Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies Evaluating Point-of-Care Tests of Coagulopathy in Cardiac Surgery

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Abstract

Treatment guidelines recommend the routine use of point-of-care diagnostic tests for coagulopathy in the management of cardiac surgery patients at risk of severe bleeding despite uncertainty as to their diagnostic accuracy. We performed a systematic review and meta-analysis of studies that evaluated the diagnostic accuracy of viscoelastometry, platelet function tests, and modified thromboelastography (TEG) tests, for coagulopathy in cardiac surgery patients. The reference standard included resternotomy for bleeding, transfusion of non red cell components, or massive transfusion. We searched MEDLINE, EMBASE, CINAHL, and Clinical Trials.gov, from inception to June 2019. Study quality was assessed using QUADAS-2. Bivariate models were used to estimate summary sensitivity and specificity with (95% Confidence Intervals). All twenty-nine studies (7,440 participants) included in the data synthesis evaluated the tests as predictors of bleeding. No study evaluated their role in the management of bleeding. None was at low risk of bias. Four were judged as low concern regarding applicability. Pooled estimates of diagnostic accuracy were; Viscoelastic tests, 12 studies, sensitivity 0.61 (0.44, 0.76), specificity 0.83 (0.70, 0.91) with significant heterogeneity. Platelet function tests, 12 studies, sensitivity 0.63 (0.53, 0.72), specificity 0.75 (0.64, 0.84) with significant heterogeneity. TEG modification tests, 3 studies, sensitivity 0.80 (0.67, 0.89), specificity 0.76 (0.69, 0.82) with no evidence of heterogeneity. Studies reporting the highest values for sensitivity and specificity had important methodological limitations. In conclusion, we did not demonstrate predictive accuracy for commonly used point-of-care devices for coagulopathic bleeding in cardiac surgery. However, the certainty of the evidence was low. Registration: PROSPERO CRD42017056032

Keywords: Cardiovascular Surgery, Coagulopathy, Point-of-care tests, Viscoelastic tests

Abbreviations: NICE - National Institute for Health and Care Excellence; AUROC - Area Under the receiver Operating Characterisitic; HSROC - Hierarchical summary receiver operating characteristics; TEG - Thromboelastography; QUADAS - Quality Assessment of Diagnostic Accuracy Studies; REML - Restricted Maximum Likelihood Estimator; GRADE - Grading of Recommendations Assessment, Development and Evaluation; IQR - Interquartile Range; CI - Confidence Interval

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Introduction

Coagulopathic haemorrhage is a common and potentially severe complication of cardiac surgery. Bleeding requiring massive transfusion or emergency reoperation occurs in up to 10% of patients, and increases mortality up to 8-fold.[1] Timely diagnosis and treatment of coagulopathy is considered an important determinant of outcome.[2] Treatment guidelines,[3] including those from the National Institute for Health and Care Excellence (NICE) in the United Kingdom,[4] and the European Associations for Cardio-Thoracic Surgery (EACTS) and Cardiothoracic Anaesthesiology (EACTA) [5] recommend the routine use of viscoelastic and other point-of-care diagnostic tests of coagulopathy in cardiac surgery. The clinical effectiveness of a point-of-care test requires that it has high sensitivity and specificity for the target condition, in this case coagulopathic bleeding, that in turn guides the administration of effective personalised interventions that reduce blood loss, massive transfusion, and prevent sequelae of haemorrhagic shock. However, point-of-care test-based treatment algorithms for coagulopthic bleeding have failed to demonstrate clinical benefits in recent systematic reviews of randomised trials.[6] [7] One possible explanation for these observations is that the diagnostic accuracy of the point-of-care tests evaluated in these trials is poor.[8] To address this uncertainty we performed a systematic review and quantitative meta-analysis of studies that have evaluated the diagnostic accuracy point-of-care tests for coagulopathy in cardiac surgery patients.

Methods

Protocol and registration

A systematic review and meta-analysis of studies evaluating the diagnostic accuracy of point-of-care devices for coagulopathic bleeding was performed as described in the Cochrane Handbook for Systematic Reviews of Diagnostic Accuracy (Version 5.1).[9] The methods were specified in advance and documented on PROSPERO International prospective register of systematic reviews (CRD42017056032) on the 25th of January 2017. Changes to the protocol after the commencement of the study are listed in the supplementary material. The study is reported as per the PRISMA Diagnostic Test Accuracy statement.[10]

Eligibility criteria

Types of studies Diagnostic accuracy studies irrespective of language, publication status, date of publication, and sample size. Studies that did not report 2x2 frequency data for the estimation of sensitivity and specificity or data for Area Under the receiver Operating Charaterisitic (AUROC) were excluded.

Participants Patients undergoing cardiac surgery for acquired or congenital cardiac disease or thoracic aorto-vascular disease with or without cardiopulmonary bypass. No age restriction was applied.

Target condition Coagulopathic bleeding after cardiac surgery.

Index tests We included point-of-care diagnostic tests of coagulopathy in clinical use:

1. **Visco-elastic tests of clot formation:** Sonoclot Analyzer (Sienco Inc., Wheat Ridge, CO, USA); Thromboelastograph (TEG, Haemonetics Corporation, Braintree, MA, USA; and Haemoscope Corporation, Niles, IL, USA); Rotational thromboelastometry (ROTEM International GmbH, Munich, Germany), WBA analyser (Mebanix, Tokyo, Japan).
2. **Point-of-Care platelet function tests using a platelet agonist**: Platelet Function Analyzer (PFA-100, Siemens,Deerfield, IL, USA); VerifyNow system (Accumetrics, San Diego, CA, USA); Platelet Works (Helena Laboratories, Beaumont, TX,USA); MultiplateTM (Dynabyte Medical, Munich,Germany). Chronolog (ChronoLog Corp., Havertown, PA, USA), Hepcon/Hemostatus (Medtronic; Minneapolis, MN, USA), Innovance-PFA2Y (Siemens Healthcare, Marburg, Germany), light transmission aggregometry (multiple devices), VASP kit (Biocytex, Marseille, France).
3. **TEG modifications:** TEG Platelet Mapping AssayTM (Haemoscope Corporation, Niles, IL, USA).

Timing We identified two clinical pathways where point-of-care tests are used routinely for the diagnosis of coagulopathic bleeding (Figure 1). These are performed either in as predictors of coagulopathic bleeding in unselected patients where positive tests can lead to pre-emptive treatment of coagulopathy or targeted treatment in the event of bleeding (**Pathway A**) OR in selected patients who are actively bleeding (**Pathway B**). In the latter case the tests are used to discriminate between coagulopathic bleeding that requires targeted treatment with pro-coagulants, and non-coagulopathic bleeding that requires surgical treatment.

Reference Standard. All self-reported definitions of coagulopathic haemorrhage were included in the quantitative synthesis. To identify studies where the reference standard was likely to reflect the target condition, and in the absence of embedded clinical consensus, we adopted a definition of coagulopathic bleeding used in a recent cohort study evaluating the diagnostic accuracy of point-of-care tests of coagulopathy in cardiac surgery.[11] The reference standard was a composite of at least 1 of the following clinical events:

1. Emergency re-sternotomy for bleeding
2. Transfusion of allogenic non-red cell components to promote haemostasis
3. Large volume red cell transfusion
4. Massive bleeding

Definitions of coagulopathy that did not include one of these events were considered unlikely to reflect the target condition. For the purposes of the analyses, True positives and True negatives were as reported by individual study authors.

Information sources and inclusion assessment

Eligible studies were identified by searching MEDLINE (Ovid), EMBASE (Ovid), and CINAHL Plus (EBSCO) from inception to June 2019. Full details of the Searches in different databases are listed in the supplement.

To identify ongoing or unpublished studies we searched Clinicaltrials.gov. We also examined the reference lists of eligible studies and reviews. Searches were not restricted by language or publication status. Three authors (CC, CT, and RA) screened the search results to identify potentially eligible studies. Full texts were obtained for these reports and assessed for inclusion by two authors (CC, CT), and checked by another (RA).

Data collection

A standardised form was used to extract data from the included studies. Two authors (CC, CT) piloted the extraction form before data extraction commenced. Extracted information included year and language of publication, country of participant recruitment, year of conduct of the study, study population; inclusion and exclusion criteria, sample size, participant demographics, baseline characteristics, type of surgery, target condition, definition of reference standard, index test, units of measurement, treatment pathway, comparator test (standard care), 2x2 contingency table data for the estimation of sensitivity, specificity, and area under the receiver operating characterisitic (AUROC). One of three authors (CC, CT, and AM) extracted study data, with checking by fourth (RA). Discrepancies were resolved through discussion (with a fifth author where necessary, GJM).

Quality Assessment

Studies were assessed for risk of bias and concerns regarding applicability using Quality Assessment of Diagnostic Accuracy Studies (QUADAS) 2[12] by two reviewers (CC and AM) and checked by a third reviewer (RA).

Statistical analysis and data synthesis

The extracted data included 2x2 test data for the calculation of specificity and sensitivity, total numbers of cases, and numbers of participants with or without the reference outcome. The values were used to calculate numbers of true and false positives, and true and false negatives. In cases where multiple measures were reported (for different indices within a test), the most favourable test results were extracted for the analysis.

Summary estimates of sensitivity and specificity with 95% confidence intervals were estimated using R version 3.3.1[13] and *madad* function from the *mada* package.[14] Hierarchical summary receiver operating characteristics (HSROC) were estimated with *reitsma* and plotted with *crosshair* functions from the *mada* package.

For Summary Area Under the Receiver Operating Characteristic (AUROC) estimates, AUROC values and standard error values were extracted. Summary AUROC were estimated using the *rma* function from *metafor* package version 2.0-0[15] to fit random effects models with restricted maximum likelihood estimator (REML[16]).

Methods for investigating heterogeneity are included in the supplementary material.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of the quality of evidence for point-of-care tests was performed as described.[17]

Investigating heterogeneity

We assessed whether high risk of bias or concerns regarding applicability as judged by the QUADAS 2 assessment could explain heterogeneity. Between study heterogeneity for sensitivity and specificity data was assessed by visual examination of the HSROC crosshair plots. Equality of sensitivities and specificities in terms of proportions across studies were assessed by Chi-square test. Meta-regression was used to investigate heterogeneity by adding the pre-specified variables as covariates in the bivariate model using the *reitsma* function from R *mada* package version 0.5.8.[14] We then compared the fit of the two models with and without the covariate using the likelihood ratio test (ANOVA). A p-value of <0.05 indicated possible source of heterogeneity. Between study heterogeneity for AUROC analysis was assessed by visual examination of Forest plots, and Cochran's Q-test[18] in random effects models without moderators. For mixed models with moderators, the QM test for residual heterogeneity was used (included in the standard output of the *rma metafor* function). Heterogeneity in AUROC models was reported as I^2 with p-value (Q-test).[19, 20]

Results

Search Results

The search identified 23,721 titles (PRISMA diagram, Figure 2). After removing duplicate reports, 16,957 articles were screened, 16,831 articles were excluded on the basis of title and abstracts, and a total of 126 publications were retrieved for further assessment. Twenty-nine studies met the inclusion criteria and were included in the quantitative synthesis. We identified one ongoing study (NCT03902275) in ClinicalTrials.gov that is expected to complete in December 2019.

Included studies

All twenty-nine studies (7,440 participants) included in the data synthesis evaluated the tests as predictors of bleeding. No study evaluated their role in the management of bleeding. The main study characteristics are summarised in Table 1, and reported in detail in Table S1. Three studies evaluated devices for both viscoelastic and platelet function tests in overlapping patient cohorts resulting in 32 individual analyses for inclusion in the quantitative synthesis. Twenty-seven analyses (12 for viscoelastic, 12 for point-of-care, three for TEG modification tests) provided 2 x 2 test data and were included in the HSROC analysis. In addition, it was possible to extract or calculate AUROC and its standard errors from 16 analyses (six analyses for viscoelastic, eight for platelet function, two for TEG modification tests)**.**

Quality Assessment

QUADAS-2 assessments are summarised in Figure 3 and reported in detail in in the online only supplement (Table S2). Overall no study was considered as low risk of bias. Twenty six out of twenty nine studies had significant concerns about applicability (Figure 3B).

Viscoelastic Tests

Fourteen studies evaluated viscoelastic tests (Table 1 and Table S1). Seven evaluated TEG devices, five evaluated ROTEG/ROTEM, and two Sonoclot. The median age (IQR), reported in 13/14 studies was 65 (63.07 - 67.57). One study was performed in children undergoing cardiac surgery. The median

(IQR) proportion of female patients, reported in 12/14 studies, was 26.54% (20.0 – 31.0). The median prevalence of the reference outcome; coagulopathic bleeding was 23.7 (13.6 – 29.7). There was marked heterogeneity with respect to the reference standard, which included postoperative bleeding with threshold volumes ranging from 200ml/hr to 1,500ml/24hrs, major life-threatening bleeding, or a post hoc definition of bleeding greater than 75th percentile, or transfusion of blood products (Table S1). For the index test, four studies reported using the manufacturers normal ranges for ROTEM, and two used the manufacturers normal ranges for TEG. There was marked heterogeneity with respect to diagnostic thresholds used in other studies.

All 14 studies evaluated the tests as predictors of bleedingin unselected cohorts (Pathway A, Figure 1), although four (28.6%) were in cohorts at increased risk of bleeding (receiving thienopyridines). Six studies were judged to be at high risk of bias; one because of inappropriate exclusions leading to a high risk of selection bias,[21] and five due to concerns about the interpretation of the index test and the conduct or interpretation of the reference standard (Table S2).

For viscoelastic tests (12 studies, 2,224 participants), the summary sensitivity was 0.61 (95%CI 0.44, 0.76) and summary specificity was 0.83 (95%CI 0.70, 0.91) with significant heterogeneity for both measures (Figure 4A and Table S4). Evaluation of heterogeneity using the likelihood ratio test indicated that none of the prespecified sources explained the heterogeneity between studies (Table S5).

For viscoelastic tests the summary estimate for AUROC (six studies, 3,022 included participants) was 0.74 (95%CI 0.72, 0.76) without heterogeneity ($I^2 = 0.0\%$, $p < 0.01$, n = 6, Figure 4B).

The study reporting highest sensitivity (0.94, 95%CI 0.63, 0.99) and specificity (0.97, 95%CI 0.88, 0.99) [22], evaluated ROTEM in a cohort of 58 patients undergoing first-time coronary artery revascularization. This study was at high risk of bias in the application of the reference standard and unclear risk of bias in domain cohort selection (**Table S2**).

GRADE assessment of the quality of evidence for viscoelastic tests was LOW (Table S3).

Platelet function testing

Fourteen studies (5,047 participants) evaluated point-of-care platelet function tests as predictors of bleeding in unselected cohorts (Table 1 and Table S1). Nine (64.3%) evaluated cohorts where at least a fraction of patients were at increased risk of bleeding (received thienopyridines within one week before surgery, Table S1). Eleven studies evaluated Multiplate, and three evaluated the PFA-100. The median age (IQR) of patients, reported in 12/14 studies, was 66.5 (63.7 – 67.9) years. All the studies were performed in adult populations, and the median (IQR) proportion of female patients in 12/14 studies where this was reported was 23.1% (19.9 – 28.9). The median prevalence of the reference outcome was 25% (12.1 – 31.5). The reference standard included postoperative bleeding with threshold volumes ranging from blood loss greater than 200ml/2hrs to greater than 1,000ml/12hrs or blood loss grater than 75th or 90th percentile; transfusion of blood or platelets products and composite

of blood loss, transfusion, delayed sternal closure, surgical reexploration and usage of factor VIIIa (Table S1). For the index test, no two studies pre-specified the same diagnostic thresholds.
Eight studies were considered at high risk of bias: one for selection bias[23], seven for the conduct or interpretation of the index test and five for the conduct or interpretation of the reference standard (Table S2).
For platelet function tests, (12 studies, 2,394 participants) summary sensitivity was 0.63 (95%CI 0.53, 0.72) and specificity was 0.75 (95%CI 0.64, 0.84) with significant heterogeneity for both measures (Figure 4C and Table S4). Meta-regression did not identify any of the prespecified sources of heterogeneity as likely to explain variance between studies (Table S5). The study with highest sensitivity 0.85 (95% CI 0.67, 0.95) and specificity 0.98 (95% CI 0.90, 0.99)[24] was performed in a case-control cohort of 84 adult patients at low risk of bleeding. The study had significant methodological limitations in relation to patient selection, the applicability of the patient cohort to the research question, and the applicability of the reference outcome to the target condition. Excluding the study from the analysis resulted in summary sensitivity 0.59 (95%CI 0.50, 0.69) and specificity 0.73 (95%CI 0.62, 0.81).
The summary estimate (eight studies, 4,157 participants) for AUROC was 0.68 (95% CI 0.63 to 0.73, Figure 4D) with high heterogeneity ($I^2 = 84.3\%$, $p < 0.001$, df = 7). All of the studies had important limitations. Evaluation of causes of heterogeneity indicated that all pre-specified sources significantly affected heterogeneity levels when included in the models as covariates (QM p-value in Figure 4D). Analysis in subgroups identified studies at high/unclear risk of selection bias or selection applicability least variable with insignificant levels of heterogeneity (I2 = 52.63%, Q p-value = 0.09, Figure 4D)
The study reporting highest sensitivity (0.85, 95%CI 0.67, 0.95) and specificity (0.98, 95%CI 0.90, 0.99) [24] was an evaluation of Multiplate in a cohort of 84 patients undergoing first time isolated CABG on CPB. In this study, the risk of bias for cohort selection, application of the index test and reference standard was unclear (**Table S2**).
GRADE assessment of the quality of evidence for platelet function tests was VERY LOW (Table S3).

TEG modification tests

Four studies, with a total of 399 participants, evaluated Modified Thromboelastography (Platelet Mapping with collagen and ADP). The median (IQR) age of patients was 63.9 years (61.6 – 66.0), and the median (IQR) proportion of female patients was 23.6% (18.1 – 30.3). The median (IQR) prevalence of the reference outcome was 22.0 (14.0 – 29.0) (Table 1 and Table S1). The reference standards included excessive bleeding or bleeding grater than 1000ml, transfusion of blood, fresh frozen plasma or platelets (Table S1).
All studies evaluated the tests as part of Pathway A (Figure 1). Three studies were performed in cohorts where all or majority of patients received thienopyridines within one week of surgery, with the prevalence of the reference outcome ranging from 10.1 – 28.7%. The fourth study by Weitzel et al.[25] recruited a cohort of low risk patients undergoing primary cardiac surgery, and reported a prevalence for the reference outcome of 30.0%. (Table S1).

Two studies were at high risk of bias, one in the conduct and interpretation of the index test, and both studies in the conduct and interpretation of the reference standard. In one study [26] the index test threshold was not prespecified and the results were not interpreted without the knowledge of the reference standard. In both studies[25, 26] there were concerns about the appropriateness of the reference standard definition, and the results of the reference standard were not interpreted without the knowledge of the index test (Table S2).

The summary estimate (three studies, 200 participants included in the analyses) for sensitivity was 0.80 (95%CI 0.67, 0.89) and for specificity was 0.76 (95%CI 0.69, 0.82) without significant heterogeneity for both measures (Figure 4E and Table S4). The summary estimate (two studies, 300 participants) for AUROC was 0.75 (95% CI 0.67, 0.82, Figure 4D)

The study reporting highest sensitivity (0.78, 95%CI 0.45, 0.94) and specificity (0.84, 95%CI 0.72, 0.92) [27] was an evaluation of TEG/Platelet mapping device in a cohort of 59 patients undergoing first-time elective or urgent CABG and treatment with anti-platelet agents. This study had unclear risk of bias in the domain cohort selection (**Table S2**).

GRADE assessment of the quality of evidence for TEG modification tests was LOW (Table S3).

Discussion

This systematic review of studies that evaluated the diagnostic accuracy of point-of-care tests for coagulopathic bleeding in cardiac surgery identified 29 studies that evaluated 6 devices in 32 analyses. All the studies evaluated the predictive accuracy of the tests for coagulopathic bleeding in unslected cohorts. No study evaluated their performance in cohorts who were not actively bleeding. Using QUADAS-2 to assess methodological quality, no study was considered at low risk of bias, and 26/29 had concerns about applicability. Summary estimates of diagnostic accuracy for viscoelastic tests and platelet function tests demonstrated significant heterogeneity, limiting their interpretation. Attempts to explore the causes of this variance in pre-specified sub-group analysis yielded little insight. Estimates of diagnostic accuracy for TEG Modification tests were limited by small sample sizes and study quality. These observations did not resolve uncertainty as to the diagnostic accuracy of existing point-of-care tests for coagulopathy in cardiac surgery.

Strengths and limitations

To our knowledge, this is the first systematic review and quantitative meta-analysis of the diagnostic accuracy of point-of-care tests of coagulopathy in cardiac surgery using Cochrane methodology.[28] The review was conducted using a pre-specified protocol, with comprehensive search strategies,[8] and used the QUADAS-2 quality assessment tool[12] for reviews of test accuracy studies as recommended by Cochrane.[9] The major limitation of the review is the limited validity of the included studies to the review question due to concerns about applicability, bias, and heterogeneity. Furthermore, many of our QUADAS-2 methodological assessments for the risk of bias were 'Unclear'. Another limitation is that all of the evaluations were of diagnostic tests used routinely in non-bleeding cohorts with heterogeneity of bleeding risk. These findings should not be generalised to

patients who are actively bleeding. A final limitation is that the test results used in the analyses do not reflect the large number of test measures per assay that are thought to reflect different components of the blood clotting pathway, or the heterogeneity in their interpretation between units. The data included in the meta-analyses were the reported parameters with the best diagnostic accuracy for each study. In the main, this was because studies only reported the diagnostic accuracy of test results that best predicted bleeding. As the sensitivity and specificity of other parameters were not reported or analysed we are unable to comment on the ability of these platforms to guide targeted treatment of different coagulopathies with specific pro-haemostatic therapies as claimed by the device manufacturers.

Meaning of the study

These limitations notwithstanding, the study identified key considerations for improved design of diagnostic accuracy studies in this setting: First, the review has identified a knowledge gap with respect to the performance of these tests in bleeding patients. Second, there is a clear need for standardisation of reference outcomes, pre-specified test thresholds, and better adherence to reporting standards for diagnostic test accuracy studies, in future research. Third, misclassification bias, or limited applicability of the reference standard to the target condition, was evident in 20/27 studies that provided data on sensitivity and specificity. Our reference outcome used the definition of coagulopathic bleeding from the largest and most comprehensive evaluation of point-of-care tests in cardiac surgery to date.[11] This includes a composite of clinical outcomes that can both under- (resternotomy) and over-estimate (plasma transfusion). The small number of studies meeting this definition identifies an important outcome for standardisation in future studies. In mitigation, uncertainty as to what constitutes a true positive or true negative for coagulaopathic bleeding is a potential limitation of all clinical studies in this field because the phenotype is so poorly defined.[29] It is likely that the molecular mechanisms underlying coagulopathic bleeding differ from patient to patient depending on the underlying cause. Better testing platforms designed to discriminate between these phenotypes may ultimately lead to more personalised treatments[30].

Existing blood management guidelines, recommend the routine use of point-of-care diagnostic tests of coagulopathy for the management of cardiac surgery patients at risk of significant bleeding.[3, 4] However, a recent systematic review of trials evaluating the clinical effectiveness of viscoelastometry failed to demonstrate a clinical benefit from the routine introduction of these devices into patient blood management algorithms in cardiac surgery.[6, 30] A contemporary cost effectiveness analysis of viscoelastic tests and platelet aggregometry in cardiac surgery indicated that their use was not more cost effective than simple clinical assessment alone.[11] Together with the current study, which demonstrates a clear knowledge gap with respect to the diagnostic accuracy of these tests, our observations suggest that existing treatment guidelines should reflect uncertainty as to the clinical utility of these tests. They also identify an unmet need for further research into better diagnostic tests or new technology for the management of patients with coagulopathic bleeding.

Conclusion

In a systematic review and meta-analysis of studies evaluating the diagnostic accuracy of point –of-care tests for coagulopathy significant methodological limitations and the heterogeneity between studies for measures of diagnostic accuracy limited the internal and external validity of the data synthesis.

Details of authors' contributions

MJW and FL performed the analysis and wrote manuscript. AM, CC and CT extracted the data with oversight by MJW and TK. TK and PW also wrote the manuscript, GJM, conceived and designed the study, supervised the analyses, and wrote the manuscript. All of the authors contributed to the writing of the manuscript and have approved the final version for submission.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

Mrs Kumar, Prof. Murphy and Dr Woźniak report grant from Zimmer Biomet for a randomised trial of inosine solution treated allogeneic red cells in cardiac surgery patients, outside the submitted work. Prof. Murphy reports grant from Terumo, outside the submitted work. Other co-authors have nothing to disclose.

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Table and figure legends

Table 1 Summary characteristics of the studies included in the qualitative and quantitative analyses; CPB – cardiopulmonary bypass, TEG – thromboelastography, ROTEM - rotational thomboelastometry, LTA - Light Transmission Aggregometry, PFA- Platelet Function analyser, Teg Mod, Modified Thromboelastography/ Platelet Mapping, HSROC Hierarchical Summary Receiver Operating Characteristic, AUC, Area Under Receiver Operating Characterisitic, *Median (IQR)

Table S1 Characteristics of included studies. CPB – cardiopulmonary bypass, CABG - coronary artery bypass graft. TEG – thromboelastography, ROTEM - rotational thomboelastometry, LTA - Light Transmission Aggregometry, Hct - haematocrit, PT – prothrombin time, aPTT - , APTT activated partial thromboplastin time, INR - International Normalized Ratio, Hb – Haemoglobin, MPV - mean platelet volume, ACT - activated clotting time, NA – not available

Table S2 : Summary of QUADAS-2 assessment of the risk of bias and sources of heterogeneity. CPB – cardiopulmonary bypass, CABG - coronary artery bypass graft. TEG – thromboelastography, ROTEM - rotational thomboelastometry, LTA - Light Transmission Aggregometry, Hct - haematocrit, PT – prothrombin time, aPTT - , APTT activated partial thromboplastin time, INR - International Normalized Ratio, Hb – Haemoglobin, MPV - mean platelet volume, ACT - activated clotting time, NA – not available.

Table S3 GRADE assessment whether point of care tests should be used to diagnose bleeding in cardiac surgery. [a] The index test threshold was not prespecified in all studies and the results were not interpreted without the knowledge of the reference standard. Results of the reference standard were not interpreted without the knowledge of the index test in all studies. [b] Low number of patients, wide confidence intervals.

Table S4 Summary of Diagnostic Accuracy Estimates (95%CI) for Viscoelastic, Platelet Function tests and TEG modification tests. TP – true positives, FN – false negatives, FP – false positives, TN – true negatives, 95% CI – 95% confidence intervals. X2 test was used to determine heterogeneity levels for sensitivities and pecificities and p-values < 0.05 indicate that estimates of sensitivity and specificity are not homogenous.

Table S5 Heterogeneity analysis for sensitivity and specificity in subgroups defined by pre-specified sources of heterogeneity. Prespecified sources of heterogeneity were included in bivariate models as covariates and compared with models without them using likelihood ratio test. P-values greater than 0.05 indicate that the included covariate does not significantly change the model and hence has no influence on the levels of heterogeneity. Due to small number of studies low risk/concern groups were compared with merged high/unclear groups.

Figure 1 Clinical pathways routinely used for the diagnosis of coagulopathic bleeding.

Figure 2 PRISMA flow diagram

Figure 3 Risk of bias and applicability concerns graph of studies evaluating point-of-care tests of coagulopathy in cardiac surgery (n = 29).

Figure 4 Hierarchical summary receiver operating characteristic of studies evaluating (**A**) viscoelastic, (**B**) platelet function and (**C**) TEG modification tests included in the quantitaive synthesis. Red dots and whiskers show point estimates for sensitivity and false positive rate, and their 95% confidence intervals. Pale purple triangles and whiskers indicate sensitivity and false positive rate, and their 95% confidence intervals for individual studies. Triangle size indicates cohort size. Forest plots of Area under ROC curve values for studies evaluating viscoelastic (**B**), platelet function tests (**D**), and TEG modification tests (**F**). Heterogeneity between AUROC measures was investigated with Cochrane Q-test and the outcome is shown below the plots. For studies evaluating Platelet Function Tests (**D**) heterogeneity was investigated within pre-specified categories. The influence of covariates on heterogeneity is indicated by QM p. Estimates are shown for each subgroup together with levels of heterogeneity. **Q** – Chochrane Q-test estimate, **n** – number of papers, ***p*** – Chochrane Q-test p-value, $\mathbf{I^2}$ – total heterogeneity.

Figure 1

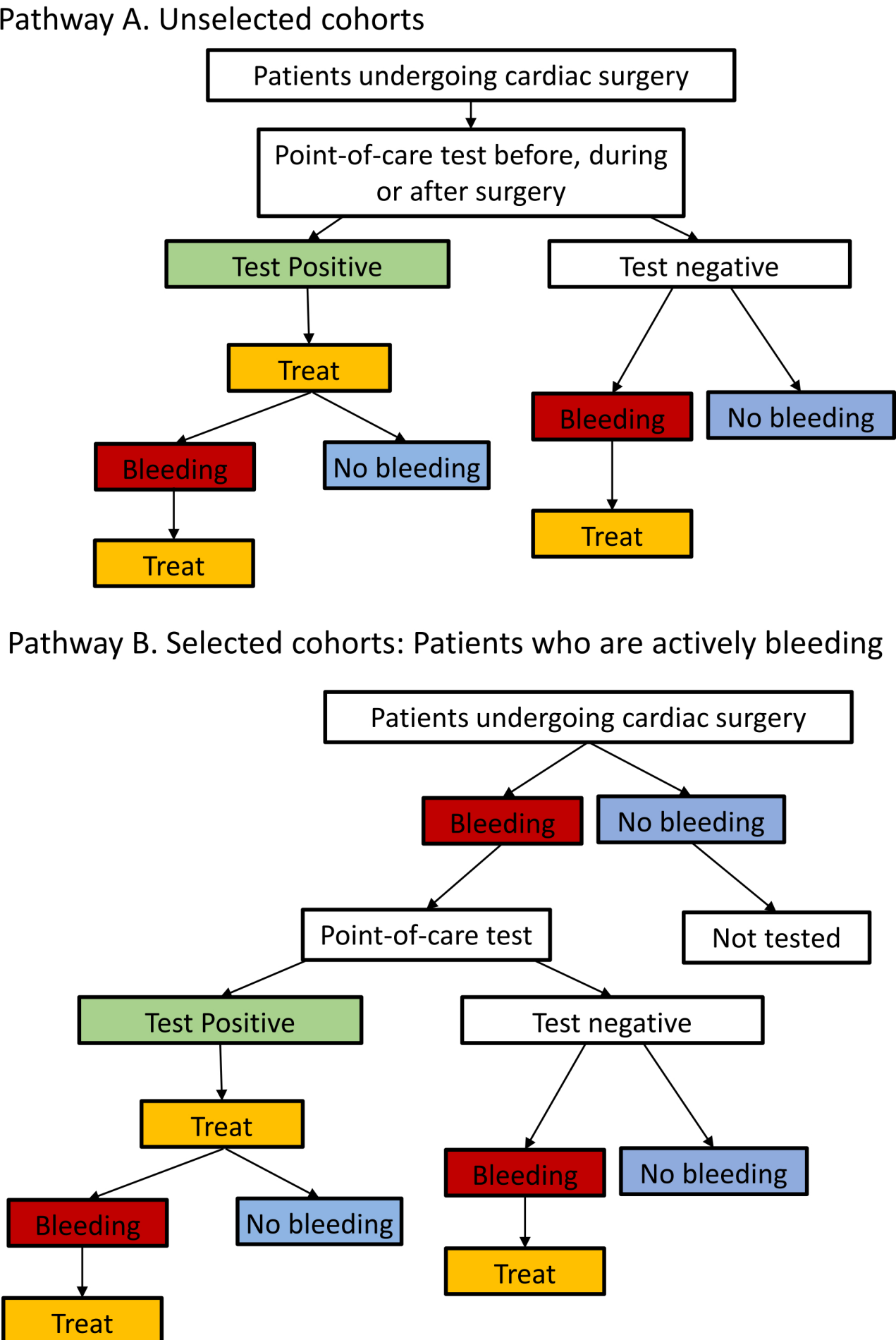

Pathway A. Unselected cohorts
Patients undergoing cardiac surgery
Point-of-care test before, during or after surgery
Test Positive
Test negative
Treat
Bleeding
No bleeding
Bleeding
No bleeding
Treat
Treat
Pathway B. Selected cohorts: Patients who are actively bleeding
Patients undergoing cardiac surgery
Bleeding
No bleeding
Point-of-care test
Not tested
Test Positive
Test negative
Treat
Bleeding
No bleeding
Bleeding
No bleeding
Treat
Treat

Figure 2

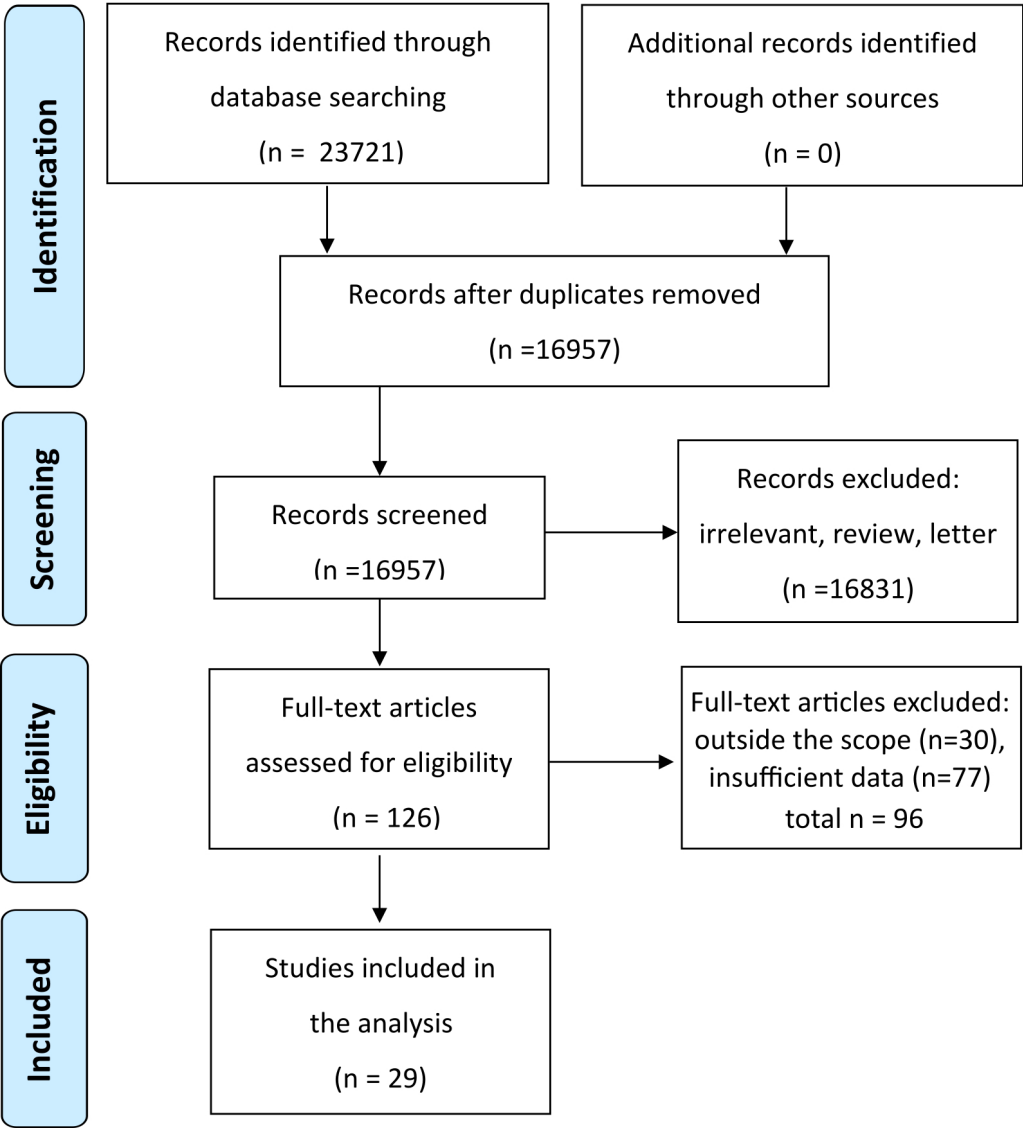

Identification
Records identified through database searching (n = 23721)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n =16957)
Screening
Records screened (n =16957)
Records excluded: irrelevant, review, letter (n =16831)
Eligibility
Full-text articles assessed for eligibility (n = 126)
Full-text articles excluded: outside the scope (n=30), insufficient data (n=77) total n = 96
Included
Studies included in the analysis (n = 29)

Figure 3

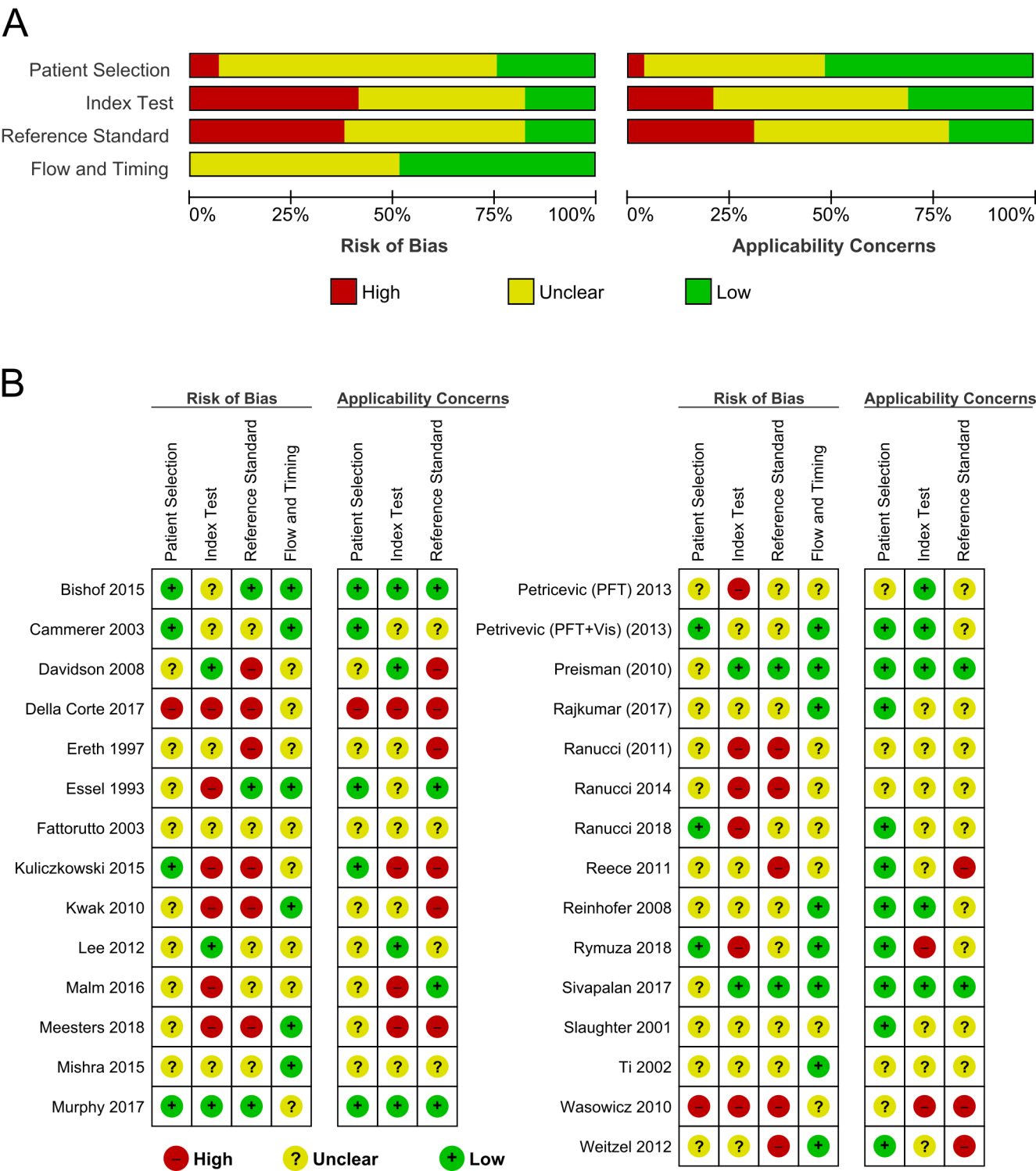
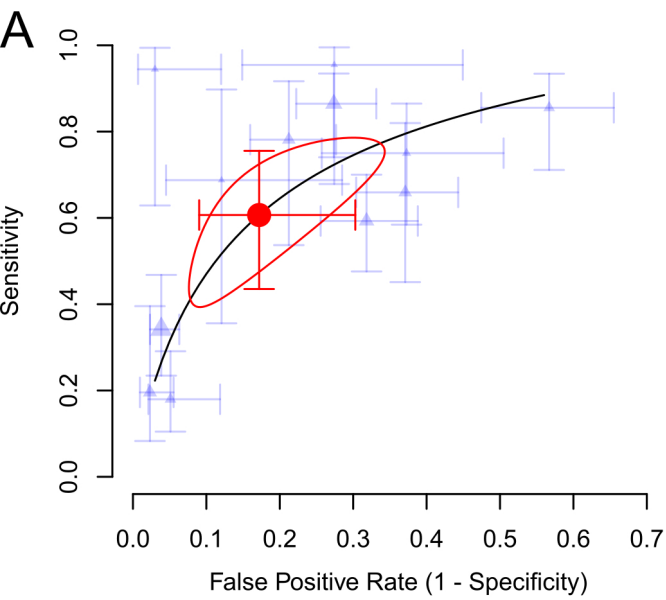
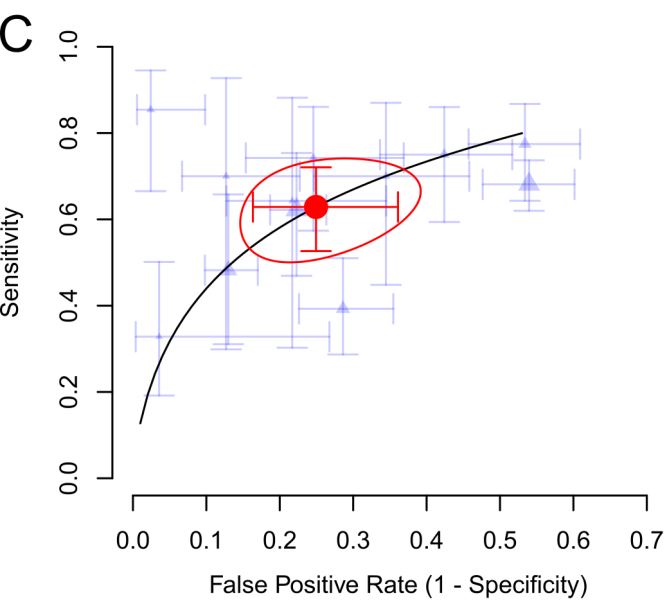
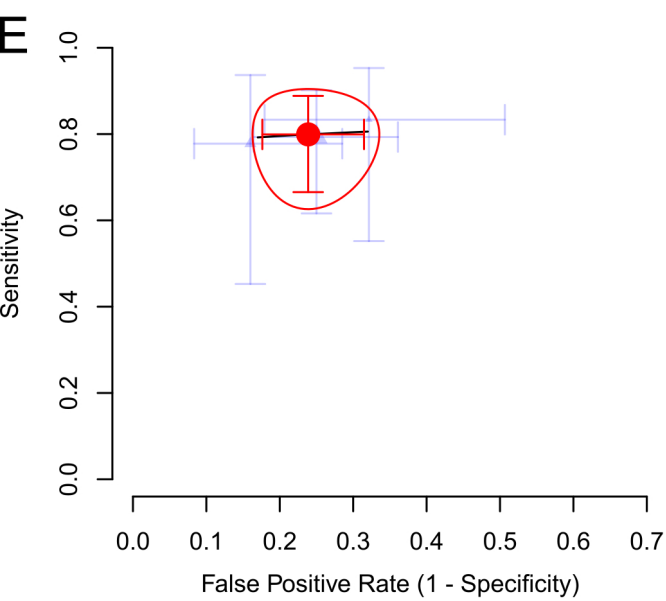
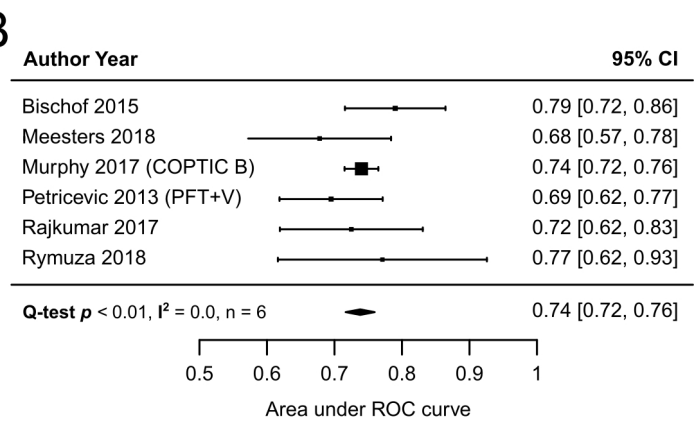

A
Patient Selection
Index Test
Reference Standard
Flow and Timing
0%
25%
50%
75%
100%
Risk of Bias
Applicability Concerns
High
Unclear
Low
B
Risk of Bias
Applicability Concerns
Patient Selection
Index Test
Reference Standard
Flow and Timing
Bishof 2015
Cammerer 2003
Davidson 2008
Della Corte 2017
Ereth 1997
Essel 1993
Fattorutto 2003
Kuliczkowski 2015
Kwak 2010
Lee 2012
Malm 2016
Meesters 2018
Mishra 2015
Murphy 2017
Petricevic (PFT) 2013
Petrivevic (PFT+Vis) (2013)
Preisman (2010)
Rajkumar (2017)
Ranucci (2011)
Ranucci 2014
Ranucci 2018
Reece 2011
Reinhofer 2008
Rymuza 2018
Sivapalan 2017
Slaughter 2001
Ti 2002
Wasowicz 2010
Weitzel 2012
High
Unclear
Low

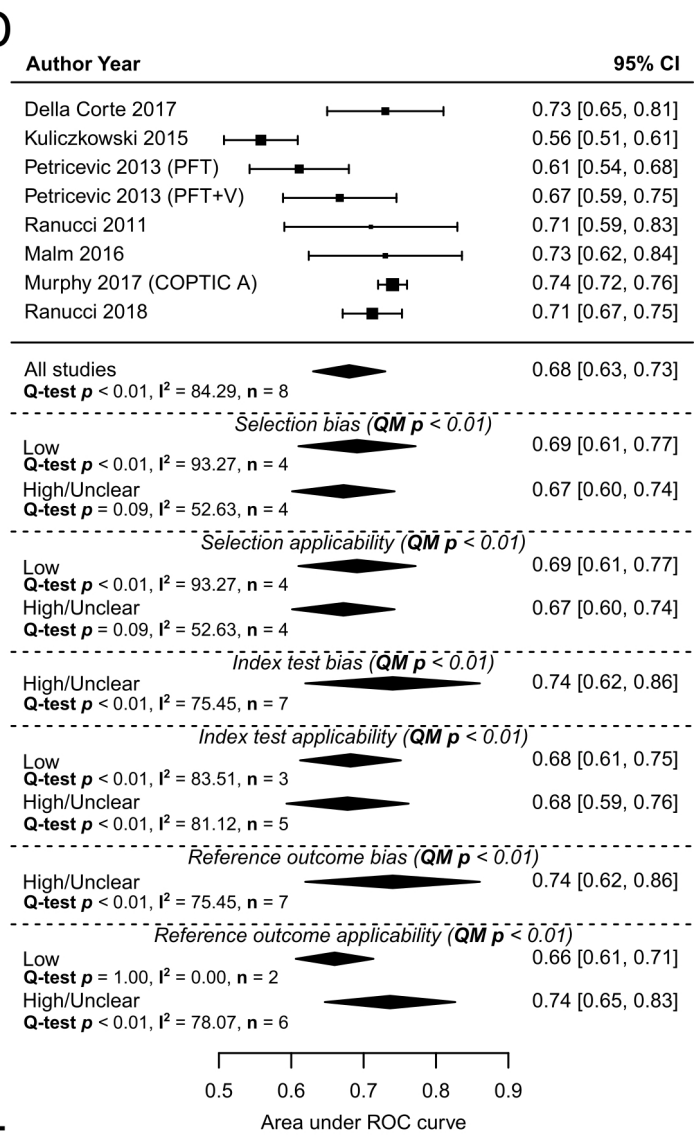
Figure 4


A
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
False Positive Rate (1 - Specificity)


C
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
False Positive Rate (1 - Specificity)


E
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
False Positive Rate (1 - Specificity)


B
Author Year
95% CI
Bischof 2015
0.79 [0.72, 0.86]
Meesters 2018
0.68 [0.57, 0.78]
Murphy 2017 (COPTIC B)
0.74 [0.72, 0.76]
Petricevic 2013 (PFT+V)
0.69 [0.62, 0.77]
Rajkumar 2017
0.72 [0.62, 0.83]
Rymuza 2018
0.77 [0.62, 0.93]
Q-test p < 0.01, I² = 0.0, n = 6
0.74 [0.72, 0.76]
0.5
0.6
0.7
0.8
0.9
1
Area under ROC curve


D
Author Year
95% CI
Della Corte 2017
0.73 [0.65, 0.81]
Kuliczkowski 2015
0.56 [0.51, 0.61]
Petricevic 2013 (PFT)
0.61 [0.54, 0.68]
Petricevic 2013 (PFT+V)
0.67 [0.59, 0.75]
Ranucci 2011
0.71 [0.59, 0.83]
Malm 2016
0.73 [0.62, 0.84]
Murphy 2017 (COPTIC A)
0.74 [0.72, 0.76]
Ranucci 2018
0.71 [0.67, 0.75]
All studies
Q-test p < 0.01, I² = 84.29, n = 8
0.68 [0.63, 0.73]
Selection bias (QM p < 0.01)
Low
Q-test p < 0.01, I² = 93.27, n = 4
0.69 [0.61, 0.77]
High/Unclear
Q-test p = 0.09, I² = 52.63, n = 4
0.67 [0.60, 0.74]
Selection applicability (QM p < 0.01)
Low
Q-test p < 0.01, I² = 93.27, n = 4
0.69 [0.61, 0.77]
High/Unclear
Q-test p = 0.09, I² = 52.63, n = 4
0.67 [0.60, 0.74]
Index test bias (QM p < 0.01)
High/Unclear
Q-test p < 0.01, I² = 75.45, n = 7
0.74 [0.62, 0.86]
Index test applicability (QM p < 0.01)
Low
Q-test p < 0.01, I² = 83.51, n = 3
0.68 [0.61, 0.75]
High/Unclear
Q-test p < 0.01, I² = 81.12, n = 5
0.68 [0.59, 0.76]
Reference outcome bias (QM p < 0.01)
High/Unclear
Q-test p < 0.01, I² = 75.45, n = 7
0.74 [0.62, 0.86]
Reference outcome applicability (QM p < 0.01)
Low
Q-test p = 1.00, I² = 0.00, n = 2
0.66 [0.61, 0.71]
High/Unclear
Q-test p < 0.01, I² = 78.07, n = 6
0.74 [0.65, 0.83]
0.5
0.6
0.7
0.8
0.9
Area under ROC curve

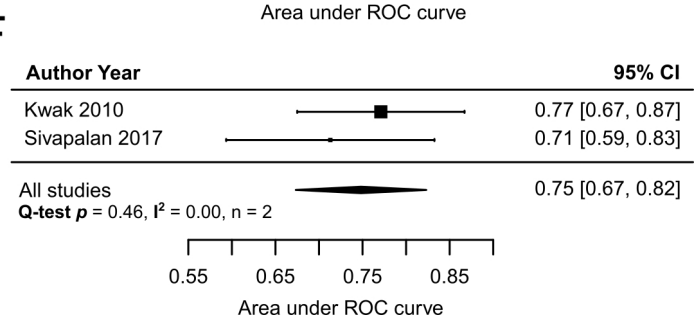

F
Author Year
95% CI
Kwak 2010
0.77 [0.67, 0.87]
Sivapalan 2017
0.71 [0.59, 0.83]
All studies
Q-test p = 0.46, I² = 0.00, n = 2
0.75 [0.67, 0.82]
0.55
0.65
0.75
0.85
Area under ROC curve

Table 1. Summary characteristics of the studies included in the qualitative and quantitative analyses; CPB – cardiopulmonary bypass, TEG – thromboelastography, ROTEM - rotational thomboelastometry, LTA - Light Transmission Aggregometry, PFA- Platelet Function analyser, Teg Mod, Modified Thromboelastography/ Platelet Mapping, HSROC Hierarchical Summary Receiver Operating Characteristic, AUC, Area Under Receiver Operating Characterisitic, *Median (IQR)

	No. of studies	No. of analyses	No. of patients	No. of studies in children	Age* Years	% female*	Prevalence of the reference outcome*	Device
All studies	29	32	7,440	1	65·00 (63·07 - 67·57)	26·54 (20·00 – 31·00)	23·70 (13·59 - 29·71)	TEG = 7 ROTEM = 5 Sonoclot = 2 Multiplate = 11 PFA-100 = 3 PlateletMapping = 4
Viscoelastic test								
All viscoelastic	14	14	4,514	1	65·00 (63·27 - 67·42)	30.03 (25·55 - 31·85)	22·04 (13·92 - 25·51)	TEG = 7 ROTEM = 5 Sonoclot = 2
HSROC analysis	12	12	2,229	1	65·00 (61·29 - 66·50)	30·03 (26·68 - 31·60)	20 (13·81 - 26·03)	TEG = 5 ROTEM = 5 Sonoclot = 2
AUROC analysis	6	6	3,022	1	66·71 (65·25 - 68·53)	29·05 (28·74 - 30·00)	24·07 (16·67 – 25·00)	TEG = 2 ROTEM = 2 Sonoclot = 2
Platelet function tests								
All Platelet function tests	14	14	5,047	0	66·50 (63·68 - 67·85)	23·10 (19·88 - 28·92)	25·00 (12·13 - 31·47)	Multiplate = 11 PFA-100 = 3
HSROC analysis	12	12	2394	0	66·50 (63·83 - 67·75)	24·27 (20·12 - 29·01)	25·00 (12·13 - 31·47)	Multiplate = 9 PFA-100 = 3
AUC analysis	8	8	4157	0	66·8 (64·10 - 68·22)	25.37 (21·5 - 28·92)	24·35 (17·99 - 32·92)	Multiplate = 8
TEG mod tests								

All TEG mod	4	4	399	0	63·92 (61·62 – 66·00)	23·55 (18·14 - 30·25)	21·98 (13·95 - 29·03)	PlateletMapping = 4
HSROC analysis	3	3	200	0	62·83 (60·42 - 63·92)	28·00 (21·63 - 32·5)	28·71 (21·98 - 29·36)	PlateletMapping = 3
AUC analysis	2	2	300	0	67·00 (66·00 – 68·00)	23·55 (21·33 - 25·77)	19·38 (14·72 - 24·05)	PlateletMapping = 2

Table S1. Characteristics of included studies. CPB – cardiopulmonary bypass, CABG - coronary artery bypass graft. TEG – thromboelastography, ROTEM - rotational thomboelastometry, LTA - Light Transmission Aggregometry, Hct - haematocrit, PT – prothrombin time, aPTT - , APTT activated partial thromboplastin time, INR - International Normalized Ratio, Hb – Haemoglobin, MPV - mean platelet volume, ACT - activated clotting time, NA – not available

Evaluation Ref.	Device	Publication language and Country	Population	Exclusion criteria	Demographics	Reference Standard: Definition of coagulopathy and Prevalence	Pathway Timing of test Definition of Abnormal Test	Data for Analyses
Bischof 2015 [1]	Sonoclot	English, Switzerland	Consecutive patients undergoing cardiac surgery.	<18 yearsand >90 years,repair of congenital heart defects, and known hereditary or acquired coagulation disorders.	Age=65; % females=31; N Patients=300; N patients with data for the analysis=300	Postop blood loss >800 mL in 4 hours 50/300 (17%)	Unselected cohort Test at end of surgery Ranges for normal test results not stated	2x2 data AUROC
Cammerer 2003 [2]	PFA-100, TEG	English, Germany	Consecutive patients scheduled for routine cardiac surgical procedures involving CPB.	emergency operation and missing consent	Age=64; % females=32; N Patients=255; N patients with data for the analysis=255	Blood loss >=500 mL (75th percentile) in 6 hour 69/255 (27%)	Unselected cohort Test during and at the end of surgery MA post-CPB 57 mm Angle α post-CPB 71° Abciximab MA post-CPB 17 mm Abciximab α post-CPB 26° PFA ADP post-CPB 118seconds	2x2 data, AUROC available but impossible to calculate standard errors
Davidson 2008 [3]	ROTEM	English, UK	Patients undergoing first-time coronary artery revascularization.	<18 years, preoperative anticoagulation, known coagulopathy, redo surgery, patients taking aspirin, ticlopidine, clopidogrel, or abciximab within the preceding 7 days.	Age=67; % females=18; N Patients=57; N patients with data for the analysis=57	Excessive bleeding post-op defined as >200ml/hr in first 4hrs. 8/58 (14%)	Unselected cohort Test pre-surgery and at 1, 2, and 3 hours after surgery Manufacturers reference ranges for ROTEM	2x2 data
Della Corte 2017 [4]	Multiplate	English, Italy	Consecutive patients undergoing isolated first-time CABG and receiving Aspirin + Clopidogrel or Aspirin + Ticagrelor	Single antiplatelet therapy with aspirin or off-pump CABG.	Age=63; % females=20; N Patients=226; N patients with data for the analysis=226	75th percentile of blood losses (>450 ml) at 6 h 72/226 (32%)	Unselected cohort Pre-surgery multiplate value ADP test >_46U was considered as the safety cut-off ADP test result of <31U indicates high bleeding risk ASPI test <30U was considered as the safety cut-off ASPI test result of <40U indicated strong cyclooxygenase inhibition.	AUROC

Ereth 1997 [5]	Platelet-Activated Clotting Test (PACT) & TEGTEG	English, USA	Adult patients undergoing cardiac surgery requiring CPB	Patients undergoing moderate or deep hypothermic CPB.	Age=NA; % females=26; N Patients=200; N patients with data for the analysis=200	>200 ml/hr chest tube drainage in 4hr 15/200 (8%)	Unselected cohort Test during and at the end of surgery PACT clot 70% to 80% TEG-MA 44 mm	2x2 data
Essel 1993 [6]	TEG	English, USA	Adult patients undergoing CPB	NA	Age=54; % females=NA; N Patients=35; N patients with data for the analysis=35	Abnormal bleeding >1500ml/24hrs or need to transfuse platelets/FFP to control haemorrhage. 7/35 (20%)	Unselected cohort Test during and at the end of surgery R = 6 to 12 minutes K = 3 to 5 minutes Angle α = 45 to 55° MA = 55 to 60 mm A60= >0.85 MA	2x2 data
Fattorutto 2003 [7]	PFA-100	English, Belgium	Patients undergoing elective heart surgery with CPB	NA	Age=NA; % females=NA; N Patients=70; N patients with data for the analysis=70	Excessive mediastinal blood loss >200 ml for two hours 4/70 (6%)	Unselected cohort Test during and at the end of surgery Collagen/epinephrine closure time >300 seconds	2x2 data
Kuliczkowski 2015 [8]	Multiplate	English, Poland	Cardiac surgery patients receiving anti-platelet agents < 10 days of surgery	Patients who stopped antiplatelet treatment >10 days before surgery	Age=64; % females=29; N Patients=478; N patients with data for the analysis=478	Post-op drainage >610mL, median for the study group 239/478 (50%)	Unselected cohort Pre-surgery multiplate value ASPI test value <407 AUC*minute in all patients ASPI test <271 AUC*minute in CABG patients ASPI test <513 AUC*minute in Valve patients	2x2 data AUROC
Kwak 2010 [9]	TEG Platelet mapping	English, Korea	Patients scheduled for isolated multi-vessel OPCABG receiving clopidogrel within 5 days of surgery	Emergency (operation priority, including emergent or salvage OPCABG), myocardial infarction, history of cardiac surgery, history of bleeding diathesis or hepatic dysfunction, left ventricular ejection fraction <40%, hematocrit <33%, platelet count <100,000 mm3, abnormal range of prothrombin time and activated partial thromboplastin time, creatinine >1.4 mg/dl, and use of glycoprotein IIb/IIIa inhibitors.	Age=65; % females=28; N Patients=100; N patients with data for the analysis=99	Transfusion rates at highest tertile (>76.5%) platelet inhibitory response to clopidogrel 29/99 (29%)	Unselected cohort Pre-surgery TEG value 70% Platelet inhibitory response to clopidogrel	2x2 data AUROC
Lee 2012 [10]	ROTEM	English, USA	Patients undergoing cardiac surgery requiring CPB	NA	Age=65; % females=32; N Patients=321; N patients with data for the analysis=215	Chest tube output at 920ml 22/215 (10%)	Unselected cohort Test during and at the end of surgery	2x2 data, AUROC available but impossible to calculate standard errors

							Manufacturers recommended reference ranges were used.	
Malm 2016 [11]	Multiplate	English, Sweden	Cardiac surgery patients with acute coronary syndrome treated with acetylsalicylic acid and ticagrelor <5 days before surgery	NA	Age=68; % females=20; N Patients=90; N patients with data for the analysis=90	At least one must apply: i) chest drain loss >1000 ml in first 12 h after surgery; ii) delayed sternal closure; iii) need for surgical re-exploration due to bleeding or tamponade; iv) use of recombinant factor VIIa; v) transfusion of >5 units of RBCs within 24 h of chest closure; or vi) transfusion of >5 units of plasma within 24 h of chest closure. 32/90 (36%)	Unselected cohort Pre-surgery multiplate value Manufacturers normal ranges for hirudin-test tubes were used: ADP-HS 43–100 U ASPI test 71–115 U TRAP test 84–128 U	2x2 data AUROC
Meesters 2018 [12]	ROTEM	English, the Netherlands	Adult patients who underwent elective cardiac surgery with CPB.	NA	Age=67; % females=NA; N Patients=202; N patients with data for the analysis=202	Major blood loss >500 mL chest tube drainage at 6hrs (90th percentile) 21/202 (10%)	Unselected cohort Test during and at the end of surgery Cut points and normal ranges not stated.	2x2 data AUROC
Mishra 2015 [13]	Multiplate, TEG	English, UK	Patients undergoing 1st time isolated CABG on CPB.	Severe liver or renal dysfunction (altered liver function test, creatinine >200 µmol/L) and patients with known bleeding diathesis.	Age=63; % females=12; N Patients=84; N patients with data for the analysis=84	Blood or platelet transfusion 23/84 (27%)	Unselected cohort Test before and at the end of surgery Manufacturers references ranges for Multiplate: ADP test 57–113U ASPI test71–115U TRAP test 84–128U Reference ranges for TEG not stated	2x2 data
Murphy 2017 (COPTIC A) [14]	Multiplate,	English, UK	Adult patients undergoing cardiac surgery who had consented to participation in the study.	Emergency and salvage surgery	Age=69; % females=24; N Patients=2463; N patients with data for the analysis=2197	Post-operative blood loss >600ml at 6hrs, intervention with haemostatic treatment i.e. platelets, FFP, cryo, additional protamine, reoperation for bleeding with no surgical cause identified	Unselected cohort Pre-surgery multiplate value Manufacturers references ranges for Multiplate	AUROC

						686/2197 (31%)		
Murphy 2017 (COPTIC B) [14]	Multiplate, TEG, ROTEM	English, UK	Patients undergoing cardiac surgery who had consented to the study and had pre-operative and post-operative ROTEM and TEG samples taken.	Emergency and salvage surgery	Age=69; % females=24; N Patients=2463; N patients with data for the analysis=1833	Post-operative blood loss >600ml at 6hrs, intervention with haemostatic treatment i.e. platelets, FFP, cryo, additional protamine, reoperation for bleeding with no surgical cause identified 535/1833 (29%)	Unselected cohort Test results at the end of surgery Manufacturers reference ranges used for all devices	AUROC
Petricevic 2013 (Plt+visco) [15]	Multiplate, ROTEM	English, Croatia	Adult patients scheduled for elective CABG requiring CPB.	Patients with cardiac surgical procedures other than isolated CABG, APT other than ASA or CLO, hematological disorders, patients on non-steroidal antiinflammatory drugs, patients with missing data, urgent and emergent surgery, off-pump CABG and Re-Do CABG.	Age=66; % females=29; N Patients=148; N patients with data for the analysis=148	24 h chest tube output >= 75th percentile 37/148 (25%)	Unselected cohort Test during and at the end of surgery ASPI ≤22 AUC ADP ≤36 AUC ExTEM α angle ≤63° FibTEM A 30 ≤11 mm	2x2 data AUROC
Petricevic 2013 (Plt) [16]	Multiplate	English, Croatia	Consecutive patients, scheduled for elective cardiac surgery (ECS) procedures requiring CPB.	<18 years old, urgent procedure, off-pump cardiac surgical procedure, on APT other than Aspirin (ASA) and CLO, patients with inaccurate APT administration documentation, urgent surgery, and patients requiring surgical exploration for excessive bleeding due to obvious surgical bleeding with a bleeding vessel identified.	Age=64; % females=27; N Patients=211; N patients with data for the analysis=211	24 h chest tube output >= 75th percentile 50/211 (24%)	Unselected cohort Test during and at the end of surgery ASPI ≤20 AUC ADP ≤73 AUC	2x2 data AUROC
Preisman 2010 [17]	TEG/Platelet mapping (Haemoscope)	English, Israel	Patients undergoing first-time elective or urgent CABG and treatment with anti-platelet agents (aspirin and/or clopidogrel) within 1 week prior to surgery.	Patients requiring emergent surgery and combined operations, grossly abnormal coagulation tests, a history of coagulopathy, preoperative treatment with other anticoagulants, enrollment in any other study.	Age=63; % females=15; N Patients=59; N patients with data for the analysis=59	Excessive Bleeding within 24 hrs 9/59 (15%)	Unselected cohort Pre-surgery Platelet Mapping Agonist resistance defined as >50% agonist activation Maximum amplitude for ADP >42.4mm considered positive test	2x2 data, AUROC available but impossible to calculate standard errors
Rajkumar 2017 [18]	Sonoclot	English, India	Patients aged 6months - 14 years, undergoing cardiac surgery using CPB for cyanotic congenital heart disease.	pre-operative deranged liver or renal function, anti-coagulant or anti-platelet drugs within one week of surgery	Age=6; % females=29; N Patients=87; N patients with data for the analysis=87	Bleeding: post-op chest drainage >8 mL/kg during the first 4 hrs in the ICU 33/87 (38%)	Unselected cohort Test before and at the end of surgery Reference ranges not stated	2x2 data AUROC
Ranucci 2011	Multiplate	English, Italy	Patients undergoing heart operations and treated with	Unable to undergo a complete preoperative MEA test.	Age=68; % females=22; N Patients=87; N	Excessive bleeding defined as >90th	Unselected cohort	2x2 data AUROC

[19]			dual anti-platelet therapy with P2Y12 inhibitors not discontinued at least 1 week before operation.		patients with data for the analysis=87	percentile of the distribution 14/87 (16%)	Pre-surgery multiplate value ADPtest <31	
Ranucci 2014 [20]	Multiplate	English, Italy	Patients undergoing heart operations and treated with dual anti-platelet therapy with P2Y12 inhibitors not discontinued at least 1 week before operation.	Not stated	Age=68; % females=21; N Patients=361; N patients with data for the analysis=361	>1l chest drain loss in 12hrs, need for surgical exploration or need for >5 units RBC or FFP 27/361 (8%)	Unselected cohort Pre-surgery multiplate value ADPtest <22 U TRAPtest ≥75	2x2 data, AUROC available but impossible to calculate standard errors
Ranucci 2018 [21]	Multiplate	English, Italy	Consecutive series of adult (≥18 years) patients undergoing cardiac surgery with cardiopulmonary bypass.	Unwillingness to participate, failure to obtain a written informed consent, surgery for congenital heart defects, and known congenital coagulopathy.	Age=median 70; % females=32; N Patients=490; N patients with data for the analysis=490	Severe bleeding = chest drain blood loss >1000 mL/12 h or need for surgical reexploration 40/490 (8%)	Unselected cohort Pre-surgery multiplate value ADPtest <8U, <16U, >18U	2x2 data AUROC
Reece 2011 [22]	Multiplate, Light transmission aggregometry (LTA)	English, UK	Patients undergoing routine CABG surgery.	Urgent or emergency surgery, previous sternotomy, severe renal or liver failure and known haemorrhagic diathesis.	Age=67; % females=14; N Patients=44; N patients with data for the analysis=44	Red cell transfusion 13/44 (30%)	Unselected cohort Test during and at the end of surgery ADTtest <31U TRAPtest >100U	2x2 data, AUROC available but impossible to calculate standard errors
Reinhofer 2008 [23]	ROTEM	English, Germany	Patients undergoing elective cardiac surgery and an expected on-pump time of at least 45 min.	Emergency surgery	Age=67; % females=31; N Patients=150; N patients with data for the analysis=150	Post-op blood loss >600ml 63/150 (42%)	Unselected cohort Test during and at the end of surgery and in ICU Normal reference ranges as proposed by the ROTEM manufacturer were used	2x2 data
Rymuza 2018 [24]	TEG	English, Poland	Patients with severe aortic stenosis treated with TAVI.	NA	Age=81; % females=56; N Patients=54; N patients with data for the analysis=54	Major or life-threatening bleeding 13/54 (24%)	Unselected cohort Test before and at the end of surgery MA < 46.6 mm	AUROC
Sivapalan 2017 [25]	TEG Platelet mapping	English, Denmark	Patients scheduled for elective CABG or combined CABG with aortic or mitral valve replacement using CPB.	Age below 18 years and non-CPB procedures	Age=69; % females=19; N Patients=199; N patients with data for the analysis=199	Fresh frozen plasma and/or platelet transfusion (FFP/PLT) 20/199 (10%)	Unselected cohort Test during and at the end of surgery and in ICU Normal ranges for Multiplate were ASPItest 92-151U ADPtest 79-141U TRAPtest 55-117U	AUROC

							Normal ranges for platelet mapping were: Maximum amplitude for ADP 45.0–69.0mm Maximum amplitude for arachidonic acid 51.0–71.0mm	
Slaughter 2001 [26]	PFA-100, Chronolog	English, USA	Adult patients scheduled to undergo elective primary CABG surgery.	Repeat or emergency surgery, pre-existing coagulation disorders, pre-operative treatment with platelet glycoprotein receptor inhibitors or fibrinolytic drugs, and hepatic or renal insufficiency.	Age=NA; % females=NA; N Patients=76; N patients with data for the analysis=58	CABG patients highest decile of bleeders (>646 ml/6 h) 6/58 (10%)	Unselected cohort Test during and at the end of surgery Collagen/ADP closure time >172 s	2x2 data
Ti 2002 [27]	TEG	English, Singapore	Patients undergoing elective multivessel CABG surgery.	Existing coagulopathies or abnormal reoperative coagulation screening tests.	Age=59; % females=20; N Patients=40; N patients with data for the analysis=40	>1000ml in 24hr or >250 within 2hrs 10/40 (25%)	Unselected cohort Test before and at the end of surgery Test positive if any parameter was >20% outside the normal range (K >16 mm, α <40°, or MA<40 mm)	2x2 data
Wasowicz 2010 [28]	TEG	English, Canada	Adult patients who underwent cardiac surgery with CPB.	Clopidogrel or warfarin within 5 days of surgery	Age=63; % females=32; N Patients=434; N patients with data for the analysis=434	Excessive blood loss was defined as transfusion of 5 units RBCs from end of CPB to 1 day post-op. 59/434 (14%)	Unselected cohort Test during and at the end of surgery MA<60 or values used as continuous variables	2x2 data, AUROC available but impossible to calculate standard errors
Weitzel 2012 [29]	Platelet mapping (Haemoscope)	English, USA	Patients undergoing primary cardiac surgery.	Known bleeding disorders; administration of direct thrombin inhibitors or clopidogrel; and re-sternotomy.	Age=58; % females=37; N Patients=40; N patients with data for the analysis=40	High bleeding (chest tube output 1000+ ml/24 h) vs low bleeding 12/40 (30%)	Unselected cohort Test during and at the end of surgery Cut points: TEG-MAthrombin post-CPB 58.2 TEG-MAcollagen pre-CPB 40.2 TEG-MAcollagen post-CPB 18.5 TEG-MAAA pre-CPB 57.5 TEG-MAAA post-CPB 9.8	2x2 data, AUROC available but impossible to calculate standard errors

Table S2: Summary of QUADAS 2 assessment of the risk of bias and sources of heterogeneity.

CPB – cardiopulmonary bypass, CABG - coronary artery bypass graft. TEG – thromboelastography, ROTEM - rotational thomboelastometry, LTA - Light Transmission Aggregometry, Hct - haematocrit, PT – prothrombin time, aPTT - , APTT activated partial thromboplastin time, INR - International Normalized Ratio, Hb – Haemoglobin, MPV - mean platelet volume, ACT - activated clotting time, NA – not available.

Paper	**Selection** **1.1 Was a consecutive or random sample of patients enrolled?** **1.2 Was a case-control design avoided?** **1.3 Did the study avoid inappropriate exclusions?** **1.4 Could the selection of patients have introduced bias?** **1.5 Are there concerns that the included patients do not match the review question?**		**Index test** **2.1 Describe the index test and how it was conducted and interpreted;** **2.2 Were the index test results interpreted without knowledge of the results of the reference standard?** **2.3 If a threshold was used, was it pre-specified?** **2.4 Could the conduct or interpretation of the index test have introduced bias?** **2.5 Are there concerns that the index test, its conduct, or interpretation differ from the review question?**		**Reference Standard** **3.1 Describe the reference standard and how it was conducted and interpreted;** **3.2 Is the reference standard likely to correctly classify the target condition?** **3.3 Were the reference standard results interpreted without knowledge of the results of the index test?** **3.4 Could the reference standard, its conduct, or its interpretation have introduced bias?** **3.5 Are there concerns that the target condition as defined by the reference standard does not match the review question?**		**Flow and Timing** **4.1 Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table** **4.2 Was there an appropriate interval between index test(s) and reference standard?** **4.3 Did all patients receive a reference standard?** **4.4 Did all patients receive the same reference standard?** **4.5 Were all patients included in the analysis?** **4.6 Could the patient flow have introduced bias?**	
Bischof 2015	1.1	Yes	2.1	Sonoclot test during and at end of surgery	3.1	Postop blood loss >800 mL in 4 hours	4.1	NA
	1.2	Yes	2.2	Unclear	3.2	Yes	4.2	Yes
	1.3	Yes	2.3	No	3.3	Yes	4.3	Yes
	1.4	RISK: LOW	2.4	RISK: UNCLEAR	3.4	RISK: LOW	4.4	Yes
	1.5	CONCERN: LOW	2.5	CONCERN: LOW	3.5	CONCERN: LOW	4.5	Yes
							4.6	RISK: Low
Cammerer 2003	1.1	Yes	2.1	PFA-100, TEG tested during and at the end of surgery. Anesthesiologists and surgeons were blinded to the results. The same person (TR) performed all measurements.	3.1	Blood loss >=500 mL (75th percentile) in 6 hour	4.1	N/A
	1.2	Yes	2.2	Unclear	3.2	No	4.2	Yes
	1.3	Yes	2.3	Yes	3.3	Unclear	4.3	Yes
	1.4	RISK: LOW	2.4	RISK: Unclear	3.4	RISK: UNCLEAR	4.4	Yes
	1.5	CONCERN: LOW	2.5	CONCERN: Unclear	3.5	CONCERN: UNCLEAR	4.5	Yes
							4.6	RISK: Low

Della Corte 2017	1.1	Yes	2.1	Pre-surgery Multiplate tests	3.1	75th percentile of blood losses (>450 ml) at 6 h.	4.1	
	1.2	Yes	2.2	Yes	3.2	No	4.2	Yes
	1.3	No	2.3	Yes	3.3	No	4.3	Yes
	1.4	RISK: High	2.4	RISK: High	3.4	RISK: High	4.4	Yes
	1.5	CONCERN: High	2.5	CONCERN: High	3.5	CONCERN: High	4.5	Unclear
							4.6	RISK: UNCLEAR
Davidson 2008	1.1	Yes	2.1	ROTEM pre-surgery and at 1, 2, and 3 hours after surgery. At the time of this study, the authors did not have access to the results and relied on laboratory assessment of coagulation.	3.1	Excessive bleeding post-op defined as >200ml/hr in one of the first four hours, or in the hour following the test	4.1	
	1.2	Unclear	2.2	Yes	3.2	No	4.2	Yes
	1.3	Yes	2.3	Yes	3.3	Yes	4.3	Yes
	1.4	RISK: Unclear	2.4	RISK: Low	3.4	RISK: High	4.4	Yes
	1.5	CONCERN: Unclear	2.5	CONCERN: Low	3.5	CONCERN: High	4.5	Unclear
							4.6	RISK: Unclear
Ereth 1997	1.1	Unclear	2.1	TEG during and at the end of surgery	3.1	>200 ml/hr chest tube drainage in 4hr plus a positive test result	4.1	
	1.2	Yes	2.2	Unclear	3.2	Yes	4.2	Yes
	1.3	Unclear	2.3	Unclear	3.3	No	4.3	Yes
	1.4	RISK: UNCLEAR	2.4	RISK: Unclear	3.4	RISK: High	4.4	No
	1.5	CONCERN: Unclear	2.5	CONCERN: Unclear	3.5	CONCERN: High	4.5	Unclear
							4.6	RISK: Unclear
Essel 1993	1.1	Yes	2.1	TEG during and at the end of surgery The surgeons were not aware of the TEG results. The need for re-exploration was based upon the clinical judgment of the attending cardiothoracic surgeon.	3.1	Abnormal bleeding >1500ml/24hrs or need to transfuse platelets/FFP to control haemorrhage.	4.1	1 patient who died was excluded
	1.2	Yes	2.2	No	3.2	Yes	4.2	Yes
	1.3	Unclear	2.3	No	3.3	Yes	4.3	Yes
	1.4	RISK: Unclear	2.4	RISK: HIGH	3.4	RISK: LOW	4.4	Yes
	1.5	CONCERN: LOW	2.5	CONCERN: UNCLEAR	3.5	CONCERN: LOW	4.5	No
							4.6	RISK: Low

Fattorutto 2003	1.1	No	2.1	PFA 100 during and at the end of surgery	3.1	Excessive mediastinal blood loss >200 ml for two hours	4.1	Following a randomization table, the aggregation studies were performed in 20 patients on platelet-rich plasma
	1.2	Yes	2.2	Unclear	3.2	No	4.2	Yes
	1.3	Yes	2.3	Unclear	3.3	Unclear	4.3	yes
	1.4	RISK: Unclear	2.4	RISK: Unclear	3.4	RISK: UNCLEAR	4.4	Yes
	1.5	CONCERN: Unclear	2.5	CONCERN: Unclear	3.5	CONCERN: UNCLEAR	4.5	No
							4.6	RISK: UNCLEAR
Kuliczkowski 2015	1.1	Yes	2.1	Pre-surgery multiplate value	3.1	Post-op drainage >610mL, median for the study group	4.1	9 patients were excluded from the study because their laboratory data were missing, and 6 patients were excluded due to missed clinical outcomes.
	1.2	Yes	2.2	No	3.2	No	4.2	Yes
	1.3	Yes	2.3	Unclear	3.3	No	4.3	Yes
	1.4	RISK: Low	2.4	RISK: HIGH	3.4	RISK: HIGH	4.4	Yes
	1.5	CONCERN: LOW	2.5	CONCERN: HIGH	3.5	CONCERN: HIGH	4.5	No
							4.6	RISK: Unclear
Kwak 2010	1.1	Unclear	2.1	Pre-surgery TEG value Anesthesiologists and cardiothoracic surgeons were were blinded to TEG platelet mapping assay results.	3.1	Red cell transfusion	4.1	1 patient not included in analysis
	1.2	Unclear	2.2	No	3.2	No	4.2	Yes
	1.3	No	2.3	No	3.3	No	4.3	Yes
	1.4	RISK: UNCLEAR	2.4	RISK: High	3.4	RISK: High	4.4	Yes
	1.5	CONCERN: UNCLEAR	2.5	CONCERN: UNCLEAR	3.5	CONCERN: High	4.5	No
							4.6	RISK: Low
Lee 2012	1.1	No	2.1	ROTEM Test during and at the end of surgery	3.1	>90th centile chest tube output	4.1	Not all patients received the index tests 16 patients had imputed reference outcome because of missing data
	1.2	Yes	2.2	Yes	3.2	No	4.2	Yes

	1.3	Unclear	2.3	Yes	3.3	Unclear	4.3	Yes
	1.4	RISK: Unclear	2.4	RISK: LOW	3.4	RISK: UNCLEAR	4.4	Yes
	1.5	CONCERN: UNCLEAR	2.5	CONCERN: LOW	3.5	CONCERN: UNCLEAR	4.5	No
							4.6	RISK: Unclear
Malm 2016	1.1	No	2.1	Pre-surgery multiplate value The findings of the preoperative platelet function tests were available to the surgical and anaesthetic team, but the analysis was always performed after the decision to operate, and consequently, not used as a decision tool for timing of surgery.	3.1	At least one must apply: i) chest drain loss >1000 ml in first 12 h after surgery; ii) delayed sternal closure; iii) need for surgical re-exploration due to bleeding or tamponade; iv) use of recombinant factor VIIa; v) transfusion of >5 units of RBCs within 24 h of chest closure; or vi) transfusion of >5 units of plasma within 24 h of chest closure..	4.1	2 patients did not undergo surgery
	1.2	No	2.2	Unclear	3.2	Yes	4.2	Unclear
	1.3	Yes	2.3	No	3.3	No	4.3	Yes
	1.4	RISK: Unclear	2.4	RISK: High	3.4	RISK: Unclear	4.4	Yes
	1.5	CONCERN: Unclear	2.5	CONCERN: HIGH	3.5	CONCERN: Low	4.5	No
							4.6	RISK: UNCLEAR
Meesters 2018	1.1	Unclear	2.1	ROTEM taken at induction and 3 minutes after protamine induction	3.1	Major blood loss >500 mL chest tube drainage at 6hrs (90th percentile)	4.1	
	1.2	Yes	2.2	No	3.2	No	4.2	Yes
	1.3	Unclear	2.3	No	3.3	No	4.3	Yes
	1.4	RISK: UNCLEAR	2.4	RISK: High	3.4	RISK: High	4.4	Yes
	1.5	CONCERN: Unclear	2.5	CONCERN: High	3.5	CONCERN: High	4.5	Yes
							4.6	RISK: LOW
Mishra 2015	1.1	Unclear	2.1	Pre and post operative Multiplate tests	3.1	Blood loss >2.5ml/kg/hr for first 3 hours	4.1	
	1.2	Yes	2.2	Unclear	3.2	Unclear	4.2	Yes
	1.3	Yes	2.3	Yes	3.3	Yes	4.3	Yes
	1.4	RISK: UNCLEAR	2.4	RISK: Unclear	3.4	RISK: UNCLEAR	4.4	Yes
	1.5	CONCERN: UNCLEAR	2.5	CONCERN: Unclear	3.5	CONCERN: UNCLEAR	4.5	Yes
							4.6	RISK: Low
Murphy 2017	1.1	Yes	2.1	Preoperative multiplate tests, and postoperatibe multiplate, TEG and ROTEM tests	3.1	Post-operative blood loss >600ml at 6hrs, intervention with haemostatic treatment i.e. platelets, FFP, cryo,	4.1	230/2427 (Coptic A) and 398/2231 (Coptic B) patients with

						additional protamine, reoperation for bleeding with no surgical cause identified		missing data were excluded
	1.2	Yes	2.2	Yes	3.2	Yes	4.2	Yes
	1.3	Yes	2.3	Yes	3.3	Yes	4.3	Yes
	1.4	RISK: Low	2.4	RISK: LOW	3.4	RISK: Low	4.4	Yes
	1.5	CONCERN: Low	2.5	CONCERN: LOW	3.5	CONCERN: Low	4.5	No
							4.6	Unclear
Petricevic 2013 (Plt. Fun. Testing)	1.1	Unclear	2.1	Pre-surgery Platelet Mapping	3.1	24 h chest tube output >= 75th percentile	4.1	2 patients excluded due to missing test results, 3 for clinical reasons
	1.2	Yes	2.2	Unclear	3.2	Unclear	4.2	Yes
	1.3	Unclear	2.3	No	3.3	Yes	4.3	Yes
	1.4	RISK: Unclear	2.4	RISK: HIGH	3.4	RISK: Unclear	4.4	Yes
	1.5	CONCERN: Unclear	2.5	CONCERN: LOW	3.5	CONCERN: Unclear	4.5	No
							4.6	RISK: Unclear
Petricevic 2013 (Plt+Visc. Fun. Testing)	1.1	Yes	2.1	Multiplate and ROTEM during and at the end of surgery	3.1	24 h chest tube output >= 75th percentile.	4.1	
	1.2	Yes	2.2	Unclear	3.2	Unclear	4.2	Yes
	1.3	Yes	2.3	Unclear	3.3	Yes	4.3	Yes
	1.4	RISK: LOW	2.4	RISK: Unclear	3.4	RISK: Unclear	4.4	Yes
	1.5	CONCERN: LOW	2.5	CONCERN: LOW	3.5	CONCERN: Unclear	4.5	Yes
							4.6	RISK: Low
Preisman 2010	1.1	Unclear	2.1	Pre-surgery Platelet Mapping	3.1	Re-exploration for bleeding	4.1	1 excluded from analysis
	1.2	Yes	2.2	Yes	3.2	Yes	4.2	Yes
	1.3	Yes	2.3	Yes	3.3	Yes	4.3	Yes
	1.4	RISK: Unclear	2.4	RISK: LOW	3.4	RISK: LOW	4.4	Yes
	1.5	CONCERN: LOW	2.5	CONCERN: LOW	3.5	CONCERN: LOW	4.5	No
							4.6	RISK: Low
Rajkumar 2017	1.1	Unclear	2.1	Sonoclot was performed on all patients at induction of anaesthesia, and after administration of	3.1	Bleeding: post-op chest drainage >8 mL/kg during the first 4 hrs in the ICU	4.1	

				protamine but before blood transfusions and closure of the chest.				
	1.2	Yes	2.2	No	3.2	Unclear	4.2	Yes
	1.3	Yes	2.3	No	3.3	Yes	4.3	Yes
	1.4	RISK: Unclear	2.4	RISK: Unclear	3.4	RISK: Unclear	4.4	Yes
	1.5	CONCERN: LOW	2.5	CONCERN: Unclear	3.5	CONCERN: Unclear	4.5	Yes
							4.6	RISK: LOW
Ranucci 2011	1.1	Unclear	2.1	Pre-surgery multiplate tests	3.1	Excessive bleeding defined as >90th percentile of the distribution	4.1	31 patients did not undergo testing or had missing data
	1.2	Yes	2.2	No	3.2	Unclear	4.2	Yes
	1.3	No	2.3	Unclear	3.3	No	4.3	Yes
	1.4	RISK: Unclear	2.4	RISK: HIGH	3.4	RISK: HIGH	4.4	Yes
	1.5	CONCERN: Unclear	2.5	CONCERN: Unclear	3.5	CONCERN: Unclear	4.5	No
							4.6	RISK: Unclear
Ranucci 2014	1.1	Yes	2.1	Pre-surgery multiplate tests	3.1	>1l chest drain loss in 12hrs, need for surgical exploration or need for >5 units RBC or FFP	4.1	74 patients with incomplete test results were excluded
	1.2	Yes	2.2	No	3.2	Yes	4.2	Yes
	1.3	Yes	2.3	No	3.3	No	4.3	Yes
	1.4	RISK: Unclear	2.4	RISK: HIGH	3.4	RISK: HIGH	4.4	Yes
	1.5	CONCERN: Unclear	2.5	CONCERN: Unclear	3.5	CONCERN: Unclear	4.5	No
							4.6	RISK: UNCLEAR
Ranucci 2018	1.1	Yes	2.1	Pre-surgery multiplate value	3.1	Severe bleeding = chest drain blood loss >1000 mL/12 h or need for surgical reexploration	4.1	490/840 potential candidates included in the analysis
	1.2	Yes	2.2	No	3.2	Yes	4.2	Yes
	1.3	Yes	2.3	No	3.3	No	4.3	Yes
	1.4	RISK: Low	2.4	CONCERN: High	3.4	RISK: Unclear	4.4	Yes
	1.5	CONCERN: Low	2.5	CONCERN: Unclear	3.5	CONCERN: Unclear	4.5	No
							4.6	RISK: Unclear
Reece 2011	1.1	Unclear	2.1	Multiplate and LTA during and at the end of surgery	3.1	Red cell transfusion	4.1	
	1.2	Yes	2.2	Yes	3.2	No	4.2	Yes

	1.3	Yes	2.3	Unclear	3.3	Yes	4.3	Yes
	1.4	RISK: Unclear	2.4	RISK: UNCLEAR	3.4	RISK: High	4.4	Yes
	1.5	CONCERN: LOW	2.5	CONCERN: UNCLEAR	3.5	CONCERN: High	4.5	Yes
							4.6	RISK: UNCLEAR
Reinhofer 2008	1.1	Unclear	2.1	ROTEM Test during and at the end of surgery and in ICU Clinical staff blinded to ROTEM data	3.1	Post-op blood loss >600ml	4.1	
	1.2	Yes	2.2	Unclear	3.2	No	4.2	Yes
	1.3	Yes	2.3	Yes	3.3	Unclear	4.3	Yes
	1.4	RISK: Unclear	2.4	RISK: UNCLEAR	3.4	RISK: Unclear	4.4	Yes
	1.5	CONCERN: Low	2.5	CONCERN: LOW	3.5	CONCERN: Unclear	4.5	Yes
							4.6	RISK: LOW
Rymuza 2018	1.1	Yes	2.1	TEG before and at the end of surgery. TAVI operators were blinded to the results of the test.	3.1	This was not specified clearly but indicated that major life-threatening bleeding was defined by VARC-2 criteria but treatment guidelines were not specified	4.1	
	1.2	Yes	2.2	No	3.2	Unclear	4.2	Yes
	1.3	Yes	2.3	No	3.3	Unclear	4.3	Yes
	1.4	RISK: LOW	2.4	RISK: High	3.4	RISK: UNCLEAR	4.4	Yes
	1.5	CONCERN: LOW	2.5	CONCERN: High	3.5	CONCERN: UNCLEAR	4.5	Yes
							4.6	RISK: Low
Sivapalan 2017	1.1	Unclear	2.1	Platelet mapping during and at the end of surgery and in ICU. MPA and PEA Results blinded to clinicians	3.1	Fresh frozen plasma and/or platelet transfusion (FFP/PLT)	4.1	
	1.2	Yes	2.2	Yes	3.2	Yes	4.2	Yes
	1.3	Yes	2.3	Yes	3.3	Yes	4.3	Yes
	1.4	RISK: UNCLEAR	2.4	RISK: LOW	3.4	RISK: Low	4.4	Yes
	1.5	CONCERN: LOW	2.5	CONCERN: LOW	3.5	CONCERN: LOW	4.5	Yes
							4.6	RISK: LOW
Slaughter 2001	1.1	Unclear	2.1	PFA-100 and chronology tests during and at the end of surgery Transfusion of blood products was left to the discretion of the patient's surgical team who were blinded to results.	3.1	CABG patients highest decile of bleeders (>646 ml/6 h).	4.1	Evaluated PFA in 58/76 patients

	1.2	Yes	2.2	Unclear	3.2	No	4.2	Yes
	1.3	Yes	2.3	No	3.3	Unclear	4.3	Unclear
	1.4	RISK: Unclear	2.4	RISK: Unclear	3.4	RISK: Unclear	4.4	Unclear
	1.5	CONCERN: Low	2.5	CONCERN: Unclear	3.5	CONCERN: Unclear	4.5	Yes
							4.6	RISK: UNCLEAR
Ti 2002	1.1	Unclear	2.1	TEG before and at the end of surgery The surgeon and anaesthesiologist were blinded to the result of thromboelastography.	3.1	>1000ml in 24hr or >250 within 2hrs.	4.1	
	1.2	Yes	2.2	Unclear	3.2	Unclear	4.2	Yes
	1.3	Yes	2.3	Yes	3.3	Yes	4.3	Yes
	1.4	RISK: UNCLEAR	2.4	RISK: UNCLEAR	3.4	RISK: Unclear	4.4	Yes
	1.5	CONCERN: UNCLEAR	2.5	CONCERN: UNCLEAR	3.5	CONCERN: Unclear	4.5	Yes
							4.6	RISK: LOW
Wasowicz 2010	1.1	Yes	2.1	TEG during and at the end of surgery. A dedicated technician performed all tests and reported the results to the attending anaesthesiologist.	3.1	Excessive blood loss was defined as transfusion of 5 units RBCs from end of CPB to 1 day post-op.	4.1	Not all patients received the tests, only high risk, as part of standard care
	1.2	Yes	2.2	No	3.2	Yes	4.2	Yes
	1.3	No	2.3	Unclear	3.3	No	4.3	Yes
	1.4	RISK: High	2.4	RISK: HIGH	3.4	RISK: High	4.4	Yes
	1.5	CONCERN: Unclear	2.5	CONCERN: HIGH	3.5	CONCERN: HIGH	4.5	No
							4.6	RISK: Unclear
Weitzel 2012	1.1	Unclear	2.1	Platelet mapping during and at the end of surgery	3.1	High bleeding (chest tube output 1000+ ml/24 h) vs low bleeding.	4.1	
	1.2	Yes	2.2	No	3.2	No	4.2	Yes
	1.3	Yes	2.3	Yes	3.3	No	4.3	Yes
	1.4	RISK: UNCLEAR	2.4	RISK: UNCLEAR	3.4	RISK: High	4.4	Yes
	1.5	CONCERN: LOW	2.5	CONCERN: UNCLEAR	3.5	CONCERN: High	4.5	Yes
							4.6	RISK: LOW

Table S3: GRADE assessment whether point of care tests should be used to diagnose bleeding in cardiac surgery. [a] The index test threshold was not prespecified in all studies and the results were not interpreted without the knowledge of the reference standard. Results of the reference standard were not interpreted without the knowledge of the index test in all studies. [b] Low number of patients, wide confidence intervals.

Type	Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
				Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
Viscoelastic tests	**True positives** (patients with Bleeding)	12 studies 391 patients	cohort & case-control type studies	serious [a]	not serious	serious [b]	not serious	none	147 (106 to 183)	⊕⊕◯◯ LOW
	False negatives (patients incorrectly classified as not having Bleeding)								94 (58 to 135)	
	True negatives (patients without Bleeding)	12 studies 1732 patients	cohort & case-control type studies	serious [a]	not serious	serious [b]	not serious	none	630 (531 to 691)	⊕⊕◯◯ LOW
	False positives (patients incorrectly classified as having Bleeding)								129 (68 to 228)	
Platelet function tests	**True positives** (patients with Bleeding)	12 studies 572 patients	cohort & case-control type studies	serious [a]	not serious	very serious [b]	not serious	none	158 (133 to 180)	⊕◯◯◯ VERY LOW
	False negatives (patients incorrectly classified as not having Bleeding)								92 (70 to 117)	
	True negatives (patients without Bleeding)	12 studies 1804 patients	cohort & case-control type studies	serious [a]	not serious	very serious [b]	not serious	none	563 (480 to 630)	⊕◯◯◯ VERY LOW
	False positives (patients incorrectly classified as having Bleeding)								187 (120 to 270)	

TEG mod. tests	**True positives** (patients with Bleeding)	3 studies 50 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	serious [b]	none	176 (147 to 196)	⨁⨁◯◯ LOW
	False negatives (patients incorrectly classified as not having Bleeding)								44 (24 to 73)	
	True negatives (patients without Bleeding)	3 studies 150 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	serious [b]	none	593 (538 to 640)	⨁⨁◯◯ LOW
	False positives (patients incorrectly classified as having Bleeding)								187 (140 to 242)	

Table S4 Summary of Diagnostic Accuracy Estimates (95%CI) for Viscoelastic, Platelet Function tests and TEG modification tests.

TP – true positives, FN – false negatives, FP – false positives, TN – true negatives, 95% CI – 95% confidence intervals. X2 test was used to determine heterogeneity levels for sensitivities and pecificities and p-values < 0.05 indicate that estimates of sensitivity and specificity are not homogenous.

Test	Paper	TP	FN	FP	TN	N	Sensitivity	Lower 95% CI	Upper 95% CI	Specificity	Lower 95% CI	Upper 95% CI
Viscoelastic	Bischof 2015	41	6	69	184	300	0.87	0.74	0.94	0.73	0.67	0.78
	Cammerer 2003	41	28	59	127	255	0.59	0.48	0.70	0.68	0.61	0.74
	Davidson 2008	8	0	1	48	57	0.94	0.63	0.99	0.97	0.88	0.99
	Ereth 1997	12	3	39	146	200	0.78	0.54	0.92	0.79	0.72	0.84
	Essel 1993	5	2	3	25	35	0.69	0.36	0.90	0.88	0.72	0.96
	Lee 2012	4	18	4	189	215	0.20	0.08	0.40	0.98	0.95	0.99
	Meesters 2018	14	7	67	114	202	0.66	0.45	0.82	0.63	0.56	0.70
	Petricevic 2013 [20]	32	5	63	48	148	0.86	0.71	0.93	0.43	0.35	0.53
	Rajkumar 2017	25	8	20	34	87	0.75	0.58	0.87	0.63	0.50	0.74
	Reinhofer 2008	11	52	4	83	150	0.18	0.11	0.29	0.95	0.88	0.98
	Ti 2002	10	0	8	22	40	0.96	0.68	1.00	0.73	0.55	0.85
	Wasowicz 2010	20	39	14	361	434	0.34	0.23	0.47	0.96	0.94	0.98
	All data					**2224**	**0.61**	**0.44**	**0.76**	**0.83**	**0.70**	**0.91**
	Chi-squared test to assess hetorogeneity						**Chi-sq = 115.689, df = 11, p <0.001**			**Chi-sq = 280.270, df = 11, p <0.001**		
Platelet function tests	Cammerer 2003	27	42	53	133	255	0.39	0.29	0.51	0.71	0.65	0.77
	Fattorutto 2003	3	1	8	58	70	0.70	0.30	0.93	0.87	0.77	0.93
	Kuliczkowski 2015	163	76	129	110	478	0.68	0.62	0.74	0.46	0.40	0.52
	Malm 2016	24	8	14	44	90	0.74	0.57	0.86	0.75	0.63	0.85
	Mishra 2015	20	3	1	60	84	0.85	0.67	0.95	0.98	0.90	0.99
	Petricevic 2013 [72]	39	11	86	75	211	0.78	0.64	0.87	0.47	0.39	0.54
	Petricevic 2013 [20]	28	9	47	64	148	0.75	0.59	0.86	0.58	0.48	0.66
	Ranucci 2011	10	4	25	48	87	0.70	0.45	0.87	0.66	0.54	0.75
	Ranucci 2014	13	14	43	291	361	0.48	0.31	0.66	0.87	0.83	0.90
	Ranucci 2018	25	15	100	350	490	0.62	0.47	0.75	0.78	0.74	0.81
	Reece 2011	10	21	0	13	44	0.33	0.19	0.50	0.96	0.73	1.00

	Slaughter 2001	4	2	11	41	58	0.64	0.30	0.88	0.78	0.66	0.87
	All data					**2376**	**0.63**	**0.53**	**0.72**	**0.75**	**0.64**	**0.84**
	Chi-squared test to assess hetorogeneity						**Chi-sq = 49.317, df = 11, p <0.001**			**Chi-sq = 219.038, df = 11, p <0.001**		
TEG modif.	Kwak 2010	23	6	18	54	101	0.79	0.62	0.90	0.75	0.64	0.84
	Preisman 2010	7	2	8	42	59	0.78	0.45	0.94	0.84	0.72	0.92
	Weitzel 2012	10	2	9	19	40	0.83	0.55	0.95	0.68	0.49	0.82
	All data					**200**	**0.80**	**0.67**	**0.89**	**0.76**	**0.69**	**0.82**
	Chi-squared test to assess hetorogeneity						**Chi-sq = 0.120, df = 2, p = 0.942**			**Chi-sq = 2.830, df = 2, p = 0.243**		

Table S5 Heterogeneity analysis for sensitivity and specificity in subgroups defined by pre-specified sources of heterogeneity.

Prespecified sources of heterogeneity were included in bivariate models as covariates and compared with models without them using likelihood ratio test (ANOVA). P-values greater than 0.05 indicate that the included covariate does not significantly change the model and hence has no influence on the levels of heterogeneity. Due to small number of studies low risk/concern groups were compared with merged high/unclear groups.

Tests	Heterogeneity source	Subgroup	N	Likelihood-ratio test p-value
Viscoelastic	Selection Bias	Low risk	3	0.155
		High/Unclear risk	9	
	Selection applicability	Low concern	6	0.282
		High/Unclear Concern	6	
	Index test bias	Low risk	2	0.060
		High/Unclear risk	10	
	Index test applicability	Low concern	5	0.566
		High/Unclear Concern	7	
	Reference outcome bias	Low risk	2	0.096
		High/Unclear risk	10	
	Reference outcome applicability	Low concern	2	0.096
		High/Unclear Concern	10	
Platelet function	Selection Bias	Low risk	4	0.112
		High/Unclear risk	8	
	Selection applicability	Low concern	6	0.083
		High/Unclear Concern	6	
	Index test bias	Low risk	0	NA
		High/Unclear risk	12	
	Index test applicability	Low concern	2	0.063
		High/Unclear Concern	10	
	Reference outcome bias	Low risk	0	NA
		High/Unclear risk	12	
	Reference outcome applicability	Low concern	1	0.650
		High/Unclear Concern	2	

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