THE USE OF FIBRINOGEN CONCENTRATE IN HIGH-RISK CARDIAC SURGERY: A PROSPECTIVE DOUBLE BLIND RANDOMIZED CONTROLLED STUDY

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BACKGROUND INFORMATION

Complex cardiac surgery (time-consuming surgeries, e.g. aortic root/arch repair or combined procedures, e.g. aortic valve replacement and coronary artery bypass grafting) is often accompanied by excessive perioperative bleeding. Contributing factors are hemodilution, platelet dysfunction and low levels of coagulation factors caused by prolonged cardiopulmonary bypass (CPB) time. Fibrinogen has a key role in maintaining and restoring hemostasis after long and complex cardiovascular surgery. One molecule of thrombin can activate 1680 molecules of fibrinogen[1]. A large amount of fibrinogen is captured by a few platelets via the abundant GPIIb/IIIa receptors (40,000-50,000 copies per platelet). [2] Clinical and in vitro data from Lang and coworkers demonstrates that even in the presence of reduced platelet count and thrombin levels (e.g. after extensive cardiopulmonary bypass) administration of fibrinogen increases clot strength. [3] Unfortunately the concentration of fibrinogen in fresh frozen plasma (FFP) is not high enough to treat hemorrhagic complications efficiently after complex cardiac surgery. [4] The average concentration of fibrinogen in FFP is 2.0 g/L. [5] The fibrinogen concentration can vary significantly between units. For the clinician it is difficult to predict the increase in patient plasma fibrinogen concentration after administration of FFP. [6] Chowdhury et al. measured a median increase of 1.0 g/L of fibrinogen after transfusion with 30ml/kg of FFP (2.4 L for 80 kg patient) in critical ill patients. [4] Those large volumes of FFP could be harmful (volume overload, hemodilution) for cardiac surgery patients who often suffer from myocardial dysfunction after complex and high-risk procedures.

The concentration of fibrinogen in cryoprecipitates (Cryo) is much higher compared to FFP. According to Canadian Blood Services each unit of Cryo is supposed to have between 150 - 450 mg of fibrinogen (7.5 g/L - 22.5 g/L). Canadian Blood Services guaranties this concentration in 75% of the provided units. [7] Thus, Cryo has the same problem as FFP the concentrations of fibrinogen do differ between units. Additionally Cryo can't be virus-inactivated. Because of the risk of transmission of

infectious agents most European countries have stopped using Cryo. [8]

RiaSTAP™ (CLS Behring, Marburg, Germany) is a new alternative source of fibrinogen. It provides purified, virus-inactivated, standardized concentration of fibrinogen. It is reconstituted with low volume of sterile water (1 g/50ml, 20 g/L). Although much anecdotal evidence exists there are few studies that provide evidence supporting its superiority to conventional treatment using FFP and Cryo. Current indication for fibrinogen concentrate has been replacement therapy in congenital fibrinogen deficiency.

Name and description of the investigational product

RiaSTAP™ (Fibrinogen concentrate (Human), FCH) is a pasteurized, preservative free, lyophilized human fibrinogen concentrate. It is derived from human plasma and presented as a white powder for reconstitution with sterile water for injection (not provided with the product) and infusion. RiaSTAP™ is to be intravenously (i.v.) administered.

RELEVANT SYSTEMATIC REVIEWS AND PUBLISHED TRIALS

There have been several articles in a cardiovascular setting. One study was comparing retrospective and prospective data in patients having aortic valve operation and ascending aorta replacement. Most patients (80%) of the prospective group who received concentrated fibrinogen did not need any allogeneic blood products. In the retrospective group without concentrated fibrinogen treatment almost everyone required blood products (41 of 42 patients). [9] A follow up study with small numbers (n=6) investigated patients with thoracoabdominal aortic aneurysm repair. Rahe-Meyer and co-workers found a significant reduction of transfusion of allogeneic blood products in patients receiving concentrated fibrinogen. [10]

A review article from Sørensen et al. gives a very detailed and critical evaluation of Cryo for replacement of fibrinogen. This

article discusses the problems of pathogen transmission, immune-mediated complications and timing issues (thawing, transportation) with the usage of Cryo in perioperative bleeding. [8] A recently (February 2012) published review article by Levy and co-workers points out that "*fibrinogen is critical for effective clot formation, and its monitoring and guided supplementation in the treatment of major bleeding is increasingly recognized... further prospective, randomized controlled studies on the use of fibrinogen concentrate are essential to help define the breadth of clinical settings in which fibrinogen supplementation may be beneficial*".[11]

Evidence supporting need for a trial

Several studies have demonstrated that the fibrinogen level is the limiting factor for postoperative hemostasis. [9,12-14] Conventional treatment of excessive perioperative bleeding after complex cardiac surgery consists of administration of FFP, platelets and Cryo. This empirical approach needs to be evaluated in view of reported unfavourable outcomes (e.g. lung injury, myocardial infarction, right-ventricular dysfunction, stroke, arrhythmia, infection) associated with FFP and platelet transfusion. [14,15] Cryo has several disadvantages compared to concentrated fibrinogen: risk of ABO incompatibility, no standardized concentration, no viral inactivation, higher thrombotic activity, more expensive, must first be thawed, and delayed administration (45 min.). [8,16]

There is evidence that side effects associated with the use of packed red cells, platelets, FFP, and Cryo significantly increases the risk of complications after surgery. The most significant evidence linking transfusion and the development of ALI/ARDS comes from the Canadian Critical Care Trial. Hebert et al. randomized 838 critically ill patients to either a liberal transfusion regime or a restrictive transfusion regime. [17] The liberal transfusion regime was associated with a higher rate of ALI/ARDS and a higher mortality. Gong and coworkers demonstrated significantly higher odds of the development of ALI/ARDS in patients treated with a blood transfusion. [18] Croce at al. showed in a retrospective analysis of 5260 trauma patients a much higher risk of ALI/ARDS in those patients who had received

any transfusion. [19] An investigation conducted by Silverboard and coworkers demonstrated a dose-dependent relationship between the number of units of blood products and the development of an acute lung injury. The risk was significantly increased after 5 units. [20] Another contributing factor for postoperative morbidity and mortality is nosocomial infections. In a prospective observational study by Taylor and coworkers the number of transfused RBC units was an independent risk factor for nosocomial infections. Mortality and length of stay (ICU and hospital) were significantly higher in transfused patients. [21]

How will the results impact clinical practice?

With the expected positive results, we hypothesize that concentrated fibrinogen will be used as first line therapy in perioperative management of bleeding during and after major surgery. With an overall blood transfusion rate of **38%** (all cardiac cases, last 5 years, n=5100) and a blood transfusion rate of higher risk cases of **60%** (aortic valve replacement (AVR) + coronary artery bypass grafting (CABG), n=386); the primary use of blood components like packed red blood cells (RBCs), platelets, FFP, and Cryo will be reduced.

RISKS AND BENEFITS TO HUMAN SUBJECTS

Risks

There are no studies published to date that clearly address the risk associated purely to fibrinogen supplementation. Based on the available literature the risk of any adverse event directly related appears to be < 1/10000 patient. The following outlines the state of knowledge regarding the use of fibrinogen products.

A review article by Dickneite et al. analyzed an extensive pharmacosurveillance database of more than 250000 treatment episodes with fibrinogen concentrate. They found an incidence of thrombotic events possibly related to fibrinogen of approximately 3.5 per 100,000 treatment episodes. [22]

Kreuz et al. analyzed 151 fibrinogen infusions in 12 patients with congenital fibrinogen deficiency (median dosage range 63.5mg/kg body weight to 105.6mg/kg body weight). One patient experienced an anaphylactic reaction after the 56th infusion. Another patient developed deep vein thrombosis and non-fatal pulmonary embolism after complex orthopedic surgery. Fibrinogen treatment could not be excluded as a contributing factor in this high-risk patient. [23]

The current indication for fibrinogen concentrate has been replacement therapy in congenital fibrinogen deficiency. Two studies with patients who suffered from congenital fibrinogen deficiency also showed a good clinical efficacy and a favourable safety profile. [23,24] Manco-Johnson et al. assessed the safety of fibrinogen concentrate in 15 patients with afibrinogenemia. They concluded that fibrinogen concentrate has a good safety profile with no evidence of serious adverse events (e.g. viral transmission, thromboembolism nor vital sign changes). Four patients experienced minor symptoms during the study (headache, pain, GERD and epistaxis) and were not related to the study drug. [24]

Benefits

The available evidence suggests that fibrinogen concentrate rapidly and safely restore hemostasis in patients with

congenital fibrinogen deficiency. [24] Perioperative fibrinogen concentrate infusion reduced bleeding after CABG without evidence of postoperative hypercoagulability in a prospective randomized pilot study by Karlsson et al. [25]

Depending on the results of our proposed study, concentrated fibrinogen will be used as first line therapy in perioperative management of bleeding during and after major surgery. The expected outcome is that primary use of blood products like packed red cells, platelets, FFP, and cryo will be reduced. The potential overall reduction of the use of blood products (RBC, platelets, and FFP) due to fibrinogen will possibly improve significantly patient's outcome after complex cardiac surgery. Blood transfusions have long been implicated as a risk factor for severe complications like acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and nosocomial infections. Probably the most significant evidence of the link between transfusion and the development of ALI/ARDS has come from the Canadian Critical Care Trial.

The studies available to date that have used concentrated fibrinogen in cardiac surgery showed a very low risk of thrombosis. Karlsson et al. demonstrated the preoperative infusion of concentrated fibrinogen reduced significantly bleeding in patients (n=20) after coronary artery bypass grafting (CABG). No adverse thrombotic events were recorded. [25] Rahe-Meyer and coworkers showed that intraoperative administration of concentrated fibrinogen reduced transfusion requirements and postoperative bleeding (n=42). [9] In a study of Solomon et al. with patients who had diffuse bleeding after cardiac surgery fibrinogen concentrate was effective in increasing plasma fibrinogen levels and contributed to the correction of bleeding after cardiac surgery (n=39).[26] In a retrospective study from Thorarinsdottir and coworkers concentrated fibrinogen administration improved coagulation parameters and reduced transfusion requirements. Most of the investigate patients had open heart surgery (n=30). [27] All those studies reported no thromboembolic complications associated to administration of concentrated fibrinogen. Other investigations demonstrated the efficacy of intravenous fibrinogen in various clinical hemorrhage scenarios (orthopedic procedures, GI

bleeding, sepsis, liver dysfunction, trauma).[28-31] In all the studies the administration of fibrinogen was well-tolerated. No severe adverse events attributable to fibrinogen concentrate were recorded.

Although the current literature shows that concentrated fibrinogen has a good safety profile the above authors have the opinion that there is a strong need for better studies because the evidence is restricted to case studies and retrospective analyses.

The expected outcome is that primary use of blood products (packed red cells, platelets, FFP, and Cryo) will be reduced. This overall reduction due to the use of fibrinogen concentrate will also reduce the side effects associated with the use of packed red cells, platelets, FFP, and Cryo and will significantly benefit patients.

ROUTE OF ADMINISTRATION, DOSAGE, DOSAGE REGIMEN, AND TREATMENT PERIOD

Fibrinogen dosing will be based on the results of the FIBTEM® analysis. The amount of fibrinogen concentrate corresponds to approximately 0.5 g of fibrinogen concentrate needed to raise MCF by 1 mm in a 70 kg patient. [9,10,26] The maximum amount of fibrinogen concentrate used in this study will be 10 g in any participant. In the placebo group, the standard hemostatic algorithm involving the use of plasma, Cryo and platelets (Figure 1), will be used as per the standard of care currently in place at CDHA.

Once randomized to treatment, the test compound will be administered through the central line (usually internal jugular vein catheter) by the anesthesiologist within 10 minutes (25-50 ml/minute). Since high doses of anticoagulants are used in this surgical population while on cardiopulmonary bypass it is important that the test compound is administered in a relatively short period of time to boost the fibrinogen level.

The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

STUDY POPULATION

All patients will be recruited from the Queen Elizabeth II Health Sciences Center (QEIIHSC), Halifax, Nova Scotia, which is the sole tertiary cardiac surgery referral center in Nova Scotia. There are approximately 1000 open heart surgical procedures performed yearly, including more than 700 isolated CABG procedures.

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TRIAL OBJECTIVES AND PURPOSE

Research question

Hypothesis: The aim of the study is to show that prophylactic first line treatment with concentrated fibrinogen prior to conventional therapy with FFP, platelets, Cryo, and other blood products such as factor VII concentrate and human prothrombin complex (factors II, VII, IX, X) has superiority over conventional therapy alone ("wait and see") in ~~perioperative management of bleeding~~ patients with low or low normal fibrinogen levels (≤3.8g/l) after complex cardiac surgery.

Primary objective: To determine the cumulative perioperative amount (number of units) of blood components used between the start of surgery and 24 hours after administration of the study drug or placebo. 'Blood Components' are defined as all fresh components of blood (PRBCs, plasma, platelets, and Cryo).

Secondary objective: To determine the effect of RiaSTAP™ on fibrinogen levels, hematocrit, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), platelet count, hemoglobin, thromboelastometry* (ROTEM®, EXTEM, INTEM, HEPTEM, FIBTEM test, Clotting Time, Clot Formation Time, Angle, Maximum Clot Firmness), CVICU-stay, Hospital-stay, In-Hospital Mortality, adverse events (anaphylaxis, stroke, myocardial infarction, pulmonary embolism, and deep vein thromboembolism) and usage of factor VII concentrate and human prothrombin complex (factors II, VII,IX, X), total avoidance of transfusion after CPB (24h after administration of study drug or placebo).

*Thromboelastometry (ROTEM®; Pentapharm GmbH, Munich, Germany) is a bedside qualitative test of whole blood coagulation (Figure 1). The Clotting Time (CT) represents the time required for initial fibrin formation. Both Clot Formation Time (CFT) and angle represent the rate of clot formation, fibrin cross-linking, and platelet-fibrin interaction. Maximum Clot Firmness (MCF) represents the overall clot quality determined by

polymerised fibrin, platelets and factor XIII. The ROTEM® system provides several tests, one of them is the FIBTEM® test. The FIBTEM® test shows the isolated fibrinogen contribution to the clot firmness (Figure 2).

TRIAL DESIGN

Primary and secondary outcomes

Primary outcome: Cumulative perioperative amount (number of units and total volume) of blood components used between the start of surgery and 24 hours after administration of the study drug or placebo. 'Blood Components' are defined as all fresh components of blood (RBCs, plasma, platelets, and Cryo).

Secondary outcomes: To determine the effect of RiaSTAP™ on fibrinogen levels, hematocrit, PT, PTT, INR, platelet count, Hemoglobin (Hb), Thromboelastometry (ROTEM®, CT, CFT, Angle, MCF), CVICU-stay, Hospital-stay, In-Hospital Mortality, Hemoglobin, adverse events (anaphylaxis, stroke, myocardial infarction, pulmonary embolism, and deep vein thromboembolism) and usage of factor VII concentrate and human prothrombin complex (factors II, VII,IX, X), total avoidance of transfusion after CPB (24h after administration of study drug or placebo).

METHODOLOGY

The proposed trial will be a prospective, single-centre, double blind, randomized, controlled trial comparing blood product utilization between patients receiving saline therapy (PLACEBO) compared to fibrinogen therapy (FIB) in the setting of perioperative ~~surgical bleeding~~ blood management in patients with low or low normal fibrinogen levels after complex cardiac surgery. Blood products refer to any manufactured product derived from blood or plasma (albumin, fibrinogen, rFVIIa, human prothrombin complex, etc.).

Intervention

Prospective, randomized controlled study involving two groups: fibrinogen group (FIB) and saline group (PLACEBO), with a standardized anaesthesia protocol. Anesthesia management, surgical technique, post-operative management and follow-up will be as per the standard of care for this surgical population.

In-Hospital Follow-up: All postoperative cardiac surgery patients will be followed for the duration of their hospital stay. Blood work and amount of blood components and products will be assessed at the end of surgery, 12hr, and 24hr after delivery of the study medication. The study endpoint for the primary outcome parameter (amount of blood components) will be 24h after administration of the study medication.

Other outcomes assessed include Thromboelastometry (ROTEM®, EXTEM, INTEM, HEPTEM, FIBTEM, CT, CFT, Angle, MCF), CVICU-stay, Hospital-stay, In-Hospital Mortality, Hemoglobin, and adverse events.

Any patients with evidence of study drug related adverse events at follow-up will be reviewed by the Data and Safety Monitoring Committee (DSMC) to review all the supporting evidence. The (DSMC) will consist of at least one anesthesiologist, one surgeon and a statistician not otherwise associated with the trial. Their role will be to review the available evidence provided by the research coordinator for the follow-up of all patients including in-hospital and follow-up study drug related adverse events. The outcomes of interest are listed above and will follow-strict study definitions as outlined. All outcomes will be based on consensus of the DSMC.

There will be an interim analysis performed by the Data and Safety Monitoring Committee. This analysis will be conducted when half of the patients have been enrolled. The final analysis will be conducted once all enrolled patients have reached their follow-up date. All final analysis will take into consideration that an interim analysis was conducted.

In case the study is terminated prematurely, the REB will be notified within 14 days in writing including the reason for the termination. If the termination is related to an emergent safety issue, the notification will be faxed to the REB office or preceded by a telephone call to the Chair or REB Coordinator. The study will be unblinded and all patients having received fibrinogen concentrate will be notified in writing and by direct contact via a telephone call of the study termination as well as

the reason for termination. Patients will also be informed of any emergent safety issues or adverse outcomes. Patients will be instructed on how to proceed in terms of medical care and follow up investigations.

RANDOMIZATION METHOD

Informed consent will be obtained from the patient prior to the operation either in the same-day surgery clinic or at the bedside if the patient has already been admitted to hospital pre-operatively. The randomization process will be performed with the help of software (G*Power version 3.1.2). Treatment allocation cards will be provided by the study Sponsor and placed in sealed, opaque envelopes for safe storage in a secure location to preserve the integrity of the blinding. The study drug designate will withdraw the envelope directing the patient's randomization to the FIB group or the PLACEBO group. Both the surgeon and anaesthesiologist will be blinded to patient randomization.

Randomization process

After eligibility and written informed consent is confirmed patients will be randomized on the day of surgery after arrival at the OR to receive either fibrinogen concentrate or placebo after heparin reversal as indicated in the algorithm (Figure 3). ~~If the patient has a diffuse medical bleed then the research coordinator will be called to inform~~ The ~~research coordinator~~ study drug designate will call the study drug designate to randomize the patient and a sequential envelope will be opened by them in the blood bank. The drug/placebo will be prepared in the Blood Transfusion Services at the Infirmary site. The drug/placebo will be transported to the OR by the study drug designate.

Dosage and Dosage Regimen

The dose of fibrinogen concentrate will be calculated based on the point of care measurement of n maximum clot firmness (MCF)

in the FIBTEM® test performed on CPB (aortic cross clamp off)[10]. According to the available literature we will use the following formula to achieve the preoperative (baseline) FIBTEM MCF (mm):

Fibrinogen dosage (g) = [Preop FIBTEM MCF (mm) - FIBTEM MCF (mm)] x bodyweight (kg) x c

$$C = \frac{0.5\ g}{1(mm)\ X\ 70}$$

The formula can be simplified to:

(Preop FIBTEM MCF – FIBTEM MCF) x bodyweight/140.

Calculation example: A patient's bodyweight is 75kg. The baseline FIBTEM MCF showed 22mm. The FIBTEM test on CPB shows a MCF of 10 mm. The overall dose of concentrated fibrinogen to achieve the baseline MCF of 22 mm would be:

Fibrinogen dosage (g) = (22 - 10) x 75/140 = 12 x 75/140 = **6.4**

Fibrinogen dosing will be based on the results of the FIBTEM® analysis. The amount of fibrinogen concentrate corresponds to approximately 0.5 g of fibrinogen concentrate needed to raise MCF by 1 mm in a 70 kg patient [9,10,26] The maximum fibrinogen concentrate dose used in this study will be 10 g. If the baseline FIBTEM® is ≤ 12 mm the fibrinogen dosage will be calculated from a minimum baseline value of 15 mm to achieve a more effective fibrinogen dosage. In the placebo group, the standard hemostatic algorithm involving the use of plasma, Cryo and platelets (Figure 3), will be used as per the standard of care currently in place at CDHA.

The test compound will be administered through the central line (usually internal jugular vein catheter) within 10 minutes (25-50 ml/minute) by the anesthesiologist. Since high doses of anticoagulants are used in this surgical population while on cardiopulmonary bypass it is important that the test compound is administered in a relatively short period of time to boost the fibrinogen level. Two studies in cardiac surgery used an infusion rate of 20ml/minute and 150ml/minute without any adverse events. [25,26]

This bolus approach interrupts the circle of hemodilution and ongoing bleeding produced from cardiopulmonary bypass. This is the practice at CDHA in the cardiovascular anesthesia group. This technique has not produced any thromboembolic complications or severe side effects in the 25+ patients that have received this product in our health centre.

Reconstitution

The RiaSTAP, and placebo, are labelled as per Health Canada regulations. The reconstituted RiaSTAP or placebo will be transported by the ~~the Research Coordinator~~ Study drug designate to the OR and the Blood Transfusion requisition will be signed and completed by the anesthesiologist and the ~~Research Coordinator~~ Study drug designate once the medication has been given.

PLANNED FREQUENCY AND DURATION OF FOLLOW-UP

In-Hospital Follow-Up

All postoperative cardiac surgery patients will be followed for the duration of their hospital stay. Blood work and amount of blood components and products will be assessed at end of surgery, 12hr and 24hr after administration of study medication or placebo. The study endpoint for the primary outcome parameter (amount of blood components) will be **24h after administration of study medication or placebo**.

Other outcomes assessed include Thromboelastometry (ROTEM®, CT, CFT, Angle, MCF), CVICU-stay, Hospital-stay, In-Hospital Mortality, Hemoglobin, and adverse events.

After Discharge Follow-up

After discharge from hospital all patients, ~~including those involuntarily withdrawn from the study by a member of the research team,~~ are followed-up in clinic six weeks postsurgery. This is currently the standard of care for patients post CABG surgery. If ~~the patient~~ a study participant does not return to

clinic at the time window of six weeks +/- 1 week, a phone visit will occur by the research coordinator. Additionally all patients will be contacted by a research coordinator at three and six months. The focus of the interviews will be to determine anginal symptoms, and ~~need for~~ if readmission to hospital for acute myocardial infarction (AMI), acute coronary syndrome (ACS) or congestive heart failure (CHF) occurred. Events of interest include: incisional wound infection, thrombosis, recurrent angina, myocardial infarction, angiography, percutaneous coronary intervention (PCI), repeat cardiac surgery, stroke and cardiac related mortality. Any patients with evidence of adverse study drug related events at follow-up will be investigated further by the Data and Safety Monitoring Committee to review all the supporting evidence.

Proposed frequency of analysis

As previously stated there will be an interim analysis performed by the data and safety monitoring committee. This analysis will be conducted when half of the patients have been enrolled. The final analysis will be conducted once all enrolled patients have reached their follow-up date. All final analysis will take into consideration that an interim analysis was conducted.

SELECTION AND WITHDRAWAL OF SUBJECTS

Inclusion criteria

Participants will be eligible to participate in this trial if they:

- are scheduled for elective complex cardiac surgical procedures including:
  - double procedures (aortic valve replacement (AVR)+CABG, mitral valve repair/replacement (MVR)+CABG, AVR+MVR),
  - redo-sternotomies, and
  - Aortic root repair +/-AVR.
- have a preoperative fibrinogen level of ≤ 3.8 g/l

Subject exclusion criteria

Participants will be excluded if they have:

- Any known congenital or pre-existing bleeding disorder,
- ~~pre-existing clinically significant abnormal fibrinogen levels~~
- ~~pre-existing clinically significant abnormal fibrinogen levels~~
- ~~pre-existing clinically significant abnormal FIBTEM MCF tests~~
- Preoperative fibrinogen level of < 1.0 g/l
- Preoperative FIBTEM® of < 5 mm
- Preoperative fibrinogen level of > 3.8 g/l
- severe liver disease (alanine aminotransferase or aspartate aminotransferase > 150 U/l),
- inability to provide informed consent,
- emergency surgery,
- self-report pregnancy or nursing,
- age under 18 years,
- intake of anti-clotting drugs within 2-5 days preoperatively (low dose ASA is allowed) based on the drug's half life or pharmacokinetic profile,
- allergy to concentrated fibrinogen or other components in the product,
- anemia (Hb < 110),
- diagnosed deep vein thrombosis (DVT),
- pulmonary embolism,
- acute stroke (within the last 3 months),
- acute myocardial infarction (within the last 3 months),
- any unstable medical condition as determined by the Principal Investigator
- within the past 30 days, participated in or currently enrolled in a clinical trial.

Subject withdrawal criteria

~~As per the intraoperative algorithm (Figure 3) the Anesthesiologist and the Surgeon complete a bleeding assessment ten minutes after the protamine is given. If the patient is not having a diffuse medical bleed they will not be randomized and will be considered a screen failure.~~ Patients who are experiencing surgical bleeding after weaning from CPB and protamine administration with requirement of a second pump run are withdrawn from the study. In case of an ongoing bleeding after step 3 of the study algorithm (Figure 3) an immediate and blinded FIBTEM is performed in order to prevent an overdosing of fibrinogen. If the FIBTEM shows an amplitude > 20 mm the patient will be unblinded and drop out of the study for safety reasons. This way it is ensured that a patient who received concentrated fibrinogen is not getting Cryoprecipitate (step 4 of study algorithm; Figure 3) leading to supraphysiologic levels of fibrinogen. Patients who have extremely rare complications like air embolism, heart perforation or heart lung machine failure will be ~~excluded~~ withdrawn from the study.

TREATMENT OF SUBJECTS

After weaning from cardiopulmonary bypass (CPB), completion of heparin reversal with protamine and surgical hemostasis either concentrated fibrinogen or saline will be given intravenously. The surgeon and anaesthesiologist will ~~the amount of blood loss that is considered diffuse (non-surgical) bleeding.~~ determine when surgical hemostasis is completed. After agreement on completion of surgical hemostasis and defined intraoperative conditions a transfusion algorithm is initiated (Figure 3). ~~After the surgeon and anesthesiologist have agreed on diffuse bleeding then the patients are randomized~~ FIB patients are treated with concentrated fibrinogen based on maximum clot firmness (MCF) in the FIBTEM test (Figures 1 and 2) performed on CPB (aortic cross clamp off).

Defined Intraoperative Conditions – Standard of Care Assessments

As per the usual standard of care/clinical assessment to treat, the following criteria must be met prior to Fibrinogen administration:

- *ACT less than 150s,*
- *body temperature higher than ~~36~~ 35.5°C,*
- *pH more than 7.3,*
- *hemoglobin level higher than 70g/l,*
- *calcium level higher than 1 mmol/l (ionized)) ~~and~~*
- ~~*no blood products given before or during CPB (Defined intraoperative conditions).*~~

Anaesthesia management

As per the standard of care in this surgical population, all patients will undergo general anaesthesia and will be induced with midazolam, fentanyl or sufentanil, propofol and rocuronium. General anaesthesia will be maintained with sevoflurane titrated to maintain an end-tidal concentration of 1-2% and boluses of fentanyl or sufentanil, until initiation of cardiopulmonary bypass.

Tranexamic acid (Sandoz Canada Inc.) will be infused at a rate of 2mg/kg/hr following an initial bolus of 1000-2000mg. During the cardiopulmonary bypass run, propofol will be infused with subsequent boluses of fentanyl or sufentanil. Prior to cardiopulmonary bypass, patients will be given unfractionated heparin (500 units/kg; PPC, Pharmaceuticals Partners of Canada Inc.) to maintain an activated clotting time (ACT) > 480 seconds. The cardiopulmonary bypass circuit includes a membrane oxygenator and roller pumps to maintain a non-pulsatile perfusion technique. Depending on the procedure, deep or moderate hypothermia (nasopharyngeal temperature of 18 or 32 to 34^{o}C) will be utilized and cardioprotection will be maintained using antegrade and retrograde cold blood cardioplegia when possible. Separation from cardiopulmonary bypass will be achieved once the patient is re-warmed to a nasopharyngeal temperature of 36.5^{o}C. Following separation from cardiopulmonary bypass, heparin will be reversed with protamine (1mg protamine/100units heparin; protamine sulphate, Sandoz Canada Inc.). A hemoglobin concentration below 70 g/l will be treated with PRBCs to maintain a hemoglobin of 70 g/l or greater throughout the procedure.

Surgical technique

As per standard of care in this surgical population and depending on the procedure, a median sternotomy or lateral thoracotomy will be performed in all patients. Surgery will be performed in a standardized fashion with CPB. During CPB, the mean arterial pressure target will be 60-70 mmHg and the body temperature will be allowed to drift to approximately 32^0C or lower. Intermittent cold blood cardioplegia (1:4 blood to crystalloid with maximal K^+ concentration 22 meq/L) will be delivered antegrade via the aortic root unless otherwise indicated. No special blood conservation technique will be utilized other than: non-hemic prime, retransfusion of all contents of the oxygenator at the end of CPB, and acceptance of normovolemic anemia. Post-operatively non-hemic volume expanders are utilized routinely (Voluven®, Kabi Fresenius Inc., Germany).

Post-operative management

As per the standard of care in this surgical population, all post-operative cardiac surgery patients will be taken immediately to a dedicated cardiovascular intensive care unit (CVICU). All patients will receive respiratory and hemodynamic support as needed. Each patient will be required to meet standard hospital criteria both prior to extubation and prior to transfer to the intermediate-care unit (IMCU). Discharged patients will be transferred to an intermediate-care unit or general-care ward under the care of the same cardiac surgical team. All patients will be monitored continuously for a minimum of 24 hours. In case of a post-operative bleeding in CVICU the same algorithm (Figure 3) like in the OR will be used. In case of surgical bleeding a re-sternotomy will be performed. Diffuse bleeding will be treated with blood components (step 2 -5, Figure 3). Patients having a valve replaced with a mechanical valve will receive heparin or warfarin 48 hours after surgery. All other patients will get ASA (acetylsalicylic acid, Aspirin®, Bayer Canada) on the first postoperative day (anticoagulation protocol, Division of Cardiac Surgery, QEII, Halifax, Canada).

ASSESSMENT OF SAFETY

Adverse Events

The following treatment-emergent and adverse effects will be captured during this study from the date ~~the consent was signed~~ of randomization to the 6 month follow-up:

Treatment-emergent adverse events

- Pleural effusion
- Atrial fibrillation
- Postoperative Delirium
- Reoperation because of surgical bleeding and unknown bleeding
- Air embolism

Adverse events (A/E) and Serious adverse events (SAE)

- Anaphylaxis
- Stroke
- Myocardial infarction
- Pulmonary embolism
- Deep vein thromboembolism
- Sternal wound infection
- Recurrent angina
- Angiography
- Percutaneous coronary intervention (PCT)
- Repeated cardiac surgery
- Cardiorespiratory arrest
- Cerebral hemorrhage
- Death

All serious unexpected adverse drug reactions will be reported to Health Canada as per ICH/GCP guidelines.

Unblinding

Unblinding for this study will occur when:

1. Clinical treatment decisions need to be made and when an unexpected serious adverse event occurs and the intervention must be made known.
2. At the request of the Data Safety Monitoring Committee.

3. After 110 participants have reached the primary endpoint for interim analysis.
4. At the conclusion of the study to determine the effect of the intervention.

The Blood Transfusion Services are able to unblind for the clinical treatment of a patient. Please refer to the site Standard operating procedure for more details of this process. If a patients treatment is unblinded before the 24 hour primary end point their data will not be used in the analysis.

STATISTICS

Sample size

The primary outcome of interest will be overall need for blood transfusion at 24hr after surgery (including all used blood components from the start of surgery). For the sample size calculations G*Power version 3.1.2 was used.

Based on the available literature [9,10,12], the investigator hypothesized a 70-90% reduction in total units of blood products in the group receiving fibrinogen compared with the group receiving conventional therapy. An estimate of blood product requirement in the group receiving conventional therapy is mean 3.4 units (standard deviation 5.9) based on our data from 2005 to 2007 for AVR+CABG, MVR+CABG, AVR+MVR, and Aortic root repair +/-AVR. Standard deviation 5.9 was used for both groups. Blood product requirement in the two groups will be compared using the Mann-Whitney U test for two independent samples. The sample size calculation was based on a two-tailed test with $\alpha = 0.05$, for $\beta = 0.2$, 0.1, and 0.05. The sample sizes shown Table 1 represent the number of patients required in each group.

Details of the planned analysis

~~Individual case forms will be completed by the research coordinator for individual patients.~~ The research coordinator will complete individual case forms for individual patients. These forms will be detailing demographic characteristics,

intra-operative, post-operative and follow-up outcomes. Outcome data and blood samples will be collected according a lab/data schedule (Table 2). ~~All data will be reviewed by the appropriate clinical outcomes committee.~~ The Sponsor will review all data. Once reviewed all data will entered and maintained electronically.

Primary outcome: Blood component requirement in the two groups will be compared using the Mann-Whitney *U* test for two independent samples.

Secondary outcomes: Univariate comparisons between patients randomized to FIB and patients randomized to PLACEBO group will be carried out based on pre-, intra-, and post-operative variables using Chi-square tests for dichotomous variables, two-tailed t-tests for continuous variables and Wilcoxon rank sum tests for nominal variables.

All statistical analyses will be performed at the QEII Health Sciences Center using SAS version 9.2 (Cary, North Carolina). Data validation will be an integral part of this protocol and will be carried out using already established clinical and administrative patient databases available through the Division of Cardiac Surgery at the QEIIHSC. This will ensure 100% follow-up of all patients and data accuracy. ~~All discrepancy will be investigated by the clinical outcomes committee.~~ The Data and Safety Monitoring Committee will investigate all discrepancies. The Maritime Heart Center (MHC) cardiac surgery database is a prospectively collected, clinical database that captures detailed information on a wide range of pre-operative, intra-operative, and in-hospital post-operative variables including post-operative complications and in-hospital mortality for all patients undergoing cardiac surgery at the QE II Health Sciences Center. It is audited on an annual basis to ensure reliability of data capture. The MHC cardiac surgery database will be linked to the Canadian Institute for Health Information (CIHI) Discharge Abstract Database and the Nova Scotia Vital Statistics database through the Population Health Research Unit (PHRU) at Dalhousie University. The CIHI Discharge Abstract Database is a national administrative database that contains extensive data on all admissions to hospital and enables us to track all

readmissions to hospital. The Nova Scotia Vital Statistics database collects information on all deaths occurring within the province of Nova Scotia and enables us to track all-cause mortality following discharge from hospital. The following data will be obtained from the MHC-PHRU data link after 6-months follow-up for all patients:

i) Cardiac related mortality
ii) Readmission to hospital for acute myocardial infarction (AMI), acute coronary syndrome (ACS), or congestive heart failure (CHF)
iii) Re-intervention including CABG and/or PCI

Estimated Recruitment Rate

Approximately 200 complex cardiac procedures are performed annually in Halifax by nine cardiac surgeons. Of these patients, conflicting studies and patients being disqualified on the basis of exclusion criteria will result in a maximal annual number of eligible patients of 100 per year. We would plan to recruit 222 patients for this study. With a length of follow up of 6 months and using administrative data of an already well established data base we are expecting a rate of loss under 5%.

DATA HANDLING AND RECORD KEEPING

Data will be collected from patient charts and health records, the anesthetic record as well as the Maritime heart center cardiac surgery database. A data collection sheet will be filled out by the study nurse for patients included in the study. Follow-up data will be collected from patients themselves. In cases where patients have adverse outcomes, this information will be obtained from hospital records and the patient.

A data collection form will be used to collect study information and will be completed by the designated study personnel for participants. These forms will be detailing demographic characteristics, intra-operative, postoperative and follow-up outcomes. Individual data forms will record: the perioperative amount of blood products used (packed red cells, FFP, platelets,

Cryo). Also fibrinogen levels, hematocrit, PTT, INR, platelet count, Hemoglobin, Thromboelastometry (ROTEM®, CT, CFT, Angle, MCF), CVICU-stay, Hospital-stay, In-Hospital Mortality, Hemoglobin, adverse events (anaphylaxis, stroke, myocardial infarction, pulmonary embolism, and deep vein thromboembolism) and usage of factor VII concentrate and human prothrombin complex will be collected for study purposes. All data will be reviewed by the appropriate outcome committee. Once reviewed all data will entered and maintained electronically on a designated CDHA computer.

Data will also be collected using the Maritime Heart Center (MHC) cardiac surgery database. This database is a prospectively collected, clinical database that captures detailed information on a wide range of pre-operative, intra-operative, and in-hospital postoperative variables including post-operative complications and in-hospital mortality for all patients undergoing cardiac surgery at the QE II Health Sciences Center.

QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

Data validation will be an integral part of this protocol and will be carried out using already established clinical and administrative patient databases available through the Division of Cardiac Surgery at the QEIIHSC. This will ensure 100% follow-up of all patients and data accuracy. The Data and Safety Monitoring Committee will investigate all discrepancies.

Monitoring

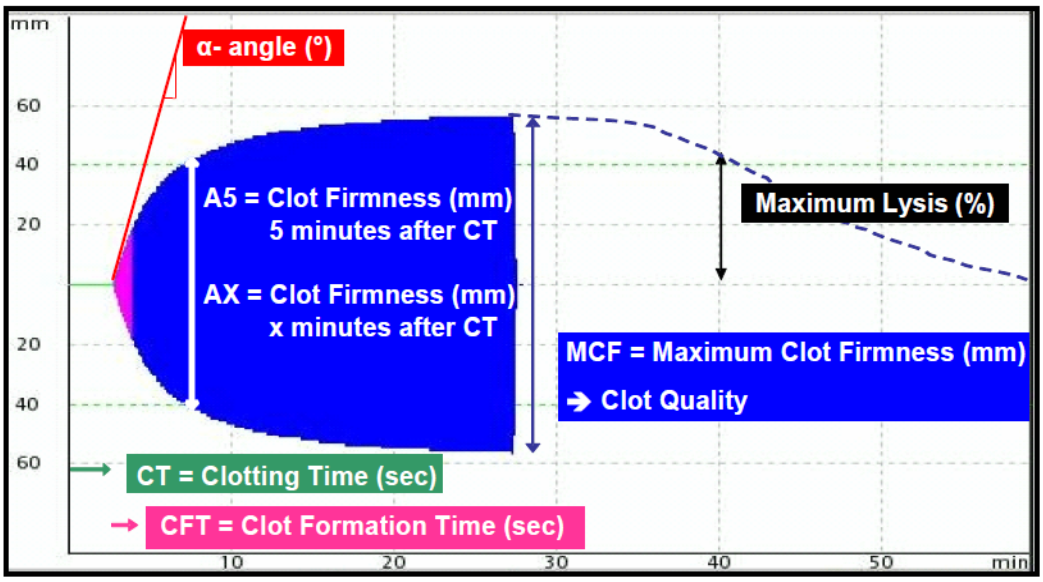
The study will be monitored in accordance with ICH-GCP guidelines that require a minimum of three visits, before the trial starts, once during the trial, and after the trial is completed.

Data Storage

During the study data will be stored in a filing cabinet in a designated office for the study nurse as well as a CDHA computer, as a data file. All other data will be stored on the CDHA network. Once the study is complete, data will be stored in a filing cabinet in the Principal investigator's office under lock and key. All other data will be stored as per current standard of practice for elective cardiac surgery patients; on the CDHA network and in the Maritime Heart Center (MHC) cardiac surgery database. De-identified information will be available to the sponsor after study completion. In case of adverse outcomes, the study will be unblinded and may be reviewed by regulatory agencies through CDHA. The research team also intends to publish de-identified in a research journal that will be available to the study participants and to the public.

~~Prior to data transfer to CSL Behring, study participant information will be de-identified using a serial number system. This unique number will be assigned to each study participant and will be stored on paper in a filing cabinet in a designated, secure office in the Department of Anesthesia.~~ The study research data will be archived for a minimum of 25 years according to the current Capital Health policy. Once the information requires destruction, paper data will be shredded through the hospital confidential waste disposal. Electronic data will be deleted from the designated CDHA computer. Data stored independently on the CDHA hospital network and the Maritime Heart Center database will be disposed of by the regulations governing those networks or databases.

Figure 1. ROTEM® Parameters



CT (clotting time): time from start of measurement until initiation of clotting
=> initiation of clotting, thrombin formation, start of clot polymerisation

CFT (clot formation time): time from initiation of clotting until a clot firmness of 20mm is detected
=> fibrin polymerisation, stabilisation of the clot with thrombocytes and F XIII

MCF (maximum clot firmness): firmness of the clot
=> increasing stabilisation of the clot by the polymerised fibrin, thrombocytes as well as F XIII

ML (maximum lysis): reduction of the clot firmness after MCF in relation to MCF
=> stability of the clot (ML < 15%) or fibrinolysis (ML > 15% within 1h)

Figure 2. FIBTEM® Test Specificities

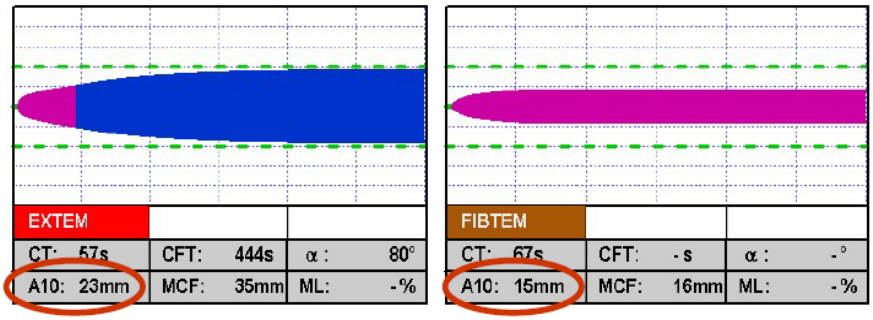
FIBTEM:
- activation as in EXTEM
- platelet inhibition reagent added

→ TEMogram shows isolated fibrinogen contribution to Clot firmness

A)
- EXTEM: amplitude low
- FIBTEM: amplitude normal

=> fibrinogen level OK

=> platelet deficiency



B)
- EXTEM: amplitude low
- FIBTEM: amplitude low

=> fibrinogen deficiency

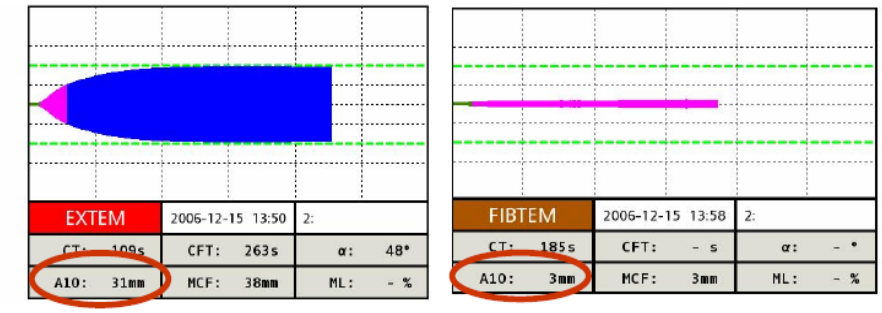


Figure 3. Treatment Algorithm

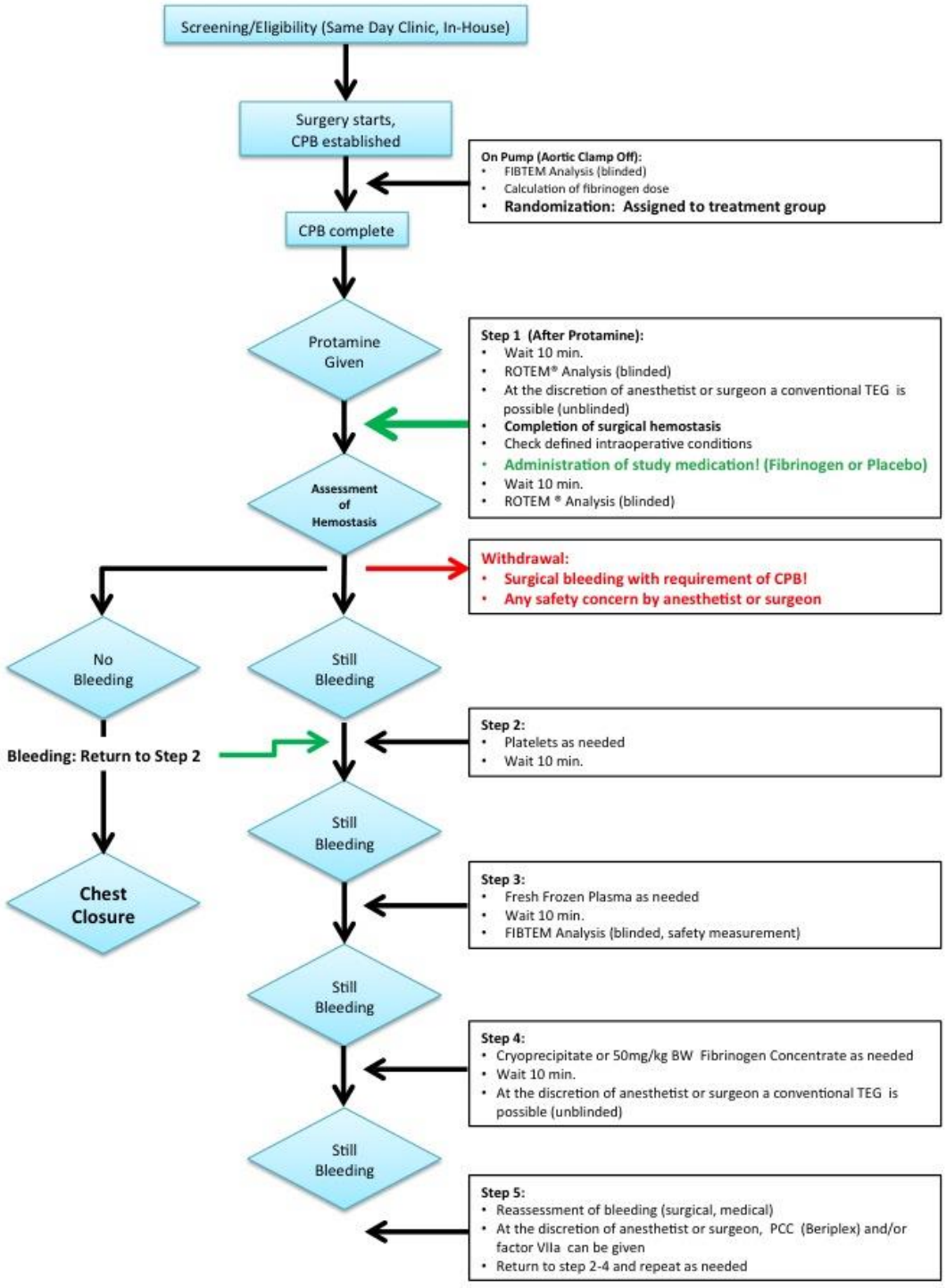


Table 1. Sample Size Calculation

	Relative Risk Reduction in Mean Number of Units Transfused			
Power = 1-beta	30% Δ = 1.0 units (3.4 to 2.4)	50% Δ = 1.7 units (3.4 to 1.7)	70% Δ = 2.4 units (3.4 to 1.0)	90% Δ = 3.1 units (3.4 to 0.3)
80%	634	220	**111**	69
90%	848	295	149	92
95%	1049	364	183	113

Table 2. Schedule of Assessments

	Preop I+II	Intraop I	Intraop II	Intraop III	Postop I	Postop II	Postop III	Postop IV
Time intervals	**Baseline**	**On Bypass Aortic Clamp Off**	**Off Bypass After Heparin reversal (5-15 minutes post protamine)**	**10 minutes after administration (+5 minutes)**	**End of Surgery (±10 minutes)**	**Blood Draw 12 Hours (±60 minutes)**	**Blood Draw 24 Hours (±60 minutes)**	**Discharge**
Primary Outcome					Total Blood Components Used	Total Blood Components Used	**Total Blood Components Used**	Total Blood Components Used
					Cryo Used	*Cryo Used*	***Cryo Used***	*Cryo Used*
					FFP Used	*FFP Used*	***FFP Used***	*FFP Used*
					Packed Red Cells Used	*Packed Red Cells Used*	***Packed Red Cells Used***	*Packed Red Cells Used*
					Platelets Used	*Platelets Used*	***Platelets Used***	*Platelets Used*
Secondary Outcomes	Fibrinogen Levels		Fibrinogen Levels	Fibrinogen Levels	Fibrinogen Levels	Fibrinogen Levels	**Fibrinogen Levels**	~~Adverse Effects:~~
	Hematocrit		Hematocrit	Hematocrit	Hematocrit	Hematocrit	**Hematocrit**	~~Anaphylaxis~~
	Hemoglobin	ABG/ Hemoglobin	ABG/ Hemoglobin	ABG/ Hemoglobin	ABG/ Hemoglobin	Hemoglobin	**Hemoglobin**	~~CVICU LOS~~
	INR/PT		INR/PT	INR/PT	INR/PT	INR/PT	**INR/PT**	~~Deep Vein Thromboembolism~~
	Platelet Count		Platelet Count	Platelet Count	Platelet Count	Platelet Count	**Platelet Count**	~~Hospital LOS~~
	PTT		PTT	PTT	PTT	PTT	**PTT**	
	*ACT	ACT	ACT	ACT	ACT		**Blood Drainage**	~~In Hospital Mortality~~
	*EXTEM	EXTEM	EXTEM	EXTEM	EXTEM	EXTEM	**EXTEM**	~~Myocardial Infarction~~
	*INTEM		INTEM	INTEM	INTEM	INTEM	**INTEM**	~~Pulmonary Embolism~~
	*FIBTEM	FIBTEM	FIBTEM	FIBTEM	FIBTEM	FIBTEM	**FIBTEM**	~~Stroke~~
			HEPTEM	HEPTEM	HEPTEM	HEPTEM	**HEPTEM**	
	AT III		Usage of Factor VII a	Usage of Factor VII a	Usage of Factor VII a	Usage of Factor VII a	**Usage of Factor VII a**	Usage of Factor VII a
	*ABG		Usage of human prothrombin complex	Usage of human prothrombin complex	Usage of human prothrombin complex	Usage of human prothrombin complex	**Usage of human prothrombin complex**	Usage of human prothrombin complex

Please Note: 24 hour blood draw = primary endpoint highlighted in green, assessments highlighted in peach are outside

the standard of care , ***Preoperative 1- assessments done in Same day admission or on the floor the day prior to OR*** ****Only these values will be done on the Preoperative II time point. Preoperative II (window is +10 minutes post art line insertion)***

Table 2. Schedule of Assessments (continued)

Time intervals	**6 week post operative clinic visit (±1week) (phone visit may occur if patient is not brought in within window)**	**3 month phone visit (±1week)**	**6 month phone visit (±1week)**
Secondary Outcomes	• Angina • Re-admission (CHF, AMI, ACS) • Incisional wound infection • Thrombosis • MI • Angiography • PCI (percutaneous conronary intervention) • Repeat cardiac surgery • Cardiac Mortality	• Angina • Re-admission (CHF, AMI, ACS) • Incisional wound infection • Thrombosis • MI • Angiography • PCI (percutaneous conronary intervention) • Repeat cardiac surgery • Cardiac Mortality	• Angina • Re-admission (CHF, AMI, ACS) • Incisional wound infection • Thrombosis • MI • Angiography • PCI (percutaneous conronary intervention) • Repeat cardiac surgery • Cardiac Mortality