NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review of DG13: Detecting, managing and monitoring haemostasis: viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems)

This guidance was issued in August 2014.

The review date for this guidance is August 2017.

A decision to review the guidance was deferred in 2017 until data from the iTACTIC trial was available.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Recommendations

The existing DG13 includes recommendations for 3 populations; only one of these populations requires updating. It is therefore proposed that the emergency control of bleeding in trauma population should separate into a rapid guidance review. This would mean:

1. Removing recommendations and reference to the use of the technologies when used for the emergency control of bleeding after trauma from DG13.

2. Leaving DG13 with the remaining extant recommendations on use of the technologies to help detect, manage and monitor haemostasis during and after cardiac surgery, and during postpartum haemorrhage. Publishing a technical supplement alongside it to describe newer versions of the technologies.

3. Producing an accelerated update to assess use of the technologies to help detect, manage and monitor haemostasis in the emergency control of bleeding after trauma which would publish as a new piece of guidance.

A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper.

2. Original objective of guidance

To assess the clinical and cost effectiveness of viscoelastometric point‑of‑care testing systems (ROTEM, TEG and Sonoclot) for detecting, managing and monitoring haemostasis.

3. Current guidance

Adoption recommendations

Cardiac surgery

Recommendation 1.1

The ROTEM system and the TEG system are recommended to help detect, manage and monitor haemostasis during and after cardiac surgery.

Recommendation 1.2

The Sonoclot system is only recommended for use in research to help detect, manage and monitor haemostasis during and after cardiac surgery. Research is recommended into the clinical benefits and cost effectiveness of using the Sonoclot system during and after cardiac surgery (see research recommendation 7.1).

Recommendation 1.3

Healthcare professionals using the ROTEM system and the TEG system during cardiac surgery should have appropriate training and experience with these devices

Emergency control of bleeding

Recommendation 1.4

There is currently insufficient evidence to recommend the routine adoption of viscoelastometric point‑of‑care testing (ROTEM, TEG and Sonoclot systems) in the NHS to help detect, manage and monitor haemostasis in the emergency control of bleeding after trauma and during postpartum haemorrhage. Research is recommended into the clinical benefits and cost effectiveness of using viscoelastometric point‑of‑care testing to help in the emergency control of bleeding after trauma or during postpartum haemorrhage (see research recommendation 7.2).

Research recommendations

Research recommendation 7.1

The Committee recommended further research to demonstrate the utility of the Sonoclot system in detecting, managing and monitoring haemostasis in cardiac surgery.

Research recommendation 7.2

The Committee recommended further research in using viscoelastometric testing in the emergency control of bleeding after trauma and during postpartum haemorrhage to assess its effectiveness compared with standard laboratory testing. The Committee recommended that outcomes should include, but may not be limited to, bleeding outcomes, mortality, duration of hospital or intensive care unit stay, transfusion rates and volumes transfused.

Research recommendation 7.3

The Committee recommended further research comparing the clinical effectiveness of all 3 viscoelastometric devices (ROTEM, TEG and Sonoclot systems) in cardiac surgery and in the emergency control of bleeding after trauma and during postpartum haemorrhage. In particular, the Committee recommended research to determine which of the parameters included in the viscoelastometric testing systems are the most significant in changing clinical decision-making and improving clinical outcomes. The degree of change needed in these parameters to affect clinical decision-making and clinical outcomes should also be considered.

Research recommendation 7.4

The Committee recommended that future trials should include longer-term follow-up, beyond the initial hospital episode, with a view to informing the cost-effectiveness modelling and reducing uncertainty.

Research recommendation 7.5

The Committee recommended further research to understand the characteristics of patients at high risk of haemostatic instability in whom viscoelastometric testing may be most cost effective.

4. Rationale

New data are available on the use of viscoelastometric point-of-care tests when used in the emergency control of bleeding after trauma. These may have a material effect on the existing recommendations on the use of these technologies in this context. .

No evidence was identified which is likely to change recommendation 1.1 but there have been changes to the available technologies which can be effectively and efficiently summarised using technical and advice products.

5. Implications for other guidance producing programmes

NICE guideline NG39 (Major trauma: assessment and initial management; published February 2016) includes a recommendation for further research to determine the clinical and cost effectiveness of point-of-care coagulation testing using ROTEM or TEG to target treatment, compared with standard laboratory coagulation testing. An update of DG13 may make this research recommendation obsolete.

No issues were raised during internal consultation.

6. New evidence

The search strategy from the original diagnostics assessment report was re-run on Embase, Ovid MEDLINE, BIOSIS Web of Science, Cochrane Libraries, ClinicalTrials.gov, ISRCTN Registry, WHO ICTRP, PROSPERO, LILACS, ASA Meetings, APC, Econlit (Proquest) and IDEAS. References from 2013 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the diagnostic and care pathways. Companies were asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. Specialist Committee Members for this guidance topic were also consulted and asked to submit any information regarding changes to the technologies, the evidence base and clinical practice. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

6.1 Technologies

Since the publication of NICE diagnostics guidance 13 in August 2014 there have been minor changes to software related to 2 of the technologies covered by the guidance. New versions of the ROTEM and TEG systems have also been released.

The ROTEM system

The ROTEM delta system (which was available when the original guideline was published) has had several software upgrades. The upgrades provide automatic quality control reminders, give the ability to encrypt data, monitor and record team training and provides additional quality control capabilities.

A further version of the system – the ROTEM sigma – was launched in the UK in September 2015. The company state that the ROTEM sigma uses the same thromboelastometry technology as the ROTEM delta but that the tests are fully automated. The ROTEM sigma uses a cartridge-based system to run 4 haemostasis tests simultaneously; with 2 versions of cartridge available to run different combinations of tests (Sigma Complete Cartridge and Sigma Complete+Hep). A clinical expert commented that the ROTEM sigma uses the same technology as the ROTEM delta but has improved ease of use for operators and minimises their involvement in testing.

The cost of the ROTEM system in diagnostic guidance 13 was £24,950, compared with the current cost of the ROTEM delta of [redacted]. The estimated cost of use of the device per test in diagnostic guidance 13 (assuming 3 years of use and including costs related to maintenance, training and assay consumables) was £46.27 for cardiac surgery and £40.69 for trauma patients. The corresponding estimated cost per test using provided current costs is [redacted] for cardiac surgery and [redacted] for trauma patient. However, these costs do not include connectivity kit or software/database costs that were included in cost estimates for diagnostics guidance 13.

The newer ROTEM system version, the ROTEM sigma, costs [redacted]. An estimated cost per test (assuming 3 years of use and including costs related to maintenance and assay consumables) is [redacted].

The TEG system

The TEG manager software, which can be used as an optional extra for the TEG system on external computers or devices to view and manage results, has been upgraded since diagnostics guidance 13 published.

In addition, a new version of the system – the TEG 6s – has been released since diagnostics guidance 13 published. The TEG 6s measures the same physical properties as the original TEG 5000 system, and furthermore now includes a resonance-based technique to assess clot strength. A clinical expert commented that this additional assay uses a different mechanism to tests used in the previous TEG 5000 device. The TEG 6s uses an all-in-one cartridge which allows several different haemostasis tests to be done simultaneously. Two cartridge versions (with different combinations of tests; the Global Haemostasis and PlateletMapping) are available. A clinical expert has commented that the all-in-one cartridge system used by the TEG 6s essentially automates the analytic process and requires minimal operator input.

The cost of the TEG 5000 system and associated assay consumables has not changed since the publication of diagnostics guidance 13. The TEG 6s costs [redacted]. The estimated cost per test (assuming 3 years of use and including costs related to maintenance and assay consumables) is [redacted] (compared with a cost

per test for the TEG system, as calculated in the original assessment, of £34.25 for cardiac surgery and £34.03 for trauma patients).

The Sonoclot system

There have been no changes to the Sonoclot system since the guidance was published.

Additional technologies

The ClotPro analyser (enicor GmbH) uses viscoelastic methods to evaluate coagulopathy. It offers testing for overall coagulation (EX-test), fibrinogen (FIB-test), heparin (IN-test), heparin inhibition (HI-test) and fibrinolysis inhibition (AP-test) and drug monitoring tests. No published studies assessing this test have been identified. But there are 2 ongoing studies:

- Investigation of Systemic and Regional Haemostasis During Liver Transplantation by Comparing ClotPro® and TEG ® Viscoelastic Tests (NCT04246307): An observational study assessing correlation between TEG and ClotPro parameters in people having liver transplant. Estimated study completion date is January 2022.

- Comparison of Viscoelastic Measurement by ROTEM® Delta and ClotPro® in Trauma Patients (NCT04107818): An observational study comparing ClotPro and ROTEM Delta measurements in trauma patients. Estimated study completion date is January 2021.

It is not known if this test is available to the NHS. In April 2020, Haemonetics (the manufacturer of the TEG system) announced that it has acquired enicor GmbH.

6.2 Clinical practice

NICE guideline NG45 (Routine preoperative tests for elective surgery; published in April 2016) includes recommendations on the use of pre-operative haemostasis point-of-care testing.

NICE guideline NG39 (Major trauma: assessment and initial management; published February 2016) includes recommendations on the management of haemorrhage in pre‑hospital and hospital settings (section 1.5). This includes a recommendation that, for patients with active bleeding, to start with a fixed‑ratio protocol for blood components and change to a protocol guided by laboratory coagulation results at the earliest opportunity. The guideline includes a recommendation for further research to determine the clinical and cost effectiveness of point‑of‑care coagulation testing using ROTEM or TEG to target treatment, compared with standard laboratory coagulation testing. Diagnostics guidance 13 also recommends further research on

the use of viscoelastometric point‑of‑care testing to help in the emergency control of bleeding after trauma.

Several NICE guidelines that published after diagnostics guidance 13 include recommendations to use, or consider the use of, tranexamic acid: NICE guideline NG24 (Blood transfusion; published November 2015), NICE guideline NG39 (Major trauma: assessment and initial management; published February 2016) and NICE guideline CG190 (Intrapartum care for healthy women and babies; published December 2014). In addition, the Association of Anaesthetists of Great Britain and Ireland's AAGBI guidelines: the use of blood components and their alternatives 2016 recommends considering intra-operative cell salvage and tranexamic acid administration in all non-obstetric patients where blood loss >500mL is possible and in traumatic and obstetric major haemorrhage. A clinical expert commented that, because tranexamic acid is an anti-fibrinolytic drug, greater use may make the fibrinolysis detection assays of the systems in diagnostics guidance 13 redundant in many cases.

The AAGBI guidelines: the use of blood components and their alternatives 2016 also recommends that:

> "*Patients who continue to actively bleed should be monitored by point-of-care and/or regular laboratory tests for coagulation, fibrinogen and platelet counts or function, and a guide for transfusion should be FFP if INR > 1.5, cryoprecipitate if fibrinogen < 1.5 g.l^{-1} and platelets if platelet count < 75 × 109.l^{-1}.*"

The guideline further states that: "*Monitoring of haemostatic function in obstetric haemorrhage is particularly important; laboratory testing is often too slow during obstetric haemorrhage, and therefore, POC testing is preferred*." The guideline also comments that point-of-care testing of coagulation status is increasingly popular for general and cardiac surgery, trauma units, intensive care and obstetrics. The ROTEM and TEG devices are mentioned in this guideline, which states that one of these devices cannot be recommended over the other.

The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition (published April 2016) also recommends early and repeated monitoring of coagulation status using either laboratory tests and/or a viscoelastic method (recommendation 12). In addition, resuscitation measures for trauma patients should be continued using a goal-directed strategy guided by standard laboratory coagulation values and/or viscoelastic tests (recommendation 26). The guideline further comments that "…*complete and rapid monitoring of blood coagulation and fibrinolysis using viscoelastic methods may facilitate a more accurate targeting of therapy compared to conventional laboratory tests alone."* In addition: "*Trauma systems without rapid point-of-care* [coagulation] *testing tend to*

use fixed ratio protocols during the phase of rapid bleeding, as central laboratory coagulation results are available too late to guide therapy."

The EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery (2017) concludes that viscoelastic point of care testing is supported by the evidence, although it is not recommended in patients without antithrombotic treatment.

The CADTH Rapid Response Report for Thromboelastography or Rotational Thromboelastography for Trauma (2017) concludes that ROTEM and TEG may be useful in guiding transfusion requirements in trauma patients

The British Society for Haematology Guideline published a guideline on the use of viscoelastic haemostatic assays in the management of major bleeding in 2018. This focussed on the use of viscoelastic haemostatic assays in 4 scenarios:

- **Obstetric and postpartum bleeding**: The assays may be used as part of an agreed algorithm to manage postpartum haemorrhage when the local institution's major obstetric haemorrhage protocol is activated. Recommendations are provided on the use of the ROTEM FIBTEM A5 assay to guide fibrinogen replacement.

- **Liver disease and Liver surgery**: ROTEM FIBTEM and TEG Functional Fibrinogen assay (TEG-FF) are recommended to guide fibrinogen replacement. Viscoelastic haemostatic assays can be used to reduce overall transfusion requirements.

- **Cardiac surgery**: Cardiac surgery services should use transfusion protocols based on VHA testing to reduce use of blood components and potentially improve clinical outcomes in bleeding patients. The assays can be used to assess fibrinogen concentration to guide fibrinogen replacement.

- **Trauma**: Normal assay results can predict need for transfusion, TEG and ROTEM measures can be used to indicate higher risk of needing red blood cell and blood components. Use of the assays may be considered for transfusion guidance in trauma haemorrhage.

The guideline states that a drawback of viscoelastic haemostatic assay machines has been the need for users to be trained in basic pipetting to introduce reagents. It further notes that newer versions of the TEG and ROTEM systems (TEG6s and the ROTEM sigma) uses cartridges that are pre-loaded with reagents.

6.3 New studies

A list of abbreviations is provided in appendix 2.

6.3.1. Cardiac surgery

Diagnostics guidance 13 includes a recommendation for further research to demonstrate the utility of the Sonoclot system in detecting, managing and monitoring haemostasis in cardiac surgery (research recommendation 7.1). An RCT which published after diagnostics guidance 13 and which compares the use of the Sonoclot to standard laboratory tests (SLTs) in cardiology patients is discussed below.

An overview of 18 studies on the use of viscoelastometric point of care testing in cardiac surgery (3 RCTs, 5 prospective cohort studies and 10 retrospective cohort studies), organised by outcome, is presented below.

6.3.1.1. Transfusions: red blood cells, fresh frozen plasma, platelets and allogenic blood products

RCTs

Karkouti et al. (2016) was a multi-centre, stepped-wedge cluster RCT carried out at 12 hospitals in Canada (n=7,402). The study compared a transfusion algorithm incorporating ROTEM (version unspecified) guided haemostatic testing with a standard approach based on institutional guidelines for managing post-surgical bleeding. Use of the ROTEM reduced transfusion of red blood cells (RBCs; relative risk [RR] 0.91, p=0.02) and platelets (RR 0.77, p<0.001). In addition, there was a 13% reduction in per-patient red blood cells transfused, a 24% reduction in platelets transfused, and an overall 16% reduction in allogenic blood products (p=0.04).

A single-centre, single-blinded RCT compared use of the TEG 5000 to activated coagulation time (ACT) testing in South Africa (Levin et al. 2014). No significant between-group differences were seen in the primary outcome of protamine dosing (p=0.057) or in secondary outcomes: postoperative transfusions, ICU length of stay or resuscitation requirements.

Observational studies

A Danish prospective cohort study (Sivapalan et al. 2017) reported that the TEG 6s was able to predict plasma and platelet transfusion needs. Several retrospective cohort studies reported that use of TEG or ROTEM devices reduced the transfusion of blood components (Fassl et al. 2013; Mehaffey et al. 2017; Pearse et al. 2015; Sun et al. 2014; Trevisan et al. 2016; Vasques et al. 2017; Yildirim et al. 2014).

6.3.1.2. Bleeding

RCTs

The multi-centre, stepped-wedge cluster RCT Karkouti et al. (2016; described above) reported a reduced risk of major bleeding (RR 0.83, p=0.004) when ROTEM

(version unspecified) guided haemostatic testing was used, compared with a standard approach based on institutional guidelines for managing post-surgical bleeding.

Yang et al. (2017) compared use of the Sonoclot to SLTs in cardiology patients randomised 1:1 in China (n=128). Sonoclot significantly reduced the incidence of thrombus (7.8% vs. 21.9%; p=0.025) and bleeding (4.7% vs. 15.6%, p=0.041) compared to the SLT group. Sonoclot also significantly reduced blood coagulation detection time compared to the SLT group (15.6 vs. 38.2 minutes; p=0.001).

Observational studies
A retrospective cohort study (Vasques et al. 2017) reported that blood loss within 24-hours was significantly reduced in patients with ROTEM-guided haemostasis management compared to those with SLTs-based care (p<0.0001). Three retrospective cohort studies reported that ROTEM parameter values measured pre-operatively were abnormal in people with higher levels of bleeding (Ghavidel et al. 2015; Petricevic et al. 2013; Sartorius et al. 2014). Mishra et al. (2014) reported that parameters measured by the TEG (version unspecified) did not correlate well with bleeding outcomes.

6.3.1.3. Mortality, complications, re-operations and length of stay

RCTs
A multi-centre RCT (Karkouti et al, 2016) reported no significant difference in complication rates (a composite of in-hospital death, acute kidney injury, sepsis, sternal infection, deep vein thrombosis, pulmonary embolism, myocardial infarction and stroke) between ROTEM and standard haemostatic management.

Levin et al. 2014 reported no significant difference in the length of stay in an ICU between groups for whom the TEG 5000 was used to assess residual heparin and those for whom activated coagulation time testing was used.

Observational studies
A retrospective cohort study (Vasques et al. 2017) reported that ICU length of stay was significantly reduced in patients with ROTEM-guided haemostasis management compared to those with SLTs-based care (43.7 hours vs. 52.5 hours). Mehaffey et al. (2017), a retrospective before-after cohort study, reported that the reoperation odds ratio for ROTEM-guided haemostasis was 0.73 (p=0.004) compared to SLT-guided haemostasis management. Two retrospective cohort studies assessed use of the ROTEM with the Roche Multiplate analyser. Pearse et al. (2015) reported significant reductions in re-exploration for bleeding, infection and mean length of stay compared to the SLTs based protocol, but no significant difference in complication and mortality rates. Trevisan et al. (2016) reported a significant reduction in ventilation (p<0.001), compared to conventional management, but no significant difference in mortality or adverse events.

A Danish retrospective cohort study (Dridi et al. 2014) reported no significant increase in the incidence of all-cause mortality, stroke and major adverse cardiac events in people with hypercoagulation as defined by the TEG 5000 (TEG-MA parameter).

6.3.1.4. Chest tube output and drainage

Observational studies
No RCTs were identified. Two prospective cohort studies (Petricevic et al. 2013 and 2014; carried out on the same group of patients in Croatia) reported that ROTEM measurements were correlated with increased chest tube output and that the ROTEM-InTEm assay results were significantly better correlated with chest tube output than ACT testing results.

A retrospective before-after cohort study (Pearse et al. 2015) reported that chest tube blood loss was significantly reduced in a group managed using a protocol incorporating ROTEM plus the Roche Multiplate compared to an SLTs based protocol ($p<0.001$). A further before-after retrospective comparative study (Yildirim et al. 2014) reported a significant reduction in drainage in groups manged using ROTEM compared with a group manged using SLTs ($p=0.001$). A non-comparative study done in the USA (Chowdhury et al. 2014) reported an association between lower preoperative TEG-MAADP values (maximum amplitude produced by adenosine diphosphate) and a higher likelihood of elevated postoperative chest tube drainage (odds ratio 0.94; $p=0.004$).

6.3.2. Trauma

Diagnostics guidance 13 includes a recommendation for further research in using viscoelastometric testing in the emergency control of bleeding after trauma (research recommendation 7.2). The committee highlighted the following outcomes as particularly important: bleeding outcomes, mortality, duration of hospital or intensive care unit stay, transfusion rates and volumes transfused.

An overview of identified studies (3 RCTs, 8 prospective cohort studies and 7 retrospective cohort studies), organised by outcome, is presented below.

During the assessment for diagnostics guidance 13, the EAG identified 1 ongoing RCT that was comparing TEG (rapid assay) with conventional coagulation testing in adults with blunt or penetrating trauma who were likely to require a transfusion of RBCs within six hours from admission (NCT01536496). No data were available at the time of the assessment, but study results have now been posted on the clinicaltrials.gov webpage for this study.

6.3.2.1. Transfusions: red blood cells, fresh frozen plasma, platelets and allogenic blood products

RCTs

Baksaas-Aasen et al. (2020) reported results of the Implementing Treatment Algorithms for the Correction of Trauma Induced Coagulopathy (iTACTIC) trial. This multi-centre RCT (which included UK hospitals) compared use of viscoelastic haemostatic assays (TEG 6S or ROTEM Sigma; n=201) with conventional coagulation tests (n=195) to guide haemostatic therapy for injured patients suspected of having haemorrhage. No statistically significant difference in the proportion of people who were alive and free of massive transfusion at 24 hours after injury (the primary outcome) was seen in pre-specified subgroups. In people with severe traumatic brain injury (n=74), 64% were alive and free of massive transfusion at 24 hours in the treatment arm compared to 46% in the control arm (odds ratio 2.12, 95% confidence interval 0.84 to 5.34).

Gonzalez et al. (2016) reports an RCT in which people with trauma requiring transfusion (n=111) had this guided by either TEG 5000 or SLTs. The TEG managed group required significantly fewer units of platelets (p=0.041) and fresh frozen plasma (FFP; p=0.022) in the first two hours of resuscitation. Similar quantities of RBCs were required.

Observational studies

Several observational cohort studies compared cohorts of trauma patients whose transfusion was guided with and without use of the TEG:

- Tapia et al. (2013) reported that for blunt trauma patients who received ≥10 units of RBC, a cohort managed without TEG (version not specified) required significantly more FFP (p=0.02) and crystalloid transfusions (p=0.04) than a TEG managed cohort. There was no difference in overall transfusion demands between the cohorts for patients who received ≥6 units of RBC.

- Wang et al. (2017) reported that significantly fewer units of RBC were used in a cohort of people with traumatic abdominal solid organ injury who had TEG-guided transfusion (version not specified) compared to a non-TEG-guided cohort (4 vs. 9 units; p<0.01).

- Hota et al (2019) reported that use of TEG (version not specified) compared to conventional coagulation testing in traumatic brain injury patients significantly reduced the use of blood products.

- Unruh et al. (2019), a before-after study of 67 patients following massive transfusion protocol, reported that TEG 5000 significantly reduced red blood cell transfusions (-5 units, p=0.001) as well as the number of patients receiving FFP (17% vs. 85%, p<0.001) and platelets (38.3% vs. 75%, p=0.006) compared to conventional coagulation testing.

- Mohamed et al. (2017), a before-after cohort study of 134 patients in the USA, reported that use of TEG5000 significantly reduced transfusions of packed red blood cells (-3.6 units, p=0.022), fresh frozen plasma (-2.13 units, p=0.0474) and platelets (-1.45 units, p=0.0476) at 24-hours.

6.3.2.2. Bleeding

RCTs
Connelly et al. (2016), a multi-centre RCT, compared the use of the TEG 5000 guided and standard trauma protocols to adjust enoxaparin dosage for people admitted to 3 trauma centres in the US (n=185). There was no significant difference in the occurrence of venous thromboembolism (6.7% vs. 6.3%; p>0.99) or bleeding complications (5.6% vs 13.5%; p=0.08). However, the study was underpowered according to the authors' sample size calculation.

6.3.2.3. Survival, complications and length of stay

RCTs
Gonzalez et al. (2016) reported significantly higher survival in a group treated using a TEG 5000 guided transfusion protocol compared to a group treated using an SLT guided transfusion protocol (log-rank p=0.032, Wilcoxon p=0.027).

Observational studies
A retrospective cohort study, Tapia et al. (2013), reported that mortality was significantly lower in patients with penetrating trauma (and who received ≥10 units of RBC) who had TEG-directed transfusion (33.3% vs. 54.1%; p=0.04). Another retrospective cohort study, Wang et al. (2017), reported that people with TEG-guided transfusion had a significantly reduced length of stay in hospital (14 vs. 19 days; p<0.05).

A prospective cohort study (Brill et al. 2017) reported that the occurrence of lower extremity deep vein thrombosis in adults admitted to a trauma centre (n=983) was higher in people with hypercoagulable TEG 5000 results (defined by local reference ranges; p=0.039). Another prospective cohort study (Connelly et al. 2017) reported that the TEG (version unspecified) was able to predict antiplatelet medication use (AUC 0.77) in patients admitted to an emergency department.

Hota et al (2019) investigated the efficacy of TEG (unspecified version) compared to conventional coagulation tests in traumatic brain injury patients (n=118). Mortality was similar between the groups. However, in the most severely injured patients, mortality was lower in the TEG group.

Unruh et al. (2019) reported that length of hospital stay and mortality outcomes were similar before and after use of the TEG5000 was adopted. In contrast, Mohamed et al. (2017) another before-after cohort study, reported that ICU and hospital length of stay were significantly shorter in the TEG group (-8.35 days, p=0.0093 and -11.37

days, p=0.0011) which also had reduced mortality mortality (odds ratio 0.33, p=0.0334).

6.3.3. Post-partum haemorrhage

Diagnostics guidance 13 includes a recommendation for further research in using viscoelastometric testing during postpartum haemorrhage (research recommendation 7.2). The committee highlighted the following outcomes as particularly important: bleeding outcomes, mortality, duration of hospital or intensive care unit stay, transfusion rates and volumes transfused.

No relevant RCTs have been identified. The results of 4 observational studies (all prospective cohort studies) that published after diagnostics guidance 13 are described below. The studies include the TEG and ROTEM systems, but not Sonoclot.

6.3.3.1. Bleeding

Karlsson et al. (2014) reported that haemostasis parameters measured by the TEG 5000 were significantly different in people with major obstetric haemorrhage, compared to people with blood loss of less than 600 ml. The maximum amplitude of clot (TEG-MA) as measured by the TEG 5000 was strongly correlated with fibrinogen tests and moderately correlated with blood loss.

6.4.3.2. Diagnostic accuracy

In Ahmad et al. (2016), a cohort study of people presenting with pre-eclampsia/eclampsia in India, TEG measured parameters (R-time and K-time) were strongly correlated with SLT results (r>0.9). TEG measured parameters were also significantly different in hypercoagulable patients (compared to normocoagulable patients). In Davies et al. (2016), ROTEM measured parameters (version unspecified) were significantly different between UK cohorts with Factor XI deficiency and a control group without the condition. Measured ROTEM parameters were moderately correlated with bleeding scores, but overall ROTEM measured parameters were not significantly correlated to haemorrhage outcomes or to blood product use. Duraj et al. (2015), a cohort study done in Slovakia, reported that maximum clot firmness measured using the ROTEM system (version unspecified) was significantly higher in a pregnant cohort (gestation 34th-36th week) compared to a non-pregnant control group (n=55). ROTEM assays (EXTEM and INTEM) showed moderate correlation with standard tests (clotting time and activated prothrombin time).

6.3.4. Other indications

Further studies have reported on the use of viscoelastometric point-of-care testing devices in liver transplant (9 studies), critical care (2 studies), lung transplant (1

study) and stoke (1 study). Use of the devices in such contexts is outside the scope of diagnostics guidance 13.

6.3.5. Economic evidence

In both the cardiac and trauma economic models produced for diagnostics assessment 13, use of viscoelastometric devices dominated standard laboratory tests (that is, they were more effective and less costly).

6.3.5.1. The ROTEM system

Trevisan et al. (2016) reported that introduction of a protocol including the ROTEM and Roche Multiplate analyser as part of a cardiac study was associated with a saving of €340 per patient. Pearse et al. (2015) reported that the implementation of a protocol involving the ROTEM and Roche Multiplate analyser to diagnose cause of bleeding and monitor treatment for cardiac patients in Australia resulted in a decrease in blood product costs.

6.3.5.2. The TEG system

Goodman et al. (2015) compared the use of point-of-care international normalized ratio (POC INR) testing to use of the TEG (version unspecified) for trauma patients in the US. Total cohort charges for POC INR testing were lower than for TEG and the authors concluded that POC INR provides a practical alternative for rapid coagulopathy assessment in the trauma patient at institutions that lack TEG capability.

6.3.6. Ongoing trials

Appendix 2 lists potentially relevant identified ongoing trials that assess the use of the ROTEM, TEG or Sonoclot systems in the context of cardiac surgery, trauma or post-partum haemorrhage.

The ROTEM-PPH trial (NCT02461251) is a randomised study in which adults with severe post-partum haemorrhage will either have ROTEM-guided treatment or treatment according to clinical decision making and conventional coagulation tests. The primary trial outcome is reduction in blood transfusions; secondary outcomes include reduction in transfusion-related side effects and number of thromboembolic events. The clinicaltrials.gov page for this trial states that it completed in January 2020, but no data are posted.

7. Summary of new evidence and implications for review

Cardiac surgery

As in the original assessment, new studies indicate that the addition of ROTEM to haemostasis management protocols significantly reduces bleeding and requirements for transfusion products. For TEG, available evidence published after diagnostics

guidance 13 was less clear. An observational study (Sun et al. 2014) reported that a cohort receiving a TEG guided transfusion protocol received significantly less fresh frozen plasma (FFP) and platelets compared to a SLT control group. However, an RCT (Levin et al. 2014) and an observational study (Dridi et al. 2014) reported that TEG 5000 was not superior to SLTs in reducing transfusions, bleeding or complications. In diagnostics guidance 13, data from 6 RCTs was available to inform estimates of the effectiveness of the TEG system to detect and treat haemostasis. Pooled estimates from these studies showed a beneficial effect of the TEG system on reducing the number of patients who received red blood cell transfusion (3 RCTs), reducing the number of patients who received any blood product transfusion (1 RCT), reducing the number of patients who received a fresh frozen plasma transfusion (3 RCTs) and reducing the number of patients who received a platelet transfusion (3 RCTs). Given the data in the original assessment for diagnostics guidance 13 showing a beneficial effect of TEG with cardiac surgery, the new data would be unlikely to have an effect on existing guideline recommendation 1.1.

Diagnostics guidance 13 includes a recommendation for further research to demonstrate the utility of the Sonoclot system in detecting, managing and monitoring haemostasis in cardiac surgery (research recommendation 7.1). One RCT (Yang et al. 2017) done in China indicated that use of the Sonoclot reduced the incidence of bleeding in comparison to use of standard laboratory tests (SLTs); however, this RCT is small, data generated in China may not be generalisable to the UK and is unlikely to provide sufficient evidence to remove the need for research recommendation 7.1.

Trauma

No RCTs relating to trauma were identified in the original assessment. An RCT (Gonzalez et al. 2016) and 3 observational studies reported that use of the TEG system could reduce transfusion demands, mortality and length of hospital stay. However, another RCT (Connelly et al. 2016) reported no significant effect of the TEG system on the occurrence of bleeding complications (although the study was potentially underpowered). The iTACTIC study was highlighted by clinical experts as likely to be very relevant to this guidance. This study has now published and includes data on outcomes highlighted by the committee in diagnostics guidance 13 as important (in research recommendation 7.2).

Post-partum haemorrhage

As in the original assessment, no RCTs were identified that compared clinical outcomes among patients with postpartum haemorrhage who were tested with viscoelastometric devices compared with those who were not tested. One ongoing RCT was identified but no data were available. This study was also small in size. The identified new studies are unlikely to provide sufficient evidence to remove the need for research recommendation 7.2.

No new studies relevant to research recommendations 7.3, 7.4 or 7.5 were identified.

Costs

Newer versions of the ROTEM and TEG systems have become available since diagnostics guidance 13 published. [redacted]. In addition, the potentially greater use of tranexamic acid (a haemostatic agent) since diagnostics guidance 13 published may make the fibrinolysis testing assays of the devices less useful, which may have a small effect on cost effectiveness. In the base case analysis for cardiac surgery in the original assessment, use of the TEG and ROTEM systems was estimated to be cost saving compared to SLTs (£43 for ROTEM and £79 for TEG) and also more effective (that is, use was estimated to produce more QALYs). The changes in cost are unlikely to change the cost-effectiveness of the TEG or ROTEM devices to the extent that they would have an effect on the existing recommendation 1.1.

In conclusion, the evidence base and clinical environment has not changed to an extent that is likely to have a material effect on the adoption recommendation for use of the ROTEM and TEG systems in cardiac surgery in the existing guidance. A new study on the use of Sonoclot for cardiac surgery, or any of the devices in the emergency control of bleeding during postpartum haemorrhage, are unlikely to provide sufficient evidence for the diagnostics advisory committee to make adoption recommendations at the present time. However, further evidence for the use of the TEG or ROTEM systems for trauma patients is now available which may allow recommendations on the use of the technologies in this context to be made by committee.

8. Implementation

The ROTEM system is currently in use in [redacted] The TEG system is in use in [redacted]. The Sonoclot system is not currently in use in the NHS.

The 1000 Lives OBS Cymru project in Wales is aiming improve the care of women suffering a postpartum haemorrhage in Wales. One of the ways it hopes to achieve this is by ‘providing a ROTEM machine to assess blood clotting and guide blood product use’.

A company stated that these devices are routinely used in cardiac, vascular and liver surgery. Furthermore, they suggested that decreased access to hospital laboratories has led to an increase in point-of-care viscoelastometric testing for incidents such as post-partum haemorrhage and major trauma injuries.

Guidelines that have published after diagnostics guidance 13 have supported the use of viscoelastic point-of-care devices to assess coagulation status (see section 6.2).

9. Equality issues

No new equality issues have been identified since the publication of the guidance.

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Appendix 1 – explanation of options

If the published Diagnostics Guidance needs updating NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
Standard update of the guidance	A standard update of the Diagnostics Guidance will be planned into NICE's work programme.	No
Accelerated update of the guidance	An accelerated update of the Diagnostics Guidance will be planned into NICE's work programme. Accelerated updates are only undertaken in circumstances where the new evidence is likely to result in minimal changes to the decision problem, and the subsequent assessment will require less time to complete than a standard update or assessment.	Yes
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Diagnostics Guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Diagnostics Guidance on the static list should be flagged for review.	No
Produce a technical supplement	A technical supplement describing newer versions of the technologies is planned into NICE's work programme.	Yes
Defer the decision to review the guidance	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Diagnostics Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Abbreviations

FFP	Fresh frozen plasma
ICU	Intensive care unit
INR	International normalised ratio
POC	Point-of-care
PPH	Post-partum haemorrhage
RBC	Red blood cells
RR	Relative risk
SLT	Standard laboratory test

Relevant Institute work

Published

Routine preoperative tests for elective surgery (2016) NICE guideline NG45

Major trauma: service delivery (2016) NICE guideline NG40

Major trauma: assessment and initial management (2016) NICE guideline NG39

Blood transfusion (2015) NICE guideline NG24

Intrapartum care for healthy women and babies (2014) NICE guideline CG190

In progress

None.

Registered and unpublished trials

The ROTEM system

Trial name and registration number	Details
Critical Evaluation of a Targeted Point of Care (POC) ROTEM (Registered Trademark) and Multiplate (Registered Trademark) Guided Coagulation and Haemostasis Management Programme in Cardiac Surgical Patients ACTRN12614000182695	Prospective observational study. Australia. Primary outcome: Blood and Blood Product Transfusion Rates Secondary outcomes include: Blood and blood product transfusion related complications, Blood and blood product cost, Mortality.
Critical Evaluation of a Targeted Point of Care (POC) ROTEM (Registered Trademark) and Multiplate (Registered Trademark) Guided Coagulation and Haemostasis Management Programme in Severe Trauma and Critical Bleeding ACTRN12614000198628	Prospective observational study. Australia. Primary outcome: Blood and Blood Product Transfusion Rates Secondary outcomes include: Blood and blood product transfusion related complications, Blood and blood product cost, Mortality.
Cost-Utility Analysis of Management of Peri Operative Haemorrhage Following Cardiac Surgery Using Conventional Blood Coagulation Tests or Thrombo-elastographic Point of Care Test - IMOTEC NCT02972684	Prospective, single blinded stepped wedge randomized study. Participants are adults having cardio-vascular surgical procedure using cardiopulmonary bypass and meeting inclusion criterion "bleeding". Participants are managed using conventional blood coagulation tests or a thromboelastometry POC test. Estimated primary completion date: November 2019. Estimated enrolment: 1000
Towards Better Prognostic and Diagnostic Strategies for Haemostatic Changes During Major Obstetric Haemorrhage (TeMpOH-2) NCT02149472	Observational prospective cohort study.

Trial name and registration number	Details
Clinical Trial: Evaluation of 2 Different Protocols of Blood Derivates Transfusion in Acute Trauma Patients in a Brazilian Tertiary Hospital. Strategy of Transfusion in Trauma Patients - STATA Trial (STATA) NCT02416817	Randomised, open-label trial investigating methods for massive transfusion in trauma patients admitted to the emergency room of a large reference hospital.
Thromboelastometry-guided Treatment Protocol Versus Standard Care of Major Haemorrhage in Obstetric Patients (ROTEM-PPH) NCT02461251	People over 18 with severe PPH randomised to either have ROTEM results used to guide treatment of major obstetric haemorrhage, or 'standard care' (clinical decision making and conventional coagulation tests). Estimated study completion date: December 2018. Estimated enrolment: 60 Finland.
Treatment of Coagulopathy Trauma-induced Guided by Thromboelastography in Politrauma Patients. NCT02864875	
Point-of-Care Testing in Coagulopathic Patients Undergoing Cardiac Surgery - a Multicenter Study (MultiPOC) NCT01826123	

The TEG system

Trial name and registration number	Details
Assessment of agreement and clinical interchangeability between the TEG5000(Registered) and TEG6S(Registered) thromboelastography haemostasis analysers: a prospective validation study ACTRN12617000062325	Australia. 25 adult patients in a tertiary level intensive care unit

Trial name and registration number	Details
Effects of thromboelastography-guided transfusion algorithm versus standard clinical practice on post-operative bleeding and blood product use after cardiac surgery: a randomised, controlled trial. ChiCTR-INR-16008740 (Chinese clinical trials registry)	
Cost-Utility Analysis of Management of Peri Operative Haemorrhage Following Cardiac Surgery Using Conventional Blood Coagulation Tests or Thrombo-elastographic Point of Care Test - IMOTEC NCT02972684	Prospective, single blinded stepped wedge randomized study. Participants are adults having cardio-vascular surgical procedure using cardiopulmonary bypass and meeting inclusion criterion "bleeding". Participants are managed using conventional blood coagulation tests or a thromboelastometry POC test. Estimated primary completion date: November 2019. Estimated enrolment: 1000

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