DEPOSITION

Decr**e**asing **P**ost**o**perative Blood Loss**s** by Topical vs. **I**ntravenous **T**ranexamic Acid **i**n **O**pe**n** Cardiac Surgery

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DEPOSITION Protocol v3.0 Approval:

By signing the below, I designate my approval of the above-named version of the DEPOSITION protocol.

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List of Abbreviations

ATACAS	Aspirin and Tranexamic Acid for Coronary Artery Surgery
BART	Blood conservation using Antifibrinolytics in a Randomized Trial
BCa	Bias-Corrected and Accelerated
CA	Competent Authority
CABG	Coronary Artery Bypass Grafting
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	Central Nervous System
CRF	Case Report Form
CT	Computed Tomography
DEPOSITION	Decreasing Postoperative Blood Loss by Topical vs. Intravenous Tranexamic Acid in Open Cardiac Surgery
DSMB	Data Safety Monitoring Board
EAC	Event Adjudication Committee
EACA	ε-aminocaproic Acid
$GABA_A$	γ-aminobutyric Acid A (receptor)
GCP	Good Clinical Practice
HHS	Hamilton Health Sciences
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive Web Randomization Service
LBBB	Left Bundle Branch Block
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NIHSS	National Institutes of Health Stroke Scale
NOAC	Novel Oral Anticoagulant
OR	Operating Room
PHRI	Population Health Research Institute
POOC	Project Office Operations Committee
RBC	Red Blood Cell
RCT	Randomized Controlled Trial
REB	Research Ethics Board
RR	Relative Risk
SC	Steering Committee
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty
TxA	Tranexamic Acid
URL	Upper Reference Limit

Study Synopsis

Title	Decreasing Postoperative Blood Loss by Topical vs. Intravenous Tranexamic Acid in Open Cardiac Surgery (DEPOSITION) Trial
Project Office	Population Health Research Institute 237 Barton Street East, Hamilton, Ontario Canada L8L 2X2
Study Size	3800 patients
Study Design	Multi-center, double-dummy, randomized controlled trial
Primary Objective	To determine in patients undergoing on-pump cardiac surgery, if topical tranexamic acid (intra-pericardial) is *superior* to the usual intravenous tranexamic acid (TxA) administration for reducing the risk of in-hospital **seizure**
Secondary Objective	To determine in patients undergoing on-pump cardiac surgery, if topical TxA (intra-pericardial) compared with intravenous TxA administration is associated with a *non-inferior* risk of in-hospital **red blood cell transfusion**
Tertiary Objectives	To determine the effect of topical TxA on other outcomes including: blood product transfusions (as a composite and individually), re-operation for bleeding or tamponade, duration of ICU stay, MACE (composite of death, non-fatal MI and non-fatal stroke)
Inclusion Criteria	1. ≥ 18 years of age 2. Undergoing a cardiac surgical procedure (i.e. isolated CABG, isolated single cardiac valve surgery or a combination of both or isolated ascending aorta replacement) **with the use of cardiopulmonary bypass (CPB) and median sternotomy** 3. Provide written informed consent
Exclusion Criteria	1. Allergy to tranexamic acid 2. Undergoing minimally invasive surgery 3. Fulfill any of the following transfusion risk factors (A-D): A. Emergency surgery B. History of bleeding disorder C. Inherited thromboembolic or hemorrhagic disease D. Infective endocarditis (active) 4. History of previous cardiac surgery 5. Estimated glomerular filtration rate <30 mL/min (CKD-EPI equation) or on dialysis 6. Pre-operative hemoglobin >170 g/L or <110 g/L 7. Pre-operative thrombocytopenia (<50,000 platelets per µL) 8. Expected circulatory arrest 9. Pregnancy or breast feeding 10. Previously enrolled in the DEPOSITION trial 11. Refusal of blood products (e.g. Jehovah's Witnesses) 12. Pericardiectomy
Treatment Intervention	**Topical TxA** (IV placebo + topical TxA) during surgery • **Topical TxA:** 5 g to 10 g TxA (50 to 100 mL) poured into the pericardial and mediastinal cavities after protamine administration. • **Intravenous Placebo:** 10 to 100 mL of saline in place of TxA administered intravenously as per standard care at the beginning and during surgery.
Control Intervention	**Intravenous TxA** (IV TxA + topical placebo) at the beginning and during surgery • **Intravenous TxA:** 1 to 10 g TxA (10 to 100 mL) administered intravenously as per standard care. The dose typically varies from 3 to 6 g TxA per patient. • **Topical Placebo**: 50 to 100 mL of saline poured into the pericardial and mediastinal cavities after protamine administration.
Study follow up	In-hospital until discharge or 10 days (whichever comes first)

1 INTRODUCTION & RATIONALE

1.1 The problem being addressed

Bleeding associated with cardiac surgery remains a major cause of morbidity and mortality in Canada and consumes a significant portion of our health care resources. For example, cardiac operations consume approximately 10% to 15% of the nation's blood supply in the United States.[1] In 2016, 35% of patients received red blood cells (RBC) in Ontario for routine coronary artery bypass graft (CABG) or valve surgery (CorHealth 2018 report, Ontario)[2] but 60% for combined surgery (Aortic valve + CABG). Excessive degradation of hemostatic fibrin (hyper-fibrinolysis) results in excessive or recurrent bleeding, which can be prevented by anti-fibrinolytic agents. TxA is an anti-fibrinolytic drug that has been used to reduce bleeding in haemorrhagic conditions for decades[3] and is a synthetic analog of the amino acid lysine. It serves as an anti-fibrinolytic by reversibly binding five to six lysine receptor sites on plasminogen.[4] This prevents plasmin from binding to and degrading fibrin (Figure 1). Transfusion of packed red cells to bleeding patients is a time-honored hemostatic practice that is limited by supply, associated with an increased risk of infection[5] and may reduce long-term survival.[6-8] Therefore, anti-fibrinolytic therapy is an important part of the multi-modal approach to blood conservation.

Although tranexamic acid is effective in reducing bleeding, its intravenous use during cardiac surgery is associated with a serious side effect—**postoperative seizures**.[8-10] In the largest clinical TxA trial (ATACAS) seizures were infrequent but significantly higher in the TxA group (15/2304 (0.7%) vs. the placebo group 2/2327 (0.1%), RR 7.62, 95% CI 1.77-68.7, P=0.002).[8] Patients who had seizures had a significant increase in the primary outcome (composite of death, MI, renal failure, stroke, pulmonary embolism, renal failure or bowel infarction; 10/17 (58.8%) vs. 796/4614 (17.3%), RR 3.4, 95% CI 2.3-5.1, P<0.001) and had lengthier stays in the ICU (116 h vs. 29 h, P=0.006) and hospital (18 d vs. 8 d, P=0.007).[11] The pro-convulsant effect of TxA is likely due to the similarity between TxA molecules and the molecules of γ-aminobutyric acid or glycine (Figure 2), leading to the occupancy of γ-aminobutyric A ($GABA_A$) and glycine receptors in the brain.[12,13] Both receptor types are mediators of inhibition within the CNS, thus the pro-convulsant property of TxA is likely mediated by neuronal hyperexcitability (disinhibition).[14]

1.2 Principal Research Question

Proposed benefits of topical (local) compared to intravenous (systemic) TxA delivery include enhanced local anti-fibrinolytic effects with reduced neurological side effects due to lower systemic levels. Prior to our DEPOSITION pilot trial, no clinical trial has evaluated the use of topical TxA versus intravenous TxA in cardiac surgery. The full-scale DEPOSITION trial will address the following important clinical question: *In patients undergoing on-pump cardiac surgery, does topical tranexamic acid (intra-pericardial) compared to the usual intravenous tranexamic acid administration reduce the risk of in-hospital seizure without increasing red blood cell transfusion?*

1.3 Previous Clinical Trials of TxA

1.3.1 Prior Large RCTs of Intravenous TxA in Cardiac Surgery

The **Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART)** was a multi-centre randomized control trial comparing the effect of three anti-fibrinolytic agents (aprotinin, ε-aminocaproic acid (EACA), and tranexamic acid) on postoperative bleeding in 2331 cardiac surgery patients.[15] All three anti-fibrinolytic agents were administered intravenously. Although aprotinin reduced the requirement for RBC transfusion compared to TxA (RR 0.82, 95% CI 0.75-0.89) and EACA (RR 0.81, 95% CI 0.75-0.88), the trial was terminated early due to a higher rate of death and renal failure with aprotinin. As a result, aprotinin was withdrawn from the market in 2007/2008 but after careful review aprotinin was re-authorized for use in CABG surgery in Canada in 2011.[16] However, aprotinin is rarely used, is expensive and is seen as a last course of action. As a result of BART, attention has shifted to the lysine derivative anti-fibrinolytic agents, specifically towards TxA, in which a 10-fold lower dose is required compared to EACA.[17]

Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) was a randomized control trial that evaluated the effects of aspirin versus placebo and intravenous tranexamic acid versus placebo using a 2-by-2 factorial design in 4662 patients scheduled to undergo coronary artery surgery.[8] TXA reduced the proportion of patients requiring RBC transfusion intraoperatively (RR 0.71, 95% CI 0.62-0.82, P<0.001), postoperatively within 24 hours (RR 0.58, 95% CI 0.52-0.64, P<0.001) and from 48 hours to discharge (RR 0.72, 95% CI 0.64-0.81, P<0.001). In addition, the authors estimated that in their patient population the use of tranexamic acid saved approximately 57 units of blood products for every 100 patients treated. These results reaffirm that TxA alone is an effective perioperative blood-conserving therapy in cardiac surgery. Despite the positive effects of TxA on transfusions and bleeding, **intravenous TxA was associated with a higher risk of seizures** compared to the placebo TxA group (15/2304 (0.7%) vs. 2/2327 (0.1%), RR 7.62, 95% CI 1.77-68.7, P= 0.002).[8] In turn, patients who had seizures had a significant increase in the primary outcome, a composite of death, stroke, myocardial infarction, renal failure, pulmonary embolism, or bowel infarction in patients with seizures (10/17 (58.8%) vs. 796/4614 (17.3%) in patients without seizures, RR 3.4, 95% CI 2.3-5.1, P<0.001) and had lengthier stays in the ICU and hospital.[11]

Mid way through the trial, anesthesiologists reduced their dosage of intravenous TxA in order to reduce seizures; however, similar rates of seizures were observed between full dose of TxA (0.5% with 100 mg/kg) and half dose of TxA (0.7% with 50 mg/kg) in comparison to the placebo group with 0% and 0.1% respectively. Furthermore, **lowering the dose of TxA decreased the antifibrinolytic effect of TxA** as the interaction for the number of units transfused was significant (P=0.017) between the full dose group (100 mg/kg) and the half dose group (50 mg/kg).[18] Similar interaction effect is noted with median blood loss (P=0.026). ATACAS demonstrated that intravenous TxA in comparison to *placebo* did not decrease or increase the primary outcome, a composite of death, stroke, myocardial infarction, renal failure, pulmonary embolism, or bowel infarction (386/2310 (16.7%) vs. 420/2320 (18.1%), RR 0.92 (0.81-1.05);

P=0.22) or any individual component. **Therefore, the safety of intravenous TxA is accepted for these outcomes, but not for seizures.**

1.3.2 Effectiveness of TxA in Other Surgical Populations—Orthopedic Surgery

Nearly 37% of patients undergoing total hip arthroplasty (THA) and 25% undergoing total knee arthroplasty (TKA) require blood transfusions for postoperative bleeding.[19] In Ontario, the use of tranexamic acid has played a large role in the dramatic reduction in the proportion of patients receiving allogeneic blood transfusions during knee replacement from 24.5% in 2002 to 0.57% in 2018.[2] In RCTs comparing 1 g of topical TxA (intra-articular) to placebo, topical TxA reduced the absolute risk of blood transfusion in THA patients by 19.6%, from 32.1% to 12.5%, (95% CI 6.9%-32.1%, P=0.004)[20], and in TKA patients by 15.4%, from 16.7% to 1.3%, (95% CI 7.5% to25.4%, P=0.001).[21]

When comparing topical TxA with intravenous TxA, there remains controversy regarding the best mode of delivery. Many small studies (<200 patients) failed to find differences between topical and intravenous TxA,[22-24] while others were in favour of topical[25-27] or intravenous.[28] In pooled data of 2034 orthopedic surgery patients, no difference in transfusion rates were reported in patients who received topical TxA compared to those who received intravenous TxA (OR 0.92, 95% CI 0.66-1.30; P=0.65)[29] and this question needs to be resolved with a large trial.

1.3.3 Small RCTs of Topical TxA in Cardiac Surgery

At least 9 relatively small (cumulative *N* ≤600 patients) randomized trials conducted between 2000 and 2019 have examined the incidence of seizures and/or red blood cell transfusions after topical TxA administration during cardiac surgery (Table 1).[30-38] Results from these trials suggest that topical TxA may reduce the incidence of seizures compared to controls but typically very few, if any, seizures were recorded given the limited number of patients observed in each trial. In the absence of a large trial there remains uncertainty regarding the seizure-sparing effects of topical TxA in cardiac surgery. With regard to RBC transfusion, only 2 trials compared topical TxA to placebo where patients were not administered intravenous TxA (i.e. a measure of the efficacy of topical TxA). In one trial topical TxA reduced transfusions (5% absolute reduction) with no difference observed in the other. Three trials compared topical TxA as adjunct therapy to intravenous TxA with mixed results (1 was inferior, 1 neutral and 1 superior). In the largest trial (N=739 patients) topical TxA was poured into the pericardial cavity for 1 min and subsequently removed by suction (i.e. a very brief exposure), largely nullifying the results.[35] Finally, in our DEPOSITION pilot trial topical TxA was compared to intravenous TxA (i.e. a comparison of the route of administration). Topical TxA was found to be superior (9% absolute reduction in RBC transfusion). Several trials in cardiac surgery also provide evidence that topical TxA reduces post-operative blood loss (Figure 3),[30,31,33,39-41] total RBC transfusion volume,[31] length of ICU/hospital stay,[31,39,42] platelet transfusion,[42] and re-exploration for bleeding.[39,42]

Trials of topical TxA in cardiac surgery thus far have had insufficient power to detect moderate but important differences in clinical events such as seizure or RBC transfusion. It is important to note that the investigations using both routes of administration (except our DEPOSITION pilot) did not directly compare topical with intravenous TxA and therefore the

effects of topical TxA were not independent of the effects of intravenous TxA, leading to uncertainty regarding the most effective route of TxA administration.

1.3.4 DEPOSITION Pilot Study (Intravenous vs. Topical TxA)

We have completed a single-centre DEPOSITION pilot trial (ClinicalTrials.gov, NCT03376061), in order to assess the feasibility of a large randomized controlled trial. The corresponding manuscript has been published in the *Journal of Cardiac Surgery* (https://doi.org/10.1111/jocs.14027).[38] Briefly, 97 patients at the Hamilton General Hospital were randomized to receive either 5 g of topical TxA or 1 to 10 g (mean of 5 g) intravenous TxA. We performed a per protocol analysis as ten patients (five in each group) were not dosed due to a lack of compliance from surgeons and anesthesiologists early in the trial. Using this experience and feedback from them, we modified our exclusion criteria to exclude patients with either too low (off-pump, minimally invasive) or too high (complex surgeries) risk of bleeding.

The baseline (Table 2) and surgical characteristics (Table 3) were similar among topical and intravenous groups. In the *per protocol* analysis, topical TxA in comparison to intravenous TxA produced an absolute risk reduction of 9.1% (19% relative risk reduction) in the proportion of patients receiving red blood cell (RBC) transfusion and an absolute risk reduction of 5.2% (10% relative risk reduction) in the proportion of patients receiving any blood products (Table 4). In addition, the median number of blood product units used per patient was reduced by one unit in the topical TxA group. The rate of seizure was low with a seizure in a patient who received intravenous TxA but none in the topical group. [18]

The mean dose of intravenous TxA used was 55 mg/kg and 54 mg/kg in the topical group. However, mean plasma TxA concentrations taken upon arrival in the ICU were significantly lower in patients who received topical TxA (45.5 µg/mL vs. 90.9 µg/mL or 0.58 vs. 1.10 µg/mL/kg). This supports the possibility that CNS exposure is likely to be reduced in the topical TxA group with lower plasma concentration, reducing the risk of seizures in patients who received topical TxA compared to intravenous TXA. The mean intravenous TxA dose in our pilot is similar to the low dose regimen used in ATACAS, which likely reflects a change in practice to lower IV TxA doses after this influential trial. The expected increase in transfusion risk at lower systemic TxA concentrations is concerning and therefore our hypothesis that the increased transfusion risk will be countered by enhanced local anti-fibrinolytic activity at the sites of bleeding (i.e. a key advantage of topical TxA exposure) needs to be thoroughly tested. Results from our pilot study support this hypothesis.

Overall, 10 patients (5 in each group) were not dosed at time of surgery due to a lack of compliance from surgeons and anesthesiologists. Unfortunately, eight of these patients received blood products (5/5 in topical TxA group and 3/5 in i.v. TxA group). All 5 patients in the topical TxA group who received blood products had crossed over (were initially assigned to topical TxA but received intravenous TxA instead as per standard care. In an *intention-to-treat* analysis, while the rate of RBC transfusions showed a smaller absolute reduction of 4.7% (9.6% relative risk reduction) in the proportion of patients receiving RBC, other results remained comparable (Table 5).

Together, these results **are encouraging** and suggest that TxA applied topically may be superior to intravenous TxA in reducing postoperative blood loss, transfusions, and seizures.

Although these results were not statistically significant due to the small sample size of the pilot, they support the need for a larger trial to evaluate the potential of topical TxA to reduce postoperative transfusions and improve safety with less seizures in cardiac surgery patients.

1.4 Need for DEPOSITION & Potential Impact

Considering all the efforts deployed in cardiac surgery to reduce blood transfusions (cell savers, smaller CPB circuits, avoiding dilution, restrictive transfusion thresholds etc.) and large trials of anti-fibrinolytics like BART and ATACAS, the use of RBC and other blood products are still very high in cardiac surgery for *routine* CABG and valve surgery. The use of blood products is deleterious for the patients, creates a significant demand on the Canadian Blood Services, and generates substantial expenses. Since ATACAS, no new improvements in preventing perioperative bleeding have been made in cardiac surgery despite widespread use of intravenous TxA. The use of **topical** TxA in orthopaedic surgery is a new and very effective approach that has significantly decreased the use of RBC in their practice.[20,21] We have successfully tested the same topical approach in our pilot study which demonstrated trial feasibility and encouraging efficacy results, and we will now undertake a large RCT to provide a definite answer to a clinically important question. Above, we have reviewed the relevant literature that highlights the current need for a large RCT to evaluate the route of TxA administration in cardiac surgery. The results of DEPOSITION are expected to have broad implications to cardiac surgery and to offer insights for other surgical disciplines in Canada and worldwide by further decreasing blood loss during surgery.

2 TRIAL OBJECTIVES

DEPOSITION is part of a larger vision—to find safer and more effective ways of achieving hemostasis during cardiac surgery that aim to improve the lives of our patients and decrease costs of care.

2.1 Primary Objective

To determine in patients undergoing on-pump cardiac surgery, if topical tranexamic acid (intra-pericardial) is *superior* to the usual intravenous tranexamic acid administration for reducing the risk of in-hospital **seizure**.

2.2 Secondary Objective

To determine in patients undergoing on-pump cardiac surgery, if topical tranexamic acid (intra-pericardial) compared with intravenous tranexamic acid administration is associated with a *non-inferior* risk of in-hospital **red blood cell transfusion**.

3 OUTCOMES

3.1 Primary Outcome

The proportion of patients experiencing an in-hospital seizure.

3.2 Secondary Outcome

The proportion of patients receiving in-hospital red blood cell transfusion.

3.3 Tertiary Outcomes

- Blood product transfusions (as a composite and individually)
- Re-operation for bleeding or tamponade
- Duration of ICU stay
- MACE (composite of death, non-fatal MI and non-fatal stroke)

Standardized definitions of these outcomes are provided below (section 18.1).

3.4 Adjudication of Trial Outcomes

The Event Adjudication Committee (EAC) is composed of clinicians with expertise in perioperative outcomes. The adjudication process will be outlined in the Adjudication Manual. We will use the decisions of the outcome adjudicators for all statistical analyses of these events.

4 TRIAL DESIGN

DEPOSITION is a multi-centre, double-dummy, randomized controlled trial comparing topical with intravenous administration of tranexamic acid in patients undergoing on-pump cardiac surgery. Subjects will be randomized in a 1:1 ratio to topical TxA (IV placebo + topical TxA) or intravenous TxA (IV TxA + topical placebo). The aim of the trial is to show that topical TxA is *superior* to the usual intravenous TxA approach (i.e. a superiority trial). A schematic diagram of the trial design, including treatment groups and the primary outcome is provided (Figure 4).

5 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

Patients will be eligible if they meet all of the following criteria:

1. ≥18 years of age

2. Undergoing a cardiac surgical procedure (i.e. isolated CABG, isolated single cardiac valve surgery or a combination of both or isolated ascending aorta replacement) **with the use of cardiopulmonary bypass (CPB) and median sternotomy**
3. Provide written informed consent

5.2 Exclusion Criteria

Patients will be excluded if they meet any of the following criteria:

1. Allergy to tranexamic acid
2. Undergoing minimally invasive surgery
3. Fulfill any of the following transfusion risk factors (A-D):
    A. Emergency surgery
    B. History of bleeding disorder
    C. Inherited thromboembolic or hemorrhagic disease
    D. Infective endocarditis (active)
4. History of previous cardiac surgery
5. Estimated glomerular filtration rate <30 mL/min (CKD-EPI equation) or on dialysis
6. Pre-operative hemoglobin >170 g/L or <110 g/L
7. Pre-operative thrombocytopenia (<50,000 platelets per µL)
8. Expected circulatory arrest
9. Pregnancy or breast feeding
10. Previous enrollment in DEPOSITION trial
11. Refusal of blood products (e.g. Jehovah's Witnesses)
12. Pericardiectomy

5.3 Medications Permitted

Patients who already took their prescribed medications on the day of surgery will still be eligible for randomization to the tranexamic acid treatments and to receive the baseline and in-hospital components of the trial. Patients will be permitted to use any medications prior to surgery as deemed appropriate by local clinical practices. The only medication not permitted before surgery is tranexamic acid (the study drug), which is to be administered according to the protocol. Pre-operative medications taken by the patients enrolled in the trial will be either their own medications, or provided by the hospital pharmacy, as per routine practice. The hospital pharmacy at each center will provide the patient's medications after surgery, as per routine practice.

6 RECRUITMENT, INFORMED CONSENT & RANDOMIZATION

Eligible patients will be approached by a trained member of the research team before surgery to obtain written informed consent to participate in the trial. The site research team will obtain written informed consent and on the day of surgery, they will randomize the patient to

receive topical or intravenous TxA via the central Interactive Web Randomization System (IWRS). The IWRS will email the site's pharmacy the patient's allocation for preparation. Site pharmacists will sign a form stating that they understand the importance of keeping the treatment allocation confidential and that they will not share this information with anyone. Randomization should occur on the day of surgery to reduce randomization errors in patients that may have their surgery cancelled or postponed. The IWRS is a computerized system maintained by the DEPOSITION Project Office at PHRI. Following stratification by centre, patients will be randomly assigned to each intervention (1:1 ratio) using random permuted blocks sizes.

7 INTERVENTIONS, DOSAGE & BLINDING

7.1 Interventions

In the **treatment intervention group**, topical TxA will be poured into the pericardial and mediastinal cavities after protamine administration. In addition, patients will receive an intravenous placebo (saline) at the induction of anesthesia as per usual care (Figure 4).

In the **control intervention group**, topical placebo (saline) will be poured into the pericardial and mediastinal cavities after protamine administration. In addition, patients will receive an intravenous administration of TxA at the induction of anesthesia as per usual care.

7.2 Dosage

The local pharmacy staff will prepare the study drug kits using standardized instructions. Each patient will receive a drug kit containing 2 syringes for the anesthesia team and 2 syringes for the surgical team. Each syringe contains 5 g (50 mL) of TxA or matching placebo (saline) for a potential dose of 10 g (100 mL) for topical or intravenous use. To ensure that patients in the intravenous TxA group receive TxA, we will require at least 1 g TxA (10 mL) be administered intravenously or 5 g TxA administered topically. Syringes containing active TxA for either topical or intravenous use are identical (clear liquids) and are indistinguishable from syringes containing placebo (saline) intended for either topical or intravenous use. Drug kits will be delivered to the operating room by the research staff. The syringes for topical use will be emptied into a sterile container on the OR table and intervention solutions transferred to sterile syringes for the surgical team to use.

The topical dose will not be fixed but is usually 5 g TxA with a maximum of 10 g of TxA. The intravenous dose can be varied based on the anesthesiologist preference. The dosage of intravenous TxA varies between anesthesiologists and hospitals across the country due to the variation in perceived risk of bleeding and seizure in each patient. In a recent survey of current practices among Canadian anesthesiologists, the mean dose varied across provinces from 22 to 55 mg/kg (P=0.001).[43] Likewise, the average dose of intravenous TxA administered by each anesthesiologists varied by nearly 3-fold (2.7 to 8.0 g TxA or 34.6 to 96.4 mg/kg) in our pilot trial (Table 6). In our experience, it is *impossible* to standardize the dose of intravenous TxA across anesthesiologists. Furthermore, we expect that both teams will adjust their dosing according to the hemostasis achieved, as per usual care. Therefore, we will allow the dose of TxA to be varied

by both the anesthesia team (1 to 10 g intravenous TxA) and the surgical team (5 to 10 g topical TxA) to accommodate their preferences and simply record the dose used in the operating room, as we did during our pilot trial. This compromise highlights an important limitation of the existing cardiac surgery literature pertaining to IV TxA use and the lack of agreement on the "optimal" dosing of TxA. Flexibility in the dosing reflects local clinical practices, will allow us to evaluate outcomes by TxA dose, will ease the recruitment, and consolidate compliance from both teams.

7.3 Blinding

Intraoperatively, we will blind the anesthesia team, the surgical team, research staff and any other medical personnel from the TxA/placebo allocation through the use of 2 matching placebos (a matching placebo for each administration route). Each patient will receive both intravenous and topical administrations (as opposed to one or the other) in order to maintain blinding. All packaging and syringes will be clearly labelled by the local pharmacy staff so that syringes for the anesthesia and surgical teams are not mistaken for one another.

7.4 Emergency Unblinding

Patients will be allowed to crossover (use both approaches or supplementary dose of TxA) in emergency situations, as they would have already contributed to the primary outcome by receiving a RBC transfusion. If the safety of the patient is at risk due to the trial blind (as determined by the anesthesiologist and surgeon) the blind may be broken. We will provide each site with 2 options for emergency unblinding, either through the use of unblinding envelopes or through a centralized 24-hour call service. If the unblinding envelopes option is chosen, then within each patient's study drug kit will be a sealed opaque envelope containing the patient's treatment allocation. In extenuating circumstances, the envelope may be opened to inform the anesthetist and surgeon of the treatment allocation. Research staff will collect the sealed opaque envelope following each surgery and document any unblinding events on the "unblinding" Case Report Form (CRF). Unblinding envelopes will be returned to the Project Office for accountability. If the centralized 24-hour call service is chosen, the site must document any unblinding events on the "unblinding" Case Report Form (CRF). Both emergency unblinding methods will prevent unintended intravenous TxA overdosing of patients.

8 TRIAL PHASES & TIMELINE

8.1 Phase I: Baseline

Upon obtaining written informed consent, research staff will collect baseline risk data from the patient's chart including demographics, relevant information from medical history and physical examination, and pre-operative medications.

8.2 Phase II: In-hospital

Research staff will prospectively collect relevant intra-operative details from observations in the OR and referring to the anesthesia and OR documentation. Participants will be followed daily in-hospital until discharge or 10 days post-operatively (whichever comes first). A schedule of patient assessments is provided in Table7.

8.3 Timeline

Patients will be recruited at each of the centres by trained research staff under the supervision of the local investigator. We have achieved a recruitment rate of 6-8 patients per week at the Hamilton General Hospital during the pilot study but have lowered our projections to a more conservative rate of recruitment of 5 patients per week per site. Therefore, we **expect to recruit 50 patients each week from approximately 11 hospitals, for a period of 18 months.** It will take approximately **6 months** to obtain the national and local regulatory and IRB/ethics approvals (Table 8). We expect an overall duration of **24 months for active recruitment** (assuming a staggered start-up of sites) for a **total trial period of 30 months.** Consented patients will undergo the intervention during their surgery. Patients will be seen in-hospital by research staff daily until discharge or 10 days (whichever comes first). Data analysis and knowledge translation is expected to take about 6 months. **From start-to-finish, we estimate the trial will take a total of 36 months (3 years) to complete.**

9 PATIENT SAFETY AND REPORTING OF ADVERSE EVENTS

9.1 Definition of Serious Adverse Drug Reaction

A serious adverse drug reaction is defined as a noxious and unintended response to the study drug that at any dose: is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; OR causes congenital malformation.

9.2 Safety Reporting

Efficacy or safety outcome events as outlined in section 3.0 will not be considered as serious adverse drug reaction, except if, because of the course or severity or any other feature of such events, the investigator, according to his/her best medical judgment, **considers these events as exceptional for their medical condition, and related to the study drug**. All events considered as part of the endpoints should be reported on the appropriate CRFs but not as a serious adverse drug reaction.

Only serious adverse drug reactions that are **not identified in nature, severity or frequency in the risk information reported on the label of the drug (i.e. serious unexpected adverse drug reactions) need to be reported** within 24 hours of knowledge of the event to the PHRI Project Office. For such events, research personnel should complete a serious adverse drug reactions CRF and immediately enter it into the Study Database System. The project office will then inform the regulatory bodies, as applicable. All other serious adverse drug reactions should

be reported within 48 hours of knowledge of the event. Patients experiencing a serious adverse drug reaction will receive standard care and be followed in-hospital until discharge.

The DSMB will provide oversight of patients' safety throughout the trial by reviewing unblinded aggregate data (including all reported study outcome events and serious adverse drug reactions) by treatment group at regular intervals throughout the duration of the trial and as defined in the DSMB Charter.

10 SUBSTUDIES

Substudies may be added at a later date based on the recommendation of the Steering Committee (SC). These substudies will not be part of the main protocol or analyses and reporting of these substudies will be separate from the main study.

11 DATA ANALYSES

11.1 General Considerations

Standard methods will be used to provide tabular and graphical summaries as appropriate for continuous and categorical variables. The intention to treat principle, in which all randomized participants will be included in their assigned treatment groups regardless of actual surgical procedure performed, will guide all analyses. Summaries of continuous variables will include the number of subjects (*N*), mean, standard deviation, median, quartiles 1 and 3, minimum and maximum. Frequency distributions (*N* and %) will be given for categorical data. Statistical significance will be determined using 2-sided p-values and all analyses will be conducted with SAS version 9.4 or higher.

11.2 Sample Size and Power

We have chosen a **sample size of 3,800 patients**. We assume a similar rate of seizure as in the placebo group of the ATACAS trial (0.7%) vs. (0.1%)[8], because the topical TxA arm of our trial should have a rate of seizures close to placebo. Moreover, a 5% non-compliance rate is applied. Thus, this sample size of 3,800 patients allows a power of 80% to detect a significant difference 0.6% in seizures between topical and intravenous TxA groups at a two-sided significance level 0.05 (Table 9). For the secondary outcome of RBC transfusion, at least 3,272 patients are required to test the non-inferiority of topical versus intravenous TxA with an 80% power at a non-inferiority margin 1.15 and a one-sided significance level 0.025 (Table 10). If the non-inferiority holds, we will also test for superiority.

The non-inferiority margin is the minimum acceptable effect ratio of topical versus intravenous TxA with regard to RBC transfusion. Guo et al. (2019)[44] reported that compared with placebo, TxA usage had a risk reduction (RR) 0.70 (95% confidence interval 0.66 to 0.74). The upper bound of the 95% confidence interval is 0.74 corresponding to a relative risk reduction (RRR) 0.26. We select a RRR 0.13, which is half of 0.26, as the minimum acceptable RRR. Converting this RRR 0.13 to a RR, we have a minimum acceptable effect ratio 1.15. Therefore, if

the entire confidence interval of the estimated effect ratio falls below 1.15, it will show that the topical route is non-inferior to the intravenous route regarding RBC transfusion. Moreover, if the confidence interval further falls below the value 1, it will show the superiority of the topical route.

11.3 Main Analysis

We will compare the topical TxA and intravenous TxA groups in order to evaluate the superiority of topical TxA over the usual intravenous TxA administration. The primary null hypothesis and alternative hypothesis are:

H_0: there is no difference in the primary outcome between the topical TxA group and the intravenous TxA group.

H_1: there is a difference in the primary outcome between the topical TxA group and the intravenous TxA group.

Comparisons will be made using Fisher's exact test, as frequencies of seizures are expected to be low (≈1%). The effect of the topical delivery route (estimated as absolute risk reduction [ARR]), corresponding 2-sided 95% confidence interval and p-value will be reported. The 95% confidence interval is calculated as:

$$ARR = P_2 - P_1,$$

Where

$$P_1 = \frac{a}{n_1}, P_2 = \frac{c}{n_2},$$

a is the number of seizures in the intravenous TxA group (control)
n_1 is the number of participants randomized to the intravenous TxA group (control)
c is the number of seizures in the topical TxA group (intervention under investigation)
n_2 is the number of participants randomized to the topical TxA group (intervention under investigation)

$$SE_{ARR} = \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}$$

The $100(1-\alpha)\%$ confidence interval is defined as

$$(P_2 - P_1 - Z_{1-\frac{\alpha}{2}} SE_{ARR}, P_2 - P_1 + Z_{1-\frac{\alpha}{2}} SE_{ARR})$$

As a sensitivity analysis, the comparison will be also done through a binomial regression model with a logarithmic link.

The secondary outcome (the proportion of patients who experience a RBC transfusion) will be analyzed using a binomial regression model with a logarithmic link. A sensitivity analysis will also be done using a logistic regression model with a random intercept for the centre. Tertiary outcomes (e.g., units of blood products and length of intensive care unit stay) will be analyzed using a linear regression model. A linear mixed-effect model with a random intercept for the centre is run as a sensitivity analysis. A Cox proportional hazard model will be used to analyze the time to the first occurrence of the composite of death, non-fatal MI, or non-fatal stroke (MACE).

11.4 Subgroup Analyses

The effect of the two routes of administration on different sub-groups i.e. age (<65 or ≥65), sex and preoperative antiplatelets usage (ASA, clopidogrel, ticagrelor) will be examined for consistency and coherence. Sub-groups will be analyzed using logistic regression with a random intercept for the centre. The effect of intravenous and topical TxA dose received will also be examined in a secondary analysis.

11.5 Interim Analyses

The Data Safety Monitoring Board (DSMB) will review the unblinded results (including recruitment, data quality, compliance, outcomes, etc.) of the study twice a year. Two formal interim analyses will be undertaken when 50% and 75% of the participants have finished their follow-up. These analyses will be based on the primary outcome (proportion of patients experiencing seizure). As a guide, the DSMB will employ the modified Haybittle-Peto stopping rule to trigger discussions about stopping the trial early: ≥ 4 standard deviations (SD) for the first and ≥ 3 SD for the second interim analysis.[45,46] If the testing statistic surpasses the monitoring boundary at one or both analyses the analysis will be repeated 3 months later to confirm that the boundary remains crossed. The DSMB will then advise the Steering Committee (SC) and ensue discussions on whether to stop the trial. The SC and DSMB, in making such a decision, will consider the consistency of the secondary and tertiary outcomes (proportion of patients experiencing RBC transfusion and number of patients receiving any blood product transfusion, respectively) and any emerging external data. With the conservative monitoring boundaries and only two interim analyses, it will be negligible to adjust the type I error for the final analysis.

There are several variations in the possible results, and so the statistical monitoring boundary that we have described should not be viewed as an absolute rule, but guideposts that should be considered along with the patterns of data observed, the types of events impacted and the potential impact on both patient safety and clinical practice. At any time during the study, if safety concerns arise the DSMB chairperson will assemble a formal meeting of the full committee. The DSMB will make their recommendations to the SC after considering all the available data.

11.6 Health Economic Analyses

A 2020 review of the current TxA evidence noted that "the efficacy and cost associated with topical use of TxA remains questionable".[47] The hypothesis of our economic analysis is that topical tranexamic acid will be cost-saving compared to intravenous delivery as a result of decreased seizures and RBC product utilization. This analysis will examine the costs associated with both arms as well as the incremental cost per patient. Since follow up is less than a year, no discounting will be required. Study drug acquisition costs and hospitalization related costs will be obtained from Hamilton Health Sciences. Costs of seizures will be estimated from additional resource utilization (e.g. imaging) and/or length of stay in hospital. Costs of blood products will be estimated from Canadian Blood Services. Unit costs will be applied to patient-level utilization data to calculate the average total cost per patient within each treatment group and the average incremental cost per patient. Since cost data is not normally distributed, a bootstrap analysis using the bias corrected and accelerated (BCa) method will be used to calculate standard error and 95% confidence intervals for the average incremental cost-effectiveness ratio (ICER).[48,49] We will be using the definition of cost-neutrality first established in the ACTIVE-A trial[50] and used subsequently in other analyses.[51-53]

12 TRIAL MANAGEMENT

12.1 The Project Office will oversee the day-to-day management of the trial

The organizational structure of DEPOSITION is illustrated in Figure 5. The Project Office at Population Health Research Institute (PHRI) is the coordinating center for this trial and is responsible for the development of the protocol, development of the randomization scheme, trial database, data consistency checks, data analysis, coordination of the trial centres and conducting the trial. The Principal Investigator, Project Officer, and Research Coordinator are responsible for the activities of the Project Office. No statistician with knowledge of the randomization code or unblinded results will participate in the management or coordination of the DEPOSITION Trial.

12.2 Operations & Steering Committees

The Project Office Operations Committee (POOC) will meet regularly to review trial progress and all pertinent issues related to the conduct of DEPOSITION. The POOC will report directly to the Steering Committee (SC). The SC will meet at least annually to discuss trial issues, and strategize to ensure the successful conduct and completion of DEPOSITION. The SC is composed of the members of the POOC and the Principal Investigator from each participating site. These committees will include a broad representation, and members may be added as the trial progresses.

12.3 Data and Safety Monitoring Board

The Data and Safety and Monitoring Board (DSMB) will include members with expertise in clinical trial methodology, statistics, surgery and anesthesiology.

12.4 Sub-study & Publication Committee

The POOC will appoint members to a Sub-study (if applicable) and Publication Committee. This committee will create guidelines for sub-studies and publications related to DEPOSITION. Subsequent publications will be authored by specific individuals on behalf of the DEPOSITION Investigators. Individuals selected to lead the writing of these subsequent publications will depend on their role in and contribution to DEPOSITION, scientific interest, and scientific expertise.

12.5 Site Principal Investigators

All participating centres will have a site Principal Investigator (PI), and this individual is responsible for ensuring compliance with respect to the interventions, visit schedule and procedures required by the protocol. The site PI will provide all information requested in the Case Report Forms (CRFs) in an accurate and timely manner according to instructions provided. The site PI will maintain patient confidentiality with respect of all information accumulated in the course of the trial, other than that information to be disclosed by law. The investigator(s) at each of the participating centres agree to permit trial-related monitoring, audits, Institutional Review Board/Independent Ethics Committee (IRB/IEC) review, regulatory inspection(s) and provide direct access to source data/documents.

13 OTHER CONSIDERATIONS

13.1 Ethical Considerations

This trial will be conducted in compliance with the protocol, the Declaration of Helsinki, Good Clinical Practice (GCP), and all applicable laws and regulations of the countries in which the study is performed. Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process and, where applicable, approval by the participating countries Competent Authority (CA) in accordance with local laws and regulations. Amendments to the protocol will also require IRB/IEC and/or CA approval, where applicable.

13.2 Data Management

Study personnel will complete CRFs electronically through computer software called iDataFax. Data will be stored on a secure computer server located at PHRI. Source documentation supporting the information reported on the CRF will be filed at the site and made available for

monitoring, IRB/IEC review, and regulatory inspections, when required. The Investigator must retain all study records/files pertaining to the trial for a period of 25 years in accordance with applicable regulatory requirements.

The Data Management Plan will outline the procedures to ensure data quality and will include the following:

1. All research personnel will undergo a training session before trial commencement to ensure consistency in trial procedures including data collection and reporting;
2. The Project Office personnel will review detailed monthly reports on enrollment, patient follow-up, data transmission, thoroughness, and completeness of data collection and they will rapidly address any identified issues;
3. Biometric programmers will create internal validity and range checks on iDataFax, which will identify any errors or omissions in received CRFs and notify the sender and Project Office of any such issues;
4. The Project Office will send investigators regular quality control reports in addition to the quality control reports being accessible to sites immediately in iDataFax upon entry.

13.3 Confidentiality and Unblinded Data

All patient information will be stored on a secure computer server and kept strictly confidential. Patients will be assigned a unique trial identification number to ensure anonymity. These ID numbers will correspond to allocation data in secure electronic files. Only the DSMB and the DSMB-reporting statistician will be aware of the unblinded data until the trial is completed. Centres will be instructed to store any patient information containing names or other personal identifiers separately and identified by their ID number. Centres will secure all local databases with password-protected access systems. Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited except for the following reason. Medical information may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of the trial are to be available for inspection on request by the participating physicians, IRB/IEC, and regulatory authorities.

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15 FIGURES

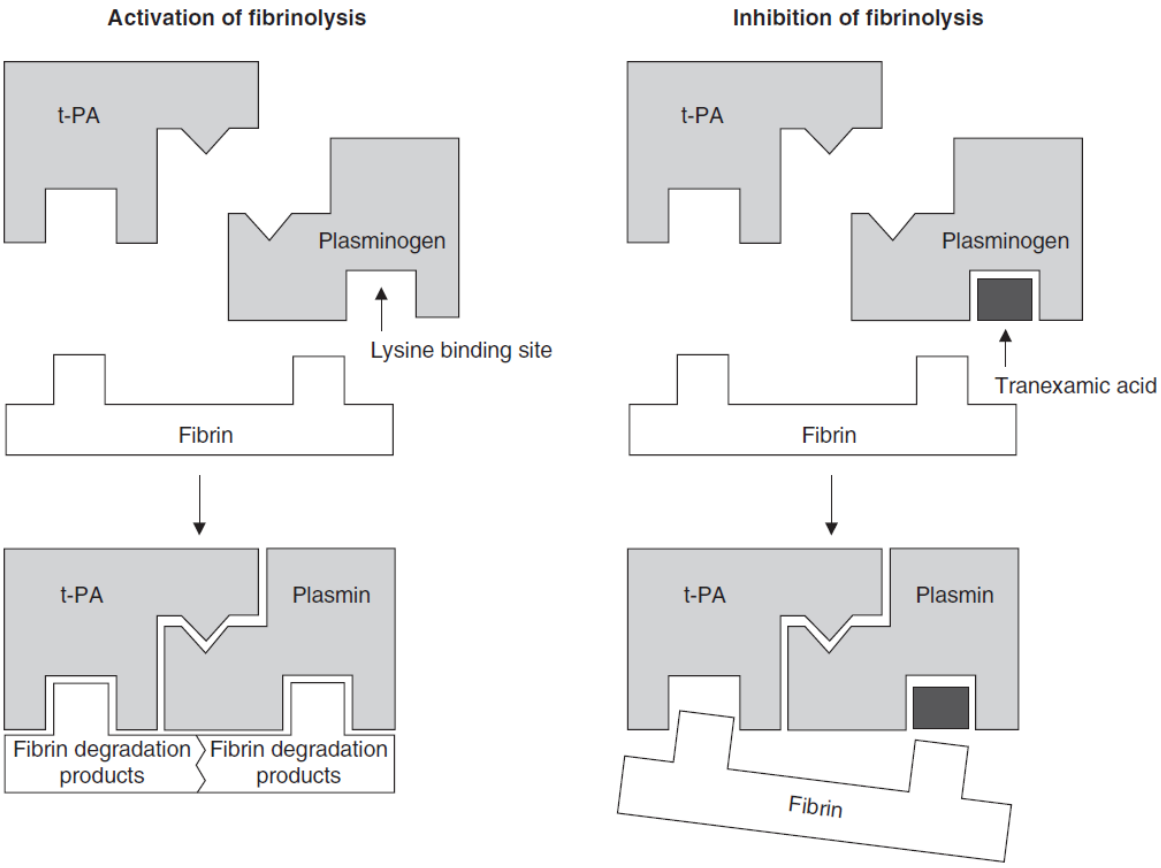


Figure 1. Schematic of anti-fibrinolytic action of TxA[3,54]

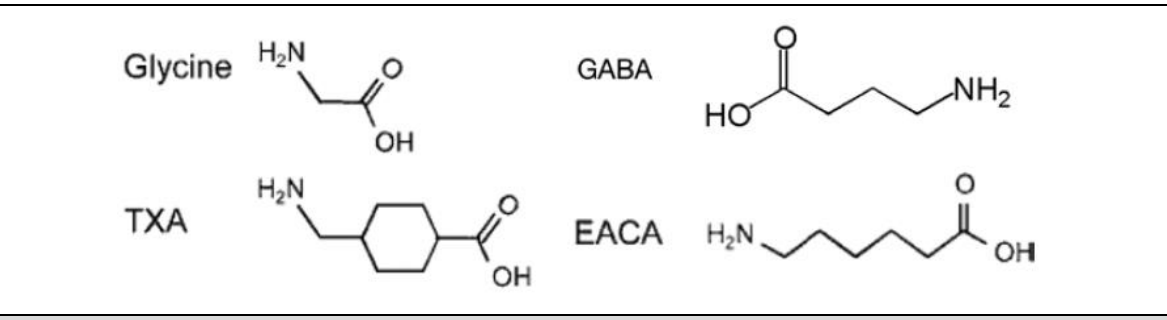


Figure 2. Chemical structure of anti-fibrinolytics, γ-aminobutyric acid (GABA), and glycine[13,55]

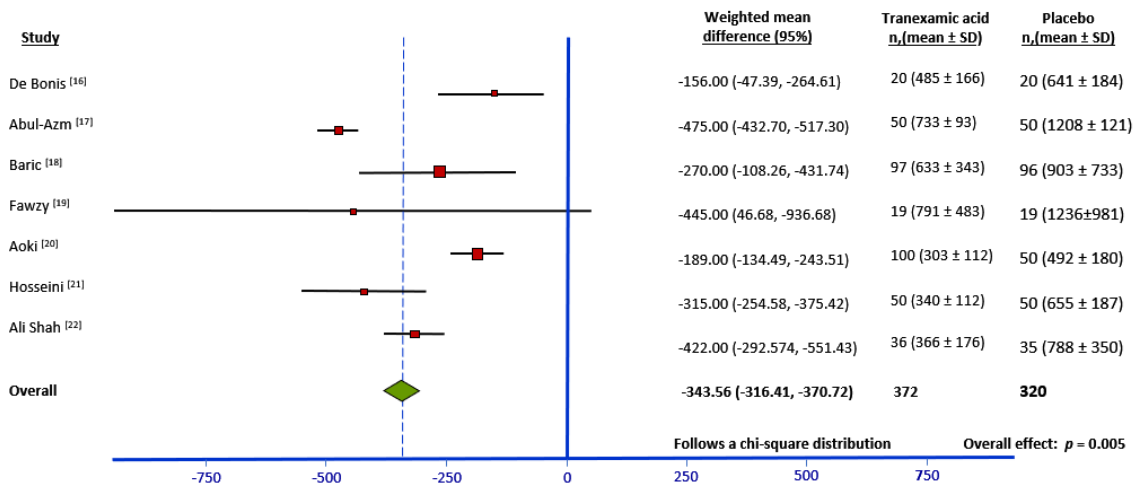


Figure 3. Pooled estimate of mediastinal (blood) loss in 7 small RCTs (topical TxA vs. placebo) in cardiac surgery.[56]

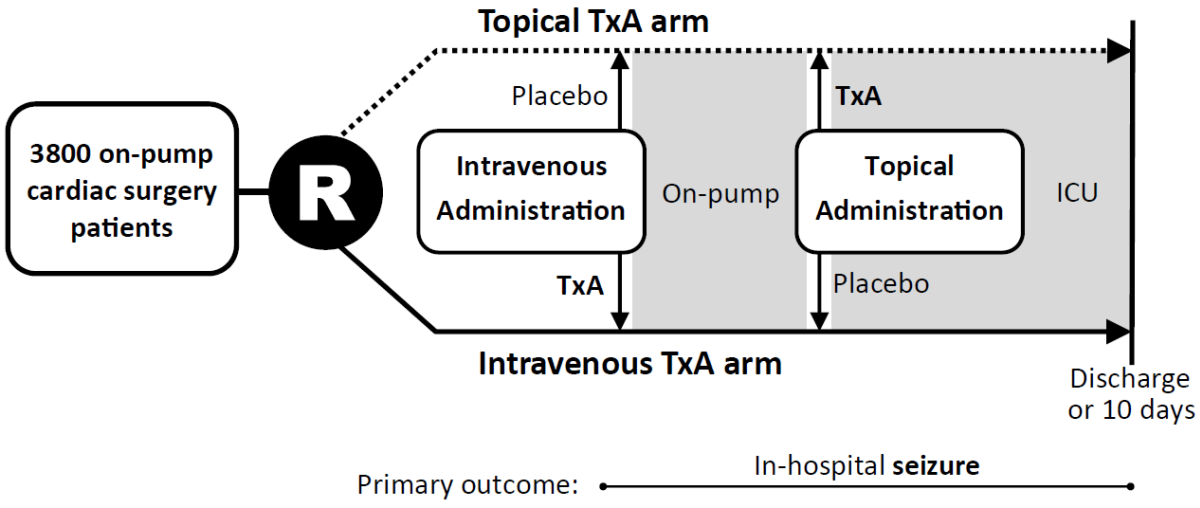


Figure 4. Schematic diagram of the trial design

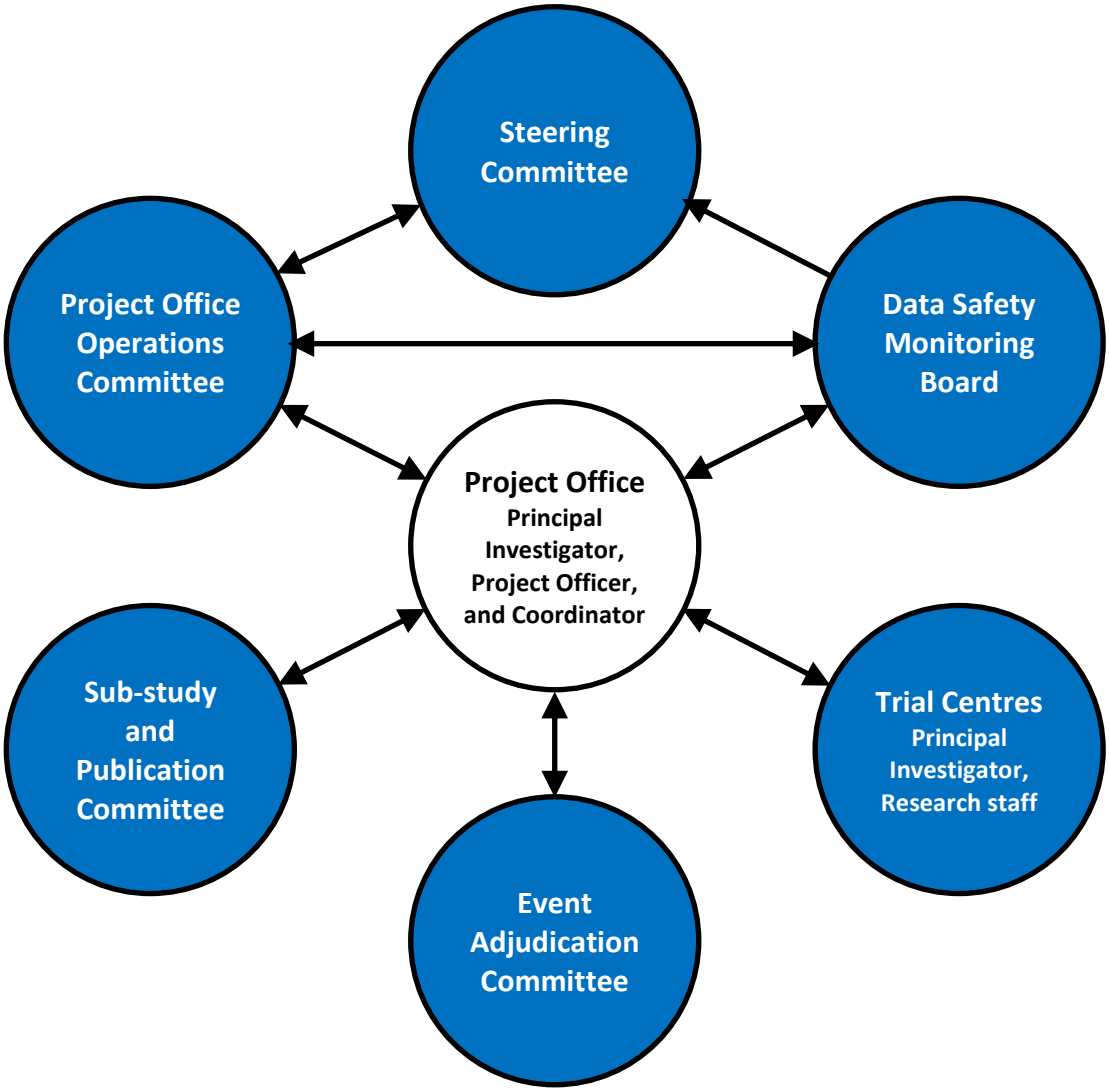


Figure 5. DEPOSITION organization structure

16 TABLES

Table 1. Summary of trials examining the incidence of seizures and/or RBC transfusions after topical TxA administration during cardiac surgery

	Seizure		RBC transfusion			
Study	**Topical**	**Intravenous**	**Topical**	**Intravenous**	**Topical TxA dose (g)***	**Intravenous TxA dose**
De Bonis[30] (2000)			3/20 (15%)	4/20 (20%)†	1	**Topical & IV:** None
Baric[31] (2007)			51/97 (53%)	51/96 (53%)†	2.5	**Topical & IV:** None
Spegar[32] (2011)			37/49 (76%)	36/51 (71%)	2.5	**Topical & IV:** 1g bolus + 0.5g in pump + 400mg/hr infusion
Aoki[33] (2012)	0/50 (0.0%)	0/50 (0.0%)†			1	**Topical & IV:** None
Taman[34] (2015)	1/60 (1.7%)	10/60 (16.7%)			2	**Topical:** 30 mg/kg over 15min + 16mg/kg/hr infusion + 2mg/kg in pump **IV:** 2 (50 mg/kg) bolus + 100mg/100 mL prime in pump
Kimenai[35] (2016)	0/245 (0.0%)	1/249 (0.4%)	94/245 (38%)	94/249 (38%)	2	**Topical & IV:** 2 (2g bolus)
Taksaudom[36] (2017)	1/40 (2.5%)	0/40 (0.0%)	8/40 (20%)	9/40 (23%)	1	**Topical & IV:** 1mg/kg/hr
Mazaheri[37] (2018)	0/59 (0.0%)	0/59 (0.0%)			1	**Topical & IV:** 2 (10mg/kg over 20min) + 1mg/kg/hr
Habbab[38] (2019)‡	0/49 (0.0%)	1/48 (2.1%)	19/49 (39%)	23/48 (48%)	5	**Topical:** None **IV:** 54.4 ± 10 mg/kg
Total	**2/503 (0.4%)**	**12/506 (2.4%)**	**212/500 (42%)**	**217/504 (43%)**		

*Topical TxA was administered before sternotomy closure

†Patients did not receive any intravenous TxA during the study

‡Results from the DEPOSITION pilot trial

Table 2. Baseline characteristics of the DEPOSITION pilot study		
Characteristic	**Topical TxA (*N* = 49)**	**Intravenous TxA (*N* = 48)**
Age (yr) – mean ± SD	67.3 ± 9.4	67.8 ± 9.2
Weight (kg) – mean ± SD	92.1 ±17.2	88.5 ± 18.5
Male sex – n (%)	44 (89.8)	42 (95.8)
Left ventricular function ejection fraction – n (%)		
≥50%	29 (59.2)	33 (68.8)
35-49%	14 (28.6)	11 (22.9)
20-34%	6 (12.2)	4 (8.3)
Coronary artery disease – n (%)		
Left main	10 (20.4)	14 (29.2)
Triple vessel	36 (73.5)	40 (83.3)
Double vessel	4 (8.2)	4 (8.3)
Single vessel	3 (6.1)	2 (4.2)
Pre-existing medical conditions – n (%)		
Diabetes	17 (34.7)	21 (43.8)
Stroke	3 (6.1)	3 (6.3)
Transient ischemic attack	2 (4.1)	2 (4.2)
Carotid endarterectomy/stent	3 (6.1)	1 (2.1)
Asymptomatic carotid stenosis	0 (0)	0 (0)
Seizure history	1 (2.0)	0 (0)
Alcohol abuse history	1 (2.0)	1 (2.1)
Atrial fibrillation	2 (4.1)	2 (4.2)
Preoperative medications (within a week) – n (%)		
Aspirin	38 (77.6)	42 (87.5)
Clopidogrel	12 (24.5)	7 (14.6)
Ticagrelor	3 (6.1)	5 (10.4)
Novel oral anticoagulant (NOAC)	3 (6.1)	4 (8.3)

Table 3. Surgical characteristics of the DEPOSITION pilot study		
Characteristic	**Topical TxA (*N* = 49)**	**Intravenous TxA (*N* = 48)**
Surgery type – n (%)		
CABG	44 (89.8)	46 (95.8)
LIMA	39 (79.6)	40 (83.3)
RIMA	2 (4.1)	5 (10.4)
Aortic valve	5 (10.2)	8 (16.7)
Mitral valve	1 (2.0)	0 (0)
Ascending aorta	3 (6.1)	2 (4.2)
Other	8 (16.3)	5 (10.4)
Laboratory test results		
Platelet count (x109/L)	227.1 (75.9)	228.1 (52.1)
INR	1.0 (0.1)	1.0 (0.1)
Serum creatinine (µmol/L)	88.9 (25.7)	93.1 (26.7)
Hemoglobin (g/L)	139.0 (18.8)	131.9 (17.8)
Number of distal grafts – mean ± SD	3.7 ± 1.0	3.7 ± 1.0
Total heparin dose (units) – mean ± SD	62073.3 ± 22433.2	68730.7 ± 59349.2
Total protamine dose (mg) – mean ± SD	681.9 ± 187.3	678.5 ± 231.6
Cross-clamp time (min) – mean ± SD	80.0 ± 23.0	78.0 ± 27.3

Table 4. Key outcomes of the DEPOSITION pilot study (*per protocol* results)		
Outcomes	**Topical TxA (*N* = 49)**	**Intravenous TxA (*N* = 48)**
Seizures – n (%)*	0	1 (2.1)
TxA dose (mg/kg) – mean ± SD	55.2 ± 10.1	54.4 ± 19.6
TxA blood level (µg/mL) – mean ± SD	46.6 ± 35.8	96.9 ± 49.5
TxA blood level (µg/mL/kg) – mean ± SD	0.58 ± 0.41	1.10 ± 0.52
Transfusions		
Red blood cells – n (%) †	19 (38.8)	23 (47.9)
Platelets – n (%)	13 (26.5)	14 (29.2)
Any blood products – n (%)	23 (46.9)	25 (52.1)
Any blood products (units) – median (Q1-Q3)	2.0 (1.0-4.0)	3.0 (2.0-5.0)
Hours in ICU – median (Q1-Q3)	23.0 (19-45)	25.5 (22-53)
Mediastinal drainage (mL) – median (Q1-Q3)	500 (350-700)	540 (420-700)
TxA blood level (µg/mL) – mean ± SD	46.6 ± 35.8	96.9 ± 49.5

* Primary outcome for DEPOSITION.

† Secondary outcome for DEPOSITION.

Table 5. Key outcomes of the DEPOSITION pilot study (*intention-to-treat* results)		
Outcomes	**Topical TxA (*N* = 54)**	**Intravenous TxA (*N* = 53)**
Seizures – n (%)	0	1 (2.1)
Transfusions		
Red blood cells – n (%)	24 (44.4)	26 (49.1)
Platelets – n (%)	16 (29.6)	16 (30.2)
Any blood products – n (%)	28 (51.9)	28 (52.18
Any blood products (units) – median (Q1-Q3)	2.0 (1.0-4.0)	3.0 (1.5-6.0)
Hours in ICU – median (Q1-Q3)	23.5 (19-47)	26.0 (22-53)
Mediastinal drainage (mL) – median (Q1-Q3)	500 (350-700)	550 (420-710)

Table 6. Mean intravenous TxA dose according to anesthesiologist in the DEPOSITION pilot study			
Anesthesiologist	**No. of cases**	**Intravenous TxA dose (g)**	**Intravenous TxA dose (mg/kg)**
1	3	2.7	34.6
2	3	2.8	28.9
3	3	3.7	38.6
4	2	4.0	51.4
5	7	4.0	42.5
6	2	4.0	54.3
7	1	4.0	49.4
8	4	4.6	68.6
9	1	5.0	46.0
10	3	5.0	53.4
11	2	5.0	57.7
12	2	5.0	77.8
13	1	5.0	50.5
14	4	5.0	59.9
15	1	5.0	56.5
16	2	6.0	51.9
17	5	7.5	82.4
18	3	8.0	96.4
Overall	49	4.8	55.6

Table 7. Schedule of patient assessments				
	Phase I		**Phase II**	
Characteristic	**Screening**	**Baseline**	**Operative**	**Post-op/Discharge**
Eligibility	✓			
Informed Consent	✓			
Randomization		✓		
Demographics		✓		
Medications		✓		✓
Medical History		✓		
Pre-operative Details			✓	
Operative Details			✓	
Outcome Events[a]			✓	✓

[a] The primary outcome will be recorded during operative and post-operative assessments.

Table 8. DEPOSITION trial timeline		
Period	**Time (months)**	**Task**
1 (Planning)	6	1. Development of protocol, case report forms, database and study aids 2. National regulatory approval 3. Local ethics committee approval 4. Develop randomization sequence 5. Investigator site training prior to starting recruitment
2 (Recruitment)	24	1. Recruitment of 3800 patients 2. Data entry 3. Two interim analyses 4. DSMB meetings twice a year
3 (Analysis & Knowledge translation)	6	1. Event adjudication 2. Data clean-up 3. Data analysis 4. Publication of key results
	Total 36 (3 years)	

Table 9. Sample size estimations for the incidence of seizures		
Seizure event rate in intravenous TxA group	**Absolute risk reduction**	**Total sample size**
0.7%	0.6%	3,800
0.8%	0.7%	3,120
1%	0.9%	2,285

Results using Fisher's exact test assuming 80% power and a secondary outcome rate of 0.1% in the topical TxA group.[57] A 5% non-compliance is applied. Alpha=0.05 (two-sided).

Table 10. Sample size estimations for the incidence of RBC transfusion		
RBC transfusion event rate in intravenous TxA group	**Non-inferiority Margin Ratio**	**Total sample size**
33%	1.12	4, 972
33%	1.15	3, 272
33%	1.24	1, 386

Assuming 80% power and a one-sided significance level 0.025, sample sizes are estimated from a non-inferiority test on the ratio of proportion of RBC transfusion rate. A non-inferiority margin ratio is chosen using a "fixed margin method": based on a risk reduction 0.70 (95% CI: 0.66 to 0.74), we select the upper bound of the 95% CI 0.74 as M1. By preserving 40%, 50% or 75% of the effect, a non-inferiority margin ratio M2 is computed as 1.12, 1.15 and 1.24.

17 SUPPLEMENTAL INFORMATION

17.1 Topical TxA Administration Guidelines

- Topical application may occur at any time after protamine administration
- At least 5 g TxA (equivalent to the entire contents of a single 50 mL syringe) must be applied topically to be considered properly dosed
- TxA applied to leg or arm wounds resulting from graft harvesting will be permitted

17.2 Intravenous TxA Administration Guidelines

- Administration of intravenous TxA as early as possible is encouraged (i.e. preinduction or preincision)
- At least 1 g TxA (10 mL) must be administered intravenously to be considered properly dosed
- All modes of intravenous administration will be permitted (e.g. infusion only, one or more boluses, bolus then infusion etc…)
- TxA incorporated into the bypass pump prime will be permitted

A supplementary dose of intravenous TxA at the end of the procedure will be permitted

18 APPENDIX A

18.1 Event Definitions

Seizure (focal or generalized) – A focal or generalized seizure that is not associated with any new neurologic deficit or acute structural change on cerebral computed tomography (CT) or magnetic resonance imaging (MRI), if done.

Red blood cell transfusion – Packed erythrocytes administered intravenously.

Death – All deaths before hospital discharge or 10 days (whichever is first) will be considered cardiovascular (CV) deaths.

Myocardial infarction (MI) – Coronary artery bypass grafting (CABG) related myocardial infarction is defined by elevation of cardiac biomarker values more than 10 times above the 99th percentile of the upper reference limit (URL) in patients with a normal baseline biomarker value (≤99th percentile URL). In addition, either (i) new pathological Q waves or new left bundle branch block or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Stroke – A new neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours as diagnosed by a physician involved in the patient's care. Stroke will be sub-classified into hemorrhagic and non-hemorrhagic stroke. Non-hemorrhagic stroke will sub-classified into ischemic, ischemic with secondary transformation, or stroke of uncertain classification.

> **Hemorrhagic stroke** – Typical clinical syndrome of sudden onset headache, with or without focal signs, and CT/MRI or cerebrospinal fluid or autopsy evidence of bleeding into the substance of the brain or ventricular/subarachnoid spaces. Subarachnoid bleeding due to ruptured intracranial aneurysms and vascular malformation are counted as hemorrhagic strokes. Secondary hemorrhage into cerebral infarct (i.e. hemorrhagic transformation which is defined separately), or intracerebral bleeding (i.e. contusions) due to trauma, or microbleeds detected by MRI are not considered hemorrhagic strokes.
>
> *Non-hemorrhagic stroke*
> **Ischemic stroke** – Brain infarction caused by an arterial (or rarely venous) obstruction and as documented by CT/MRI that is normal or shows an infarct in the clinically expected area.
>
> **Ischemic stroke with secondary hemorrhagic transformation** – A hematoma occupying 30% or more of the infarcted tissue associated with a significant neurologic deterioration (consistent with a decrease of 4 points in the NIHSS – National Institutes of Health Stroke

Scale) compared to immediately before the worsening and an absence of an alternative explanation for deterioration.

Undetermined stroke – Definite stroke that does not meet the criteria for ischemic or hemorrhagic stroke because CT scan or MRI are not done and there are no autopsy data. Rarely it cannot be determined with confidence whether the stroke was ischemic vs. hemorrhagic, even after review of CT/MRI images (e.g., primary intracerebral hemorrhage vs. severe hemorrhagic transformation); these stroke events will be classified as undetermined.

Major Adverse Cardiac Events (MACE) – Composite of death, non-fatal MI and non-fatal stroke.

Blood transfusions – All blood products (except albumin) will be recorded and analyzed as a composite but also individually by type. Usage of factor VII, Octoplex®(Human prothrombin complex concentrate) and Fibrinogen (Factor I) concentrate will be also recorded.

Re-operation for bleeding/tamponade – All causes of return to the operating room for bleeding.

Duration of ICU stay – Length of time (hours) spent in ICU until the first occurrence of either discharge or 10 days.