Prediction of bleeding in paediatric cardiac surgery using clinical characteristics and prospective coagulation test results

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| Corresponding Author: | andrew mumford, MB ChB PhD  
University of Bristol School of Clinical Science  
UNITED KINGDOM |
| Corresponding Author's Institution: | University of Bristol School of Clinical Science |
| First Author:      | Jessica Harris, BSc |
| Order of Authors:  | Jessica Harris, BSc  
Karen Sheehan, Msc  
Chris Rogers, BSc, PhD  
Tim Murphy, MBBS, FRCA  
Massimo Caputo, MD, MCh  
Andrew Mumford, MB ChB PhD |
| Keywords:          | Coagulation testing; paediatric cardiac surgery; bleeding; predictive models; coagulopathy |

**Question**

**Response**

Prospective coagulation testing offers little additional benefit to prediction of bleeding in children undergoing cardiac surgery when compared to prediction using clinical characteristics alone.

Excessive bleeding from coagulopathy causes adverse outcomes in children having cardiac surgery. Rapid coagulation testing for diagnosis of coagulopathy improves outcomes but has uncertain utility for prediction of bleeding. We show that prospective coagulation testing does predict bleeding but has little additional value compared to prediction using the clinical characteristics of children alone.

Bleeding prediction models improves little after including coagulation test results

Is this manuscript a clinical trial that requires registration at www.clinicaltrials.gov per ICMJE rules?

**Response:** no
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<td>Do you have any patents, whether planned, pending or issued, broadly relevant to the work?</td>
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<td>Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?</td>
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Prediction of bleeding in paediatric cardiac surgery using clinical characteristics and prospective coagulation test results

Jessica M Harris BSc, MSc, PhD¹, Karen Sheehan MSc², Chris A Rogers BSc, PhD¹, Tim Murphy MBBS FRCA², Massimo Caputo MD MCh²,³,⁴, Andrew D Mumford MB ChB PhD⁵

1. Bristol Trials Centre, Faculty of Health Sciences, University of Bristol, Bristol, UK.
2. Department of Paediatric Cardiac Surgery, Bristol Royal Hospital for Children, University Hospitals Bristol, Bristol, UK.
3. Bristol Heart Institute, University Hospitals Bristol, Bristol, UK.
4. Department of Paediatric Cardiac Surgery, School of Translational Sciences, University of Bristol, Bristol, UK.
5. Department of Haematology, School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK.

Conflicts of Interest: The authors declare no relevant conflicts of interest

Funding statement: The study was supported by the UK National Institute for Health Research through the Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol, and the British Heart Foundation.

Corresponding author: Professor Andrew Mumford, School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK. Email a.mumford@bristol.ac.uk

Clinical trial registration: ISRCTN55439761

NHS Research Ethics Committee: approval 13/LO/0504 (2013)

Key Words: Coagulation testing; Paediatric Cardiac Surgery; Bleeding; Predictive models; Coagulopathy

Manuscript length: Total 3498 words; Abstract 250 words; Figures 3; Tables 4; Supplementary file 1; References 34
Prediction of bleeding in paediatric cardiac surgery using clinical characteristics and coagulation test results

1. Response to Seminars editor's comments

There is interest in considering your paper for publication in Seminars given its relevance to the field. However, reviewer comments have pointed out some persistent concerns. In particular, the authors should address the concerns raised by reviewer #2 with respect to the data as presented. The manuscript should also more clearly recognize the limited generalizability, especially given the study design and the very small number of neonates/circulatory arrest procedures. A final decision to publish will be made if these major concerns are adequately addressed.

Response: Thank you for giving us a further opportunity to respond to the reviewer’s comments. We are encouraged by the overall positive responses from reviewer 1 and 3 and the statistical editor. Reviewer 4 has highlighted some cautions about interpretation that we have highlighted clearly in the strengths and weaknesses section.

We have now carefully addressed the additional comments from reviewer 2. For most comments, we have made positive changes to the manuscript and in a minority clarified with the reviewer.

The major criticism for reviewer 2 concerned exclusion of neonates (<2.5 Kg) because of a necessary research ethics constraint caused by the relatively large blood volume required for comprehensive coagulation testing. Despite this constraint, we chose not to proceed with a smaller blood sample volume because this would have compromised the scope of coagulation testing for all children in the study. This potentially could have resulted in an underestimate of the utility of prospective coagulation testing.

For complete transparency, we have acknowledged in our discussion that our findings cannot be generalised to the neonatal group (new sentence at lines 381-383 This constraint precluded inclusion of neonates in which bleeding is prevalent and prevents generalisation of our findings to this age group’). We don’t believe that this devalues the importance of our findings in any of the other age groups which were well represented in our study.

We have made some further small changes to the text without alteration of meaning in order to maintain the word limit of 3,500.
2. **Response to reviewers**

**Reviewer #1:** The only suggestion I would make for further clarifying or improving the paper is to further emphasize the difference between the use of coagulation testing to predict vs to treat excessive bleeding. I believe this could be effectively done by stating the former as "prospective laboratory testing" or something similar. This would ensure that the reader is aware of the difference between laboratory testing before any clinical evidence of bleeding is noted.

**Response:** Thank you for this helpful suggestion. We have amended the manuscript throughout where appropriate.

**Changes:** The term ‘prospective’ or ‘prospective coagulation tests’ has been inserted at the following positions:

| Title- page 1 |
| Central picture legend- page 3 |
| Central Message- page 3 |
| Perspective statement- page 3 |
| Abstract-page 4 |
| Introduction- pages 5 and 6 |
| Results- page 12 |
| Discussion- pages 14,15, 16, 17,18 |
| Figure 2 legend- page 24 and 25 |
| Figure 4 (graphical abstract) legend- page 26 |

**Reviewer #2:**

1. Clinical management of patients: The authors have revised their primary endpoint from excessive bleeding to clinical concern for bleeding (CCB), parallel to that from a previous adult study by the same group. Their response is still unsatisfactory. The following issues beg for either clarification in the methods, or at the very least some mention of them in the discussion as weaknesses in the study design.

   a. Clinical decision making remains subjective, and no clear algorithm or protocol for guiding the decision making has been outlined. This reviewer joins Reviewer 4, in asking for further clarification regarding institutional practices and protocols.

**Response:** In our revised manuscript, we significantly increased the description of the institutional practices and protocols. Within the manuscript length constraint, we believe that this gives the reader sufficient information relevant to our blood management practice. We have now introduced a new reference from our centre that give more detail about other aspects of anaesthetic and surgical management in place at the time of the study.
b. The authors clarify that any transfusion treatment not specifically documented as a response to bleeding is not classified as the primary outcome. This opens the possibility for undermeasurement of the primary outcome. Some estimation of how often this occurred, or inclusion of this as a limitation is requested.

Response: The reviewer correctly identifies that accurate capture of the primary outcome required our clinical teams to identify whether a pro-haemostatic treatment was ‘in response to bleeding’ or was a ‘pre-planned preventative treatment’. For every treatment administered during the study interval this was actively recorded on the case report form. All ‘treatments in response to bleeding’ identified on the case report form (crf) were checked by the research team to ensure correct designation as part of the primary outcome. This procedure is documented in Methods page 8, paragraph 1.

As expected, the vast majority of pro-haemostatic interventions (eg protamine at the end of CPB) were pre-planned preventative treatments and therefore were not part of the primary outcome. Haemostatic treatments give at times other than the well demarcated periods during the study interval when pre-planned preventative treatments are usually given would have been obvious during the crf review process and correct designation ensured. Therefore, the likelihood of incorrect designation leading to underestimation of the primary outcome is likely zero or very low. We have amended the ‘strengths and limitations’ section to recognise this as a small possibility.

Changes: Sentence ‘Conversely a very small number of children may have received treatments in response to bleeding that were not documented as such.’ Has now been inserted into Discussion page 17, paragraph 1.

2. Clarity of the models: Although the authors explain to the statistical editor that the fractional polynomial method was chosen to account for nonlinearity of terms, the very process of the fractional polynomial regression method remains totally opaque. Statistical processes should be explained to the readership in sufficient detail such that if the authors were to send the reader a copy of their data file, the reader should be able to follow their methods and reproduce their findings. If the details are lengthy or technically tedious, then a supplemental online file or reference to previously published methods (again, with sufficient detail) may be provided.

Response: In the previous revision we included a reference for readers who may be unfamiliar with this approach (reference #27). We have also edited the text slightly and named the Stata command. We believe the information provided details the steps taken in sufficient detail that would allow for reproduction by a
a. The number of proposed variables, in light of a population of 225 subjects, provokes the question of overfitting of the model. This could be addressed if the authors were to show their methods for selection of the clinical variables with their predefined integer and fractional power terms (intrinsic to the fractional polynomial method), and describe in detail the stepwise iterative technique.

Response: The backward elimination process was automated by the software and we have edited the text (line 217) to reflect this. The number of proposed variables was minimised by wrapping the baseline characteristics into a single “score”, then models only included this score plus 17 laboratory parameters which we believe is not excessive. The specific laboratory parameters were selected a priori from a more extensive list, with the aim of avoiding over-fitting the data. Final models only included one or two predictive laboratory parameters (see Table S5) so we feel there is little concern about over-fitting.

Response: The models that quantified the associations between the pre-operative characteristics and the primary outcome are displayed in Figures 2 and 3. The final models after automated backwards stepwise selection are shown in Table S5. There are no iterative summaries available in Stata and we believe there is sufficient reporting of the models.

Changes: No changes have been made to the manuscript

b. The resulting model, with iterative summary, needs to be shown even if the primary aim of the study was to evaluate solely the contribution of coagulation tests. The reason is this: Suppose the study involved risk factors for postoperative atrial fibrillation in adults cardiac surgery. If the primary aim involved some medical or surgical intervention, the results would be meaningless (if not undetectable) if the authors did not account for the overwhelming impact of age, and show the magnitude of age (and other clinical factors) on their measured outcomes. Showing the models would also reveal the amount of variability accounted for, some measure of goodness-of-fit, and whether overfitting was a problem. The readership deserves to see these features in the statistical approach.

Response: The models that quantified the associations between the pre-operative characteristics and the primary outcome are displayed in Figures 2 and 3. The final models after automated backwards stepwise selection are shown in Table S5. There are no iterative summaries available in Stata and we believe there is sufficient reporting of the models.

Changes: No changes have been made to the manuscript

c. The authors claim that at the time of study design, evidence for resternotomy as a bleeding risk factors was not as strong as it is now. In response, resternotomy has been recognized as a strong bleeding risk factor for decades. Resternotomy was
identified as a major risk factor by Williams et al in their classic study in 1999 (Anesth Analg 89:57), and many times since then (Gomez et al, Transfus Alt Transfus Med 2002 4:27). Duke's DCRI identified resternotomy as a specific risk group in children, and the role of aprotinin in alleviating this risk specifically. This was in 2012, the year before the current study enrollment began. Inclusion of significant clinical risk factors may, again despite what the authors claim, alter the results of the study since accounting for more variability in the outcome often allows the detection of other weaker risk factors. Again, in studies involving postoperative atrial fibrillation, inclusion of strong risk factors, such as age and beta blocker withdrawal, is done so that the impact of weaker risk factors can be detected. This reviewer would like to see either (1) resternotomy included in the clinical models (with the models shown), or (2) a more defensible reason why resternotomy was not included (it was captured, as the authors mention).

Response: We thank this reviewer for presenting evidence of the importance of sternotomy as a risk factor. We accept this as a fair criticism because in retrospect we gave this insufficient priority in the original study design resulting in its omission from the clinical predictive models.

In our revised manuscript, we included the frequency of resternotomy in the description of the clinical characteristics of the cases (table 1) after reinspection of clinical records. However, since this characteristic was not *pre-specified* in our statistical analysis plan we believe that it is inappropriate to repeat the analyses with resternotomy included post hoc. We highlight to the reviewer that the main objective of the study was to examine the effect of adding prospective coagulation test results to a baseline clinical predictive model. Omission of resternotomy may have slightly reduced the predictive value of the baseline clinical characteristics models, but also the combined models which included the coagulation test results. Therefore, this omission is very unlikely to have altered the difference between the models and the overall conclusion. This point is made in our revised manuscript in the strengths and limitations section discussion, page 17, lines 383-388.

Changes: We have made no further changes to the manuscript.

e. Table S5 again contains odds ratios less than one for two anti-Xa terms which are inversely related to each other. The interpretation of this is that both high anti-Xa levels and low anti-Xa levels are protective for CCB. Linear or nonlinear, this makes no clinical sense. In addition, there is an odds ratio of 10^-28, which is essentially zero, while the same variable raised to the -3/2 power has an odds ratio no different from 1 (it should be closer to infinity since the two variables are inversely related). Aside from being implausible, this truly makes one wonder about spurious associations arising from algebraic manipulations (fractional powers) of the data, and whether the fractional polynomial regression method is appropriate here.
Response: The nature of fractional polynomial regression models mean that the most-complex permitted fractional polynomial model is fitted and then simplified as much as possible by the statistical software. Whilst it appears that these two factors are in conflict, the terms would always be fitted together not in isolation, and together best describe the relationship between anti-Xa and the primary outcome. Table S5 presents a transparent summary of the multivariate fractional polynomial models and highlights which laboratory terms are selected as contributing to the final model. We believe the key message to the reader is which terms are selected rather than the final estimates as these are complex to attempt to interpret in isolation.

Changes: No changes to the manuscript

3. (Incorrectly listed as 4 in original critique) Patient population:
   a. Again, the authors argue that refinements in clinical prediction would not alter their conclusions regarding the contribution of coagulation testing. See 2c above. The acknowledgement in the limitations regarding additional age classifications is appreciated.

Response: Thank you

b. It should be pointed out that this population, having very few neonates, is missing the segment of the cardiac surgery population most at risk for bleeding complications, so application to populations which have appreciable numbers of neonates may be limited.

Response: We have already highlighted the likely reason why neonates were underrepresented in the study population in the strengths and limitations section of Discussion. To be explicit about the potential effect of this we have inserted a further sentence to this section.

Changes: Discussion page 17, lines 381-383: insertion of the sentence ‘This constraint precluded inclusion of neonates in which bleeding is prevalent and prevents generalisation of our findings to this age group’.

Reviewer #3: No further points raised

Response: Thank you

Reviewer #4: The authors have addressed many of the reviewers’ concerns. They have put considerable effort into clarifying the outcome measures employed specifically changing the primary outcome from excessive bleeding (EB) to clinical concern of bleeding (CCB). However, the subjective nature of this outcome measure
remains a major flaw in study design. Furthermore, the generalizability of the results is questionable given the low incidence of significant bleeding (99% of patients received 0-1 units of allogenic blood products), the low number of neonates, and the avoidance of deep hypothermia. Ultimately, the results of this work must be interpreted with caution. While coagulation testing may not be superior to clinical characteristic modeling in the prediction of bleeding, it has been consistently linked to improve outcomes through goal direction of component therapy.

**Response:** We thank the reviewer for articulating these concerns. We believe that the specific changes requested by reviewer 1 and 2 further clarify the message and that the current manuscript adequately highlights the se points in the improved 'strengths and limitations' section.

**Associated Statistical Editor:** No additional points

**Response:** Thank you
Revision Requirements

Please revise your manuscript promptly. Revised manuscripts fare best when the
care concerns are fresh in the mind of the reviewer. Your revision must be submitted
by Dec 02, 2020. You may request a deadline extension if extensive revisions or
new experiments are requested by the reviewers.

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Please provide a point-by-point response to the Editors’ and reviewers’ comments
and for each comment indicate what changes were made to the manuscript.
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   2. The author(s) response
   3. What Changes were made to the manuscript (and specify the lines) or explain
      why no changes were made.

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Clearly identify each version by using different file names.

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8. Be sure that all figures meet the requirements for print publication. All figures must be in a .tiff or .jpeg format; line art and illustration need to be at 1200 dpi resolution, and photographs must be at 300 dpi resolution. Failure to do this at the revision stage will mean delay in publication if your manuscript is accepted.

In the event that the revisions raise additional concerns, we will take the liberty to have the manuscript re-reviewed.

Thank you for submitting this excellent study to the Journal. We look forward to hearing from you.

Regards,

Richard D. Weisel, MD, Editor
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David Zurakowski, MSc, PhD, Associate Statistical Editor
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1. Bristol Trials Centre, Faculty of Health Sciences, University of Bristol, Bristol, UK.
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Clinical trial registration: ISRCTN55439761

NHS Research Ethics Committee: approval 13/LO/0504 (2013)

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Supplementary file 1; References 34
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<thead>
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<th>Abbreviation</th>
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<td>Anti-Xa</td>
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<td>Activated partial thromboplastin time</td>
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<td>Clinical concern about bleeding</td>
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<td>MUF</td>
<td>Modified ultra-filtration</td>
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CENTRAL PICTURE LEGEND: Bleeding prediction models improves little after including prospective coagulation test results.

CENTRAL MESSAGE: Prospective coagulation testing offers little additional benefit to prediction of excessive bleeding in children undergoing cardiac surgery when compared to prediction using clinical characteristics alone.

PERSPECTIVE STATEMENT: Excessive bleeding because of coagulopathy causes adverse outcomes in children having cardiac surgery. Rapid coagulation testing to help selection of treatments for bleeding improves outcomes but has uncertain utility for predicting whether bleeding will occur. We show that prospective coagulation testing has little additional value compared to prediction using the clinical characteristics of children alone.
ABSTRACT

Objective: Bleeding caused by coagulopathy is common in children undergoing cardiac surgery and causes adverse outcomes. Coagulation testing assists selection of treatments to stop bleeding but has an uncertain role for predicting bleeding. We aimed to evaluate how well prospective coagulation testing predicted excessive bleeding during and after cardiac surgery compared to prediction using clinical characteristics alone.

Methods: A single centre, prospective cohort study in children having a range of cardiac surgery procedures with coagulation testing at anaesthetic induction and immediately after cardio-pulmonary bypass. The primary outcome was clinical concern about bleeding (CCB), a composite of either administration of pro-haemostatic treatments in response to bleeding or a high chest drain volume after surgery.

Results: In 225 children, CCB occurred in 26 (12%) during surgery and in 68 (30%) after surgery. Multivariable fractional polynomial models using the clinical characteristics of the children alone predicted CCB during surgery (c-statistic 0.64; 95% confidence interval 0.53, 0.76) and after surgery (0.74; 0.67, 0.82). Incorporating coagulation test results into these models improved prediction (c-statistics 0.79; 0.70, 0.87 and 0.80; 0.74, 0.87 respectively). However, this increased the overall proportion of children classified correctly as CCB or not CCB during surgery by only 0.9% and after surgery by only 0.4%. Incorporating coagulation test results into predictive models had no effect on prediction of blood transfusion or post-operative complications.

Conclusions: Prospective coagulation testing marginally improves prediction of CCB during and after cardiac surgery but the clinical impact of this is small when compared to prediction using clinical characteristics.
INTRODUCTION

Microvascular bleeding caused by coagulopathy and blood transfusion in response to bleeding are common after cardiac surgery in children\(^1\),\(^2\) and are independent predictors of morbidity and mortality.\(^3\),\(^4\) Coagulopathy is typically complex and may include reduced levels or reduced function of platelets, coagulation factors or fibrinogen.\(^5\) These changes may relate to the age of children, underlying cardiac disease or medication before cardiac surgery\(^6\),\(^7\) or to interventions that occur during surgery, particularly heparin anticoagulation, hypothermia and cardiopulmonary bypass (CPB).\(^8\)-\(^10\)

Coagulation testing using point-of-care viscoelastometry or rapid platelet function testing detects major components of coagulopathy during cardiac surgery in children.\(^7\),\(^11\),\(^12\) In retrospective case control studies, viscoelastometry-assisted selection of treatments reduced blood component use in children who developed excessive bleeding.\(^13\),\(^14\) In a randomised controlled trial of children with excessive bleeding, viscoelastometry resulted in less bleeding and blood transfusion.\(^15\) Further support for the utility of blood management algorithms that include diagnostic coagulation test results has been reproduced in other recent studies\(^16\)-\(^18\).

An alternative strategy is to perform **prospective testing** before bleeding occurs, potentially enabling preventative treatments in children at greatest risk or the pre-ordering of treatments for immediate administration if bleeding starts. However, most previous studies of **prospective testing** for prediction of bleeding have evaluated only small patient cohorts using limited repertoires of coagulation tests and have yielded inconsistent findings.\(^15\),\(^19\)-\(^21\) In studies of larger cohorts of children, predictive models for excessive bleeding have
incorporated both coagulation test results and the clinical characteristics of children, thereby obscuring the utility of coagulation testing alone.\textsuperscript{1, 22, 23}

We performed the Detection of Coagulopathy in Paediatric Heart Surgery (DECISION) study to investigate how well prospective coagulation testing predicts excessive bleeding in children undergoing cardiac surgery, compared with prediction using clinical characteristics alone.

\section*{METHODS}

\textbf{Study design and patients}

The DECISION study was a prospective single-centre observational cohort study conducted at University Hospitals NHS Foundation Trust between May 2013 and April 2015 in accordance with the Declaration of Helsinki and United Kingdom NHS Research Ethics Committee approval 13/LO/0504.

Children were eligible if they were aged 16 years or younger, had a body weight of more than 2.5 Kg and were listed for any non-emergency cardiac surgery procedure requiring CPB. Children were ineligible if undergoing isolated ostium secundum ASD repair in which bleeding risk is very low, or if they required emergency cardiac surgery. Parental consent was obtained for children younger than 16 years. Direct consent was obtained for children aged 16 years. A detailed study protocol is reported elsewhere.\textsuperscript{24}

\textbf{Surgical and blood management procedures}

All the children were managed according to a standard institutional anaesthetic protocol described previously\textsuperscript{25}. A bolus dose of heparin 300–400 units/Kg was administered before
aortic cannulation with additional doses of 100 units/kg to maintain an activated clotting time (ACT) >400 s. Protamine (10 mg/1000 units of heparin administered) was given at the end of CPB with additional boluses of 2-4 mg given sequentially until the ACT was <150s. Protamine was also administered after return of pump blood (5mg/100ml) which was also ultra-filtrated for all neonates and children <10Kg. Tranexamic acid (30-80 mg/kg total dose) and cell-savers for redo procedures and for complex aortic valve procedures were used according to the discretion of the anaesthesiologist. The administration of tranexamic acid and protamine as part of this standard protocol was planned before surgery and not given in response to abnormal bleeding. These interventions were classified as pre-planned preventative treatments.

Anesthesiologists also administered pro-haemostatic treatments hereafter termed treatments in response to bleeding in two circumstances: i.) during surgery if there was excessive chest cavity bleeding unattributable to a surgical bleeding point, or ii.) after surgery if there was concern about the rate of blood loss from chest drains or if there was indirect evidence of bleeding such as unexplained hypotension or anaemia. These treatments were usually selected using thromboelastography or ACT tests performed in the operating theatre of intensive care unit but in some emergency circumstances, treatments were selected empirically based on clinical circumstances. The results of the coagulation tests performed in the study were unavailable to clinicians and did not influence the choice of whether or not to administer pro-haemostatic treatments.

The clinical teams recorded administration and the indication for any pro-haemostatic treatment (fresh frozen plasma, cryoprecipitate, platelet concentrates, or additional protamine given after initial correction of the ACT at the end of CPB) that was administered between
anaesthetic induction and the first 12 hours after insertion of chest drains. Case report forms and where necessary the primary anaesthetic records were subsequently inspected by senior clinical members of the research team for all interventions recorded as treatments in response to bleeding to confirm correct classification.

### Outcomes

The primary outcome was clinical concern about bleeding (CCB) defined as either of the following events in the interval between the start of surgery and 12 hours after insertion of chest drains: i.) administration of any pro-haemostatic treatment in response to bleeding, or, ii.) a chest drain volume of either >5ml/Kg/hr in any 1 hour interval or >3ml/kg/hr for 3 consecutive hours (relevant for the post-operative interval only).

Pro-haemostatic treatments in response to bleeding were included in the primary outcome since it was not otherwise possible to capture excessive bleeding that occurred before the insertion of chest drains or when excessive bleeding was detected and treated after chest drain insertion before reaching the pre-designated volume threshold. Pre-planned preventative pro-haemostatic treatments were not included in the primary outcome because they were administered to children before any excessive bleeding occurred and were planned before surgery according to the blood management protocol.

The secondary outcomes were administration of any blood transfusion given within 12 hours of surgery or post-operative complications (Supplementary table S1). Post-operative complications were classified as serious if they were judged by the treating clinicians as likely to have increased the length of hospital stay, to have been life threatening or if the complication caused persistent or significant disability or resulted in death.
Blood samples and laboratory testing

A pre-operative blood sample was taken after anaesthetic induction but before anticoagulation with heparin. A post-CPB blood sample was taken after completion of protamine reversal of heparin anticoagulation at the end of CPB, but before the return of pump blood, insertion of chest drains and chest closure. Both blood samples were analysed using Sysmex XN and CS-2100 series blood count and coagulation analysers (Sysmex Corp. Kobe, Japan), a Multiplate platelet function analyser (Roche Diagnostics, Switzerland) and a ROTEM delta thromboelastometer (TEM International GmbH, Germany). A total of 17 test results or derived parameters were pre-specified as potential predictors of the primary outcome. The blood test results were unavailable to the clinicians responsible for the care of the patients.

Selection of clinical predictors

The baseline characteristics of the children that were pre-specified as potential predictors of CCB were those characteristics known to the surgical teams at the start of surgery. These comprised patient age (0-28 days old vs older), sex, RACHS-1 category of the planned procedure27 weight-for-age z-score using the British 1990 Growth Reference data, pre-operative anti-thrombotic medication (aspirin, warfarin or other anticoagulants at admission for surgery), pre-operative prostin, and pre-operative haemoglobin level. The surgical characteristics were potential predictors only known to the surgical teams at the end of cardiac surgery and comprised total CPB time, aortic cross-clamp time, minimum temperature during CPB, use of cell saver, return of pump blood, blood transfusion during surgery and the presence of CCB during surgery.
Statistical analysis

In order to evaluate how well coagulation test results predicted CCB during surgery and after surgery, three sets of predictive models were generated: i.) pre-operative test results versus CCB during surgery; ii.) post-CPB test results versus CCB after surgery, and, iii.) pre-operative test results versus CCB after surgery. For each set of models, the association between the coagulation test results and CCB was assessed alongside the association between the clinical characteristics and CCB. Finally, both the clinical characteristics and coagulation test results were assessed in the same model, to test whether there was improvement in model fit.

The analysis population for the models of CCB during surgery was all children who had collection of the pre-operative blood sample and for the models of CCB after surgery was all children who had collection of the post-CPB blood sample. Multiple imputation methods using predictive mean matching and ten imputations was used for children with missing clinical characteristics or coagulation test results. Multivariable fractional polynomial models were used to allow for non-linearity of terms using the mfp command in Stata, which builds multivariable fractional polynomial models in multiply imputed data. In addition to adjustment for the pre-specified predictors of CCB, the models were additionally adjusted for whether the patient was in the intervention arm of either of two concurrent trials (Thermic-2 ISRCTN81773762: (22 children) and OXIC-2 ISRCTN13467772: 11 children). In the models that included the coagulation test results, automated backward elimination was used to identify the test results that contributed significantly to the final model using cut-off of 0.05 in most cases, but this was increased to 0.10 if this did not result in the selection of terms. The overall effectiveness of the models in predicting CCB was reported using the c-statistic with 95% confidence intervals (95% CI) with differences between these tested using
the DeLong method. The percentage of children correctly classified in each model has having CCB or no CCB was calculated using the non-imputed data. These analyses were repeated for assessing the associations with the secondary outcomes.

RESULTS

Study population

Of the 441 children who were assessed for eligibility, 75 were ineligible and 58 were eligible but were not approached for other reasons (Figure 1). Of the 308 children who were approached, consent to participate was obtained for 242 (79%). The overall analysis population for which data were collected was 225 children. Coagulation test results from all 225 children were included in the CCB during surgery models. For the CCB after surgery models, results from three children were excluded because the post-CPB blood samples could not be collected at the correct time. Imputation of at least one missing test result or clinical characteristic was required for seven of 225 (3%) children for the CCB during surgery models and for 20 of 222 (9%) children for the CCB after surgery models.

Baseline and surgical clinical characteristics

The clinical characteristics of the overall study group are shown in Table 1 and in Supplementary tables S2 and S3. The median age of the children was 1.3 years (range 2 days to 16.9 years). A total of 119 the children (53% of the overall analysis population) were male. The most common surgical procedures were bidirectional Glenn shunts or the Fontan procedure (14%) and repair of tetralogy of Fallot (13%). Most procedures had RACHS-1 category of two or three (88%). For 33% of procedures, the children had had at least one previous cardiac surgery procedure.
Of the 225 children in the overall analysis population, 26 (12%) had CCB during surgery, because they received a pro-haemostatic treatment in response to bleeding. A total of 68 (30%) had CCB after surgery of which 53 had a pro-haemostatic treatment in response to bleeding without having high chest-drain loss (Table 2). Sixty children (27%) had the secondary outcome of any blood transfusion after surgery, 99 (44%) any post-CPB complication and 62 (28%) any serious post-CPB complication (Table 2).

Coagulation test results

The prospective coagulation test results from the overall analysis population are shown in Table 3, in Supplementary Tables S2 and S4 and Figures S1 and S2. The main differences in the post-CPB results compared to the pre-operative results were reduced platelet count and platelet function (reduced PLT and reduced AUCs for the Multiplate tests), dysfunctional coagulation pathway (prolonged PT or APTT and reduced ETP), reduced fibrinogen (reduced FIB) and the persistent heparin after protamine reversal (increased anti-Xa). These changes were reflected in the ROTEM results which showed higher CT and lower MCF (EXTEM and INTEM) and lower MCF (FIBTEM) in the post-CPB samples, compared to the pre-operative samples (Table 3).

Prediction of clinical concern about bleeding during surgery

When considered individually, none of the baseline characteristics were associated with a statistically significant difference in odds ratio of CCB during surgery (Figure 2A), but when incorporated into a model they enabled prediction of CCB during surgery with a $c$-statistic of 0.64 (95% confidence interval 0.53, 0.76). The alternative model incorporating the pre-operative coagulation test results alone enabled prediction of CCB during surgery with a $c$-statistic of 0.65 (0.56, 0.76). A combined model that incorporated both the baseline
characteristics and the pre-operative coagulation test results had a \textit{c-statistic} of 0.79 (0.70, 0.87), representing a statistically significant (p=0.01) improvement in model fit (Figure 2B). However, the number of children correctly predicted to have either CCB or no CCB during surgery was 198 with the baseline characteristics alone model and 200 with combined model, corresponding to an uplift in correct classification in only 0.9% of children.

**Prediction of clinical concern about bleeding after surgery**

The baseline characteristics female sex, higher RACHS1 category, and the surgical characteristics increased total CPB time and no use of cell saver were independent predictors of CCB after surgery (Figure 3A). The model incorporating the baseline and surgical characteristics enabled prediction of CCB after surgery with a \textit{c-statistic} of 0.74 (0.67, 0.82). The model incorporating only the post-CPB coagulation test results enabled prediction of CCB after surgery with a \textit{c-statistic} of 0.59 (0.51, 0.68). The combined model that incorporated the baseline and surgical characteristics and also the post-CPB coagulation test results had a \textit{c-statistic} of 0.80 (0.74, 0.87), representing a statistically significant (p=0.02) improvement in model fit (Figure 3B). The number of children correctly predicted to have CCB or no CCB after surgery was 163 with the baseline and surgical characteristics alone model and 164 children with the combined model, corresponding to an uplift in correct classification in only 0.4% of children. The final fitted combined models are shown in Supplementary Table S5.

A similar analysis was performed to assess whether CCB after surgery could be predicted using only the baseline characteristics of the children and the pre-operative coagulation test results. Similar to the previous findings, CCB after surgery could be predicted using a model incorporating baseline characteristics alone (\textit{c-statistic} 0.72 CI 0.64, 0.79), but this was not
improved by incorporating the pre-operative coagulation test results \((c\text{-}statistic \ 0.74 \ CI \ 0.66, 0.81; \text{test \ of \ equality} \ p=0.25)\) (Supplementary Figures S3 and S4).

**Prediction of the secondary outcomes**

The clinical characteristics of the children and the post-CPB coagulation test results according to presence or absence of each secondary outcomes are reported in Supplementary tables S6 and S7. For all of the secondary outcomes, the predictive models incorporating the clinical characteristics alone had higher \(c\text{-}statistics\) than the corresponding models incorporating the post-CPB coagulation test results (Table 4). There was no further increase in \(c\text{-}statistic\) after combining the clinical and test result models.

**DISCUSSION**

In this prospective study of 225 children having a wide range of cardiac surgery procedures, we evaluated how well prospective coagulation testing at anaesthetic induction or just after CPB improved the prediction of CCB, when compared to prediction using clinical characteristics alone. The main finding was that the predictive models that incorporated clinical characteristics were improved after coagulation test results were included in the models. However, this resulted in an increase in correct prediction in only 0.9% of children for CCB during surgery and 0.4% of children for CCB after surgery. Incorporation of prospective coagulation test results did not improve prediction of blood transfusion or post-CPB complications (Figure 4).

**Predictive models using clinical characteristics**

We found a trend towards more frequent CCB in younger children and those receiving anti-thrombotic drugs at the point of admission for surgery, similar to previously reports.\(^1,22\) CCB after surgery was associated with more complex planned surgery (high RACHS-1 score),
increased total CPB time and no use of cell saver, which also reproduces previous findings.\textsuperscript{1,15,22,23} The association between CCB after surgery and increased duration of CPB supports previous observations that activation and consumption of platelets, clotting factors and fibrinogen by the extracorporeal CPB circuit results in significant coagulopathy.\textsuperscript{5} The association between CCB after surgery and no use of cell saver likely reflects that without a cell saver, blood volume is typically restored using crystalloid or red cell blood transfusion which have no haemostatic activity and have previously been shown to increase pro-haemostatic treatments when compared to cell saver blood.\textsuperscript{30}

**Contribution of prospective coagulation test results**

The coagulation test results showed complex abnormalities in platelet number and function, coagulation pathway function and in fibrinogen activity that frequently co-existed in the same blood sample, similar to previous studies.\textsuperscript{8-10} Although there were abnormalities in some pre-operative blood test results, abnormal results were more frequent in the post-CPB blood samples, indicating development of coagulopathy during surgery and consistent with the known effects of CPB and interventions such as heparin anticoagulation.\textsuperscript{5}

Coagulation test results consistently associated with bleeding in previous studies including low platelet count\textsuperscript{22}, viscoelastometric clot strength reflecting the contribution of both platelet and fibrinogen to haemostasis (ROTEM MCF or TEG MA tests)\textsuperscript{15,19,22} or low fibrinogen (ROTEM FIBTEM MCF or FIB)\textsuperscript{15,23} were included in the test panel evaluated in our study. However, uniquely in our study we revealed that the additional value of using these and other test results for prediction of CCB is very low if prediction is already performed using clinical characteristics alone. This conclusion was the same for the secondary outcomes of blood transfusion or post-operative complications which are potential
consequences of bleeding.\textsuperscript{3,4,31,32} This suggests that the main underlying causes of
cogulopathy were reflected in the clinical characteristics of the cases which were thereby
sufficient to drive the predictive models and that demonstration of an abnormal results in
prospective coagulation tests provided little clinically useful information.

\textbf{Strengths and weaknesses}

The main strength of the DECISION study was the features of the study design that
minimised the risk of bias: (i) the study enrolled unselected children having a wide range of
procedures, (ii) 79\% of the eligible children who were approached were enrolled into the
study and had data collected, and (iii) the coagulation tests were performed using
standardised methodology in a remote laboratory so that the results could not influence the
study outcomes.

It is also a strength that the primary outcome was a composite of high blood loss observed
from chest drains in the post-operative period but also the administration of any pro-
haemostatic product for the treatment of bleeding. This pragmatic definition enabled
identification of children with excessive bleeding during surgery before chest drain insertion,
but also after surgery when pro-haemostatic treatments early in the course of bleeding
frequently arrest bleeding before the threshold values for chest drain blood loss are reached.
Although this approach is likely to have captured all episodes of excessive bleeding, it is
possible that some pro-haemostatic treatments may have been given without evidence of
excessive bleeding resulting in incorrect classification of children as having reached the
primary outcome. Conversely a very small number of children may have received treatments
in response to bleeding that were not documented as such. We minimised the impact of these
potential errors by ensuring that a contemporaneous record was made of the indication for
each pro-haemostatic treatment and by reviewing the clinical record to ensure that these were correctly classified.

It is a potential weakness of the study that since it was conducted in a single centre the findings may not be generalizable to other centres. However, the characteristics of the children were similar to those in other predictive modelling studies\textsuperscript{22, 23} and to children at other Paediatric cardiac surgery centres\textsuperscript{33}, with the exception that the number of neonates enrolled to our study was lower. This is a likely consequence of exclusion of patients with body weight <2.5 Kg, which was an ethical constraint to minimise the impact of large blood samples needed for comprehensive coagulation testing. This precluded inclusion of neonates in which bleeding is prevalent and prevents generalisation of our findings to this age group.

Incorporation of more recently validated procedural complexity scores such as EACTS STAT instead of RACHS-1 and including repeat sternotomy and more detailed age classifications as terms may potentially have improved performance of the clinical characteristics models. However, these measures would have been unlikely to influence the impact of including coagulation test results to these models, which was the main subject of study.

**Clinical impact of the study findings**

There is now abundant evidence that incorporation of coagulation test results into blood management algorithms assists selection of targeted pro-haemostatic treatments and reduces blood component use.\textsuperscript{34} In this study, we evaluated the utility of prospective coagulation testing to predict excessive bleeding. Our findings support the use of clinical characteristics that are readily available either before surgery or during the course of surgery to assist prediction of bleeding. However, our findings do not currently support prospective coagulation testing to improve prediction if clinical characteristics are already considered.
REFERENCES


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Figure 1: Flow of study participants. The flow chart indicates the number of children who were assessed for eligibility, approached to participate, consented to join the study and the number for which complete study datasets were collected (white boxes). The gray boxes indicate the reasons why some children who were assessed for eligibility were not part of the analysis population.
Figure 2: Prediction of excessive bleeding during surgery. A. Associations between the baseline clinical characteristics and clinical concern about bleeding (CCB) during surgery presented as adjusted odds ratios with 95% confidence intervals (CI). B. Receiver operator characteristic (RoC) curves of the predictive models for CCB during surgery incorporating the baseline clinical characteristics alone and for a combined model that also incorporated the prospective pre-operative coagulation test results. The areas under the curves (c-statistics) indicate better prediction for the combined model. RACHS-1: Risk adjustment in Congenital Heart Surgery-1. The test of equality value indicates evidence of difference between the RoC curves.
Figure 3: Prediction of excessive bleeding after surgery. A. Associations between the baseline and surgical clinical characteristics of the children and clinical concern about bleeding (CCB) after surgery presented as adjusted odds ratios with 95% confidence intervals (CI). B. Receiver operator characteristic (RoC) curves of the predictive models for CCB after surgery incorporating the baseline and surgical characteristics alone and for a combined model that also incorporated the prospective post-CPB coagulation test results. The areas under the curves (c-statistics) indicate better prediction for the combined model. RACHS-1: Risk adjustment in Congenital Heart Surgery-1. The test of equality value indicates evidence of difference between the RoC curves.
This study overview highlights that from a study population of 225 children undergoing a wide range of cardiac surgery procedures, candidate predictors of bleeding were pre-selected from either the clinical characteristics of the children and from the results of a panel of prospective coagulation tests performed at anaesthetic induction and just after the end of cardiopulmonary bypass. The primary outcome was clinical concern about bleeding, a composite endpoint to reflect excessive bleeding. Predictive models were generated using clinical characteristics alone or in combination with prospective coagulation test results. Although including coagulation test results to the models that already included clinical characteristics improved prediction of CCB, the clinical impact expressed as the improvement in the number of children with correct classification was very small.
Prediction of bleeding in paediatric cardiac surgery using clinical characteristics and prospective coagulation test results

Jessica M Harris BSc, MSc, PhD¹, Karen Sheehan MSc², Chris A Rogers BSc, PhD¹, Tim Murphy MBBS FRCA², Massimo Caputo MD MCh²,³,⁴, Andrew D Mumford MB ChB PhD⁵

1. Bristol Trials Centre, Faculty of Health Sciences, University of Bristol, Bristol, UK.
2. Department of Paediatric Cardiac Surgery, Bristol Royal Hospital for Children, University Hospitals Bristol, Bristol, UK.
3. Bristol Heart Institute, University Hospitals Bristol, Bristol, UK.
4. Department of Paediatric Cardiac Surgery, School of Translational Sciences, University of Bristol, Bristol, UK.
5. Department of Haematology, School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK.

Conflicts of Interest: The authors declare no relevant conflicts of interest

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Corresponding author: Professor Andrew Mumford, School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK. Email a.mumford@bristol.ac.uk

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Supplementary file 1; References 34
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<th>Abbreviation</th>
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<td>Anti-Xa</td>
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<td>APTT</td>
<td>Activated partial thromboplastin time</td>
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<td>ASD</td>
<td>Atrial septal defect</td>
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<td>Modified ultra-filtration</td>
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CENTRAL PICTURE LEGEND: Bleeding prediction models improves little after including prospective coagulation test results.

CENTRAL MESSAGE: Prospective coagulation testing offers little additional benefit to prediction of excessive bleeding in children undergoing cardiac surgery when compared to prediction using clinical characteristics alone.

PERSPECTIVE STATEMENT: Excessive bleeding because of coagulopathy causes adverse outcomes in children having cardiac surgery. Rapid coagulation testing to help selection of treatments for bleeding improves outcomes but has uncertain utility for predicting whether bleeding will occur. We show that prospective coagulation testing has little additional value compared to prediction using the clinical characteristics of children alone.
ABSTRACT

Objective: Bleeding caused by coagulopathy is common in children undergoing cardiac surgery and causes adverse outcomes. Coagulation testing assists selection of treatments to stop bleeding but has an uncertain role for predicting bleeding. We aimed to evaluate how well prospective coagulation testing predicted excessive bleeding during and after cardiac surgery compared to prediction using clinical characteristics alone.

Methods: A single centre, prospective cohort study in children having a range of cardiac surgery procedures with coagulation testing at anaesthetic induction and immediately after cardio-pulmonary bypass. The primary outcome was clinical concern about bleeding (CCB), a composite of either administration of pro-haemostatic treatments in response to bleeding or a high chest drain volume after surgery.

Results: In 225 children, CCB occurred in 26 (12%) during surgery and in 68 (30%) after surgery. Multivariable fractional polynomial models using the clinical characteristics of the children alone predicted CCB during surgery (c-statistic 0.64; 95% confidence interval 0.53, 0.76) and after surgery (0.74; 0.67, 0.82). Incorporating coagulation test results into these models improved prediction (c-statistics 0.79; 0.70, 0.87 and 0.80; 0.74, 0.87 respectively). However, this increased the overall proportion of children classified correctly as CCB or not CCB during surgery by only 0.9% and after surgery by only 0.4%. Incorporating coagulation test results into predictive models had no effect on prediction of blood transfusion or post-operative complications.

Conclusions: Prospective coagulation testing marginally improves prediction of CCB during and after cardiac surgery but the clinical impact of this is small when compared to prediction using clinical characteristics.
INTRODUCTION

Microvascular bleeding caused by coagulopathy and blood transfusion in response to bleeding are common after cardiac surgery in children\textsuperscript{1,2} and are independent predictors of morbidity and mortality.\textsuperscript{3,4} Coagulopathy is typically complex and may include reduced levels or reduced function of platelets, coagulation factors or fibrinogen.\textsuperscript{5} These changes may relate to the age of children, underlying cardiac disease or medication before cardiac surgery\textsuperscript{6,7} or to interventions that occur during surgery, particularly heparin anticoagulation, hypothermia and cardiopulmonary bypass (CPB).\textsuperscript{8-10}

Coagulation testing using point-of-care viscoelastometry or rapid platelet function testing detects major components of coagulopathy during cardiac surgery in children.\textsuperscript{7,11,12} In retrospective case control studies, viscoelastometry-assisted selection of treatments reduced blood component use in children who developed excessive bleeding.\textsuperscript{13,14} In a randomised controlled trial of children with excessive bleeding, viscoelastometry resulted in less bleeding and blood transfusion.\textsuperscript{15} Further support for the utility of blood management algorithms that include diagnostic coagulation test results has been reproduced in other recent studies\textsuperscript{16-18}.

An alternative strategy is to perform prospective testing before bleeding occurs, potentially enabling preventative treatments in children at greatest risk or the pre-ordering of treatments for immediate administration if bleeding starts. However, most previous studies of prospective testing for prediction of bleeding have evaluated only small patient cohorts using limited repertoires of coagulation tests and have yielded inconsistent findings.\textsuperscript{15,19-21} In studies of larger cohorts of children, predictive models for excessive bleeding have
incorporated both coagulation test results and the clinical characteristics of children, thereby obscuring the utility of coagulation testing alone.\textsuperscript{1, 22, 23}

We performed the Detection of Coagulopathy in Paediatric Heart Surgery (DECISION) study to investigate how well prospective coagulation testing predicts excessive bleeding in children undergoing cardiac surgery, compared with prediction using clinical characteristics alone.

METHODS

Study design and patients

The DECISION study was a prospective single-centre observational cohort study conducted at University Hospitals NHS Foundation Trust between May 2013 and April 2015 in accordance with the Declaration of Helsinki and United Kingdom NHS Research Ethics Committee approval 13/LO/0504.

Children were eligible if they were aged 16 years or younger, had a body weight of more than 2.5 Kg and were listed for any non-emergency cardiac surgery procedure requiring CPB. Children were ineligible if undergoing isolated ostium secundum ASD repair in which bleeding risk is very low, or if they required emergency cardiac surgery. Parental consent was obtained for children younger than 16 years. Direct consent was obtained for children aged 16 years. A detailed study protocol is reported elsewhere.\textsuperscript{24}

Surgical and blood management procedures

All the children were managed according to a standard institutional anaesthetic protocol described previously\textsuperscript{25}. A bolus dose of heparin 300-400 units/Kg was administered before
aortic cannulation with additional doses of 100 units/kg to maintain an activated clotting time (ACT) >400 s. Protamine (10 mg/1000 units of heparin administered) was given at the end of CPB with additional boluses of 2-4 mg given sequentially until the ACT was <150s.

Protamine was also administered after return of pump blood (5mg/100ml) which was also ultra-filtrated for all neonates and children <10Kg. Tranexamic acid (30-80 mg/kg total dose) and cell-savers for redo procedures and for complex aortic valve procedures were used according to the discretion of the anaesthesiologist. The administration of tranexamic acid and protamine as part of this standard protocol was planned before surgery and not given in response to abnormal bleeding. These interventions were classified as *pre-planned preventative treatments*.

Anesthesiologists also administered pro-haemostatic treatments hereafter termed *treatments in response to bleeding* in two circumstances: i.) during surgery if there was excessive chest cavity bleeding unattributable to a surgical bleeding point, or ii.) after surgery if there was concern about the rate of blood loss from chest drains or if there was indirect evidence of bleeding such as unexplained hypotension or anaemia. These treatments were usually selected using thromboelastography or ACT tests performed in the operating theatre of intensive care unit but in some emergency circumstances, treatments were selected empirically based on clinical circumstances. The results of the coagulation tests performed in the study were unavailable to clinicians and did not influence the choice of whether or not to administer pro-haemostatic treatments.

The clinical teams recorded administration and the indication for any pro-haemostatic treatment (fresh frozen plasma, cryoprecipitate, platelet concentrates, or additional protamine given after initial correction of the ACT at the end of CPB) that was administered between
anaesthetic induction and the first 12 hours after insertion of chest drains. Case report forms and where necessary the primary anaesthetic records were subsequently inspected by senior clinical members of the research team for all interventions recorded as treatments in response to bleeding to confirm correct classification.

**Outcomes**

The primary outcome was clinical concern about bleeding (CCB) defined as either of the following events in the interval between the start of surgery and 12 hours after insertion of chest drains: i.) administration of any pro-haemostatic treatment in response to bleeding, or, ii.) a chest drain volume of either >5ml/Kg/hr in any 1 hour interval or >3ml/kg/hr for 3 consecutive hours²⁶ (relevant for the post-operative interval only).

Pro-haemostatic treatments in response to bleeding were included in the primary outcome since it was not otherwise possible to capture excessive bleeding that occurred before the insertion of chest drains or when excessive bleeding was detected and treated after chest drain insertion before reaching the pre-designated volume threshold. Pre-planned preventative pro-haemostatic treatments were not included in the primary outcome because they were administered to children before any excessive bleeding occurred and were planned before surgery according to the blood management protocol.

The secondary outcomes were administration of any blood transfusion given within 12 hours of surgery or post-operative complications (Supplementary table S1). Post-operative complications were classified as serious if they were judged by the treating clinicians as likely to have increased the length of hospital stay, to have been life threatening or if the complication caused persistent or significant disability or resulted in death.
Blood samples and laboratory testing

A pre-operative blood sample was taken after anaesthetic induction but before anticoagulation with heparin. A post-CPB blood sample was taken after completion of protamine reversal of heparin anticoagulation at the end of CPB, but before the return of pump blood, insertion of chest drains and chest closure. Both blood samples were analysed using Sysmex XN and CS-2100 series blood count and coagulation analysers (Sysmex Corp. Kobe, Japan), a Multiplate platelet function analyser (Roche Diagnostics, Switzerland) and a ROTEM delta thromboelastometer (TEM International GmbH, Germany). A total of 17 test results or derived parameters were pre-specified as potential predictors of the primary outcome. The blood test results were unavailable to the clinicians responsible for the care of the patients.

Selection of clinical predictors

The baseline characteristics of the children that were pre-specified as potential predictors of CCB were those characteristics known to the surgical teams at the start of surgery. These comprised patient age (0-28 days old vs older), sex, RACHS-1 category of the planned procedure, weight-for-age z-score using the British 1990 Growth Reference data, pre-operative anti-thrombotic medication (aspirin, warfarin or other anticoagulants at admission for surgery), pre-operative prostin, and pre-operative haemoglobin level. The surgical characteristics were potential predictors only known to the surgical teams at the end of cardiac surgery and comprised total CPB time, aortic cross-clamp time, minimum temperature during CPB, use of cell saver, return of pump blood, blood transfusion during surgery and the presence of CCB during surgery.
Statistical analysis

In order to evaluate how well coagulation test results predicted CCB during surgery and after surgery, three sets of predictive models were generated: i.) pre-operative test results versus CCB during surgery; ii.) post-CPB test results versus CCB after surgery, and, iii.) pre-operative test results versus CCB after surgery. For each set of models, the association between the coagulation test results and CCB was assessed alongside the association between the clinical characteristics and CCB. Finally, both the clinical characteristics and coagulation test results were assessed in the same model, to test whether there was improvement in model fit.

The analysis population for the models of CCB during surgery was all children who had collection of the pre-operative blood sample and for the models of CCB after surgery was all children who had collection of the post-CPB blood sample. Multiple imputation methods using predictive mean matching and ten imputations was used for children with missing clinical characteristics or coagulation test results. Multivariable fractional polynomial models were used to allow for non-linearity of terms using the mfpmi command in Stata, which builds multivariable fractional polynomial models in multiply imputed data. In addition to adjustment for the pre-specified predictors of CCB, the models were additionally adjusted for whether the patient was in the intervention arm of either of two concurrent trials (Thermic-2 ISRCTN81773762: (22 children) and OXIC-2 ISRCTN13467772: 11 children). In the models that included the coagulation test results, automated backward elimination was used to identify the test results that contributed significantly to the final model using cut-off of 0.05 in most cases, but this was increased to 0.10 if this did not result in the selection of terms. The overall effectiveness of the models in predicting CCB was reported using the c-statistic with 95% confidence intervals (95% CI) with differences between these tested using
the DeLong method. The percentage of children correctly classified in each model has having CCB or no CCB was calculated using the non-imputed data. These analyses were repeated for assessing the associations with the secondary outcomes.

RESULTS

Study population
Of the 441 children who were assessed for eligibility, 75 were ineligible and 58 were eligible but were not approached for other reasons (Figure 1). Of the 308 children who were approached, consent to participate was obtained for 242 (79%). The overall analysis population for which data were collected was 225 children. Coagulation test results from all 225 children were included in the CCB during surgery models. For the CCB after surgery models, results from three children were excluded because the post-CPB blood samples could not be collected at the correct time. Imputation of at least one missing test result or clinical characteristic was required for seven of 225 (3%) children for the CCB during surgery models and for 20 of 222 (9%) children for the CCB after surgery models.

Baseline and surgical clinical characteristics
The clinical characteristics of the overall study group are shown in Table 1 and in Supplementary tables S2 and S3. The median age of the children was 1.3 years (range 2 days to 16.9 years). A total of 119 the children (53% of the overall analysis population) were male. The most common surgical procedures were bidirectional Glenn shunts or the Fontan procedure (14%) and repair of tetralogy of Fallot (13%). Most procedures had RACHS-1 category of two or three (88%). For 33% of procedures, the children had had at least one previous cardiac surgery procedure.
Of the 225 children in the overall analysis population, 26 (12%) had CCB during surgery, because they received a pro-haemostatic treatment in response to bleeding. A total of 68 (30%) had CCB after surgery of which 53 had a pro-haemostatic treatment in response to bleeding without having high chest-drain loss (Table 2). Sixty children (27%) had the secondary outcome of any blood transfusion after surgery, 99 (44%) any post-CPB complication and 62 (28%) any serious post-CPB complication (Table 2).

Coagulation test results
The prospective coagulation test results from the overall analysis population are shown in Table 3, in Supplementary Tables S2 and S4 and Figures S1 and S2. The main differences in the post-CPB results compared to the pre-operative results were reduced platelet count and platelet function (reduced PLT and reduced AUCs for the Multiplate tests), dysfunctional coagulation pathway (prolonged PT or APTT and reduced ETP), reduced fibrinogen (reduced FIB) and the persistent heparin after protamine reversal (increased anti-Xa). These changes were reflected in the ROTEM results which showed higher CT and lower MCF (EXTEM and INTEM) and lower MCF (FIBTEM) in the post-CPB samples, compared to the pre-operative samples (Table 3).

Prediction of clinical concern about bleeding during surgery
When considered individually, none of the baseline characteristics were associated with a statistically significant difference in odds ratio of CCB during surgery (Figure 2A), but when incorporated into a model they enabled prediction of CCB during surgery with a $c$-statistic of 0.64 (95% confidence interval 0.53, 0.76). The alternative model incorporating the pre-operative coagulation test results alone enabled prediction of CCB during surgery with a $c$-statistic of 0.65 (0.56, 0.76). A combined model that incorporated both the baseline
characteristics and the pre-operative coagulation test results had a \textit{c-statistic} of 0.79 (0.70, 0.87), representing a statistically significant (p=0.01) improvement in model fit (Figure 2B). However, the number of children correctly predicted to have either CCB or no CCB during surgery was 198 with the baseline characteristics alone model and 200 with combined model, corresponding to an uplift in correct classification in only 0.9% of children.

\textbf{Prediction of clinical concern about bleeding after surgery}

The baseline characteristics female sex, higher RACHS1 category, and the surgical characteristics increased total CPB time and no use of cell saver were independent predictors of CCB after surgery (Figure 3A). The model incorporating the baseline and surgical characteristics enabled prediction of CCB after surgery with a \textit{c-statistic} of 0.74 (0.67, 0.82). The model incorporating only the post-CPB coagulation test results enabled prediction of CCB after surgery with a \textit{c-statistic} of 0.59 (0.51, 0.68). The combined model that incorporated the baseline and surgical characteristics and also the post-CPB coagulation test results had a \textit{c-statistic} of 0.80 (0.74, 0.87), representing a statistically significant (p=0.02) improvement in model fit (Figure 3B). The number of children correctly predicted to have CCB or no CCB after surgery was 163 with the baseline and surgical characteristics alone model and 164 children with the combined model, corresponding to an uplift in correct classification in only 0.4% of children. The final fitted combined models are shown in Supplementary Table S5.

A similar analysis was performed to assess whether CCB after surgery could be predicted using only the baseline characteristics of the children and the pre-operative coagulation test results. Similar to the previous findings, CCB after surgery could be predicted using a model incorporating baseline characteristics alone (\textit{c-statistic} 0.72 CI 0.64, 0.79), but this was not
improved by incorporating the pre-operative coagulation test results (c-statistic 0.74 CI 0.66, 0.81; test of equality p=0.25) (Supplementary Figures S3 and S4).

Prediction of the secondary outcomes

The clinical characteristics of the children and the post-CPB coagulation test results according to presence or absence of each secondary outcomes are reported in Supplementary tables S6 and S7. For all of the secondary outcomes, the predictive models incorporating the clinical characteristics alone had higher c-statistics than the corresponding models incorporating the post-CPB coagulation test results (Table 4). There was no further increase in c-statistic after combining the clinical and test result models.

DISCUSSION

In this prospective study of 225 children having a wide range of cardiac surgery procedures, we evaluated how well prospective coagulation testing at anaesthetic induction or just after CPB improved the prediction of CCB, when compared to prediction using clinical characteristics alone. The main finding was that the predictive models that incorporated clinical characteristics were improved after coagulation test results were included in the models. However, this resulted in an increase in correct prediction in only 0.9% of children for CCB during surgery and 0.4% of children for CCB after surgery. Incorporation of prospective coagulation test results did not improve prediction of blood transfusion or post-CPB complications (Figure 4).

Predictive models using clinical characteristics

We found a trend towards more frequent CCB in younger children and those receiving anti-thrombotic drugs at the point of admission for surgery, similar to previously reports.\textsuperscript{1, 22} CCB after surgery was associated with more complex planned surgery (high RACHS-1 score).
increased total CPB time and no use of cell saver, which also reproduces previous findings.\textsuperscript{15,22,23} The association between CCB after surgery and increased duration of CPB supports previous observations that activation and consumption of platelets, clotting factors and fibrinogen by the extracorporeal CPB circuit results in significant coagulopathy.\textsuperscript{5} The association between CCB after surgery and no use of cell saver likely reflects that without a cell saver, blood volume is typically restored using crystalloid or red cell blood transfusion which have no haemostatic activity and have previously been shown to increase pro-
haemostatic treatments when compared to cell saver blood.\textsuperscript{30}

**Contribution of prospective coagulation test results**

The coagulation test results showed complex abnormalities in platelet number and function, coagulation pathway function and in fibrinogen activity that frequently co-existed in the same blood sample, similar to previous studies.\textsuperscript{8-10} Although there were abnormalities in some pre-
operative blood test results, abnormal results were more frequent in the post-CPB blood samples, indicating development of coagulopathy during surgery and consistent with the known effects of CPB and interventions such as heparin anticoagulation.\textsuperscript{5}

Coagulation test results consistently associated with bleeding in previous studies including low platelet count\textsuperscript{22}, viscoelastometric clot strength reflecting the contribution of both platelet and fibrinogen to haemostasis (ROTEM MCF or TEG MA tests)\textsuperscript{15,19,22} or low fibrinogen (ROTEM FIBTEM MCF or FIB).\textsuperscript{15,23} were included in the test panel evaluated in our study. However, uniquely in our study we revealed that the additional value of using these and other test results for prediction of CCB is very low if prediction is already performed using clinical characteristics alone. This conclusion was the same for the secondary outcomes of blood transfusion or post-operative complications which are potential
consequences of bleeding.\textsuperscript{3, 4, 31, 32} This suggests that the main underlying causes of coagulopathy were reflected in the clinical characteristics of the cases which were thereby sufficient to drive the predictive models and that demonstration of an abnormal results in prospective coagulation tests provided little clinically useful information.

**Strengths and weaknesses**

The main strength of the DECISION study was the features of the study design that minimised the risk of bias: (i) the study enrolled unselected children having a wide range of procedures, (ii) 79\% of the eligible children who were approached were enrolled into the study and had data collected, and (iii) the coagulation tests were performed using standardised methodology in a remote laboratory so that the results could not influence the study outcomes.

It is also a strength that the primary outcome was a composite of high blood loss observed from chest drains in the post-operative period but also the administration of any pro-haemostatic product for the treatment of bleeding. This pragmatic definition enabled identification of children with excessive bleeding during surgery before chest drain insertion, but also after surgery when pro-haemostatic treatments early in the course of bleeding frequently arrest bleeding before the threshold values for chest drain blood loss are reached. Although this approach is likely to have captured all episodes of excessive bleeding, it is possible that some pro-haemostatic treatments may have been given without evidence of excessive bleeding resulting in incorrect classification of children as having reached the primary outcome. Conversely a very small number of children may have received treatments in response to bleeding that were not documented as such. We minimised the impact of these potential errors by ensuring that a contemporaneous record was made of the indication for
each pro-haemostatic treatment and by reviewing the clinical record to ensure that these were correctly classified.

It is a potential weakness of the study that since it was conducted in a single centre the findings may not be generalizable to other centres. However, the characteristics of the children were similar to those in other predictive modelling studies\textsuperscript{22, 23} and to children at other Paediatric cardiac surgery centres\textsuperscript{33}, with the exception that the number of neonates enrolled to our study was lower. This is a likely consequence of exclusion of patients with body weight <2.5 Kg, which was an ethical constraint to minimise the impact of large blood samples needed for comprehensive coagulation testing. This precluded inclusion of neonates in which bleeding is prevalent and prevents generalisation of our findings to this age group. Incorporation of more recently validated procedural complexity scores such as EACTS STAT instead of RACHS-1 and including repeat sternotomy and more detailed age classifications as terms may potentially have improved performance of the clinical characteristics models. However, these measures would have been unlikely to influence the impact of including coagulation test results to these models, which was the main subject of study.

**Clinical impact of the study findings**

There is now abundant evidence that incorporation of coagulation test results into blood management algorithms assists selection of targeted pro-haemostatic treatments and reduces blood component use.\textsuperscript{34} In this study, we evaluated the utility of prospective coagulation testing to predict excessive bleeding. Our findings support the use of clinical characteristics that are readily available either before surgery or during the course of surgery to assist prediction of bleeding. However, our findings do not currently support prospective coagulation testing to improve prediction if clinical characteristics are already considered.
REFERENCES


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Figure 1: Flow of study participants. The flow chart indicates the number of children who were assessed for eligibility, approached to participate, consented to join the study and the number for which complete study datasets were collected (white boxes). The gray boxes indicate the reasons why some children who were assessed for eligibility were not part of the analysis population.
**Figure 2: Prediction of excessive bleeding during surgery.** A. Associations between the baseline clinical characteristics and clinical concern about bleeding (CCB) during surgery presented as adjusted odds ratios with 95% confidence intervals (CI). B. Receiver operator characteristic (RoC) curves of the predictive models for CCB during surgery incorporating the baseline clinical characteristics alone and for a combined model that also incorporated the prospective pre-operative coagulation test results. The areas under the curves (c-statistics) indicate better prediction for the combined model. RACHS-1: Risk adjustment in Congenital Heart Surgery-1. The test of equality value indicates evidence of difference between the RoC curves.
Figure 3: Prediction of excessive bleeding after surgery. A. Associations between the baseline and surgical clinical characteristics of the children and clinical concern about bleeding (CCB) after surgery presented as adjusted odds ratios with 95% confidence intervals (CI). B. Receiver operator characteristic (RoC) curves of the predictive models for CCB after surgery incorporating the baseline and surgical characteristics alone and for a combined model that also incorporated the prospective post-CPB coagulation test results. The areas under the curves (c-statistics) indicate better prediction for the combined model. RACHS-1: Risk adjustment in Congenital Heart Surgery-1. The test of equality value indicates evidence of difference between the RoC curves.
Figure 4: Graphical abstract

This study overview highlights that from a study population of 225 children undergoing a wide range of cardiac surgery procedures, candidate predictors of bleeding were pre-selected from either the clinical characteristics of the children and from the results of a panel of prospective coagulation tests performed at anaesthetic induction and just after the end of cardiopulmonary bypass. The primary outcome was clinical concern about bleeding, a composite endpoint to reflect excessive bleeding. Predictive models were generated using clinical characteristics alone or in combination with prospective coagulation test results. Although including coagulation test results to the models that already included clinical characteristics improved prediction of CCB, the clinical impact expressed as the improvement in the number of children with correct classification was very small.
CENTRAL PICTURE LEGEND: Bleeding prediction models improves little after including coagulation test results.
FIGURE 1

Assessed for eligibility (n=441)

Ineligible (n=75)
Not approached (n=58)
Recruitment ended (n=20); trial staff unavailable (n=11); parental anxiety (n=7); patients arrived too late (n=5); previously stated not interested (n=4); surgical list changed (n=2); missed (n=1); other (n=4).

Approached to participate (n=308)

Did not consent (n=66)
Not interested (n=28); parental anxiety (n=20); not enough time to consider study (n=6); concern about blood sample volume (n=4); personal reasons (n=3); concern about participation in multiple studies (n=1); no laboratory staff available (n=1); other (n=5).

Consented to participate (n=242)

Withdrawals before surgery (n=17)
Trial staff unavailable (n=9); recruitment ended (n=4); no cardiopulmonary bypass (n=2); operation cancelled (n=2).

Consented to participate and data collected (n=225)

No post-operative blood sample (n=3)
Not taken at correct time (n=2); cardiopulmonary bypass continued after surgery (n=1)

Final dataset with pre-operative blood test results and primary outcome data recorded during surgery (n=225)

Final dataset with post-operative blood test results and primary outcome data recorded after surgery (n=222)
Prediction of bleeding using clinical characteristics improves little after including coagulation test results

<table>
<thead>
<tr>
<th>Patients</th>
<th>Candidate predictors</th>
<th>Primary outcome</th>
<th>Predictive models</th>
<th>Clinical impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>225 Children having a range of cardiac surgery procedures</td>
<td>Clinical characteristics</td>
<td>Clinical Concern about Bleeding (CCB)</td>
<td>CCB during cardiac surgery</td>
<td>Clinical characteristics predicted CCB during and after cardiac surgery</td>
</tr>
<tr>
<td>17 coagulation test results at two timepoints</td>
<td>High blood loss or Need for extra prohaemostatic treatment</td>
<td>CCB after cardiac surgery</td>
<td>Including coagulation test results improved prediction but this had little overall clinical impact</td>
<td></td>
</tr>
<tr>
<td>VS</td>
<td></td>
<td></td>
<td>Improved correct classification of &lt;1% of children</td>
<td></td>
</tr>
</tbody>
</table>
# Table 1: Description of the study cohort

<table>
<thead>
<tr>
<th>Category</th>
<th>All patients (n=225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex; n (%) males</td>
<td>119 (53%)</td>
</tr>
<tr>
<td>Age categories</td>
<td></td>
</tr>
<tr>
<td>Neonate (0-28 days)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Older child (&gt;28 days)</td>
<td>213 (95%)</td>
</tr>
<tr>
<td>Weight-for-age z-scores</td>
<td>-1.3 (-2.5, -0.3)</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
</tr>
<tr>
<td>Bidirectional Glenn shunts or Fontan</td>
<td>31 (14%)</td>
</tr>
<tr>
<td>Tetralogy of Fallot repair</td>
<td>30 (13%)</td>
</tr>
<tr>
<td>VSD repair</td>
<td>23 (10%)</td>
</tr>
<tr>
<td>Atroventricular septal defect repair</td>
<td>22 (10%)</td>
</tr>
<tr>
<td>Complex or multiple procedures</td>
<td>16 (7%)</td>
</tr>
<tr>
<td>Sub- or supra- aortic stenosis repair</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>VSD + minor defect repair</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Conduit replacements</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Pulmonary valve replacement</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>VSD + major defect repair</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Transposition of great arteries repair</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Ross-Konno procedure</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>RVOT repair</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>AV valve repair/replacement</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Aortic valve repair</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Atrial septal defect repair all</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Interrupted arch repair</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>PAPVD or TAPVD repair</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Norwood procedure</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Truncus repair</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>RACHS-1 complexity</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>2</td>
<td>115 (51%)</td>
</tr>
<tr>
<td>3</td>
<td>83 (37%)</td>
</tr>
<tr>
<td>4</td>
<td>20 (9%)</td>
</tr>
<tr>
<td>6</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Repeat sternotomy</td>
<td>75 (33%)</td>
</tr>
<tr>
<td>Pre-operative antithrombotic medication</td>
<td>44 (20%)</td>
</tr>
<tr>
<td>Pre-operative haemoglobin (g/dL)</td>
<td>122 (108, 137)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>92 (71, 130)</td>
</tr>
<tr>
<td>Cross clamp time (if used) (min)</td>
<td>60 (36, 88)</td>
</tr>
<tr>
<td>Minimum temperature during CPB (°C)</td>
<td>32 (31, 34)</td>
</tr>
<tr>
<td>Cell saver used (yes)</td>
<td>33 (15%)</td>
</tr>
<tr>
<td>If yes, volume returned (mL)/weight (kg)</td>
<td>8.3 (5.5, 11.8)</td>
</tr>
<tr>
<td>Pump blood returned (yes)</td>
<td>140 (63%)</td>
</tr>
<tr>
<td>If yes, volume (mL)/weight (kg)</td>
<td>8.9 (5.9, 12.1)</td>
</tr>
<tr>
<td>Red cell transfusion during surgery (units*)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>168 (75%)</td>
</tr>
<tr>
<td>1</td>
<td>55 (24%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

AVSD, Atrioventricular Septal Defect; VSD, Ventricular Septal Defect; AV, atrioventricular; PAPVD, Partial Anomalous Pulmonary Venous drainage; TAPVD, Total Anomalous Pulmonary Venous Drainage; RACHS, Risk adjustment for congenital heart surgery. The continuous variables are described as median and interquartile ranges. * data refer to the number of allogenic red cell units administered
Table 2: The frequencies of the primary and secondary outcomes

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>26 (12%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical concern about bleeding during surgery</td>
<td></td>
</tr>
<tr>
<td>Pro-haemostatic treatment in response to bleeding during surgery</td>
<td></td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>1</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>16</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>15</td>
</tr>
<tr>
<td>Additional protamine</td>
<td>3</td>
</tr>
<tr>
<td>Clinical concern about bleeding after surgery</td>
<td>68 (30%)</td>
</tr>
<tr>
<td>Pro-haemostatic treatment in response to bleeding after surgery</td>
<td>53 (24%)</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>9</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>33</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>41</td>
</tr>
<tr>
<td>Additional protamine</td>
<td>7</td>
</tr>
<tr>
<td>High chest-drain volume(^1)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>High chest-drain volume(^1) and non-routine pro-haemostatic treatment after surgery</td>
<td>9 (4%)</td>
</tr>
</tbody>
</table>

Secondary outcomes

<table>
<thead>
<tr>
<th>i. Any blood transfusion after surgery</th>
<th>60 (27%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ii. Any post-operative complications</td>
<td>99 (44%)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>58 (26%)</td>
</tr>
<tr>
<td>Pulmonary complication</td>
<td>27 (12%)</td>
</tr>
<tr>
<td>Haemodynamic support required</td>
<td>23 (10%)</td>
</tr>
<tr>
<td>Renal complication</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Neurological complication</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Infective complication</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Death during hospital admission</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Gastrointestinal tract complication</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>iii. Any serious post-operative complications</td>
<td>62 (28%)</td>
</tr>
</tbody>
</table>

Frequencies are expressed relative to the overall analysis population of 225 children. 1 Defined as chest drain volume >5mL/Kg/hr in any one hour interval after surgery or chest drain volume >3mL/Kg/hr for 3 consecutive hours after surgery.
Table 3: Coagulation test results

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-operative blood sample (n=225)</th>
<th>Post-CPB blood sample (n=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLT (x10^9/L)¹</td>
<td>269.5 (220.5, 348.5)</td>
<td>152.0 (114.0, 198.0)</td>
</tr>
<tr>
<td>PT (s)²</td>
<td>11.5 (11.1, 12.2)</td>
<td>14.3 (13.4, 15.4)</td>
</tr>
<tr>
<td>APTT (s)²</td>
<td>30.5 (28.7, 32.8)</td>
<td>40.3 (34.7, 51.2)</td>
</tr>
<tr>
<td>FIB (g/L)¹</td>
<td>1.9 (1.6, 2.3)</td>
<td>1.1 (0.9, 1.4)</td>
</tr>
<tr>
<td>anti-Xa (u/mL)³</td>
<td>0.1 (0.0, 0.1)</td>
<td>0.3 (0.2, 0.5)</td>
</tr>
<tr>
<td>ADP-test AUC (U)⁴</td>
<td>724.0 (571.0, 889.0)</td>
<td>362.5 (242.0, 526.0)</td>
</tr>
<tr>
<td>TRAP-test AUC (U)⁴</td>
<td>1047.0 (905.0, 1238.0)</td>
<td>888.5 (599.0, 1169.0)</td>
</tr>
<tr>
<td>COLL-test AUC (U)⁵</td>
<td>631.0 (502.0, 747.0)</td>
<td>478.5 (321.5, 676.0)</td>
</tr>
<tr>
<td>ETP (nM/min)</td>
<td>823.1 (643.9, 980.4)</td>
<td>193.4 (47.4, 383.1)</td>
</tr>
<tr>
<td>INTEM CT (s)⁶</td>
<td>198.0 (176.0, 223.0)</td>
<td>241.0 (204.0, 286.0)</td>
</tr>
<tr>
<td>INTEM MCF (mm)⁶</td>
<td>66.0 (62.0, 69.0)</td>
<td>56.0 (51.0, 62.0)</td>
</tr>
<tr>
<td>INTEM ML (%⁶)</td>
<td>7.0 (4.0, 10.0)</td>
<td>2.0 (0.0, 5.0)</td>
</tr>
<tr>
<td>EXTEM CT (s)⁷</td>
<td>58.0 (50.0, 67.0)</td>
<td>80.0 (67.0, 99.0)</td>
</tr>
<tr>
<td>EXTEM MCF (mm)⁷</td>
<td>66.0 (62.0, 69.0)</td>
<td>57.0 (52.0, 63.0)</td>
</tr>
<tr>
<td>EXTEM ML (%⁶)</td>
<td>9.0 (6.0, 13.0)</td>
<td>3.0 (1.0, 7.0)</td>
</tr>
<tr>
<td>FIBTEM MCF (mm)⁷</td>
<td>13.0 (11.0, 16.0)</td>
<td>8.0 (6.0, 10.0)</td>
</tr>
<tr>
<td>INTEM CT-HEPTEM CT (s)⁸</td>
<td>-2.0 (-18.0, 17.0)</td>
<td>2.0 (-18.0, 24.0)</td>
</tr>
</tbody>
</table>

PLT, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen level, anti-Xa, anti-Xa heparin level; AUC, area under curve in Multiplate platelet function test; ETP, endogenous thrombin potential; CT, ROTEM thromboelastometry INTEM/EXTEM reagent clot time; MCF, ROTEM INTEM/EXTEM/FIBTEM maximum clot firmness, ML, ROTEM INTEM/EXTEM maximum lysis. Data are expressed as median and interquartile range. Missing data: ¹ 4 children; ² 5 children; ³ 34 children; ⁴ 6 children; ⁵ 8 children; ⁶ 6 children; ⁷ 5 children; ⁸ 7 children; ⁹ 2 children.
Table 4: The *c*-statistics from the predictive models for the secondary outcomes.

<table>
<thead>
<tr>
<th>Model components</th>
<th>Red cell transfusion after surgery</th>
<th>Post-operative complication</th>
<th>Serious post-operative complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative and surgical clinical characteristics</td>
<td>0.67 (0.59, 0.75)</td>
<td>0.72 (0.66, 0.79)</td>
<td>0.73 (0.66, 0.80)</td>
</tr>
<tr>
<td>Post-CPB blood sample test results</td>
<td>0.59 (0.51, 0.69)</td>
<td>0.56 (0.48, 0.64)</td>
<td>0.52 (0.43, 0.62)</td>
</tr>
<tr>
<td>Combined clinical characteristics and blood test results</td>
<td>0.71 (0.63, 0.79)</td>
<td>0.75 (0.69, 0.82)</td>
<td>0.73 (0.66, 0.80)</td>
</tr>
<tr>
<td><em>P</em> value for combined model vs clinical characteristics only model</td>
<td>0.15</td>
<td>0.09</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Based on “A new standard for authorship” from The Council of Science Editors (http://tinyurl.com/lkab4jp).

By submitting this manuscript, each author certifies that:

They made a direct and substantial contribution to the work reported in the manuscript by participating in at least the following three areas:

- made substantial contributions to conception and design and/or acquisition of data and/or analysis and interpretation of data;
- participated in drafting and/or revising the paper and provided important intellectual contributions; and
- gave final approval of the submitted version and any revised versions submitted prior to acceptance.

They participated to a sufficient degree to take public responsibility for the work and believe that the manuscript describes truthful facts. They declare that they shall produce the data on which the manuscript is based for examination by the editors or their assignees, should it be requested. Each author also agrees to allow the corresponding author to make decisions regarding submission of the manuscript to the Journal, changes to galley proofs, and prepublication release of information in the manuscript to the media, federal agencies, or both.

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<table>
<thead>
<tr>
<th>Name:</th>
<th>University of Bristol, Bristol, UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution:</td>
<td>Bristol Trials Centre</td>
</tr>
<tr>
<td>Department:</td>
<td><a href="mailto:Jessica.harris@bristol.ac.uk">Jessica.harris@bristol.ac.uk</a></td>
</tr>
<tr>
<td>Email:</td>
<td></td>
</tr>
</tbody>
</table>

Area(s) of Statistical Expertise:

Dr Harris and Professor Rogers are the Senior statistician and Director of the Bristol Trials Centre (https://bristoltrialscentre.blogs.bristol.ac.uk/) which is a UKCRC-registered clinicla trial unit with extensive expertise of design delivery and statistical analysis of observational and clinical trails.

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