; σ=0.0043		μ=0.0366; σ=0.0037	
Excessive bleeding re-operation	μ=0.0428; σ=0.0043		μ=0.0366; σ=0.0037	
Wound complications	μ=0.0428; σ=0.0043		μ=0.0366; σ=0.0037	
Septicaemia	μ=0.0428; σ=0.0043		μ=0.0366; σ=0.0037	
Transfusion-associated graft versus host disease	1	SHOT[94]	μ=0.0366; σ=0.0037	
Incorrect blood component	μ=0.0428; σ=0.0043	Calibration	μ=0.0366; σ=0.0037	
Haemolytic transfusion reactions - acute	μ=0.111; σ= 0.0113	SHOT[94]	μ=0.0366; σ=0.0037	
Haemolytic transfusion reactions – delayed	μ=0.0428; σ=0.0043	Calibration	μ=0.0366; σ=0.0037	
PTP	μ=0.0667; σ=0.0068	SHOT[94]	μ=0.0366; σ=0.0037	
TRALI	μ=0.0938; σ=0.0095	SHOT[94]	μ=0.0366; σ=0.0037	
Febrile reaction	μ=0.0428; σ=0.0043	Calibration	μ=0.0366; σ=0.0037	
Bacterial contamination	μ=0.2750; σ=0.0280	SHOT[94]	μ=0.0366; σ=0.0037	
vCJD	NA	Assumption	μ=0.0366; σ=0.0037	
HAV	NA		μ=0.0366; σ=0.0037	
Malaria	NA		μ=0.0366; σ=0.0037	
HTLV	NA		μ=0.0366; σ=0.0037	
HIV	NA		μ=0.0366; σ=0.0037	
HBV	NA		μ=0.0366; σ=0.0037	
HCV	NA		μ=0.0366; σ=0.0037	

NA=not applicable

4.3.1.6 Health benefits

Health benefits were expressed in terms of life years and quality-adjusted life years (QALYs) gained at one month and one year. For the calculation of the life years, patients were assumed to die in the middle of the period where death occurred. Thus, for patients who

[5] Standard deviations were derived assuming a 95% CI with limits deviating 20% from the mean.

died in month 1 we distinguish between those who die halfway the hospitalisation period and those who die halfway between hospital discharge and end of the month. For patients who survived the first month but died subsequently, it was assumed that death occurred halfway between month 1 and month 12 (i.e. at 6.5 months).

Life years were then valued with different utilities depending on the health state of the patient. We followed the approach used in the Davies[92] and Scottish HTA reports.[12] Except for stroke, we used utility values from the 1996 Health Survey for England:[98]

1) During the hospitalisation period the value for the health state associated with 'limiting long-standing illness' (0.64) was used.
2) For the period between hospital discharge and one month, the mean utility value associated with the health state 'non-limiting long-standing illness' (0.88) was used.
3) For month 1 to month 12, the mean utility value associated with the health state 'no long-standing illness' (0.93) was used, except for patients with transfusion associated infection for whom the mean utility value associated with the health state 'non-limiting long-standing illness' (0.88) was used.

For patients with a stroke, we used a utility value of 0.64 from a study Luengo-Fernandez et al[99] for hospital discharge to month 12. The utilities used in the model are summarised in Table 24.

Table 24: Utilities per health state and time period.

Health states	Mean value	Distribution	Distribution parameters
From surgery to hospital discharge			
All patients	0.64	Beta	$\alpha = 0.7898$; $\beta = 0.4443$
From hospital discharge to 1 month			
All patients except stroke	0.88	Beta	$\alpha = 2.9799$; $\beta = 0.4063$
Stroke patients[6]	0.64	Normal	$\mu=0.64$; $\sigma= 0.0653$
Month 1 to 12 (after surgery and hospital discharge)			
All patients except stroke and transmitted infections	0.93	Beta	$\alpha = 5.6187$; $\beta = 0.4229$
Stroke	0.64	Normal	$\mu=0.64$; $\sigma= 0.0653$
Transmitted infections	0.88	Beta	$\alpha = 2.9799$; $\beta = 0.4063$

[6] Standard deviation for stroke was derived assuming a 95% CI with limits deviating 20% from the mean.

4.3.1.7 Costs

Short (one month) and long-term (one year) costs were considered in the model. Short-term costs included the following four groups: (1) pre- and peri-operative costs of transfusion, (2) costs of blood products, (3) test costs for the identification of patients at risk of bleeding during or after transfusion and (4) costs related to complications due to surgery and blood loss, transfusion-related complications and infections due to bacterial contamination. Long-term costs included those related to the other transfusion-transmitted infections, i.e. vCJD, HAV, malaria, HTLV, HIV, HBV and HCV, and disabling stroke.

Pre and peri-operative costs of transfusion

Pre-operative and peri-operative costs of transfusion were taken from the Davies report[92] and inflated to 2013 prices (Table 25).[100] These included blood group tests, screening, cross-matching, additional allogeneic blood matching and those related to the use of transfusion sets. These costs inflated to 2013 prices can be seen in Table 25.

Table 25: Pre and peri-operative costs associated with transfusion.

Type of service	Cost	Source
Pre-operative costs of allogeneic blood per transfusion	£27.97	Davies et al. 2006.[92]
Peri-operative costs of transfusion services: Additional allogeneic blood match Use of transfusion sets	 £0.65 £3.21	Davies et al. 2006.[92]

Cost of blood products

We included three types of blood products in the model. The prices for standard red blood cells, adult platelets and clinical FFP were obtained from the NHS Blood and Transplant price list 2013-2014[101] and these are £122.09, £208.09, and £27.98, respectively.

Data on units of blood transfused (see Table 26) were obtained from Shore-Lesserson et al. 1999.[51] Although several other studies also provided information on this parameter, most provided data on the median rather than mean units of blood transfused per patient enrolled in the study. We needed to estimate the average number of units of blood per transfused patient, however, all RCTs reported the mean or median number of units of blood per patient enrolled in the study. It was only possible to use these data to calculate the average volume of blood transfused per transfused patient for studies that reported this information as a mean rather than median value and that also provided data on the proportion of patients in the study who received a transfusion. The only study able to provide the required information was the study by Shore-Lesserson.[51] This study provided

data on the volume of blood transfused in mL per patient enrolled in the study. To estimate the number of units of blood transfused per transfused patient we divided this number by 300 (the number mL of blood in one unit) and then divided this number by the proportion of patients who received a transfusion.

For example, for RBCs Shore-Lesserson reported an average transfusion of 475mL per patient (transfused or not) for the SLTs group. This is equivalent to 1.58 units (475/300). The proportion of patients in the SLTs arm who received a transfusion was 59% and so the average number of units per transfused patient was 1.58/0.59 = 2.65. The mean number of units of RBC transfused for patients in the VE group was slightly higher than in the SLTs group, whereas the units of FFP and platelets were lower. This might suggest that VE testing leads to some substitution of one blood product by another.

Table 26: Units of blood transfused[7] in patients undergoing cardiac surgery

Technology	Mean value	Distribution[8]	Distribution parameters	Source
ROTEM, TEG and Sonoclot				
Red blood cell	2.84	Gamma	α =180.03; β =4.73	Shore-Lesserson et al. 1999.[51]
FFP	0.29	Gamma	α =62.14; β =1.40	
Adult Platelet Pack	0.27	Gamma	α =28.12; β =2.88	
Standard Laboratory Tests				
Red blood cell	2.66	Gamma	α =94.46; β =8.23	Shore-Lesserson et al. 1999.[51]
FFP	1.21	Gamma	α =53.75; β =6.78	
Adult Platelet Pack	0.47	Gamma	α =17.34; β =8.17	

Cost of VE devices

To estimate acquisition costs of the different VE devices, we assumed that four channel devices were used. This is because, at the time of writing, this is the only version which is available for all three devices (ROTEM, TEG and Sonoclot). It should be noted that these are more expensive than one and two channel versions which are available for TEG and Sonoclot. Each of the manufacturers quoted a number of extra cost items in addition to the cost of the device itself. Only those extras that were available (and comparable) for the

[7] In Shore-Lesserson et al. 1999 (Table 4)[51] Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg* 1999;88(2):312-9.

[8] The probability distribution is used to model the millimeters of blood component transfused in each treatment arm (including both patients transfused and not transfused). It is further adjusted according to the probability of being transfused and converted into units.

three devices, were included in the acquisition costs in order to maintain consistency. After-care and training costs were also included although the equivalency of these between devices was difficult to assess. As in the Scottish HTA[12] we assumed that a machine would be used for three years (the total acquisition cost are then divided by three to obtain the cost per year). An important variable in the estimation of equipment costs per test is the number of tests per device per year. In the Scottish report, an assumption was made that 200 test would be done per year. However, experts indicted values much higher, ranging from 600 to 8,000 per year (with the 8,000 performed on an eight channel machine). We have therefore assumed that, on average, 500 tests are performed per centre per year. Table 27 presents the estimated equipment costs for ROTEM, TEG and Sonoclot.

Table 27: Comparison of costs of ROTEM, TEG and Sonoclot based on 2013 costs.

Cost component	ROTEM	TEG	Sonoclot
4 channel device	£24,950	£20,000	£14,950
Connectivity kit	£4,078	Included in	Included in
Software/ Database commander	£2,415	device cost	device cost
Printer	£126		
Trolley	£1,015		£750
Total Device Cost	***£32,584***	***£20, 000***	***£15,700***
Years of use	3	3	3
Total cost ROTEM + Extras per year	£10,861	£6,667	£5,233
After care cost per year	£1,750	£2,000	£933
Training cost per year (advanced)	£725	£0	£0
Total cost ROTEM per year	£13,336	£8,677	£6,633
Number of tests per year with the 4 channel device	500	500	500
Material cost per test	***£26.67***	***£17.33***	***£13.27***

The number of VE tests conducted on each patient in the RCTs included in the systematic reviews varied from one to six; five studies reported that patients received three tests with three of these studies performing more tests if patients continued to bleed (Table 7). We therefore assumed that each patient was tested three times in total during and after surgery. To estimate the total average cost of each VE test, the estimated equipment cost of (Table 27) has to be added to the cost of a basic test, which has to be defined. The assays that can potentially be used by ROTEM, TEG and Sonoclot are described in Table 2, 3 and 4, respectively. Only three of the five studies that assessed ROTEM reported on the assays used. One used INTEM, HEPTEM, FIBTEM and APTEM,[54] one used EXTEM, INTEM, FIBTEM and HEPTEM,[35] and the third used EXTEM and FIBTEM.[53] For the model, we assumed that INTEM, EXTEM, FIBTEM and HEPTEM would be used. Five of the six studies that used TEG provided details on the assays used: all ran standard kaolin assays with and without heparinise. We therefore assumed a basic kaolin and heparinase test for TEG. As there

were no RCTs of Sonoclot we did not have data on the assays that might be used in practice. We assumed that the gbACT and kACT would be used as these are similar to the assays selected for ROTEM and TEG; the kACT assay can be used for high dose heparin management. It should be noted that in clinical practice various other combinations of assays may be used, depending on the patient. The total cost of a test for the cardiac surgery model is summarised in Table 28.

Table 28: Comparison of costs of ROTEM, TEG and Sonoclot basic test (cardiac surgery).

Basic Test Cost	
ROTEM intem	£1.13
ROTEM extem	£1.22
ROTEM fibtem	£2.22
ROTEM heptem	£2.43
Cup and pin (x4)	£3.15 x 4
Equipment cost	£26.67
Total cost ROTEM test	£46.27
Kaolin vial	£2.72
Heparinase cup and pin	£8.75
Plain cup and pin	£5.45
Equipment cost	£17.33
Total cost TEG test	£34.25
gbACT	£2.20
kACT	£2.20
Equipment cost	£12.33
Total cost Sonoclot test	£16.73

Cost of standard laboratory tests

As described in Section 2.4, the comparator for this technology appraisal is a combination of clinical judgement and standard laboratory tests (SLTs). SLTs generally include the following five tests: prothrombin time – also used to derive measures prothrombin ratio (PR) and international normalised ratio (INR), activated partial thromboplastin time (aPTT), platelet count (PC), plasma fibrinogen concentration (PFC) and activated clotting/coagulation time (ACT). The total cost per set of SLTs inflated to 2013 prices[100] was taken from the Scottish HTA[12] and was equal to £26 for fibrinogen concentration, PT, PC, ACT and APTT combined.

Hospitalisation costs

Four studies included in the systematic review reported the mean length of hospital stay of patients undergoing cardiac surgery.[35, 46, 47, 54] However, these studies reported data inconsistently, in a format that did not permit pooling, making it difficult to produce a summary estimate across studies. As more contemporary UK-specific data were available on

length of stay we selected this data for inclusion in the model. The average length of hospital stay was sourced from the Hospital Episode Statistics 2012/2013[102] which reports a mean stay of 10.53 days per patient undergoing cardiac surgery. The cost per day (inflated to 2013 prices) was £198 for patients without complication, according to Davies et al. 2006.[92] Since none of the studies including the effectiveness review reported significant differences between VE groups and SLTs in terms of length of hospital stay we assumed equal average length of hospital stay for each of the different strategies. This assumption is conservative towards the VE testing groups as you would expect patients with complications to have a longer hospital stay than those without.

To estimate the costs associated with complications and infections due to bacterial contamination during the hospitalisation period, we assumed that the days of hospitalisation were valued at different unit costs depending on the type of event experienced. For example, where a patient experienced renal dysfunction, it was assumed an overall mean length of stay of 10.53 days where 5.68 days were valued at £335 (as shown in Table 29 below) and the remaining 3.88 days were valued at £198. When a certain complication had an associated length of stay longer than 10.53 days (e.g. wound complications) it was assumed that the overall length of stay was the period of hospitalisation associated with the complication and the days were valued at the unit cost of the corresponding complication (e.g. 12 days in case of wound complications, each day valued at £245). In the case of bacterial contamination we assumed an additional hospitalisation period of 8.4 days, each day valued at £212.

Finally, as described above, patients who died were assumed to die in the middle of the hospitalisation period (including patients requiring re-operation). Thus, patients experiencing a complication were assumed to die in the middle of the period for which the complication lasted and only the cost corresponding to the complication was used (e.g. for renal dysfunction 2.84 days valued at £335 each day). When the cause of death was a re-operation, it was assumed that patients survived half of the hospitalisation period but the total cost of the re-operation was considered.

It should be noted that, as in the Davies and Scottish studies, costs of ICU stay were not considered and thus the total costs may be underestimated. Four RCTs included in the effectiveness review evaluated the length of ICU stay and all reported shorted stays in the VE group compared to control (although this difference was only statistically significant in

one study). Thus, we may expect that if the costs of ICU stay had been included that the results would be more favourable for the VE tested group.

Table 29: Length of stay (in days) and associated costs per day of complications and bacterial contamination during the hospitalization period.

Health states	Mean (SD[9]) length of stay	Mean (SD[9]) cost per day (inflated to 2013 prices)
Renal dysfunction	μ=5.68; σ=0.57	μ=£335; σ=34.18
Myocardial infarction	μ=8.91; σ=0.90	μ=£198; σ=20.20
Stroke	μ=8.76; σ=0.89	μ=£270; σ=27.55
Thrombosis	μ=3.32; σ=0.33	μ=£319; σ=32.55
Excessive bleeding re-operation	μ=0.13; σ=0.01	μ=£2922; σ=298.19
Wound complications	μ=12.00; σ=1.22	μ=£245; σ=25.00
Septicaemia	μ=7.00; σ=0.71	μ=£271; σ=27.65
Transfusion-associated graft versus host disease	μ=6.80; σ=0.69	μ=£1173; σ=119.69
Incorrect blood component	μ=11.90; σ=1.21	μ=£212; σ=21.63
Haemolytic transfusion reactions - acute	μ=11.90; σ=1.21	μ=£818; σ=83.47
Haemolytic transfusion reactions – delayed	μ=11.90; σ=1.21	μ=£818; σ=83.47
PTP	μ=2.50; σ=0.25	μ=£818; σ=83.47
TRALI	μ=1.98; σ=0.20	μ=£1173; σ=119.69
Febrile reaction	μ=1.00; σ=0.10	μ=£998; σ=101.84
Bacterial contamination	μ=8.40; σ=0.85	μ=£212; σ=21.63

Costs between hospital discharge and one year after surgery

Long-term costs (during month 1 and 12 after cardiac surgery) due to all transfusion-transmitted infections with the exception of bacterial contamination were included in the model. The number and the duration of hospitalisations and outpatient visits associated with each type of infection and the corresponding unit costs were obtained from the Davies Report (Table 30).[92] For HAV, HBV, HCV and HIV we assumed two acute hospitalisations and three outpatient visits during the first 12 months after surgery. For malaria and HTLV we assumed two acute hospitalisations with no outpatient visits. For the costs of stroke, we used recently published estimates of costs based on UK data in the first year after a stroke. The first study reported costs of £8,302 (exchange rate 1$=£0.64)[103] and the second of £9,248[104], yielding an average of £8,775. Finally, patients were assumed to die in the middle of the period between month 1 and month 12 after hospitalisation.

[9] Standard deviations were derived assuming a 95% CI with limits deviating 20% from the mean.

Table 30: Length of stay (in days) and associated costs per day of transfusion-transmitted infections (excluding bacterial contamination) during month 1 and 12 after the hospitalisation period.

Health states	Mean (SD[10]) length of stay	Mean (SD[10]) cost per day
vCJD	0	NA
HAV acute hospitalization (x2) HAV outpatient visit (x3)	μ=5.10; σ=0.52 μ=1.00;σ=0.10	μ=£475; σ=48.47 μ=£266; σ=27.14
Malaria hospitalization (x2) Malaria outpatient visit (x0)	μ=3.40; σ=0.34 μ=1.00; σ=0.10	μ=£475; σ=48.47 μ=£266; σ=27.14
HTLV hospitalization (x2) HTLV outpatient visit (x0)	μ=1.00; σ=0.10 μ=1.00; σ=0.10	μ=£598; σ=61.02 μ=£266; σ=27.14
HIV hospitalization (x2) HIV outpatient visit (x3)	μ=6.97; σ=0.71 μ=1.00; σ=0.10	μ=£598; σ=61.02 μ=£966; σ=98.57
HBV chronic hospitalization (x2) HBV outpatient visit (x3)	μ=7.40; σ=0.75 μ=1.00; σ=0.10	μ=£475; σ=48.47 μ=£266; σ=27.14
HCV chronic hospitalization (x2) HCV outpatient visit (x3)	μ=3.50; σ=0.35 μ=1.00; σ=0.10	μ=£341; σ=34.79 μ=£266; σ=27.14

4.3.2 Patients with coagulopathy induced by trauma

The model in patients with coagulopathy induced by trauma was based on the model that we developed for patients undergoing cardiac surgery. The difference between the models relates to the surgery and/or transfusion related complications, which we have replaced with trauma and/or transfusion related complications i.e. acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF). Where possible we have used trauma specific data as inputs to the model. Where these data were not available, including the impact of VE testing on the various parameters, we have used the same input values as for the cardiac surgery population.

4.3.2.1 Probability of RBC transfusion

We estimated the baseline risk of RBC transfusion for the SLTs group using data from the studies included in the effectiveness review (section 3.2.4) that reported data on the proportion of patients who received an RBC transfusion. We used a random effects model to estimate the mean proportion of patients who received an RBC transfusion. This gave a summary estimate of 0.321 (95% CI 0.209, 0.444) (Figure 29). As there were no data comparing the proportion of transfused patients in a trauma population who received VE testing compared to those who received SLTs, we applied the same RR as in the cardiac surgery population. These data are summarised in Table 31.

[10] Standard deviations were derived assuming a 95% CI with limits deviating 20% from the mean.

Figure 29: Forest Plot showing RBC transfusion rates (95% CI) in trauma patients

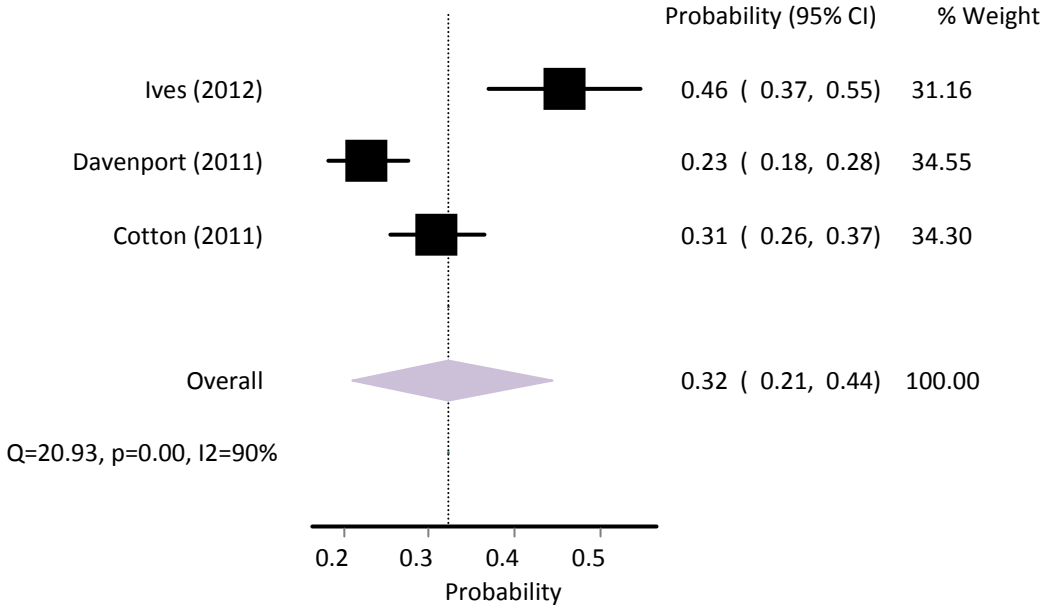


Table 31: Probability of transfusion for trauma patients according to SLTs management and RR associated with VE technologies.

Technology	Mean value	Distribution	Distribution parameters	Source
Baseline risk: Standard laboratory tests	Base case: 0.321	Normal[11] (prob. of RBC transfusion)	μ =0.321; σ = 0.056	Estimated
Relative risk: ROTEM, TEG and Sonoclot	Base case RR=0.88	Normal[12]	μ =0.88; σ =0.08[13]	Section 3.2.1.3 & assumption

4.3.2.2 Complications related to trauma and/or transfusion

We included the two main reported complications that can occur due to trauma which also show a relationship with transfusion.[105] These complications are ARDS and MOF. While other complications may also be relevant, they were not reported in the studies in trauma patients that were included in the systematic review (section 3.2.4).

Estimates for the incidence of ARDS were obtained from a study by Chaiwat et al. of 14,070 trauma patients conducted in the USA.[106] This study reported an overall incidence of ARDS of 4.6%. It also allowed calculation of the data on ARDS related to transfusion as it provided the incidence in patients who did not receive a transfusion i.e. 1.7%, which allowed us to

[11]The 95% CI reported for the mean probability of RBC transfusion suggests a Normal distribution.

[12]Although theoretically lognormal, the 95% CI reported for the RR suggests a Normal distribution.

[13] This is 0.04 in the cardiac surgery model (see Table 19). We have doubled it in order to account in the PSA for the uncertainty about the assumption that the RR for the cardiac surgery population is also valid for trauma.

estimate the proportion of patients with ARDS among those who received a transfusion as 15.5%. For MOF, no studies were found that either provided estimates or allowed direct calculation of incidence for those transfused. However, the overall incidence of MOF in trauma patients is higher than that of ARDS ranging from 15-25%, which is 3 to 5 times higher than the ARDS incidence.[107-110] Assuming that the same ratio applies for the incidence in the transfused patients, an estimate of about 45% to 75% MOF would follow, with a simple average of 60%. However, the only trauma study retrieved on MOF that reported the transfusion rate[110] found this rate to be double (45.8%) that of the ARDS study by Chaiwat (21%).[106] Therefore, it might be suggested that an MOF incidence rate of 30% is a more realistic assumption, however, it is clear that this assumption is very uncertain.

4.3.2.3 Transfusion-related complications

The probability of transfusion-related complications was assumed to be the same as that for the cardiac surgery patients (see Table 21).

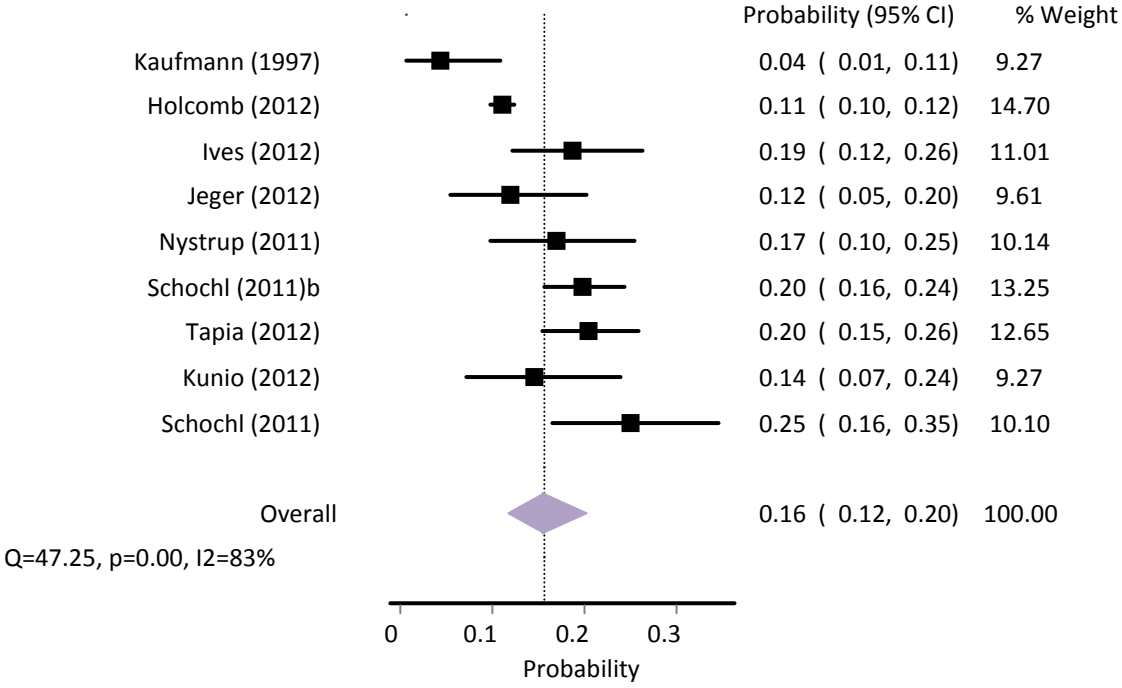
4.3.2.4 Transfusion-transmitted infections

The probability of transfusion-transmitted infections was assumed to be the same as that for the cardiac surgery population (see Table 22). This is likely to be an underestimation, as patients with trauma receive on average more units of blood than cardiac surgery patients (see Table 26 and 33), increasing the exposure to various donors.

4.3.2.5 Mortality

At one month, we estimated the baseline risk of morality for the SLTs group using the same method used to estimate the baseline risk of RBC transfusion. We identified studies included in the effectiveness review (section 3.2.4) that reported data on 30 day or in-hospital mortality; if the time frame for mortality was not reported it was assumed to be longer term (i.e. up to 30 day) mortality. We then used a random effects model to estimate the mean one month mortality in the SLTs group of 15.7% (95% CI 11.7%, 20.1%) (Figure 30).

Figure 30: Forest Plot showing overall one month mortality rates (95% CI) in trauma patients



As for the cardiac patients, we aimed to assign one month mortality rates to transfused and non-transfused patients such that the overall mortality rate would be equal to 15.7%. We were able to retrieve one study that reported mortality rates separately for transfused and non-transfused.[111] This study included 1,172 trauma patients that were admitted to an ICU of whom 67% received a transfusion. In-hospital mortality was reported for patients who received a blood transfusion (21.4%) and those who did not (6.5%), showing that mortality was 3.3 times higher among patients who received a transfusion. It should be noted that the number of days in hospital for transfused patients was also higher (18.6 versus nine), so the mortality rates are less easy to interpret than if mortality had been reported for a fixed time period (e.g. 30 days). The severity of the trauma was also more severe in these patients than might be seen in a general trauma population (mean ISS=24), however, as similar data were not available in a general trauma population, this was the best estimate available.

Thus we assumed that the ratio of mortality for transfused ($Mort_{trans}$) to non-transfused ($Mort_{not\ trans}$) was 3.3. Therefore the goal was to estimate mortality rates such that the weighted average of these yielded an overall mortality of 15.7%, the mean mortality in the SLTs group derived from the systematic review. i.e. 32% $Mort_{trans}$ + 68% $Mort_{not\ trans}$ = 15.7%.

From this it follows that mortality was 9.1% in patients who did not receive a transfusion and 29.8% in those that did.

We then estimated mortality for the two trauma and/or transfusion related complications, ARDS and MOF. As none of the papers included in the systematic review reported on the incidence of ARDS or MOF and their associated mortality rates, we estimated these data from other sources. We estimated the probability of mortality in patients with ARDS from a trial in ARDS patients which reported a mortality rate of 83/385 = 21.6%.[112] We pooled data from two studies to estimate the mortality rate in patients with MOF (Table 32):[107, 108], a 12 year prospective studies of 339 patients with postinjury MOF[107] and a prediction modelling study of 104 trauma patients of whom 21 developed MOF[108]. This yielded an overall MOF mortality rate of 26.2%.

Table 32: Probability of death due to multiple organ failure

Study	Number dead	Number MOF	Mean
Dewar[108]	5	21	0.238
Ciesla[107]	90	342	0.263
Overall mean (inverse variance)			0.262
SE			0.023

SE: standard error

One month mortality rates for transfusion-related complications and transfusion-transmitted infections were derived when possible from the SHOT survey,[94], and, as in the cardiac surgery population, it was assumed that all infections apart from bacterial contamination would only manifest themselves after one month, implying a zero mortality rate in the first month.

However, as we calculated earlier, the overall mortality in the transfused group had to be 29.8% in order to achieve an overall mortality of 15.7% after one month. The ARDS and MOF mortality that we estimated from published studies were lower than this, which would imply that having ARDS or MOF lowers the mortality rate. As this is clinically implausible, we were confronted with a consistency issue caused by using data from various studies all with slightly different populations and ways of reporting. Any way of dealing with this issue involves arbitrary choices. We made the decision that all complication mortality rates that were below the overall mortality rate for the transfused patients would become part of a calibration similar to that applied in the cardiac population. *De facto* this means that only the mortality rate for Transfusion-associated graft versus host disease (which is 1) was not

included in the calibration. The calibration procedure itself meant that all other transfusion related mortality parameters were set to x, and a value of x was sought such that the transfusion mortality was 29.8%.

As in the cardiac population, the one month mortality for each sub-group of patients in the VE group (see Table 33) was assumed to be the same as in the SLTs group, implying that any mortality benefit in the VE group was due to fewer patients being transfused.

Table 33: Probability of patient dying within 1 month per complication or infection (trauma population).

Type of complication or infection	1 month (SLTs and VE)	
	Mean value and SD[14]	**Source**
No transfusion	μ=0.091; σ=0.009	Bochicchio 2008 [111] and calibration
Transfusion and no complications	μ=0.296; σ=0.030	Calibration
Multiple organ failure	μ=0.296; σ=0.030	
Acute respiratory distress syndrome	μ=0.296; σ=0.030	
Transfusion-associated graft versus host disease	1	SHOT[94]
Incorrect blood component	μ=0.296; σ=0.030	Calibration
Haemolytic transfusion reactions - acute	μ=0.296; σ=0.030	
Haemolytic transfusion reactions – delayed	μ=0.296; σ=0.030	
PTP	μ=0.296; σ=0.030	
TRALI	μ=0.296; σ=0.030	
Febrile reaction	μ=0.296; σ=0.030	
Bacterial contamination	μ=0.296; σ=0.030	
vCJD	NA	Assumption
HAV	NA	
Malaria	NA	
HTLV	NA	
HIV	NA	
HBV	NA	
HCV	NA	

NA: Not applicable

For mortality between one and 12 months after trauma little data were available. One study was identified, this reported 3% mortality for this period. [113] However, no information was identified on how this mortality is distributed over transfused and non-transfused patients. We therefore applied the same ratio as for 1 month mortality (3.3). Now we need to solve 32% $Mort_{trans}$ + 68% $Mort_{not\ trans}$ = 3.0%. This yielded a mortality in the non-transfused of

[14] Standard deviations were derived assuming a 95% CI with limits deviating 20% from the mean.

1.7% and mortality in the transfused of 5.7%. These values were assumed to apply to both the SLTs and VE group.

4.3.2.6 Health benefits

The calculation of life years was done in the same way as for the cardiac surgery patients. For the calculation of QALYs, we explored trauma specific utilities. We used a review paper by Hofhuis and Spronk to identify relevant studies on utilities in trauma patients.[114] This paper lists various studies in trauma patients reporting on health-related quality of life.

We selected studies that reported a mean EQ-5D utility. Most studies only collected EQ-5D data two to seven years after the trauma. Only one study,[115] collected EQ-5D utilities 12 to 18 months after trauma. This study included patients with severe trauma (ISS scores >=16) and reported a mean utility of 0.69 (SE 0.016) in these patients 12 to 18 months after the trauma. None of the studies reported utilities for the period of hospitalisation and shortly afterwards. We therefore assumed the same utility for the period of hospitalisation as for the cardiac population during hospitalisation, i.e. 0.64, and a utility of 0.69, the value obtained in trauma patients at 12-18 months, after discharge. It is likely that these utility values are overestimations. It is reasonable to assume that trauma patients will have a worse quality of life than cardiac patients. However, no published data were available to show how much lower that utility should be. Similarly, the value of 0.69 was derived from a group of patients evaluated 12-18 months after the trauma; it is likely that the utility would be worse closer to the event. We opted for conservative estimates as lower utility values would have resulted in larger QALY gains for VE testing.

For ARDS patients we used the results of a prospective cohort study that measured quality adjusted survival in 200 patients in the first year after ARDS.[116] This study reported utilities of 0.60 (SE 0.01) and 0.64 (SE 0.01) at six months and one year after onset of ARDS respectively. We applied the first value to the period of one month, and the latter to the period between months 1 and 12. As with the utility values for the general trauma population, these values, especially that for the period of hospitalisation, are likely to be an overestimation as the utility would be expected to be worse closer to the trauma. Additionally, patients with a long stay on the ventilator would be expected to have utility values close to 0 whilst on the ventilator and this is not taken into account in these values. However, in the absence of more reliable estimates of utilities for these patients we adopted these conservative values.

We were unable to find similar data for patients with MOF and so applied the same utilities as for patients with ARDS, based on the assumption that both complications are similar in their severity. For patients with transfusion related complications, we assumed that after discharge, as in the cardiac population, the utility would be equivalent to patients without complications. We assumed that the additional disutility from having a transfusion related infection was estimated by multiplying the utility of trauma patients having no transfusion complications or infection with the utility applied in the cardiac population for patients with infections.[117] Table 34 summarises the utilities used in the trauma model.

Table 34: Utilities per health state and time period (trauma population).

Health states	Mean value	Distribution	Distribution parameters	Source
During hospitalisation				
All patients except transfusion and trauma complications	0.64	Beta	$\alpha = 0.7898$; $\beta = 0.4443$	Assumed same as cardiac population
Transfusion and trauma Complications	0.60	Normal	$\mu = 0.60$; $\sigma = 0.091$	Angus et al. 2001 [116]
From hospital discharge to 1 month				
All patients except transfusion and trauma complications	0.69	Normal	$\mu = 0.69$; $\sigma = 0.1056$	Holtslag et al. [115]
Transfusion and trauma Complications	0.60	Normal	$\mu = 0.60$; $\sigma = 0.091$	Angus et al. 2001 [116]
Month 1 to 12 (after surgery and hospital discharge)				
All patients except transfusion and trauma complications or transfusion transmitted infection	0.69	Normal	$\mu = 0.69$; $\sigma = 0.1056$	Holtslag et al. [115]
Transfusion and trauma Complications	0.64	Normal	$\mu=0.64$; $\sigma= 0.0979$	Angus et al. 2001 [116]
Transfusion transmitted infection	0.69*0.88=0.61	Normal	$\mu = 0.61$; $\sigma = 0.0933$	Holtslag et al. [115] and Davies et al. 2006[92]

4.3.2.7 Costs

Similarly to the model in cardiac surgery patients, the trauma model also considered short (one month) and long-term (one year) costs. Short-term costs included the following four groups: (1) peri-trauma costs of transfusion, (2) costs of blood products, (3) test costs for the identification of patients at risk of bleeding during or after transfusion and (4) costs related to complications due to surgery and blood loss, transfusion-related complications and

infection due to bacterial contamination. Long-term costs included those related to the other transfusion-transmitted infections (i.e. vCJD, HAV, malaria, HTLV, HIV, HBV and HCV).

Peri-trauma costs of transfusion

We applied the same pre-operative and peri-operative costs of transfusion as for the cardiac surgery population, under the assumption that tests that are done pre-operatively in the cardiac population, such as cross-matching, are now done while the patient receives trauma care (see Table 25 in cardiac section).

Cost of blood products

As with the cardiac surgery population, we included three types of blood products in the model: standard red blood cells, adult platelets and clinical FFP. We used data from the only two trauma studies in the effectiveness review that reported volumes of blood products used to estimate the average number of units transfused per transfused patient (Table 35).[73, 74] As both studies[73, 74] included a similar number of patients, a simple average was taken to estimate the number of units transfused per patient. This was adjusted by the proportion of patients who received a transfusion to give an estimate per transfused patient. To estimate the number of units for the VE testing strategy, we calculated the ratio of units transfused among cardiac patients tested with VE device (2.84) to the number of units transfused among cardiac patients tested with SLTs (2.65) based on Shore-Lesserson et al. 1999.[51] i.e. 1.07 and assumed that this would also be applicable to the trauma population.

Table 35: Units of blood products transfused per transfused trauma patient

	RBC	FFP	Platelets
Ives[74]	9.5	10.9	3.3
Nystrup[73]	3.4	2.2	1.6
Average units per patient	6.45	6.55	2.45
Average units per transfused patient SLTs group	**20.09**	**20.40**	**7.63**
Ratio of units transfused among VE tested patients compared to SLTs tested patients (cardiac surgery population)	1.07	0.24	0.57
Average units per transfused patient VE group	**21.50**	**4.90**	**4.35**

Cost of VE devices

In line with the study protocol of the ongoing RCT in trauma patients[64] we assumed that each patient was tested five times. In addition, we assumed that the acquisition costs would

be the same as in the cardiac population as the material costs of the device would be the same and we again assumed that 500 tests would be performed per year.

The only difference in costs in terms of device was for the types of assays used to define a basic test (Table 36). We assumed that trauma patients would not be tested using the heparin assays. Therefore for ROTEM we assumed that a basic test would consist of INTEM, EXTEM and FIBTEM; this was similar to the assays evaluated in the predictive accuracy studies included in the systematic review. For Sonoclot we assumed that patients would just receive a basic glass bead activated test. For TEG, we assumed that the regular kaolin test would be replaced by the rapidTEG assay as this was used by almost all the predictive accuracy studies included in the systematic review and is also the assay used in the ongoing RCT.[63, 64]

Table 36: Comparison of costs of ROTEM, TEG and Sonoclot basic test (trauma patients).

Basic Test Cost	
ROTEM intem	£1.13
ROTEM extem	£1.22
ROTEM fibtem	£2.22
Cup and pin (x3)	£3.15 x 3
Equipment cost	£26.67
Total cost ROTEM test	£40.69
Rapid TEG	£11.25
Plain cup and pin	£5.45
Equipment cost	£17.33
Total cost TEG test	£34.03
gbACT	£2.20
Equipment cost	£12.33
Total cost Sonoclot test	£14.53

Cost of standard laboratory tests

These were assumed to be the same as for the cardiac population. The costs for SLTs for the cardiac population were based on a general battery of coagulation tests and it is likely that similar tests would be run in trauma patients.

Hospitalisation costs

Data on length of hospital stay for trauma patients were taken from the only two trauma studies included in the effectiveness review that reported on this parameter.[73, 74] One reported a mean stay of 10.8 days and the other of 10.3 days, which give a simple average of 10.55 in-hospital days. Of these days, on average 4.9 were spent on the ICU.[74] For the ICU costs we assumed costs per day of £1,173, based on National Schedule of Reference Costs - Year 2012-13.[118] For hospital stay beyond the stay in ICU, it was difficult to define a cost per

day, as trauma patients can have a wide variety of injuries and may thus be admitted to various departments. As we were unable to define a more reliable estimate, we assumed the same per-day unit costs as for the cardiac surgery patients.

For patients with ARDS, we used data from Angus et al [112] who reported an ICU length of stay of 18.8 days, while hospital length of stay was 26.8 days. For patient with MOF, we used data from Dewar et al who reported an ICU length of stay of 19.1 days.[108] No data were reported on overall length of stay, so we assumed that after ICU discharge the patient spent the same amount of time in regular care as the ARDS trauma patients (i.e. 26.8-18.8 = eight days).

As the incidence of MOF and ARDS is high and their mean length of ICU stay and hospital stay was much longer than the overall mean length of ICU stay, we estimated the length of ICU and hospital stay for patients who did not experience either MOF or ARDS, so that the overall mean length of hospital stay was 10.55 days and the mean length of ICU stay was 4.9 days. This gave ICU and hospital lengths of stay for patients without ARDS or MOF as estimated at 2.2 days and 7.4 days, respectively.

We had no data on how transfusion related complications and bacterial infection would affect length-of-stay. We therefore assumed the same length of stay for these complications as for cardiac surgery patients and the same unit costs per day. While patients remained in ICU for their trauma, we did not apply any hospital costs for complications as we assumed that the level of care was already such that the marginal resource use due to the complications was relatively small. Once patients were no longer on the ICU, we applied the per day costs for complications in the same way we did for cardiac patients.

Costs between hospital discharge and one year after surgery

Long-term costs (during month one and 12 after trauma) due to all transfusion-transmitted infections with the exception of bacterial contamination were included in the model in the same way as for the cardiac population.

4.4 Sensitivity and scenario analyses

4.4.1 Probabilistic sensitivity analysis

The impact of statistical uncertainties regarding the model's input parameters was explored through probabilistic sensitivity analysis (PSA). PSA results were presented in the cost-effectiveness plane for all the technologies compared. Cost-effectiveness acceptability

curves (CEACs) were used to determine the probability of a strategy being considered cost-effective given a threshold incremental cost-effectiveness ratio (ICER). The probability distributions used in the PSA are listed in the tables presented throughout Section 4.2 and 4.3.

4.4.2 EVPI

For the trauma model, we explored the value of information associated with the model uncertainty by estimating the expected value of perfect information (EVPI), which is the amount the decision-maker should be willing to pay to eliminate all uncertainty in the decision. The decision is made based on the expected net monetary benefit given current information, i.e. the technology with the highest expected net monetary benefit is chosen as optimal. The EVPI per patient was calculated as the average of the maximum net benefits across all PSA outcomes (expected net benefit of perfect information) minus the maximum average net benefit for the different technologies (expected net benefit given current information). Additional research might be justified when the expected net benefit for future patients, defined as the population EVPI, exceeds the expected costs of additional research. Therefore the per patient EVPI is multiplied by the population size to give the population EVPI. This is then summed over the lifetime for which the research recommendation is expected to be valid, discounted at 3.5% to give the net present value.[119] We selected a period of five years for this value. For the trauma model a potential population of 16,825 adult patients in the UK was assumed based on data from the National Audit Office.[120] This was calculated as follows:

- Total number of major trauma (ISS >16) patients in England was approximately 20,000 per year
- Number who die before they get to hospital is 2,400
- Proportion aged 15 years or less is 4.4%

Note that this provides an upper limit of the potential population, as SLTs and VE testing will probably not be indicated for the whole trauma population. We distinguished two approaches to the population EVPI depending on whether the problem to be addressed was which of the four different strategies should be recommended, or whether to recommend VE testing (e.g. ROTEM) instead of SLTs. In the former case, all four technologies were included in the EVPI estimation. For the latter situation we only compared ROTEM as it the most expensive strategy.

4.4.3 Scenario analyses

Scenario analyses were performed to investigate the influence of number of years of machine usage, number of tests performed per year, number of tests per patient, relative risk of be probability of transfusion, baseline prevalence of RBC transfusion, units of blood product transfused, one month mortality, and the probability of experiencing complications related to trauma and/or transfusion (trauma model only). We only performed these analyses for the most expensive VE device (ROTEM) as if the results were cost-effective for this device then they would also be cost-effective for the other devices (TEG and Sonoclot).

4.4.3.1 Number of years of machine usage

The base case assumed that the hospital would use the VE device for three years. In this scenario, we increased the time that the hospital would use the device for to five years. Increasing the number of years that the machine would be used for only affects the costs of ROTEM reducing it from £2,588 to £2,562 for the cardiac model and from £6,973 to £6,929.

4.4.3.2 Number of tests per year

The usage of the machine determines the material cost of a VE test: the higher the number of tests per machine per year the lower the material cost (and therefore the higher the likelihood of being cost-effective). In the base case we assumed that on average, 500 tests would be run on each VE device per year. In the sensitivity analysis, we reduced the number of tests per year to 200, the value used in the Scottish HTA report.[12] We used iterative analysis to investigate the minimum number of tests per device year that would need to be performed for the VE devices to be considered cost-saving and cost-effective (ICER of £0 and ICER of £30 000).

4.4.3.3 Number of tests per patient

In the base case scenario we assumed that each patient was tested three times in the cardiac surgery population and five times in the trauma population, based on the testing protocols used in the included RCTs. However, clinical experts suggested that in practice the number of tests performed per patient may be lower. In this scenario we therefore investigated the effects of changing the number of tests per patients. For the cardiac surgery population we reduced the number of tests so that non-transfused patients were tested once and transfused patients twice. For the trauma population we assumed that non-transfused patients would be tested two times and transfused patients would be tested three times. Reducing the number of tests per patients reduces the costs of both VE testing and SLTs.

4.4.3.4 Relative risk of the probability of transfusion

The base case scenario in both the cardiac and trauma models was based on the summary RR of RBC transfusion equal to 0.88 (95% CI 0.80, 0.96) estimated in the systematic review (Figure 6). We investigated the effects of this replacing 0.88 with the lower and upper limits of the CI. For the trauma population we assumed that the RR of RBC transfusion was equivalent to that in the cardiac surgery population. We conducted additional analyses to investigate the validity of the assumption. We used iterative analysis to investigate the minimum RR that would be needed for VE devices to be considered cost-saving and cost-effective (ICER of £0 and ICER of £30 000). For this analysis, we assumed that equal blood volumes would be transfused in the VE tested and SLTs groups.

4.4.3.5 Baseline prevalence of RBC transfusion

We varied the baseline prevalence of RBC transfusion by selecting one value lower than the base case and one value higher. For the lower estimate in cardiac surgery patients, we used the estimate from Murphy et al (2007)[15] which evaluated all patients who underwent cardiac surgery at the Bristol Royal Infirmary between 1996 and 2003 (n=8,598). This study reported a probability of RBC transfusion of 0.429. We did not have a reliable estimate for a higher prevalence of RBC transfusion in cardiac surgery patients and so selected an arbitrary value of 1.5 times the base case value, equivalent to a probability of RBC transfusion of 0.89 in the SLTs group. For the trauma model, we did not identify any reliable sources for estimates of RBC transfusion in these patients. The baseline prevalence used in the trauma model (0.321) was estimated from studies included in the systematic review and had an accompanying 95% CI of 0.209, 0.444. We investigated the effects of replacing the value in the base case with the upper (0.444) and lower (0.209) confidence limits around this estimate. As estimates in the trauma population were considered to be more uncertain, we conducted additional analyses in this population. We used iterative analysis to investigate the minimum baseline prevalence of RBC transfusion that would be required for VE devices to be considered cost-saving and cost-effective (ICER of £0 and ICER of £30 000). For this analysis, we assumed that equal blood volumes would be transfused in the VE tested and SLTs groups. We repeated this analysis for a RR of RBC transfusion in VE tested compared to SLTs tested patients of 0.95 (compared to 0.88 used in the base case analysis), as the estimates of RR was uncertain in this population.

4.4.3.6 Units of blood product transfused

The estimate for the average units of blood transfused per transfused patient for the base case for both trauma and cardiac surgery were derived from studies included in the systematic review (Table 26). In both the cardiac surgery and trauma populations the number of units of RBC transfused for patients in the VE group was slightly higher than in the SLTs group, whereas the number of units of FFP and platelets were lower. We investigated the effects of changing the average units of blood transfused so that the average number of units transfused was the same in the SLTs and VE testing groups.

4.4.3.7 Probability of experiencing complications related to trauma and/or transfusion (trauma model only)

The mean probability of experiencing ARDS and MOF included in the model were 0.155 and 0.30 respectively. In this scenario we investigated the effect of reducing and increasing these probabilities by half; we replaced the base case values by 0.0775 (ARDS) and 0.15 (MOF) and 0.2325 (ARDS) and 0.45 (MOF). We also investigated the effect of reducing the probability of complications related to trauma and/or transfusion, transfusion-related complications and transfusion related-infections to zero.

4.4.3.8 One month mortality

For the base case in both the cardiac surgery and trauma populations, the one month mortality for transfused patients was calibrated to obtain an overall one month mortality figure. In the cardiac surgery patients this was equal to 0.027 overall (the value reported by Murphy et al [15](Table 23) and 0.0428 in the transfused patients (Table 23). In the trauma population the overall mortality figure was 0.157 and 0.296 in the transfused patients. We investigated the halving and doubling the mortality in the transfused patients (and making associated changes to the non-transfused such that overall mortality remained the same); we replaced the base case value with 0.0214 and 0.0642 in the cardiac surgery model and with 0.1483 and 0.4450 in the trauma model.

4.5 Model assumptions

The assumptions used in the model are summarised below (Table 37):

Table 37: Model assumptions

General	
1.	ROTEM, TEG and Sonoclot were assumed to be equally effective.
2.	Complications related to surgery and/or transfusion, transfusion-related complications and infection caused by bacterial contamination were assumed to occur during the hospitalisation period.

3.	For the transfusion-transmitted infections (except bacterial contamination), one month mortality was assumed to be zero since these infections were assumed to manifest themselves after the hospitalisation period.
4.	Patients were assumed to die in the middle of the period where death occurred.
5.	We assumed that four channel VE devices were used.
6.	Only those extra items that were available (and comparable) for the three devices, were included in the acquisition costs. After-care and training costs were also included.
7.	We assumed 3 years of machine usage.
8.	We assumed that, on average, 500 tests were performed per machine per year.
9.	We assumed equal average length of hospital stay for the VE and SLTs groups.
10.	For HAV, HBV, HCV and HIV we assumed two acute hospitalisations and three outpatient visits during the first 12 months after surgery. For malaria and HTLV we assumed two acute hospitalisations with no outpatient visits.
Cardiac surgery population	
11.	We assumed that there was no difference in the risk of having a complication between those tested with VE devices and those tested with SLTs (except for the probability of re-operation), except due to transfusion.
12.	The probability of experiencing septicaemia was sourced from Karkouti et al. 2006[93] but reduced by an arbitrary factor of 0.5.
13.	The mortality associated with 'Incorrect blood component', 'delayed haemolytic transfusion reactions', 'febrile reaction', all surgery and/or transfusion complications, and patients with transfusion but without complications was estimated using the calibration procedure described in Section 4.3.1.4.
14.	We assumed that any mortality benefit from VE testing resulted from fewer patients receiving a transfusion, which meant that the one month mortality for each patient group (not transfused, transfused without complications, transfused with complications) in the VE group was assumed to be the same as in the SLTs group.
15.	The one year mortality for patients in each category (not transfused, transfused without complications, transfused with complications) for the VE group was assumed to be the same as in the SLTs group.
16.	A basic test for ROTEM was defined as a combination of the INTEM, EXTEM, FIBTEM and HEPTEM assays. A basic test for TEG was defined as a standard Kaolin and a heparinise assays. A basic test for Sonoclot was a combination of the gbACT and kACT would be used for this population.
17.	It was assumed that each patient is tested 3 times in total during and after surgery.
18.	For parameters where standard errors were not reported, estimates for the PSA assumed a 95% CI with limits deviating 20% from the mean.
Trauma population	
19.	For the proportion of patients who received VE testing compared to the ones who received SLTs, we applied the same RR as in the cardiac surgery population.
20.	An MOF incidence rate of 30% was assumed.
21.	The probability of transfusion-related complications and the probability of transfusion-transmitted infections were assumed to be the same as for cardiac surgery patients.
22.	The ratio between mortality for transfused and non-transfused was assumed to be the same as in the Bochicchio et al. [111] study.
23.	We assumed that all complication mortality rates that were below the overall mortality rate for transfused were part of a calibration, resulting in equal probabilities.
24.	The one month and one year mortality for patients in each category (not transfused, transfused without complications, transfused with complications) for the VE group was assumed to be the same as in the SLTs group.
25.	For the period of hospitalisation and the period from discharge to 1 month we assumed the same utility as for the cardiac population during hospitalisation.
26.	We applied the same pre-operative and peri-operative costs of transfusion as for the cardiac surgery population.
27.	To estimate the number of units of blood transfused for the VE testing strategy, we estimated the ratio of units transfused in the VE group and the units transfused in the SLTs

group found in the cardiac group, and applied this to the SLTs trauma volumes.
28. A basic test for ROTEM was defined as a combination of the INTEM, EXTEM and FIBTEM assays. The rapidTEG assay was considered as the basic test for TEG. A basic test for Sonoclot was the gbACT assay
29. We assumed that each patient was tested 5 times.
30. For parameters where standard errors were not reported, estimates for the PSA assumed a 95% CI with limits deviating 30% from the mean.

4.5 Results of cost-effectiveness analyses

4.5.1 Base case results for model in cardiac surgery patients

The base case results from the analysis reported as life years (LYs), quality adjusted life years (QALYs) and costs per technology for patients undergoing cardiac surgery are summarised in Table 38.

Table 38: Cardiac surgery model outputs (base case)

	SLTs	ROTEM	TEG	Sonoclot
LY	0.9624	0.9660	0.9660	0.9660
QALY	0.8726	0.8773	0.8773	0.8773
Cost	£2,631	£2,588	£2,552	£2,499
Incr. QALYs vs. SLTs		0.0047	0.0047	0.0047
Incr. costs vs. SLTs		-£43	-£79	-£132

LY, life years; QALY, quality-adjusted life year

Under the assumptions made in Section 4.2, all the VE technologies dominated SLTs. As the same treatment effects were assumed for each VE testing device, effectiveness (measured using LYs and QALYs) was the same for each device. The cost of Sonoclot was lower than that of ROTEM or TEG and so this device was associated with greater cost-savings (£132) compared to TEG (£79) or ROTEM (£43).

The total cost of testing per patient undergoing cardiac surgery for the four technologies included in the base case analysis was £139 for ROTEM, £103 for TEG, £78 for SLTs, and £50 for Sonoclot. Other outputs of interest from the base case analysis were overall one month and one year mortality, the percentage of patients experiencing surgery and/or transfusion complications, the percentage of patients experiencing transfusion-related complications, the percentage of patients experiencing transfusion-transmitted infections, transfusion costs and hospitalization costs. These are summarised in Table 39. Note that for these outputs there is no difference between the three VE devices. These results show that compared with SLTs, the use of VE devices is associated with less mortality, a reduced probability of experiencing complications and less transfusion and hospitalisation costs. The probability of

experiencing transfusion-transmitted infections was very low (almost zero) in both groups but was lower in the VE group.

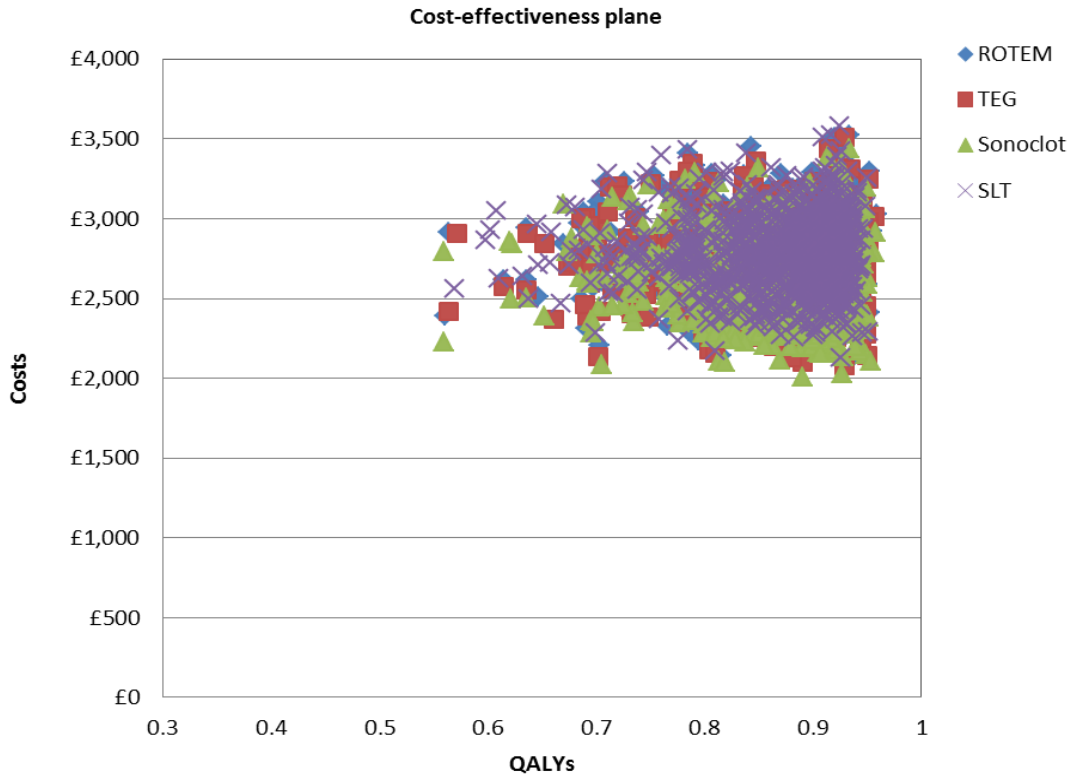
Table 39: Cardiac surgery additional model outputs (base case)

Outcome	VE	SLTs
One month mortality	2.4%	2.7%
One year mortality	4.6%	5.1%
Percentage surgery and/or transfusion complications	11.9%	14.4%
Percentage transfusion-related complications	0.04%	0.04%
Percentage transfusion-transmitted infections	0.00%	0.00%
Transfusion costs	£231	£290
Hospitalisation cots	£2,174	£2,213

4.5.2 Results of the probabilistic sensitivity analyses in cardiac surgery patients

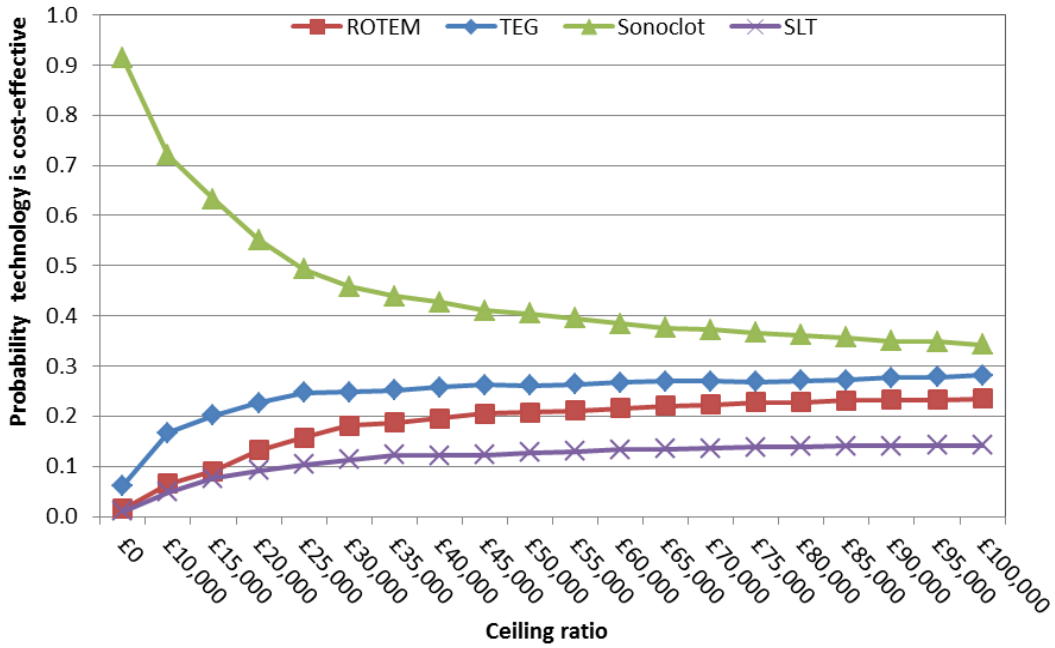
The impact of the statistical uncertainties in the model was investigated in the PSA. As the model only assumed differences in technology costs between the three VE technologies, the scatter plot of the PSA outcomes in the cost-effectiveness (CE) plane was not very informative (Figure 31).

Figure 31: Cost-effectiveness plane with PSA outcomes for all technologies in cardiac surgery patients



The cost-effectiveness acceptability curves (CEACs) for each technology are shown in Figure 32. PSA confirmed that SLTs is the strategy with the lowest probability of being cost-effective. This is to be expected as the base-case scenario suggested that all three of the VE devices were both cheaper and more effective than SLTs. The CEACs for ROTEM, TEG and Sonoclot are very close together, especially at higher ceiling ratios, which would be expected as the only difference between the three strategies assumed in the model was a difference in technology cost. At lower ceiling ratios, larger differences were observed as Sonoclot was the cheapest technology in our model and so had the highest probability of being cost-effective.

Figure 32: Cost-effectiveness acceptability curves for all technologies in cardiac surgery patients



The information presented in Figure 32 is helpful to address the question of which of the four different testing strategies should be recommended. However, if the actual question is whether to recommend VE testing instead of SLTs, then pairwise comparisons may be more informative. The deterministic pairwise results are presented in Table 38. The CEACs in Figures 33 to 35 illustrate the difference between ROTEM, TEG or Sonoclot and SLTs in terms of the probability of being cost effective. At a cost-effectiveness threshold of £30,000 per QALY, the probability of cost-effectiveness for each of the three VE technologies was 0.79 for ROTEM, (the most expensive device), 0.82 for TEG and 0.87 for Sonoclot (the cheapest device). At higher thresholds, the cost-effectiveness probabilities converged to around 0.8 for all technologies.

Figure 33: Cost-effectiveness acceptability curves: ROTEM vs. SLTs (cardiac surgery)

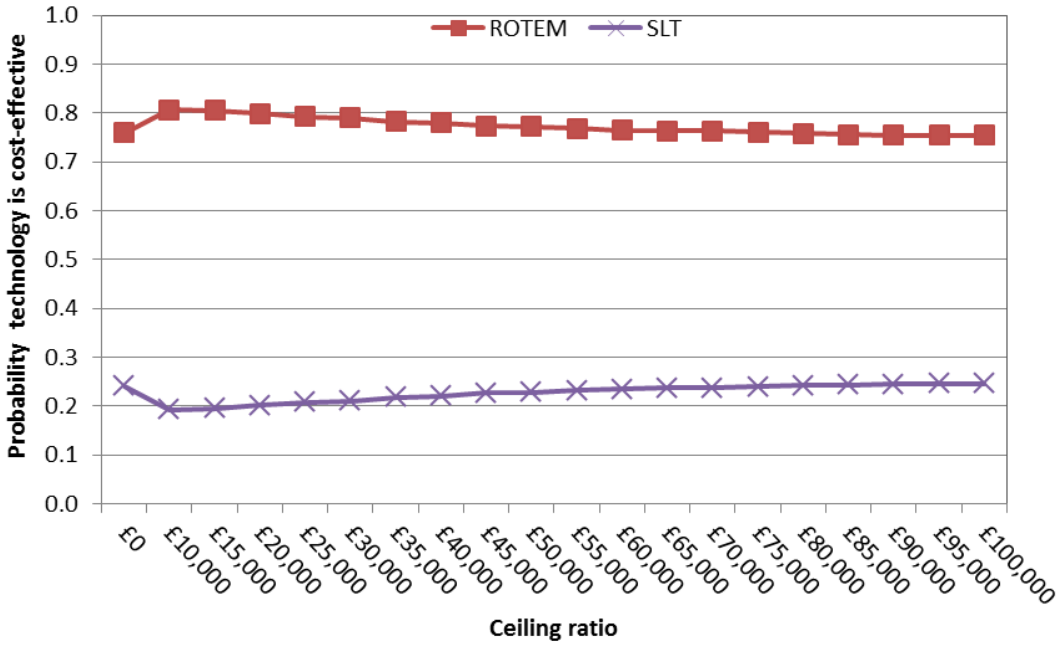


Figure 34: Cost-effectiveness acceptability curves: TEG vs. SLTs (cardiac surgery)

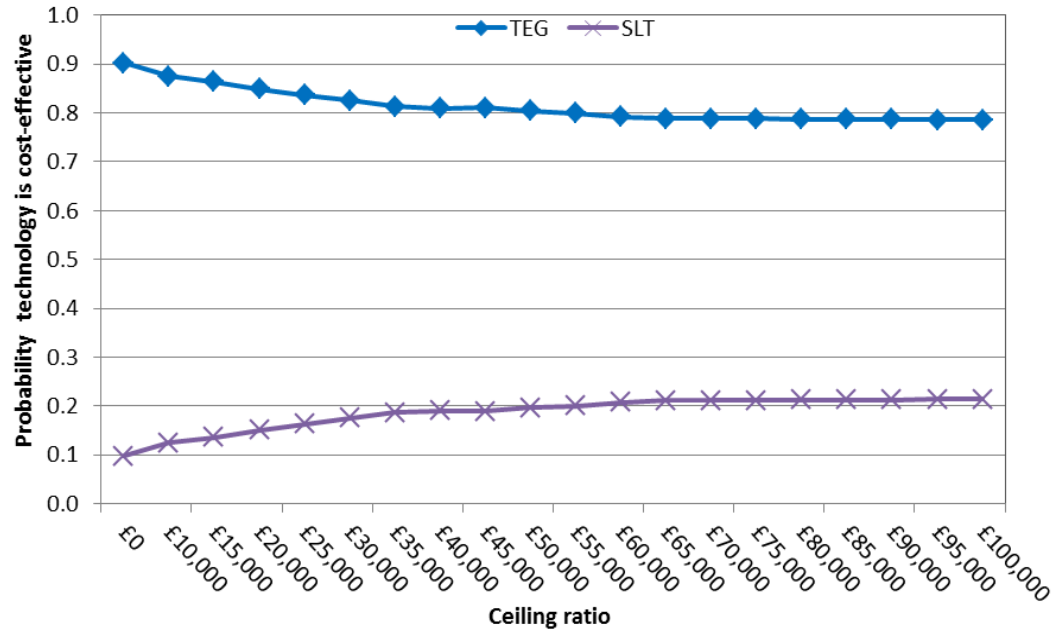
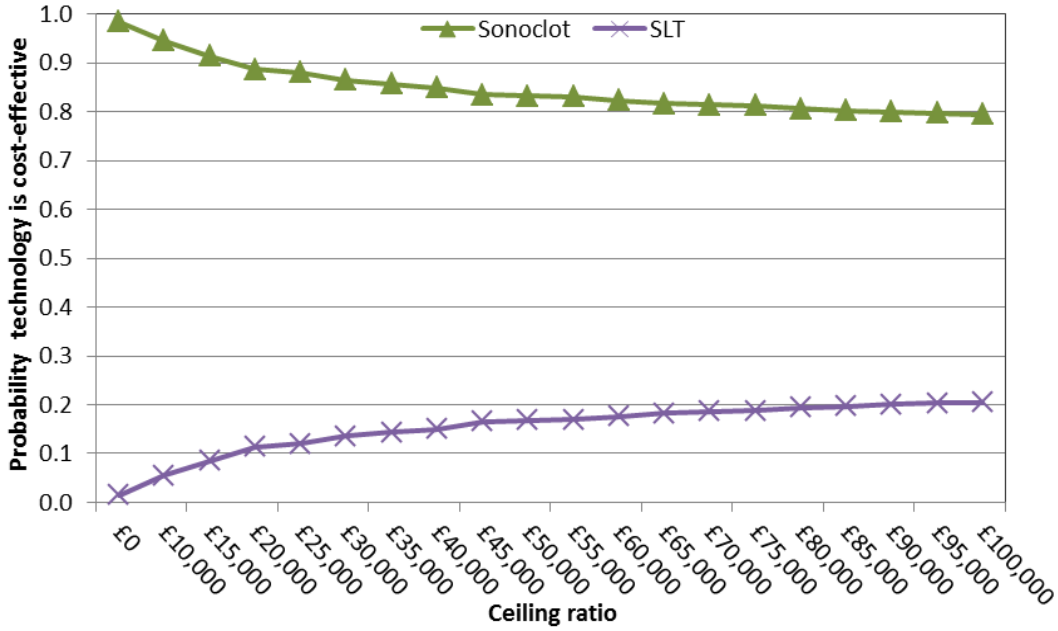


Figure 35: Cost-effectiveness acceptability curves: Sonoclot vs. SLTs (cardiac surgery)



4.5.3 Results of scenario analyses in cardiac surgery patients

All scenario analyses suggested that ROTEM remained cost saving (Table 40). CEACs for all analyses (not shown) were similar to those in Figure 33. The only exception was the number of tests run on each device per year. After reducing the number of tests run on each device from 500 to 200, ROTEM no longer dominated SLTs, and an ICER of £16,487 is found (Table 40 and Figure 36). At a cost-effectiveness threshold of £30,000 per QALY, the probability of cost-effectiveness for ROTEM was 0.62. As the cost-effectiveness threshold increased, the probability of cost-effectiveness for ROTEM converged to around 0.70. We estimated, using iterative analysis, that if all other parameters in the model remain unchanged, the costs of ROTEM and SLTs would be equal if 326 tests were run on ROTEM each year. At this level the ICER would be £0. If number of tests per year is reduced to 152 then the ICER is around £30,000.

Figure 36: Cost-effectiveness acceptability curves ROTEM vs. SLTs. Scenario based on 200 tests per year

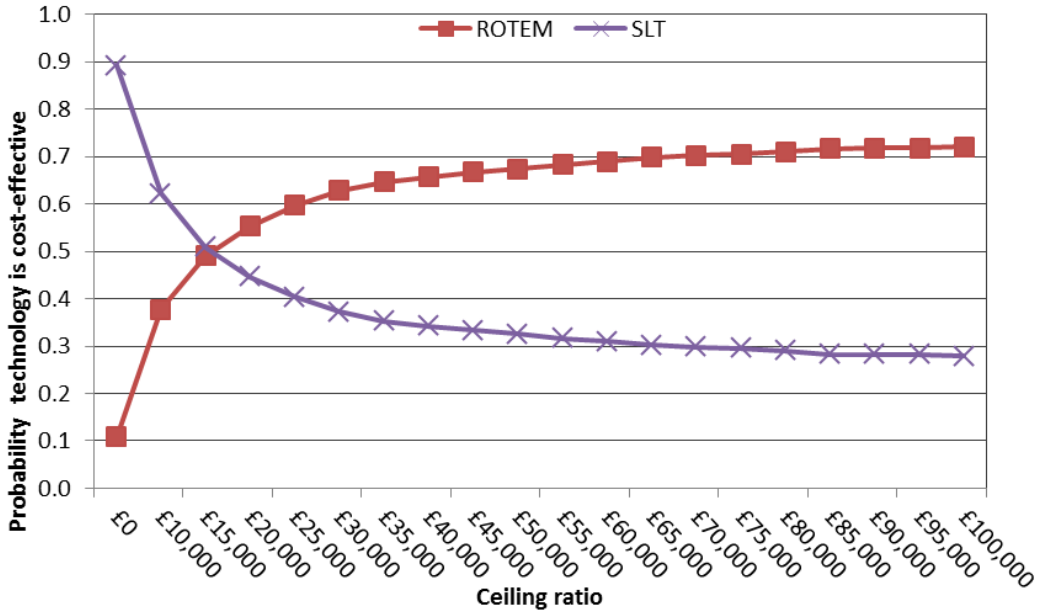


Table 40: Cardiac surgery model outputs - scenarios

Scenario	ROTEM LYs	ROTEM QALYs	ROTEM Cost	SLTs LYs	SLTs QALYs	SLTs Cost	Incr. QALY	Incr. Cost	ICER
Base case	0.9660	0.8773	£2,588	0.9624	0.8726	£2,631	0.0047	-£43	Dominance
5 years machine usage	0.9660	0.8773	£2,562	0.9624	0.8726	£2,631	0.0047	-£69	Dominance
200 tests per year	0.9660	0.8773	£2,708	0.9624	0.8726	£2,631	0.0047	£77	£13,679
Number of tests per patient decreased (1 no transfusion, 2 transfusion)	0.9660	0.8773	£2,519	0.9624	0.8726	£2,620	0.0047	-£101	Dominance
RR transfusion = 0.80 (lower limit)	0.9684	0.8804	£2,554	0.9624	0.8726	£2,631	0.0078	-£77	Dominance
RR transfusion = 0.96 (upper limit)	0.9636	0.8742	£2,621	0.9624	0.8762	£2,631	0.0016	-£10	Dominance
Lower probability of transfusion (0.429)	0.9733	0.8867	£2,486	0.9707	0.8833	£2,501	0.0034	-£14	Dominance
Higher probability of transfusion (0.890)	0.9527	0.8601	£2,773	0.9473	0.8530	£2,868	0.0070	-£95	Dominance
Equal volumes of blood products transfused	0.9660	0.8773	£2,612	0.9624	0.8726	£2,631	0.0047	-£18	Dominance
Calibrated one month mortality (0.0214)	0.9768	0.8870	£2,601	0.9747	0.8837	£2,646	0.0033	-£45	Dominance
Calibrated one month mortality (0.0642)	0.9552	0.8676	£2,574	0.9501	0.8616	£2,616	0.0060	-£41	Dominance

LY, life years; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

4.5.4 Base case results for model in patients with coagulopathy induced by trauma

The base case results from the analysis reported as LYs, QALYs and costs per technology for patients with coagulopathy induced by trauma are summarized in Table 41.

Table 41: Trauma model outputs (base case)

	SLTs	ROTEM	TEG	Sonoclot
LY	0.8343	0.8425	0.8425	0.8425
QALY	0.5644	0.5713	0.5713	0.5713
Cost	£7,661	£6,973	£6,940	£6,842
Incr. QALYs vs. SLTs		0.0069	0.0069	0.0069
Incr. costs vs. SLTs		-£688	-£721	-£818

LY, life years; QALY, quality-adjusted life year

All the VE technologies dominated SLTs. As with the cardiac surgery model, the cost of Sonoclot was lower than that of ROTEM or TEG and so this device was associated with greater cost-savings (£818) than TEG (£721) or ROTEM (£688). The total cost of testing per trauma patient for the four technologies was £203 for ROTEM, £170 for TEG, £130 for SLTs, and £73 for Sonoclot (£84). Other intermediate outcomes are summarised in Table 42.

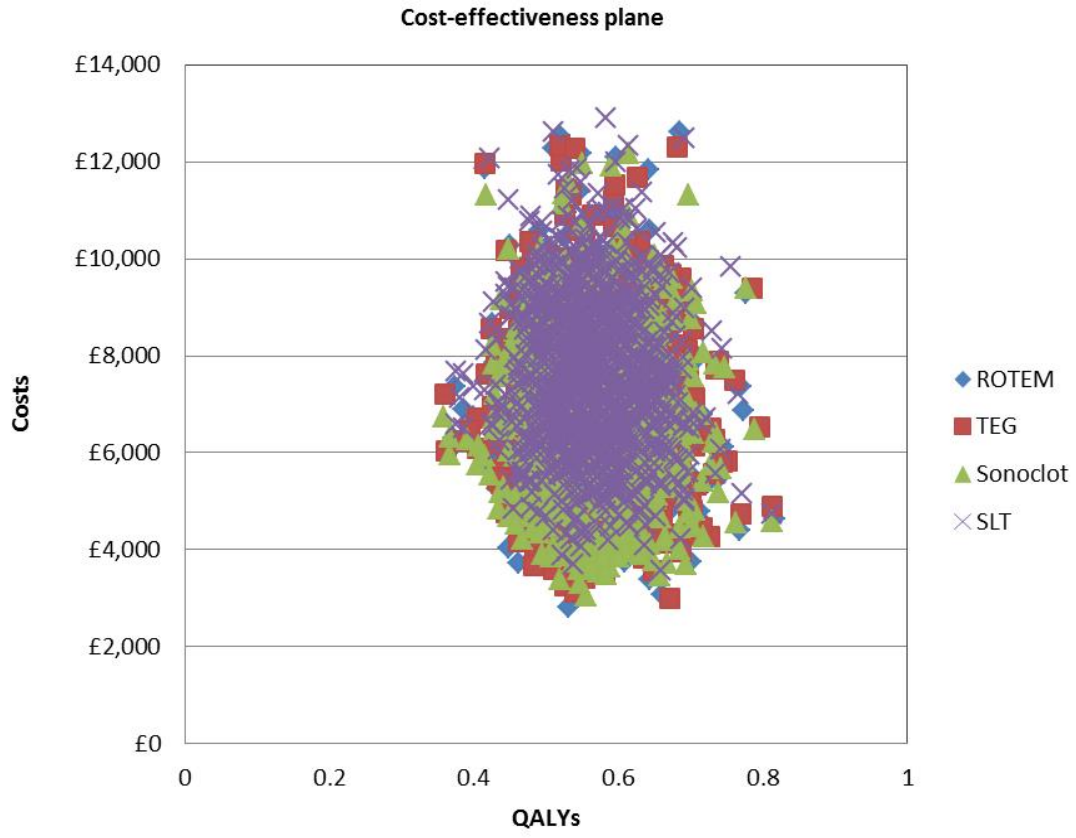
Table 42: Coagulopathy induced by trauma additional model outputs (base case)

Outcome	VE device	SLTs
One month mortality	14.9%	15.7%
One year mortality	17.3%	18.2%
Percentage trauma and/or transfusion complications	12.9%	14.6%
Percentage transfusion-related complications	0.02%	0.02%
Percentage transfusion-transmitted infections	0.00%	0.00%
Transfusion costs	£1,045	£1,491
Hospitalisation cots	£5,724	£6,040

4.5.5 Results of the probabilistic sensitivity analyses in patients with coagulopathy induced by trauma

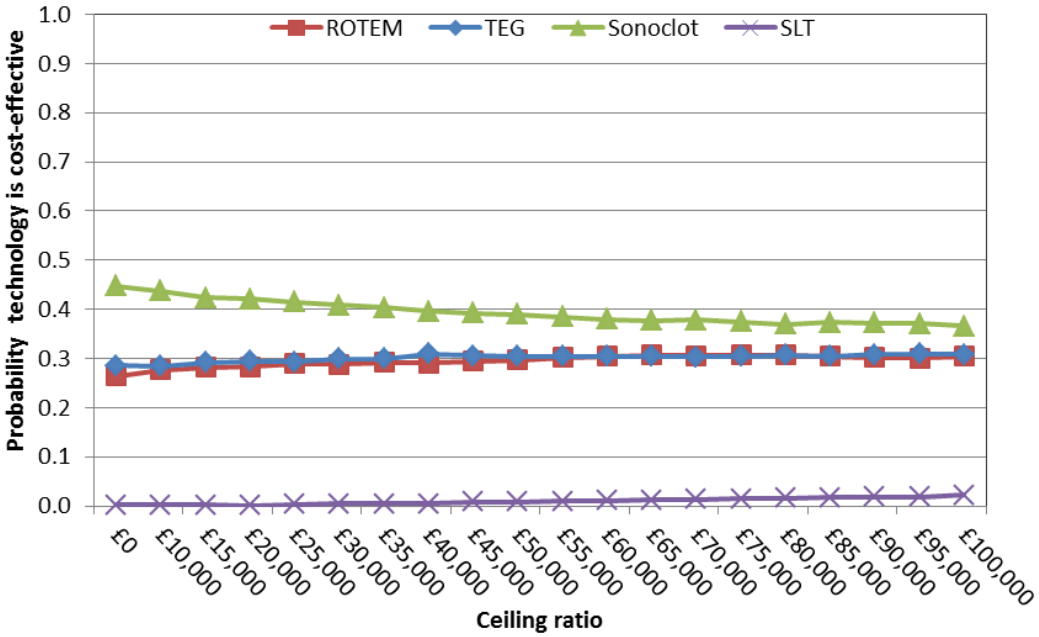
The impact of statistical uncertainties in the model was investigated in the PSA. The scatter plot of the PSA outcomes in the CE plane (Figure 37) did not show clear preference for any one of the VE technologies.

Figure 37: Cost-effectiveness plane with PSA outcomes for all technologies in trauma population



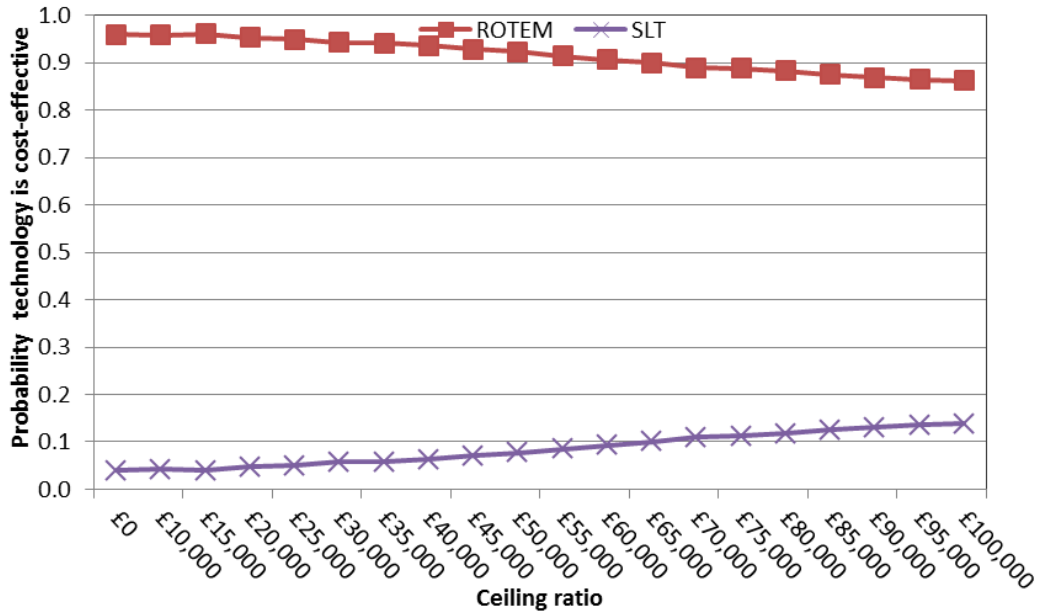
The cost-effectiveness acceptability curves (CEACs) for each strategy are shown in Figure 38. The PSA confirmed that SLTs was the strategy with the lowest probability of being cost-effective (0.022 at most). This is to be expected as the base-case scenario suggested that all three of the VE devices were both cheaper and more effective than SLTs. As with the cardiac surgery model, the CEACs for ROTEM, TEG and Sonoclot were very close together, which would be expected as the only difference between the three strategies assumed in the model was a difference in technology cost. At lower ceiling ratios, larger differences were observed as Sonoclot was the cheapest technology in our model.

Figure 38: Cost-effectiveness acceptability curves for all technologies in trauma population



A comparison of ROTEM with SLTs found a cost effectiveness probability equal to 0.96 for ROTEM for a ceiling ratio equal to £0 (see CEAC in Figure 39). As the ceiling ratio increased, the CEAC for ROTEM converged to 0.87. A similar pattern was observed for TEG and Sonoclot (CEACs not shown).

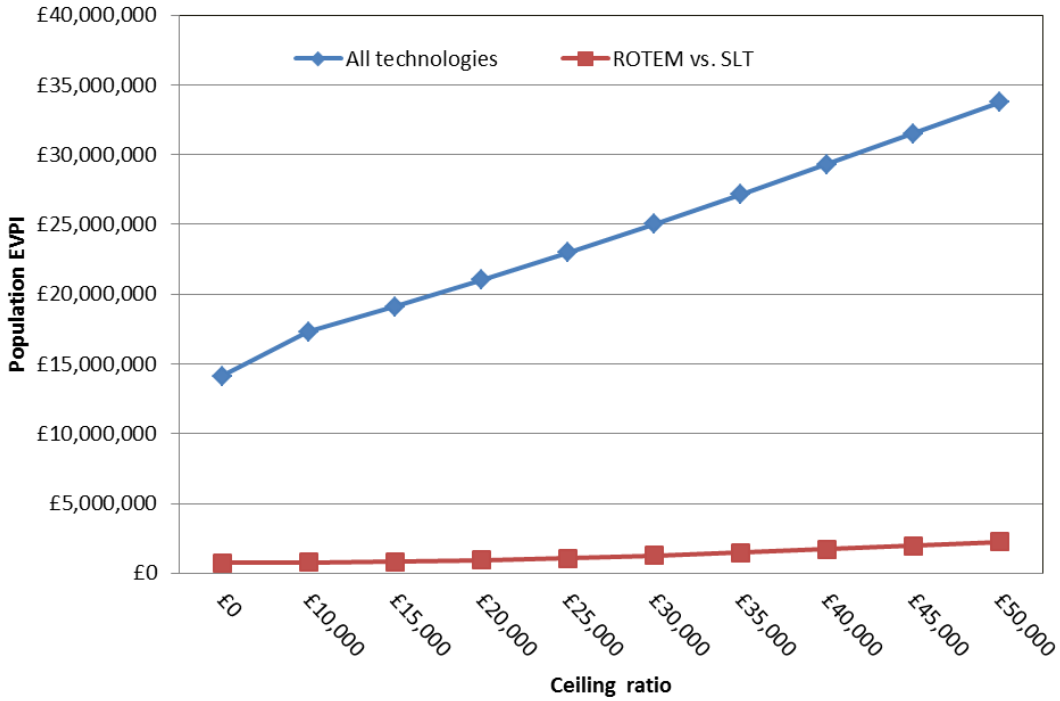
Figure 39: Cost-effectiveness acceptability curves: ROTEM vs. SLTs trauma population



4.5.6 Results of the EVPI analysis

The population EVPI results are presented in Figure 40. This shows that, at a cost-effectiveness threshold of £30,000 per QALY, the population EVPI when all four technologies are considered was £25,017,471, whilst the population EVPI when only ROTEM and SLTs were compared was more than 22 times lower at £1,263,131. This huge difference in EVPI is to be expected given that there is little uncertainty as to whether any one of the VE devices is superior to SLTs, but much uncertainty as to which of three devices is the optimal device. This is illustrated in the results of the PSA (Figures 37, 38 and 39).

Figure 40: Population EVPI in trauma model (all technologies and ROTEM vs. SLTs only)



4.5.7 Results of scenario analysis in patients with coagulopathy induced by trauma

All scenario analyses outlined in section 4.4.3 suggested that ROTEM remained cost saving (Table 43). CEACs and population EVPI curves for all analyses (not shown) were very similar to those shown in Figure 39 and 40. The iterative analysis performed to estimate the number of tests per year such that ROTEM would still be cost-saving suggested a break-even value of 81 tests per year; at this level the ICER was £0. When the number of tests per year was reduced to 65 the ICER was approximately £30,000.

Threshold analysis on the combined effect of a reduction in the percentage transfused and the blood volumes transfused, where we assumed that equal volumes of blood were transfused in the VE testing and SLTs groups, showed that at a RR of transfusion of 0.9822 or

more ROTEM was no longer cost-saving (ICER was zero). When the RR of transfusion increased to 0.9874, the ICER of ROTEM versus SLTs was £30,000.

Reducing baseline transfusion risk in the SLTs group, assuming that equal volumes of blood were transfused in the VE testing and SLTs group, showed that ROTEM was no longer cost-saving at a transfusion rate of 5%, and the ICER was £30,000 for a transfusion rate of 4%. This compares to a transfusion rate of 32% used in the base case analysis. We repeated the analysis but increased the RR of RBC transfusion from 0.88 to 0.95. For this analysis, the ICER was above £30,000 for a transfusion rate of 8% or less. After reducing the probability of complications related to trauma and/or transfusion, transfusion-related complications and transfusion related-infection to zero ROTEM remained cost-saving with a reduction in costs of £372.

Table 43: Trauma model outputs - scenarios

Scenario	ROTEM LYs	ROTEM QALYs	ROTEM Cost	SLTs LYs	SLTs QALYs	SLTs Cost	Incr. QALY	Incr. Cost	ICER
Base case	0.8425	0.5713	£6,973	0.8343	0.5644	£7,661	0.0069	-£688	Dominance
5 years machine usage	0.8425	0.5713	£6,929	0.8343	0.5644	£7,661	0.0069	-£731	Dominance
200 tests per year	0.8425	0.5713	£7,173	0.8343	0.5644	£7,661	0.0069	-£488	Dominance
Number of tests per patient decreased (2 no transfusion, 3 transfusion)	0.8425	0.5713	£6,862	0.8343	0.5644	£7,591	0.0069	-£729	Dominance
RR transfusion = 0.80 (lower limit)	0.8480	0.5759	£6,668	0.8343	0.5644	£7,661	0.0115	-£993	Dominance
RR transfusion = 0.96 (upper limit)	0.8370	0.5667	£7,278	0.8343	0.5644	£7,661	0.0023	-£383	Dominance
Lower probability of transfusion SLTs group (0.209)	0.8636	0.5889	£5,802	0.8582	0.5844	£6,224	0.0045	-£422	Dominance
Higher probability of transfusion SLTs group (0.444)	0.8194	0.5520	£8,259	0.8080	0.5425	£9,238	0.0095	-£979	Dominance
Equal volumes of blood products transfused	0.8425	0.5713	£7,240	0.8343	0.5644	£7,661	0.0069	-£421	Dominance
Probability experiencing ARDS (0.0775) and MOF (0.15)	0.8420	0.5731	£5,814	0.8337	0.5665	£6,344	0.0066	-£530	Dominance
Probability experiencing ARDS (0.2325) and MOF (0.45)	0.8430	0.5695	£8,132	0.8349	0.5624	£8,977	0.0071	-£846	Dominance
Calibrated one month mortality (0.1483)	0.8823	0.5969	£7,144	0.8794	0.5935	£7,855	0.0034	-£711	Dominance
Calibrated one month mortality (0.4450)	0.8028	0.5457	£6,801	0.7891	0.5354	£7,466	0.0104	-£664	Dominance

5. DISCUSSION

5.1 Statement of principal findings

5.1.1 Clinical effectiveness

All completed RCTs identified by our systematic review were conducted in patients undergoing cardiac surgery. Pooled estimates, derived from meta-analyses of dichotomous data, indicated that viscoelastic testing (TEG or ROTEM) was associated with significant reductions in the numbers of patients receiving red blood cell transfusion, platelet transfusion and FFP transfusion, compared with an SLTs-based strategy. There were no significant differences between the VE testing and SLTs in terms of factor VIIa transfusion, any blood product transfusion, or prothrombin transfusion; although data suggested a beneficial effect associated with VE testing, these outcomes were only evaluated in two studies.[35, 54] There was no apparent difference in the rates of fibrinogen transfusion between patients managed using VE testing and those managed using SLTs. Continuous data on blood product use, although inconsistently reported across studies, supported these findings; the only blood product that was not associated with a reduced volume of use in the VE testing group was fibrinogen. There were no apparent differences in clinical outcomes (re-operation, surgical cause of bleed on re-operation and mortality) between patients managed using VE testing and those managed using SLTs. There was some evidence of reduced bleeding[35, 50] and ICU stay[35] in the VE testing groups compared to SLTs groups, but this was not consistently reported across studies. There was no apparent difference in the length of hospital stay between groups. All meta-analyses, with the exception of factor VIIa transfusion, fibrinogen transfusion and prothrombin transfusion, which included only studies of ROTEM, included both studies of TEG and studies of ROTEM; summary estimates were similar when stratified by VE device, thus, there was no evidence to indicate a difference in effectiveness between the two devices. However, it should be noted that none of the included RCTs reported a direct comparison between TEG and ROTEM.

As none of the RCTs described above evaluated the Sonoclot VE test, we included lower levels of evidence for this device. Three prediction studies which evaluated Sonoclot were included in the review,[61, 62, 121] two of these also evaluated TEG and SLTs enabling a direct comparison between the two devices and between VE devices and SLTs.[61, 62] Data reported by the three studies in this group were not suitable for meta-analyses. All three studies used measures of bleeding as the reference standard or as the dependent variable in multivariable models. Positive results on conventional tests, TEG and Sonoclot were

generally associated with an increased risk of bleeding with no clear differences according to test. The limited available data do not suggest a significant difference in the ability of Sonoclot and TEG to predict bleeding, however, there were insufficient data to rule out a difference in the overall clinical effectiveness of these two devices. No studies reported any data comparing Sonoclot and ROTEM.

With the exception of one small, non-randomised controlled trial,[65] all studies conducted in trauma patients or women with PPH included in our systematic review were prediction studies. These studies either reported the predictive accuracy of different VE device parameters and/or SLTs with a reference standard consisting of clinical outcome or measure of transfusion requirements. These 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 product and massive transfusion) and death. There was no clear difference 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 hypocoaguable was the strongest predictor of any blood product transfusion. The presence of hyperfibrinolysis was the strongest predictor of mortality. No studies of the Sonoclot device were identified that fulfilled inclusion criteria for the either the trauma or PPH populations.

A previous Cochrane review, last up-dated in 2011, evaluated the effectiveness of transfusion strategies guided by VE devices in patients with severe bleeding.[21] This review concluded that there was no evidence that TEG or ROTEM improved morbidity or mortality and that, whilst transfusion strategies guided by VE devices appeared to reduce the amount of bleeding, the clinical implications of this remained uncertain.[21] Our systematic review differs from the Cochrane review on a number of key points. The Cochrane review was not restricted to any specific clinical groups. As a result it included one study of patients undergoing liver surgery, as well as eight RCTs of patients undergoing cardiac surgery, all of which were also included in our review. Our review represents an advance on the Cochrane review in that it identified three further RCTs conducted in patients undergoing cardiac surgery.[35, 53, 55] In addition, because the Cochrane review was restricted to RCTs, it did not include any studies assessing Sonoclot, whereas we were able to include some limited data on this device. A key difference in approach between our systematic review and the Cochrane review was in the handling of continuous data. The Cochrane review converted median values to means in order to allow pooled estimates to be generated, even though

the Cochrane handbook includes a specific recommendation that this approach should not be used; the Cochrane handbook (section 7.7.3.6) states that "Ranges are very unstable and, unlike other measures of variation, increase when the sample size increases. They describe the extremes of observed outcomes rather than the average variation. Ranges should not be used to estimate standard deviations. One common approach has been to make use of the fact that, with normally distributed data, 95% of values will lie within 2×SD either side of the mean. The SD may therefore be estimated to be approximately one quarter of the typical range of data values. This method is not robust and we recommend that it should not be used."[122] We do not believe that this approach can be justified and have therefore reported individual study results in forest plots and summarised findings in a narrative synthesis. Finally we noted two specific errors in data extraction in the Cochrane review. Firstly, the study by Westbrook et al was included in a meta-analysis of the proportion of patients undergoing surgical re-intervention for exploration of bleeding; data from this study had been erroneously extracted from the baseline characteristics table which reported the number of patients in each arm who were undergoing a repeat cardiac surgical intervention.[47] Secondly, meta-analyses of the proportion of patients undergoing FFP transfusion and the proportion of patients undergoing platelet transfusion, which were reported in the Cochrane review, included data derived from a graph reported in Nuttal et al.[50] The graph recorded the numbers of patients in each arm of the trial who received FFP only, platelets only, or platelets and FFP and/or cryoprecipitate;[50] this means that the graph cannot be used to derive either the total number of patients who received FFP or the total number who received platelets. The Cochrane review appeared to have extracted the numbers of patients receiving FFP and the numbers of patients receiving platelets as though these were the total numbers of patients receiving each blood product. As more patients in the control (SLTs) arm received multiple blood products,[50] this error had the effect of producing an RR which favoured the control group, a result which was in the opposite direction to all three of the other studies included in the meta-analysis.[21] A systematic review conducted for a Health Technology Assessment report, published in 2008, included studies of VE devices in cardiac surgery, but did not restrict inclusion by study design;[91] the two RCTs included in this assessment, which met the inclusion criteria for our review,[48, 50] were also included in both our review and the Cochrane review. The Health Technology Assessment report concluded that, assuming 200 tests per annum, the use of VE devices appeared to be clinical and cost-effective, reducing the need for inappropriate transfusions, decreasing blood product requirements and reducing the number of deaths, complications

and infections.[91] The results of our systematic review are consistent with previous reviews[21, 91] in that they suggest that the use of VE devices may be a clinically effective approach to the management haemostasis in patients undergoing cardiac surgery.

We are not aware of any previous systematic reviews assessing the effectiveness of VE devices for the management of patients with trauma-induced coagulopathy or PPH. A Cochrane Diagnostic Test Accuracy protocol has recently been published with the title 'Thromboelastography (TEG) and thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding.'[22]

5.1.2 Cost-effectiveness

We assessed the cost-effectiveness of VE devices in two key populations: patients undergoing cardiac surgery and patients with trauma acquired coagulopathies. There were insufficient data from the clinical effectiveness review to construct a model to assess the cost-effectiveness of VE devices in women with PPH. There were no data on the clinical effectiveness of Sonoclot; we therefore assumed that the TEG- and ROTEM-based estimates used in the model would also be applicable to Sonoclot; thus the same health effect estimates were used for all three VE devices.

The cost-effectiveness model suggested that VE testing is cost saving and more effective than standard laboratory testing in cardiac surgery patients. The per-patient cost-saving was slightly smaller for ROTEM (£43) than for TEG (£79) and Sonoclot (£132). This finding was entirely dependent on material costs which are slightly higher for ROTEM. When all uncertainties included in the model were taken into account, at a cost-effectiveness threshold of £30,000 per 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). At higher thresholds, probabilities converged to around 0.8 for all technologies. Scenario analyses were used to assess the potential impact of changing various input values for the model. In these scenarios the results remained largely unchanged. Only when the number of tests performed per machine per year was VE testing was no longer cost-saving when the number of test performed per machine was less than 326. When this number was 152, the ICER was around £30,000.

For the trauma population, the per-patient cost savings due to VE testing were more substantial, amounting to £688 for ROTEM compared to SLTs, £721 for TEG and £818 for Sonoclot. A comparison of the most expensive technology, ROTEM, with SLTs found a cost

effectiveness probability equal to 0.96 for ROTEM for a ceiling ratio of £0. As the ceiling ratio increased, this probability converged on 0.87. The increased cost savings observed for the trauma compared to the cardiac population were primarily due to the higher blood volumes that are transfused in the trauma patients. Scenario analyses constructed to assess the impact of various parameters showed similar results. Given the lack of effectiveness data in trauma patients, the current results should only be regarded as indicative of the potential cost-effectiveness of VE testing in trauma patients.

5.2 Strengths and limitations of assessment

5.2.1 Clinical effectiveness

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts to identify unpublished studies. Because of the known difficulties in identifying test accuracy studies using study design-related search terms,[123] and potential need to include non-randomised controlled trials and prediction modelling studies, search strategies were developed to maximise sensitivity at the expense of reduced specificity. Thus, large numbers of citations were identified and screened, many of which did not meet the inclusion criteria of the review.

The possibility of publication bias remains a potential problem for all systematic reviews. Publication bias was not formally assessed in this review because, for RCTs, the number of studies was too small for such an assessment to be meaningful and, for prediction studies, there is no reliable method of assessing publication bias. However, our search strategy included a variety of routes to identify unpublished studies and resulted in the inclusion of a number of conference abstracts and the identification of one ongoing RCT. Considerations may differ for systematic reviews of test accuracy studies. It is relatively simple to define a positive result for studies of treatment, e.g. a significant difference between the treatment and control groups which favours treatment. This is not the case for test accuracy studies, which measure agreement between index test and reference standard, or prediction modelling studies, which measure the extent to which a particular test result is predictive of outcome(s) once other potentially predictive variables have been adjusted for. However, it would seem likely that studies finding greater agreement between the index test and reference standard (high estimates of sensitivity and specificity), or that the index test is a significant, independent predictor of outcome will be published more often.

Clear inclusion criteria were specified in the protocol for this review and the one protocol modification that occurred during the assessment has been documented in the methods section of this report (section 3.1.2 Table 6) and in the protocol section (Appendix 7). The eligibility of studies for inclusion is therefore transparent. In addition, we have provided specific reasons for excluding all of the studies considered potentially relevant at initial citation screening (Appendix 4). The review process followed recommended methods to minimise the potential for error and/or bias;[37] studies were independently screened for inclusion by two reviewers and data extraction and quality assessment were done by one reviewer and checked by a second (MW and PW). Any disagreements were resolved by consensus.

Studies included in this review were assessed for risk of bias using published tools appropriate to study design and/or the type of data extracted. Studies which provided data on the accuracy of VE testing to predict clinical outcomes and/or transfusion requirements were assessed using the QUADAS-2 tool.[45] QUADAS-2 is structured into four key domains covering participant selection, index test, reference standard, and the flow of patients through the study (including timing of tests). Each domain is rated for risk of bias (low, high, or unclear); the participant selection, index test and reference standard domain are also, separately rated for concerns regarding the applicability of the study to the review question (low, high, or unclear). Although designed specifically for this type of study, QUADAS-2 was also considered the best option for assessment of the prediction modelling studies. This was because the prediction modelling studies included in this assessment are unusual in that they generally present the results of several multivariable models for each outcome/dependent variable; a separate model is needed for each VE testing parameter or SLTs, as parameters and tests frequently measure the same or similar coagulation properties and cannot be considered independent. In addition, studies aimed to assess the ability of individual VE testing parameters or SLTs to predict the occurrence of very short term outcomes. For these reasons, the studies were considered to have more in common with diagnostic accuracy studies than with classic prognostic/prediction modelling studies. RCTs were assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials.[44] The results of the risk of bias and QUADAS-2 assessments are reported, in full, for all included studies (Appendix 3) and in summary in the results (sections 3.2.1.2, 3.2.4.2 and 3.2.6.2, Tables 8, 16 and 18, and Figures 5 and 17).

Although we identified 11 RCTs which compared the effectiveness of VE testing with an SLTs-based approach for the management of haemostasis in patients undergoing cardiac surgery, the potential to produce summary effect estimates was limited by the wide variety of outcomes reported and a lack of standardisation of the way in which these were measured. No summary estimates of continuous data (e.g. duration of hospital or ICU stay, or volume of blood products transfused) were possible as the majority of these data were appropriately reported as medians with range or IQR. Pooling only those studies which reported continuous outcomes as mean ± standard deviation would be un-representative of the group as a whole and would be likely to result in greater weight being given to studies which reported data as mean ± standard deviation without consideration of whether or not these data were normally distributed.

At the start of this assessment the role of VE testing in the care pathway was considered to be unclear; it could be used either as an *add-on* to, or *replacement* for SLTs. Three of the RCTs included in our systematic review compared the effectiveness of VE testing combined with SLTs (two studies using TEG[50, 51] and one using ROTEM[55]) to SLTs alone, i.e. these studies provided data on the *add-on* value of VE testing. For all outcomes assessed, the results of these studies were consistent with those of studies which compared VE testing alone with SLTs. These findings indicate performing SLTs in addition to VE testing is unlikely to give further benefit over that provided by VE testing alone. VE testing can therefore be regarded as a *replacement* for SLTs.

All of the studies conducted in trauma patients or women with PPH included in this review have considerable limitations in respect of their ability to address the overall aim of assessing the clinical effectiveness of VE devices for assessment of haemostasis in these patient groups. With the exception of one small, non-randomised controlled trial,[65] all studies in these patient groups were prediction studies, which either reported the predictive accuracy of different SLTs and/or VE device parameters where the reference standard was a clinical outcome or measure of transfusion requirements, or the results of prediction models where each test or parameter was modelled separately, as described above, with clinical outcome or transfusion requirement as the dependent variable. Where the reference standard or dependent variable in the model was a measure of transfusion requirements, it is not possible for studies to be rated as both 'low risk of bias' and 'low applicability concerns' with respect to the reference standard. This is because, in order for such a study to reflect clinical practice and be rated 'as low applicability concerns,' the decision to

transfuse would need to be made with knowledge of the test results, however, there is then an inevitable risk of incorporation bias leading to a rating of 'high risk of bias.' The need for a separate model for each VE testing parameter or SLTs, as described above, creates a further problem in that prediction studies cannot adequately assess the overall predictive performance of VE devices compared to SLTs as they would be used in practice. Finally, any type of prediction study is sub-optimal in that these studies can only ever provide an indication of the ability of VE testing or SLTs to predict clinical outcomes or transfusion requirements. These studies cannot provide information on how interventions and subsequent clinical outcomes may differ according to whether a point-of-care VE testing or SLTs-based strategy is used; these data can only be derived from controlled trials.

5.2.2 Cost-effectiveness

Our study can be regarded as an important update of the cardiac surgery aspect of the evaluation undertaken for NHS Scotland,[12] and is the first cost-effectiveness analysis of VE devices in trauma patients. It was informed by an up to date high quality systematic review that included a number of RCTs published since the NHS Scotland evaluation. We also added a probabilistic sensitivity analysis to the model in order to assess the simultaneous impact of the various uncertainties. A further strength of our model is that we included longer term mortality data than were included in previous evaluations which only included mortality up to one month. Our cardiac surgery model used data based on a large study by Murphy et al[15] which showed that the effects of transfusion on mortality continued up to and beyond one year. Similar data were not available for the trauma population. We therefore had to make some assumptions for this population. We extrapolated the ratio of mortality in transfused to non-transfused patients found in a study which provided this information up to hospital discharge to one year follow-up and then applied this data to the overall mortality rate for this period from another study in trauma patients. It would be expected that a RR at hospital discharge is too high at one year; the study in cardiac patients showed that the difference in mortality between transfused and non-transfused patients decreased over time. Scenario analyses showed that changing the ratio of mortality in transfused versus non-transfused did not affect results. We might reasonably assume, given that mortality is low between one month and one year, that this would also be the case if we had made similar changes to one year mortality.

The main outcome used in the economic models was the proportion of patients at risk of RBC transfusion. From this, it was possible to impute other effects such as units of blood

transfused, adverse events, complications, changes to quality of life, and overall survival. This is consistent with the only cost-effectiveness study in the field, the Scottish HTA report.[12 91] It is also consistent with the study by Davies et al.[92], on which the Scottish HTA was based, where costs and effects of methods of minimising perioperative allogeneic RBC transfusion were assessed for cardiac patients as a subpopulation. In order to estimate the mortality for VE testing, we assumed that any mortality benefit from VE testing resulted only from fewer patients receiving an RBC transfusion. It should be noted that, differential mortality between VE and SLTs could result from reasons other than differential rates of transfusion, such as reduced volume transfused or differential transfusion of other blood products e.g. FFP and platelets. However, we validated the method of only using mortality data associated with RBC transfusion by comparing the estimated RR of mortality (VE versus SLTs) with the results of the systematic review. This showed a RR of mortality for ROTEM and TEG of 0.90 which was almost identical to the RR estimated in the systematic review (0.87).

A strength of our study was the detailed consultation with manufacturers regarding the costs of each VE device. This was important as each device is available with different numbers of channels and runs different assays which are not directly comparable between devices. We decided which assays and number of tests to model based on the combination of assays and numbers of tests used in the trials so that the costs included in the model correspond to the source of the effectiveness data. However, it is unclear whether the results found in the trials would also be applicable to different assay combinations and numbers of tests used in clinical practice. We found that varying the number of tests, which could also be a proxy for assay combinations, did not alter the conclusions in terms of cost-effectiveness. The length of time that a machine is used for and the average number of tests run per machine per year influences the material cost of a test. However, scenario analysis showed that the number of tests had to be very low before VE testing was no longer cost-effective.

A major limitation of both models was the lack of data on the effectiveness of the Sonoclot device. None of the RCTs included in our review assessed this device. As the only difference in the models was the costs of the devices, and Sonoclot was the cheapest device, Sonoclot was the most likely to be cost-effective. However, this should be interpreted with extreme caution due to the lack of evidence.

There were no data on the clinical effectiveness of any of the VE devices in trauma patients. We therefore assumed equivalent clinical effectiveness to the cardiac surgery population. Clinical experts were consulted regarding their views on the validity of this assumption. They indicated that patients undergoing (elective) cardiac surgery are likely to differ from trauma patients which may affect the relative effectiveness of the VE devices. Specifically, it was noted that trauma patients are likely to have higher blood loss and therefore have greater blood transfusion requirements. We were able to estimate the baseline risk of RBC transfusion in trauma patients from the predictive accuracy studies included in the systematic review, but these studies could not inform the RR of transfusion in patients who were and were not tested with a VE device. There was general agreement that an assumption of equivalent clinical effectiveness in terms of the RR of RBC transfusion between the cardiac surgery and trauma populations was a reasonable assumption given the lack of other reliable data. Although this assumption may be clinically problematic, scenario analysis indicated that if the RR of RBC transfusion was as high as 0.98 VE testing would still be cost-saving in this population. This compares to a value of 0.88 derived from the systematic review of cardiac surgery patients and used in the base case analysis.

The one year time horizon used by our model could be regarded as a further limitation. However, we would argue that extrapolation over a longer time horizon is unnecessary. This is because at one year all VE devices where shown to be both more effective and cheaper than SLTs and with little uncertainty (probabilities of at least 0.68 of being cost effective); effectiveness would only increase and costs would be likely to decrease over a lifetime. The expected increase in effectiveness is based on the avoidance of transfusions supported by Murphy et al (2007),[15] who showed transfusion continues to increase mortality beyond one year. In addition, long term complications such as stroke, which are likely to be avoided by fewer transfusions, would also imply lower cost.

Where possible we used cardiac surgery and trauma specific utility and cost estimates in our models. However, for some of the short term utility parameters we were unable to find trauma specific data. We made the conservative assumption that during the first month trauma patients would have the same utility of cardiac surgery patients. Given that many trauma patients spent quite some time on an ICU, often being ventilated, the true utility is likely to be lower. In addition, we had no good data on costs of a hospital stay once trauma patients leave the ICU. This is related to the fact that these patients may go to a wide variety of departments, depending on the type of trauma (e.g. brain trauma or mainly

orthopaedic trauma). We therefore made the assumption that costs per day would also be the same as for cardiac patients; it was unclear whether this was likely to be an over- or underestimation. However, given that these utilities and costs only apply to a very short time period they are unlikely to have influenced whether VE testing was cost-effective.

We conducted an EVPI analysis for the trauma population as we felt there less evidence and therefore greater uncertainty for this population. This showed that it may be worth spending money on further primary research given that, when comparing all four technologies (ROTEM, TEG, Sonoclot, and SLTs) the population EVPI was around £25 million for an ICER of £30,000. However, the EVPI should be interpreted with caution given that the value when comparing only a single VE device (ROTEM) with SLTs was 22 times lower at just over £1.25 million. This would suggest that there is relatively little uncertainty as to whether ROTEM would be cost-effective in comparison to SLTs. This is inconsistent with the evidence, as the data to inform the trauma model was derived from trials conducted in cardiac surgery patients. The full uncertainty associated with this limitation, as well as other assumptions, may not have been captured by this analysis.

5.3 Uncertainties

5.3.1 Clinical effectiveness

The results of our systematic review are consistent with previous reviews[21, 91] in that they suggest that the use of VE devices may be a clinically effective approach to the management haemostasis in patients undergoing cardiac surgery. Our results indicate that the use of VE devices may be associated with a reduction in transfusion rates, however, whether or not this reduction represents a decrease in inappropriate transfusions and whether it translates into changes in important clinical outcomes (e.g. duration of ICU/hospital stay, morbidity and mortality) remains less clear. Studies included in our review provided some indication that the use of VE devices may be associated with a reduction in the duration of ICU stay. However, data were not considered suitable for meta-analyses and only one study showed a statistically significant decrease in the length of ICU stay for patients managed using an algorithm based on a VE device compared to those managed using an algorithm based on SLTs; this study restricted inclusion to patients who were bleeding from capillary beds or had blood loss >250mL/h or 50mL/10 min.[35]

The existence of a link between the use of VE devices and clinical outcome is even more uncertain where these devices are used in the management of trauma patients or women with PPH. Studies in trauma patients or women with PPH included in our review consistently

indicated a link between a positive test result (VE device of SLTs) and transfusion outcomes or mortality. However, we did not identify any completed RCTs in these patient groups, although we did identify one ongoing RCT (recruitment has reached 105 participants out of a target of 120) and additional information on this study was provided by the authors in the form of the study protocol.[64] As described in the 'strengths and limitations' section above, prediction studies cannot provide information on how interventions and subsequent clinical outcomes may differ according to whether a point-of-care VE testing or SLTs-based strategy is used. Further, in contrast to the RCTs conducted in patients undergoing cardiac surgery, cannot provide data on how transfusion rates may differ according to whether the decision to transfuse is based on the use of a VE device or on SLTs. Our systematic review included one small (n=50) controlled clinical trial which compared the effectiveness of an 'institutional massive transfusion protocol' (details not reported) to a TEG-guided protocol (details not reported) for the management of trauma patients.[65] This study was only published as a conference abstract and no numerical data were reported, however, the results section stated that there were no statistically significant differences, or trends towards differences, between groups in mortality, ARDS, SIRS, multi-organ failure, sepsis, cardiovascular events, or duration of hospitalisation; a trend towards reduced pneumonia, reduced days on ventilation and reduced duration of ICU stay in the TEG-guided group was reported.[65] We did not include studies of VE devices with a historical control group in our review, as it is not possible to attribute any observed differences between groups in these studies solely to the introduction of the VE device. One such study, from a German level I trauma centre, reported reductions in the annual use of transfusion products from 2002 to 2010 (PRBC -33%, FFP -79%, platelet concentrates -65%), following the introduction of an algorithm for coagulation management in trauma patients based on point-of-care ROTEM combined with calculated goal-directed therapy with fibrinogen and prothrombin complex concentrate; the number of study participants was unclear, but approximately 250 trauma patients per year were treated in the emergency room.[124] The study protocol provided by the authors of the ongoing trial[64] also reported the results of a before and after study, conducted in their institution. Although much smaller than the German study, this study had the advantage of assessing two immediately consecutive populations, before (n=34) and after (n=34) r-TEG was added to the institution's massive transfusion protocol; unlike the German study, this implies that r-TEG was the only change to management strategy. Results from this study indicated that patients managed with a protocol that included r-TEG had more effective resuscitation than those managed using the standard massive transfusion

protocol; median improvement in lactate from presentation to six hours was 2% for the standard massive transfusion protocol and 44% for the standard massive transfusion protocol + r-TEG, and median improvement in pH from presentation to six hours was 1% for the standard massive transfusion protocol and 2% for the standard massive transfusion protocol + r-TEG.[64] Rates of transfusion of all blood products were consistently less after the introduction of r-TEG, but differences did not reach statistical significance.[64] Finally, mortality fell from 65% to 29% (p=0.04) after the introduction of r-TEG.[64] Taken together, the results of these studies could be considered to indicate that further investigation of the clinical utility of VE devices in trauma patients and women with PPH is warranted.

There is currently a lack of adequate information on the potential role of VE devices in the early detection of hyperfibrinolysis and any consequent effects on clinical outcomes and this is an area which may particularly warrant further investigation. Data from the CRASH-2 trial indicate that greatest survival benefit from anti-fibrinolytic therapy in trauma patients is seen with very early (<1 hour after injury) intervention.[125] There are also some published data indicating that the risk of death from bleeding increases at levels of clot lysis below the 7.5% (at 30 minutes post-maximum clot strength) generally regarded as normal. [126, 127] The ROTEM FIBTEM assay and the TEG functional fibrinogen assay use a reagent specific for the fibrin polymerisation process, which decline more rapidly than fibrinogen levels as measured in the laboratory.[128] This adds the potential to detect the pathology at an earlier stage in its evolution to the time gained from using point-of-care testing compared to laboratory-based testing.[129, 130] A small observational study, which did not meet the criteria for inclusion in our systematic review, reported that primary fibrinolysis, as diagnosed by TEG, occurred <1 hour post-injury in 18% of a series of severely injured patients requiring massive transfusion, and was associated with increased blood product requirements, coagulopathy, and haemorrhage-related death. VE devices therefore have the potential to provide a sufficiently timely and sensitive method of detecting fibrinolysis to enable optimally effective intervention. Fibrinogen is also thought to play a major role in the evolution of PPH and can be an early predictor of severity,[128] however, data in this population are even more sparse than for trauma. Neither of the two PPH studies included in review[84, 85] reported hyperfibrinolysis as an outcome, although one did evaluate the ROTEM FIBTEM assay.[85]

The extent to which VE devices may be considered to be clinically equivalent remains uncertain. As outlined in the background section of this report (section 2.2, Tables 2-4) the range of parameters measured differs between the three devices included in this

assessment (TEG, ROTEM and Sonoclot). Despite these differences the available data provide no strong evidence of a difference in clinical effectiveness between TEG and ROTEM, however, it should be noted that there is no strong evidence that the devices are equivalent as there were no studies providing a direct comparison between the two devices. Data on Sonoclot were very sparse, limited to three studies in the cardiac surgery population;[61, 62, 121] data from two of these studies, which provided a direct comparison with TEG, did not suggest a significant difference in the ability of the two devices to predict bleeding.[61, 62]

Issues of training requirements and implementation are outside the scope of this assessment, however, a 2010 published report of studies undertaken by the UK National External Quality Assessment Scheme (NEQAS) for Blood Coagulation on the use of TEG and ROTEM devices in operating theatres has indicated that there may be some areas of concern.[131] The published article reported the results of a series of four quality assurance studies, with up to 18 TEG users and 10 ROTEM users involved in testing two samples per study. The samples were normal plasmas, factor VIII or XI deficient samples, or normal plasmas spiked with heparin. The precision of the tests varied greatly for both devices, with coefficients of variances ranging from 7.1 to 39.9% for TEG and 7.0 to 83.6% for ROTEM.[131] Some centres returned results that were judged to be sufficiently different from those obtained by other participants to predict alterations in patient management decisions.[131] Based on these findings it would seem that staff training requirements are likely to be an important consideration for the implementation of these devices. A UK study published in 2009 compared users' experience of TEG and ROTEM over a one week period; the study included seven consultant anaesthetists, one consultant haematologist, one associate specialist anaesthetist and two senior trainee anaesthetists, all of whom were trained by the manufacturers.[132] The summary of the opinions of study participants suggested that the TEG training programme was preferred and that better service support was provided for this device.[132] However, this is a very small study and may not be reflective of current experience in the NHS.

5.3.2 Cost-effectiveness

Substantial uncertainties around the cost-effectiveness of VE devices for the identification and management of coagulopathies remain, particularly with respect to the trauma population. The main uncertainties in the cost-effectiveness analyses follow directly from those described for the review of clinical effectiveness. Uncertainties are caused by lack of clinical effectiveness data for Sonoclot in the cardiac surgery population and by a lack of

clinical effectiveness data for any of the VE devices in the trauma and PPH populations. Once the results of the ongoing RCT, and any future RCTS, in the trauma population become available, our trauma model can readily be updated.

Other uncertainties pertain particularly to the trauma patients. As well as a requirement for data on the clinical effectiveness of VE testing in this population, this also includes data on trauma specific costs and utilities. The influence of RBC transfusion on longer term mortality (beyond in hospital mortality) in trauma patients is also unclear.

6. CONCLUSIONS

6.1 Implications for service provision

For patients undergoing cardiac surgery, there was evidence from RCTs that viscoelastic testing (TEG or ROTEM) may be effective in reducing the numbers of patients receiving red blood cell transfusion, platelet transfusion and FFP transfusion, compared with an SLTs-based management strategy. Trial data also indicated that VE testing may be associated with a reduction in the number of patients receiving factor VIIa transfusion, any blood product transfusion, or prothrombin transfusion, compared to SLTs, but for these outcomes differences did not reach statistical significance. There was no apparent difference in the rates of fibrinogen transfusion between patients managed using VE testing and those managed using SLTs. The available data did not support an improvement in clinical outcomes (re-operation, surgical cause of bleed on re-operation and mortality), or length of hospital stay, for patients managed using VE testing compared with those managed using SLTs. There was some evidence of reduced bleeding and reduced length of ICU stay for patients managed with VE testing compared to those managed using SLTs, but this was not consistently reported across studies. There was no evidence to indicate a difference in clinical effectiveness between the TEG and ROTEM devices, on any measure. No data were identified on the clinical effectiveness of Sonoclot. The limited available data on the ability of Sonoclot and TEG to predict bleeding (as opposed to clinical effectiveness) did not indicate a significant difference between the two devices. There was no evidence to indicate that performing SLTs in addition to VE testing gave any further benefit over that provided by VE testing alone. VE testing can therefore be regarded as a *replacement* for SLTs.

The base case results of the cost-effectiveness analysis indicated that VE testing is cost saving and more effective than SLTs, in patients undergoing cardiac surgery. The per-patient cost-saving was slightly smaller for ROTEM (£43) than for TEG (£79) and Sonoclot (£132). This finding was entirely dependent on material costs which were slightly higher for ROTEM. Scenario analyses, used to assess the potential impact of varying the way in which VE devices were used, did not alter the overall conclusion that VE testing is cost-saving.

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 product and massive transfusion) and death. This implies a potential for improved intervention based on VE testing, however, there were no data showing that the use of VE

devices could change outcomes. There were no clear differences between ROTEM, TEG or SLTs. No studies of the Sonoclot device were identified that fulfilled inclusion criteria for the either the trauma or PPH populations.

Cost-effectiveness analyses indicated that the per-patient cost savings due to VE testing were more substantial for the trauma population than for patients undergoing cardiac surgery. This finding was primarily due to the much higher blood volumes that are transfused in trauma patients. As with the cardiac surgery population, scenario analyses did not alter the overall conclusion that VE testing is cost-saving. However, given the potentially problematic assumption that the clinical effectiveness of VE testing is the same in trauma patients as it in cardiac surgery patients, these results should only be regarded as indicative of the potential cost-effectiveness of VE testing in trauma patients.

6.2 Suggested research priorities

The clinical- and cost-effectiveness of VE testing in trauma patients and women with PPH remains uncertain. Clinical trials are urgently required in these populations, in order to assess the effectiveness of VE testing compared with management based on SLTs. Outcomes assessed should include, but may not be limited to, bleeding outcomes, transfusion rates, volumes transfused, duration of hospital/ICU stay and mortality. The trauma model included in this assessment could readily be adapted to utilise data from such trials. It is also likely that the model structure could be adapted for women with PPH, as there is no reason to believe that effect categories would be substantially different.

No studies providing data on the clinical effectiveness of Sonoclot were identified in any of the populations considered by this assessment (patients undergoing cardiac surgery, trauma patients and women with PPH). Therefore, if the adoption of Sonoclot were to be considered, trials of this device would have high priority.

This assessment found no evidence to support any difference in clinical effectiveness between the three VE devices considered (ROTEM, TEG and Sonoclot). However, there was no strong evidence of equivalent clinical effectiveness between the devices for any of the populations considered (patients undergoing cardiac surgery, trauma patients and women with PPH). This was because no trial reported a direct comparison between VE devices. Trials comparing more than one VE device with SLTs would therefore be particularly useful.

None of the studies included in the clinical effectiveness review reported follow-up of participants to assess the potential effects of different testing regimens on longer term

transfusion-related complications and mortality. Future trials should include longer term follow-up, beyond the initial hospital episode, with a view to informing improved cost-effectiveness modelling.

7. REFERENCES

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APPENDIX 1: LITERATURE SEARCH STRATEGIES

a. Clinical effectiveness searches

RCT searches

Embase (OvidSP): 1974-2013/09/30
Searched 1.10.13

1 Random$.tw. or clinical trial$.mp. or exp health care quality/ (3200870)
2 animal/ (1889848)
3 animal experiment/ (1717916)
4 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5819410)
5 or/2-4 (5819410)
6 exp human/ (14983864)
7 human experiment/ (316823)
8 or/6-7 (14985305)
9 5 not (5 and 8) (4638337)
10 1 not 9 (3047951)
11 thromboelastography/ (4910)
12 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw,dv. (5750)
13 (thromb$ adj2 elastogra$).ti,ab,ot,hw,dv. (45)
14 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw,dv. (2)
15 TEG.ti,ab,ot,dv. (1769)
16 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw,dv. (993)
17 whole blood h?emosta$ system$.ti,ab,ot,hw,dv. (2)
18 whole blood h?emo-sta$ system$.ti,ab,ot,hw,dv. (0)
19 (ROTEM$ or ROTEG).ti,ab,ot,hw,dv. (782)
20 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw,dv. (778)
21 (thromb$ adj2 elastom$).ti,ab,ot,hw,dv. (6)
22 (thromb$ adj2 elasto?m$).ti,ab,ot,hw,dv. (6)
23 (Sonoclot or sono-clot).ti,ab,ot,hw,dv. (158)
24 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw,dv. (17)
25 or/11-24 (7601)
26 10 and 25 (1163)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE (best sens). J Med Libr Assoc 2006;94(1):41-7.

Medline (OvidSP): 1946-2013/09/wk 3
Searched 27.9.13

1 randomized controlled trial.pt. or "randomized controlled trials as topic"/ (482025)
2 controlled clinical trial.pt. (89224)
3 random$.ti,ot. (111186)
4 placebo.ab. (155394)

5 drug therapy.fs. (1753686)
6 random$.ab. (658632)
7 trial.ab. (299080)
8 groups.ab. (1263660)
9 or/1-8 (3415580)
10 animals/ not (animals/ and humans/) (3941632)
11 9 not 10 (2911473)
12 Thrombelastography/ (3421)
13 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw. (4232)
14 (thromb$ adj2 elastogra$).ti,ab,ot,hw. (24)
15 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw. (0)
16 TEG.ti,ab,ot. (933)
17 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw. (459)
18 whole blood h?emosta$ system$.ti,ab,ot,hw. (1)
19 whole blood h?emo-sta$ system$.ti,ab,ot,hw. (0)
20 (ROTEM$ or ROTEG).ti,ab,ot,hw. (260)
21 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw. (360)
22 (thromb$ adj2 elastom$).ti,ab,ot,hw. (3)
23 (thromb$ adj2 elasto?m$).ti,ab,ot,hw. (3)
24 (Sonoclot or sono-clot).ti,ab,ot,hw. (108)
25 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw. (12)
26 or/12-25 (5052)
27 11 and 26 (1051)

Trials filter based on:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Medline In-Process & Other Non-Indexed Citations (OvidSP): up to 26.9.13
Medline Daily Update (OvidSP): up to 26.9.13
Searched 27.9.13

1 randomized controlled trial.pt. or "randomized controlled trials as topic"/ (864)
2 controlled clinical trial.pt. (38)
3 random$.ti,ot. (10417)
4 placebo.ab. (6835)
5 drug therapy.fs. (1577)
6 random$.ab. (52321)
7 trial.ab. (18616)
8 groups.ab. (94330)
9 or/1-8 (143469)
10 animals/ not (animals/ and humans/) (1886)
11 9 not 10 (143057)
12 Thrombelastography/ (4)

13 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw. (114)
14 (thromb$ adj2 elastogra$).ti,ab,ot,hw. (0)
15 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw. (0)
16 TEG.ti,ab,ot. (119)
17 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw. (8)
18 whole blood h?emosta$ system$.ti,ab,ot,hw. (0)
19 whole blood h?emo-sta$ system$.ti,ab,ot,hw. (0)
20 (ROTEM$ or ROTEG).ti,ab,ot,hw. (28)
21 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw. (36)
22 (thromb$ adj2 elastom$).ti,ab,ot,hw. (0)
23 (thromb$ adj2 elasto?m$).ti,ab,ot,hw. (0)
24 (Sonoclot or sono-clot).ti,ab,ot,hw. (5)
25 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw. (1)
26 or/12-25 (211)
27 11 and 26 (53)

Trials filter based on:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Biosis Previews (Web of Knowledge): 1956-2013/09/26
Searched 27.9.13

1 2,539 TS=(thrombo-elastogra* or thrombelastogra* or thrombelasto-gra* or thromboelastogra*)
2 426 TS=(thromb$ NEAR elastogra*)
3 1 TS=(thromb* NEAR elasto-gra*)
4 638 TS=(TEG NEAR/10 thromb*)
5 452 TS=(haemoscope* or hemoscope* or haemonetics or hemonectics)
6 812 TS=(whole blood hemosta* system*)
7 191 TS=(whole blood haemosta* system*)
8 278 TS=(ROTEM* or ROTEG*)
9 302 TS=(thrombo-elastomet* or thrombelastomet* or thromboelastomet*)
10 11 TS=(thromb* NEAR/2 elastom*)
11 0 TS=(thromb* NEAR/2 elasto-m*)
12 99 TS=(Sonoclot or sono-clot)
13 17 TS=((viscoelastic or visco-elastic) NEAR/3 (detection or coagulation) NEAR/3 (system* or process or test or tests or analyz* or analys* or assay* or device* or measurement*))
 # 14 4,142 #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

Science Citation Index (SCI) (Web of Science): 1970-2013/09/26
Conference Proceedings Citation Index (CPCI-S) (Web of Science): 1990-2013/09/26
Searched 27.9.13

1 2,373 TS=(thrombo-elastogra* or thrombelastogra* or thrombelasto-gra* or thromboelastogra*)
2 26 TS=(thromb$ NEAR elastogra*)
3 0 TS=(thromb* NEAR elasto-gra*)
4 639 TS=(TEG NEAR/10 thromb*)
5 321 TS=(haemoscope* or hemoscope* or haemonetics or hemonectics)
6 285 TS=(whole blood hemosta* system*)
7 91 TS=(whole blood haemosta* system*)
8 403 TS=(ROTEM* or ROTEG*)
9 458 TS=(thrombo-elastomet* or thrombelastomet* or thromboelastomet*)
10 10 TS=(thromb* NEAR/2 elastom*)
11 0 TS=(thromb* NEAR/2 elasto-m*)
12 126 TS=(Sonoclot or sono-clot)
13 29 TS=((viscoelastic or visco-elastic) NEAR/3 (detection or coagulation) NEAR/3 (system* or process or test or tests or analyz* or analys* or assay* or device* or measurement*))
14 3,407 #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 10. October/2013
Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 10. October/2013
Database of Abstracts of Reviews of Effects (DARE) (Wiley): Issue 4. October/2013
Health Technology Assessment Database (HTA) (Wiley): Issue 4. October/2013
Searched 5.11.13

#1 MeSH descriptor: [Thrombelastography] this term only 151
#2 (thrombo-elastogra* or thrombelastogra* or thrombelasto-gra* or thromboelastogra*):ti,ab,kw 252
#3 (thromb* near/2 elastogra*):ti,ab,kw 1
#4 (thromb* near/2 elasto-gra*):ti,ab,kw 0
#5 TEG:ti,ab 87
#6 (haemoscope* or hemoscope* or haemonetics or hemonectics):ti,ab,kw 52
#7 whole blood h?emosta* system*.ti,ab,kw 0
#8 whole blood h?emo-sta* system*:ti,ab,kw 0
#9 (ROTEM* or ROTEG):ti,ab,kw 22
#10 (thrombo-elastomet* or thrombelastomet* or thromboelastomet*):ti,ab,kw 27
#11 (thromb* near/2 elastom*):ti,ab,kw 4
#12 (thromb* near/2 elasto?m*):ti,ab,kw 0
#13 (Sonoclot or sono-clot):ti,ab,kw 12
#14 ((viscoelastic or visco-elastic) near/3 (detection or coagulation) near/2 (system* or process or test or tests or analyz* or analys* or assay* or device* or measurement*)):ti,ab,kw 0
#15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 326

CDSR search retrieved 3 references.
CENTRAL search retrieved 313 references.
DARE search retrieved 3 references.
HTA search retrieved 3 references.

NIH Clinical Trials.gov (Internet): up to 2013/09/27
http://clinicaltrials.gov/ct2/search
Searched 27.9.13

Search terms	Records
Interventions: (thrombo-elasto* OR thrombelasto* OR thromb* elasto* OR thromboelasto* OR TEG OR haemoscope* OR hemoscope* OR haemonetics OR hemonectics OR ROTEM* OR ROTEG OR Sonoclot OR sono-clot)	46
Interventions: ("whole blood" AND (hemosta* OR haemosta* OR hemo-sta* OR haemo-sta*) AND system*)	0
Interventions: ((viscoelastic OR visco-elastic) AND (detection OR coagulation) AND (system* OR process OR test OR tests OR analyz* OR analys* OR assay* OR device* OR measurement*))	1
Total	**47**

mRCT – metaRegister of Controlled Trials (Internet): up to 2013/09/27
http://www.controlled-trials.com/
Searched 27.9.13

Search terms	Records
(thrombo-elasto* OR thrombelasto* OR thromb* elasto* OR thromboelast* OR TEG OR haemoscope* OR hemoscope* OR haemonetics OR hemonectics OR ROTEM* OR ROTEG OR Sonoclot OR sono-clot)	**69**
("whole blood" AND (hemosta* OR haemosta* OR hemo-sta* OR haemo-sta*) AND system*)	**8**
((viscoelastic OR visco-elastic) AND (detection OR coagulation) AND (system* OR process OR test OR tests OR analyz* OR analys* OR assay* OR device* OR measurement*))	**3**
Total	**80**

WHO International Clinical Trials Registry Platform (ICTRP) (Internet): up to 2013/09/26
http://www.who.int/ictrp/en/
Searched 26.9.13

Title	Records
(thrombo-elasto* OR thrombelasto* OR thromb* elasto* OR thromboelasto* OR TEG)	57
(haemoscope* OR hemoscope* OR haemonetics OR hemonectics)	0
(ROTEM* OR ROTEG OR Sonoclot OR sono-clot)	31
("whole blood" AND (hemosta* OR haemosta* OR hemo-sta* OR haemo-sta*) AND system*)	67
(viscoelastic AND detection AND system*)	0

(viscoelastic AND detection AND process)	0
(viscoelastic AND detection AND test)	0
(viscoelastic AND detection AND tests)	0
(viscoelastic AND detection AND analyz*)	0
(viscoelastic AND detection AND analys*)	0
(viscoelastic AND detection AND assay*)	0
(viscoelastic AND detection AND device*)	0
(viscoelastic AND detection AND measurement*)	0
(visco-elastic AND detection AND system*)	0
(visco-elastic AND detection AND process)	0
(visco-elastic AND detection AND test)	0
(visco-elastic AND detection AND tests)	0
(visco-elastic AND detection AND analyz*)	0
(visco-elastic AND detection AND analys*)	0
(visco-elastic AND detection AND assay*)	0
(visco-elastic AND detection AND device*)	0
(visco-elastic AND detection AND measurement*)	0
(viscoelastic AND coagulation AND system*)	0
(viscoelastic AND coagulation AND process)	0
(viscoelastic AND coagulation AND test)	0
(viscoelastic AND coagulation AND tests)	0
(viscoelastic AND coagulation AND analyz*)	0
(viscoelastic AND coagulation AND analys*)	0
(viscoelastic AND coagulation AND assay*)	0
(viscoelastic AND coagulation AND device*)	0
(viscoelastic AND coagulation AND measurement*)	0
(visco-elastic AND coagulation AND system*)	0
(visco-elastic AND coagulation AND process)	0
(visco-elastic AND coagulation AND test)	0
(visco-elastic AND coagulation AND tests)	0
(visco-elastic AND coagulation AND analyz*)	0
(visco-elastic AND coagulation AND analys*)	0
(visco-elastic AND coagulation AND assay*)	0
(visco-elastic AND coagulation AND device*)	0
(visco-elastic AND coagulation AND measurement*)	0
Totals	**155**

Aggressive Research Intelligence Facility (ARIF) (Internet): 1996-2013/09/27
http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/databases/index.aspx
Searched 27.9.13

Search terms	All indexed fields	All Non-Indexed Text fields	Records
Thromboelastograph*	0	1	1
thrombo-elastograph*	0	0	0
Thrombelastograph*	0	0	0
thrombelasto-graph*	0	0	0
Thrombo elastograph*	0	0	0
Thromboelasto graph*	0	0	0

TEG	0	ERROR message	0
Haemoscope*	0	0	0
Hemoscope*	0	0	0
Haemonetics	0	0	0
Hemonectics	0	0	0
ROTEM*	0	0	0
ROTEG	0	0/1 -> irrelevant (Osteop**roteg**erin)	0
thrombo-elastomet*	0	0	0
Thrombelastomet*	0	0	0
Thromboelastomet*	0	0	0
Thrombo elastomet*	0	0	0
Sonoclot	0	0	0
sono-clot	0	0	0
viscoelastic	0	1	1
visco-elastic	0	0	0
Total	**0**	**2/3**	**2**

NIHR Health Technology Assessment Programme (HTA) (Internet): up to 2013/9/27
Searched 27.9.13

Browsed with ROTEM terms.
N = 0

International Prospective Register of Systematic Reviews (PROSPERO) (Internet): up to 2013/09/27
http://www.crd.york.ac.uk/prospero/search.asp
Searched 27.9.13

Search in All fields

Search terms	**Records**
thromboelastography	0
thrombo-elastography	0
Thrombelastography	0
thrombelasto-graphy	0
Thrombo elastography	0
Thromboelasto graphy	0
TEG	2
Haemoscope	0
hemoscope	0
Haemonetics	0
Hemonectics	0
ROTEM	1
ROTEG	0
thrombo-elastometry	0
Thrombelastometry	0

Thromboelastometry	0
Thrombo elastometry	0
Sonoclot	1
sono-clot	1
viscoelastic	1
visco-elastic	1
Total	**7**
Total after deduplication	**2**

International Network of Agencies for Health Technology Assessment (INAHTA): up to 2013/09/27
http://www.inahta.org/
Searched 27.9.13

Search Term	Results
Thromboelastog*	0
Thrombelastog*	0
Thrombelastomet*	0
Thromboelastomet*	0
Rotem	0
Roteg*	0
Sonoclot	0
Haemoscope*	0
Hemoscope*	0
Haemonetics	0
Hemonetics	0
viscoelastic	0
Total	**0**

LILACS (Latin American and Caribbean Health Sciences): up to 2013/09/26
http://regional.bvsalud.org/php/index.php?lang=en
Searched 27.9.13

Terms	Records
(thrombelastogra$ or thromboelastogra$ or tromboelastogra$ or thrombo-elastogra$ or trombo-elastogra$ or MH:E01.370.225.625.115.830 or MH:E05.200.625.115.830 or TEG or haemoscop$ or hemoscop$ or haemonetics or hemonetics or Rotem$ or Roteg or Sonoclot or sono-clot or thromboelastomet$ or thrombelastomet$ or thrombo-elastomet$ or tromboelastomet$ or trombo-elastomet$)	61
((viscoelastic or visco-elastic) AND (detection OR coagulation) AND (system$ OR process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$))	0
("whole blood" AND ((haemosta$ or hemosta$) AND (system$)))	1
Total	**62**

Spanish and portuguese translations of MeSH terms identified using the DECS (Health Sciences Descriptors) thesaurus:
http://decs.bvs.br/I/homepagei.htm

MEDION (Internet): up to 2013/09/27
http://www.mediondatabase.nl/
Searched 27.9.13

Searched in 'Whole Database'

Search Term in 'Topics'	**Results**
Thromboelastograph	0
Thrombelastograph	0
Thromboelastography	0
Thrombelastography	0
Thrombelastomet*	0
Thromboelastomet*	0
Rotem	0
Roteg*	0
Sonoclot	0
Haemoscope*	0
Hemoscope*	0
Haemonetics	0
Hemonetics	0
viscoelastic	0
Total	**0**

Post-partum haemorrhage searches

Embase (OvidSP): 1974-2013/09/30
Searched 1.10.13
1 animal/ (1889848)
2 animal experiment/ (1717916)
3 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5819410)
4 or/1-3 (5819410)
5 exp human/ (14983864)
6 human experiment/ (316823)
7 or/5-6 (14985305)
8 4 not (4 and 7) (4638337)
9 thromboelastography/ (4910)
10 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw,dv. (5750)
11 (thromb$ adj2 elastogra$).ti,ab,ot,hw,dv. (45)
12 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw,dv. (2)
13 TEG.ti,ab,ot,dv. (1769)

14 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw,dv. (993)
15 whole blood h?emosta$ system$.ti,ab,ot,hw,dv. (2)
16 whole blood h?emo-sta$ system$.ti,ab,ot,hw,dv. (0)
17 (ROTEM$ or ROTEG).ti,ab,ot,hw,dv. (782)
18 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw,dv. (778)
19 (thromb$ adj2 elastom$).ti,ab,ot,hw,dv. (6)
20 (thromb$ adj2 elasto?m$).ti,ab,ot,hw,dv. (6)
21 (Sonoclot or sono-clot).ti,ab,ot,hw,dv. (158)
22 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw,dv. (17)
23 or/9-22 (7601)
24 23 not 8 (6789)
25 exp obstetric haemorrhage/ (9038)
26 exp labor complication/ (131568)
27 obstetric emergency/ (316)
28 labor stage 3/ (568)
29 exp instrumental delivery/ (64245)
30 exp childbirth/ (47045)
31 exp pregnancy disorder/ (421205)
32 exp pregnancy/ (620411)
33 exp obstetric procedure/ (335160)
34 ((postpartum or post-partum or "after birth" or afterbirth or "third stage" or "3rd stage" or "final stage" or birth or childbirth or labour or labor or perinatal$ or per-natal$ or Caesar$ or cesar$ or c-section or obstetric$ or placenta$ or parturi$ or puerpal$ or puerper$ or intra-partum$ or intrapartum$ or preeclamp$ or pre-eclamp$ or eclamp$) adj3 (haemorr$ or hemorr$ or bleed$ or blood$)).ti,ab,ot,hw. (21313)
35 (lochia or cruenta or purulenta or Lochiorrhea$ or ((postpartum or post-partum) adj3 fluxus)).ti,ab,ot. (609)
36 or/25-35 (942425)
37 24 and 36 (455)

Medline (OvidSP): 1946-2013/09/Wk3
Searched 1.10.13
1 animals/ not (animals/ and humans/) (3941632)
2 Thrombelastography/ (3421)
3 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw. (4232)
4 (thromb$ adj2 elastogra$).ti,ab,ot,hw. (24)
5 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw. (0)
6 TEG.ti,ab,ot. (933)
7 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw. (459)
8 whole blood h?emosta$ system$.ti,ab,ot,hw. (1)
9 whole blood h?emo-sta$ system$.ti,ab,ot,hw. (0)
10 (ROTEM$ or ROTEG).ti,ab,ot,hw. (260)
11 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw. (360)
12 (thromb$ adj2 elastom$).ti,ab,ot,hw. (3)
13 (thromb$ adj2 elasto?m$).ti,ab,ot,hw. (3)
14 (Sonoclot or sono-clot).ti,ab,ot,hw. (108)

15 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw. (12)
16 or/2-15 (5052)
17 16 not 1 (4427)
18 exp Labor, Obstetric/ (38786)
19 exp delivery, Obstetric/ (60793)
20 exp Obstetric Labor Complications/ (51037)
21 exp pregnancy/ (714444)
22 ((postpartum or post-partum or "after birth" or afterbirth or "third stage" or "3rd stage" or "final stage" or birth or childbirth or labour or labor or perinatal$ or per-natal$ or Caesar$ or cesar$ or c-section or obstetric$ or placenta$ or parturi$ or puerpal$ or puerper$ or intra-partum$ or intrapartum$ or preeclamp$ or pre-eclamp$ or eclamp$) adj3 (haemorr$ or hemorr$ or bleed$ or blood$)).ti,ab,ot,hw. (13888)
23 (lochia or cruenta or purulenta or Lochiorrhea$ or ((postpartum or post-partum) adj3 fluxus)).ti,ab,ot. (530)
24 or/18-23 (727283)
25 17 and 24 (254)

Medline In Process & Other Non-Indexed Citations (OvidSP): up to 2013/09/30
Medline Daily Update (OvidSP): up to 2013/09/30
Searched 1.10.13
1 animals/ not (animals/ and humans/) (2696)
2 Thrombelastography/ (6)
3 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw. (118)
4 (thromb$ adj2 elastogra$).ti,ab,ot,hw. (0)
5 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw. (0)
6 TEG.ti,ab,ot. (122)
7 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw. (8)
8 whole blood h?emosta$ system$.ti,ab,ot,hw. (0)
9 whole blood h?emo-sta$ system$.ti,ab,ot,hw. (0)
10 (ROTEM$ or ROTEG).ti,ab,ot,hw. (29)
11 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw. (37)
12 (thromb$ adj2 elastom$).ti,ab,ot,hw. (0)
13 (thromb$ adj2 elasto?m$).ti,ab,ot,hw. (0)
14 (Sonoclot or sono-clot).ti,ab,ot,hw. (5)
15 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw. (1)
16 or/2-15 (215)
17 16 not 1 (214)
18 exp Labor, Obstetric/ (19)
19 exp delivery, Obstetric/ (46)
20 exp Obstetric Labor Complications/ (45)
21 exp pregnancy/ (487)
22 ((postpartum or post-partum or "after birth" or afterbirth or "third stage" or "3rd stage" or "final stage" or birth or childbirth or labour or labor or perinatal$ or per-natal$ or Caesar$ or cesar$ or c-section or obstetric$ or placenta$ or parturi$ or puerpal$ or puerper$ or intra-partum$ or intrapartum$ or preeclamp$ or pre-eclamp$ or eclamp$) adj3 (haemorr$ or hemorr$ or bleed$ or blood$)).ti,ab,ot,hw. (743)

23 (lochia or cruenta or purulenta or Lochiorrhea$ or ((postpartum or post-partum) adj3 fluxus)).ti,ab,ot. (15)
24 or/18-23 (1242)
25 17 and 24 (2)

Trauma searches

Embase (OvidSP): 1974-2013/9/30
Searched 1.10.13
1 animal/ (1889848)
2 animal experiment/ (1717916)
3 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5819410)
4 or/1-3 (5819410)
5 exp human/ (14983864)
6 human experiment/ (316823)
7 or/5-6 (14985305)
8 4 not (4 and 7) (4638337)
9 thromboelastography/ (4910)
10 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw,dv. (5750)
11 (thromb$ adj2 elastogra$).ti,ab,ot,hw,dv. (45)
12 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw,dv. (2)
13 TEG.ti,ab,ot,dv. (1769)
14 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw,dv. (993)
15 whole blood h?emosta$ system$.ti,ab,ot,hw,dv. (2)
16 whole blood h?emo-sta$ system$.ti,ab,ot,hw,dv. (0)
17 (ROTEM$ or ROTEG).ti,ab,ot,hw,dv. (782)
18 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw,dv. (778)
19 (thromb$ adj2 elastom$).ti,ab,ot,hw,dv. (6)
20 (thromb$ adj2 elasto?m$).ti,ab,ot,hw,dv. (6)
21 (Sonoclot or sono-clot).ti,ab,ot,hw,dv. (158)
22 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw,dv. (17)
23 or/9-22 (7601)
24 23 not 8 (6789)
25 exp injury/ (1492208)
26 wound/ or bite wound/ or gunshot injury/ or knife cut/ or missile wound/ or stab wound/ (32224)
27 exp blunt trauma/ (20182)
28 multiple trauma/ (10361)
29 exp rupture/ (76335)
30 exp traumatic shock/ (5045)
31 exp accident/ (143084)
32 seatbelt/ or traffic safety/ (6329)
33 seatbelt injury/ (446)

34 traffic/ or bicycle/ or exp car driving/ or dangerous goods transport/ or motorized transport/ or patient transport/ or traffic accident/ or traffic noise/ or exp traffic safety/ (91387)
35 exp motor vehicle/ (27510)
36 emergency/ (34524)
37 exp emergency treatment/ (161412)
38 emergency health service/ (66643)
39 intensive care/ (83265)
40 emergency medicine/ (25513)
41 exp traumatology/ (7325)
42 paramedical personnel/ or paramedical profession/ (13231)
43 rescue personnel/ (5523)
44 emergency nursing/ (4949)
45 emergency physician/ or emergency/ or emergency ward/ or emergency nurse practitioner/ (88148)
46 (Trauma$ or accident$ or crash or crashed or crashes or collision$ or collide$ or smash or pile-up).ti,ab,ot. (430019)
47 ((Car$ or motorcar$ or cycle$ or cycling or bicycl$ or bike$ or motorbike$ or motorcycle$ or motor-bike$ or motor-cycle$ or vehic$ or motor$ or traffic or road or pedestrian$ or lorry or lorries or truck or trucks or van or vans or pick-up$) adj8 (injur$ or accident$ or crash$ or collide$ or collision$ or smash$ or bump$ or shunt$ or trauma$ or crush$ or compress$ or impact$)).ti,ab,ot. (167496)
48 (multiple?trauma$ or poly?trauma$ or multiple?injur$ or complex?injur$).ti,ab,ot,hw. (4371)
49 (wound$ or injur$ or fractur$ or burn or burns or burned or scald$ or stab$ or shot$ or shoot$ or lacerat$ or gunshot$).ti,ab,ot. (1816547)
50 (dogbite$ or animalbite$ or bite$ or bitten).ti,ab,ot. (28226)
51 (splenosis or splenoses).ti,ab,ot. (556)
52 (h?emothorax or h?emo-thorax or pneumothorax or pneumo-thorax).ti,ab,ot,hw. (33993)
53 (h?emoperiton$ or h?emo-periton$ or free?fluid or intraperiton$ or retroperiton$ or intra-periton$ or retro-periton$).ti,ab,ot,hw. (230854)
54 ((spleen or splenic or liver or hepatic or abdomen or abdominal or stomach or thorax or thoracic or chest or chests) adj5 (trauma$ or injur$ or ruptur$ or bleed$ or crush$ or penetrate$ or perforat$ or blunt or force or compress$ or tear$)).ti,ab,ot,hw. (135217)
55 mechanical trauma$.ti,ab,ot. (1571)
56 ((thermal or blast or crush or avulsion or compress$) adj2 injur$).ti,ab. (11436)
57 (open fractur$ or compound fractur$).ti,ab,ot,hw. (6437)
58 (ATLS or ALS or BLS or EMST).ti,ab,ot. (56748)
59 Advanced life support.ti,ab,ot. (1991)
60 basic life support.ab,ti,ot. (1623)
61 ((emergency or trauma or critical or casualty) adj3 (care or treat$ or unit or units or department$)).ab,ti,ot. (122678)
62 ("emergency room" or "emergency rooms" or er or ers or "emergency department" or "emergency departments" or "casualty department" or "casualty departments" or "accident and emergency" or "accidents and emergencies" or "A&E" or "A & E").ti,ab,ot. (175800)
63 ((trauma adj3 system$) or (life adj3 support$) or (primary adj3 survey$) or (golden adj3 hour) or (first adj3 aid$)).ab,ti,ot. (24907)
64 (management adj3 trauma).ab,ti,ot. (3484)
65 ((prehospital or pre-hospital or preclinical or pre-clinical) adj3 (care or support or treat$)).ab,ti,ot. (5298)

66 (para-medic$ or paramedic$).ab,ti,ot,hw. (20661)
67 ((emergency or critical or trauma or triage or ambulanc$) adj3 (doctor$ or crew$ or staff or team$ or technician$ or worker$ or nurs$ or specialist$)).ab,ti,ot. (17195)
68 ((head or crani$ or cerebr$ or capitis or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj5 (injur$ or trauma$ or damag$ or wound$ or fracture$ or contusion$)).ab,ti,ot. (141857)
69 ((head or crani$ or cerebr$ or brain$ or intra-cran$ or inter-cran$) adj5 (haematoma$ or hematoma$ or haemorrhag$ or hemorrhag$ or bleed$ or pressure)).ti,ab,ot. (40456)
70 ("diffuse axonal injury" or "diffuse axonal injuries").ti,ab,ot. (1109)
71 ((brain or cerebral or intracranial or intra-cranial) adj3 (oedema or edema or swell$)).ab,ti,ot. (15857)
72 ((spine$ or spinal) adj3 (fracture$ or injury$ or break$ or broke$)).ti,ab,ot. (36019)
73 ((head or crani$ or cerebr$ or brain$ or skull$) adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ti,ab,ot. (129021)
74 ((femur$ or femoral$) adj3 (fracture$ or injur$ or trauma$ or broke$ or break$)).ti,ab,ot. (19819)
75 ((pelvis or pelvic) adj3 (fracture$ or injur$ or trauma$ or broke$ or break$)).ti,ab,ot. (6332)
76 ((crush$ or burn$) adj3 (injur$ or trauma$)).ti,ab,ot. (14324)
77 Advanced trauma life support.ti,ab,ot. (583)
78 ((emergency or trauma or critical or casualty) adj3 (center$ or centre$)).ab,ti,ot. (13571)
79 ((unconscious$ or coma$ or concuss$ or "persistent vegetative state") adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ti,ab,ot. (3493)
80 (MVA or MVC or RTA or RTC).ti,ab,ot. (10618)
81 exp military phenomena/ (58197)
82 military medicine/ (26478)
83 soldier/ (21784)
84 (complex emergenc$ or man-made hazard$ or complex hazard$).ti,ab,ot,hw. (237)
85 (war$ or conflict or violence or fighting or genocid$ or massacre$ or mass killing$).ti,ab,ot,hw. (594563)
86 (Military or battlefield$ or battle-field$ or medevac or med-evac or "medical evacuation" or "medical evacuations" or army or armies).ti,ab,ot. (44427)
87 or/25-86 (4167681)
88 24 and 87 (1620)

Medline (OvidSP): 1946-2013/9/Wk 3
Searched 1.10.13
1 animals/ not (animals/ and humans/) (3941632)
2 Thrombelastography/ (3421)
3 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw. (4232)
4 (thromb$ adj2 elastogra$).ti,ab,ot,hw. (24)
5 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw. (0)
6 TEG.ti,ab,ot. (933)
7 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw. (459)
8 whole blood h?emosta$ system$.ti,ab,ot,hw. (1)
9 whole blood h?emo-sta$ system$.ti,ab,ot,hw. (0)
10 (ROTEM$ or ROTEG).ti,ab,ot,hw. (260)
11 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw. (360)

12 (thromb$ adj2 elastom$).ti,ab,ot,hw. (3)
13 (thromb$ adj2 elasto?m$).ti,ab,ot,hw. (3)
14 (Sonoclot or sono-clot).ti,ab,ot,hw. (108)
15 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw. (12)
16 or/2-15 (5052)
17 16 not 1 (4427)
18 exp "Wounds and Injuries"/ (689154)
19 exp Accidents/ (138755)
20 Seat Belts/ (3324)
21 exp Motor Vehicles/ (14903)
22 Emergencies/ (33912)
23 exp Emergency Treatment/ (93377)
24 exp Emergency Medical Services/ (94125)
25 Intensive Care/ (15220)
26 Traumatology/ (2101)
27 emergency medical technicians/ (4761)
28 Emergency Nursing/ (5484)
29 exp Emergency Service, Hospital/ (48577)
30 (Trauma$ or accident$ or crash or crashed or crashes or collision$ or collide$ or smash or pile-up).ti,ab,ot. (319055)
31 ((Car$ or motorcar$ or cycle$ or cycling or bicycl$ or bike$ or motorbike$ or motorcycle$ or motor-bike$ or motor-cycle$ or vehic$ or motor$ or traffic or road or pedestrian$ or lorry or lorries or truck or trucks or van or vans or pick-up$) adj8 (injur$ or accident$ or crash$ or collide$ or collision$ or smash$ or bump$ or shunt$ or trauma$ or crush$ or compress$ or impact$)).ti,ab,ot. (124403)
32 (multiple?trauma$ or poly?trauma$ or multiple?injur$ or complex?injur$).ti,ab,ot,hw. (2912)
33 (wound$ or injur$ or fractur$ or burn or burns or burned or scald$ or stab$ or shot$ or shoot$ or lacerat$ or gunshot$).ti,ab,ot. (1430203)
34 (dogbite$ or animalbite$ or bite$ or bitten).ti,ab,ot. (23110)
35 (splenosis or splenoses).ti,ab,ot. (457)
36 (h?emothorax or h?emo-thorax or pneumothorax or pneumo-thorax).ti,ab,ot,hw. (22295)
37 (h?emoperiton$ or h?emo-periton$ or free?fluid or intraperiton$ or retroperiton$ or intra-periton$ or retro-periton$).ti,ab,ot,hw. (129878)
38 ((spleen or splenic or liver or hepatic or abdomen or abdominal or stomach or thorax or thoracic or chest or chests) adj5 (trauma$ or injur$ or ruptur$ or bleed$ or crush$ or penetrate$ or perforat$ or blunt or force or compress$ or tear$)).ti,ab,ot,hw. (99682)
39 mechanical trauma$.ti,ab,ot. (1206)
40 ((thermal or blast or crush or avulsion or compress$) adj2 injur$).ti,ab. (9177)
41 (open fractur$ or compound fractur$).ti,ab,ot,hw. (3113)
42 (ATLS or ALS or BLS or EMST).ti,ab,ot. (38646)
43 ((emergency or trauma or critical or casualty) adj3 (care or treat$ or unit or units or department$)).ab,ti,ot. (86241)
44 ("emergency room" or "emergency rooms" or er or ers or "emergency department" or "emergency departments" or "casualty department" or "casualty departments" or "accident and emergency" or "accidents and emergencies" or "A&E" or "A & E").ti,ab,ot. (127879)
45 ((trauma adj3 system$) or (life adj3 support$) or (primary adj3 survey$) or (golden adj3 hour) or (first adj3 aid$)).ab,ti,ot. (19387)

46 (management adj3 trauma).ab,ti,ot. (2663)
47 ((prehospital or pre-hospital or preclinical or pre-clinical) adj3 (care or support or treat$)).ab,ti,ot. (3931)
48 (para-medic$ or paramedic$).ab,ti,ot,hw. (5379)
49 ((emergency or critical or trauma or triage or ambulanc$) adj3 (doctor$ or crew$ or staff or team$ or technician$ or worker$ or nurs$ or specialist$)).ab,ti,ot. (13364)
50 ((head or crani$ or cerebr$ or capitis or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj5 (injur$ or trauma$ or damag$ or wound$ or fracture$ or contusion$)).ab,ti,ot. (105502)
51 ((head or crani$ or cerebr$ or brain$ or intra-cran$ or inter-cran$) adj5 (haematoma$ or hematoma$ or haemorrhag$ or hemorrhag$ or bleed$ or pressure)).ti,ab,ot. (29545)
52 ("diffuse axonal injury" or "diffuse axonal injuries").ti,ab,ot. (792)
53 ((brain or cerebral or intracranial or intra-cranial) adj3 (oedema or edema or swell$)).ab,ti,ot. (11773)
54 ((spine$ or spinal) adj3 (fracture$ or injury$ or break$ or broke$)).ti,ab,ot. (27922)
55 ((head or crani$ or cerebr$ or brain$ or skull$) adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ti,ab,ot. (95593)
56 ((femur$ or femoral$) adj3 (fracture$ or injur$ or trauma$ or broke$ or break$)).ti,ab,ot. (15098)
57 ((pelvis or pelvic) adj3 (fracture$ or injur$ or trauma$ or broke$ or break$)).ti,ab,ot. (4724)
58 ((crush$ or burn$) adj3 (injur$ or trauma$)).ti,ab,ot. (11152)
59 Advanced trauma life support.ti,ab,ot. (458)
60 ((emergency or trauma or critical or casualty) adj3 (center$ or centre$)).ab,ti,ot. (10437)
61 ((unconscious$ or coma$ or concuss$ or "persistent vegetative state") adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ti,ab,ot. (2590)
62 (MVA or MVC or RTA or RTC).ti,ab,ot. (8602)
63 exp Military Personnel/ (23530)
64 War/ (18376)
65 Military Medicine/ (25794)
66 (complex emergenc$ or man-made hazard$ or complex hazard$).ti,ab,ot,hw. (203)
67 (war$ or conflict or violence or fighting or genocid$ or massacre$ or mass killing$).ti,ab,ot,hw. (364591)
68 (Military or battlefield$ or battle-field$ or medevac or med-evac or "medical evacuation" or "medical evacuations" or army or armies).ti,ab,ot. (36008)
69 or/18-68 (2862142)
70 17 and 69 (699)

Medline In Process & Other Non-Indexed Citations (OvidSP): up to 2013/09/30
Medline Daily Update (OvidSP): up to 2013/09/30
Searched 1.10.13
1 animals/ not (animals/ and humans/) (2696)
2 Thrombelastography/ (6)
3 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw. (118)
4 (thromb$ adj2 elastogra$).ti,ab,ot,hw. (0)
5 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw. (0)
6 TEG.ti,ab,ot. (122)
7 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw. (8)

8 whole blood h?emosta$ system$.ti,ab,ot,hw. (0)
9 whole blood h?emo-sta$ system$.ti,ab,ot,hw. (0)
10 (ROTEM$ or ROTEG).ti,ab,ot,hw. (29)
11 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw. (37)
12 (thromb$ adj2 elastom$).ti,ab,ot,hw. (0)
13 (thromb$ adj2 elasto?m$).ti,ab,ot,hw. (0)
14 (Sonoclot or sono-clot).ti,ab,ot,hw. (5)
15 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw. (1)
16 or/2-15 (215)
17 16 not 1 (214)
18 exp "Wounds and Injuries"/ (606)
19 exp Accidents/ (142)
20 Seat Belts/ (1)
21 exp Motor Vehicles/ (13)
22 Emergencies/ (21)
23 exp Emergency Treatment/ (128)
24 exp Emergency Medical Services/ (113)
25 Intensive Care/ (31)
26 Traumatology/ (2)
27 emergency medical technicians/ (2)
28 Emergency Nursing/ (2)
29 exp Emergency Service, Hospital/ (62)
30 (Trauma$ or accident$ or crash or crashed or crashes or collision$ or collide$ or smash or pile-up).ti,ab,ot. (26819)
31 ((Car$ or motorcar$ or cycle$ or cycling or bicycl$ or bike$ or motorbike$ or motorcycle$ or motor-bike$ or motor-cycle$ or vehic$ or motor$ or traffic or road or pedestrian$ or lorry or lorries or truck or trucks or van or vans or pick-up$) adj8 (injur$ or accident$ or crash$ or collide$ or collision$ or smash$ or bump$ or shunt$ or trauma$ or crush$ or compress$ or impact$)).ti,ab,ot. (9256)
32 (multiple?trauma$ or poly?trauma$ or multiple?injur$ or complex?injur$).ti,ab,ot,hw. (167)
33 (wound$ or injur$ or fractur$ or burn or burns or burned or scald$ or stab$ or shot$ or shoot$ or lacerat$ or gunshot$).ti,ab,ot. (134477)
34 (dogbite$ or animalbite$ or bite$ or bitten).ti,ab,ot. (1574)
35 (splenosis or splenoses).ti,ab,ot. (19)
36 (h?emothorax or h?emo-thorax or pneumothorax or pneumo-thorax).ti,ab,ot,hw. (1069)
37 (h?emoperiton$ or h?emo-periton$ or free?fluid or intraperiton$ or retroperiton$ or intra-periton$ or retro-periton$).ti,ab,ot,hw. (5116)
38 ((spleen or splenic or liver or hepatic or abdomen or abdominal or stomach or thorax or thoracic or chest or chests) adj5 (trauma$ or injur$ or ruptur$ or bleed$ or crush$ or penetrate$ or perforat$ or blunt or force or compress$ or tear$)).ti,ab,ot,hw. (4052)
39 mechanical trauma$.ti,ab,ot. (57)
40 ((thermal or blast or crush or avulsion or compress$) adj2 injur$).ti,ab. (504)
41 (open fractur$ or compound fractur$).ti,ab,ot,hw. (248)
42 (ATLS or ALS or BLS or EMST).ti,ab,ot. (1434)
43 ((emergency or trauma or critical or casualty) adj3 (care or treat$ or unit or units or department$)).ab,ti,ot. (6953)

44 ("emergency room" or "emergency rooms" or er or ers or "emergency department" or "emergency departments" or "casualty department" or "casualty departments" or "accident and emergency" or "accidents and emergencies" or "A&E" or "A & E").ti,ab,ot. (10753)
45 ((trauma adj3 system$) or (life adj3 support$) or (primary adj3 survey$) or (golden adj3 hour) or (first adj3 aid$)).ab,ti,ot. (1077)
46 (management adj3 trauma).ab,ti,ot. (204)
47 ((prehospital or pre-hospital or preclinical or pre-clinical) adj3 (care or support or treat$)).ab,ti,ot. (282)
48 (para-medic$ or paramedic$).ab,ti,ot,hw. (261)
49 ((emergency or critical or trauma or triage or ambulanc$) adj3 (doctor$ or crew$ or staff or team$ or technician$ or worker$ or nurs$ or specialist$)).ab,ti,ot. (830)
50 ((head or crani$ or cerebr$ or capitis or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj5 (injur$ or trauma$ or damag$ or wound$ or fracture$ or contusion$)).ab,ti,ot. (6315)
51 ((head or crani$ or cerebr$ or brain$ or intra-cran$ or inter-cran$) adj5 (haematoma$ or hematoma$ or haemorrhag$ or hemorrhag$ or bleed$ or pressure)).ti,ab,ot. (1534)
52 ("diffuse axonal injury" or "diffuse axonal injuries").ti,ab,ot. (39)
53 ((brain or cerebral or intracranial or intra-cranial) adj3 (oedema or edema or swell$)).ab,ti,ot. (551)
54 ((spine$ or spinal) adj3 (fracture$ or injury$ or break$ or broke$)).ti,ab,ot. (1784)
55 ((head or crani$ or cerebr$ or brain$ or skull$) adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ti,ab,ot. (5788)
56 ((femur$ or femoral$) adj3 (fracture$ or injur$ or trauma$ or broke$ or break$)).ti,ab,ot. (970)
57 ((pelvis or pelvic) adj3 (fracture$ or injur$ or trauma$ or broke$ or break$)).ti,ab,ot. (310)
58 ((crush$ or burn$) adj3 (injur$ or trauma$)).ti,ab,ot. (712)
59 Advanced trauma life support.ti,ab,ot. (31)
60 ((emergency or trauma or critical or casualty) adj3 (center$ or centre$)).ab,ti,ot. (704)
61 ((unconscious$ or coma$ or concuss$ or "persistent vegetative state") adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ti,ab,ot. (168)
62 (MVA or MVC or RTA or RTC).ti,ab,ot. (495)
63 exp Military Personnel/ (20)
64 War/ (11)
65 Military Medicine/ (7)
66 (complex emergenc$ or man-made hazard$ or complex hazard$).ti,ab,ot,hw. (12)
67 (war$ or conflict or violence or fighting or genocid$ or massacre$ or mass killing$).ti,ab,ot,hw. (24821)
68 (Military or battlefield$ or battle-field$ or medevac or med-evac or "medical evacuation" or "medical evacuations" or army or armies).ti,ab,ot. (2894)
69 or/18-68 (200579)
70 17 and 69 (66)

Conference proceeding searches

International Society on Thrombosis and Haemostasis (ISTH) (Internet): 2009, 2011
http://www.isth.org/?PastMeetings
Searched 28.11.13

Searched Annual meetings abstract books for:
2009 - http://onlinelibrary.wiley.com/doi/10.1111/jth.2009.7.issue-s2/issuetoc
2010 - not available online

2011 - http://onlinelibrary.wiley.com/doi/10.1111/jth.2011.9.issue-s2/issuetoc
2012 – not available online
2013 - not available online

Year	Abstracts
2009	39
2010	n/a
2011	49
2012	n/a
2013	n/a
Total	**88**

Terms browsed include:
ROTEM
ROTEG
Sonoclot
TEG
Viscoelastic
Visco-elastic

American Society of Anesthesiologists (ASA) (Internet): 2009-2013
http://www.asaabstracts.com/strands/asaabstracts/search.htm;jsessionid=FF1E2F6EA4FF34468F5594FA255F3423
Searched 28.11.13

Term	Title	Abstract
ROTEM	8	28
ROTEG	0	0
TEG	8	43
SONOCLOT	0	0
Viscoelastic	1	7
Visco-elastic	0	1
Subtotal	**17**	**79**
Total	**96**	

European Association of Cardiothoracic Anaesthetists (EACTA) (Internet): 2009-2013
Searched 28.11.13

2013 - http://www.applied-cardiopulmonary-pathophysiology.com/acp-2-2013.html
2012 – http://www.applied-cardiopulmonary-pathophysiology.com/acp-supp1-2012.html
2011 – Searched via publisher's website

2010 - http://www.applied-cardiopulmonary-pathophysiology.com/fileadmin/downloads/acp-2010-1/10_abstracts.pdf
2009 - http://www.applied-cardiopulmonary-pathophysiology.com/fileadmin/downloads/acp-2009-S1/EACTA-2009-abstracts.pdf

Term	2009	2010	2011	2012	2013
ROTEM	0	0	0	1	0
ROTEG	0	0	0	0	0
TEG	0	0	0	0	0
SONOCLOT	0	0	0	0	0
Viscoelastic	0	0	0	0	0
Visco-elastic	0	0	0	0	0
Thrombo	0	0	1	1	0
Subtotal	**0**	**0**	**1**	**2**	**0**
Total	**3**				

Additional searches

PubMed Related Citations search undertaken for included studies
Results sorted by Link Ranking
http://www.ncbi.nlm.nih.gov/pubmed/
Searched 28.11.13

Of 42 included studies, only 21 references were indexed on PubMed.
For each reference, the first 20 references were retrieved by carrying out a Related Citations search using PubMed's similarity matching algorithm. These records were downloaded for screening. All related citations were checked against the Endnote Library to remove duplicate, and only new unique references were imported and screened.

Reference	PMID	Result retrieved
#28. Ak[46]	19583608	20/45
#30. Avidan[48]	14722166	20/519
#8034. Cotton[75]	21825945	20/249
#5582. Davenport[72]	21765358	20/149
#1107. Girdauskas[54]	20951260	20/221
#5470. Holcomb[76]	22868371	20/299
#5464. Ives[74]	22766227	20/121
#7985. Jeger[79]	22547997	20/93
#3851. Kaufmann[66]	9137263	20/354
#8574. Kunio[69]	22425448	20/94
#5727. Leemann[67]	21150521	20/125
#48. Nuttall[61]	9412876	20/233
#32. Nuttall[50]	11388527	20/350

#498. Pezold[82]	21899867	20/184
#31. Royston[49]	11573637	20/120
#5707. Schochl[78]	22078266	20/153
#33. Shore [51]	9972747	20/598
#78. Tauber[68]	21705350	20/237
#4261. Tuman[62]	2742171	20/195
#35. Weber[35]	22914710	20/108
#29. Westbrook[47]	19117801	20/202
Total		**440**
Following duplicate removal, number of records screened		**101**

b. Health economics searches

Embase (OvidSP): 1974-2013/11/05
Searched 6.11.13

1 health-economics/ (33331)
2 exp economic-evaluation/ (206551)
3 exp health-care-cost/ (198226)
4 exp pharmacoeconomics/ (170054)
5 or/1-4 (473269)
6 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (592569)
7 (expenditure$ not energy).ti,ab. (23436)
8 (value adj2 money).ti,ab. (1327)
9 budget$.ti,ab. (23658)
10 or/6-9 (616419)
11 5 or 10 (889041)
12 letter.pt. (846057)
13 editorial.pt. (450524)
14 note.pt. (589815)
15 or/12-14 (1886396)
16 11 not 15 (802081)
17 (metabolic adj cost).ti,ab. (878)
18 ((energy or oxygen) adj cost).ti,ab. (3167)
19 ((energy or oxygen) adj expenditure).ti,ab. (20058)
20 or/17-19 (23290)
21 16 not 20 (796999)
22 exp animal/ (19435707)
23 exp animal-experiment/ (1729328)
24 nonhuman/ (4161134)
25 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (5024049)
26 or/22-25 (20785461)
27 exp human/ (15078566)
28 exp human-experiment/ (317907)
29 27 or 28 (15080007)
30 26 not (26 and 29) (5706423)
31 21 not 30 (737003)

32 thromboelastography/ (4953)
33 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw,dv. (5797)
34 (thromb$ adj2 elastogra$).ti,ab,ot,hw,dv. (46)
35 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw,dv. (2)
36 TEG.ti,ab,ot,dv. (1801)
37 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw,dv. (1003)
38 whole blood h?emosta$ system$.ti,ab,ot,hw,dv. (2)
39 whole blood h?emo-sta$ system$.ti,ab,ot,hw,dv. (0)
40 (ROTEM$ or ROTEG).ti,ab,ot,hw,dv. (793)
41 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw,dv. (790)
42 (thromb$ adj2 elastom$).ti,ab,ot,hw,dv. (7)
43 (thromb$ adj2 elasto?m$).ti,ab,ot,hw,dv. (7)
44 (Sonoclot or sono-clot).ti,ab,ot,hw,dv. (159)
45 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw,dv. (17)
46 or/32-45 (7669)
47 31 and 46 (238)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Embase (Ovid) weekly search. York: Centre for Reviews and Dissemination; 2010.

Medline (OvidSP): 1946-2013/10/wk 4
Searched 6.11.13
1 economics/ (27117)
2 exp "costs and cost analysis"/ (182817)
3 economics, dental/ (1866)
4 exp "economics, hospital"/ (19436)
5 economics, medical/ (8580)
6 economics, nursing/ (3880)
7 economics, pharmaceutical/ (2607)
8 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (428332)
9 (expenditure$ not energy).ti,ab. (17575)
10 (value adj1 money).ti,ab. (22)
11 budget$.ti,ab. (17221)
12 or/1-11 (552792)
13 ((energy or oxygen) adj cost).ti,ab. (2756)
14 (metabolic adj cost).ti,ab. (800)
15 ((energy or oxygen) adj expenditure).ti,ab. (16687)
16 or/13-15 (19533)
17 12 not 16 (548438)
18 letter.pt. (804607)
19 editorial.pt. (335541)
20 historical article.pt. (299905)
21 or/18-20 (1425550)
22 17 not 21 (520378)
23 animals/ not (animals/ and humans/) (3962474)

24 22 not 23 (486879)
25 Thrombelastography/ (3453)
26 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw. (4267)
27 (thromb$ adj2 elastogra$).ti,ab,ot,hw. (24)
28 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw. (0)
29 TEG.ti,ab,ot. (951)
30 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw. (459)
31 whole blood h?emosta$ system$.ti,ab,ot,hw. (1)
32 whole blood h?emo-sta$ system$.ti,ab,ot,hw. (0)
33 (ROTEM$ or ROTEG).ti,ab,ot,hw. (269)
34 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw. (370)
35 (thromb$ adj2 elastom$).ti,ab,ot,hw. (3)
36 (thromb$ adj2 elasto?m$).ti,ab,ot,hw. (3)
37 (Sonoclot or sono-clot).ti,ab,ot,hw. (109)
38 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw. (12)
39 or/25-38 (5091)
40 24 and 39 (90)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search. York: Centre for Reviews and Dissemination; 2010.

Medline In-Process Citations (OvidSP): up to 2013/11/05
Medline Daily Update (OvidSP): up to 2013/11/05
Searched 6.11.13
1 economics/ (4)
2 exp "costs and cost analysis"/ (260)
3 economics, dental/ (0)
4 exp "economics, hospital"/ (28)
5 economics, medical/ (2)
6 economics, nursing/ (2)
7 economics, pharmaceutical/ (5)
8 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (41521)
9 (expenditure$ not energy).ti,ab. (1256)
10 (value adj1 money).ti,ab. (5)
11 budget$.ti,ab. (1905)
12 or/1-11 (43580)
13 ((energy or oxygen) adj cost).ti,ab. (235)
14 (metabolic adj cost).ti,ab. (70)
15 ((energy or oxygen) adj expenditure).ti,ab. (974)
16 or/13-15 (1238)
17 12 not 16 (43222)
18 letter.pt. (26653)
19 editorial.pt. (15882)
20 historical article.pt. (186)
21 or/18-20 (42699)
22 17 not 21 (42728)

23 animals/ not (animals/ and humans/) (3186)
24 22 not 23 (42660)
25 Thrombelastography/ (6)
26 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$ or thromboelastogra$).ti,ab,ot,hw. (129)
27 (thromb$ adj2 elastogra$).ti,ab,ot,hw. (0)
28 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw. (0)
29 TEG.ti,ab,ot. (123)
30 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw. (9)
31 whole blood h?emosta$ system$.ti,ab,ot,hw. (0)
32 whole blood h?emo-sta$ system$.ti,ab,ot,hw. (0)
33 (ROTEM$ or ROTEG).ti,ab,ot,hw. (30)
34 (thrombo-elastomet$ or thrombelastomet$ or thromboelastomet$).ti,ab,ot,hw. (39)
35 (thromb$ adj2 elastom$).ti,ab,ot,hw. (0)
36 (thromb$ adj2 elasto?m$).ti,ab,ot,hw. (0)
37 (Sonoclot or sono-clot).ti,ab,ot,hw. (6)
38 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw. (1)
39 or/25-38 (232)
40 24 and 39 (3)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search. York: Centre for Reviews and Dissemination; 2010.

NHS Economics Evaluation Database (NHS EED) (Wiley): Issue 4. October/2013
Searched 5.11.13
#1 MeSH descriptor: [Thrombelastography] this term only 151
#2 (thrombo-elastogra* or thrombelastogra* or thrombelasto-gra* or thromboelastogra*):ti,ab,kw 252
#3 (thromb* near/2 elastogra*):ti,ab,kw 1
#4 (thromb* near/2 elasto-gra*):ti,ab,kw 0
#5 TEG:ti,ab 87
#6 (haemoscope* or hemoscope* or haemonetics or hemonectics):ti,ab,kw 52
#7 whole blood h?emosta* system*.ti,ab,kw 0
#8 whole blood h?emo-sta* system*:ti,ab,kw 0
#9 (ROTEM* or ROTEG):ti,ab,kw 22
#10 (thrombo-elastomet* or thrombelastomet* or thromboelastomet*):ti,ab,kw 27
#11 (thromb* near/2 elastom*):ti,ab,kw 4
#12 (thromb* near/2 elasto?m*):ti,ab,kw 0
#13 (Sonoclot or sono-clot):ti,ab,kw 12
#14 ((viscoelastic or visco-elastic) near/3 (detection or coagulation) near/2 (system* or process or test or tests or analyz* or analys* or assay* or device* or measurement*)):ti,ab,kw 0
#15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 326

NHS EED search retrieved 3 references.

EconLIT (EBSCO): 1990-2013/09/01

Searched 7.11.13

S1 TX ((thrombo-elastogra* or thrombelastogra* or thrombelasto-gra* or thromboelastogra*)) OR TX (thromb* N2 elastogra*) OR TX (thromb* N2 elasto-gra*) 0

S2 TX ((haemoscope* or hemoscope* or haemonetics or hemonectics)) OR TX whole blood h#emosta* system* OR TX whole blood h#emo-sta* system* 0

S3 TX ((TEG or ROTEM* or ROTEG)) OR TX ((thrombo-elastomet* or thrombelastomet* or thromboelastomet*) OR TX (thromb* N2 elastom*) 0

S4 TX (thromb* N2 elasto#m*) OR TX ((Sonoclot or sono-clot)) OR TX (((viscoelastic or visco-elastic) N3 (detection or coagulation) N2 (system* or process or test or tests or analyz* or analys* or assay* or device* or measurement*))) 0

S5 s1 or s2 or s3 or s4 0

IDEAS via Research Papers in Economics (REPEC) (Internet): up to 2013/11/07
Searched 7.11.13
http://repec.org/

Search terms	Results
(thrombo-elastogram | thrombo-elastograph | thrombelastogram | thrombelastograph)	0
(thrombelasto-graph | thromboelastogram | thrombelasto-gram | thromboelastograph)	0
(haemoscope | hemoscope | haemonetics | hemonectics | haemoscopes | hemoscopes)	0
"whole blood haemostasis system" | "whole blood haemostatic system"	0
"whole blood hemostasis system" | "whole blood hemostatic system"	0
(TEG | ROTEM | ROTEG)	26
(thrombo-elastometry | thrombelastometry | thromboelastometry)	0
(Sonoclot | sono-clot)	0
(viscoelastic | visco-elastic) + (detection | coagulation) + (system | process | test | tests | analyz | analysis | assay | device | measurement)	58
Total	**84**

Health Economic Evaluation Database (HEED) (Wiley): up to 2013/11/07
http://onlinelibrary.wiley.com/book/10.1002/9780470510933
Searched 7.11.13
Compound search, (all data)

All data	All data	Results
thrombo-elastogra* or thrombelastogra* or thrombelasto-	-	5

gra* or thromboelastogra*		
thromb*	AND elastogra* OR elasto-gra* OR elastom*	0
haemoscope* or hemoscope* or haemonetics or hemonectics OR Sonoclot or sono-clot	-	7
whole blood haemosta* system*	OR whole blood hemo-sta* system*	0
TEG OR ROTEM* or ROTEG	-	2
thrombo-elastomet* or thrombelastomet* or thromboelastomet*	-	0
(viscoelastic or visco-elastic) AND (detection or coagulation)	AND (system* or process or test or tests or analyz* or analys* or assay* or device* or measurement*)	0
Total		**14**

APPENDIX 2: DATA EXTRACTION TABLES

a. Baseline details cardiac surgery studies

Study Details	Selection criteria	Participant Details	Intervention	Control
Ak(2009)[46] **Country:** Turkey **Funding:** Not reported **Study Design:** RCT **Recruitment:** NR **Number of participants:** 228	**Inclusion criteria:** Consecutive patients undergoing elective first-time CABG **Exclusion criteria:** Preoperative hemodynamic instability, malignancies, history of bleeding diathesis, use of low-molecular-weight heparin molecules until the day of operation, recent treatment (<5 days) with a glycoprotein IIb/IIIa antagonist or clopidogrel, impaired renal function (creatinine >2mg/dL) and any liver disease resulting in elevated liver function tests.	**Patient category:** CABG **Previous anti-coagulation therapy:** 65% of standard group and 59% of TEG group received aspirin until the day before the operation. **Mean age (sd)** 64(20) **% Male:** 76	**Test:** TEG (Kaolin and heparinase) **Parameters:** r, MA, LY30 r≥14mm then FFP (1 unit)*; r≥21mm then FFP (2 units)*; r≥28mm then FFP (4 units)*; MA<48mm then platelets (1 unit); MA<40mm then platelets (2 units); LY30>7.5% then tranexamic acid. *If the r time on the h-kTEG was less than one-half of the nonheparinase r time on the kTEG. **Test timing** t1, before induction of general anaesthesia; t2, after institution of CPB; t3, 15 minutes after administration of protamine sulphate; t4, on admission to the intensive care unit (ICU); t5, 6 hours after CPB; and lastly t6, 24 hours after CPB	Clinician directed transfusion. Decision for blood product (platelet suspension and/or FFP) was determined by using the criteria obtained from abnormal conventional laboratory tests, absence of visible clots, and presence of generalized oozing-type bleeding in the surgical field. Platelet suspension was ordered if the platelet count was less than 100,000/µL. FFP was given if the prothrombin time (PT) was over 14 seconds or activated partial thromboplastin time (APTT) was >1.5× normal. After complete neutralization of systemic heparin, an additional dose of protamine sulphate was given according to the control activated clotting time (ACT) values (25 mg if the ACT was between 120 and 150 seconds or 50 mg if it was over 150 seconds). In this group, the appropriate amount of blood products was judged according to the clinical discretion of the anaesthesiologist responsible for the postoperative care of the patient. TA requirement was determined by absence of visible clots and presence of generalized oozing-type bleeding in the surgical field. **Test timing** Same as group 1

Study Details	Selection criteria	Participant Details	Intervention	Control	Comments
Avidan(2004)[48] **Country:** UK **Funding:** Medicell UK provided TEG consumables at discounted prices, Medtronic provided consumables for the Hepcon machine, other funding was provided by the Royal College of Anaesthetists UK, and National Blood Services UK. **Study Design:** RCT **Recruitment:** NR **Number of participants:** 102	**Inclusion criteria:** Patients having elective, first-time CABG with CPB, who were treated by the same surgeon and anaesthetic team. **Exclusion criteria:** Pre-operative abnormal clotting tests (INR >1.5, APTT ratio >1.5, or platelet count <150 x 10^9/L). Medication affecting coagulation within 72 hours of surgery (warfarin, heparin, low molecular weight heparin, aspirin and clopidogrel).	**Patient category:** CABG **Previous anti-coagulation therapy:** None within 72 hours before surgery **Mean age (range)** 64(57, 71) **% Male:** 78	**Test:** TEG (Heparinase) **Parameters:** R, α angle, MA and LY30. The intervention (POC) protocol also included Hepcon (heparin dose response and heparin/protamine titration tests), platelet function testing (PFA-100 (Dade Behring, Deerfield, IL, USA) analyser) and ACT (Hemochron; ITC, Edison, NJ, USA). Bleeding was managed and transfusion triggers were set based on POC alone; algorithm reported as a flow chart in the paper. TEG: LY30 (>7.5%) plus bleeding >100 mL/h, response 2 Mu aprotinin i.v.; R (>10 min) plus excessive bleeding, response 4 units FFP. RBC transfusion was triggered by haemoglobin concentration <8 g/dL. **Test timing** TEG after 5 min and after 1 hour on CPB and 20 min post-protamine administration and 2 hours post-surgery if excessive bleeding continued	Laboratory tests included Act, INR, APTT ratio and FBC. Laboratory tests were requested only for patients with increased bleeding and investigators were blinded to POC test results. The full management algorithm was reported as a flow chart in the paper. Bleeding >100 mL/hour in the first 24 hours after surgery, response 2 Mu aprotinin and 0.4 µg/kg body weight desmopressin; still bleeding >100 mL/hour and INR or APTT >1.5 x control value, response 4 units FFP; excessive bleeding persists or platelet count <50 x 10^9/L, response platelet transfusion. RBC transfusion was triggered by haemoglobin concentration <8 g/dL. **Test timing** ACT at baseline, every 30 min on CPB and post-protamine; INR, aPTT and FBC 2hours post-surgery if excessive bleeding continued	Data were also reported for an additional, retrospective, matched control group, which comprised patients undergoing CABG who received blood products at the individual clinician's discretion.

Study Details	Selection criteria	Participant Details	VE test	Conventional tests
Bischof(2009)[60] **Country:** Switzerland **Funding:** Not reported **Study Design:** prediction study **Recruitment:** July 2007 - December 2008 **Number of participants:** 300	**Inclusion criteria:** Patients undergoing cardiac surgery **Exclusion criteria:** Known coagulopathy or anticoagulant medication	**Patient category:** Any cardiac surgery **Details:** CPB 61%, off pump 39% **Previous anti-coagulation therapy:** **Mean age (sd or range)** 65(11 27, 87) **% Male:** 69 **%White:** NR	Sonoclot (glass bead activated): CR, PF, ACT	None

Study Details	Selection criteria	Participant Details	Intervention	Control
Girdauskas(2010)[54] **Country:** Germany **Funding:** Not stated **Study Design:** RCT **Recruitment:** July 2007 - January 2008 **Number of participants:** 56	**Inclusion criteria:** > 18 years undergoing aortic surgery requiring HCA, including urgent and emergency surgery **Exclusion criteria:** Pregnant, known (inherited) coagulation disorders (haemophilia A or B, activated protein C resistance, etc.), or were unable to give informed consent.	**Patient category:** Aortic surgery **Previous anti-coagulation therapy:** Preoperative aspirin 33% in ROTEM and 28% in control; preoperative warfarin 1 patient (4%) in each group. No patients were receiving clopidogrel or heparin. **Mean age (sd)** 62(16) **% Male:** 57	**Test:** ROTEM (INTEM,HEPTM, FIBTEM and APTEM run simultaneously on 4 ROTEM channels) **Parameters:** CT or MTF CT by HEPTEM (>260s), response FFP (15 mL/kg body mass); CT by APTEM (>120 s), response 3000 IU PPSB; MCF by HEPTEM (<=45 mm) or FIBTEM (>8mm), response 1 platelet concentrate; MCF by FIBTEM (<8mm), response 2g fibrinogen; MCF by APTEM or HEPTEM (>1.5), response 3g tranexamic acid; CT by INTEM or HEPTEM (>1.5), response 5000 IU protamine. Average 3.6 tests per patient performed. **Test timing** During rewarming phase of CPB, second ROTEM carried out for documentation of transfusion effect irrespective of bleeding. If no microvascular bleeding was determined, the chest was closed, and further ROTEM tests were performed in the ICU only in case of increased bleeding. In cases of persistent microvascular bleeding in the operating room, ROTEM coagulation analysis was performed 15 minutes after administration of all appropriate coagulation products.	Patients in the control group received the initial transfusion in the operating room on the basis of clinical judgment (empirically) and subsequently on the basis of standard coagulation test results: ACT (>160s), response 5000 IU protamine; PTT >60s or INR >1.5, response FFP (15mL/kg body mas); platelets (<100 000 cells/ul), response 1 platelet concentrate; fibrinogen (<1.2 mg/dL), response 2g fibrinogen; alpha-2 antiplasmin <80%, response 3g tranexamic acid **Test timing** Blood samples for laboratory tests drawn after administration of protamine.

Study Details	Selection criteria	Participant Details	Intervention	Control	Comments
Kultufan Turan(2006)[52] **Country:** Turkey **Funding:** Not for profit **Study Design:** RCT **Recruitment:** NR **Number of participants:** 40	**Inclusion criteria:** Open heart surgery - either CABG or valve surgery **Exclusion criteria:** None stated	**Patient category:** Mixed cardiac surgery **Details:** CABG or valve surgery **Previous anti-coagulation therapy:** Unclear **Mean age (sd or range)** 53(18, 78) **% Male:** 90	**Test:** Rotational thromboelastography (ROTEG) **Parameters:** Performed preoperative and 1 hour post-op Transfusion algorithm based on ROTEG. Postoperative transfusion indicated if bleeding was >400mL with an hour or >1000ml within 4 hours. **Test timing** Performed preoperative and 1 hour post-op	Routine transfusion therapy, standard laboratory coagulation testing. Postoperative transfusion indicated if bleeding was >400mL with an hour or >1000ml within 4 hours.	Turkish language - extraction based on data in Cochrane review, paper abstract and tables

Study Details	Selection criteria	Participant Details	VE test	Conventional tests
Nuttall(1997)[61] **Country:** USA **Funding:** Not reported **Study Design:** prediction study **Recruitment:** NR **Number of participants:** 82	**Inclusion criteria:** adult men and women scheduled for elective cardiac surgery requiring CPB **Exclusion criteria:** NR	**Patient category:** Mixed cardiac surgery **Details:** coronary artery bypass graft (CABG) and/or valve replacement or repair, or congenital heart surgery. **Previous anti-coagulation therapy:** 11 patients received preoperative heparin, 3 received preoperative coumadin, 18 received preoperative aspirin **Mean age (sd or range)** 63 (NR) **% Male:** 61 **%White:** NR	TEG (NR): MA, R, R + k, α angle, MA + 30 Sonoclot (NR): P1 (time to shoulder), P2 (time to peak), P1-P2, Onset, R1, R2, R3	Bleeding time, Platelet MPV, Plasma fibrinogen concentration, Platelet count, PT, aPTT, Platelet haematocrit

Study Details	Selection criteria	Participant Details	Intervention	Control
Nuttall(2001)[50] **Country:** USA **Funding:** Not stated **Study Design:** RCT **Recruitment:** NR **Number of participants:** 92	**Inclusion criteria:** Adults scheduled for elective cardiac surgery requiring CPB. **Exclusion criteria:** Pregnancy	**Patient category:** Mixed cardiac surgery **Details:** Elective cardiac surgery requiring CPB; 58% CABG, 72% valve surgery, 37% other cardiac surgery **Previous anti-coagulation therapy:** 34% in intervention and 15.7% in control were receiving warfarin. 42% in intervention and 45% in control receive preoperative aspirin. 34% in intervention and 16% in control received preoperative coumadin. 34% in intervention and 18% in control received preoperative IV heparin. **Mean age (sd or range)** 68(NR) **% Male:** 73	**Test:** TEG (NR) **Parameters:** MA Point of care algorithm incorporating: TEG - maximum amplitude (<48mm) available in 30 mins & platelet counts (<102K/mm3) (Coulter MD II) available in 5-10 mins for platelet transfusion or DDAVP administration; whole blood prothrombin time (>16.6 sec) and APTT (>57 sec)(Biotrack 512 Coagulation monitor) available in 3-6 minutes for fresh frozen plasma transfusion; fibrinogen concentration (<144 mg/dL) available within 1 hour for cryoprecipitate transfusion. **Test timing** Tests performed on arrival in ICU.	Transfusion of blood products based on clinician's judgment with or without guidance from laboratory tests.

Study Details	Selection criteria	Participant Details	Intervention	Control
Paniagua(2011)[53] **Country:** Spain **Funding:** NR **Study Design:** RCT **Recruitment:** NR **Conference abstract only** **Number of participants:** 22	**Inclusion criteria:** All patients scheduled to cardiac surgery with extracorporeal circulation who had major postoperative bleeding (≥300 ml in first post-operative hour) **Exclusion criteria:** NR	**Patient category:** Mixed cardiac surgery **Details:** NR **Previous anti-coagulation therapy:** NR **Mean age (sd or range)** NR **% Male:** NR	**Test:** ROTEM (EXTEM and FIBTEM) **Parameters:** MCF Hypofibrinogenemia: MCF in ECTEM <50 and FIBTEM <9; Thrombocitopenia MCF EXTEM <50 of and FIBTEM >=9. **Test timing** All measurements done at time of inclusion and 10 mins after each treatment until bleeding stopped (<150m/h).	Standard laboratory measurements: Hypofibrinogenemia: Fibrinogen (Clauss method) <1g/L; Thrombocitopenia platelet count $<80x10^9$/L **Test timing** All measurements done at time of inclusion and 10 mins after each treatment until bleeding stopped (<150m/h).

Study Details	Selection criteria	Participant Details	Intervention	Control
Rauter(2007)[55] **Country:** Austria **Funding:** Not stated **Study Design:** RCT **Recruitment:** NR **Conference abstract only** **Number of participants:** 213	**Inclusion criteria:** Patients scheduled for routine on-pump cardiac surgery **Exclusion criteria:** NR	**Patient category:** Mixed cardiac surgery **Details:** NR **Previous anti-coagulation therapy:** NR **Mean age (sd or range)** NR **% Male:** NR	**Test:** ROTEM (NR) **Parameters:** NR ROTEM + clinical signs **Test timing** Not reported	Routine management for substitution of blood products (apTT, Quick, fibrinogen, haemoglobin, clinical signs of anaemia) **Test timing** Not reported

Study Details	Selection criteria	Participant Details	Intervention	Control
Royston(2001)[49] **Country:** UK **Funding:** Not reported **Study Design:** RCT **Recruitment:** NR **Number of participants:** 60	**Inclusion criteria:** Not reported; appears to be patients undergoing heart surgery **Exclusion criteria:** Not reported	**Patient category:** Mixed cardiac surgery **Details:** 10% heart transplantation, 50% revascularisation, 40% Ross procedure, multiple valve or valve and revascularisation surgery. No patients were having repeat operations. **Previous anti-coagulation therapy:** 10% were taking aspirin and/or warfarin immediately before surgery a further 50% were taking aspirin. **Mean age (sd or range)** (21, 83) **% Male:**	**Test:** TEG (with and without heparinase) **Parameters:** r, MA, LYS30 r>14 mm then 1 unit FFP; r>21 mm then 2 units FFP; r>28mm then 4 units FFP; MA <48mm then 1 platelet pool; MA <40 mm then 2 platelet pools; LYS30>7.5% then aprotonin **Test timing** Sample 1 prior to surgery; sample 2 at bypass (included heparinase); sample 3 10-15 minutes after protamine, developed with and without heparinase	Wishes of the clinician. Standard laboratory tests performed included APTT, platelet count and fibrinogen concentration. **Test timing** 10-15 minutes after protamine

Study Details	Selection criteria	Participant Details	Intervention	Control
Shore-Lesserson(1999)[51, 56, #6501, #3778, 57, 58] **Country:** USA **Funding:** Not reported **Study Design:** RCT **Recruitment:** NR **Number of participants:** 107	**Inclusion criteria:** Adult patients undergoing a cardiac surgical procedure that had a moderate to high risk for requiring a transfusion (single valve replacement, multiple valve replacement, combined coronary artery bypass plus valvular procedure, cardiac reoperation, or thoracic aortic replacement) **Exclusion criteria:** Significant pre-existing hepatic disease (transaminase levels >2 times control), renal disease requiring dialysis, or requirement for pre-operative inotropic support	**Patient category:** Mixed cardiac surgery **Details:** Moderate transfusion risk procedures (single valve, repeat CABG) 32% High transfusion risk procedures (combined procedures, repeat valve) 66% **Previous anti-coagulation therapy:** Patients receiving preoperative heparin infusion and those who had taken aspirin within the past 7 days were included. **Mean age (sd or range)** 66(15) **% Male:** 58	**Test:** TEG (heparin and non-heparin TEG) Heparinase-modified TEG R time <50% of non-heparinase R time, response additional protamine (50 mg); platelet count (<100,000/µL) AND TEG MA (<45 mm), response if bleeding persisted 6 units platelets transfused; R time (>20 mm), response 2 units FFP transfused if bleeding persisted; fibrinogen (<100 mg/dL), response 10 units cryoprecipitate if bleeding persisted; TEG evidence of fibrinolysis (LY30 >7.5%), response 10 g EACA at clinician's discretion if bleeding persisted **Test timing** Baseline: Celite- and TF-activated TEG. During re-warming on CPB: celite- and TF-activated TEG with heparinase After protamine administration: celite- and TF-activated TEG + heparinase-modified TEG to rule out residual heparinisation	ACT (>15% above baseline), response 50 mg additional protamine; platelet count (<100,000/µL), response 6 units of platelets if bleeding persisted; PT (>150% of control), response 2 units of FFP if bleeding persisted; fibrinogen (<100 mg/dL), response 10 units cryoprecipitate if bleeding persisted; persistent bleeding and failure of all previous therapies, response 10 g EACA at physician's discretion **Test timing** Baseline: platelet count; fibrinogen; PT; aPTT During re-warming on CPB: platelet count After protamine administration: PT; aPTT; fibrinogen

Study Details	Selection criteria	Participant Details	VE test	Conventional tests
Tuman(1989)[62] **Country:** USA **Funding:** NR **Study Design:** Prediction study **Recruitment:** NR **Number of participants:** 42	**Inclusion criteria:** Adult cardiac surgical patients prospectively felt to be at high risk for excessive post-CPB bleeding. Patients were considered to be at high risk for bleeding if they were undergoing preoperative cardiac procedures, valve replacement, ventricular or aortic arch aneurysm resection, or other complex cardiac procedures. **Exclusion criteria:** Abnormal preoperative coagulation or liver function studies, anticoagulant or antiplatelet medications 7 days before surgery.	**Patient category:** Mixed cardiac surgery **Details:** **Previous anti-coagulation therapy:** No patients received previous anticoagulation therapy **Mean age (sd or range):** NR **% Male:** NR **%White:** NR	Sonoclot (NR): ACT, R1, R2, PEAK and R3 TEG (NR): R, k, MA, alpha value, A60	ACT, PT, PTT, PLT, and FIB

Study Details	Selection criteria	Participant Details	Intervention	Control	Comments
Weber(2012)[35] **Country:** Germany **Funding:** Not reported **Study Design:** RCT **Recruitment:** May 2009 - April 2010 **Number of participants:** 100	**Inclusion criteria:** A two stage inclusion process was used: Stage 1: Patients (≥18 yr) scheduled for elective, complex cardiothoracic surgery (combined CABG and valve surgery, double or triple valve procedures, aortic surgery or redo surgery) with cardiopulmonary bypass (CPB). Stage 2: Patients were enrolled in the study after heparin reversal following CPB if at least one of the following two criteria were fulfilled: (1) diffuse bleeding from capillary beds at wound surfaces requiring hemostatic therapy as assessed by the anaesthesiologist and surgeon by inspecting the operative field; (2) intraoperative or postoperative (during the first 24 postoperative hours) blood loss exceeding 250 ml/h or 50 ml/10 min. **Exclusion criteria:** Pregnancy	**Patient category:** Mixed cardiac surgery **Details:** Redo surgery 27% Combined CABG and valve surgery 44% Double valve surgery 23% Triple valve surgery 3% Aortic surgery 14% **Previous anti-coagulation therapy:** Pre-operative antiplatelet therapy, including aspirin was stopped at least 6 days before surgery **Mean age (sd)** 71(8) **% Male:** 62	**Test:** ROTEM (EXTEM, INTEM, FIBTEM, HEPEM) CT(s) for EXTEM (<80s), INTEM and HEPTEM (<240s), response 15 mL/kg body weight FFP particularly if CT prolongation didn't respond to administration of PCC, response 20-30 IU/kg body weight (EXTEM only); A10 (mm) for all four tests, including FIBTEM (<40 mm EXTEM and >10 mm FIBTEM), response 25-50 mg/kg body weight in bleeding patients, platelet concentrates. In addition to ROTEM, the intervention group received aggregometric POC testing for platelet function. **Test timing** Platelet count, fibrinogen, aPTT, and INR performed pre-operatively, at admission to ICU and after 24 hours in ICU. Timing of ROTEM test unclear, but appears to be after declampling of the aorta, before weaning off CPB, after protamine administration, and to guide therapy in ongoing bleeding.	Laboratory coagulation tests: platelet count; haemoglobin concentration, response packed erythrocytes transfused to maintain haemoglobin concentration >6 g/dL during CBP and >8 g/dL after CBP, 15 mL/kg body weigh FFP if bleeding did not stop after fibrinogen and 4 units RBC; fibrinogen concentration (<150-200 mg/dL), response, 25-50 mg/kg body weight in bleeding patients fibrinogen; INR (>1.4), response 20-30 IU/kg body weight; activated partial thromboplastin time (>50s), response 20-30 IU/kg body weight. Detailed flow chart of management algorithm reported in article. **Test timing** Platelet count, fibrinogen, aPTT, and INR performed pre-operatively, at admission to ICU and after 24 hours in ICU. Serial ACT intra-operatively. Additional coagulation tests if bleeding persisted after intervention.	88 patients included in the OR and 12 in the ICU. Study terminated early due to interim analysis showing between group difference for primary outcome ($p<0.001$)

Study Details	Selection criteria	Participant Details	Intervention	Control
Westbrook(2009)[47] **Country:** Australia **Funding:** Not reported **Study Design:** RCT **Recruitment:** NR **Number of participants:** 69	**Inclusion criteria:** Patients presenting for cardiac surgery **Exclusion criteria:** Patients undergoing cardiac surgery with lung transplantation	**Patient category:** Mixed cardiac surgery **Details:** Redo surgery: intervention group 6.3%, control group 2.5% Urgent presentation: intervention 9.4%, control 10% **Previous anti-coagulation therapy:** Pre-operative aspirin: intervention 23.6%, control 23.6% Pre-operative heparin: intervention 9.38%, control 5.0% Pre-operative warfarin: intervention 15.6%, control 10,0% Pre-operative clopidogrel: intervention 6.25%, control 2.5% **Mean age (sd or range)** 63(NR) **% Male:** 71	**Test:** TEG (Kaolin + Heparinase) **Parameters:** R, MA, LY30 Blood products were administered in accordance with a coagulation correction protocol (reported as a flow chart), which was based on TEG measurements (R, MA, LY30) alone. **Test timing** Where possible, patients taking clopidogrel or aspirin had platelet mapping studies before anaesthesia. Plain and heparinised TEG before the bypass, in the re-warming phase and after protamine administration Additional TEG for refractory bleeding in theatre or ICU	Blood products were given at the discretion of the attending physician, based on previous experience and standard laboratory coagulation tests (APTT, INR, fibrinogen level, platelet count) **Test timing** Timing at the discretion of physicians.

b. Baseline details trauma Studies

Study Details	Selection criteria	Participant Details	VE test	Conventional tests
Cotton(2011)[75] **Country:** USA **Funding:** Not reported **Study Design:** Prediction study **Recruitment:** October 2009 - February 2010 **Number of participants:** 272	**Inclusion criteria:** All adult (≥18 years) trauma patients who arrived directly from the scene and were the institution's highest level of trauma activation. **Exclusion criteria:** Patients who had burn wounds >20% total body surface area, or who died within 30 minutes of arrival were excluded.	**Patient category:** Trauma **Details:** Blunt trauma 72% **Previous anti-coagulation therapy:** NR **Mean age (sd or range)** 34(24, 50) **% Male:** 74; **%White:** 50; **GCS:** 14 (3 to 15); **ISS:** 14 (8 to 25)	TEG (rTEG): ACT	None
Davenport(2011)[72, 80] **Country:** UK **Funding:** Partially funded by an NIHR programme grant **Study Design:** Prediction study **Recruitment:** January 2007 - June 2009 **Number of participants eligible (enrolled):** 325(300)	**Inclusion criteria:** All adult trauma patients (>15 yrs) who met the local criteria for full trauma team activation were eligible for enrolment and recruited into the study when research personnel were present (08:00 –20:00 daily). **Exclusion criteria:** Exclusion criteria were: arrival in the emergency department >2 hrs after injury; the administration of >2000 mL of intravenous fluid before emergency department arrival; transfer from another hospital; and burns covering >5% of the total body surface area	**Patient category:** Trauma **Details:** Penetrating injuries 21% **Previous anti-coagulation therapy:** patients were excluded if they were taking anticoagulation therapy **Mean age (range):** 33(23, 48) **% Male:** 82; **%White:** NR; **GCS:** NR; **ISS:** 12 (4 to 25)	ROTEM (EXTEM): CA5, CT, α	Prothrombin Time ratio (PTr)

Study Details	Selection criteria	Participant Details	VE test	Conventional tests
Holcomb(2012)[76] **Country:** USA **Funding:** Government Funding **Study Design:** Prediction study **Recruitment:** September 2009 - February 2011 **Number of participants:** 1974	**Inclusion criteria:** All adult trauma patients admitted to single unit who met the institution's highest-level trauma activation. **Exclusion criteria:** Younger than 18 years or admitted directly to the burn unit.	**Patient category:** Trauma **Details:** 207 had isolated traumatic brain injury no further details **Previous anti-coagulation therapy:** 17 had pre-injury exposure to warfarin **Mean age (range):** 33(23, 49) **% Male:** 75; **%White:** 54; **GCS:** 12 (3, 15); **ISS:** 17 (9, 26)	TEG (rTEG): ACT, k-time, LY30, MA, r-value, α-angle	Plasma fibrinogen concentration, Platelet count, PT, aPTT, INR
Ives(2012)[74] **Country:** USA **Funding:** Not stated **Study Design:** Prediction study **Recruitment:** November 2010 - April 2011 **Number of participants eligible (enrolled):** 260(118)	**Inclusion criteria:** Institution's highest tier of trauma team activation criteria (systolic blood pressure <90 mmHg, or heart rate >120 bpm, or respiratory rate <10 breaths/min or >29 breaths/min, or unresponsive to pain [excluding isolated traumatic brain injury with normal vital signs], or age older than 70 years [excluding ground-level fall], or gunshot wound to chest or abdomen, or stab wound to anterior chest) **Exclusion criteria:** None stated	**Patient category:** Trauma **Details:** 52% penetrating trauma **Previous anti-coagulation therapy:** NR **Mean age (range):** 37(8, 91) **% Male:** 77; **%White:** NR; **GCS:** 11.8(4.8); **ISS:** 15.9	TEG (Kaolin): Estimated percent lysis (EPL), MA or clot strength	None

Study Details	Selection criteria	Participant Details	VE test	Conventional tests
Jeger(2012)[79, 81] **Country:** Switzerland **Funding:** Government research grant **Study Design:** Prediction study **Recruitment:** November 2009 - May 2010 **Number of participants eligible (enrolled):** 85(76)	**Inclusion criteria:** Patients were included if they were older than 16 years and had suspected multiple injuries, and a physician with TEG experience was available **Exclusion criteria:** None reported	**Patient category:** Trauma **Details:** Blunt trauma 83% Craniocerebral injury 43% **Previous anti-coagulation therapy:** NR **Mean age (sd):** 49(21) **% Male:** NR; **%White:** NR; **GCS:** NR; **ISS:** 18 ± 10	TEG (Kaolin): G, k, MA, Time to peak, α TEG (rTEG): G, k, MA, Time to peak, α	aPTT, INR, Plasma fibrinogen, concentration, Thrombin time
Kaufmann(1997)[66] **Country:** USA **Funding:** Nonmonetary support provided by Haemoscope Corporation **Study Design:** prediction study **Recruitment:** August 1994 - January 1995 **Number of participants:** 69	**Inclusion criteria:** Blunt trauma patients; trauma code criteria; age >14 years; examined using TEG **Exclusion criteria:** None stated	**Patient category:** Blunt trauma **Previous anti-coagulation therapy:** 3 patients had recently taken aspirin; no patients on warfarin. **Mean age (range)** 40(16, 82) **% Male:** 59; **%White:** NR; **GCS:** NR; **ISS:** 12.3 (1, 75)	TEG: r, K, alpha angle, and MA	None

Study Details	Selection criteria	Participant Details	VE test	Conventional tests
Korfage(2011)[77] **Country:** Netherlands **Funding:** Not reported **Study Design:** Prediction study **Recruitment:** NR **Conference abstract only** **Number of participants:** 142	**Inclusion criteria:** Trauma patients admitted to the emergency department of VUMC, Amsterdam **Exclusion criteria:** None reported	**Patient category:** Trauma **Previous anti-coagulation therapy:** Five patients used anticoagulant medication **Mean age (sd):** 46(18) **% Male:** 61; **%White:** NR; **GCS:** NR; **ISS:** NR	ROTEM (EXTEM): CFT	None
Kunio(2012)[69] **Country:** USA **Funding:** Not stated **Study Design:** Prediction study **Recruitment:** February 2010 - April 2011 **Number of participants:** 69	**Inclusion criteria:** Level 1 trauma centre; traumatic brain injury with intracranial haemorrhage on admission noncontrast head CT; >= 16 years. **Exclusion criteria:** Use of clopidogrel or warfarin within 30 days of admission	**Patient category:** Traumatic brain injury **Previous anti-coagulation therapy:** Patients taking clopidogrel or warfarin within 30 days of admission excluded. 16% were taking aspirin before admission. **Mean age (range):** 46(30, 64) **% Male:** 81; **%White:** NR; **GCS:** 13 (7, 15); **ISS:** 21 (17, 33)	TEG (Not stated): R	None

Study Details	Selection criteria	Participant Details	VE test	Conventional tests
Leemann(2010)[67] **Country:** Switzerland **Funding:** Not reported **Study Design:** retrospective prediction study **Recruitment:** January 2006 - December 2006 **Number of participants:** 53	**Inclusion criteria:** ISS ≥16 and ROTEM measurements on admission available **Exclusion criteria:** Isolated head injury (AIS head ≥3 and AIS chest, abdomen and extremity <3); penetrating mechanism of injury	**Patient category:** Blunt trauma **Details:** Severe traumatic brain injury present in 64% of patients **Previous anti-coagulation therapy:** NR **Mean age (sd):** 40(2) **% Male:** 76; **%White:** NR; **GCS:** GCS ≤8 79%; **ISS:** 31.1 ± 1.7	ROTEM (EXTEM and INTEM): A10, A20, CFT, MCF, α	aPTT, INR, platelet count
Messenger (2011)[65] **Country:** Canada **Funding:** NR **Study Design: C**CT **Conference abstract only** **Recruitment:** NR **Number of participants:** 50	**Inclusion criteria:** Adult trauma patients requiring massive transfusion (>12 RBC units in 24 hours or >4 units in 4 hours) **Exclusion criteria:** None reported	**Patient category:** Mixed trauma; high risk of bleeding **Previous anti-coagulation therapy:** NR **% Male, %White, GCS, and ISS:** NR	**Test:** TEG-guided protocol and haematocrit assay **Parameters:** rapid TEG (r, MA, LY30) **Test timing:** NR	Treatment according to institutional massive transfusion protocol based on point of care haematocrit assay **Test timing** NR

Study Details	Selection criteria	Participant Details	Intervention	Control
Moore (ongoing)[63] **Country:** USA **Funding:** Denver Health and Hospital Authority and Haemonetics Corporation **Study Design:** RCT **Recruitment:** September 2010 - Ongoing **Number of participants:** Target 120	**Inclusion criteria:** age >18 years admitted to Denver Health Medical Center, blunt or penetrating trauma sustained < 6 hours before admission, with Injury Severity Score > 15 (ISS>15), likely to require transfusion of RBC within 6 hours from admission as indicated by clinical assessment. **Exclusion criteria:** Chronic liver disease (total bilirubin >2.0 mg/dL). Advanced cirrhosis discovered on laparotomy will be a criterion for study withdrawal and exclusion of conventional coagulation or r-TEG/TEG data from the analysis); known inherited defects of coagulation function (e.g. haemophilia, Von Willebrand's disease), pregnancy	**Patient category:** **Previous anti-coagulation therapy:** Not available **% Male, %White, GCS, and ISS:** Not yet available	**Test:** TEG (r-TEG) **Parameters:** [TEG-ACT, alpha angle, K value, MA (maximum amplitude), G value (clot strength), and fibrinolysis (EPL=estimated percent lysis) **Test timing** Blood component therapy per usual clinical practice. The test arm involves the use of rapid-TEG to diagnose and describe post-injury coagulopathy and to guide blood product replacement per institutional algorithm. The current institutional massive transfusion protocol will be followed. Test timing: On hospital admission (usually within an hour), twice within first 6 hours post-injury, 12 and 24 hours post-injury.	INR, PTT, fibrinogen, D-dimer: Blood component therapy guided by conventional coagulation tests (aPTT, INR, fibrinogen level, D-dimer) per usual clinical practice. The current institutional massive transfusion protocol will be followed. **Test timing** Same as TEG

Study Details	Selection criteria	Participant Details	Intervention	Control
Nystrup(2011)[73] **Country:** Denmark **Funding:** Not reported **Study Design:** Retrospective prediction study **Recruitment:** 2006 - 2007 **Number of participants:** 89	**Inclusion criteria:** Patients on the European Trauma Audit and Research Network (TARN) database, who had a TEG analysis performed along with the initial blood tests, on admission and before any blood products are administered. The TARN database only includes patients with severe traumatic injuries. **Exclusion criteria:** None reported	**Patient category:** Trauma **Details:** Blunt trauma 85%. Cause of trauma: RTA 73%; fall from height 11%; assault 11%; suicide attempt 4.5% Type of trauma: thoracic 17%; abdominal 8%; extremities 4.5%; cerebral 20%; multiple trauma 41.5%; other 9% **Previous anti-coagulation therapy:** NR **Mean age (range):** 39(35, 43) **% Male:** 66; **%White:** NR; **GCS:** NR; **ISS:** 21 (95% CI: 19 to 23)	TEG (Not stated): clot strength, MA	aPTT, INR
Pezold(2012)[82] **Country:** USA **Funding:** Government research grants **Study Design:** Prediction study **Recruitment:** May 2008 - September 2010 **Number of participants:** 80	**Inclusion criteria:** Trauma activations, patients age >15 years, injury severity score (ISS) >15, and both BD and rapid TEG (r-TEG) obtained on arrival at the emergency department. **Exclusion criteria:** None reported	**Patient category:** Trauma **Details:** Blunt trauma 38% Penetrating trauma 62% **Previous anti-coagulation therapy:** **Mean age (sd):** 34(2) **% Male:** 81; **%White:** NR; **GCS:** NR; **ISS:** 29 ± 1	TEG (rTEG): G (global measure of clot strength) dynes/cm^2	aPTT INR

Study Details	Selection criteria	Participant Details	Intervention	Control
Schochl(2011)[78, 83] **Country:** Austria **Funding:** Not reported **Study Design:** Retrospective prediction study **Recruitment:** January 2005 - December 2010 **Number of participants:** 323	**Inclusion criteria:** All patients with an injury severity score (ISS) ≥16, from whom blood samples were taken immediately upon admission to the ER, were eligible for inclusion in the study **Exclusion criteria:** Therapy withheld due to non-survivable injuries; patient suffered from burns; patient transferred from other hospitals	**Patient category:** Trauma **Details:** None reported **Previous anti-coagulation therapy:** Not reported **Mean age (range):** 44(26, 59) **% Male:** 79; **%White:** NR; **GCS:** NR; **ISS:** NR	ROTEM (INTEM): CT MCF CFT ROTEM (EXTEM): MCF CFT CT ROTEM (FIBTEM): A10, MCF	Platelet count aPTT Plasma fibrinogen concentration
Schochl(2011)[70, 78] **Country:** Austria **Funding:** Not reported **Study Design:** Cohort **Recruitment:** NR **Conference abstract only** **Number of participants:** 88	**Inclusion criteria:** Patients with isolated severe traumatic brain injury (Abbreviated Injury Scale AIShead 92 and AISextracranial G3) at admission to the emergency room **Exclusion criteria:** None reported	**Patient category:** Traumatic brain injury **Previous anti-coagulation therapy:** NR **Mean age (sd or range):** NR **% Male:** NR; **%White:** NR; **GCS:** NR; **ISS:** NR	ROTEM (FIBTEM): MCF	aPTT

Study Details	Selection criteria	Participant Details	Intervention	Control
Tapia(2012)[71] **Country:** USA **Funding:** Not stated **Study Design:** Prediction study **Recruitment:** January 2008 - June 2011 **Conference abstract only** **Number of participants eligible (enrolled):** 291(230)	**Inclusion criteria:** Patients on Urban Level 1 trauma center database who had received >= 6 units RBC in 1st 24 hours of admission **Exclusion criteria:** Traumatic brain injury	**Patient category:** Trauma **Details:** 58% had penetrating injury **Previous anti-coagulation therapy:** Not stated **Mean age (sd or range):** NR **% Male:** NR; **%White:** NR; **GCS:** NR; **ISS:** NR	TEG (Not specified)	None

Study Details	Selection criteria	Participant Details	Intervention	Control
Tauber(2011)[68] **Country:** Austria **Funding:** Not stated **Study Design:** prediction study **Recruitment:** July 2005 - July 2008 **Number of participants:** 334	**Inclusion criteria:** Adult polytrauma (Injury Severity Score (ISS) of ≥15 resulting from injury of at least two body regions. Isolated head injury was defined as a Glasgow Coma Score of ≤14 after blunt head trauma in patients with an Abbreviated Injury Score (AIS) of 3 in any other body region) patients, who were admitted to the Level I Trauma Center. Patients with isolated traumatic brain injury were enrolled from 2006. **Exclusion criteria:** Age <18 yr, with penetrating injuries, admitted to the study hospital later than 12 h after trauma, pre-existing coagulopathy, burn injury, malignant disease, were avalanche victims, or exhibited non-head single trauma	**Patient category:** Blunt trauma **Details:** 274 blunt polytrauma and 60 isolated brain injury **Previous anti-coagulation therapy:** Patients who had previously received anticoagulation therapy (warfarin/platelet aggregation inhibitors n=3) were excluded **Mean age (sd or range)** 43(27, 56) **% Male:** 78; **%White:** NR; **GCS:** 11 (6, 15); **ISS:** 34 (24, 45)	ROTEM (FIBTEM): Hyperfibrinolysis only	None

Study Details	Selection criteria	Participant Details	Intervention	Control
Tuman(1989)[62] **Country:** USA **Funding:** NR **Study Design:** Prediction study **Recruitment:** NR **Number of participants:** 42	**Inclusion criteria:** Adult cardiac surgical patients prospectively felt to be at high risk for excessive post-CPB bleeding. Patients were considered to be at high risk for bleeding if they were undergoing reoperative cardiac procedures, valve replacement, ventricular or aortic arch aneurysm resection, or other complex cardiac procedures. **Exclusion criteria:** Abnormal preoperative coagulation or liver function studies, anticoagulant or antiplatelet medications 7 days before surgery.	**Patient category:** Mixed cardiac surgery **Details:** **Previous anti-coagulation therapy:** No patients received previous anticoagulation therapy **Mean age (sd or range):** NR; **% Male:** NR; **% White:** NR	Sonoclot (NR): ACT, R1, R2, PEAK and R3 TEG (NR): R, k, MA, alpha value, A60	ACT, PT, PTT, PLT, and FIB

c. Baseline details PPH studies

Study Details	Selection criteria	Participant Details	VE test	Conventional tests
Bolton(2011)[84] **Country:** UK **Funding:** Not stated **Study Design:** Prediction study **Recruitment:** NS **Conference abstract only** **Number of participants:** 66	**Inclusion criteria:** Patients with major obstetric haemorrhage (>=1500 mL) requiring standard laboratory tests for suspected coagulopathy. **Exclusion criteria:** Not stated	**Patient category:** PPH **Previous anti-coagulation therapy:** NR **Mean age (sd or range)** NR	ROTEM (NR): NR	None
Lilley(2013)[85] **Country:** UK **Funding:** ROTEM provided by TEM international **Study Design:** Prediction study **Recruitment:** April 2012 - September 2012 **Conference abstract only** **Number of participants:** 179	**Inclusion criteria:** Women with PPH >=1000 mL **Exclusion criteria:** NR	**Patient category:** PPH **Previous anti-coagulation therapy:** NR **Mean age (sd or range)** NR	ROTEM(FIBTEM): MCF	Clauss fibrinogen

d. Results from RCTs in cardiac surgery patients

Study Details	Outcome	Data available	VE testing arm results	Control results	RR or MD (95% CI)	P-value
Ak(2009)[46]	RBC transfusion	Number of patients/ Number of events	52/114	60/110	0.8 (0.64, 1.08)	0.181
	FFP transfusion		19/114	31/110	0.5 (0.36, 0.99)	0.038
	Platelet transfusion		17/114	29/110	0.5 (0.34, 0.97)	0.033
	Bleeding: Mediastinal blood loss > 400 mL in the first hour after surgery or >100 mL/hour for 4 consecutive hours		11/114	9/110	1.1 (0.52, 2.65)	0.700
	Need for additional protamine		62/114	47/110	1.2 (0.97, 1.67)	0.080
	Tranexamic acid use		10/114	21/110	0.4 (0.24, 0.94)	0.007
	Re-operation: Re-exploration for bleeding		6/114	5/110	1.1 (0.38, 3.44)	NR
	Re-thoracotomy for bleeding		6/114	4/110	1.3 (0.43, 4.51)	0.574
	Surgical source of bleed (identified on re-exploration)		6/114	2/110	2.5 (0. 60, 10.54)	NR
	Death		3/114	2/110	1.3 (0.27, 6.70)	NR
	RBC transfusion (units transfused)	Median/IQR	1(0, 1)	1(1, 2)	NA	0.599
	Any blood product transfusion (Total allogeneic exposure (unit))		2(1, 3)	3(2, 4)	NA	0.001
	FFP transfusion (units transfused)		1(1, 1)	1(1, 2)	NA	0.001
	Platelet transfusion (units transfused)		1(1, 1)	1(1, 2)	NA	0.001
	Bleeding (mediastinal test tube drainage (mL) within 12 hours)	Mean (sd)	480.50(351)	591.40(339.20)	-110.9(-201.3, -20.5)	0.017
	Mean length of ICU stay(hours)		23.30(5.70)	25.30(11.20)	-2.0 (-4.34, 0.34)	0.099
	Number of days in hospital		6.20(1.10)	6.30(1.40)	-0.1 (-0.43, 0.23)	0.552
Avidan(2004)[48]	RBC transfusion within 24 hours	Number of patients/ Number of events	34/51	35/51	0.9 (0.75, 1.27)	NR
	FFP transfusion within 24 hours		2/51	0/51	4.9 (0.25, 101.61)	NR
	Platelet transfusion within 24 hours		2/51	1/51	1.6 (0.23, 12.16)	NR
	Re-operation for suspected surgical bleeding		1/51	1/51	1.0 (0.11, 9.30)	NR
	Bleeding (Blood loss in 24 hours (mL))	Median/IQR	755 (606, 975)	850(688, 1095)	NA	>0.05

Study Details	Outcome	Data available	VE testing arm results	Control Results	RR or MD (95% CI)	P-value
Girdauskas(2010)[54]	RBC transfusion within 24 hours	Number of patients/ Number of events	24/27	27/29	0.9 (0.81, 1.12)	0.80
	FFP transfusion within 24 hours		9/27	25/29	0.3 (0.23, 0.68)	<0.001
	Fibrinogen within 24 hours		21/27	26/29	0.8 (0.69, 1.10)	0.20
	Factor VIIa transfusion		1/27	2/29	0.6 (0.09, 4.55)	0.80
	Massive transfusion (>20 units) within 24 hours		5/27	10/29	0.5 (0.23, 1.37)	0.03
	Platelet transfusion within 24 hours		14/27	23/29	0.6 (0.44, 0.99)	0.03
	Prothrombin complex concentrate within 24 hours		4/27	26/29	0.1 (0.08, 0.43)	<0.001
	Allogeneic blood products transfused within 24 hours		24/27	29/29	0.8 (0.78, 1.02)	0.06
	Re-exploration for bleeding within 24 hours		5/27	7/29	0.7 (0.30, 2.08)	0.70
	Dialysis dependent renal failure		5/27	7/29	0.7 (0.30, 2.08)	0.6
	Mean length of ICU stay		6/27	7/29	0.9 (0.37, 2.32)	0.80
	Postoperative confusion		4/27	7/29	0.6 (0.23, 1.83)	0.50
	Reintubation		7/27	5/29	1.4 (0.55, 3.86)	0.40
	Stroke		4/27	3/29	1.3 (0.38, 5.04)	0.60
	Surgical source of bleed (found on re-exploration)		4/27	5/29	0.8 (0.28, 2.72)	0.80
	Death In hospital		4/27	5/29	0.8 (0.28, 2.72)	0.80
	RBC transfusion (perioperative transfusion within 24 hours)	Median/IQR	6(2, 13)	9(4, 14)	NA	0.20
	Any blood product transfusion (perioperative transfusion within 24 hours)		9(2, 30)	16(9, 23)		0.02
	FFP transfusion (perioperative transfusion within 24 hours)		3(0, 12)	8(4, 18)		0.01
	Fibrinogen (perioperative transfusion within 24 hours)		2(2, 3)	2(2, 3)		0.70
	Platelet transfusion (perioperative transfusion within 24 hours)		1(0, 4)	2(1, 3)		0.70
	Prothrombin complex concentrate (perioperative transfusion within 24 hours)		0(0, 2000)	3000(2000, 3000)		<0.001
	Bleeding (ml) within 24 hours		890(600, 1250)	950(650, 1400)		0.50
	Mean length of ICU stay (number staying >10 days)	Mean	7.3(9.1)	8.1(8.4)	-0.8 (-5.4, 3.8)	0.6
	Number of days in hospital		16.6(16.4)	17.0(14.8)	-0.4 (-8.6, 7.8)	0.80

Study Details	Outcome	Data available	VE testing arm results	Control Results	RR or MD (95% CI)	P-value
Kultufan Turan(2006)[52]	RBC transfusion within 24 hours	Number of patients/ Number of events	7/20	12/20	0.6 (0.31, 1.17)	0.031
	Platelet transfusion within 24 hours		1/20	0/20	3.0 (0.13, 69.42)	1.00
	Whole fresh blood transfusion within 24 hours		3/20	5/20	0.6 (0.19, 2.10)	0.422
	Bleeding (postoperative within 24 hours)	Mean (SD)	837.50(494.1)	711.10(489.2)	126.4 (-178.3, 431.1)	0.581
	FFP transfusion (units within 24 hours)	Mean (SD)	2.80(0.95)	2.70(1.46)	0.1 (-0.66, 0.86)	0.403
Nuttall(2001)[50]	Surgical source of bleed	Number of patients/ Number of events	0/41	2/51	0.2 (0.01, 5.03)	0.50
	Re-operation		0/41	6/51	0.0 (0.005, 1.65)	0.032
	RBC transfusion	Median/Range	2(0, 9)	3(0, 70)	NA	0.039
	Platelet transfusion	Median/Range	6(0, 18)	6(0, 144)		0.0001
	FFP transfusion	Median/Range	2(0, 10)	4(0, 75)		0.005
	Bleeding (mediastinal tube drainage (mL) within 24 hours)	Median/Range	590(240, 2335)	850(290, 10190)		0.019
Paniagua(2011)[53]	RBC transfusion	Mean	3.80	6.40	NA	NR
	Platelet transfusion	Total transfused	0.50	1.57		<0.05
	FFP transfusion	Total transfused	3.10	3.40		NR
Rauter(2007)[55]	RBC transfusion: Units (intraoperative + 48 hours post op)	Mean	0.8	1.3	NA	p<0.05
	FFP transfusion: Units (intraoperative + 48 hours post op)	Total transfused	0	4		NR
	Platelet transfusion: Units (intraoperative + 48 hours post op)		0	0		NR
	Prothrombin complex concentrate: IU (intraoperative + 48 hours post op)		3000	13600		NR
	Fibrinogen: g (intraoperative + 48 hours post op)		31	30		NR

Study Details	Outcome	Data available	VE testing arm results	Control Results	RR or MD (95% CI)	P-value
Royston(2001)[49]	Haemostatic blood product transfusion within 12 hours	Number of patients/ Number of events	5/30	10/30	.5 (0.21, 1.29)	NR
	Re-operation (Return to theatre for control of surgical bleed) within 48 hours		1/30	1/30	1.0 (0.11, 9.09)	NR
	Death within 48 hours		0/30	0/30	1.0 (0.02, 48.80)	NR
	FFP transfusion (units within 12 hours)	Total	5	16	NA	<0.05
	Platelet transfusion (platelet pools within 12 hours)	Total	1	9		<0.05
	Bleeding (Chest tube losses within 12 hours)	Median/IQR	470(295, 820)	390(240, 820)		NR
Shore-Lesserson(1999)[51]	RBC transfusion (total within 24 hours)	Number of patients/ Number of events	22/53	31/52	0.7 (0.48, 1.03)	NR
	RBC transfusion (post-operative)		10/53	16/52	0.6 (0.32, 1.22)	
	RBC transfusion (intra-operative)		17/53	23/52	0.7 (0.45, 1.19)	
	Any blood product transfusion		22/53	34/52	0.6 (0.44, 0.93)	
	FFP transfusion (total within 24 hours)		4/53	16/52	0.2 (0.10, 0.70)	
	FFP transfusion (post-operative)		2/53	11/52	0.2 (0.06, 0.79)	
	FFP transfusion (intra-operative)		3/53	8/52	0.4 (0.12, 1.32)	
	Platelet transfusion (intra-operative)		5/53	8/52	0.6 (0.23, 1.73)	
	Platelet transfusion (total within 24 hours)		3/53	9/52	0.3 (0.11, 1.16)	
	Platelet transfusion (total within 24 hours)		7/53	15/52	0.4 (0.22, 1.04)	
	Re-operation for post-operative bleeding		0/53	2/52	0.1 (0.01, 3.99)	
	Surgical source of bleed found on re-exploration		0/53	1/52	0.3 (0.01, 7.85)	
	Death		0/53	2/52	0.1 (0.009, 3.99)	
	RBC transfusion (total mL within 24 hours)	Mean (sd)	354(487)	475(593)	-121(-329, 87)	0.12
	Platelet transfusion (total mL within 24 hours)		34(94)	83(160)	-49(-99,1)	0.16
	FFP transfusion (total mL within 24 hours)		36(142)	217(463)	-181(-313,-50)	<0.04
	Bleeding (mediastinal tube drainage + reinfusion (mL) within 24 hours)		702(500)	901(847)	-199(-466,68)	0.27

Study Details	Outcome	Data available	VE testing arm results	Control Results	RR or MD (95% CI)	P-value
Weber(2012)[35]	RBC transfusion (24 hours post-operative)	Number of patients/ Number of events	32/50	41/50	0.7 (0.61, 1.00)	0.07
	RBC transfusion (total within 24 hours)		42/50	49/50	0.8 (0.76, 0.97)	0.031
	RBC transfusion (intra-operative)		33/50	45/50	0.7 (0.59, 0.91)	0.007
	Factor VIIa transfusion (total within 24 hours)		1/50	12/50	0.1 (0.02, 0.62)	0.002
	Factor VIIa transfusion (24 hours post-operative)		0/50	4/50	0.1 (0.06, 2.01)	0.117
	Factor VIIa transfusion (intra-operative)		1/50	9/50	0.1 (0.02, 0.84)	0.016
	FFP transfusion (total within 24 hours)		20/50	40/50	0.5 (0.35, 0.73)	<0.001
	FFP transfusion (intra-operative)		16/50	39/50	0.4 (0.27, 0.64)	<0.001
	FFP transfusion (24 hours post-operative)		7/50	19/50	0.3 (0.18, 0.81)	0.011
	Fibrinogen (intra-operative)		23/50	26/50	0.8 (0.60, 1.32)	0.689
	Fibrinogen (total within 24 hours)		32/50	30/50	1.0 (0.79, 1.44)	0.837
	Fibrinogen (24 hours post-operative)		16/50	14/50	1.1 (0.63, 2.05)	0.828
	Platelet transfusion (total within 24 hours)		28/50	33/50	0.8 (0.62, 1.16)	0.412
	Platelet transfusion (24 hours post-operative)		23/50	26/50	0.8 (0.60, 1.32)	0.689
	Platelet transfusion (intra-operative)		10/50	24/50	0.4 (0.23, 0.79)	0.006
	Prothrombin complex concentrate (intra-operative)		13/50	16/50	0.8 (0.45, 1.50)	0.66
	Prothrombin complex concentrate (24 hours post-operative)		12/50	16/50	0.7 (0.41, 1.41)	0.504
	Prothrombin complex concentrate (total within 24 hours)		22/50	26/50	0.8 (0.57, 1.27)	0.433
	Desmopressin treatment (intra-operative)		26/50	27/50	0.9 (0.677, 1.39)	1.0
	Desmopressin treatment (total within 24 hours)		36/50	35/50	1.0 (0.80, 1.32)	1.0
	Desmopressin treatment (24 hours post-operative)		10/50	9/50	1.1 (0.50, 2.43)	1.0
	Re-operation		5/50	8/50	0.6 (0.24, 1.76)	NR
	RBC transfusion (within 24 hours)	Median/IQR	3(2, 6)	5(4, 9)	NA	<0.001
	FFP transfusion (units within 24 hours)		0(0, 3)	5(3, 8)		<0.001
	Fibrinogen (g within 24 hours)		2(0, 4)	2(0, 6)		0.481
	Platelet transfusion (units within 24 hours)		2(0, 2)	2(0, 5)		0.010
	Prothrombin complex concentrate (IU within 24 hours)		0(0, 1800)	1200(0, 1800)		0.155
	Bleeding (post-op chest tube blood loss, mL within 24 hours)		600(263, 875)	900(600 1288)		0.021
	Mean length of ICU stay (hours)		21(18, 31)	24(20, 87)		0.019
	Number of days in hospital		12(9, 22)	12(9, 23)		0.718

Study Details	Outcome	Data available	VE testing arm results	Control Results	RR or MD (95% CI)	P-value
Westbrook (2009)[47]	RBC transfusion (units)	Total number of units	14	33	NA	0.12
	Any blood product transfusion (units)		37	90		NR
	FFP transfusion (units)		22	18		NR
	Platelet transfusion (units)		5	15		NR
	Bleeding (mL)	Median/IQR	875(755, 1130)	960(820)		0.437
	Mean length of ICU stay (hours)		29.4(14.3, 56.4)	32.5(22.0, 74.5)		0.369
	Number of days in hospital		9(7, 13)	8(7, 12)		>0.05

e. Results from prediction studies in cardiac surgery patients

Study Details	VE or conventional test	Test assay, parameters and threshold	Outcome/Reference standard details and timing	Crude DOR (95% CI)	AUC (95% CI or SE)
Bischof(2009)[60]	Sonoclot	glass bead activated, PF	Bleeding (>800 mL) Chest tube drainage recorded hourly for the first 4 hours after surgery	18.6 (7.6, 45.7)	0.79(0.72, 0.87)
	Sonoclot	glass bead activator, ACT		10.2 (4.7, 21.9)	0.76(0.70, 0.82)
	Sonoclot	glass bead activated, CR		8.2 (3.9, 17.2)	0.72(0.63, 0.81)
Nuttall(1997)[61]	Conventional	Bleeding time: 5 minutes	Bleeding (Subjective): anaesthesiologist and surgeon evaluated blood loss 10 minutes after protamine administration. The patient was characterized as a "bleeder" if both physicians determined the surgical field was "wet" (microvascular bleeding). If both physicians determined the surgical field was dry, the patient was labelled as a "nonbleeder." If there was disagreement between the physicians on the condition of the surgical field, the patient was excluded from data analysis.	4.6(1.7, 12.5)	0.69(0.07)
		PT: 15.3 seconds		11.0 (3.7, 32.9)	0.81(0.05)
		aPTT: 41.3 seconds		11.2 (3.6, 34.8)	0.80(0.04)
		Platelet MPV: 7.8fL		5.0 (1.9, 13.3)	0.72(0.06)
		Platelet count: 102K/mm^3		6.2 (2.3, 16.7)	0.77(0.06)
		Platelet haematocrit: 0.08%		6.4 (2.3, 17.5)	0.78(0.07)
		Plasma fibrinogen concentration: 144 mg/dL		4.2 (1.6, 11.2)	0.72(0.06)
	Sonoclot	R1: 16cm/min		4.3 (1.4, 13.0)	0.68(0.05)
		P1-P2: 774 seconds		5.1 (1.6, 16.6)	0.58(0.07)
		P2 (time to peak): 1182 seconds		5.5 (1.8,16.8)	0.62(0.07)
		P1 (time to shoulder): 408 seconds		6.4 (1.8, 22.4)	0.59(0.07)
		R2: 5.1cm/min		3.4 (1.3, 8.8)	0.73(0.05)
		Onset: 220sec		1.3 (0.5, 3.2)	0.42(0.07)
		R3: -1.6cm/min		5.0 (1.9, 13.1)	0.30(0.06)
	TEG	MA + 30: 46mm		2.6 (1.0, 6.6)	0.64(0.06)
		R: 17mm		2.1 (0.8, 5.4)	0.59(0.06)
		MA: 48mm		5.3 (2.0, 14.3)	0.71(0.06)
		α angle: 42 degrees		4.1 (1.6, 10.7)	0.67(0.06)
		R + k: 25mm		3.3 (1.3, 8.6)	0.67(0.06)

Study Details	VE or conventional test	Test assay, parameters and threshold	Outcome/Reference standard details and timing	Crude DOR (95% CI)	AUC (95% CI or SE)
Tuman(1989)[62]	Conventional	ACT, PT, PTT, PLT, and FIB: Abnormalities of coagulation were defined as values exceeding 20% reduction from the lowest values of the normal range (FIB, PLT), or exceeding 20% of the highest values of the normal range	Bleeding defined as chest tube drainage greater than 150 mL/hr for 2 consecutive hr or greater than 300 mL/hr in 1 hr during the first 8 hr after surgery	0.5 (0.1, 2.2)	NR
	Sonoclot	ACT, R1, R2, PEAK and R3: Abnormalities of coagulation were defined as values exceeding 20% reduction from the lowest values of the normal range or 20% of the highest values (ACT)		37.2 (NR)	NR
	TEG	NR, R, k, MA, alpha value, A60: Abnormalities of coagulation were defined as values exceeding 20% reduction from the lowest values of the normal range		98.5 (NR)	NR

f. Results from prediction studies in trauma patients

Study Details	VE or conventional test	Test assay, parameters and threshold	Outcome/Reference standard details and timing	DOR (95% CI)	AUC (95% CI)	Variables Adjusted for
Cotton(2011)[75]	TEG	Rapid_TEG, ACT: <105 s	Massive transfusion (≥10 units PRBC) : 6 hours	5.15(1.36, 19.49)	NR	Age (yrs), gender, blunt mechanism of injury, race, ED systolic blood pressure, ED heart rate, positive FAST (focussed assessment for the sonography of trauma) examination
			RBC transfusion: 6 hours	1.85(1.07, 3.19)	NR	
Davenport(2011)[72]	Conventional	PTr: >1.2	RBC transfusion (any PRBC) : 12 hours	5.2 (2.1, 13.0)	NR	Crude
	ROTEM	EXTEM, CT: >94 s		1.8 (0.9, 3.8)	NR	Crude
		EXTEM, CA5: ≤35 mm		3.7 (2.0, 7.0)	NR	Crude
		EXTEM, α angle: <65°		3.9 (1.8, 8.2)	NR	Crude
	Conventional	PTr: >1.2	Massive transfusion (>10 units PRBC) : 12 hours	13.2 (3.6, 47.6)	NR	Crude
	ROTEM	EXTEM, CA5: ≤35 mm		13.4 (3.4, 52.5)	NR	Crude
		EXTEM, CT: >94 s		3.0 (0.7, 11.7)	NR	Crude
		EXTEM, α angle: <65		7.5 (2.1, 26.0)	NR	Crude
	Conventional	PTr: >1.2	FFP transfusion (any) : 12 hours	6.1 (2.4, 15.4)	NR	Crude
	ROTEM	EXTEM, CA5: ≤35 mm		3.5 (1.7, 7.0)	NR	Crude
		EXTEM, CT: >94 s		1.4 (0.6, 3.4)	NR	Crude
		EXTEM, α angle: <65		3.9 (1.8, 8.7)	NR	Crude
Holcomb(2012)[76]	Conventional	aPTT: >35	Massive transfusion (Continuous) >=10 units RBC: 6 hours	3.08(1.52, 6.26)	NR	age, sex, mechanism of injury, base deficit, weighted, revised trauma score, and injury severity score
		INR: >1.5		3.44(1.75, 6.77)	NR	
		Plasma fibrinogen concentration: <180		2.03(.63, 6.55)	NR	
		Platelet count: <150		2.39(1.00, 5.75)	NR	
		PT: >18		2.89(1.41, 5.95)	NR	
	TEG	Rapid_TEG, ACT: >128		1.95(1.08, 3.54)	NR	
		Rapid_TEG, k: >2.5		2.48(1.32, 4.65)	NR	

Study Details	VE or conventional test	Test assay, parameters and threshold	Outcome/Reference standard details and timing	DOR (95% CI)	AUC (95% CI)	Variables Adjusted for
		Rapid_TEG, LY30: >3%		1.99(1.01, 3.89)	NR	
		Rapid_TEG, MA: <55		3.63(1.81, 6.98)	NR	
		Rapid_TEG, r-value: >1.1		2.34(1.21, 4.55)	NR	
		Rapid_TEG, α-angle: <56		8.99(2.86, 28.29)	NR	
	Conventional	aPTT: >35	Massive transfusion of cryoprecipitate (Continuous) >=20 units: 6 hours	2.26(.73, 7.09)	NR	
		INR: >1.5		4.25(1.58, 11.48)	NR	
		Plasma fibrinogen concentration: <180		1.36(.26, 7.01)	NR	
		Platelet count: <150		2.44(.79, 7.55)	NR	
		PT: >18		2.25(.96, 6.76)	NR	
	TEG	Rapid_TEG, ACT: >128		1.83(.19, 4.25)	NR	
		Rapid_TEG, k: >2.5		4.04(1.74, 9.36)	NR	
		Rapid_TEG, LY30: >3%		3.50(1.47, 8.36)	NR	
		Rapid_TEG, MA: <55		4.71(1.97, 11.28)	NR	
		Rapid_TEG, r-value: >1.1		1.81(.71, 4.64)	NR	
		Rapid_TEG, α-angle: <56		7.96(2.20, 18.85)	NR	
	Conventional	aPTT: >35	Massive transfusion of plasma (Continuous) >=6 units: 6 hours	3.34(1.58, 7.09)	NR	
		INR: >1.5		3.72(2.16, 6.41)	NR	
		Plasma fibrinogen concentration: <180		1.33(.45, 3.99)	NR	
		Platelet count: <150		2.19(1.02, 4.72)	NR	
		PT: >18		3.49(1.84, 6.63)	NR	
	TEG	Rapid_TEG, ACT: >128		1.63(1.02, 2.61)	NR	
		Rapid_TEG, k: >2.5		2.20(1.33, 3.65)	NR	
		Rapid_TEG, LY30: >3%		1.48(.85, 2.59)	NR	
		Rapid_TEG, MA: <55		3.10(1.77, 5.35)	NR	
		Rapid_TEG, r-value: >1.1		1.95(1.15, 3.34)	NR	
		Rapid_TEG, α-angle: <56		6.06(2.13, 11.26)	NR	
	Conventional	aPTT: >35	Massive transfusion of platelets (Continuous) >=2 apheresis units: 6 hours	5.02(2.42, 10.44)	NR	
		INR: >1.5		4.91(2.68, 9.01)	NR	
		Plasma fibrinogen concentration: <180		2.44(.84, 7.13)	NR	

Study Details	VE or conventional test	Test assay, parameters and threshold	Outcome/Reference standard details and timing	DOR (95% CI)	AUC (95% CI)	Variables Adjusted for
		Platelet count: <150		4.01(1.92, 8.38)	NR	
		PT: >18		5.04(2.65, 9.59)	NR	
	TEG	Rapid_TEG, ACT: >128		1.70(.99, 2.91)	NR	
		Rapid_TEG, k: >2.5		2.45(1.39, 4.32)	NR	
		Rapid_TEG, LY30: >3%		2.02(1.10, 3.70)	NR	
		Rapid_TEG, MA: <55		2.47(1.32, 4.62)	NR	
		Rapid_TEG, r-value: >1.1		1.95(1.06, 3.56)	NR	
		Rapid_TEG, α-angle: <56		6.70(2.34, 10.02)	NR	
	Conventional	Plasma fibrinogen concentration: <180	Substantial bleeding defined as (1) receiving first RBC unit within 2 hours of Emergency Department arrival and (2) at least 5RBC transfusion or death from haemorrhage within 4 hours of Emergency Department arrival.	2.01(.68, 5.97)	NR	
		PT: >18		2.55(1.59, 4.10)	NR	
		aPTT: >35		2.68(1.62, 4.45)	NR	
		INR: >1.5		3.40(1.66, 7.00)	NR	
		Platelet count: <150		2.52(1.22, 5.25)	NR	
	TEG	Rapid_TEG, LY30: >3%		1.94(1.16, 3.24)	NR	
		Rapid_TEG, MA: <55		2.42(1.41, 4.15)	NR	
		Rapid_TEG, α-angle: <56		2.66(1.13, 6.28)	NR	
		Rapid_TEG, k: >2.5		1.75(1.16, 2.66)	NR	
		Rapid_TEG, r-value: >1.1		2.52(1.43, 4.43)	NR	
		Rapid_TEG, ACT: >128		1.70(1.04, 2.77)	NR	
Ives(2012)[74]	TEG	Kaolin, EPL: Hyperfibrinolysis defined as EPL >15%	Death within 24 hours	25.0(2.8, 221.4)	NR	Packed red blood cells in 24h >10U
		Kaolin, r, K, alpha angle, and MA; Hypocoagulable: 2 or more of the following: prolonged reaction time, prolonged amplitude, and decreased angle and/or MA.		7.0 (1.7, 29.2)	NR	

Study Details	VE or conventional test	Test assay, parameters and threshold	Outcome/Reference standard details and timing	DOR (95% CI)	AUC (95% CI)	Variables Adjusted for
		Kaolin, r, K, alpha angle, and MA; Hypercoagulable: short reaction time, short amplitude, increased angle and/or MA		0.33 (0.04, 2.7)	NR	
		Kaolin, EPL: Hyperfibrinolysis defined as EPL >15%	RBC transfusion	42.0	NR	
			Plasma transfusion	8.3 (2.3, 29.6)	NR	
			Platelet transfusion	7.8 (2.2, 27.8)	NR	
Jeger(2012)[79]	Conventional	INR: >1.2	Any blood product transfusion (patients receiving blood products) : 24 hours	4.5 (NR)	73 (NR)	Crude
		INR: >1.5		5.6 (NR)	73 (NR)	Crude
		Thrombin time: >13.2 s		2.5 (NR)	53 (NR)	Crude
		aPTT: >60 s		2.6 (NR)	74 (NR)	Crude
		Plasma fibrinogen: <3 g/L		8.3 (NR)	74 (NR)	Crude
	TEG	Kaolin, k: >1.7		3.1 (NR)	67 (NR)	Crude
		Rapid_TEG, k: >1.8 min		7.5 (NR)	79 (NR)	Crude
		Rapid_TEG, α angle: <74.7		7.0 (NR)	77 (NR)	Crude
		Rapid_TEG, MA: <59.6 mm		8.5 (NR)	75 (NR)	Crude
		Rapid_TEG, G: <7374 d/s		7.5 (NR)	73 (NR)	Crude
		Kaolin, α angle: <58.5		4.0 (NR)	66 (NR)	Crude
		Kaolin, MA: <58.4 mm		9.3 (NR)	70 (NR)	Crude
		Kaolin, Time to peak: >24.7 min		3.0 (NR)	58 (NR)	Crude
		Kaolin, G: <7073 d/s		9.3 (NR)	70 (NR)	Crude
		Rapid_TEG, Time to peak: >17.3 min		4.2 (NR)	69 (NR)	Crude
Kaufmann(1997)[66]	TEG	r, K, alpha angle, and MA: Hypocoagulable defined as two or more of the following: long r and/or K time, decreased alpha-angle, and decreased MA.	Any blood product transfusion (Any) Any products transfused from the time of presentation to the ED until 24 hours later: 24 hours	104.9 (8.2, 1333.6)	NR	Crude

Study Details	VE or conventional test	Test assay, parameters and threshold	Outcome/Reference standard details and timing	DOR (95% CI)	AUC (95% CI)	Variables Adjusted for
		r, K, alpha angle, and MA: Hypercoagulable: 2 or more of the following - short r and/or K time, increased alpha angle, and increased MA		0.2 (0.0, 0.9)	NR	Crude
Korfage(2011)[77]	ROTEM	EXTEM, CFT: NR	Any blood product transfusion ("prolonged EXTEM CFT") "need for transfusion": 48 hours	15.26 (1.47, 158.30)	NR	multinomial regression analyses unclear which variables included in the final model.
Kunio(2012)[69]	TEG	R >9 minutes	Neurosurgical intervention (Intracranial pressure monitor, ventriculostomy, craniotomy, craniectomy)	6.8(0.7, 61.6)	NR	Crude
			Death in hospital	7.5 (1.3, 44.8)	NR	Crude
Leemann(2010)[67]	Conventional	aPTT >36 s	Massive transfusion (≥10 units PRBC) within 24 hours	7.75(1.93,31.18)	NR	Crude
		Platelet count <100 x 10^3		4.71(.77,28.77)	NR	Crude
		INR >1.2		10.11(2.63,38.81)	NR	Crude
	ROTEM	INTEM, MCF: abnormal (normal range 50-72 mm)		5.63(1.37,23.06)	NR	Crude
		INTEM, A20: abnormal (normal range 50-71 mm)		5.16(1.01,26.45)	NR	Crude
		INTEM, A10: abnormal (normal range 44-66 mm)		11.20(1.33,94.49)	NR	Crude
		INTEM, α angle: abnormal (normal range 70-83)		5.23(.60,45.67)	NR	Crude
		EXTEM, MCF: abnormal (normal range 50-72 mm)		3.95(.96,16.21)	NR	Crude
		EXTEM, A20: abnormal (normal range 50-71 mm)		4.29(.83,22.03)	NR	Crude
		EXTEM, A10: abnormal (normal range 43-65 mm)		4.36(.86,22.26)	NR	Crude

Study Details	VE or conventional test	Test assay, parameters and threshold	Outcome/Reference standard details and timing	DOR (95% CI)	AUC (95% CI)	Variables Adjusted for
		EXTEM, α angle: abnormal (normal range 63-83)		2.80(.67,11.79)	NR	Crude
		EXTEM, CFT: abnormal (normal range 34-159 s)		4.38(1.05,18.32)	NR	Crude
		INTEM, MCF: abnormal (normal range 50-72 mm)		8.47(1.19, 62.50)	0.82(0.71, 0.94)	haemoglobin ≤10 g/dL
Nystrup(2011)[73]	Conventional	aPTT: NR	Death within 30 days	1.10(1.00, 1.20)	0.78(0.61, 0.95)	age and ISS
		INR: NR		NR	0.63(0.44, 0.81)	Crude
	TEG	MA: maximum clot strength <50 mm		5.00(1.22, 20.45)	NR	age and ISS
		MA: NR		NR	0.70(0.53, 0.86)	Crude
Pezold(2012)[82]	Conventional	aPTT	Death (NA) Coagulation-related mortality (death after receiving a MT ≥10 PRBC units): 6 hours	NR	0.89(0.81, 0.97)	age, ISS and systolic blood pressure
		INR		NR	0.88(0.80, 0.97)	
	TEG	Rapid_TEG, G		NR	0.93(0.87, 0.98)	
	Conventional	aPTT	Massive transfusion (≥10 units PRBC) : 6 hours	NR	0.90(0.83, 0.97)	
		INR		NR	0.92(0.86, 0.98)	
	TEG	Rapid_TEG, G		NR	0.89(0.83, 0.96)	
Schochl(2011)[70]	Conventional	aPTT	Death; overall mortality	NR	0.76(0.64, 0.88)	Crude
	ROTEM	FIBTEM, MCF		NR	0.73(0.59, 0.87)	Crude
Schochl(2011)[78]	Conventional	aPTT: ≤35.2 s	Massive transfusion (≥10 RBC units) : 24 hours	18.9	0.85(.81, .89)	Crude
		Plasma fibrinogen: ≤148 mg/dL		11.2	0.83(0.78, 0.87)	Crude
		Platelet count: ≤161 x 10^3/μL		4.6	0.70(0.65, 0.75)	Crude
	ROTEM	INTEM, CT: ≤167 s		5.9	0.71(0.65, 0.76)	Crude
	ROTEM	INTEM, MCF: ≤51 mm		6.5	0.78(0.73, 0.83)	Crude
	ROTEM	FIBTEM, MCF: ≤7 mm		10.6	0.84(0.79, 0.88)	Crude
	ROTEM	INTEM, CFT: ≤111 s		6.1	0.78(0.73, 0.82)	Crude
	ROTEM	FIBTEM, A10: ≤4 mm		8.3	0.83(0.78, 0.87)	Crude

Study Details	VE or conventional test	Test assay, parameters and threshold	Outcome/Reference standard details and timing	DOR (95% CI)	AUC (95% CI)	Variables Adjusted for
	ROTEM	EXTEM, CT: ≤72 s		4.6	0.71(0.66, 0.76)	Crude
	ROTEM	EXTEM, CFT: ≤147 s		5.6	0.74(0.68, 0.79)	Crude
	ROTEM	EXTEM, MCF: ≤52 mm		5.0	0.76(0.71, 0.81)	Crude
Tapia(2012)[71]	TEG	Presence of Hyperfibrinolysis; no further details	Death within 30 days	98.7 (12.7, 765.1)	NR	Crude
Tauber(2011)[68]	ROTEM	FIBTEM: Fulminant hyperfibrinolysis	Death (NA) Overall mortality: 24 hours	40.2 (8.6, 187.1)	NR	Crude
		FIBTEM: Any hyperfibrinolysis		10.3 (4.2, 25.4)	NR	Crude
		FIBTEM: Moderate hyperfibrinolysis		1.1 (0.1, 8.7)	NR	Crude

g. Results from prediction studies in PPH patients

Study Details	VE or conventional test	Test assay, parameters and threshold	Outcome/Reference standard details and timing	DOR (95% CI)	AUC (95% CI)	Variables Adjusted for
Bolton(2011)[84]	ROTEM	NR	Coagulopathy requiring treatment	102.8 (9.5, 1110.6)	NR	Crude
			FFP transfusion	76 (NR)	NR	Crude
			Platelet transfusion	19.0 (NR)	NR	Crude
Lilley(2013)[85]	Conventional	Clauss fibrinogen	RBC transfusion (Any transfusion) :	NR	0.72(NR)	Crude
	ROTEM	FIBTEM, MCF: <18mm	RBC transfusion (Any) :	33.7 (7.3, 155.7)	0.74(NR)	Crude
	Conventional	Clauss fibrinogen	RBC transfusion (>=4 units) :	NR	0.84(NR)	Crude
	ROTEM	FIBTEM, MCF	RBC transfusion (>=4 units) :	NR	0.80(NR)	Crude
	Conventional	Clauss fibrinogen	Invasive Procedures () :	NR	0.93(NR)	Crude
	ROTEM	FIBTEM, MCF	Invasive Procedures () :	NR	0.89(NR)	Crude

APPENDIX 3: RISK OF BIAS ASSESSMENTS

a. Cochrane Risk of Bias Assessments for RCTs in cardiac patients

Study Name: Ak(2009)[46]

	Support for judgement	Risk of bias
Random sequence generation	No details on randomisation method	Unclear
Allocation concealment	No details on concealment of allocation	Unclear
Participant/Personnel blinding	Transfusions were performed by the anaesthesiologist who was blinded to the patient's group assignment. Unclear whether patient was blinded but would have been unlikely to influence results.	Low
Outcome assessor blinding	Transfusions (outcome) were performed by the anaesthesiologist who was blinded to the patient's group assignment.	Low
Incomplete Outcome Data	No withdrawals reported, all patients randomised appear to be included in the analysis	Low
Selective outcome reporting	All outcomes specified in the methods reported in the results; no mention of study protocol.	Low

Study Name: Avidan(2004)[48]

	Support for judgement	Risk of bias
Random sequence generation	No details on randomisation method	Unclear
Allocation concealment	No details on concealment of allocation	Unclear
Participant/Personnel blinding	Investigators were not blind to group allocation	High
Outcome assessor blinding	Blood loss into the chest tube and post-surgical blood product use were recorded by staff in the recovery unit who were unaware of group allocation.	Low
Incomplete Outcome Data	No withdrawals reported, all patients randomised appear to be included in the analysis	Low
Selective outcome reporting	Outcomes were not specified in the methods section; no mention of study protocol	Unclear

Study Name: Girdauskas(2010)[54]

	Support for judgement	**Risk of bias**
Random sequence generation	Patients were randomly assigned using a computer generated list	Low
Allocation concealment	No details on concealment of allocation	Unclear
Participant/Personnel blinding	No details on blinding	Unclear
Outcome assessor blinding	No details on blinding	Unclear
Incomplete Outcome Data	No withdrawals reported, all patients randomised appear to be included in the analysis	Low
Selective outcome reporting	All outcomes specified in the methods reported in the results; no mention of study protocol.	Low

Study Name: Kultufan Turan(2006)[52]

	Support for judgement	**Risk of bias**
Random sequence generation	No details on randomisation method	Unclear
Allocation concealment	No details on concealment of allocation	Unclear
Participant/Personnel blinding	Physician in charge of ROTEG and ICU physician were blinded.	Low
Outcome assessor blinding	No details on blinding	Unclear
Incomplete Outcome Data	No withdrawals reported, all patients randomised appear to be included in the analysis	Low
Selective outcome reporting	All outcomes specified in the methods reported in the results; no mention of study protocol.	Low

Study Name: Nuttall(2001)[50]

	Support for judgement	Risk of bias
Random sequence generation	Computer-generated randomisation list with a block size of four to one of two groups. Four of the patients initially randomised to the algorithm group were converted to the control group because of unavailability of study personnel.	High
Allocation concealment	No details on concealment of allocation	High
Participant/Personnel blinding	No details on blinding	Unclear
Outcome assessor blinding	The surgeons and anaesthesiologists were not made aware of which group the patients were placed in until after they decided that the patient had abnormal bleeding after CPB and they felt the patient needed to have transfusion of non-erythrocyte components. Therefore, the people making the transfusion decisions were blinded to group designation of the patients until after the determination of abnormal bleeding after CPB.	Low
Incomplete Outcome Data	Four of the patients initially randomised to the algorithm group were converted to the control group because of unavailability of study personnel. An ITT analysis was conducted for a small number of the outcomes but not all; data were extracted for the per protocol analyses for consistency. ITT analyses reported similar results to per protocol analyses. No additional dropouts reported.	Low
Selective outcome reporting	Outcomes were not specified in the methods section; no mention of study protocol	Unclear

Study Name: Paniagua(2011)[53]

	Support for judgement	Risk of bias
Random sequence generation	No details on randomisation method	Unclear
Allocation concealment	No details on concealment of allocation	Unclear
Participant/Personnel blinding	No details on blinding	Unclear
Outcome assessor blinding	No details on blinding	Unclear
Incomplete Outcome Data	No withdrawals reported, all patients randomised appear to be included in the analysis	Low
Selective outcome reporting	Abstract only, limited data reported	High

Study Name: Rauter(2007)[55]

	Support for judgement	Risk of bias
Random sequence generation	No details on randomisation method	Unclear
Allocation concealment	No details on concealment of allocation	Unclear
Participant/Personnel blinding	Unblinded	High
Outcome assessor blinding	Unblinded	High
Incomplete Outcome Data	Five patients were excluded due to protocol violations and were not included in the analysis	High
Selective outcome reporting	Outcomes were not specified in the methods section; no mention of study protocol. Abstract only so appears that some outcomes missing and no measure of significance of results.	High

Study Name: Royston(2001)[49]

	Support for judgement	Risk of bias
Random sequence generation	"Allocation by means of series of sealed envelopes" - no further details. Patients who returned to theatre for control of surgical bleeding or who died within 48h of surgery were discarded and replaced by measurements from an additional patient.	High
Allocation concealment	"Allocation by means of series of sealed envelopes" - no further details	Unclear
Participant/Personnel blinding	No details on blinding	Unclear
Outcome assessor blinding	No details on blinding	Unclear
Incomplete Outcome Data	Patients who returned to theatre for control of surgical bleeding or who died within 48h of surgery were discarded and replaced by measurements from an additional patient. Two patients had excessive bleeding, none died.	High
Selective outcome reporting	Outcomes not pre-specified in methods and no mention of protocol	Unclear

Study Name: Shore-Lesserson(1999)[51]

	Support for judgement	Risk of bias
Random sequence generation	Patients were randomly assigned in a prospective fashion, using a table of random numbers	Low
Allocation concealment	No details on concealment of allocation	Unclear
Participant/Personnel blinding	No details on blinding	Unclear
Outcome assessor blinding	No details on blinding	Unclear
Incomplete Outcome Data	All 105 participants appear to have been included in the analyses. One patient in the control group had a surgical bleed and was excluded from the bleeding and transfusion analyses.	Low
Selective outcome reporting	Outcomes were not specified in the methods section; no mention of study protocol	Unclear

Study Name: Weber(2012)[35]

	Support for judgement	**Risk of bias**
Random sequence generation	The randomisation list was computer-generated using a balanced (allocation ratio 1:1) blockwise (20*10) randomisation by the software BiAS for Windows 9.07©(Epsilon Inc., Darmstadt, Germany).	Low
Allocation concealment	No details on concealment of allocation	Unclear
Participant/Personnel blinding	The attending physicians in the POC group were blinded to the results of conventional coagulation tests. Not clear whether conventional group were blinded to POC results	Unclear
Outcome assessor blinding	No details on blinding	Unclear
Incomplete Outcome Data	No withdrawals reported, all patients randomised appear to be included in the analysis	Low
Selective outcome reporting	All outcomes specified in the methods reported in the results; no mention of study protocol.	Low

Study Name: Westbrook(2009)[47]

	Support for judgement	Risk of bias
Random sequence generation	No details on randomisation method	Unclear
Allocation concealment	No details on concealment of allocation	Unclear
Participant/Personnel blinding	Surgeons were blinded to the method of haemostasis assessment	Low
Outcome assessor blinding	Decisions about the administration of blood products were based on TEG alone or standard laboratory tests alone, depending on group allocation; blinding was not explicitly reported	Unclear
Incomplete Outcome Data	No withdrawals were reported and all participants appear to have been included in the analyses	Low
Selective outcome reporting	Outcomes were not specified in the methods section; no mention of study protocol	Unclear

b. QUADAS-2 assessments for prediction studies in cardiac patients

Study: Bischof(2009)[60]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Patients undergoing cardiac surgery. Patients with known coagulopathy or anticoagulant medication were excluded

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: High**

B. APPLICABILITY

Limited details provided

Do the included patients match the question?	**Concerns: Unclear**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

Sonoclot (ACT, CR and PF), glass bead activated and celite/clay activated, pre-operative and post-protamine testing. Full data were only reported for post-protamine, glass bead activated tests The reference standard (bleeding) occurred after testing. No threshold was reported.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

Bleeding (chest tube drainage >800 mL in the first four hours after surgery), objective reference standard; unclear whether blinded to Sonoclot results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

No withdrawals were reported	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Low**

Study: Nuttall(1997)[61]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Adult men and women scheduled for elective cardiac surgery requiring CPB No exclusion criteria were reported

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Mixed cardiac surgery

Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

TEG and Sonoclot, methods described in detail Standard thresholds used Data only reported for individual TEG and Sonoclot parameters

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

Bleeding; patients classified as bleeders or non-bleeders by two anaesthetists, classification was subjective. The physicians evaluating the haemostatic condition of the operative field were blinded to the results of all coagulation tests.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

If there was disagreement on whether or not the patient was a bleeder the patient was excluded from the analysis.	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Study: Tuman(1989)[62]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Adult cardiac surgical patients prospectively considered to be at high risk for excessive post-CPB bleeding Exclusion criteria: abnormal preoperative coagulation or liver function studies; anticoagulant or antiplatelet medications within 7 days before surgery.

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Adult cardiac surgical patients

Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

Sonoclot and TEG Interpreted before bleeding had occurred Standard pre-specified thresholds used Data reported as the predictive accuracy of the whole test

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

Occurrence of bleeding measured objectively; unclear whether blinded to Sonoclot and TEG results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

All patients enrolled were included in the 2x2 table	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

c. Cochrane Risk of Bias Assessments for CCT in trauma patients

Study Name: Messenger(2011)[65]

	Support for judgement	**Risk of bias**
Random sequence generation	Not randomised	High
Allocation concealment	Not randomised and so allocation not concealer	High
Participant/Personnel blinding	No details on blinding reported	Unclear
Outcome assessor blinding	No details on blinding reported	Unclear
Incomplete Outcome Data	Numerical outcome data were not reported and so	Unclear
Selective outcome reporting	Outcomes were not pre-specified and so it was unclear whether only selected outcomes were reported	Unclear

d. QUADAS-2 assessments for prediction studies in trauma patients

Study: Cotton(2011)[75]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Consecutive major trauma activations, adult patients	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**

B. APPLICABILITY

Major trauma, no specific categories	
Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

rTEG full data only reported for ACT as this is the earliest result available. Reference standard (transfusion outcomes) assessed after rTEG. Thresholds derived from study data.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: High**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

MT or absence of any transfusion within 6 hrs	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

No drop outs reported	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Low**

Study: Davenport(2011)[72]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Trauma patients were only included if they presented when research staff were present (08:00 to 20:00), i.e. not a consecutive sample.

Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: High**

B. APPLICABILITY

Trauma patients including blunt and penetrating injuries

Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

Three ROTEM EXTEM parameters plus PTr. Each parameter analysed separately. Reference standard (transfusion) occurred after testing. ROTEM thresholds were derived from patients with normal PTr values within study.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: High**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Transfusion requirements. Unclear whether transfusion requirements were determined with knowledge of ROTEM and/or PTr results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

325 Patients were enrolled. 25 Were missing from the analyses: 3 ROTEM sample analysis incomplete; 15 consent process could not be completed; 7 retrospective exclusions

Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Low**

Study: Holcomb(2012)[76]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

all adult trauma patients admitted between September 2009 and February 2011

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**

B. APPLICABILITY

Trauma patients described as institution's highest level trauma activation. Injuries not described in detail except that 297 had traumatic brain injury.

Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

Rapid TEG assays and thresholds described but unclear how thresholds were derived.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Multiple reference standards relating to bleeding and transfusion requirements

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

No withdrawals reports

Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Low**

Study: Ives(2012)[74]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Convenience sample; only 45% of those eligible enrolled reasons for not enrolling remainder not reported.

Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: High**

B. APPLICABILITY

Mixed trauma patients

Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

TEG evaluated at standard thresholds

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Primary outcome mortality within 24 hours. Secondary outcomes were transfusion requirements - details on timing and thresholds not reported.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low/Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low/High**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

5 patients did not contribute to the regression model; reasons for this were not reported.

Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Study: Jeger(2012)[79]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

prospective, non-consecutive observational study of trauma patients; patients included where a physician with TEG experience was available on admission. No exclusion criteria reported

Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: High**

B. APPLICABILITY

Trauma patients, mainly blunt trauma.

Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

TEG, rTEG, and conventional laboratory tests. Data reported separately for each parameter. Reference standard (transfusion requirements determined after testing). Not clear whether TEG thresholds were pre-defined.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: High**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

transfusion requirements. Physicians were blinded to TEG results. The decision to transfuse was based on clinical evaluation and pre-defined thresholds for conventional laboratory coagulation tests.
NB: risk of bias is high for conventional laboratory tests.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

Nine patients were excluded due to technical problems and handling errors

Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Low**

Study: Kaufmann(1997)[66]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Prospective study of blunt trauma patients	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Mixed blunt trauma patients; some had received aspirin.	
Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

TEG detailed description of execution including machine.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Transfusion of any blood product, timing specified, decision reported to be blind to TEG result.	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

All patients included in 2x2 table	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Korfage(2011)[77]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Trauma patients admitted to an emergency department in Amsterdam	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Limited details reported	
Do the included patients match the question?	**Concerns: Unclear**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

Data appear to have been collected for ROTEM INTEM, EXTEM and FIBTEM, plus conventional laboratory tests, but predictive data were only reported for EXTEM CFT. Reference standard (transfusion requirements) occurred after testing. No threshold was reported.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Transfusion requirements. Not clear whether need for transfusion was determined with knowledge of ROTEM results.	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

No drop outs reported	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Low**

Study: Kunio(2012)[69]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Methods of patient enrolment unclear.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Only patients with traumatic brain injury; no use of specified anticoagulants prior to enrolment.	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

TEG; no details on assays used. State that manufacturers reference ranges used for all parameters	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Unclear**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Mortality and need for neurosurgical intervention	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

All patients appear to have been included in the 2x2 table	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Leemann(2010)[67]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Retrospective review of trauma patients for whom admission ROTEM results were available. Patients with isolated head injury were excluded.

Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: High**

B. APPLICABILITY

Trauma patients (excluding isolated head injury) ISS ≥16

Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

Various ROTEM parameters, analysed individually. Reference standard (MT) occurred after testing. Thresholds appear to have been based on pre-defined normal reference ranges.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Massive transfusion within 24 hours.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

No drop outs reported

Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Low**

Study: Nystrup(2011)[73]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Retrospective study of patients from a trauma registry, for whom admission TEG results were available	
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: High**

B. APPLICABILITY

Severe trauma, variety of causes and types reported	
Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

Limited details of TEG. Data only reported for overall clot strength and MA. Reference standard (30 day mortality) occurred after testing.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Reference standard 30 day mortality	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

No drop outs reported	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Low**

Study: Pezold(2012)[82]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Review of trauma activations at a single centre between May 2008 and September 2010; appears retrospective. Three patients who died from traumatic brain injury were excluded.

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: High**

B. APPLICABILITY

Trauma patients ISS >15

Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

rTEG only one parameter reported (G, global measure of clot strength). Reference standards (outcomes) occurred after testing. Only ROC AUC data were reported.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: High**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

reference standard MT and coagulation-related mortality

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

No drop outs reported

Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Low**

Study: Schochl(2011)[78]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Retrospective analysis of patients admitted to a trauma centre between 2005 and 2010, for whom blood samples were taken on admission.

Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: High**

B. APPLICABILITY

Trauma patients with an ISS ≥16

Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

ROTEM and conventional laboratory tests. Data reported separately for each assay parameter. Blinding of interpretation unclear. Optimal thresholds derived from ROC curves.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: High**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Reference standard was MT within 24 hours in all cases

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

No drop outs reported. Retrospective study, so data likely to have been complete.

Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Study: Schochl(2011)[70]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Retrospective study of patients with isolated severe traumatic brain injury	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

No details reported	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

data reported for one parameter of ROTEM (FIBTEM MCF) and aPTT only. Reference standard (mortality) occurred after testing. Only ROC AUC data reported	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: High**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Reference standard overall mortality	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

No drop outs reported	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Low**

Study: Tapia(2012)[71]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Retrospective analysis of database patients	
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: High**

B. APPLICABILITY

No details on included patients	
Do the included patients match the question?	**Concerns: Unclear**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

TEG; no details on how the test was performed the threshold used to who interpreted the results	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Unclear**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Mortality; no details on how mortality was assessed.	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

Not all patients had data on TEG	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Study: Tauber(2011)[68]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Adult polytrauma patients with an ISS ≥15	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Patients with non-head single trauma excluded	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

ROTEM FIBTEM and EXTEM; data only extractable for hyperfibrinolysis on FIBTEM as a predictor of early mortality. Exact details on how hyperfibrinolysis was defined were not reported. Reference standard was death which would have occurred after the index test as interpreted	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Unclear**

DOMAIN 3: REFERENCE STANDARD
A. RISK OF BIAS

Reference standard was death within 24 hours	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING
A. RISK OF BIAS

All participants appear to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

e. QUADAS-2 assessments for prediction studies in women with PPH

Study: Bolton(2011)[84]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Not stated	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Major obstetric haemorrhage	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

ROTEM, no further details on assay, result parameter or threshold	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: Unclear**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

Coagulopathy requiring treatment, FFP transfusion and platelet transfusion, assessed according to standard criteria	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

All patients appear to have received the reference standard but little detail on patient flow	
Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Low**

Study: Lilley(2013)[85]

DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

Consecutive patients, no further details	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Low**

B. APPLICABILITY

Women with PPH >=1000 mL	
Do the included patients match the question?	**Concerns: Low**

DOMAIN 2: INDEX TEST(S)
A. RISK OF BIAS

ROTEM with FIBTEM assay, only MCF evaluated	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Concerns: High**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

RBC transfusion and invasive procedures; no details on how these were assessed	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Unclear**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

All patients appear to have received the reference standard but little detail on patient flow	
Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Low**

APPENDIX 4: TABLE OF EXCLUDED STUDIES WITH RATIONALE

Study Details	Population	VE Test	Study Design	Comments
Brohi(2009)[133]	Trauma	Unclear	Not primary study	
Carroll (2009)[134]	Trauma	TEG	DTA - outcome	TEG parameters not dichotomised
Chevannes(2012)[135]	PPH	ROTEM	Unclear	
Craft2008)[136]	Trauma	TEG	Correlation	
Curry2010)[137]	Trauma	ROTEM	Correlation	
Dietrich(1998)[138]	Cardiac	Unclear	Unclear	
Ducloy-Bouthors[139]	PPH	ROTEM	Correlation	PPH case-control; insufficient data to include
Ducloy-Bouthors(2012)[140]	PPH	ROTEM	Other/unclear comparative	PPH case-control; insufficient data to include
Pivalizza(1997)[141]	Cardiac	Sonoclot	Correlation	
Plotkin(2008)[142]	Trauma	TEG	Correlation regression	
Forestier (2001)[143]	Cardiac	TEG, Sonoclot	Unclear	
Grassetto(2012)[144]	Trauma	ROTEM	Unclear	
Hagemo(2010)[145]	Trauma	ROTEM, TEG	Correlation	
Huissoud(2009)[146]	PPH	TEG	Case-control	Case-control predicting PPH
Jeong(2011)[147]	Unclear	TEG	Unclear	
Johansson(2010)[148]	Unclear	Unclear	Not primary study	
Karlsson(2013)[149]	PPH	TEG	Case-control	PPH case-control; insufficient data to include
Kashuk(2010)[150]	Trauma	TEG	DTA - outcome	Wrong outcome - thrombosis
Levrat(2008)[151]	Trauma	ROTEM	DTA - other	Hyperfibrinolysis based on laboratory tests
Miles(2007)[152]	Cardiac	ROTEM	Unclear	
Miyashita(1998)[153]	Cardiac	Sonoclot	DTA - other	Correlation only
Newland(1987)[154]	Cardiac	TEG, Sonoclot	Correlation	
Nix(2011)[155]	PPH	TEG	Case series	
Porite(2004)[156]	Cardiac	TEG	Unclear	
Rourke(2012)[157]	Trauma	ROTEM	DTA - other	Fibrinogen based on standard laboratory tests as

Study Details	Population	VE Test	Study Design	Comments
				outcome
Rugeri(2007)[158]	Trauma	ROTEM	DTA - other	
Schochl(2009)[159]	Trauma	ROTEM	DTA - outcome; positive test only	Hyperfibrinolysis patients only (test positive on ROTEM) then looked at relationship with mortality
Shah(2012)[160]	Trauma	TEG	Case series	
Shah(2011)[161]	Trauma	TEG	DTA - other	
Shore-Lesserson(1992)[162]	Cardiac		RCT of treatment	
Stanworth(2010)[163]	Trauma	Unclear	DTA - outcome	
Tanaka(2012)[16]	Unclear	ROTEM	Unclear	
Tapia(2013)[164]	Trauma	TEG	Historical control	Selected patient group; all had received massive transfusion
Thai(2011)[165]	Cardiac	TEG	Unclear	
Traverso(1993)[166]	Cardiac	TEG, Sonoclot	Animal study	
Woolley(2013)[167]	Trauma	ROTEM	DTA - other	
Yamada(2007)[168]	Cardiac	Sonoclot	Correlation	

APPENDIX 5: SUMMARY OF STUDIES INCLUDED IN THE COST-EFFECTIVENESS REVIEW

Study details	Craig et al. 2008 [12]	Davies et al. 2006 [92]
Time horizon	1 month for the base case and 1 year for further analyses	1 month for the primary analysis and 1, 10 and 30 years for secondary analyses
Objective	To evaluate the clinical and cost-effectiveness of using thromboelastography and thromboelastometry analysers compared with standard laboratory tests/assays and clinical discretion used alone, to diagnose the cause of unexplained bleeding during or after surgery	To compare patient outcomes, resource use and costs to the NHS and NHS Blood Transfusion Authority (BTA) associated with cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion
Source of effectiveness information/testing accuracy data	Systematic literature review	Systematic literature review
Comparators	1. Standard laboratory tests 2. Clinical discretion	1. Preoperative autologous donation (PAD) 2. Recombinant human erythropoietin (EPO) 3. PAD plus EPO 4. Acute normovolaemic haemodilution (ANH) 5. Cell salvage plus ANH 6. Antifibrinolytics (aprotinin, tranexamic acid, ε-aminocaproic acid) 7. Fibrin sealants 8. Restrictive transfusion thresholds or protocols
Reference standard	Standard laboratory tests	NA
Unit costs	Sources: NHS Department of Health, NHS Blood and Transplant Service, Davies (2006)[92], Sharma (2000), [169] Llewelyn et al. 2004 [170] VE manufacturer and clinical experts. All costs were adjusted for inflation to reflect costs related to the year 2005/2006. The 2006 PSSRU inflation indices for Hospital and Community Health Services[171] were used to adjust for costs reported in price years different to 2005/2006.	Sources: NHS reference costs, South Manchester University Hospital Trust, NHS Blood Transfusion Authority, Department of Health Reference Costs, Chartered Institute of Public Finance and Accountancy, manufacturer of cell salvage equipment and clinical experts.
Measure of benefit	Life years lived and quality-adjusted life years	Quality-adjusted life years
Study type	Cost-effectiveness study	Cost-effectiveness study

Study details	Craig et al. 2008 [12]	Davies et al. 2006 [92]
Model assumptions	1. Complications related to surgery or transfusion, transfusion-related complications and infection due to bacterial contamination occur during the hospitalisation period. 2. For liver transplantation all patients would receive transfusion. 3. In cardiac surgery, probabilities of experiencing transfusion or surgical complications are the same across strategies. 4. Mortality rate for patients not transfused is the same for all strategies. 5. For patients with no complications or infections, a zero mortality rate during the hospitalisation period is considered. 6. Half-cycle correction applied to death events. 7. Utility associated to no transfusion is the same as utility associated to transfusion without adverse events. 8. A 3-year contract leasing programme is arranged with the manufacturer (to include the costs of a service contract for potential repairs and replacement). 9. On average, the hospital performs 200 tests per year. 10. Only one test is performed per patient not requiring transfusion, while for those patients requiring transfusion an intra-operative and a post-operative test are conducted. 11. The set of SLTs is defined following Scottish clinical Practice. 12. The calculation of the total cost per set of SLTs considers that the costs on the ward to take the blood and record the results are the same. 13. CD blood product usage is the same as that of SLTs in cardiac surgery. 14. The costs are zero if patients are managed by means of CD. No laboratory tests or supplies are used in this scenario and any opportunity costs of labour time are negligible. 15. Average length of hospital stay is the same across all strategies. 16. TE tests are independent of clinical judgement. 17. Some of the parameters used to populate the liver transplantation model are based on data used for the cardiac model.	1. The pathways for strategies to minimise blood loss or the need for a blood transfusion and those that rely on transfusion of allogeneic blood are identical. 2. The probability of needing a blood transfusion differs between strategies. 3. The risk difference between cell salvage and each of the alternative transfusion strategies is the same as the risk difference between each strategy and the control (allogeneic blood). 4. Patients treated by autologous transfusion strategies who required a transfusion would have an autologous transfusion first followed by an allogeneic transfusion if necessary. 5. For those strategies that did not use autologous blood, if there were insufficient data to estimate a strategy specific probability of an adverse event, the probability for the allogeneic comparison was used to approximate the probability of the adverse event. 6. The probability of IBCT for PAD transfusion is equal to the probability of IBCT of any blood transfusion. 7. If an adverse event was not reported to SHOT, the probability of this event was zero. 8. Transfusion transmitted infections only apply to people having an allogeneic blood transfusion. 9. Cost of allogeneic blood in the EPO strategy is equal to that of the allogeneic strategy. 10. Adverse events caused by either transfusion or surgery, transfusion only and bacterial contamination would occur within 1 day of the transfusion. 11. Additional annual cost for non-disabling stroke is zero. 12. With the exception of bacterial contamination, transfusion-transmitted infections were assumed to be diagnosed after discharge from the index admission.
Perspective	NHS Scotland	NHS
Discount rate	Not applicable	Not reported

Study details	Craig et al. 2008 [12]	Davies et al. 2006 [92]
Uncertainty around cost-effectiveness ratio expressed	Not applicable	The associated likelihood that cell salvage is cost-effective compared with the allogeneic blood transfusion strategy, PAD, PAD plus EPO, FSs, AFs and EPO is over 50%. ANH was associated with a probability of being cost-effective compared with cell salvage of around 80%.
Sensitivity analysis	One-way and multi-way (deterministic)	Wherever possible, probability distributions were obtained from the systematic review. If not available, minimum and maximum estimates were used to estimate a triangular distribution.
Outcome (cost and Lys/QALYs) per comparator	Thromboelastography and thromboelastometry analysers is the dominant strategy	The net benefit of cell salvage was between £112 and £359 per person, compared with the allogeneic blood transfusion strategy, PAD, PAD plus EPO, FSs, AFs and EPO. ANH was associated with a net benefit compared with cell salvage of £97.
Summary of incremental analysis	Thromboelastography and thromboelastometry analysers is the dominant strategy	Primary analysis: Incremental cost-effectiveness: all cell salvage versus allogeneic transfusion strategies, all surgical procedures, 1-month timeframe: 1. Cell salvage dominates allogeneic blood no restrictive transfusion protocol. 2. Cell salvage dominates antifibrinolytics. 3. Cell salvage vs. fibrin sealants: £629 per QALY gained. 4. Cell salvage dominates EPO.

APPENDIX 6: DRUMMOND ASSESSMENT FOR STUDIES INCLUDED IN THE COST-EFFECTIVENESS REVIEW

Quality item	Craig et al. 2008 [12]	Davies et al. 2006 [92]
Study design		
The research question is stated	√	√
The economic importance of the research question is stated	√	√
The viewpoint(s) of the analysis are clearly stated and justified	√	√
The rationale for choosing alternative programmes or interventions compared is stated	√	√
The alternatives being compared are clearly described	√	√
The form of economic evaluation used is stated	√	√
The choice of form of economic evaluation is justified in relation to the questions addressed	√	√
Data collection		
The source(s) of effectiveness estimates used are stated	√	√
Details of the design and results of effectiveness study are given (if based on a single study)	NA	NA
Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	√	√
The primary outcome measure(s) for the economic evaluation are clearly stated	√	√
Methods to value benefits are stated	√	√
Details of the subjects from whom valuations were obtained were given	NA	NA
Productivity changes (if included) are reported separately	NA	NA
The relevance of productivity changes to the study question is discussed	NA	NA
Quantities of resource use are reported separately from their unit costs	√	√
Methods for the estimation of quantities and unit costs are described	√	√
Currency and price data are recorded	√	√
Details of currency of price adjustments for inflation or currency conversion are given	√	√
Details of any model used are given	√	√
The choice of model used and the key parameters on which it is based are justified	√	√
Analysis and interpretation of results		
Time horizon of costs and benefits is stated	√	√
The discount rate(s) is stated	NA	X
The choice of discount rate(s) is justified	NA	X
An explanation is given if costs and benefits are not discounted	√	X
Details of statistical tests and confidence intervals are given for stochastic data	X	√
The approach to sensitivity analysis is given	Deterministic: √ PSA: X	Deterministic: x PSA: √
The choice of variables for sensitivity analysis is justified	Deterministic: √ PSA: X	Deterministic: x PSA: √
The ranges over which the variables are varied are justified	Deterministic: √ PSA: X	Deterministic: x PSA: √
Relevant alternatives are compared	√	√
Incremental analysis is reported	√	√
Major outcomes are presented in a disaggregated as well as aggregated form	√	√
The answer to the study question is given	√	√
Conclusions follow from the data reported	√	√

Quality item	Craig et al. 2008 [12]	Davies et al. 2006 [92]
Conclusions are accompanied by the appropriate caveats	*√*	*√*

√, yes; *x*, no; NA, not applicable.

APPENDIX 7: PROTOCOL

We made the following protocol modification: In addition to diagnostic cohort studies, our review identified a number of studies which used multi-variate regression modelling to assess the ability of VE tests to predict outcomes in trauma patients; data from studies of this type were considered to be useful and the inclusion criteria were expanded accordingly.

Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence – Protocol

Title of project

Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis

Name of External Assessment Group (EAG) and project lead

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Plain English Summary

Two situations associated with a high risk of bleeding are trauma (including excessive bleeding after childbirth) and surgery. Bleeding can occur as a result of the surgery or injury itself or due to problems with the blood's clotting process. The risk of bleeding varies according to type of surgery with cardiac surgery, liver transplant, major vascular surgery, hip replacement, and obstetric interventions associated with a high risk of bleeding. Patients with bleeding usually require a blood transfusion and/or (re)-operation, both of which may lead to increased morbidity and mortality. It is therefore important to appropriately treat the cause of the bleed and reduce the blood loss. Knowledge of the exact cause of the bleed allows treatment to be tailored rather than replacing blood loss with transfusion.

ROTEM® Delta is a "viscoelastic" method developed to monitor the clotting process. It is performed near the patient during surgery and can help differentiate between surgical bleeding and a clotting disorder. A blood sample is placed in a disposable cup containing the reagent(s) and a sensor pin oscillates in the blood sample. As the blood starts clotting, the clot restricts the rotation of the pin with increasing resistance as the firmness of the clot increases. This is measured by the ROTEM® system and translated to the output which consist of graphical displays and numerical parameters. Other viscoelastic (VE) devices include thromboelastography (TEG®) and the Sonoclot® analyser. These have slight differences compared to ROTEM® in terms of whether it is the pin or the cup that oscillates and the direction in which the oscillation occurs. They also use different chemicals. However, they provide similar information on clot formation.

Standard laboratory clotting tests have a number of limitations for detecting problems with the clotting process. In general, they are only able to identify that the blood is not clotting properly, not what part of the clotting process is not working. They generally take between 40 and 90 minutes from taking the blood sample to give a result; this compares to less than 30 minutes for full results of VE testing methods which can give initial results in less than 10 minutes. VE can be repeatedly performed during and after surgery and so can provide a dynamic picture of the clotting process. VE testing methods offer two key potential benefits over standard laboratory tests: the shorter timescale in which they are able to provide results and the additional information on the clotting process which they offer compared to standard tests. Additional information and quicker results mean requirements for specific blood products could be targeted and so the patient is not subjected to risks associated with unnecessary transfusion. Time in theatre, resource use, length of stay in a

critical care unit, length of hospital stay, blood product usage, and the associated costs may therefore be reduced.

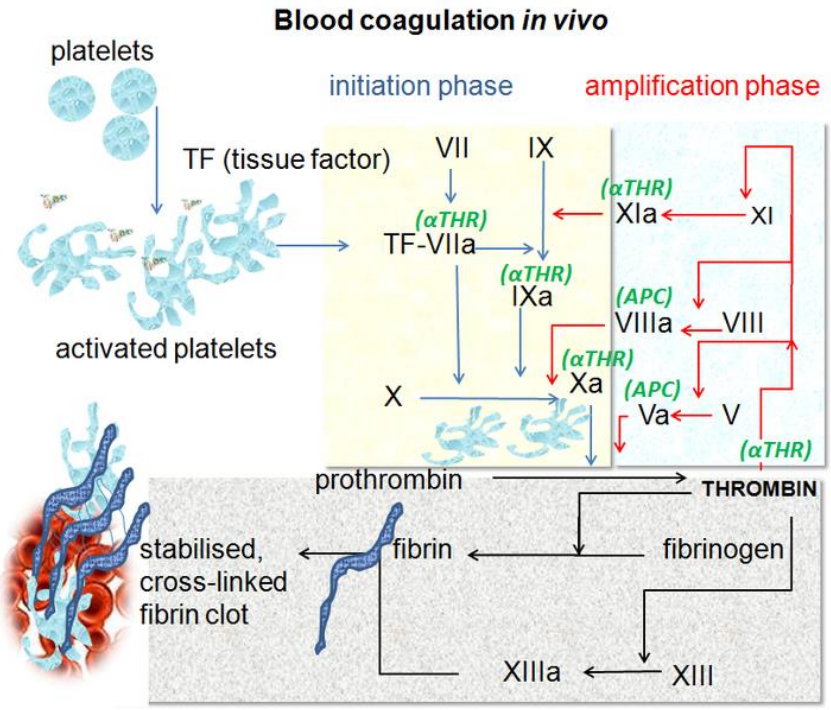
This assessment aims to determine the effectiveness of VE devices to assist with the diagnosis, management and monitoring of clotting disorders during and after surgery or trauma and may include information on the management of excessive bleeding post-childbirth. The assessment will consider both clinical effectiveness (improvement in patients' symptoms and adverse events) and cost effectiveness (cost of treatment). In addition, a cost effectiveness analysis of VE versus standard laboratory tests only will be conducted.

Decision problem

Population

There are two broad patient groups at high risk of bleeding: those who have experienced trauma (including post-partum haemorrhage) and those undergoing surgery. Patients undergoing surgery commonly present with bleeding complications which can have a negative impact on their clinical outcome in terms of increased peri-operative and post-operative morbidity and mortality. Bleeding can occur either as a result of the surgery/injury itself or due to perioperative or trauma induced coagulopathy. Coagulopathy occurs when the normal clotting mechanism (haemostasis) is interrupted impairing the blood's ability to clot. The normal clotting process starts with platelets which, combined with a number of clotting proteins, go through a series of steps to produce a solid fibrin clot (Figure 1). If any of these steps are interrupted this may result in prolonged or excessive bleeding. While coagulopathy can be caused by genetic disorders such as haemophilia it can also occur following injury as occurs in perioperative or trauma induced coagulopathy. The underlying mechanism of coagulopathy can include hyperfibrinolysis (markedly enhanced fibrinolytic activity), hypofibrinogenaemia (fibrinogen deficiency), thrombocytopenia (low levels of platelets), factor deficiency, and heparin effect.[1] There are several factors that increase the risk of coagulopathy during surgery. In cardiac surgery the use of heparin to prevent clotting whilst on cardiopulmonary bypass (CPB), preoperative anticoagulation medication, the dilution, activation and consumption of coagulation factors, and the use of cardiopulmonary bypass machines which may result in acquired platelet dysfunction, hypothermia (body temperature <35^{o}C), and hyperfibrilation are all associated with an increased risk of coagulopathy.[2] In patients undergoing liver transplantation, advanced cirrhosis is associated with decreased levels of haemostatic proteins, low synthesis of anticoagulants, thrombocytopenia, and variations in levels of some clotting proteins.[3, 4] Various stages of the liver transplant surgery itself, especially the anhepatic phase and immediately after organ reperfusion, can be associated with marked changes in haemostasis mainly in hyperfibrinolysis.[4] In major trauma the following are associated with an increased risk of coagulopathy: consumption of coagulation factors and platelets during clot formation in an attempt to prevent loss of blood through damaged vessels; dilution of whole blood as a consequence of red cell transfusion; hormonal and cytokine induced changes; hypoxia, acidosis and hypothermia which predispose to further bleeding; and ongoing bleeding. [5]

Figure 1 Blood coagulation *in vivo*[6]



The risk of bleeding varies according to type of surgery with cardiac surgery, liver transplant, major vascular surgery, hip replacement, and obstetric interventions associated with a high risk of bleeding. There were 36 702 cardiac surgery cases (based on Specialised Services National Definitions Set), [7] 638 liver transplants, 72 542 hip replacements, and 175 997 obstetric operations in England and Wales in 2011-2012 based on Hospital Episode Statistics data.[6] There are approximately 20 000 major trauma cases in England every year[8] and injuries account for over 700 000 hospital admission each year.[9] This assessment will focus on two patient groups identified by NICE as clinical priority areas: those undergoing cardiac surgery and trauma patients.

Patients with substantive bleeding usually require transfusion and/or re-operation. Table 1 summarises the number of patients undergoing various cardiac surgeries in Scotland over a 2 year period and shows the proportion of these patients who received a blood transfusion and the number of red blood cell units per episode transfused.[10] Cardiothoracic surgery uses 5% of all donated blood in the UK, [11] and the proportion of patients requiring re-operation for bleeding is estimated at 2-8% of cardiac surgery patients.[12] The increased morbidity and mortality associated with bleeding following surgery has been shown to be related to both blood transfusion and re-operation for bleeding. [12] Patients with a diagnosis of trauma induced coagulopathy on admission to hospital have a 3 to 4 fold greater mortality risk and it is independently associated with increased

transfusion requirements, organ injury, septic complications, and longer critical care stays.[5] Trauma is the leading cause of death and disability in adults aged under 36 years around the world,[13] and haemorrhage is the cause of 40% of all trauma deaths in the UK. [14]

Red blood cell transfusion is independently associated with a greater risk of both infection and ischemic postoperative morbidity, hospital stay, increased early (30 day post-operative) and late mortality (up to 1 year post-operative), and hospital costs.[15] It is therefore important to appropriately treat the coagulopathy and reduce the blood loss thus reducing the requirement for blood transfusion and reducing the risks of transfusion-related adverse events and saving costs.[2] Knowledge of the exact cause of the bleed allows treatment to be tailored to the cause of the coagulopathy rather than replacing blood loss with transfusion. For example, if thrombocytopenia is identified as the cause of the bleed this can be treated by platelet transfusion.[16] Furthermore, the cost of donor blood and blood has increased and availability has reduced and there is also the risk of blood borne infection.[11]

Protocol Table 1 Surgical blood use in 2005-6

Procedure	Number of episodes	% Episodes transfused	RBC units/episode transfused
Coronary replacement operations (minus revisions)	2 359	47.9	1.6
Heart and lung transplant	8	75.0	11.3
Revision coronary replacement operations	29	44.8	2.1
Valves and adjacent structures	758	54.5	2.5

Intervention technology

The ROTEM® Delta point-of-care analyser

The ROTEM® Delta (trademark of TEM International GmbH; www.rotem.de) is a point-of-care (POC) analyser which uses thromboelastometry, a viscoelastic method, to test for haemostasis in whole blood. It is performed near the patient during surgery or when admitted following trauma. It is used to assist with the diagnosis, management and

monitoring of haemostasis disorders during and after surgery associated with high blood loss. It is an integrated all-in-one system and analyses the coagulation status of a blood sample to differentiate between surgical bleeding and a haemostasis disorder.[17] It uses a combination of five assays to characterise the coagulation profile of a citrated whole blood sample (Table 2). Initial screening is performed using the INTEM and EXTEM assays, if these are normal then it is an indication that surgical bleeding rather than coagulopathy is present. The use of different assays allows for rapid differential diagnosis between different haemostasis defects and anticoagulant drug effects.[17] Training in use of the technology is required but specialist laboratory staff are not needed.

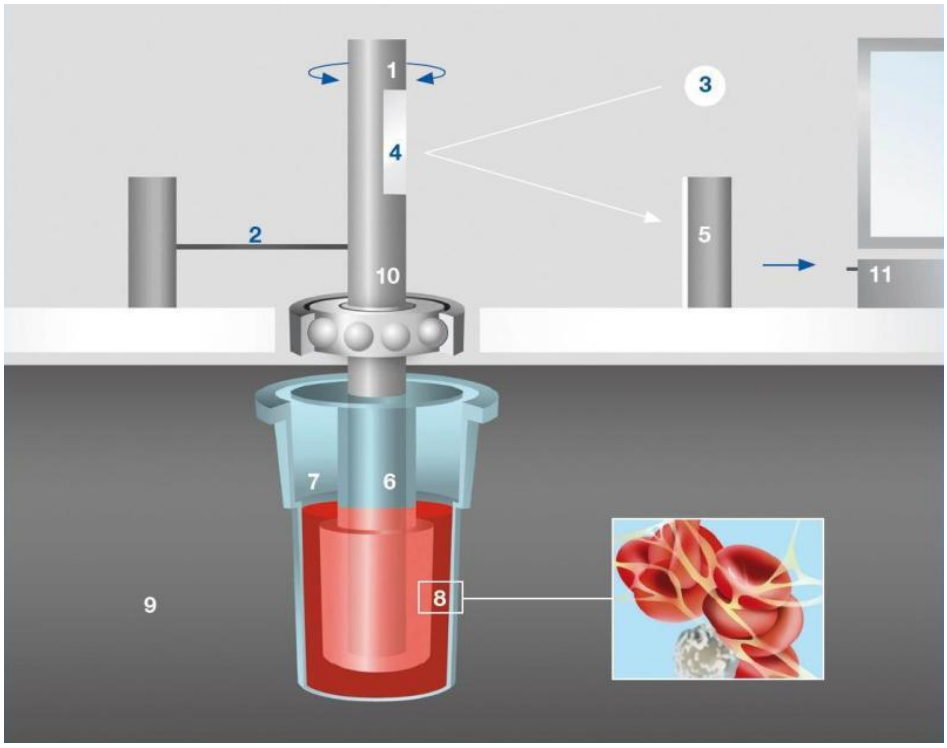
Protocol Table 2 Summary of ROTEM® Delta assays

Assay	Activator/Inhibitor	Role
INTEM	Ellagenic acid (contact activator)	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the intrinsic pathway.
EXTEM	Tissue factor	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the extrinsic pathway. Not influenced by heparin. EXTEM is also the base activator for FIBTEM and ABTEM.
HEPTEM	Ellagenic acid + heparinase	Assessment of clot formation in heparinised patients. INTEM assay performed in the presence of heparinise; the difference between HEPTEM and INTEM confirms the presence of heparin.
FIBTEM	Tissue factor + platelet antagonist	Assessment of fibrinogen status allows detection of fibrinogen deficiency or fibrin polymerisation disorders
APTEM	Tissue factor + fibrinolysis inhibitor (aprotonin)	In-vitro fibrinolysis inhibition: Fast detection of lysis when compared to EXTEM.
Na-TEM	None	Non-activated assay. Can be used to run custom haemostasis tests.

Figure 2 shows the ROTEM® system. A 340 µl blood sample that has been anticoagulated with citrate is placed into the disposable cuvette (sample cup) (7) using an electronic pipette. A disposable sensor pin (6) is attached to the shaft which is connected with a thin spring (2) and slowly oscillates back and forth (1) suspended in the blood sample. The signal from the pin is transmitted via an optical detector system (3,4, 5). The test is started by adding the reagents described above. Although the typical test temperature is 37°C, different temperatures can be selected, for example for patients with hypothermia. Whilst

the blood remains liquid the movement is unrestricted, as the blood starts clotting, the clot restricts the rotation of the pin with increasing resistance as the firmness of the clot increases. This is measured by the ROTEM® system and translated to the output which consist of graphical displays and numerical parameters.

Figure 2 ROTEM® system[18]



1 Oscillating axis
2 Counterforce spring
3 Light beam from LED
4 Mirror
5 Detector (electr. Camera)
6 Sensor Pin
7 cuvette with blood sample
8 Fibrin strands & platelet aggregates
9 Heated cuvette holder
10 Ball bearing
11 Data processing unit

The graphical output of results produced by the ROTEM® system is shown in Figure 3. A separate graphical display is produced for each reagent by an integrated computer (Appendix A). Numerical values for each of the following are also calculated and presented below the graph. Initial results are available within 5-10 minutes and full qualitative results are available in 20 minutes:

CT: Clotting time – time from adding the start reagent until the blood starts to clot. A prolonged clotting time indicates abnormal clot formation.

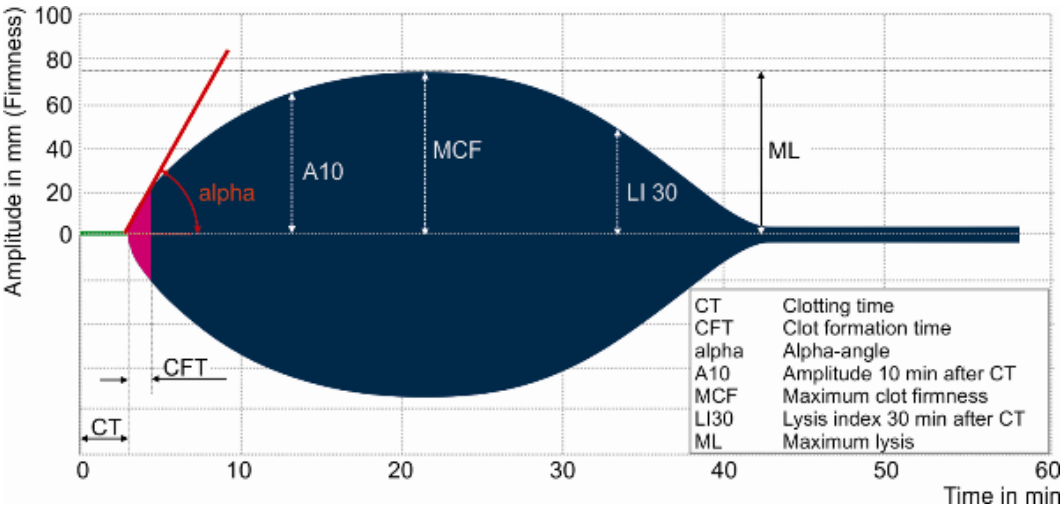
CFT: Clot formation time – time from CT until a clot firmness of 20 mm point has been reached and a: *Alpha angle* – angle of tangent between 2 and the curve. These measures indicate the speed at which the clot is forming and are mainly influenced by platelet function but are also affected by fibrinogen and coagulation factors.

A10: Amplitude 10 minutes after CT – used to predict MCF at an earlier stage and so allows earlier therapeutic decisions.

MCF: maximum clot firmness – the greatest vertical amplitude of the trace. A low MCF value suggests decreased platelet numbers or function, decreased fibrinogen levels of fibrin polymerisation disorders, or low factor XIII activity.

ML: maximum lysis. Fibrinolysis is detected by ML >15% or by better clot formation in APTEM compared to EXTEM.

Figure 3 ROTEM® Analysis and interpretation of results[19]



Alternative technologies

Thromboelastography

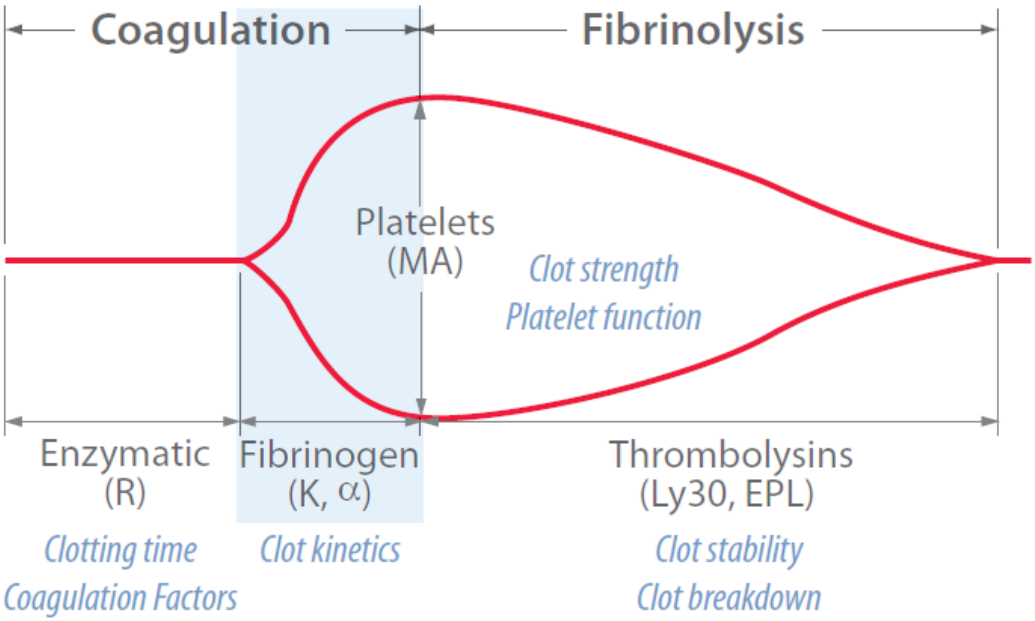
The ROTEM® system is a variant of the traditional thromboelastography (TEG®) method developed by Hartert in 1948.[20] The two techniques are generally considered as equivalent technologies and other recent reviews have evaluated them as a single intervention class. [10, 21, 22] Like ROTEM®, thromboelastography is a viscoelastic method and provides a graphical representation of the clotting process. Thromboelastography is used in the TEG® 5000 analyser (trademark of Haemonetics Corporation, IL, USA; www.haemonetics.com). The rate of fibrin polymerisation and the overall clot strength is assessed.[1] Like ROTEM®, TEG® is able to provide an analysis of platelet function, coagulation proteases and inhibitors, and the fibrinolytic system within 30 minutes, or within 15

minutes if the rapid assay is used. The nomenclature used in TEG® differs from that used in ROTEM®; differences are summarised in Table 3. The practical differences between TEG® and ROTEM® are that TEG® uses a torsion wire rather than the optical detector used in ROTEM® to measure the clot formation, and while the movement in ROTEM® is initiated with the pin, with TEG® it is initiated from the cuvette.[1] The assays used in TEG® also differ (Table 3).[3, 23] The platelet mapping function means that TEG® is able to measure platelet function which cannot be assessed using ROTEM®. Sample size requirements do not differ substantially between TEG® and ROTEM®; TEG® uses a 360µl blood sample compared to the 340µl sample used in ROTEM®.[23]

Table 3 Summary of TEG® assays

Assay	Activator/Inhibitor	Role
Kaolin	Kaolin	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the intrinsic pathway.
Heparinase	Kaolin + heparinise	Assessment of clot formation in heparinised patients (both unfractionated and low molecular weight)
Platelet Mapping	ADP Arachidonic acid	To assess platelet function and monitor antiplatelet therapy (e.g. aspirin)
RapidTEG	Kaolin + tissue factor	Provides more rapid results than standard kaolin assay (mean 20 minutes versus 30 minutes for standard TEG® with initial results in less than one minute)
Functional fibrinogen assay	Lyophilized tissue factor + platelet inhibitor	Partitions clot strength (MA) into contributions from platelets and contribution from fibrin
Native	None	Non-activated assay. Can be used to run custom haemostasis tests.

Figure 4 TEG® Analysis and interpretation of results[24]



Sonoclot® Coagulation and Platelet Function Analyser

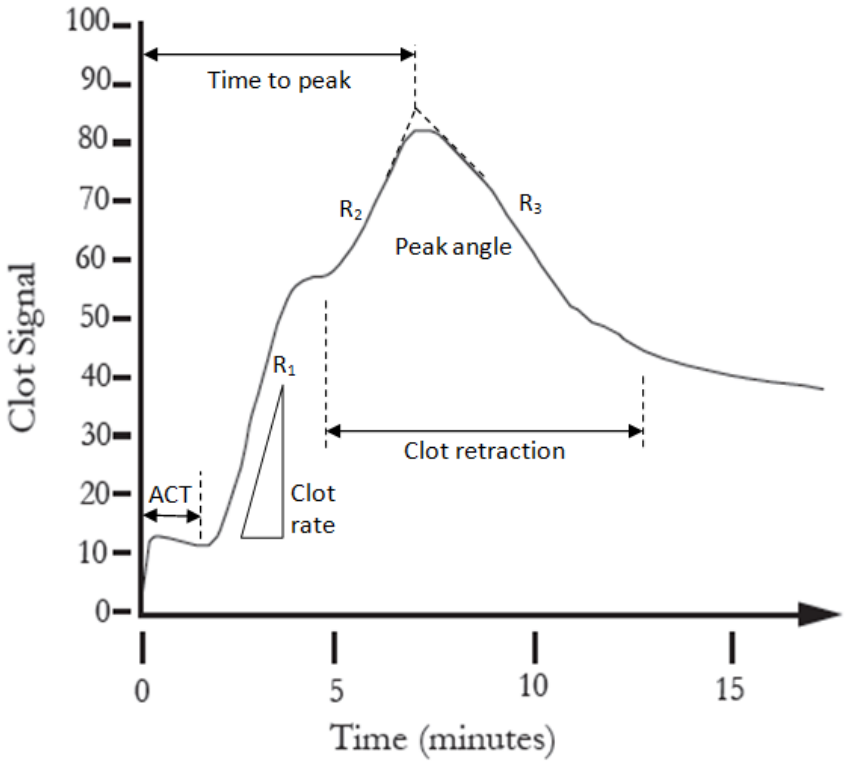
Another method that uses viscoelastometry to measure coagulation is the Sonoclot® coagulation and platelet function analyser (Sienco Inc., Arvada, CO). This analyser was first introduced in 1975 by von Kualla et al.[25] It provides information on the haemostasis process including coagulation, fibrin gel formation, fibrinolysis, and, like TEG®, is also able to assess platelet function. The Sonoclot® process is similar to ROTEM® and TEG®, although Sonoclot® is able to use either a whole blood or plasma sample, citrated blood samples can be used but are not required.[26] A hollow, open-ended disposable plastic probe is mounted on the transducer head. The test sample (blood or plasma) is added to the cuvette containing the reagents. A similar volume to ROTEM® and TEG® is used – 330 to 360 µl. As with ROTEM® it is the probe that moves within the sample, however, rather than moving horizontally the probe moves up and down along the vertical axis. As the sample starts to clot changes in impedance to movement are measured. Like TEG® and ROTEM®, Sonoclot® produces a qualitative graphical display of the clotting process and also produces quantitative results of activated clotting time, the clot rate and the platelet function (Figure 3, Table 4).[3] However, the measure of activated clotting time (ACT) produced by Sonoclot® reflects initial fibrin formation whereas the equivalent measures produced by TEG® and

ROTEM® reflects a more developed and later stage of initial clot formation.[3] Most information on clot formation is available after 15 minutes. If details on platelet function are required this may take up to 20-30 minutes.[26]

Protocol Table 4: Summary of Sonoclot® assays

Assay	Activator/Inhibitor	Role
SonACT	Celite	Large-dose heparin management without aprotonin
kACT	Kaolin	Large-dose heparin management with/without aprotonin
aiACT	Celite + Clay	Large-dose heparin management with aprotonin
gbACT+	Glass beads	Overall coagulation and platelet function assessment for use on non-heparinised patients.
H-gbACT+	Glass beads + Heparinase	Overall coagulation and platelet function assessment in presence of heparin
Native	None	Non-activated assay. Can be used to run custom haemostasis tests.

Figure 5 Sonoclot® Analysis and interpretation of results



Comparison of viscoelastic testing devices

We will refer to the three technologies, ROTEM®, TEG® and Sonoclot®, as a class as "viscoelastic testing point of care coagulation testing devices" or "VE devices," however, data from each device will be analysed separately and the devices will not be treated as equivalent. Table 6 provides an overview of the different terms used by each device to refer to the different test outputs. This table also summarises the factors affecting clot formation at each stage and the different therapeutic options. A recent study comparing the costs of TEG® and ROTEM® found that TEG® was cheaper than ROTEM® based on costs provided by the manufacturers in 2008.[27] However, it should be noted that the platelet function assay costs £70 so if this assay is used the cost of TEG® is greatly increased. A detailed breakdown of costs is provided in Table 5. Similar costs were not available for Sonoclot®.

Protocol Table 5 Comparison of costs of TEG® and ROTEM® based on 2008 costs[27]

Cost	TEG®	ROTEM®
List Price	£13 500 for 2 channel unit; £26 000 for 4 channel unit	£21 662 for standard 4 channel unit
Cost of reagents	Kaolin vials (for standard testing) £2.52 each, functional fibrinogen £8.33 each, platelet function £70 each.	Varies according to test: £0.29-£2.68
Cost of single test	£7.57 (only 1 cup/channel required for basic test)	£8.83 (2 cups channels required for basic test)
After care cost	£2000/year for 2 channel single unit; £1700 for each additional unit	£1400/year
Training	Minimum 2 days on-site with 24-h on call facility; as many follow-up training days as required in first 6 months; 1 day/month for next 6 months	Two days on site + 1 refresher day for 4 operators; any further training £1500/day plus expenses

Protocol Table 6 Stages of clot formation, factors affecting the clot, therapeutic options and terms used in TEG®, ROTEM® and Sonoclot®[1, 3]

Development of clot	Factors affecting clot[28]	Therapeutic Options	ROTEM®	TEG®	Sonoclot®
Measurement period	NA	NA	RT	-	-
Initial clot/fibrin formation	Factor XII and X1 activity; reflective of intrinsic pathway if activators not used	Administration of plasma, coagulation factors, fibrinogen or platelets.	Clotting time (CT)	R	ACT
Development of clot or rapidity of clot formation	Factor II and VIII activity; platelet count and function, thrombin, fibrinogen, HCT		Clot formation time (CFT) and α angle (α)	Kinetics (k) and α angle (α)	CR
Maximum clot strength	Fibrinogen, platelet count and function, thrombin, factor XIII activity, HCT		Maximum clot firmness (MCF)	Maximum amplitude (MA)	Peak amplitude
Time to maximum clot strength			MCF-t	TMA	Time to peak
Amplitude (at set time)			A5, A10…	A (A5, A10..)	-
Clot elasticity			MCE	G	-
Maximum lysis	Fibrinolysis	Antifibrinolytic drugs and additional measures such as administration of fibrinogen or platelets.	ML	-	R_3
Lysis at fixed time			LY30, LY45, LY60	CL30, CL45, CL60	
Time to lysis			CLT (10% from MCF)	TTL (2mm drop from MA)	
Maximum lysis			CLR	_	
Platelet function	Platelet function	Platelets	_	Platelet function	PF

Platelet function tests

VE tests are often performed in combination with platelet function tests in patients receiving antiplatelet drugs such as aspirin and clopidogrel. Whilst light transmission aggregometry in platelet rich plasma is the gold standard test for platelet function, a number of rapid near patient tests are available.[29] One of the most commonly used is the platelet function analyser (PFA) 100 (Dade-Behring, Marburg, Germany).[30] A more recently developed test which is commonly used in combination with ROTEM® is the Multiplate analyzer (Roche), a near patient test designed to detect platelet dysfunction. [31] It uses whole blood and is based on the principle of impedance platelet aggregometry (IPA). It has a turnaround time of 10 minutes and can process up to 30 tests per hour. As mentioned above, both TEG® and Sonoclot® can run specific platelet mapping assays – the TEG® platelet mapping assay and gbACT+ assay for Sonoclot®. However, some centres prefer to use a separate platelet function test such as the Multiplate analyser instead of these assays.

Comparator

The comparator for this technology appraisal is a combination of clinical judgement and standard laboratory tests.

Standard laboratory tests for coagulopathy

Standard laboratory coagulation analyses include the following:

Prothrombin time – also used to derive measures *prothrombin ratio (PR)* and i*nternational normalised ratio (INR).* Measure of the extrinsic pathway of coagulation. It measures factors I (fibrinogen), II (prothrombin), V, VII, and X in blood plasma at 37^{o}C. The sample is added to a test tube containing liquid sodium citrate and centrifuged, tissue factor is then added and the time the sample takes to clot is measured. The prothrombin ratio is the prothrombin time for a patient, divided by the result for control plasma. The INR is the ratio of a patient's prothrombin time to a normal (control sample) raised to the power of the ISI value for the analytical system used. The ISI value indicates how a particular batch of tissue factor compares to an international reference tissue factor.

Activated partial thromboplastin time (aPTT) – measures the "intrinsic" or contact activation pathway and the common coagulation pathway. An activated matrix (e.g. silica, celite, kaolin, ellagic

acid) and calcium are mixed into the plasma sample and the time the sample takes to clot is measured.

Activated clotting/coagulation time (ACT) – based on ability of whole blood to form a visible fibrin monomer in a glass tube. Used to measure heparin anticoagulation.

Platelet count – In general a low platelet count is associated with an increased risk of bleeding. It is a purely quantitative measure and cannot detect pre-existing, drug-induced, or perioperatively acquired platelet dysfunction.[2]

Plasma fibrinogen concentration – a number of assays are available to assess plasma fibrinogen levels, the Clauss fibrinogen assay is the most common and is based on the thrombin clotting time. Diluted plasma is clotted with a high concentration of thrombin at 37°C and the clotting time is measured. The result is compared with a calibration curve prepared by clotting a series of dilutions of a reference plasma sample of known fibrinogen concentration to give a result in g/L. Most laboratories use an automated method in which clot formation is considered to have occurred when the optical density of the mixture has exceeded a certain threshold.[32]

These test have a number of limitations for prediction and detection of perioperative coagulopathy as they were not developed to predict bleeding or guide coagulation management in a surgical setting. In general, they are only able to identify that the blood is not clotting properly but are not able to identify what part of the clotting process is disrupted. They are performed at a standardised temperature of 37^{o}C which limits the detection of coagulopathies induced by hypothermia.[2] The aPTT and INR tests only affect the initial formation of thrombin in plasma without the presence of platelets or other blood cells. These tests are also not able to provide any information regarding clot formation over time or on fibrinolysis and so they cannot detect hyperfibrinolysis. They generally take between 40 and 90 minutes from taking the blood sample to give a result; this turnaround time may be so long that it does not reflect the current state of the coagulation system when the results are reported.[2]

Care pathway

Current care pathway

The exact care pathway and use of standard coagulation testing before, during, and after surgery, will vary according to the specific type of surgery. Some centres routinely screen all patients pre-operatively for coagulation disorders using standard laboratory coagulation tests such as the PT and aPTT tests.[33] However, UK guidelines published in 2008 do not recommend routine coagulation tests to predict perioperative bleeding risk in unselected patients before surgery.[34] Instead, preoperative testing should only be considered in patients at risk of a bleeding disorder, for example those with liver disease, family history of inherited bleeding disorder, sepsis, diffuse intravascular coagulation, pre-eclampsia, cholestasis and those at risk of vitamin k deficiency.[33]

It is generally recommended that patients stop taking anticoagulant medications (clopidogrel, warfarin, and aspirin) a number of days before surgery to reduce the risk of bleeding during surgery.[11, 35] In the event of emergency surgery this may not be possible in which case coagulation testing should be performed.[33] If the surgery involves cardiopulmonary bypass (CPB) then heparin may be administered prophylactically to reduce the risk of clotting whilst on CPB.[35] It is essential to monitor heparin anticoagulation if this has been administered. An initial ACT test should be performed after the first surgical incision and be repeated at regular intervals during surgery.[36] Standard coagulation tests (platelet count, fibrinogen concentration, INR, PT, aPTT) are most commonly used to assess the coagulation status of patients who are experiencing high blood loss during surgery. However, these generally take too long to give a result that can inform treatment decisions. Instead decisions on how to treat the bleed have to be based largely on clinical judgement. The same tests are used after surgery to monitor coagulation status.

If bleeding occurs surgical intervention may be needed or packed erythrocytes are transfused if required. This is generally to maintain a haemoglobin concentration above 6g/dL during CPB and 8g/dL after CPV or according to other requirements as indicated by national guidelines. Other therapeutic options depending on laboratory test results include fibrinogen concentrate (bleeding patients with abnormal fibrinogen), fresh frozen plasma (if after transfusion of packed erythrocytes new laboratory results were not available and/or bleeding did not stop after fibrinogen administration), prothrombin complex concentrate (abnormal INR or aPTT), antithrombin concentrate (when ACT analyses not controlled by heparin alone), desmopressin (suspected platelet dysfunction), platelet concentrates (low platelet count).[35] If bleeding continues despite these

treatments then additional treatment options include factor XIII concentrate and activated recombinant factor VII or factor VIIa.[11, 35] Heparin does adjustments may be made to try and control the bleeding.

Role of VE in the care pathway

VE can be repeatedly performed during and after surgery and so can provide a dynamic picture of the coagulation process during and after surgery. The role of VE in the care pathway is unclear. It could be used either as an *add-on* test in which case it would be performed as well as standard laboratory tests, or it could be as *replacement* test in which case standard laboratory tests would no longer be needed.

If VE does not prevent the need for standard laboratory tests and provides complementary findings then it should be performed in addition to any laboratory coagulation tests already recommended for specific populations. However, if the standard laboratory tests do not offer any supplementary information to that provided by VE then there should no longer be a need for standard tests and VE should replace some or all of the standard laboratory tests. VE offers two key potential benefits over standard laboratory tests: the shorter timescale in which they are able to provide results and the additional information on the clotting process which they offer compared to standard tests. It is hypothesised that by providing additional information and quicker results that requirements for blood products could be targeted and so the patient is not subjected to risks associated with unnecessary transfusion. Time in theatre, resource use, length of stay in a critical care unit, length of hospital stay, blood product usage, and the associated costs may therefore be reduced.

Objectives

The overall objective of this project is to summarise the evidence on the clinical- and cost-effectiveness of VE devices to assist with the diagnosis, management and monitoring of haemostasis disorders during and after cardiac surgery or trauma induced coagulopathy. We have 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 to those who are not tested?

2 If there are no data on one of more of the VE devices we will evaluate the accuracy of that or those VE device(s) for the prediction of relevant clinical outcomes (e.g. transfusion requirement) during or after cardiac surgery.

3 How do clinical outcomes differ among patients with coagulopathy induced by trauma (including post-partum haemorrhage) who are tested with VE devices compared to those who are not tested?

4 If there are no data on one of more of the VE devices we will evaluate the accuracy of that or those VE device(s) for the prediction of relevant clinical outcomes (e.g. transfusion requirement) in patients with trauma induced coagulopathy.

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

6 What is the cost-effectiveness of VE devices in patients with trauma induced coagulopathy? If sufficient data are available from the systematic review, scenario analyses may be run using data from the post-partum haemorrhage population in the trauma model. All analyses in trauma and post-partum haemorrhage populations will be limited to those outcomes (e.g. transfusion requirement) which are considered applicable to all included populations; this is a pragmatic approach adopted because any long term consequences are likely to differ widely both within a heterogeneous general trauma population and between general trauma and post-partum haemorrhage populations.

Methods for assessing clinical effectiveness

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[37] and NICE Diagnostic Assessment Programme manual.[38]

Inclusion and exclusion criteria

Inclusion criteria for each of the three clinical review questions are summarised in Table 7. Studies which fulfil these criteria will be eligible for inclusion in the review.

Protocol Table 7 Inclusion criteria

Question	1. How do clinical outcomes differ among patients who are tested with VE devices during or after cardiac surgery compared to those who are not tested?	a. What is the accuracy of VE devices for the prediction of relevant clinical outcomes during or after cardiac surgery?	2. How do clinical outcomes differ among patients with coagulopathy induced by trauma (including post-partum haemorrhage) who are tested with VE devices compared to those who are not tested?	2a. What is the accuracy of VE devices for the prediction of relevant clinical outcomes in patients with coagulopathy induced by trauma (including post-partum haemorrhage)?
Participants	Adult (age ≥18 years) patients undergoing cardiac surgery		Adult (age ≥18 years) with clinically suspected coagulopathy induced by trauma (including post-partum haemorrhage). Studies in both military and civilian settings will be included.	
Index test	VE devices (ROTEM®, TEG® or Sonoclot®) alone or combined with platelet testing (e.g. multiplate test) or standard testing protocol, performed during or after surgery.	VE devices (ROTEM®, TEG® or Sonoclot®)	VE devices (ROTEM®, TEG® or Sonoclot®) or standard testing protocol	VE devices (ROTEM®, TEG® or Sonoclot®)
Comparators	No testing, standard testing protocol, or other VE device	Any other VE device or None	No testing, standard testing protocol, or other VE device	Any other VE device or None
Reference standard	NA	Patient relevant outcomes e.g. Massive transfusion, any transfusion	NA	Patient relevant outcomes e.g. Massive transfusion, any transfusion
Outcomes	Any reported outcomes. We anticipate that outcomes will include postoperative mortality, bleeding and transfusion outcomes, complications and re-intervention outcomes.	Sufficient data to construct a 2x2 table of test performance	Any reported outcomes. We anticipate that outcomes will include postoperative mortality, bleeding and transfusion outcomes, complications and re-intervention outcomes.	Sufficient data to construct a 2x2 table of test performance
Study design	Randomised controlled trials; if insufficient RCTs are available then lower levels of evidence will be considered	Diagnostic cohort studies	Randomised controlled trials; if insufficient RCTs are available then lower levels of evidence will be considered	Diagnostic cohort studies

Clinical effectiveness search methods

Search strategies will be based on index test (ROTEM® Delta), as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[37] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[39] Searches for studies for cost and quality of life will be developed separately.

Candidate search terms will be identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase Emtree), existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches will be used to generate test sets of target references, which will inform text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development will involve an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies will be developed specifically for each database and the keywords associated with ROTEM®, thromboelastography and thromboelastometry will be adapted according to the configuration of each database.

The following databases will be searched for relevant studies from inception to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (Internet)
- Health Technology Assessment Database (HTA) (Internet)
- Science Citation Index (SCI) (Web of Science)
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet)
  http://regional.bvsalud.org/php/index.php?lang=en
- International Network of Agencies for Health Technology Assessment (INAHTA) Publication (Internet)
  http://www.inahta.org/
- Biosis Previews (Web of Science)
- Conference Proceedings Citation Index – Science (Web of Knowledge)
- NIHR Health Technology Assessment Programme (Internet)
- Aggressive Research Intelligence Facility (ARIF) database (Internet)

http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/index.aspx

- MEDION database (Internet)
  http://www.mediondatabase.nl/
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet)
  http://www.crd.york.ac.uk/prospero/

Completed and ongoing trials will be identified by searches of the following resources (2000-present):

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- Current Controlled Trials (http://www.controlled-trials.com/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)

Key conference proceedings, to be identified in consultation with clinical experts, will be screened for the last five years. We will also screen the website set up by the manufacturers of ROTEM® Delta which lists relevant studies.[40] References in retrieved articles and relevant systematic reviews will be checked.

No restrictions on language or publication status will be applied. Searches will take into account generic and other product names for the intervention. Examples of the search strategies to be used are presented in Appendix 2; these will be adapted as necessary following consultation with clinical experts. It is anticipated that the core device terms strategy may be combined with additional facets to retrieve specific targeted topics, such as randomised controlled trials or studies of use in trauma care. Additional supplementary searches will be carried out as necessary. The main Embase strategy for each search will be independently peer reviewed by a second Information Specialist, using the CADTH Peer Review checklist.[41] Identified references will be downloaded in Endnote X4 software for further assessment and handling. References in retrieved articles will be checked for additional studies. The final list of included papers will also checked on PubMed for retractions, errata and related citations.[42-45]

Review strategy

Two reviewers will independently screen titles and abstracts of all reports identified by the searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant will be

obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following (where applicable): study design/details, participants, VE device, specific reagents used, clinical outcomes, accuracy for the prediction of clinical outcomes and test failure rates. Data will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

Quality assessment strategy

The methodological quality of included RCTs will be assessed using the Cochrane Risk of Bias Tool.[46] Diagnostic accuracy studies will be assessed for methodological quality using QUADAS-2.[47] Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

Methods of analysis/synthesis

We will provide a narrative synthesis involving the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by research question addressed and VE device. A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological limitations of the existing evidence base.

If sufficient data are available meta-analysis will be used to pool data. For studies comparing VE testing with no testing, summary estimates of treatment effect (e.g. hazard ratios, odds ratio, relative risks, weighted mean differences) together with 95% CIs will be estimated using DerSimonian and Laird random effects models. For diagnostic accuracy studies, summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions will be calculated. We will use the bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an SROC curve.[48-50] Forest plots will used to display results from individual studies and summary estimates to allow visual assessment of heterogeneity. Heterogeneity will be assessed statistically using the tau^2 and I^2

statistics. If sufficient data are available, any observed heterogeneity will be investigated using meta-regression or stratified analysis. Variables that will be investigated as possible sources of heterogeneity include patient demographics (age, gender, surgery type), type of VE device (ROTEM®, TEG®, Sonoclot®), time point of surgery (during surgery only, during and after surgery, if sufficient data are available the time frame following surgery will also be investigated) and risk of bias domains.

Methods for synthesising evidence of cost-effectiveness

Identifying and reviewing published cost-effectiveness studies

Exploration of the literature regarding published economic evaluations, utility studies and cost studies will be performed. A review of published economic evaluations will be undertaken on the following databases, utilising a methodological study design filter where appropriate (see Appendix 2):

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (Wiley)
- Health Economic Evaluation Database (HEED (Wiley)
- EconLit (EBSCO)
- Research Papers in Economics (REPEC) (Internet) http://repec.org/

Supplementary searches may be undertaken to focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses that study VE devices. For our assessment cost studies, utility studies and full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model and estimation of model input parameters that will aim to answer the research questions of this project.

The results and the methodological quality of the studies selected will be summarised. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance.[38, 51] Data extraction will focus on technologies compared,

indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

Evaluation of costs, quality of life and cost-effectiveness

This project aims to assess the value of VE devices in two different patient populations: cardiac surgery patients and trauma patients with suspected coagulopathy. Therefore two separate economics models will be defined, constructed, analysed, and reported independently. Both models will evaluate the cost-effectiveness of ROTEM®, TEG®, and Sonoclot® compared to no VE devices as described in section 3.1 If sufficient data are available from the systematic review, scenario analyses may be run using data from the post-partum haemorrhage population in the trauma model. The perspective will be that of the NHS and for the base case analysis a timeframe of one year will be used, as this time frame captures all relevant outcomes. Consequences will be expressed in quality adjusted life years (QALY) and potentially also the number of blood transfusions required. If evidence is found on any important mortality effects of transfusion reduction a lifetime time horizon will be explored in a separate scenario. All analyses in trauma and post-partum haemorrhage populations will be limited to those outcomes (e.g. transfusion requirement) which are considered applicable to all included populations; this is a pragmatic approach adopted because any long term consequences are likely to differ widely both within a heterogeneous general trauma population and between general trauma and post-partum haemorrhage populations. Any assumption used in the models and any parameter value will be based on the literature if possible and supplemented by clinical expert opinion as required.

Model structure

A Cochrane review of TEG® and ROTEM® showed that they are associated with a significant reduction in blood loss during cardiac surgeries. Blood loss can lead to complications such as stroke, renal dysfunction and re-operation to stop excessive bleeding. Also, due to blood transfusion following blood loss, complications such as febrile reaction, haemolytic transfusion reactions and transfusion-transmitted infections can occur. A study by Spalding et al. (2007) showed that the use of ROTEM® led to decreased costs for blood products in their hospital.[52] Hence, it is important to model transfusion rate for each scenario, and relate blood loss and transfusion related complications to this. A possible structure is suggested by the HTA study done for the NHS Scotland in 2008, [10] see Appendix 4. Input for this model was largely derived from a study by Davies (2006)[53] concerning the

cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion. Where possible, more recent data sources will be investigated to populate the model.

Final choices and definitions regarding the structure of the model will depend on the findings from the literature review and consultation with clinical experts.

Issues relevant to analyses:

- One way sensitivity analyses will be performed for all key parameters, especially for parameters in the models which are based on expert opinion.
- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values and sources of assumptions will be documented.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

Health outcomes

Utility values, based on literature or other sources, will be incorporated in the economic model for the various health states. QALYs will be calculated from the economic modelling.

Costs

Resource utilisation will be estimated for the diagnostic tests, blood products and treatments related to complications and infections. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of the comparators.

Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 18/11/2013. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in

parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

Competing interests of authors

None

Timetable/milestones

Milestones	**Completion data**
Draft protocol	25/07/2013
Final protocol	21/08/2013
Progress report	18/11/2013
Draft assessment report	16/01/2014
Final assessment report	13/02/2014

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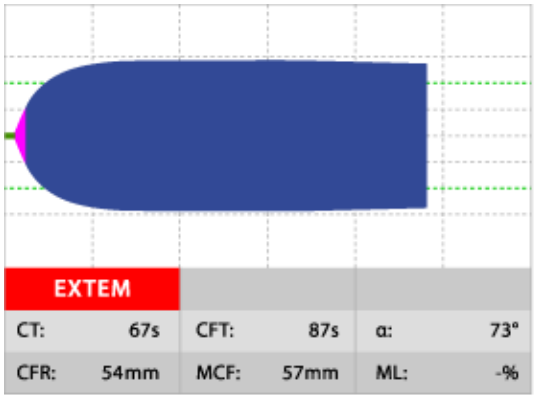
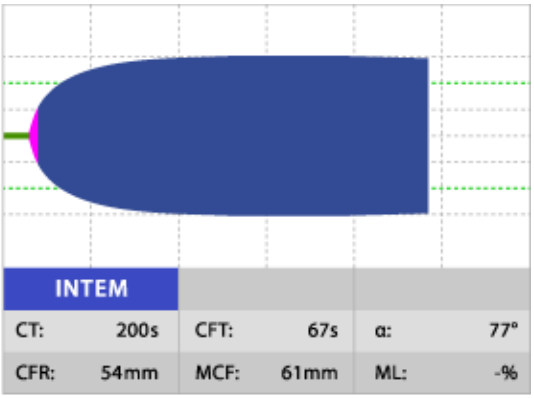
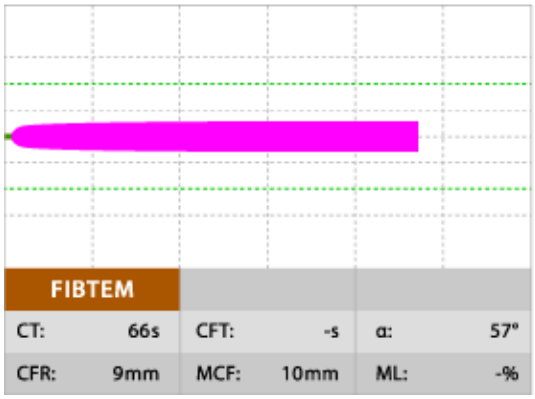
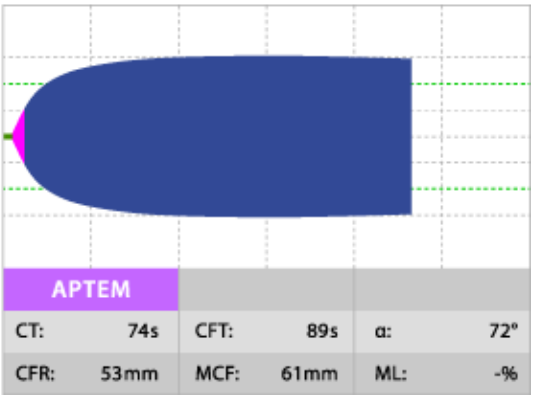
Protocol Appendix 1: ROTEM® Result interpretation[54]

Normal Patient

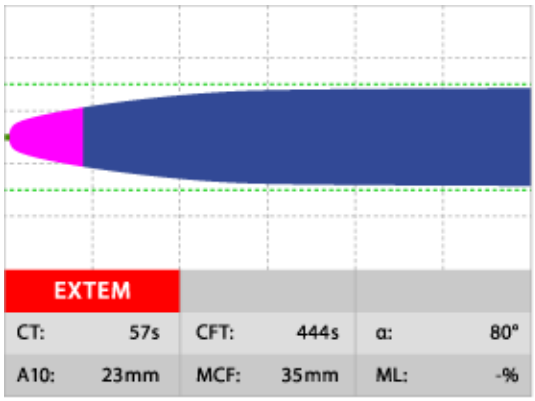


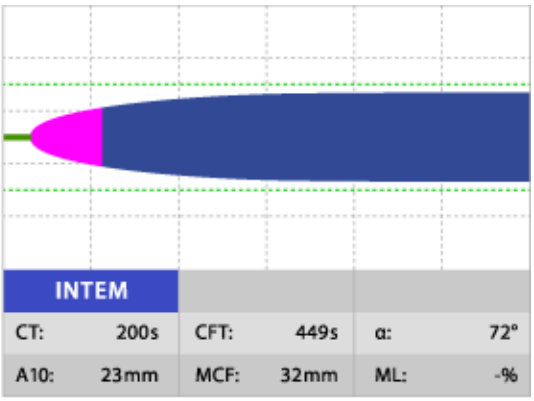


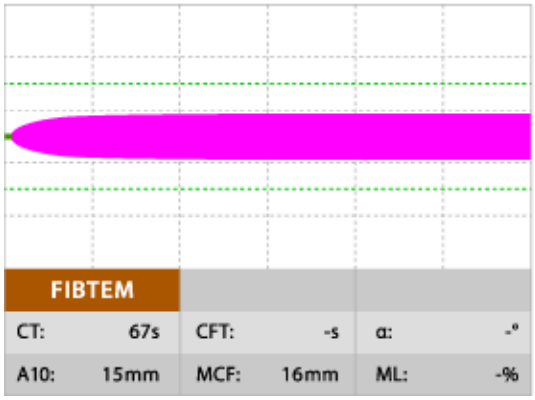


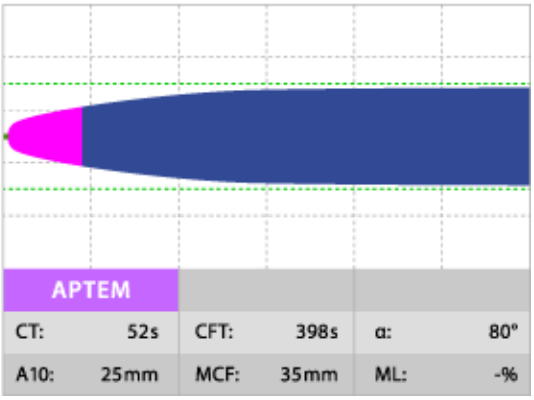


Platelet deficiency

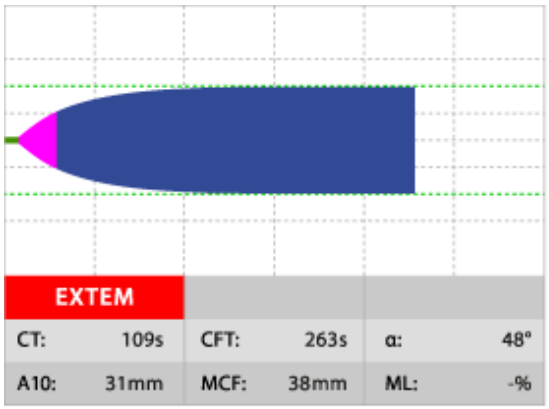








Fibrinogen deficiency



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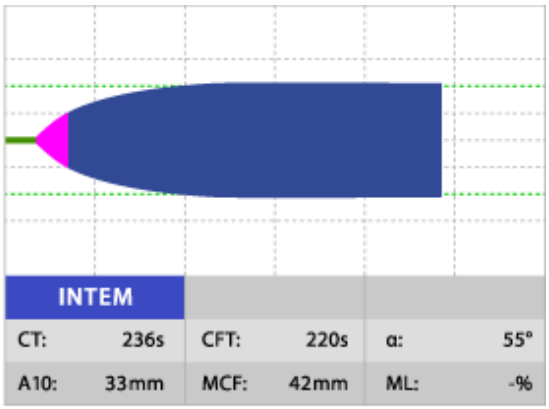

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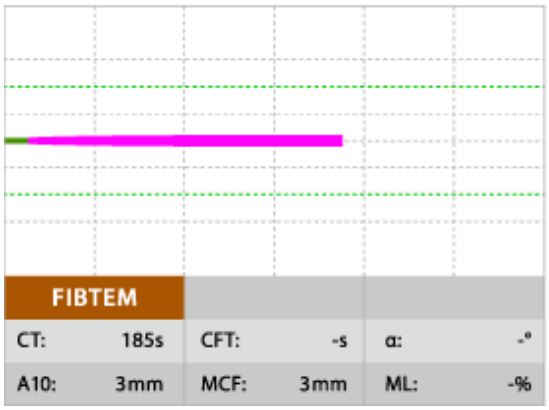

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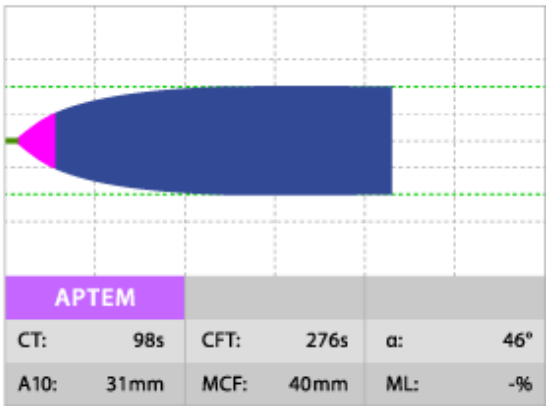

APTEM					
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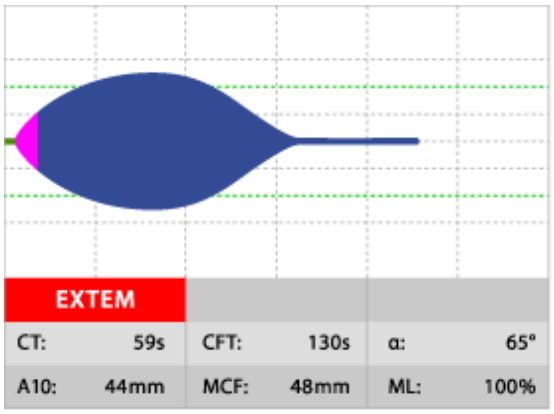
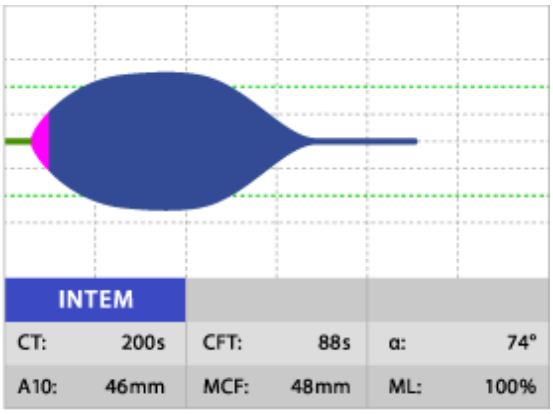
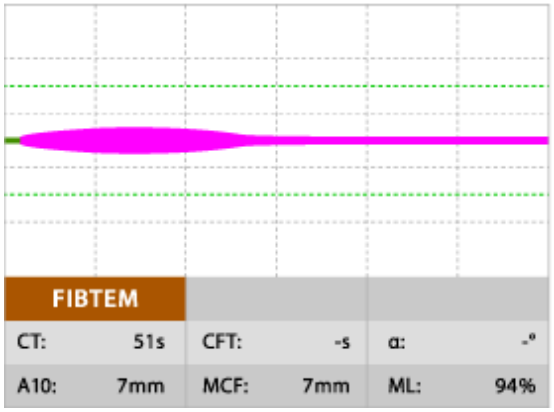
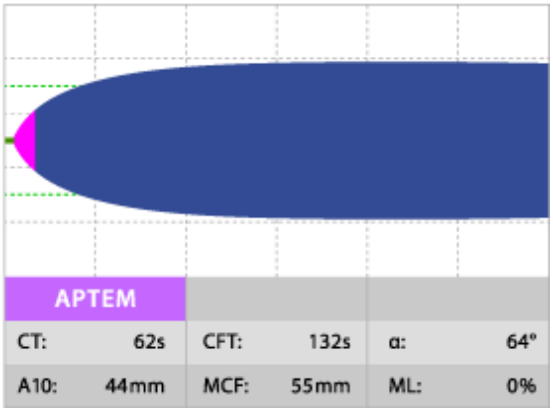
Hyperfibrinolysis

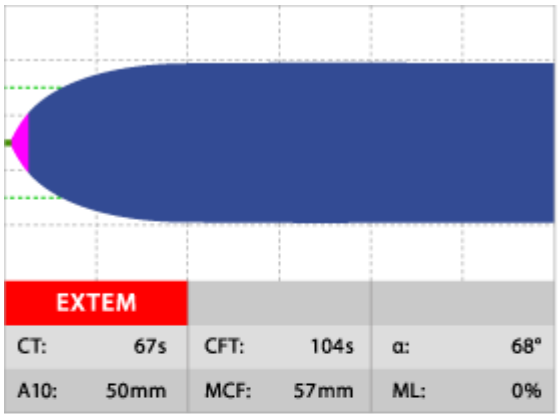


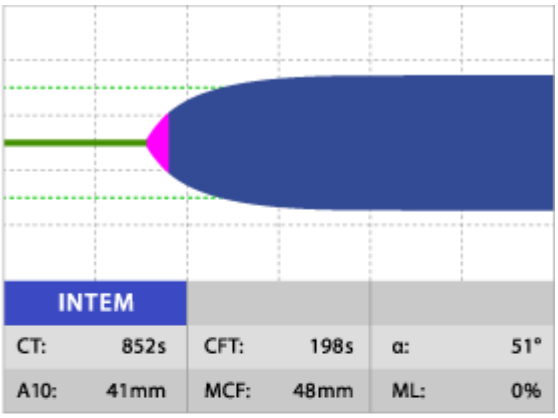


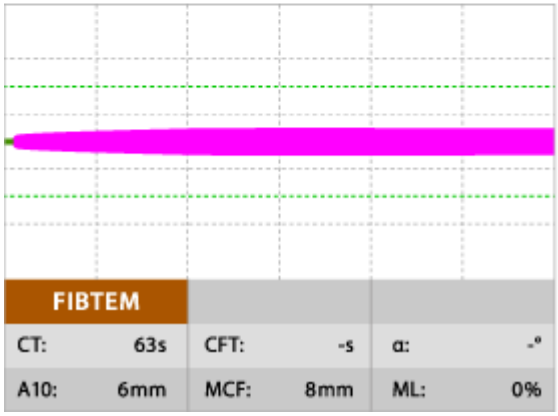


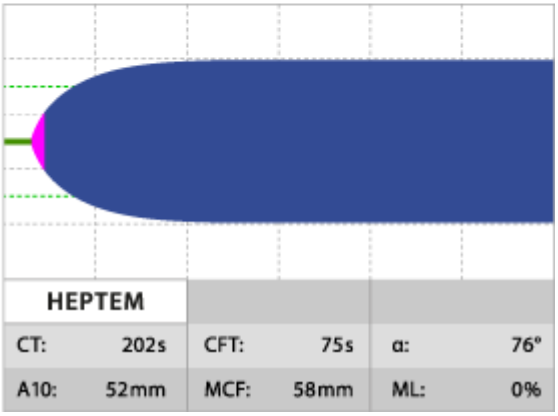


Heparin Influence









Protocol Appendix 2: Example search strategies

Clinical effectiveness search

Embase (OvidSP): 1974-2013/08/21
Searched 19.7.13

1 Random$.tw. or clinical trial$.mp. or exp health care quality/ (3173962)
2 animal/ (1884192)
3 animal experiment/ (1708883)
4 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5789666)
5 or/2-4 (5789666)
6 exp human/ (14881414)
7 human experiment/ (315546)
8 or/6-7 (14882855)
9 5 not (5 and 8) (4617774)
10 1 not 9 (3022408)
11 thromboelastography/ (4852)
12 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$).ti,ab,ot,hw,dv. (1536)
13 (thromb$ adj2 elastogra$).ti,ab,ot,hw,dv. (45)
14 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw,dv. (2)
15 TEG.ti,ab,ot,dv. (1737)
16 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw,dv. (988)
17 whole blood h?emosta$ system$.ti,ab,ot,hw,dv. (2)
18 whole blood h?emo-sta$ system$.ti,ab,ot,hw,dv. (0)
19 (ROTEM$ or ROTEG).ti,ab,ot,hw,dv. (758)
20 (thrombo-elastomet$ or thrombelastomet$).ti,ab,ot,hw,dv. (181)
21 (thromb$ adj2 elastom$).ti,ab,ot,hw,dv. (6)
22 (thromb$ adj2 elasto?m$).ti,ab,ot,hw,dv. (6)
23 (Sonoclot or sono-clot).ti,ab,ot,hw,dv. (158)
24 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw,dv. (17)
25 or/11-24 (6973)
26 10 and 25 (1081)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE (best sens). J Med Libr Assoc 2006;94(1):41-7.

Cost- effectiveness search

Embase (OvidSP): 1974-2013/08/21
Searched 19.7.13

1 health-economics/ (33085)
2 exp economic-evaluation/ (203646)
3 exp health-care-cost/ (195297)
4 exp pharmacoeconomics/ (168266)
5 or/1-4 (467212)
6 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (581623)
7 (expenditure$ not energy).ti,ab. (23068)
8 (value adj2 money).ti,ab. (1294)
9 budget$.ti,ab. (23345)
10 or/6-9 (605163)
11 5 or 10 (874842)
12 letter.pt. (837410)
13 editorial.pt. (445235)
14 note.pt. (580574)
15 or/12-14 (1863219)
16 11 not 15 (789071)
17 (metabolic adj cost).ti,ab. (857)
18 ((energy or oxygen) adj cost).ti,ab. (3132)
19 ((energy or oxygen) adj expenditure).ti,ab. (19689)
20 or/17-19 (22873)
21 16 not 20 (784067)
22 exp animal/ (19202400)
23 exp animal-experiment/ (1712313)
24 nonhuman/ (4113850)
25 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (4976072)
26 or/22-25 (20539135)
27 exp human/ (14881414)
28 exp human-experiment/ (315546)
29 27 or 28 (14882855)
30 26 not (26 and 29) (5657249)
31 21 not 30 (725363)
32 thromboelastography/ (4852)
33 (thrombo-elastogra$ or thrombelastogra$ or thrombelasto-gra$).ti,ab,ot,hw,dv. (1536)
34 (thromb$ adj2 elastogra$).ti,ab,ot,hw,dv. (45)
35 (thromb$ adj2 elasto-gra$).ti,ab,ot,hw,dv. (2)
36 TEG.ti,ab,ot,dv. (1737)
37 (haemoscope$ or hemoscope$ or haemonetics or hemonectics).ti,ab,ot,hw,dv. (988)
38 whole blood h?emosta$ system$.ti,ab,ot,hw,dv. (2)
39 whole blood h?emo-sta$ system$.ti,ab,ot,hw,dv. (0)
40 (ROTEM$ or ROTEG).ti,ab,ot,hw,dv. (758)
41 (thrombo-elastomet$ or thrombelastomet$).ti,ab,ot,hw,dv. (181)
42 (thromb$ adj2 elastom$).ti,ab,ot,hw,dv. (6)
43 (thromb$ adj2 elasto?m$).ti,ab,ot,hw,dv. (6)

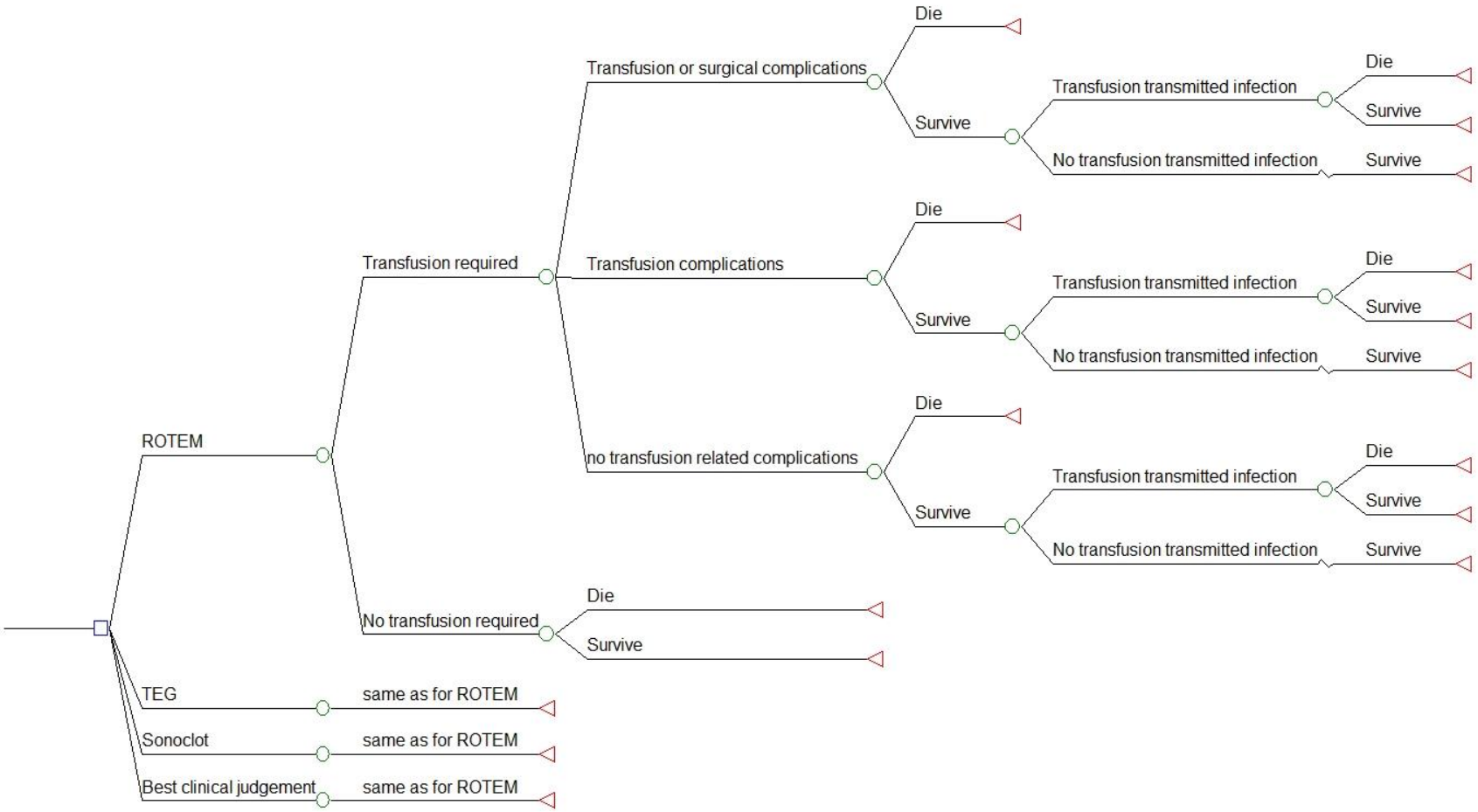
44 (Sonoclot or sono-clot).ti,ab,ot,hw,dv. (158)
45 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system$ or process or test or tests or analyz$ or analys$ or assay$ or device$ or measurement$)).ti,ab,ot,hw,dv. (17)
46 or/32-45 (6973)
47 31 and 46 (225)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Embase (Ovid) weekly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 17.3.11]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

Protocol Appendix 3: Related NICE guidance

There is no related NICE guidance on this topic. We have screened all guidance related to blood and the immune system.

Protocol Appendix 4: Draft model structure



APPENDIX 8: PRISMA CHECK LIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	17
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	25
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	24
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	39
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	43
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	39-40
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	40 and Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	44

Section/topic	#	Checklist item	Reported on page #
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	44
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	44
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	44
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	44
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	44-45
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	45
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	49
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 2 (a-c)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix 3; various sections within results (section 3.2 from p45)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix 2 (d-f)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Various sections within results (section 3.2 from p45)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Various sections within results (section 3.2 from p48)
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	148
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	152
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	162-163
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2