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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Thromboelastography or Rotational Thromboelastography for Trauma: A Review of the Clinical and Cost-Effectiveness and Guidelines

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Authors: Erika MacDonald, Melissa Severn

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Context and Policy Issues

Coagulopathy of trauma occurs in an estimated 25% to 35% of trauma patients presenting to the emergency room.[1] Its ethology is often multifactorial and overlapping; most commonly attributable to acidosis related to shock, hypothermia related to cold exposure and administration of intravenous fluids, and hemodilution due to fluid administration.[1]

Traditional tests of coagulation include prothrombin time / international normalization ratio (PT/INR), activated partial thromboplastin time (aPTT), fibrinogen, and platelet count. These traditional tests remain the standard tests for diagnosis of coagulopathy. However, they were designed for use in diagnosis of heritable coagulopathies and/or monitoring of anticoagulant therapy, and an important limitation to their use in assessment of coagulopathy of trauma is their slow turnaround time.[1]

Point of care tests, on the other hand, are available at the patients' bedside with near immediate results.[1] Thromboelastography (TEG) and rotational thromboelastography (ROTEG) (also known as thromboelastometry [ROTEM]) are viscoelastic assays that offer a global picture of clot formation and dissolution, with rapid turnaround time.[2]

Both ROTEG and TEG assess the entire process of clot formation and dissolution. The amount of a continuously applied rotational force is continuously measured and displayed, allowing for evaluation of clot initiation, propagation, stabilization through to dissolution.[2] Although the same information on kinetics and strength of clot formation is provided by each test, some notable differences exist between TEG and ROTEG. TEG can analyze two samples simultaneously, requires manual pipetting of blood, and is sensitive to vibration; therefore it must be performed on a level and stable surface. ROTEG systems can analyze four samples simultaneously, and pipetting is automated.[2] Although the same parameters are measured by each test, nomenclature differs, and results are not interchangeable.[2] For example, clotting time (CT) / reaction rate (R), clot formation time (CFT) / kinetics time (K), maximum clot firmness (MCF) / maximum amplitude (MA), and CL 30 / LY 30, are the corresponding terms for TEG / ROTEG, respectively.[2,3]

The identification of specific hemostatic defects using these point of care tests allows for rapid treatment with appropriately targeted interventions. TEG or ROTEG-guided algorithms for management of bleeding are attractive alternative to liberal unguided blood transfusions, the latter of which is associated with adverse effects and mortality.[2,3]

The purpose of this review is to provide evidence surrounding effectiveness and cost effectiveness of ROTEG and TEG in trauma, and to identify relevant evidence-based guidelines.

Research Questions

1. What is the clinical effectiveness evidence regarding the use of thromboelastography (TEG) or rotational thromboelastography (ROTEG) to guide transfusion requirements for trauma patients with bleeding?
2. What is the cost-effectiveness of TEG or ROTEG to guide transfusion requirements for trauma patients with bleeding?
3. What are the evidence-based guidelines regarding TEG or ROTEG to guide transfusion requirements for trauma patients with bleeding?

Key Findings

The clinical effectiveness of TEG or ROTEG to guide transfusion requirements in trauma patients is unclear, due to lack of high quality studies.

Both TEG and ROTEG may be cost-effective in comparison to conventional coagulation assays in trauma patients according to a single economic analysis, however a lack of evidence surrounding their clinical effectiveness limits its validity.

Evidence-based guidelines found that evidence was insufficient to recommend the use of TEG and ROTEG in trauma patients.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2012 and Aug 10, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Trauma patients (adult and pediatric) in the emergency department setting with bleeding
Intervention	Thromboelastography (TEG) or Rotational Thromboelastography (ROTEG)
Comparator	Traditional measures of clotting/conventional coagulation tests (e.g., prothrombin time ratio/international normalized ratio [PTr/INR], activated partial prothrombin time [APTT]) TEG or ROTEG compared with each other
Outcomes	Q1 - Clinical effectiveness (accuracy and speed of diagnosing trauma-induced coagulopathy; ability to guide and monitor transfusion requirements for bleeding trauma patients; bleeding events; patient outcomes – impact on morbidity & mortality, safety and harms) Q2 - Cost-effectiveness Q3 - Evidence-based guidelines
Study Designs	Health Technology Assessments, Systematic Reviews, Meta-Analyses, Economic Evaluations, Evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR checklist,[4] clinical studies were critically appraised using Downs and Black checklist,[5] economic evaluations were assessed using the Drummond checklist,[6] and guidelines were assessed with the AGREE II instrument.[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 390 citations were identified in the literature search. Following screening of titles and abstracts, 373 citations were excluded and 17 potentially relevant reports from the electronic search were retrieved for full-text review. Ten potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 22 publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

A summary of characteristics of included articles is presented in Appendix 2.

Study Design

Three systematic reviews,[8-10] one economic evaluation,[11] and one evidence-based guideline[12] met eligibility criteria for this report.

Systematic reviews

Veigas et al.[8] conducted a systematic review aiming to summarize evidence on ROTEG parameters and threshold ROTEG values for diagnosing coagulopathy, predicting or guiding transfusion, and predicting mortality in trauma patients. Quality of included studies was assessed by the authors using both the QUADAS-2 instrument and the Newcastle-Ottawa Scale. Nine prospective cohort studies and four retrospective cohort studies were included. Results of the thirteen included studies were presented narratively.

Hunt et al.[9] conducted a systematic review aiming to assess diagnostic accuracy of TEG and ROTEG in adult trauma patients with bleeding. Quality of included studies was assessed by the authors using the QUADAS-2 instrument. The three included studies were of cross-sectional design. There were too few studies to perform a valid assessment of heterogeneity to consider meta-analysis of results, therefore results of individual studies were presented narratively.

Da Luz et al.[10] performed a systematic review aiming to evaluate the evidence surrounding the use of TEG and ROTEG for diagnosis of trauma coagulopathies, transfusion guidance, and reduction of mortality in adult trauma patients admitted to hospital. Quality of included studies was assessed by the authors using the Newcastle-Ottawa Scale, and QUADAS-2 instrument for diagnostic studies. Fifty-five studies met inclusion criteria. Of the included studies, 38 were prospective cohort studies, 15 were retrospective cohort studies, and two were before-and-after studies.

Economic evaluations

Whiting et al. conducted an economic evaluation,[11] which was used to inform guidelines surrounding the use of viscoelastic assays (including TEG and ROTEG).[12] The investigators performed a literature search for prior cost-effectiveness studies, and none were identified. A decision tree model started with choice of strategy (ROTEG, TEG, Sonoclot, or standard laboratory tests). Cost-effectiveness was evaluated from the perspective of the National Health Service (NHS) in the United Kingdom (UK), with time horizons of 1 month and 1 year. Parameters were obtained from results of the systematic review, presented within the same publication, where possible.

Guidelines

Guidelines from the National Institute for Health and Care Excellence (NICE), "Detecting, managing and monitoring haemostasis: viscoelastometric point-of-care testing (ROTEG, TEG and Sonoclot systems)", were published in August 2014.[12] NICE diagnostic guidance documents are developed according to a rigorous process described in the *Diagnostics Assessment Programme Manual*, 2011.[13]

Country of Origin

The systematic reviews were conducted by groups in Canada,[8] UK[9] and United States.[10]

The economic evaluation was conducted by a group in the UK and Netherlands.[11]

The evidence-based guidelines were developed by a group in the UK.[12]

Patient Population

Systematic Reviews

Veigas et al.[8] included studies of adult patients with blunt and penetrating injuries, in either the civilian or military setting (total n=2835). Two of total the 13 studies (n=25 and n=48) were in the military setting. Hunt et al.[9] included three studies with both military and civilian trauma patients with suspected trauma-induced coagulopathy (total n= 430). The military study was the smallest of the three (n=40). Severity of trauma ranged from moderate to severe, with more severe injuries in the military population. DaLuz et al.[10] included studies of adult trauma patients admitted to hospital.

Economic evaluations

The economic evaluation[11] assessed cost-effectiveness of interventions in patients with coagulopathy induced by trauma.

Guidelines

The included guidelines[12] addressed the broad trauma population.

Interventions and Comparators

Two of the three systematic reviews[8,9] compared ROTEG to conventional coagulation assays, whereas the third systematic review[10] compared both ROTEG and TEG to conventional coagulation assays.

The economic evaluation compared use of TEG, ROTEG and Sonoclot assays to standard laboratory tests.

Outcomes

One of the systematic reviews[9] reported sensitivity and specificity of ROTEG for diagnosis of trauma induced coagulopathy, whereas another sought to determine ROTEG parameter thresholds to diagnose coagulopathy.[8] The third considered a broad range of outcomes related to diagnosis, coagulopathy, transfusion management, and mortality.[10]

Summary of Critical Appraisal

A summary of the critical appraisal of included reports is presented in Appendix 3.

Systematic reviews

The systematic review by Veigas et al.[8] was of moderate quality according to assessment using AMSTAR. Several criteria were not fulfilled (no 'a priori design, restricted to published evidence, no list of excluded studies provided, likelihood of publication bias was not addressed, and conflict of interest of included studies was not described). Additionally, authors' ability to draw conclusions was limited due to risk of bias of included studies, which was assessed using both the Newcastle Ottawa Scale and QUADAS-2. Quality of included studies was described as 'moderate' overall; no randomized controlled trials (RCTs) or controlled clinical trials were identified by the systematic review.

The systematic review by Hunt et al.[9] was of high quality. However, authors' ability to draw conclusions was again limited by the quality of evidence of the three included cross-sectional studies. Specifically, the authors' quality assessment using QUADAS-2 found that bias was of concern with respect to the domains of 'index test' (which asks whether its results are interpreted without knowledge of the reference standard results, whether any threshold values were pre-specified, whether its conduct or interpretation could have introduced bias overall, and whether the test, its conduct, or interpretation differ from the review question) and 'reference standard' (which asks whether it is likely to correctly classify the condition, whether its results were interpreted without knowledge of the results of the index test, any risk of bias overall, and whether the target condition differs from the review question). Additionally, many of the estimates of accuracy from the included studies were imprecise, with wide confidence intervals surrounding point estimates of sensitivity and specificity.

The systematic review by Da Luz et al.[10] was of low to moderate quality, failing to meet several of the AMSTAR criteria (no 'a priori design, check of data abstraction was not described, search for unpublished literature not described, no list of excluded studies was provided, likelihood of publication bias was not addressed, and conflict of interest of included studies was not described). Authors' ability to draw conclusions was again limited by the quality of evidence. Although 55 studies met eligibility, only three of the 55 included observational studies had compared interventions to control groups managed without TEG

or ROTEG. Quality of studies included within the review was reported to be moderate overall by the authors, according to the Newcastle Ottawa Scale assessment, and QUADAS-2 assessment for diagnostic studies.

Economic evaluations

The economic evaluation[11] employed rigorous methodology that was well-reported. A systematic review was performed to identify studies relevant to the economic analysis, and to identify whether prior economic analyses had been performed. There was a clear description of the model as well as sources of costs, other model inputs, and assumptions made. There was also a clear description of probabilistic sensitivity analyses and scenario analyses performed. However parameters included in the sensitivity analysis were not justified, nor was the range of values used. Due to the limited evidence available surrounding effectiveness of TEG and ROTEG in the trauma population, several key assumptions were made, many of which were extrapolations from the cardiac surgery population. This limits the validity of the results.

Guidelines

The NICE guidelines for "Detecting, managing and monitoring haemostasis"[12] were developed according to the rigorous methodology detailed in the *Diagnostics Assessment Programme Manual*.[13] The guideline had a clear scope and purpose, rigorous methods of development, and support for their application is provided. The guideline development committee and involved stakeholders included individuals from a variety professional and patient groups. Limitations included a lack of declaration of competing interests of authors, and no description of external review by clinical experts, although experts were engaged in guideline development. Although recommendations were clear and concise, specific recommendations surrounding use of TEG and ROTEG in trauma were not made due to insufficient evidence.

Summary of Findings

A summary of main findings of included reports is presented in Appendix 4.

What is the clinical effectiveness evidence regarding the use of thromboelastography (TEG) or rotational thromboelastography (ROTEG) to guide transfusion requirements for trauma patients with bleeding?

The systematic review by Veigas et al.[8] presented results of its 13 included cohort studies descriptively; results of individual studies were presented separately, with no statistical pooling of data. In summary, clot amplitude (CA) and maximal clot firmness (MCF) were consistently associated with diagnosis of coagulopathy, and also were consistently predictive of bleeding, massive transfusion, and mortality.

The systematic review by Hunt et al.[9] reported accuracy of ROTEG-measured clot amplitude at 5, 10 and 15 minutes (C5, C10, and C15 respectively), as reported in the three included individual studies, with no statistical pooling of data. CA5 sensitivity was reported in two studies: 70% (95% CI, 47% to 87%) and specificity 86% (95% CI, 82% to 90%) in one study, and sensitivity 96% (95% CI, 88% to 100%) and specificity 58% (95% CI, 44% to 72%) in another. CA10 sensitivity was reported in one of the studies as 100% (95% CI, 94% to 100%) and specificity 70% (95% CI, 56% to 82%), and CA15 sensitivity was reported in one of the studies as 88% (95% CI, 69% to 97%) and specificity 100% (95% CI, 94% to 100%).

The systematic review by Da Luz et al.[10] presented results of its 55 included observational studies descriptively, grouping outcomes for each study by findings related to diagnosis, transfusion and mortality in table format. Only three of the 55 studies compared an intervention group using ROTEG or TEG to a control group who did not receive TEG or ROTEG -guided transfusions. The first was a retrospective cohort study of 681 patients, comparing ROTEG -guided transfusion of prothrombin complex concentrate and fibrinogen complex versus standard administration of fresh frozen plasma. Red blood cell (RBC) transfusion was statistically significantly less in the ROTEG group (29% vs 3%, respectively; $p < 0.001$), as well as transfusion of platelets (91% vs 56%; $p < 0.001$). There was no statistically significant difference in mortality (7.5% vs. 10.0%; $p = 0.69$). The second was a before and after study of 68 patients comparing TEG-guided resuscitation versus a pre-TEG protocol. In patients with maximal rate of thrombin formation (MRTG) greater than 9.2, TEG-guided transfusion was associated with statistically significantly decreased RBC, fresh frozen plasma, and cryoprecipitate infusions. The third was a before and after study of 289 patients comparing TEG-guided resuscitation prior to the development of a massive transfusion protocol, to resuscitation guided by the massive transfusion protocol (without use of TEG). TEG-guided resuscitation was associated with a decrease in mortality in the subgroup of penetrating trauma patients receiving greater than 10 units of RBC, but there was no difference in blunt trauma patients, or patients receiving 6 or more units of RBC. In summary, the authors found that abnormalities detected by TEG and ROTEG were associated with massive transfusion and death. TEG and ROTEG were not consistently superior to conventional coagulation assays for predicting these outcomes, however. One observational study suggested that a ROTEG -based transfusion algorithm reduced blood-product transfusion, and TEG-guided resuscitation was associated with a decrease in mortality in another, however these results were not consistent across other studies.

What is the cost-effectiveness of TEG or ROTEG *to guide transfusion requirements for trauma patients with bleeding?*

The economic evaluation[11] was performed to inform the NICE guidance document for detecting, managing and motoring hemostasis.[12]

Both TEG and ROTEG dominated standard laboratory tests (they were found to be less costly and more effective). In a probabilistic sensitivity analysis, in which the impact of statistical uncertainty is explored, the probability of cost-effectiveness of ROTEG versus standard laboratory tests was 0.96 using a ceiling ratio of £0. As the ceiling ratio increased, the cost-effectiveness acceptability curve converged at 0.87. Similar results were found with TEG, however these were not presented. Several different scenario analyses were performed for ROTEG, the most expensive assay, and similar results were found. The per patient cost savings were estimated to be £688 for ROTEG and £721 for TEG compared to standard laboratory tests. Due to the lack of evidence specific to the trauma population, several assumptions were made, extrapolating data from other populations. The investigators noted that “Given the lack of effectiveness data in trauma patients, the current results should be regarded as indicative of the potential cost-effectiveness of viscoelastic testing only in trauma patients.”[11]

What are the evidence-based guidelines regarding TEG or ROTEG *to guide transfusion requirements for trauma patients with bleeding?*

A systematic review of evidence for TEG and ROTEG in trauma patients was done to inform the NICE guidance for detecting, managing and motoring hemostasis.[12] The

systematic review identified a single relevant controlled trial that was reported only in abstract form without numerical outcome data, and 15 “prediction” studies (differences in clinical outcomes between tested and untested populations were not evaluated). Risk of bias with respect to processes of patient selection and applicability of the index test and reference standard was of concern. Evidence was deemed to be insufficient to make recommendations surrounding the use of TEG or ROTEG in trauma. The guideline includes a recommendation for research into clinical and cost effectiveness of TEG and ROTEG in this population. A cost-effectiveness model was also developed as part of the development of the guidance document, the results of which are described above.

Limitations

There were no randomized controlled trials addressing the question of clinical effectiveness of TEG or ROTEG in trauma patients in any of the systematic reviews. The three systematic reviews[8-10] identified only observational studies, evaluating a broad range of clinical outcomes as well as accuracy of tests compared to conventional coagulation assays. Concerns regarding risk of bias related to the index test and reference standard, as assessed using the QUADAS-2 instrument, limited authors’ ability to draw conclusions regarding clinical effectiveness.

A single economic study[11] evaluated the cost-effectiveness of TEG and ROTEG. Several key assumptions were made due to lack of evidence, including extrapolation of clinical effectiveness of TEG and ROTEG in trauma from other populations, which limits the validity of the results.

A single evidence based guideline was identified,[12] and evidence was deemed to be insufficient to make recommendations surrounding the use of TEG and ROTEG in trauma.

The economic evaluation was performed from the perspective of the NHS in the UK,[11] as were the guidelines.[12] This limits applicability to health care in Canada.

Conclusions and Implications for Decision or Policy Making

Low-quality evidence supports the clinical effectiveness of TEG and ROTEG to guide transfusion requirements for trauma patients with bleeding as compared to conventional coagulation assays. There was no evidence directly comparing clinical effectiveness of TEG versus ROTEG in trauma patients.

Both TEG and ROTEG may be cost-effective as compared to conventional coagulation assays in trauma patients. However, a lack of available evidence surrounding the clinical effectiveness of TEG and ROTEG in trauma limits the ability to draw firm conclusions regarding their cost effectiveness.

Rigorously developed evidence-based guidelines found insufficient evidence surrounding clinical and cost effectiveness of TEG and ROTEG in trauma patients to recommend their use.

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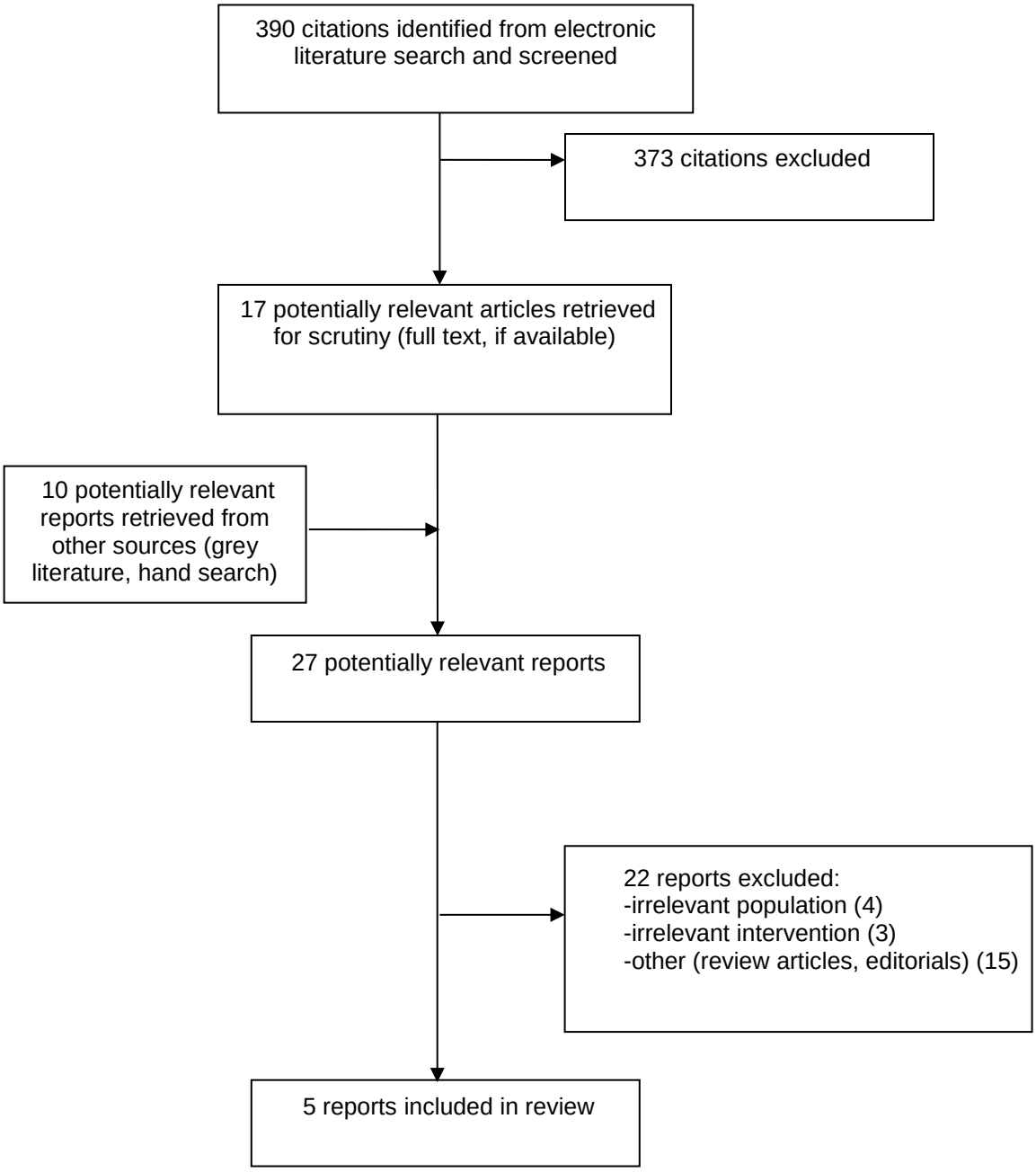
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Author, Year Country	Aim	Search date Number of included studies and study type	Summary of population characteristics	Intervention(s) vs. comparison(s)	Outcome(s) assessed
Veigas, 2016[8] **Canada**	"to determine evidenced based thresholds that could be incorporated into ROTEM® algorithms in the trauma resuscitation protocols."[8](page 115)	1946 to March 2016 Included 9 prospective cohort studies and 4 retrospective cohort studies (total n= 2835)	Adult patients with blunt and penetrating injuries in the civilian or military setting. Age (years): Median ranged from 21 (IQR 18–35) to 47 (IQR 26–66) Male (%): ranged from 67 to 100 Median ISS ranged from 12 (IQR 4–25) to 75 (IQR 75–75)	ROTEG vs. other coagulation tests such as PT, INR, aPTT, platelet count, fibrinogen level, euglobin lysis time	ROTEG parameter thresholds for diagnosing coagulopathy, predicting or guiding transfusion, or predicting mortality
Hunt, 2015[9] **UK**	"To determine the diagnostic accuracy TEG and ROTEM for TIC in adult trauma patients with bleeding, using a reference standard of prothrombin time ratio and/or the international normalized ratio"[9](page 5)	1970 to 4 March 2013 Included 3 cross-sectional studies (total n=430)	Patients with clinically suspected TIC. In the 3 included studies of n=300, 90 and 40 respectively: Age (years): Median 33 (IQR 23-48), mean 34 (SD 16), and mean 24 (IQR 21-26) Male (%): 82, 77, and 100 Median ISS 12 (IQR 4 to 24), 22 (IQR 12 to 34), and median New Injury Severity Score 34 (IQR 17 to 43)	ROTEG for diagnosis of TIC vs. TIC defined by standard clotting times of PT and INR (studies assessing accuracy of TEG were eligible, but none were identified)	Sensitivity and specificity of diagnosis of TIC using ROTEG clot amplitude at 5, 10 and 15 minutes

Table 2: Characteristics of Included Systematic Reviews

Author, Year Country	Aim	Search date Number of included studies and study type	Summary of population characteristics	Intervention(s) vs. comparison(s)	Outcome(s) assessed
Da Luz, 2014[10]	"To evaluate the evidence that the use of TEG® and ROTEM® in adult traumatically injured patients (a) diagnoses trauma coagulopathies on admission to hospital, (b) guides transfusion, and (c) reduces mortality."[10] (page 519)	Up to February 2014 Included 38 prospective cohort studies,15 retrospective cohort studies, and 2 before-and-after studies (total n=12489)	Adult trauma patients admitted to hospital Age (years): mean or median ranged from 24 to 74 years Male (overall): 78.9% Mean ISS ranged from 9 to 55	ROTEG or TEG parameter vs. other coagulation tests or no comparison; ROTEG or TEG-guided transfusion vs. any comparison or no comparison	Outcomes related to diagnosis of coagulopathies, transfusion management, and mortality.

aPTT= activated partial prothrombin time; INR = international normalized ratio; IQR = interquartile range; ISS = injury severity score; prothrombin time = PT; ROTEG = rotational thromboelastography; ROTEM = rotational thromboelastometry; TEG= thromboelastography; TIC = trauma-induced coagulopathy

Table 3: Characteristics of Included Economic Evaluations

First author, publication year, country	Type of analysis, perspective, time horizon	Study population	Intervention, comparator, outcomes	Main assumptions
Whiting, 2015[11] **UK**	Cost-effectiveness (cost-utility) From the perspective of NHS 1 month and 1 year	Patients with coagulopathy induced by trauma	TEG, ROTEG, and Sonoclot vs. standard laboratory tests Life years (LY), Quality-adjusted life years (QALY)	ROTEG, TEG and Sonoclot were assumed to be equally effective. Several extrapolations from cardiac surgery population to trauma population, including clinical effectiveness of assays.

ROTEG = rotational thromboelastography; TEG= thromboelastography

Table 4: Characteristics of Included Guidelines

First author/group, year, country	Objectives	Guideline development group, target users	Methodology
NICE, 2014[12] **UK**	"The purpose of this assessment is to evaluate the clinical and cost effectiveness of viscoelastometric testing (using the ROTEM, TEG or Sonoclot systems) to detect, manage and monitor haemostasis in cardiac surgery, and in the emergency control of bleeding after trauma and during postpartum haemorrhage."[12] (page 7)	A Diagnostics Advisory Committee included 22 members with a variety of backgrounds, plus specialists. A guideline development team consisting of a Technical Analyst (topic lead), Technical Adviser and a Project Manager.	NICE diagnostic guidance documents are developed according to a rigorous process described in the Diagnostics Assessment Programme Manual, 2011.[13]

ROTEM = rotational thromboelastometry; TEG= thromboelastography

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[4]

Strengths	Limitations
Veigas 2016[8]	
Two independent reviewers assessed articles for eligibility Comprehensive literature search strategy provided Characteristics of included studies provided Detailed quality assessment results provided, and study quality was considered in conclusions	No 'a priori' design provided Restricted inclusion to published evidence (no search for unpublished studies or grey literature described) List of excluded studies not provided Presence of conflicts of interest for included studies was not described Ability to draw conclusions was limited by quantity and quality of evidence available
Hunt 2015[9]	
Published protocol Three independent reviewers for eligibility, one reviewer extracted data and a second checked Comprehensive literature search strategy provided Not restricted by publication status or language List of included and excluded studies provided Characteristics of included studies provided Detailed quality assessment results provided, and study quality was considered in conclusions Conflicts of interest stated for included studies as well as the authors of the review	Ability to draw conclusions was limited by quantity and quality of evidence available
Da Luz 2014[10]	
Two independent reviewers assessed for eligibility Comprehensive literature search strategy provided Characteristics of included studies provided Detailed quality assessment results provided, and study quality was considered in conclusions	No 'a priori' design provided No description of data abstraction check by a second reviewer Restricted inclusion to published evidence (no search for unpublished studies or grey literature described) List of excluded studies not provided Presence of conflicts of interest for included studies was not described Ability to draw conclusions was limited by quantity and quality of evidence available

Table 6: Strengths and Limitations of Guidelines using AGREE II[7]

Strengths	Limitations
NICE 2014[12]	
Clear objectives, clinical question, and population Committee and stakeholders included individuals from a variety professional and patient groups Rigorous methodology; systematic review and economic evaluation were performed and considered by the guideline committee Detailed manual available describing the process of diagnostic guidance document development A separate document supporting adoption of guidelines is available	Recommendations not directly linked to evidence with a rating of level of evidence or strength of recommendation No description of external review by experts Potential competing interests of guideline team/committee not listed

Table 7: Strengths and Limitations of Economic Studies using Drummond[6]

Strengths	Limitations
Whiting 2015[11]	
Systematic review performed to inform the economic analysis Relevant outcomes: Quality adjusted life years (QALY), life years (LYs) Clear description of model Clear description of source of costs, other model inputs, and any assumptions made Probabilistic sensitivity analysis and scenario analyses performed	Choice of variables used in sensitivity analysis not justified, and justification of range of values used in sensitivity analysis not provided Several assumptions were made, including extrapolation of effectiveness of assays from cardiac surgery population, due to lack of evidence in the trauma population

Appendix 4: Main Study Findings and Author's Conclusions

Table 8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Veigas, 2016[8]	
9 prospective cohort studies and 4 retrospective cohort studies were included. 10 studies reported on diagnosis of coagulopathy, 6 on prediction of massive transfusion or transfusion guidance and 6 on prediction of mortality. In summary, although ROTEG threshold parameter values varied across studies, clot amplitude (CA) and maximal clot firmness (MCF) were consistently associated with diagnosis of coagulopathy, and also consistently predictive of bleeding, massive transfusion, and mortality.	"Thus, based on the current available evidence we reviewed, it could be extrapolated that clinical practice guidelines using ROTEM® parameters thresholds to guide blood component transfusion could be clinically useful. Goal-directed component transfusion approach guided by ROTEM® may reduce the exposure to allogeneic blood products and the complications derived from inappropriate resuscitation. However, due to the use of arbitrary cut-off values, lack of randomized controlled trials, cohort studies with small sample sizes, without comparable controls, and heterogeneous patient populations, no further conclusions can be drawn from the literature to date."[8](p. 125)
Hunt, 2015[9]	
3 cross-sectional studies were included. ROTEG accuracy for diagnosis of TIC: CA5 was reported in two studies: Sensitivity 70% (95% CI, 47% to 87%) and specificity 86% (95% CI, 82% to 90%) for one study, and sensitivity 96% (95% CI, 88% to 100%) and specificity 58% (95% CI, 44% to 72%) for another CA10 sensitivity was reported in a single study: 100% (95% CI, 94% to 100%) and specificity 70% (95% CI, 56% to 82%) CA15 sensitivity was reported in a single study: 88% (95% CI, 69% to 97%) and specificity 100% (95% CI, 94% to 100%)	"We found no evidence on the accuracy of TEG and very little evidence on the accuracy of ROTEM. The value of accuracy estimates are considerably undermined by the small number of included studies, and concerns about risk of bias relating to the index test and the reference standard. We recognize that the reference standards of PT and INR are imperfect, but in the absence of embedded clinical consensus these are judged to be the best reflection of current clinical practice. We are unable to offer advice on the use of global measures of haemostatic function for trauma based on the evidence on test accuracy identified in this systematic review. This evidence strongly suggests that at present these tests should only be used for research."[9](p. 15)
Da Luz, 2014[10]	
55 observational studies were included, including three relevant comparative studies 1. ROTEG-guided transfusion of prothrombin complex concentrate and fibrinogen complex versus standard administration of fresh frozen plasma (n=681), retrospective cohort study: -RBC transfusion ROTEG vs. standard group, 29% vs. 3%, respectively; p < 0.001 -Transfusion of platelets, 91% vs. 56%; p < 0.001 -Mortality, 7.5% vs. 10.0%; p = 0.69 2. TEG-guided resuscitation versus a pre-TEG protocol (n=68), before and after study: -In patients with MRTG greater than 9.2, TEG-guided transfusion was associated with statistically significantly decreased RBC, fresh frozen plasma, and cryoprecipitate infusions (effect sizes not reported) .	"In summary, our systematic review demonstrated limited but rapidly growing observational evidence on the use of TEG® and ROTEM® in trauma. Both methods may be useful for diagnosis of early trauma coagulopathies, specifcally hypocoagulability, hypercoagulability, hyperfibrinolysis, and platelet dysfunction. They may also be used to direct blood and blood-product transfusion; effects on patient-important outcomes are uncertain. The existing literature helps clinicians to appreciate the potential impact of these novel methods on transfusion guidance and outcomes in trauma. However, adequately powered and methodologically sound RCTs will be required to prove positive effects on blood-product transfusion and patient-important outcomes."[10](p. 540)

Table 8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
3. TEG-guided resuscitation prior to the development of a massive transfusion protocol versus resuscitation guided by the massive transfusion protocol (without use of TEG) (n=289), before and after study: -TEG-guided resuscitation was associated with a statistically significant decrease in mortality in the subgroup of penetrating trauma patients receiving greater than 10 units of RBC, but there was no difference in blunt trauma patients, or patients receiving 6 or more units of RBC (effect sizes not reported)	
Whiting, 2015[11]	
Cost-effectiveness of TEG vs standard laboratory tests: Dominant (less costly, more effective) Cost-effectiveness of ROTEG vs standard laboratory tests: Dominant (less costly, more effective) Cost savings per patient vs. standard laboratory tests: TEG: £721 ROTEG: £688 Probability of cost-effectiveness of ROTEG vs standard laboratory tests using a ceiling ratio of £0: 0.96 (cost-effectiveness acceptability curve converged at 0.87)	"There was no evidence on the clinical effectiveness of VE testing, using any device, in trauma patients or women with PPH. Available data generally indicated that a positive result on each of the TEG or ROTEM parameters or on SLTs was predictive of transfusion (RBC, any blood component and massive transfusion) and death. This implies a potential for improved intervention based on VE testing; however, there were no data showing that the use of VE devices could change outcomes. There were no clear differences between ROTEM, TEG or SLTs. No studies of the Sonoclot device were identified that fulfilled inclusion criteria for the either the trauma or PPH populations. Cost-effectiveness analyses indicated that the per-patient cost-savings attributed to VE testing were more substantial for the trauma population than for patients undergoing cardiac surgery. This finding was primarily a result of the much higher blood volumes that are transfused in trauma patients. As with the cardiac surgery population, scenario analyses did not alter the overall conclusion that VE testing is cost-saving. However, given the potentially problematic assumption that the clinical effectiveness of VE testing is the same in trauma patients as it is in cardiac surgery patients, these results should be regarded as indicative of the potential cost-effectiveness of VE testing only in trauma patients."[11](p. 99)

CA5 = clot amplitude at 5 minutes; CA10 = clot amplitude at 10 minutes; CA15 = clot amplitude at 15 minutes; CI = confidence interval; INR = international normalized ratio; MRTG = maximal rate of thrombin formation; PT = prothrombin time; RBC= red blood cell; RCT = randomized controlled trial; ROTEG = rotational thromboelastography; ROTEM = rotational thromboelastometry; TEG= thromboelastography; VE = viscoelastic; SBP = systolic blood pressure

Table 9: Summary of guideline recommendations

Evidence	Relevant Recommendations
NICE 2014[12]	
Evidence to inform recommendations consisted of a single relevant controlled trial reported only in abstract form without numerical outcome data, and 15 "prediction" studies (differences in clinical outcomes between tested and untested populations were not evaluated). Risk of bias with respect to processes of patient selection, and applicability of the index test and reference standard was of concern.	"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."[12](p. 5)

ROTEM = rotational thromboelastometry; TEG= thromboelastography

Appendix 5: Additional references of potential interest

Clinical studies:

Gonzalez E, Moore EE, Moore HB, Chapman MP, Chin TL, Ghasabyan A, et al. Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. Ann Surg [Internet]. 2016 Jun [cited 2017 Aug 15];263(6):1051-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5432433

This pragmatic open-label trial compared a TEG-guided massive transfusion protocol to one guided by conventional coagulation assays in 111 patients admitted to single academic level-1 trauma centre. Although the study is labelled as a randomized controlled trial, assignment to treatment was not truly random; the type of transfusion protocol alternated weekly, so that treatment assignment was dependent on which week a patient was admitted to hospital.

Guidelines, not evidence-based:

Inaba K, Rizoli S, Veigas PV, Callum J, Davenport R, Hess J, et al. 2014 Consensus conference on viscoelastic test-based transfusion guidelines for early trauma resuscitation: Report of the panel. J Trauma Acute Care Surg. 2015 Jun;78(6):1220-9.

These consensus conference recommendations sought to address nine questions on the impact of viscoelastic testing in the early resuscitation of trauma patients. The recommendations were developed and reviewed in an open forum of experts, and via a two-round Delphi poll.