Health Policy Advisory Committee on Technology

Technology Brief

Rotational thromboelastometry (ROTEM®) – targeted therapy for coagulation management in patients with massive bleeding

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This brief was prepared by Hong Ju from HPACT Secretariat.
Technology, Company and Licensing

Register ID  WP024
Technology name  Rotational thromboelastometry (ROTEM® delta)
Patient indication  Patients undergoing major surgery who are at high risk of bleeding

Description of the technology

ROTEM® delta is a point of care (POC) testing device measuring the viscoelastic properties on multiple aspects of blood coagulation in a sample of citrated whole blood. The principle of ROTEM is related to classic thromboelastography (TEG) as both provide continuous viscoelastic profiles of blood clot formation adopting various assay compositions. However, ROTEM® system is an enhancement of TEG and differs in the way they record the viscoelastic changes occurring during the coagulation process: in the TEG, the plastic cup is slowly oscillated and changes in viscoelasticity are detected by a pin attached to a suspended torsion wire; whereas, in ROTEM, the pin is oscillated and the cup remains fixed. The improved design of ROTEM allows it to be used as a mobile unit that can be transported easily to the operation theatre for POC coagulation management. The system has four independent measurement channels which enable the simultaneous independent tests, an integrated computer for automatic analysis and an electronic pipette for interactive test operation (Figure 1).

Figure 1  ROTEM® system

The system has four independent measurement channels which enable the simultaneous independent tests, an integrated computer for automatic analysis and an electronic pipette for interactive test operation (Figure 1).
ROTEM tests are started by re-calcification and accelerated by adding an activator of the intrinsic (eg. INTEM and HEPTEM) or extrinsic (eg. EXTEM, FIBTEM and APTEM) coagulation pathway. Apart from the basic screening tests (INTEM and EXTEM), differential diagnostic options are enabled by adding specific system reagents:

- **INTEM**: coagulation is activated via the contact phase to monitor the coagulation process via the intrinsic pathway (eg. factor VIII) and for the presence of heparin in the sample.

- **HEPTEM**: coagulation is activated as in INTEM to monitor the coagulation process via the intrinsic pathway in the presence of heparin. By comparing HEPTEM to INTEM results, heparin-related coagulation disturbance can be detected.

- **EXTEM**: coagulation is activated by a small amount of tissue factor to monitor the coagulation process via the extrinsic pathway.

- **FIBTEM**: coagulation is activated as in EXTEM to monitor the clot firmness after blocking platelet contribution to the clot firmness. FIBTEM is always used in conjunction with EXTEM. Therefore, the resulting clot is only dependent on the fibrin formation and fibrin polymerisation.

- **APTEM**: coagulation is also activated as in EXTEM. Intend to monitor the clot firmness after blocking hyperfibrinolysis by aprotinin. APTEM is always used in conjunction with EXTEM. The comparison of EXTEM and APTEM enables rapid detection of fibrinolysis.

ROTEM provides information on the cause of bleeding, allows flexible screening of whole blood coagulation property, and ROTEM-guided therapy can optimise blood products usage, avoiding unnecessary risks by minimising blood transfusions. Unlike conventional clotting assays, ROTEM assesses the coagulation system as a dynamic process by determining not only the clotting time, but also the dynamics of clot formation, the mechanical clot stability and its lysis over time. Specifically, it provides information on particular aspects of coagulation, including, speed of initial fibrin formation, influence of clotting factors and anticoagulants; the kinetics of clot formation and influence of platelet and fibrinogen levels; and clot firmness (available on [http://www.rotem.de/site/index.php](http://www.rotem.de/site/index.php)). Figure 2 shows the reactive curve, together with the coagulation parameters, produced by ROTEM.
The reference ranges proposed for the main parameters are presented in Table 1. Multi-centre investigation on the reference ranges demonstrated that the data appear to be quite consistent across centres and the established ranges can be used as a guideline for clinical use and as a basis for first estimates to supplement medical decision. In addition, sex-specific reference ranges were shown not to be necessary for the activated tests in ROTEM; however, the general trend of increased clot firmness with rising age deserves attention in clinical interpretation of ROTEM results.

### Table 1  Reference ranges of main parameters for ROTEM tests

<table>
<thead>
<tr>
<th>ROTEM tests</th>
<th>CT (s)</th>
<th>CFT (s)</th>
<th>MCF (mm)</th>
<th>ML (% MCF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTEM</td>
<td>100-240</td>
<td>30-110</td>
<td>50-72</td>
<td>&lt;15</td>
</tr>
<tr>
<td>EXTEM</td>
<td>40-80</td>
<td>34-160</td>
<td>50-72</td>
<td>&lt;15</td>
</tr>
<tr>
<td>HEPTEM&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100-240</td>
<td>30-110</td>
<td>50-72</td>
<td>-</td>
</tr>
<tr>
<td>APTEM&lt;sup&gt;b&lt;/sup&gt;</td>
<td>40-80</td>
<td>34-160</td>
<td>50-72</td>
<td>-</td>
</tr>
<tr>
<td>FIBTEM&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>9-25</td>
<td>-</td>
</tr>
</tbody>
</table>

CT=clotting time, CFT=clot formation time, MCF=maximum clot firmness, ML=maximum lysis

<sup>a</sup> a significantly shortened CT in HEPTEM, compared to INTEM, is indicative to a heparin effect

<sup>b</sup> a shortened CT and higher MCF in APTEM, compared to EXTEM, is a sign of hyperfibrinolysis

<sup>c</sup> in FIBTEM, MCF<9mm: reduced fibrinogen level or impaired polymerisation, MCF>25mm: increased fibrinogen level

ROTEM not only provides a global picture of the patient’s haemostatic status, but also allows differential diagnosis of the major underline pathomechanism of coagulopathy. By combining and comparing the results from different ROTEM tests, it is possible to identify singular or multiple coagulation factor deficiencies within a few minutes of obtaining samples and goal-directed coagulation therapy can, therefore, be readily initiated. Coupled with standard algorithms for coagulation management, the technology may be able to reduce bleeding and the transfusion of blood and blood products.<sup>2,3</sup>

The test time of ROTEM is typically 10-20 minutes and the analyses can be repeated 10 minutes after administration of coagulation factors or blood products to guide further management. Compared with routine coagulation tests, ROTEM has several advantages:
• is easier to use by adequately trained non-laboratory personnel as a POC test in the perioperative and emergency setting;
• can produce rapid graphical and numerical results of the haemostatic status;
• is able to detect and quantify the underlying cause of coagulopathy and the anti-coagulant effect of acidosis, hypo- or hyperthermia; and
• can be used to predict the efficiency of a risky or expensive therapy.  

ROTEM can also monitor the substitution requirement for either fibrinogen or platelet, and heparin and protamine dosage. The information can then be used by clinicians to assess the cause of bleeding and to improve the diagnosis and subsequent management of patients who experience unexplained blood loss resulting from surgery or trauma. It should be noted, however, that impaired primary haemostasis because of von Willebrand syndrome or the effect of antiplatelet drugs (eg. ASA or clopidogrel) cannot be detected by ROTEM alone; a combination of ROTEM and platelet function analysis (by PFA-100 or Multiplate Analyser) is preferred for POC coagulation management, especially in cardiac surgery.  

A brief comparison of these systems is presented in Table 2.

Table 2 Comparison of POC tests for platelet function analysis

<table>
<thead>
<tr>
<th></th>
<th>ROTEM</th>
<th>Multiplate</th>
<th>PFA-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood sample</td>
<td>Citrated whole blood</td>
<td>Heparin or thrombin inhibitor whole blood</td>
<td>Buffered citrated whole blood</td>
</tr>
<tr>
<td>Main parameters</td>
<td>CT, CFT, MCF, ML</td>
<td>AUC; aggregation, velocity</td>
<td>Closure time</td>
</tr>
<tr>
<td>Mainly examines platelet function</td>
<td>Platelet-fibrin interaction</td>
<td>Platelet aggregation</td>
<td>Platelet adhesion</td>
</tr>
<tr>
<td>Sensitive for</td>
<td>Severe platelet function disorders with resistance to thrombin stimulation, fibrinogen deficiency and polymerisation disorders, hyperfibrinolysis, heparin and hirudin effects, severe coagulation factor deficiency</td>
<td>ASA and clopidogrel effects, GPIIb/IIIa receptor inhibitors, platelet function disorders</td>
<td>von Willebrand syndrome, Bernard-Soulier syndrome, Morbus Glanzmann; storage pool disease, ASA effects (&gt;7 days), GPIIb/IIIa receptor inhibitors (over sensitive)</td>
</tr>
<tr>
<td>Limitations</td>
<td>Low sensitivity to antiplatelet drugs, oral anticoagulants and low weight heparin</td>
<td>von Willebrand syndrome (type I)</td>
<td>Low sensitivity to clopidogrel effects, over sensitive to GPIIb/IIIa receptor inhibitors; flow errors due to platelet aggregation during surgery</td>
</tr>
<tr>
<td>Main field of application</td>
<td>Perioperative coagulation management; whole blood coagulation test with special consideration of clot firmness and stability</td>
<td>Perioperative platelet function analysis; control of success for ASA, DDAVP, clopidogrel or GPIIb/IIIa receptor inhibitor therapy</td>
<td>Perioperative screening in cases of positive bleeding history, von Willebrand syndrome, control of success for ASA or DDAVP therapy</td>
</tr>
</tbody>
</table>

ACT=activated clotting time, CFT=clot formation time, CR=clot rate, CT=clotting time, DDAVP=desamino-delta-D-arginine vasopressin; MCF=maximum clot firmness, ML=maximum lysis, PFA=Platelet Function Analyser
Company or developer
The ROTEM® delta is marketed by TEM Systems, Inc., the US subsidiary of TEM Innovations GmbH, the developer and manufacturer of the ROTEM® homeostasis analyser.

Reason for assessment
Jurisdiction representative nominated the technology for assessment.

Stage of development in Australia
☐ Yet to emerge ☐ Established
☐ Experimental ☐ Established but changed indication or modification of technique
☐ Investigational ☐ Should be taken out of use
☒ Nearly established

Licensing, reimbursement and other approval
The ROTEM® analyser was cleared under the 510(k) premarket notification (K083842) by the FDA in the fall of 2010 for patients undergoing cardiovascular, trauma and liver transplant procedures (http://www.fda.gov/default.htm).

The ARTG number is currently not applicable under previous TGA framework. However, the device (ROTEM® delta) will need to be listed before 1st July 2014 under the new TGA framework for IVD, which came into operation on July 2010. The Australian sponsor is working with the regulatory authority aiming to have the device listed on the ARTG under Class I IVD (no public risk or low personal risk) by December 2012.

Currently no reimbursement is available for ROTEM tests.

Australian Therapeutic Goods Administration approval
☐ Yes ARTG number (s)
☐ No
☒ Not applicable

Technology type
Device

Technology use
Diagnostic

Patient Indication and Setting

Disease description and associated mortality and morbidity
ROTEM is mainly used in adult patients undergoing major surgeries (cardiac or liver transplant) who are at high risk of bleeding.
Critical or massive blood loss is a frequent and serious complication and is associated with a significant increase in in-hospital mortality. There are no universally accepted definitions of critical bleeding, a term used to describe a range of clinical scenarios where bleeding may result in significant patient morbidity or mortality. Surgical bleeding or arterial injury is often the dominant reason for blood loss resulting in a high transfusion requirement of blood products. In patients undergoing major surgery, severe bleeding is usually managed by fluid (volume) replacement to stabilise systemic circulation, erythrocyte (RBC) concentrates to sustain haemoglobin level and, when possible, purified factor concentrates of plasma origin and from recombinant synthesis for a rapid restoration of targeted factors.

Massive transfusion is defined as the total replacement of a patient’s blood volume in 24 hours, transfusion of at least four red blood cell concentrated within one hour, or the replacement of 50 per cent of the total blood volume within three hours. Although blood transfusion can be life-saving, its numerous adverse effects have been well documented. Coagulopathy as a result of a massive transfusion and uncontrolled bleeding occurs frequently. The vicious cycle of coagulopathy leads to defects in clot firmness and due to fibrinogen deficiency and thrombocytopenia, impaired clot stability due to hyperfibrinolysis and factor VIII deficiency, and prolonged clot generation due to various coagulation factor deficiencies. The multifactorial nature of coagulation disorders complicates clinical management, and treatment is often empirical. Table 3 shows the number of bleeding episodes, the percentage transfused and the number of RBS units transfused for different type of cardiac surgery and liver transplant in Scotland. It can be seen that a high percentage of transfusion occurred for each type of procedure and all have received RBC.

### Table 3 Surgical bleeding episodes and blood use in Scotland in 2005-06

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of episodes</th>
<th>% Episodes transfused</th>
<th>RBCs units/episode transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary replacement operations (minus revisions)</td>
<td>2,359</td>
<td>47.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Heart and lung transplant</td>
<td>8</td>
<td>75.0</td>
<td>11.3</td>
</tr>
<tr>
<td>Revision coronary replacement operations</td>
<td>29</td>
<td>44.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Valves and adjacent structures</td>
<td>758</td>
<td>54.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Transplantation of liver</td>
<td>37</td>
<td>83.8</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Similar information for Australia was not identified during the evaluation. The following figures from the National Blood Authority (NBA) Australia demonstrated the units of RBCs (Figure 3) and platelets (Figure 4) issued by the NBA per 1,000 head of population by state and territory from 2007-08 to 2010-11. Overall a total of 800,570 units of RBCs were issued in 2010-11, an increase of 4,706 units from 2009-10 although an decreased pattern of issue was seen in some states (eg. QLD, VIC, WA). Over the same period, 134,705 units of platelets were issued, an increase of 6,293 units from 2009-10 with an increased pattern of...
issue seen for each states or territory except ACT. However, FFP issued decreased by 106.1 litres from 2009-10 with 47,209.5 litres issued in 2010-11.

Figure 3  Units of red cells issued per 1000 head of population by state and territory, 2007–08 to 2010–11

There is some evidence that cardiac surgery is responsible for nearly 20 per cent all transfusion in Australasia and more than 50 per cent of patients received transfusion during or within 72 hours of their cardiac surgery. Massive transfusion is an independent risk factor of death and with a nearly linear correlation between the mortality of cardiосurgical patients and the number of transfused packed RBC and the association of fresh frozen product with the risk of transfusion-related acute lung injury and cardiocirculatory overload.
Number of patients

The exact number of patients who will use ROTEM is difficult to estimate. However, the quota from a cardiac unit from a local Queensland Health hospital is 500-600 cardiac surgery patients who are at high risk of bleeding. Given that the device is to be used in other units, such as liver transplant, obstetrics and trauma, there will be a substantial number of potential patients. Data from the company indicated that, within Australia and New Zealand, there are 72 cardiac units, 9 liver transplant units, 10 obstetrics units and 10 trauma units that may benefit from using the device.

According to data from Australia & New Zealand Liver Transplant Registry, 4,034 orthotopic liver transplants were performed on 3,735 patients (3,065 adults and 670 children) in Australia and New Zealand between 1985 to 2011. In 2011, 253 transplants were performed (on 225 new patients), a slight increase from 248 transplants (on 233 patients) in 2010.

The following figure (Figure 5) shows that the (age-standardised) national rate for coronary artery bypass graft surgery was 839 per million population in Australia in 1999\textsuperscript{13}. This rate varies across States, from 613 per million population in South Australia (including Northern Territory) to 922 per million population in New South Wales (including the Australian Capital Territory).

![Figure 5](image-url)

**Figure 5** Regional rates for coronary artery bypass graft operations, 1999\textsuperscript{13}

**Speciality**  

**Technology setting**  
Specialist hospital, mainly in the operating room, but also deployed in central laboratory.
Impact

Alternative and/or complementary technology

ROTEM is proposed as an alternative technology to the conventional laboratory coagulation tests. However, it is realised that it may be beneficial to conduct standard laboratory tests (SLTs) concomitantly at the early stage of using ROTEM to cross-validate the ROTEM tests, as well as to help to establish local reference ranges for ROTEM tests. Policies and protocols should be in place regarding whether the SLTs should be continuously used and if so, how to deal with the use of different ranges and interpretation of results.

Current technology

Transfusion of blood products is currently guided by clinical judgment and SLTs. Generally SLTs include activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR), platelet count, and plasma fibrinogen. However, none of these tests were developed to predict bleeding or to guide coagulation management in the surgical setting, with the major limitations being lack of real-time monitoring (with a turnaround time of 60 to 90 minutes); inability to identify singular or multiple coagulation factor deficiencies; and no rapid assessment of fibrinolysis, platelet dysfunction, or haemostatic response to injury or surgery.

Conventional coagulation tests are performed in plasma at a temperature of 37°C without the presence of platelets and other blood cells, whereas the haemostatic response to injury or surgery is a complex interaction of plasma proteins, platelets and the vessel wall and is also affected by hypothermia. Most importantly, conventional coagulation tests cannot differentiate the predominant cause of bleeding in the complex scenario of trauma-associated or massive intraoperative blood loss. POC tests by ROTEM, on the other hand, enable a timely distinction between surgical bleeding and bleeding caused by coagulopathy. A change in clinical management of severe bleeding may reduce transfusion-related risks and provide improved patient health outcomes, with the potential to reduce transfusion requirements, re-exploration rates, health resources consumption and healthcare costs.

Diffusion of technology in Australia

Personal communication with HaemoVIEW Diagnostics Pty Ltd, Australian distributor of ROTEM® delta, indicated that there are 14 ROTEM (and 40-45 TEGs) currently available across Australia, most of which are for routine clinical use. Approximately half of the devices are deployed in the operating room and the other half in the centre laboratory. In addition, two ROTEM devices are available in New Zealand.
International utilisation

<table>
<thead>
<tr>
<th>Country</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia / New Zealand</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe (except France)</td>
<td></td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle East</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It is not clear the exact diffusion status around the world; however, over 3,000 ROTEM systems with its five pre-packaged assays (INTEM®, EXTEM®, HEPTEM®, FIBTEM® and APTEM®) have been used at 1,600 sites in more than 50 countries since it was first introduced in 2003 (per. communication).

Cost infrastructure and economic consequences

According to data from Queensland Health, monthly costs for fresh blood usage varied between A$250,000-350,000 in Royal Brisbane Hospital, A$200,000-300,000 in Princess Alexandra Hospital, and A$100,000-180,000 in the Prince Charles Hospital (TPCH) for year 2010-11. In TPCH in 2011 alone, the real cost of all blood products to the hospital (37% of the total cost of the product) for patients who had cardiac surgery was A$674,898. The remaining 63 per cent of the cost of blood products, which amounted to A$1,149,150, was borne by Commonwealth (per. communication).

An indicative cost estimate for the establishment and running ROTEM is presented in Table 4. Regardless of the setting up costs, the costs of performing the set of tests are comparable between ROTEM and SLTs. However, an increased cost during the initial stage of adopting ROTEM to guide coagulation management is expected, as it is recommended that SLTs will still be performed as a mean to cross-validate the test results. With time, a standard protocol should be developed clearly stating whether SLTs should be continuously performed when ROTEM is used for POC test.

In addition, further costs will occur if a platelet function analyser is going to be used concurrently, especially for cardiac surgeries. The current quota for a Multiplate analyser is approximately A$25,000, with the current costs for individual tests (eg. ADP, ASPI, TRAP) being A$11.23.
Table 4  Summary of the estimated costs for ROTEM

<table>
<thead>
<tr>
<th>Item</th>
<th>ROTEM® delta</th>
<th>Standard laboratory tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>$37,000</td>
<td>-</td>
</tr>
<tr>
<td>Costs of tests</td>
<td>EXTEM - $13.40</td>
<td>aPPT - $10.69</td>
</tr>
<tr>
<td></td>
<td>INTEM - $13.40</td>
<td>PT - $10.69</td>
</tr>
<tr>
<td></td>
<td>FIBTEM - $16.77</td>
<td>Platelet count - $15.95</td>
</tr>
<tr>
<td></td>
<td>HEPTEM - $17.08</td>
<td>Fibrinogen - $44.58</td>
</tr>
<tr>
<td></td>
<td>APTEM - $19.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(costs inclusive of ROTEM pin, pipettes and reagents required)</td>
<td></td>
</tr>
<tr>
<td>Total: $80.10 per set of tests</td>
<td></td>
<td>Total: $81.91 per set of tests</td>
</tr>
<tr>
<td>Maintenance Agreements</td>
<td>ROTEM - $3190.00 per annum</td>
<td>-</td>
</tr>
</tbody>
</table>

aPPT=activated partial thromboplastin time, PT=prothrombin time.

Ethical, cultural or religious considerations

No issues identified.

Evidence and Policy

Safety and effectiveness

There is a large body of literature on the performance of ROTEM/TEG and/or its impact on blood management outcomes. Due to the Cochrane review and the NHS HTA report identified, only recent large studies evaluating the clinical and/or blood management outcomes of using ROTEM are included in this brief.

Safety

The safety results from the studies are summarised in Table 5.

A recent Cochrane review\(^7\) systematically assessed the benefits and harms of TEG or ROTEM guided transfusion strategy, compared with transfusion guided by clinical judgment and/or standard laboratory tests, in randomised controlled trials involving patients with severe bleeding. Primary outcome of the review is the overall mortality. Nine trials that randomised a total of 776 adult patients were included in the review, with one trial conducted in a liver transplant setting while the remaining trials conducted in cardiac surgery settings. The trials were published between 1999 and 2010. The follow-up period varied between 24 hours to 3 years, however, only four trials provided information on the length of follow-up. The majority of the included studies were with moderate risk of bias mainly due to unclear randomisation sequence generation, allocation concealment and blinding. Furthermore, only two trials actually used ROTEM as the intervention and the other trials used TEG.
### Table 5  Summary of adverse events in the studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study level</th>
<th>No. of Participants</th>
<th>Outcome</th>
<th>TEG / ROTEM</th>
<th>Control</th>
<th>Effect size (95% CI)/p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afshari et al (2011)</td>
<td>I</td>
<td>708 (7 studies)</td>
<td>Surgical re-intervention</td>
<td>5.2% (18/348)</td>
<td>6.4% (23/360)</td>
<td>RR 0.91 [0.44, 1.87]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>280 (2 studies)</td>
<td>Prop excessive bleeding events &amp; massive transfusion</td>
<td>11.4% (16/141)</td>
<td>13.7% (19/139)</td>
<td>RR 0.82 [0.38, 1.77]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>161 (2 studies)</td>
<td>Postoperative cerebrovascular ischaemic event &amp; stroke</td>
<td>6.3% (5/80)</td>
<td>3.7% (3/81)</td>
<td>RR 1.66 [0.46, 5.93]</td>
</tr>
<tr>
<td>Gorlinger et al 2011</td>
<td>III-3</td>
<td>3,865 from a single centre in 2004 &amp; 2009</td>
<td>Massive transfusion</td>
<td>1.3% (27/2147)</td>
<td>2.5% (43/1718)</td>
<td>RR 0.50 [0.31, 0.81]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reexploration rate (within 48 hrs)</td>
<td>2.2% (48/2147)</td>
<td>4.2% (72/1718)</td>
<td>RR 0.53 [0.37, 0.76]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Composite thrombotic/thromboembolic adverse events</td>
<td>1.8% (28/1582)</td>
<td>3.2% (46/1441)</td>
<td>RR 0.55 [0.35, 0.88]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal replacement therapy</td>
<td>8.0% (127/1582)</td>
<td>8.5% (122/1441)</td>
<td>RR 0.95 [0.75, 1.20]</td>
</tr>
<tr>
<td>Anderson et al (2006)</td>
<td>III-3</td>
<td>990 patients (488 6-mon prior &amp; 502 6-mon after ROTEM) in cardiac ICU in one centre</td>
<td>Re-exploration</td>
<td>3% (127/1582)</td>
<td>4% (122/1441)</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR=not reported; RR=relative risk

Adverse events were variably reported by the included trials, such as surgical wound infection, post-operative cerebrovascular events and acute respiratory distress and dialysis-dependent renal failure, coagulopathy and massive transfusion. However, none reached statistical significance. In addition, the review also failed to show any difference in the rate for surgical re-intervention due to bleeding with RR of 0.91 (95% CI 0.44, 1.87). Of note is that generally these adverse events occurred infrequently and a large sample would be needed to detect a statistically significant between-group difference.
Since the publication of the Cochrane review, a retrospective before-and-after study compared transfusion parameters in patients who underwent cardiovascular surgery in a university hospital in Germany before (2004) and after (2009) the implementation and refinement of ROTEM-supported coagulation management algorithm (interventional III-3 evidence). The algorithm proposes first-line therapy with specific coagulation factors (see Appendix 1 for details). A total of 3,865 cardiovascular patients were included in the study. It is not clear whether there is patient exclusion from the analysis, as no total surgery numbers were reported for each study period. The data were limited to the in-hospital period only. The primary endpoints were the incidence of any intra-operative allogeneic blood transfusion, the incidence of transfusion of PRBC, FFP and platelet concentrates, and the incidence of massive transfusion (≥ 10 units of PRBC transfused intra-operatively). There were some marked differences between the two study periods in terms of patient demographics and surgical characteristics, such as the mean age of the patients, proportion of females, patients on oral anticoagulants or dual antiplatelet therapy, emergency cases, and complex cardiac surgery. It is not clear whether any of these differences have been adjusted for in the final analysis. Further, potential conflict of interest exists as the principal author received a fee for consultation from the manufacturer.

The study reported approximately 50% reduction in the incidence of massive transfusion (1.3% vs 2.5%, p=0.006) and of re-exploration (2.2% vs 4.2%, p=0.0007) after implementation of POC-coagulation management algorithm (in 2009). The incidence of composite thrombotic/thromboembolic adverse events also decreased significantly in 2009 compared to 2004 (1.8% vs 3.2%, respectively, p=0.012); however, none of the incidence of the individual events differed between the two periods. Similarly, no difference was detected in the incidence of renal replacement therapy between the two groups.

Anderson et al reported the audit results of blood product use six-month prior to and after the introduction of ROTEM in a cardiac ICU in their hospital in UK (interventional III-3 evidence). Trained anaesthetic personnel performed the ROTEM tests and a standard transfusion protocol was used for the first 24 hours post-surgery over the 12-month period. There was no difference in the re-exploration rates between the two study periods (Table 5). No other adverse events were reported in the study.

Effectiveness

The effectiveness outcomes from the studies are summarised in Table 6.

The Cochrane review found no significant difference for overall mortality on longest follow-up period between the ROTEM/TEG group and the control group with a relative risk (RR) of death of 0.77 (95% CI 0.35, 1.72), although the authors acknowledged that no trial was powered to detect a statistically significant difference in mortality. Similarly, no difference in mortality was detected in any of the subgroup analyses conducted when looking only at cardiac surgery patients with a RR of death of 0.81 (95% CI 0.32, 2.01) or when including
studies comparing ROTEM only with the control with a RR of 0.86 (95% CI 0.26, 2.87). Once again, the number of patients included in the ROTEM trial was only 56 patients.

Among cardiac surgery patients, statistically significantly reduced bleeding was detected favouring ROTEM/TEG group, with a reduced bleeding of 85mL on longest follow-up (mean difference in -85 [95% CI -140.16, -28.89]). However, the clinical meaningfulness of such reduction in severe bleeding may need to be determined. The authors detected a statistically significant reduction in the proportion of patients receiving transfusion as a combination of fresh frozen plasma (FFP) and platelets in the ROTEM/TEG group (RR 0.39, 95% CI 0.27 to 0.57); however, the proportions of patients receiving FFP, platelets or red blood cells (RBC) were similar between the two groups when the products were examined separately. The only exception is that significantly fewer patients received FFP when comparing ROTEM only with the control (RR 0.39, (95% CI 0.22 to 0.67)). Similarly, analyses examining the amount of blood products transfused did not show any statistically significant difference between the groups. In addition, the review failed to show any significant differences in the length of stay in either ICU or hospital. Caution should apply when interpreting the review results given that the moderate heterogeneity among the included trials, in terms of differences in management algorithm, assays used, additional treatment and duration of the trials, may impact on the results of pooled analyses. Furthermore, the average blood loss in the control groups in the trials included patients undergoing elective cardiac surgery ranged from 390 to 960mL, raising the question whether these patients are truly at high risk of requiring massive transfusion. The review authors concluded that currently there is weak to moderate evidence to support the use of TEG/ROTEM in the cardiac surgery and liver transplantation settings.

Hvas et al evaluated the use of blood products before (2008) and after (2009) implementation of ROTEM in the cardiothoracic intensive care unit in a university hospital (interventional III-3 evidence). Standard anaesthesia, surgical procedures coronary artery bypass grafting, and transfusion protocol were used throughout the study periods. A ROTEM-guided treatment algorithm was applied to guide coagulation management. In the adjusted analysis (for type of surgery, acute surgery and use of antithrombotic medications), the percentage of patients receiving any or specific blood products did not differ significantly between the two periods. However, among patients who received blood products, the use of RBC decreased significantly from 2008 to 2009 (4.1 units vs 5.1 units, p=0.04), while no difference was detected for FFP and platelets. Furthermore, the use of fibrinogen increased (OR 4.55, 95% CI 2.86-7.21) and recombinant factor VIIa decreased significantly (OR 0.50, 95% CI 0.26-0.98) after the implementation of ROTEM. The authors noted that only a small proportion of patients (17%) in 2009 had ROTEM performed during surgery or within the first 24 hours post-surgery and this may account for the similar blood product use before and after ROTEM-guided coagulation management.
## Table 6  Summary of effectiveness result of in the studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study level</th>
<th>No. of Participants</th>
<th>Outcome</th>
<th>TEG / ROTEM</th>
<th>Control</th>
<th>Effect size (95% CI)/p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afshari et al (2011)</td>
<td>I</td>
<td>473 (5 studies)</td>
<td>Mortality</td>
<td>3.78% (9/238)</td>
<td>5.11% (12/235)</td>
<td>RR 0.77 [0.35, 1.72]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>748 (8 studies)</td>
<td>Mediastinal tube drainage or post-operative bleeding (mL)</td>
<td>NR</td>
<td>NR</td>
<td>MD -84.53 [-140.16, -28.89]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac surgery</td>
<td>Surgical re-intervention</td>
<td>18/348 (5.2%)</td>
<td>6.4% (23/360)</td>
<td>RR 0.91 [0.44, 1.87]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>708 (7 studies)</td>
<td>Prop receiving FFP</td>
<td>14.3% (41/286)</td>
<td>24.9% (73/293)</td>
<td>RR 0.64 [0.29, 1.42]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>579 (5 studies)</td>
<td>Prop receiving platelets</td>
<td>16.3% (50/306)</td>
<td>23% (72/313)</td>
<td>RR 0.77 [0.47, 1.26]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>619 (6 studies)</td>
<td>Prop receiving RBC</td>
<td>52.5% (139/265)</td>
<td>63.0% (165/262)</td>
<td>RR 0.88 [0.76, 1.02]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prop receiving transfusion of FFP &amp; platelet</td>
<td>20.2% (25/124)</td>
<td>54.1% (72/133)</td>
<td>RR 0.39 [0.27, 0.57]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>527 (5 studies)</td>
<td>Combined transfusion volume of FFP</td>
<td>NR</td>
<td>NR</td>
<td>MD -96.35 [-277.54, 84.84]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>257 (3 studies)</td>
<td>Combined transfusion volume of platelets</td>
<td>NR</td>
<td>NR</td>
<td>MD -31.95 [-70.43, 6.52]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>545 (6 studies)</td>
<td>Length of ICU stay (hours)</td>
<td>NR</td>
<td>NR</td>
<td>MD -2.03 [-4.35, 0.29]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>619 (6 studies)</td>
<td>Length of stay (days)</td>
<td>NR</td>
<td>NR</td>
<td>MD -0.07 [-0.40, 0.26]</td>
</tr>
<tr>
<td>Study ID</td>
<td>Study level</td>
<td>No. of Participants</td>
<td>Outcome</td>
<td>TEG / ROTEM</td>
<td>Control</td>
<td>Effect size (95% CI)/p value</td>
</tr>
<tr>
<td>------------------</td>
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<td>-----------------------------</td>
</tr>
<tr>
<td>Hvas et al (2012)</td>
<td>III-3</td>
<td>811 patients in 2008 and 865 patients undergoing cardiac surgery</td>
<td>Prop receiving RBC</td>
<td>2009</td>
<td>2008</td>
<td>p=0.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prop receiving FFP</td>
<td>29.3%</td>
<td>31.7%</td>
<td>p=0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prop receiving platelets</td>
<td>22.7%</td>
<td>24.9%</td>
<td>p=0.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prop receiving any blood products</td>
<td>21.7%</td>
<td>25.5%</td>
<td>p=0.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prop receiving fibrinogen</td>
<td>36.3%</td>
<td>38.6%</td>
<td>OR 4.55 [2.86, 7.21] p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prop receiving recombinant FVIIa</td>
<td>11.6%</td>
<td>3.6%</td>
<td>OR 0.50 [0.26, 0.98] p=0.04</td>
</tr>
<tr>
<td>Gorlinger et al 2011</td>
<td>III-3</td>
<td>3,865 patients from a single cardiac surgery centre in 2004 &amp; 2009 (with ROTEM)</td>
<td>Allogeneic blood products transfusion rate</td>
<td>42.2% (906/2147)</td>
<td>52.5% (902/1718)</td>
<td>RR 0.80 [0.75, 0.86] p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PRBC transfusion rate</td>
<td>40.4% (868/2147)</td>
<td>49.7% (854/1718)</td>
<td>RR 0.81 [0.76, 0.87] p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FFP transfusion rate</td>
<td>1.1% (24/2147)</td>
<td>19.4% (333/1718)</td>
<td>RR 0.06 [0.04, 0.09] p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Platelet transfusion rate</td>
<td>13.0% (280/2147)</td>
<td>10.0% (173/1718)</td>
<td>RR 1.30 [1.08, 1.55] p=0.0041</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PRBCs transfused (units)</td>
<td>2959</td>
<td>3276</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FFP transfused (units)</td>
<td>102</td>
<td>1986</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Platelets transfused (units)</td>
<td>581</td>
<td>336</td>
<td>p=0.085</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In-hospital mortality</td>
<td>5.2% (112/2147)</td>
<td>5.2% (90/1718)</td>
<td>RR 0.996 [0.760-1.305] p=0.9756</td>
</tr>
<tr>
<td>Gorlander et al 2010 abstract</td>
<td>III-3</td>
<td>1105 patients from visceral surgery and liver transplant unit from</td>
<td>RBC transfused (units)</td>
<td>2009</td>
<td>1999</td>
<td>-60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FFP transfused (units)</td>
<td>1365</td>
<td>3454</td>
<td>-89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>499</td>
<td>4465</td>
<td></td>
</tr>
</tbody>
</table>

ROTEM: November 2012
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study level</th>
<th>No. of Participants</th>
<th>Outcome Description</th>
<th>TEG / ROTEM</th>
<th>Control</th>
<th>Effect size (95% CI)/p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Platelets transfused (units)</td>
<td>181</td>
<td>433</td>
<td>-58%</td>
</tr>
<tr>
<td>Anderson et al (2006)</td>
<td>III-3</td>
<td>990 patients (488 6-mon prior &amp; 502 6-mon after ROTEM) in cardiac ICU in one centre</td>
<td>Prop receiving RBC</td>
<td>53%</td>
<td>60%</td>
<td>p=0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prop receiving FFP</td>
<td>12%</td>
<td>17%</td>
<td>p=0.037</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prop receiving platelets</td>
<td>11%</td>
<td>16%</td>
<td>p=0.033</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICU stay</td>
<td>24±5</td>
<td>23±4</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOS</td>
<td>7±3</td>
<td>7±2</td>
<td>NR</td>
</tr>
</tbody>
</table>

FFP=fresh frozen plasma; MD=mean difference; PRBC=packed red blood cells; RR=relative risk.

Gorlinger et al, in a historical controlled study, reported that an increased number of annual surgery cases and a higher rate of complex cardiac surgery after the implementation of ROTEM-guided coagulation management algorithm in 2009. Compared to 2004 where ROTEM-guided coagulation management was not used, the incidence of intraoperative transfusion of any allogeneic blood product, of PRBC and of FFP decreased significantly, whereas the incidence of platelet transfusion increased moderately in 2009. Similarly, the amount of transfusion requirement per year of PRBC (2959 units vs 3276 units respectively, p<0.0001) and of FFP (102 units vs 1986 units respectively, p<0.0001) decreased significantly in 2009 compared to in 2004. In contrast, there was a non significant increase in the amount of platelets transfused in year 2009 (Figure 6). Furthermore, the incidence of administration of both fibrinogen concentrate and prothrombin complex concentrate (PCC) increased substantially whereas that of factor XIII concentrates decreased in year 2009. Therapy with antithrombin concentrate did not change over the study periods.

The authors concluded that implementation of a ROTEM-guided coagulation management algorithm, and first-line therapy with specific coagulation factor concentrates, was associated with substantial reduction of allogeneic blood transfusion and with decreased incidence of composite thrombotic/thromboembolic adverse events. However, the study results should be interpreted within the context of historical control used and the potentially unadjusted analysis despite the marked differences between the two study periods on patient demographics and surgery characteristics.
The same author also compared their experience in an abstract using ROTEM-guided coagulation management algorithm (2009) in 1105 patients undergoing visceral and liver transplant surgery prior to implementation of ROTEM (1999) (interventional III-3 evidence).\(^{17}\) Compared to 1999, transfusion requirements decreased by 60% for RBC, 89% for FFP, and 58% for platelet concentrations. Over the same time, substantial increases in the use of fibrinogen concentration and prothrombin complex concentration were seen. It is not clear from the abstract whether the analyses were adjusted for the differences from the two time periods, thus caution should apply when interpreting the results.

Anderson et al\(^{15}\), in their clinical audit, reported that compared with the period prior to the introduction of ROTEM, significantly fewer patients received RBC, FFP and platelets after the use of ROTEM (Table 6). There were also significant reductions in the overall units of RBC, FFP and platelets transfused after the introduction of ROTEM. However, there was no difference in the length of ICU and hospital stay between the two periods. The authors noted that there were some observed differences in patient characteristics in terms of EuroSCORE risk index, type of surgery performed and bypass time at baseline; however, these differences were not adjusted for in the analysis.
Economic evaluation

A HTA report from NHS Scotland conducted a cost-effectiveness analysis of using ROTEM or TEG, compared with SLTs and/or clinical judgment alone, to guide coagulation management in patients experience unexplained bleeding during or after surgery. The HTA includes a systematic review of literature on the clinical benefits of ROTEM/TEG; however, it mainly focuses on modelled economic analyses comparing the cost effectiveness of using the technology in cardiac surgery and liver transplantation with a time horizon of one year. The results are summarised in Table 7. The HTA concluded that management of transfusion guided by ROTEM/TEG was the dominant strategy in both cardiac surgery and liver transplantation patients.

Table 7 Summary of results from NHS Scotland HTA report

<table>
<thead>
<tr>
<th>HTA Agency</th>
<th>Findings</th>
<th>Recommendations</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craig et al. 2008</td>
<td><strong>Effectiveness:</strong> ROTEM/TEG appeared to be clinically effective since it reduced the need for inappropriate transfusion and to decrease blood product requirements, thus improving transfusion management; however the improvement in health outcomes did not appear to be as relevant in liver transplant as in cardiac surgery; There was a reduction in number of deaths, complications and infections, and an increase in the number of years lived and QALYs gained by patients in cardiac surgery;</td>
<td>The use of ROTEM/REG is recommended in cardiac and liver transplant surgery in intra- or post-operative bleeding where the cause of bleeding is uncertain; The results from ROTEM/REG, together with clinical judgment and any results from other lab tests, should inform transfusion decisions in accordance with validated transfusion algorithms; POC test should be routinely used pre-operatively before elective surgery to risk stratify patients likely to bleed excessively; Recommendations are related to organisational perspective and are discussed in the relevant sections.</td>
<td>No differentiation made between TOREM and TEG, most studies are using TEG; Various level of studies were used as data source for economic analyses, with unknown quality; There is disagreement in the literature on using ROTEM for screening tests.</td>
</tr>
<tr>
<td></td>
<td><strong>Cost-effectiveness:</strong> In cardiac surgery, ROTEM/TEG was the dominant strategy for management of transfusion, independent of the time horizon or the measures of health benefit considered; the results were sensitive to variations in the number of tests conducted annually and to whether the tests were conducted during or after surgery; In liver transplant, ROTEM/TEG was a cost-effective strategy, the results were sensitive to the No. of units of blood transfused;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Budget impact:</strong> In terms of budget impact, savings are expected with the use of ROTEM/REG. For cardiac surgery, the most significant savings are from costs of hospitalization not related to complications and the costs of blood products transfused; in liver transplant, the savings were mainly due to blood products transfused;</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>Others:</strong> From a patient’s perspective, any intervention to reduce blood transfusion is likely to be welcomed; Variation in operating practices and policies is identified, highlighting the need for a consistent approach to training and quality control.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A few studies compared the costs related to coagulation therapy before and after the implementation of ROTEM, the results are summarized in Table 8.

Gorlinger et al compared the costs of coagulation therapy one year before (2004) and one year after (2009) the implementation of ROTEM-guided coagulation management algorithm and first-line treatment with specific coagulation factors for patients undergoing cardiac surgery in a university hospital in Germany. As a consequence of significantly reduced transfusion requirements for allogeneic blood products, an overall reduction on the costs of 6.5 per cent per patient resulted, corresponding to a cost-saving of about €50,000 per year for the hospital in year 2009.

Table 8  Results of the cost analysis

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Population</th>
<th>Costs (€)</th>
<th>Difference [p valur]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Gorlinger et al 2011</td>
<td>III-3</td>
<td>3,865 cardiac surgery 2004 &amp; 2009</td>
<td>Allogeneic blood products/per patient 286.12</td>
<td>187.89 -80.23 (-34.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coagulation factor concentrates/per patient 71.67</td>
<td>146.66 74.99 (104.6%)</td>
</tr>
<tr>
<td>Görlinger et al 2008</td>
<td>III-3</td>
<td>NR visceral and transplantation 1999 vs 2000-2006</td>
<td>All blood products NR</td>
<td>NR -411,120 (-59%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coagulation factor NR</td>
<td>NR 152,637 (353%)</td>
</tr>
<tr>
<td>Spalding et al 2007</td>
<td>III-3</td>
<td>729 (before) 693 (after) cardiac surgery 6-mon before/after ROTEM use</td>
<td>All blood products 66,000</td>
<td>45,000 -21,000 (-32%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coagulation factor 60,000</td>
<td>30,000 -30,000 (-50%)</td>
</tr>
</tbody>
</table>

In another retrospective analysis, the authors compared the costs of blood products and coagulation factors before (1999) and after (2000-2006) the implementation of ROTEM for coagulation management in visceral and transplantation surgery, particularly for liver transplantation in Germany. Similar to the cardiac surgery setting, a reduction of costs for blood products of €-411,120 (-59%) was seen after implementation of ROTEM, as well as an increase in costs of coagulation factors of €152,637 (353%). Overall, a cost-saving of €258,482 (-35%) was realised for the hospital during the study period.
Spalding et al, in a retrospective study, compared the costs of blood products and coagulation factors six months before and after the implementation of ROTEM as a bedside coagulation management system for early identification and targeting of particular coagulation disorders resulting from reduced transfusion rate in cardiac surgery patients. Compared with before ROTEM implementation, a 25 per cent reduction in cumulative expenditure in RBC and 50 per cent in platelet was shown after ROTEM implementation. However, FFP use remained stable during the study period. In addition, average monthly costs of all blood products reduced by €21,000 (32%) and those of coagulation factors reduced by €30,000, a 50 per cent reduction, yielding a combined cost-saving of 44 per cent during the study period.

Of note is the historical control design of the studies, the results should be interpreted with some caution giving that the data were obtained from before and after the intervention, a range of factors may impact on the study results apart from the intervention itself.

**Ongoing research**
Currently Queensland Health is trialling a ROTEM (in combination with Multiplate) through the Coagulation Management Project in the cardiac surgery unit in the Prince Charles Hospital. The preliminary results show that the overall transfusion rate has dropped by 10 per cent over the four months of using ROTEM. Specifically, the changes in patients receiving specific blood products (in the year) before and (four months) after implementing ROTEM are:

- Red Blood Cell use down from 49 to 36 per cent;
- Platelets down from 37 to 16 per cent;
- Fresh Frozen Plasma down from 29 to 11 per cent;
- Cryoprecipitate down from 10 to 6 per cent.

These results are indicative only as they are raw data and have not taking into consideration of other variations in time periods and clinical practice.

**Other issues**

**ROTEM vs TEG**
Despite ROTEM being the enhanced version of TEG, TEG is still widely used worldwide. There are reports suggesting that there is considerable divergence in transfusion outcomes from ROTEM and TEG, and it may be speculated that differences in diagnostic performance of the applied TEG assays may contribute to the disparity observed. Larsen et al. investigated the diagnostic performance of TEG (kaolin-activated whole blood) against ROTEM (a panel of activated whole blood) in disclosing isolated coagulopathies of dilutional coagulopathy, thrombocytopenia, hyperfibrinolysis, and heparin and compared consequent
treatment strategies based on two published algorithms. The study revealed that ROTEM assays readily distinguished all investigated coagulopathies and provided faster diagnosis, whereas the profiles based on kaolin (TEG) failed to distinguish dilutional coagulopathy from thrombocytopenia and might lead to unnecessary transfusion with platelets.

Organisational challenges of using ROTEM

There are concerns on the use of POC coagulation tests because these tests can be hard to standardise in terms of blood collection, sample processing, that the devices may not be adequately maintained, supervised and that the quality controls are not done on a regular basis. Furthermore, non-laboratory personnel are running the tests, which may lead to further error if they are not adequately trained. The NHS Scotland report has stressed the importance of some key issues in adopting the POC test, including the clinical governance relating to the set-up and management of POC test, the need for local pathology laboratory involvement in all aspects of a POC test service, the need for training, updating and monitoring all staff involved in POC test, and the need for quality control practice.

Training

As the validity and efficacy of the test rely entirely on the interpretation of the results by health professionals at the point of care, the tests should be performed by trained staff who are able to analyse and interpret the results to ensure the consistency of application. Depending on specific circumstances, those able to conduct the analysis and interpretation of results could include biomedical scientists, ICU nurses, perfusionists, anaesthetists, surgeons and others alike. Apart from the initial training, the need for retraining as required, continuing professional development and training for those involved in maintenance and repair service should be addressed. The importance of interpretation of ROTEM results were further confirmed by study indicating the importance of the availability of experienced personnel on a 24-hour basis in ICU due to the challenges in interpreting the test results.

Quality assurance and governance

- The use of POC test should be put in the broader context of patient blood management;
- Both the internal quality control (to ensure test precision and accuracy) and external quality assessment (to compare test performance across centres) of the devices are of extreme importance;
- Standard operation procedures to guide the operators as to how to perform the tests, when to perform quality control and assessment, and what to do if the quality control parameters are outside the limit of internal quality control or acceptable external quality assessment performance;
• Rigorously defined and managed clinical guidelines or algorithms which are linked to blood transfusion protocols should be developed to cover all organisational aspects of POC test, with one person who is clearly responsible for overseeing compliance;

• Policies and protocols should be in place regarding whether the SLTs should be continuously used and if so, how to deal with the use of different ranges and interpretation of results. It is realised that it may be beneficial to conduct SLTs concomitantly at the early stage of using ROTEM, the experience from NHS Scotland indicates otherwise even though this is also proposed by some manufacture;

• Tests should be performed and results interpreted by appropriately trained staff;

• Clearly document POC test results and any subsequent activities to ensure smooth communication between clinical and laboratory information system, between clinicians who use or do not use ROTEM, and to make auditing process easier;

• Quality control and assurance procedures and robust arrangements for regular preventive maintenance and prompt repair of analysers must be in place.

The UK National External Quality Assessment Scheme (NEQAS) for Blood Coagulation has undertaken a series of four studies, involving 18 TEG users and 10 ROTEM users, to evaluate the provision of external quality assessment materials for TEG and ROTEM.\(^\text{22}\) The results showed that the precision of the tests varied considerably for both devices, with coefficients of variance ranging from 7.1 to 39.9 per cent for TEG and 7.0 to 83.6 per cent for ROTEM. Results from some centres differed sufficiently from other centres to influence patient management decisions. The authors emphasised the importance of regular external quality assessment and/or proficiency testing for these devices.

**Summary of findings**

Most included studies are retrospective with historical controls conducted in cardiac settings. No significant benefits in mortality and length of ICU or hospital stay of using ROTEM-guided coagulation management, compared with SLTs and/or clinical judgment, were demonstrated in the included literature. However, a significantly reduced rate of combined allogeneic blood products transfusion was evident in the literature. The substantial reduction in the incidence of PRBC or FFP transfusion, when examined separately, for ROTEM-guided coagulation management demonstrated in the observational study has not yet been confirmed by the systematic review of RCTs. However, caution should apply when interpreting systematic review results due to its limitations.

Current economic analysis has indicated that coagulation management guided by ROTEM/TEG is cost-effective in cardiac surgery or liver transplantation settings, resulting in cost savings.
Organisational challenges of using ROTEM has been highlighted in terms of the appropriately trained personnel to perform the tests and interpret the results, the standard operation procedures, rigorous quality control activities, and well defined and managed clinical algorithms to guide coagulation management.

**Recommendation**

ROTEM appears to have been diffused around the world. The benefits of ROTEM-guided coagulation management and its impact on blood management appear to be high, although no direct patient-related outcomes have been demonstrated. It is likely that it will be continuously taken up by different surgical settings whether or not large RCTs will be conducted to demonstrate benefits in final patient outcomes. Therefore, it is recommended that the following be conducted:

- Horison Scanning Report
- Full Health Technology Assessment
- Monitor
- Archive

**HealthPACT assessment**

As ROTEM has widely diffused into clinical practice worldwide and there is recognised benefits for patient management related to its use in different surgical settings. There is no further assessment on behalf of HealthPACT will be conducted.

**Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

- Total number of studies: 8
- Total number of Level I studies: 1
- Total number of Level III-3 studies: 6
- Number of HTA: 1

**References**


**HealthPACT decision**

- [ ] New and Emerging Health Technology Report
- [ ] Full Health Technology Assessment
- [ ] Monitor
- [ ] Archive
- [ ] Refer
- [ ] Decision pending
Appendix 1  Algorithm for POC coagulation management in cardiac surgery

Part 1: Management before weaning from cardiopulmonary bypass

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Part 2

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1) 10 min after every specific intervention a reexamination of ROTEM®/Multiplate® analysis has to be done for control of success.
Part 1

No therapy !

No Diffuse bleeding after protamine ?

Yes

CT_{IN} > 240 s and CT_{IN}/CT_{IN} < 0.8

Yes

Redosage of protamine 1)

No

MCF_{EBS} < 50 mm

and

MCF_{FBS} < 12 mm

Yes

Application of fibrinogen concentrate or cryoprecipitate 1)

No

MCF_{EBS} < 60 mm

and

MCF_{FBS} < 12 mm

Yes

Application of PCC (FPSB) concentrate or FFP 1)

No

AUG-ASPI < 200

AUC-COL < 200

AUG-ADP < 300

AUC-TRAP < 500

( or )

No

Ongoing bleeding ?

Yes

Surgical bleeding ?

Yes

Optimize surgical blood attenuation 1)

No

Precord, or and CT_{IN} > 80 s

and

MCF_{EBS} > 16 mm

and

MCF_{FBS} > 60 mm

Yes

Consider application of DDAVP, vWF: concentrate, FXIII or tPA 1)

No

Improvement by active rewarming or application of NaHCO_3, CaCl_2, RBC, fibrinogen, cryoprecipitate, PCC(FPSB), FFP or platelets 1)

Reexamination of ROTEM®/Multiplate® analysis (control of success) 1)

Part 2: Management after weaning from cardiopulmonary bypass 2

1) 10 min after every specific intervention a reexamination of ROTEM®/Multiplate® analysis has to be done for control of success.