# REDUCING TRANSFUSION WHILE PRESERVING CANADA'S BLOOD SUPPLY: USE OF TRANEXAMIC ACID IN MAJOR NON-CARDIAC SURGERIES AT HIGH RISK OF TRANSFUSION


**BY**

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## ABSTRACT

**BACKGROUND**: Tranexamic acid (TXA) inhibits fibrinolysis and has been shown to consistently reduce red blood cell (RBC) transfusion in cardiac and orthopedic surgery, where it is now incorporated into standard of care. Its efficacy and safety in other major surgeries at high risk of RBC transfusion is largely unknown. A randomized controlled trial (RCT) is needed to inform best practice. If TXA reduces RBC transfusion in this diverse surgical population, it is expected that this inexpensive and widely available medication will be incorporated into routine surgical care.

**OBJECTIVES:** The overall objective was to inform the design and conduct of a registry-based RCT of TXA use to reduce RBC transfusion in major non-cardiac surgery. Specifically, we aimed to define a surgical population at high risk of RBC transfusion, evaluate real-world TXA use and variability in this at-risk population, examine TXA effectiveness, efficacy and safety in our at-risk surgical population and validate key transfusion variables critical to the planned RCT.

**METHODS:** To evaluate surgery-specific RBC transfusion risk and TXA use we completed retrospective cohort studies of adult patients undergoing major non-cardiac surgery at 5 Canadian hospitals between January 2014 and December 2016. Variability in TXA use was further characterized using multivariable logistic regression analyses in 3 common orthopedic surgeries with higher rates of RBC transfusion (>5%) and TXA utilization (>10%). Real-world TXA effectiveness was studied using propensity analysis. A systematic review and meta-analysis was performed to evaluate TXA efficacy and safety. Agreement between RBC transfusion variables was assessed by comparing different measures of RBC transfusion in the patient record, discharge abstract database and transfusion databases.

**RESULTS:** We identified 85 unique non-cardiac surgeries with an RBC transfusion rate ≥ 5%. We observed that prophylactic use of TXA varies widely according to surgical subtype, with limited use outside of orthopedic and spine surgery. We noted that TXA was most commonly administered as a bolus, with a median total dose of 1 gram. Variability in TXA use was higher among surgeries where TXA use was lower. Propensity analysis resulted in mixed results for TXA effectiveness to reduce RBC transfusion among 3 orthopedic surgeries, although methodologic limitations precluded robust interpretation of these results. We meta-analyzed 69 RCTs of TXA use in non-cardiac surgeries at increased risk for RBC transfusion, and found that TXA reduces both the proportion of patients transfused RBCs, as well as the volume of RBCs transfused. TXA use was not associated with differences in deep vein thrombosis or pulmonary embolism, although effect estimates were limited by lack of systematic screening and short duration of follow-up. Lastly, there was excellent agreement for documentation of RBC exposure between the patient record and transfusion databases, although agreement decreased with increasing number of RBC units transfused.

**CONCLUSION:** This thesis has comprehensively informed the design and conduct of an RCT evaluating TXA use in non-cardiac surgeries at increased risk for RBC transfusion by informing trial inclusion criteria, equipoise, TXA dosing, outcomes, feasibility and sample size calculations. This trial has the potential to change the standard of care in perioperative medicine in Canada and around the world.

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## LIST OF MANUSCRIPTS

The PhD thesis is based on the following manuscripts:

1. Houston BL, Fergusson DA, Falk J, Krupka E, Perelman I, Breau RH, McIsaac DI, Rimmer E, Houston DS, Garland A, Ariano RE, Tinmouth A, Balshaw R, Turgeon AF, Jacobsohn E, Park J, Buduhan G, Johnson M, Koulack J, Zarychanski R. Evaluation of Transfusion Practices in Noncardiac Surgeries at High Risk for Red Blood Cell Transfusion: A Retrospective Cohort Study. Transfus Med Rev. 2021 Jan;35(1):16-21. doi: 10.1016/j.tmrv.2020.08.001. PMID: 32994103.

2. Houston BL, Fergusson DA, Falk J, Krupka E, Perelman I, Breau RH, McIsaac DI, Rimmer E, Houston DS, Garland A, Ariano RE, Tinmouth A, Balshaw R, Turgeon AF, Jacobsohn E, Zarychanski R. Prophylactic tranexamic acid use in non-cardiac surgeries at high risk for transfusion. Transfus Med. 2021 May 2. doi: 10.1111/tme.12780. Online ahead of print. PMID: 33938051.

3. Houston BL, Fergusson DA, Falk J, Ariano R, Houston DS, Krupka E, Blankstein A, Perelman I, Breau RH, McIsaac DI, Rimmer E, Garland A, Tinmouth A, Turgeon AF, Jacobsohn E, Bohm E, Zarychanski R. Variation in prophylactic tranexamic acid administration among anethesiologists and surgeons in orthopedic surgery: a retrospective cohort study. Can J Anaesth. 2021 Feb 16. Doi: 10.1007/s12630-01939-x. Online ahead of print. PMID: 33594597.

4. Houston BL, Fergusson DA, Falk J, Ariano RE, Houston DS, Krupka E, Blankstein A, Perelman I, Breau RH, McIsaac DI, Rimmer E, Garland A, Tinmouth A, Balshaw R, Turgeon AF, Jacobsohn E, Bohm E, Zarychanski R. The association between perioperative tranexamic acid use and red blood cell transfusion in orthopedic surgery: a retrospective cohort study. [not submitted for publication]

5. Houston BL, Uminski K, Mutter T, Rimmer E, Houston DS, Menard CE, Garland A, Ariano R, Tinmouth A, Abou-Setta AM, Rabbani R, Neilson C, Rochwerg B, Turgeon AF, Falk J, Breau RH, Fergusson DA, Zarychanski R. Efficacy and Safety of Tranexamic Acid in Major Non-Cardiac Surgeries at High Risk for Transfusion: A Systematic Review and Meta-Analysis. Transfus Med Rev. 2020 Jan;34(1):51-62. doi: 10.1016/j.tmrv.2019.10.001. Epub 2019 Oct 23. PMID: 31982293.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| CABG | Coronary artery bypass graft |
| CCI | Canadian Classification of Health Interventions |
| CI | Confidence interval |
| CI^ | Comorbidity index |
| DAD | Discharge abstract database |
| DSM | Diagnostic Services Manitoba |
| DVT | Deep vein thrombosis |
| g | Gram |
| g/L | Grams per litre |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluations |
| Hb | Hemoglobin |
| Hr | Hour |
| $I^2$ | Heterogeneity statistic |
| ICD | International Classification of Diseases |
| iCT | Innovative clinical trial |
| ICTRP | International Clinical Trials Registry Platform |
| IPTW | Inverse probability of treatment weighting |
| IQR | Interquartile range |
| Kg | Kilogram |
| L | Litre |
| LIS | Laboratory Information System |
| M-H | Mantel-Haenszel |
| MD | Mean difference |
| mg | Milligrams |
| mL | Millilitre |
| N | Number |
| OR | Odds ratio |
| ORIF | Open reduction internal fixation |
| p | p-value |
| PE | Pulmonary embolism |
| Pre-op | Preoperative |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analysis |
| Q | Quartile |
| RBC | Red blood cells |
| RCT | Randomized controlled trial |
| RD | Risk difference |
| REaCT | Rethinking Clinical Trials |
| Ref | Reference |
| RevMan | Review Manager |
| RR | Risk ratio |
| SD | Standard deviation |
| SIMS | Surgical Information Management System |
| SPOR | Strategy for Patient Oriented Research |
| THA | Total hip arthroplasty |

| | |
|---|---|
| TRACTION | Phase IV trial of a hospital policy of tranexamic acid to reduce transfusion in major non-cardiac surgery |
| TXA | Tranexamic acid |
| VPC | Variance partition coefficient |
| VTE | Venous thromboembolism |
| WHO | World Health Organization |
| # | Number |
| % | Percent |

# 1.0 BACKGROUND

## 1.1 INTRODUCTION

Allogeneic red blood cell (RBC) transfusion is a scarce and costly resource associated with risk of adverse clinical outcomes[1]. Approximately 700,000 RBC transfusions are administered annually in Canada, with an estimated cost of approximately $1 billion in Canadian health care expenditure each year [2-4]. While transfusions can be life-saving, they are not without potential harm[5]. Transfusions are associated with both allergic and non-allergic transfusion reactions, infection, immune dysregulation, prolonged post-operative length of stay, and increased morbidity[6-11].

## 1.2 INCIDENCE OF PERIOPERATIVE BLEEDING

Perioperative bleeding is a major indication for allogeneic RBC transfusion and is the third most common reason for transfusion in US hospital inpatients[12, 13]. Approximately 50% of patients undergoing major cardiac and orthopedic surgery require perioperative RBC transfusion[14, 15]. Data that describes the rate of RBC transfusion in other major non-cardiac surgeries is lacking; moreover, earlier published estimates do not reflect recent efforts to minimize perioperative transfusion[8, 16-19]. Contemporary assessment of transfusion patterns in non-cardiac surgery is needed and presents an opportunity to further reduce allogeneic RBC exposure.

## 1.3 STRATEGIES TO MINIMIZE PERIOPERATIVE BLEEDING

Strategies to mitigate perioperative RBC transfusion include pre-operative anemia correction, advances in surgical technique, acute normovolemic hemodilution, autologous blood donation, intraoperative blood salvage, and pharmacologic interventions (e.g. tranexamic acid), both topical and systemic[8, 16, 20]. These strategies vary in both cost and efficacy.

*1.3.1 Tranexamic acid mechanism of action and rationale*

Tranexamic acid (TXA) is Health Canada approved for use in states of hyperfibrinolysis, a term for which there is no standardized definition. TXA is an inexpensive and widely available synthetic lysine analog that reversibly blocks lysine binding sites on plasminogen inhibiting plasmin formation and consequent fibrinolysis[21]. Surgery is associated with increased fibrinolytic activity due to thrombin generation and fibrin deposition[22]. Whether this increase in fibrinolysis is physiologic or pathologic can be studied with trial evaluating antifibrinolytic agents; if bleeding is reduced in the context of surgery, this would suggest the degree of fibrinolysis is excessive. As there is a balance of clot formation and breakdown, by stabilizing clot, there is a theoretical risk of stabilizing pathologic clot such as deep vein thrombosis and/or pulmonary embolism. Because of this, safety should be an important endpoint in trials evaluating the efficacy of TXA.

*1.3.2 TXA dosing*

TXA is renally cleared, with a half-life of 80 minutes after intravenous administration of 10 mg/kg in healthy volunteers[23]. Among healthy volunteers, a threshold of 10mg/L has been reported as necessary to inhibit fibrinolysis[24, 25]. Dosing of TXA has been variable in clinical trials, including variability in total dose, determination of dose (weight-based versus fixed-dose), and method of administration (bolus versus bolus and infusion). In a systematic review evaluating TXA use in cardiac surgery (34 randomized control trials (n = 3006 patients)), the loading dose ranged from 2.5 mg/kg to 100 mg/kg, and maintenance dose ranged from 0.25 mg/kg/hr to 4.0 mg/kg/hr delivered over 1-12 hours[26]. In a recent large randomized trial by *Myles et al*. evaluating TXA in cardiac surgery, the TXA dose was reduced from 100 mg/kg to 50 mg/kg due to concerns of a dose-dependent association of TXA and seizures, which is in keeping with the general trend to reduce TXA dosage in clinical trials over time[27]. In the CRASH-2 study, a large randomized controlled trial evaluating TXA in bleeding trauma patients, TXA was administered as a loading dose of 1g intravenously, followed by a 1g infusion over 8 hours[28]. The recently completed PORTO study evaluated variations in TXA dosing (1g intravenous bolus followed by 1g infusion versus TXA 1g intravenous bolus followed by placebo) in total hip arthroplasty, and found no difference in perioperative blood loss between these two groups[29]. An ongoing Canadian trial of TXA in cystectomy (TACT trial) is

evaluating a TXA 10 mg/kg bolus, followed by 5 mg/kg infusion[30]. Variability in TXA dosing is ongoing in trials, and the optimal administration regimen remains unknown.

### *1.3.3 Tranexamic acid efficacy*

TXA has been consistently shown to reduce RBC transfusion in cardiac surgery, orthopedic surgery, and trauma, where it is now routinely incorporated into standard of care[20, 28, 31-37]. In a 2011 Cochrane meta-analysis evaluating 65 randomized controlled trials (n = 4842 patients) of TXA use in surgical patients, TXA reduced the relative risk of transfusion by 39% (0.61, 95% CI 0.53 to 0.70) with an absolute risk reduction of 18% (RD 0.18, 95% CI -0.22 to -0.14), although heterogeneity between trials was high ($Chi^2$ = 249.33, df = 63, P <0.0001; $I^2$ = 75%)[26]. TXA also reduced transfused RBC volume by 0.87 units per patient (MD -0.87 units, 95% CI -1.20 to -0.53 units) and perioperative blood loss by 414 milliliters (mL) per patient (MD -414.06 mL, 95% CI -525.19 to -302.92 mL). Most patients underwent cardiac (n = 3006) or orthopedic (n = 1381) surgery, and therefore TXA efficacy in other surgical populations is less clear. In the above systematic review[26], the number of non-cardiac and non-orthopedic surgeries was small, and limited to liver (2 trials, n = 296 patients), vascular (1 trial; n = 59 patients), and gynecologic surgeries (1 trial; n = 100 patients).

### *1.3.4 Tranexamic acid safety*

TXA is commonly used in cardiac surgery, orthopedic surgery, and trauma, and has a well-established side-effect profile[38]. Based on TXA's mechanism of action, there is a theoretical risk of increased risk of venous and arterial thromboembolic events. Data from a meta-analysis that evaluated perioperative TXA in 65 trials found there was no increase in adverse events including myocardial infarction (21 trials; n = 2186 patients), stroke (18 trials; n = 2027 patients), deep vein thrombosis (23 trials; n = 1472 patients), pulmonary embolism (14 trials; n = 1006 patients) or renal failure (9 trials; n = 912 patients)[26]. A recent meta-analysis of complications of TXA in lower limb orthopedic surgery similarly did not identify an increase in VTE[39]. Further, in a large meta-analysis of intravenous TXA use across all medical disciplines (216 trials; n=125,550 patients), TXA was not associated with an increase in thromboembolic events, regardless of TXA dose[40].

Recently, an association between TXA and post-operative seizures in patients undergoing non-cardiac surgery has been observed. A large (n=4662) randomized trial evaluating TXA use in cardiac surgery found increased incidence of postoperative seizure in the TXA arm (0.7%) compared to the placebo arm (0.1%)[27]. This trial initially studied a TXA dose of 100 mg/kg, although this was decreased mid-trial to 50 mg/kg due to concern regarding dose-related seizures. Post-operative seizure has been observed primarily in the cardiac surgery population, and retrospective studies and a meta-analysis of non-randomized studies support a dose-response relationship between TXA dose and seizure association[41-45]. The mechanism by which TXA predisposes to seizures is unclear, and both ischemic and non-ischemic hypotheses have been proposed[46].

### 1.4 KNOWLEDGE GAPS:

#### *1.4.1 An RCT evaluating TXA use in non-cardiac surgeries at high risk for RBC transfusion is needed*

While TXA use is common in cardiac and orthopedic surgery, its use and efficacy in other major surgeries associated with high rates of RBC transfusion is largely unknown. A randomized controlled trial is needed to inform best-practice. If TXA reduces RBC transfusion in this diverse surgical population, it is expected that this inexpensive and widely available agent would be adopted as part of routine surgical care in a variety of health care settings. My proposed research program comprehensively evaluates key clinical questions needed to inform such a trial.

#### *1.4.2 Pragmatic electronic registry-based RCT methodology*

The process of developing and conducting randomized trials is notoriously inefficient and expensive; novel trial methodologies are needed[47]. Canadian Institutes of Health Research, Canada's federal funding agency for health research, has recognized this inefficiency and has launched the SPOR (Strategy for Patient Oriented Research) innovative Clinical Trials (iCT) initiative, focused on the development and implementation of innovative randomized trial methodology[48]. Pragmatic, registry-based (electronic) randomized controlled trials utilize readily available electronic patient data to decrease cost and increase the power and efficiency of evaluating hypotheses designed to improve patient-oriented outcomes[49-51]. In Ontario, pilot

trials within the Rethinking Clinical Trials (REaCT) initiative are ongoing to evaluate pragmatic, cost-efficient registry-based RCTs for comparative efficacy research[52]. Pragmatic electronic clinical trial research methodology is novel and facilitates high-quality research at a fraction of standard costs, but requires comprehensive, highly organized and linked electronic datasets.

During hospitalization, electronic patient data is routinely captured in high-fidelity pre-existing databases. These datasets are underutilized and could provide an opportunity to electronically monitor a trial intervention in an efficient and cost-effective manner. The evaluation of TXA utilization in major non-cardiac surgery is conducive to such a strategy, and as such, is an opportunity to demonstrate how these methods could transform the conduct of clinical trial research in Manitoba.

### *1.4.3 Opportunity for innovation in Manitoba*

TXA use in high-risk non-cardiac surgery has the potential to substantially reduce perioperative transfusion, improve patient outcomes and preserve our blood supply. This research program will systematically and comprehensively identify surgical populations at high risk of perioperative transfusion, and will investigate the utilization, efficacy, and safety of TXA in this population. These studies will collectively inform the design and conduct of a pragmatic, registry-based (electronic) randomized controlled trial. Altogether, the research program has potential to change the standard of care in both perioperative medicine and research methodology in Canada and around the world.

## 2.0 OBJECTIVES

### OVERALL OBJECTIVE:

To comprehensively inform the design and conduct of a Phase IV trial of a hospital policy of TXA to reduce transfusion in major non-cardiac surgery (TRACTION) trial, a pragmatic, registry-based (electronic) randomized controlled trial of TXA use in high-risk non-cardiac surgery **(Figure 1)**.

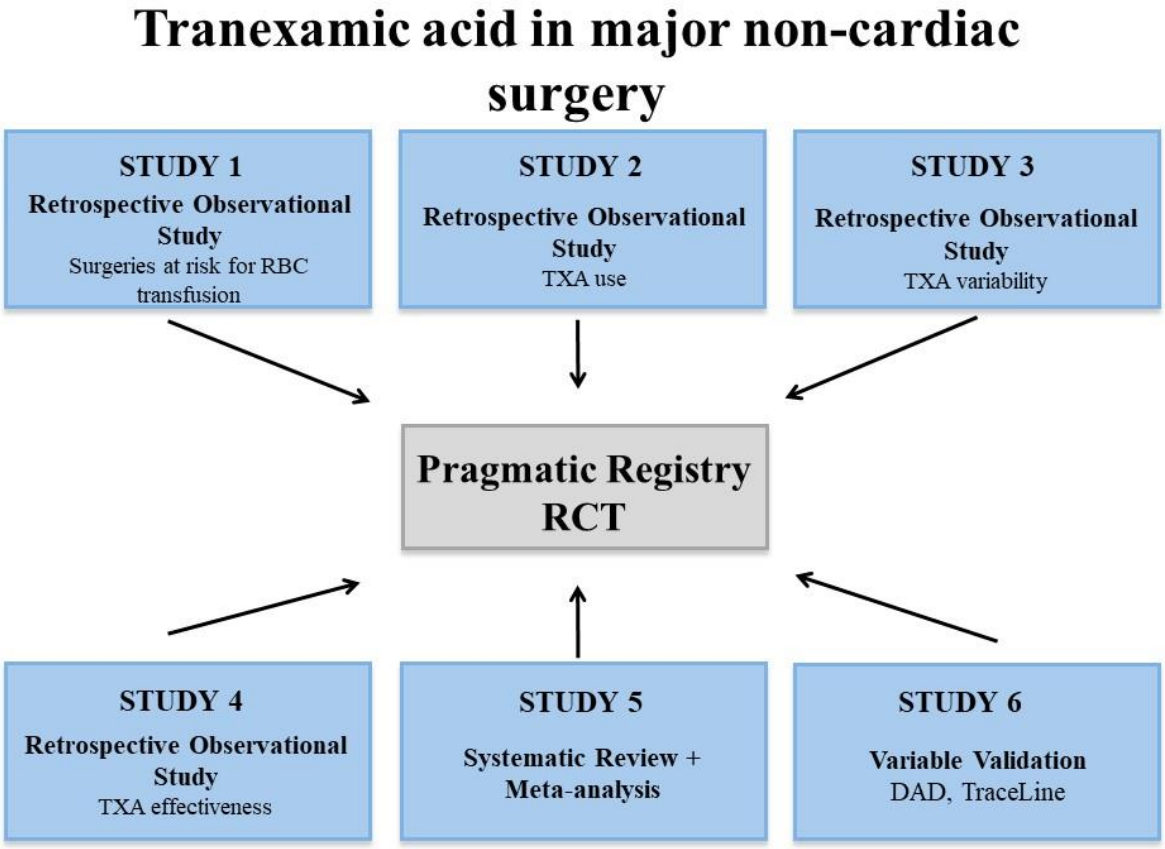



**Figure 1.** Research program

### OBJECTIVE 1: DEFINE A SURGICAL POPULATION AT HIGH RISK OF RBC TRANSFUSION

Identification of this high-risk surgical population is a foundation for the research program and will facilitate and inform subsequent Objectives. Ultimately, this high-risk surgical population will inform the enrollment criteria in the TRACTION trial by identifying patients who are most likely to benefit. Further, event rates in the control arm will contribute to sample size calculations and estimation of trial feasibility.

### OBJECTIVE 2: EVALUATE REAL-WORLD TXA USE IN PATIENTS AT HIGH RISK OF RBC TRANSFUSION

Understanding current TXA utilization patterns and practice variations in the identified at-risk surgical population will inform the extent to which clinical equipoise may (or may not) exist. These estimates will help us understand whether randomization of specific patient populations is ethically justifiable. Ultimately, this will inform the inclusion and exclusion criteria and TXA dosing in the TRACTION trial.

### OBJECTIVE 3: EXAMINE TXA EFFECTIVENESS IN PATIENTS AT HIGH RISK OF RBC TRANSFUSION

We will investigate whether the efficacy of TXA demonstrated in prior clinical trials is consistent when applied to a real-world population in the context of an observational cohort study.

### OBJECTIVE 4: EXAMINE TXA EFFICACY IN PATIENTS AT HIGH RISK OF RBC TRANSFUSION

In addition to the study of real-life TXA effectiveness, we will synthesize and meta-analyze the body of evidence from all randomized controlled trials performed in the high-risk population identified in Objective 1. Information on TXA efficacy is important to inform the TRACTION trial's sample size calculations. Information on TXA dosing in RCTs will supplement Objective 2 to inform TXA dosing in TRACTION. Additionally, this systematic review and meta-analysis will evaluate TXA safety specific to our study population.

### OBJECTIVE 5: EVALUATE KEY TRANSFUSION VARIABLES

In anticipation of a registry-based (electronic) randomized-controlled trial, it is important to evaluate the agreement between key transfusion variables captured in the clinical databases to ensure the trial results accurately represent truth. Using the patient record, electronic transfusion databases and the discharge abstract database, we will evaluate agreement in documentation of RBC transfusion among our cohort of patients undergoing non-cardiac surgery at high risk for RBC transfusion.

## 3.0 METHODS

This section briefly summarizes the methods for each of the studies. Detailed descriptions of the methods are available in the published manuscripts and their accompanying protocols and are included in **Section 9.0** [53-56]. A list of the data sources used throughout the thesis is included in **Table 1**.

**Table 1.** Summary of data sources for key variables

| Data | Winnipeg | Ottawa |
|---|---|---|
| Patient demographics, clinical and administrative hospitalization data | Discharge abstract database | The Ottawa Hospital Data Warehouse |
| ICD codes | Discharge abstract database | The Ottawa Hospital Data Warehouse |
| CCI codes | Discharge abstract database | The Ottawa Hospital Data Warehouse |
| Transfusion data | TraceLine | The Ottawa Hospital Data Warehouse |
| TXA administration | Manual chart review of random subset of non-cardiac surgeries at high risk for RBC transfusion | The Ottawa Hospital Data Warehouse (sourced from the Surgical Information Management System) |
| Laboratory data | Laboratory Information System | The Ottawa Hospital Data Warehouse |
| Transfusion variable validation | Manual chart review of random subset of non-cardiac surgeries at high risk for RBC transfusion | Not applicable |

### 3.1 STUDY 1: IDENTIFICATION OF NON-CARDIAC SURGERIES AT HIGH RISK FOR RBC TRANSFUSION

*Study design*

We completed a retrospective cohort study to evaluate adult patients undergoing major non-cardiac surgery at 5 Canadian hospitals between January 2014 and December 2016. We obtained patient demographics, clinical and administrative hospital data from the Discharge Abstract Database (DAD), which contains Canadian Classification of Health Interventions (CCI) coding for surgical procedures[57]. Manitoba transfusion and laboratory data were obtained from a provincial transfusion database (TraceLine®) and the Laboratory Information System,

respectively. Ontario transfusion and laboratory data were obtained from the Ottawa Hospital Data Warehouse.

*Study population*

We evaluated all patients undergoing a major non-cardiac surgery at ≥5% risk of perioperative RBC transfusion.

*Outcomes*

For each surgical specialty and individual surgery type, we characterized the percentage of patients exposed to RBC transfusion, and the mean/median number of RBC units transfused. We summarized the distribution of RBC transfusions by describing the non-cardiac surgeries with the highest risk of transfusion, as well as those with the highest annual number of RBC units transfused (ie, transfusion burden). This identifies common surgeries where a high percentage of patients are transfused a low number of RBC units, and lower frequency surgeries where patients receive larger numbers of RBC units. For each surgery we also evaluated the percentage of patients requiring ≥5 RBC units, RBC timing in relation to surgery, and the percentage of patients exposed to platelets and plasma.

### 3.2 STUDY 2: PROPHYLACTIC TXA USE IN NON-CARDIAC SURGERIES AT HIGH-RISK FOR RBC TRANSFUSION

*Study design*

We completed a retrospective cohort study to evaluate adult patients undergoing types of major non-cardiac surgery associated with ≥5% risk of perioperative RBC transfusion (as identified in Study 1) at 5 Canadian hospitals between January 2014 and December 2016. We obtained patient demographics, clinical and administrative hospital data from the Discharge Abstract Database (DAD), which contains Canadian Classification of Health Interventions (CCI) coding for surgical procedures[57]. The DAD was linked to transfusion and laboratory databases. Prophylactic intraoperative intravenous TXA use was ascertained electronically from The Ottawa Hospital Data Warehouse, and via manual chart review for Winnipeg hospitals.

*Study population*

As intraoperative TXA use is not electronically captured in Manitoba, the population was limited to a randomly selected subset (n = 1,653 / 12,960) of patients who underwent a major non-cardiac surgery at ≥5% risk of perioperative RBC transfusion.

*Outcomes*

We described the percentage of patients who received intraoperative TXA by surgical specialty and individual surgery type, as well as specifics of TXA dose (mg/kg/hr and mg/hr) and administration. We used pharmacokinetic modelling to examine the ability of a bolus dose to maintain TXA concentrations above the reported threshold concentration of 10 mg/L necessary to inhibit fibrinolysis[58, 59]. We chose a one-compartment open-model of drug distribution as the distributional phase of a two-compartment model ends before 30 minutes [54], and would therefore be insignificant in the surgical setting after the first few hours.

### 3.3 STUDY 3: VARIATION IN PROPHYLACTIC TXA ADMINISTRATION AMONG ANESTHESIOLOGISTS AND SURGEONS IN ORTHOPEDIC SURGERY

The original intention of Objective 2 was to perform a multivariable logistic regression analysis to evaluate factors associated with practice variation in TXA use as it relates to non-cardiac surgeries at high risk of RBC transfusion. However, upon further data exploration it was apparent that there was vast discrepancy in TXA use by surgical specialty, with very little use outside of orthopedic surgery. We were therefore unable to model predictors of TXA administration outside of orthopedic surgery as use was low and the surgery itself strongly predicted use. Objective 2 was therefore modified to evaluate predictors of TXA use in three frequently performed orthopedic surgeries where use was common (>10%).

*Study design*

We completed a retrospective cohort study of all adult patients undergoing primary total hip arthroplasty (THA), hip fracture surgery and spine fusion ± vertebrectomy at two Canadian hospitals between January 2014 and December 2016. These orthopedic surgeries were chosen because they are high frequency surgeries (n >150 per year) with higher rates of RBC transfusion

(>5%) and TXA utilization (>10%) within the cohort[53, 54]. We used CCI procedure codes within the DAD, which we linked to the Ottawa Data Warehouse to obtain hospitalization information, transfusion, laboratory and TXA administration data.

*Study population*

We evaluated patients undergoing primary THA, hip fracture surgery and spine fusion ± vertebrectomy. Analysis was restricted to Ottawa because of limited sample size in Manitoba due to the manual chart review (n <200 patients). Prophylactic TXA administration was defined as intravenous TXA initiated within 1 hour before or after the start of surgery, with the intent to exclude cases where TXA was administered in response to surgical bleeding.

*Outcomes*

To estimate the effect of anesthesiologists and surgeons on prophylactic TXA utilization, we performed separate multivariable mixed-effects logistic regression analyses for primary total hip arthroplasty, hip fracture surgery and spinal fusion ± vertebrectomy. Our exposure of interest was the anesthesiologist and surgeon; the outcome was the administration of TXA.

*Statistical analysis*

To account for patient and surgical risk, we adjusted for patient age, sex, comorbidities, preoperative hemoglobin, surgical urgency, hospital and year. For hip fracture surgery, the model was adjusted for the specific surgery subtypes, including THA (in patients with a diagnosis of hip fracture), hip hemi-arthroplasty and hip open reduction internal fixation (ORIF). The exposures of interest, the anesthesiologist and surgeon, were included as random effects[60].

To characterize the relative contributions of anesthesiologists, surgeons and patient-level factors on variation in TXA administration, we used the random intercepts to calculate the variance partition coefficient (VPC) and the median odds ratio (OR) for the receipt of TXA[61]. The variance partition coefficient characterizes the proportion of variation attributable to the anesthesiologists, surgeons, and patient and other factors, and was calculated using the linear threshold model method. We used modified Wald p-values to test if the variance was significantly different from zero[62]. The median odds ratio is a standardized measure of the variability in the odds of TXA use among surgeons or anesthesiologists. It represents the median

amount by which the odds of TXA administration would change given two different anesthesiologists (or surgeons), one with a higher probability of TXA use, and one with a lower probability of TXA use.

To more clearly illustrate how widely TXA use varies by anesthesiologist and surgeon, we plotted practitioner-specific estimated rates of TXA use for a hypothetical, but typical patient, whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population. To examine anesthesiologists, we set the surgeon to the surgeon with the median predicted likelihood of TXA use; for surgeons, we used the median anesthesiologist. We then plotted these predicted likelihoods using a box-and-whisker plot.

### 3.4 STUDY 4: ASSOCIATION BETWEEN PERIOPERATIVE TXA USE AND RBC TRANSFUSION IN ORTHOPEDIC SURGERY

The original intention of Objective 3 was to evaluate the real-world effectiveness of TXA to reduce perioperative RBC transfusion among patients undergoing non-cardiac surgery at high risk for RBC transfusion. Similar to Study 3, this was infeasible because of low TXA use outside of orthopedic surgery. We therefore modified the population of interest to three common orthopedic surgeries where TXA use was high.

*Study design*

We completed a retrospective cohort study of all adult patients undergoing primary THA, hip fracture surgery and spine fusion ± vertebrectomy at two Canadian hospitals between January 2014 and December 2016. These orthopedic surgeries were chosen because they are high frequency surgeries (n >150 per year) with higher (>10%) rates of TXA use[53, 54]. We used CCI procedure codes within the DAD, which we linked to the Ottawa Data Warehouse to obtain hospitalization information, transfusion, laboratory and TXA administration data.

*Study population*

We evaluated patients undergoing primary total hip arthroplasty (THA), hip fracture surgery and spine fusion ± vertebrectomy. Analysis was restricted to Ottawa because of limited

sample size in Manitoba due to the need for manual chart review (n <200 patients). Prophylactic TXA administration was defined as intravenous TXA initiated within 1 hour before or after the start of surgery, with the intent to exclude cases where TXA was administered in response to surgical bleeding.

*Outcomes*

The outcome of interest was the proportion of patients exposed to a perioperative RBC transfusion, defined as from the start of surgery to 7 days post-operatively.

*Statistical analysis*

Our propensity score estimates the patient's likelihood of receiving prophylactic TXA given their baseline characteristics. We estimated the propensity score using a logistic regression model in which TXA status (receipt of prophylactic TXA versus no prophylactic TXA) was regressed on 17 baseline covariates (Appendices 2-4 of manuscript)[63]. With input from content experts, variables were included if they affected either the outcome (possible confounder), or both the treatment and outcome (confounder)[64-66].

The success of a propensity score is determined by its ability to balance measured covariates between treatment groups. Prior to performing the analysis, we conducted a feasibility assessment to evaluate the overlap of the propensity score distribution between treated and untreated individuals. For each surgery, we used 3 distinct analytic approaches to assess the relationship between TXA use and perioperative RBC transfusion: (1) stabilized inverse probability weighting (IPTW); (2) propensity matching; and (3) stratification based on propensity score. We considered IPTW the primary analysis, as it estimates the average treatment effect, which more closely approximates that of a trial, resulted in the best overall covariate balance between treatment groups, and used most of the patient data. This was determined prior to estimation of the treatment effect.

Weighting attempts to use weights to create a pseudo-sample in which the distribution of measured covariates is independent of treatment assignment. Each patient is assigned a weight equal to the inverse of the probability of receiving the treatment that the subject received. As such, treated patients with very small propensity scores (ie, close to 0), and untreated patients with large propensity scores (ie, close to 1) can be assigned a large weight with significant

influence. To minimize disproportionate weighting on patients with extreme propensity score values, we weighted our study population using the stabilized inverse probability of treatment weights derived from the propensity score[67]. To assess for potential concerns regarding non-positivity of mis-specification of the propensity score, we calculated the mean stabilized weight as well as the range of weights.

To evaluate the ability of the propensity score to balance observed covariates across treatment groups, we compared the differences in means or prevalence in continuous and dichotomous covariates between treatment groups. Standardized differences were calculated to quantify the differences in means or prevalences between the treatment groups[68]. An absolute standardized difference <0.1 and variance ratio between 0.5 and 2 were used as thresholds for adequate covariate balance[69]. The distribution of continuous covariates were compared by side-by-side plots, quantile-quantile plots and cumulative density plots[70].

### 3.5 STUDY 5: EFFICACY AND SAFETY OF TXA IN NON-CARDIAC SURGERIES AT HIGH RISK OF TRANSFUSION

*Study design*

Using an *a priori* published protocol (CRD42018094409) we conducted a systematic review using methodologic approaches outlined in the *Cochrane Handbook for Systematic Reviewers* and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria[71, 72]. We searched Medline (Ovid), Embase (Ovid), CENTRAL (Cochrane Library - Wiley) and CAB Abstracts (CAB International) from inception to June 2019 to identify relevant citations of published trials. We searched the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP), clinicaltrials.gov and conference proceedings (American Society of Hematology and American Society of Anesthesiology from 2015-2018) to identify planned, ongoing, or recently completed but unpublished trials.

*Study population, interventions, and comparators*

We included randomized controlled trials (RCTs) of adults (age ≥ 18 years) undergoing surgeries at high risk for RBC transfusion (≥5% baseline transfusion rate), for which TXA use is

not standard of care. To determine trial eligibility (≥5% transfusion rate), we preferentially obtained the baseline transfusion rates from the placebo/usual care arm of each trial, as transfusion risk depends on both patient and surgical factors. However, if an individual trial did not report the transfusion rate in the control arm, we utilized surgery-specific transfusion rates obtained from Study 1. To identify surgeries where TXA is not standard of care, we excluded surgeries with TXA utilization rates were ≥50%, which included total hip and knee arthroplasty based on the results from Study 2. Our intervention included intravenous prophylactic perioperative (within one hour of start of surgery) TXA regardless of dose, frequency and duration. Comparators included placebo, usual care (i.e. open-label), or active comparators.

*Outcomes*

Our primary outcome measures were the proportion of patients transfused at least one RBC transfusion, and the number of allogeneic RBC units transfused. Our main safety outcome was incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE).

*Statistical analyses*

Data analysis were performed using Review Manager (RevMan v5.3.5, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) and Stata/IC 14.2 (StataCorp. College Station, TX). Study level summary effect comparisons of dichotomous outcomes were presented as risk ratios (RR) and risk difference (RD) with 95% confidence intervals (CI) using a Mantel-Haenszel random-effects model with constant continuity correction of 0.5 for zero events[73]. Summary effect-estimates for continuous data were expressed as the mean difference (MD) with 95% CIs. Statistical heterogeneity was quantified using the $I^2$ statistic and visual inspection of the forest plot[74]. Statistical heterogeneity, if detected ($I^2$ >50%), was explored using sensitivity analyses. For the primary outcomes, we evaluated potential publication bias using funnel plot analysis[75]. We assessed the certainty of the evidence for our primary outcomes using the GRADE methodology[76].

### 3.6 STUDY 6: EVALUATION OF AGREEMENT BETWEEN RBC TRANSFUSION VARIABLES

*Study design*

We completed a retrospective cohort study to assess the extent of agreement between different measures of RBC transfusion in the patient record, DAD, and transfusion databases.

*Study population*

We evaluated adult patients undergoing major non-cardiac surgery at ≥5% risk of perioperative RBC transfusion at 5 Canadian hospitals between January 2014 and December 2016. We obtained patient demographics, clinical and administrative hospital data from the DAD, which contains an RBC transfusion variable. We queried TraceLine® and The Ottawa Hospital Data Warehouse to obtain electronic transfusion records. Additionally, in Winnipeg transfusion information was also ascertained via chart review in a randomly selected subset (n = 1,554 / 12,960) of patients who underwent major non-cardiac surgery at ≥5% risk of perioperative RBC transfusion.

*Study variables*

We identified the presence/absence of RBC transfusion from the DAD. The DAD flags this variable as 'yes' if the patient required an RBC transfusion at any time during hospital admission. TraceLine includes more detailed transfusion data, including date/time and the product code for all dispensed or transfused blood products. The transfusion status (e.g. dispensed or transfused) relies on manual return of a 'receipt of transfusion' from the hospital to Canadian Blood Services. This has been considered accurate based on internal validation at Canadian Blood Services, however the accuracy of the 'dispensed' and 'transfused' status has not been externally evaluated. We reviewed the patient record and recorded the date/time and product code of all transfused RBCs. This information was primarily gathered from the transfusion administration record and operating room record.

*Analysis*

We evaluated the agreement between the patient record and TraceLine for documentation of RBC transfusion exposure and number of RBCs transfused from surgery start to 7 days post-operatively. We evaluated agreement in the context of differential transfusion volume (ie. <5 RBC units vs. ≥ 5 RBC units). Agreement was measured using the kappa statistic.

We compared the documentation of in-hospital RBC exposure in the DAD with TraceLine. We computed several common measures of agreement including the sensitivity, specificity, positive predictive value and negative predictive value.

## 4.0 STUDY SUMMARIES

This section briefly highlights the main findings of the manuscripts included in this thesis. Detailed analyses are reported in the manuscripts **(Section 9.0)**.

### 4.1 STUDY 1: IDENTIFICATION OF NON-CARDIAC SURGERIES AT HIGH RISK FOR RBC TRANSFUSION

Houston BL, Fergusson DA, Falk J, Krupka E, Perelman I, Breau RH, McIsaac DI, Rimmer E, Houston DS, Garland A, Ariano RE, Tinmouth A, Balshaw R, Turgeon AF, Jacobsohn E, Park J, Buduhan G, Johnson M, Koulack J, Zarychanski R. Evaluation of Transfusion Practices in Noncardiac Surgeries at High Risk for Red Blood Cell Transfusion: A Retrospective Cohort Study. Transfus Med Rev. 2021 Jan;35(1):16-21. doi: 10.1016/j.tmrv.2020.08.001. PMID: 32994103.

In our 5 centres we captured 82,971 patient admissions for major surgery and identified 85 types of non-cardiac surgeries with an RBC transfusion rate ≥ 5% representing 25,607 patient admissions. The surgical distribution between the two cities was comparable. Most surgeries were elective (n=16,383; 64%) and performed using an open surgical approach (69/85; 81%). The mean patient age was 63 years (SD 17 years), and 55% were female. Baseline demographics categorized by surgical domain are included in **Table 2.**

**Table 2.** Baseline demographics categorized by surgical domain

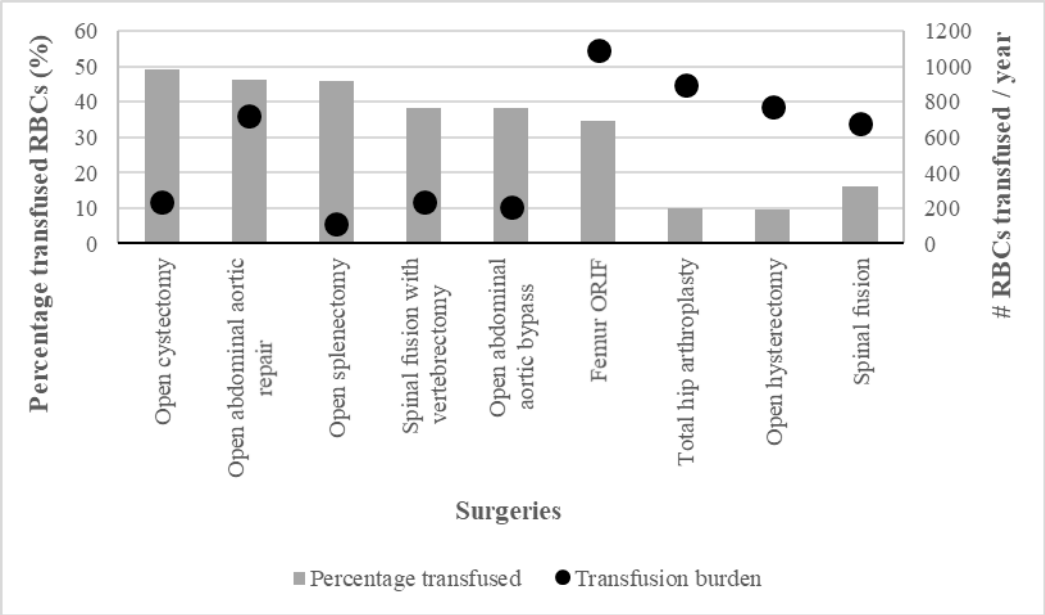
| **Surgical domain** | **Surgical volume (# surgeries / year)** | **Mean age (SD)** | **Sex (% female)** | **Mean pre-op Hb (g/L) (SD)** | **% transfused** | **Mean # RBC units* (SD)** | **RBC burden (# units / year)** |
|---|---|---|---|---|---|---|---|
| General surgery | 4907 | 62.1 (16.3) | 48 | 121 (23) | 17.5 | 2.5 (2.7) | 719 |
| Gynecology | 3792 | 52.3 (13.2) | 100 | 125 (18) | 9.5 | 2.4 (1.7) | 285 |
| Neurosurgery | 296 | 56.7 (12.1) | 71.0 | 133 (17) | 11.6 | 2.2 (1.6) | 25 |
| Orthopedic Surgery | 8515 | 70.0 (17.1) | 56.7 | 121 (20) | 17.2 | 1.9 (1.2) | 929 |
| Otolaryngology | 187 | 61.2 (13.9) | 44.4 | 130 (15) | 8.1 | 2.0 (0.8) | 10 |
| Plastic Surgery | 416 | 56.5 (16.8) | 44.7 | 118 (24) | 9.4 | 2.2 (1.1) | 28 |
| Spine Surgery | 2233 | 56.6 (15.3) | 43.1 | 133 (19) | 16.6 | 2.9 (2.2) | 352 |
| Thoracic Surgery | 736 | 59.5 (16.5) | 43.2 | 124 (22) | 17.3 | 2.4 (2.6) | 103 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Urology | 1775 | 63.2 (14.3) | 25.4 | 121 (22) | 16.2 | 2.8 (2.5) | 272 |
| Vascular Surgery | 2750 | 70.1 (11.9) | 30.3 | 128 (21) | 22.2 | 3.1 (3.8) | 636 |

* Mean # of RBC transfusions in those patients who received a RBC transfusion; SD = standard deviation; CI = comorbidity index; Pre-op = pre-operative; Hb = hemoglobin; RBC = red blood cells

In our surgical cohort, the baseline RBC transfusion rate was 16%, and ranged from 5% to 49% among individual types of surgeries. Of those transfused, the median (Q1, Q3) number of RBCs transfused was 2 units (1, 3 units); 39% received 1 RBC unit, 36% received 2 RBC units, and 8% were transfused ≥5 units. The surgeries with the highest transfusion risk differed from the surgeries with the highest annual number of RBCs transfused **(Figure 2)**. Of those who received an RBC transfusion, 27% were transfused intraoperatively, 60% were transfused postoperatively, and 13% were transfused both intraoperatively and postoperatively. This was consistent across surgical domains. Platelet and plasma transfusion were overall low, with 4% (3/85) and 12% (10/85) of surgeries associated with a platelet and plasma transfusion rate ≥5%, respectively.

**Figure 2.** The top 5 surgeries ranked according to the proportion of patients transfused RBCs (%) and the number of RBC units transfused annually. This captures the distinct surgical populations with differential impact on patients and the health care system.



### 4.2 STUDY 2: PROPHYLACTIC TXA USE IN NON-CARDIAC SURGERIES AT HIGH-RISK FOR RBC TRANSFUSION

Houston BL, Fergusson DA, Falk J, Krupka E, Perelman I, Breau RH, McIsaac DI, Rimmer E, Houston DS, Garland A, Ariano RE, Tinmouth A, Balshaw R, Turgeon AF, Jacobsohn E, Zarychanski R. Prophylactic tranexamic acid use in non-cardiac surgeries at high risk for transfusion. Transfus Med. 2021 May 2. doi: 10.1111/tme.12780. Online ahead of print. PMID: 33938051.

In five hospitals we identified 14,300 patients undergoing non-cardiac surgeries with an RBC transfusion risk ≥5%, for which TXA use was evaluable. Of these, 12,647 (88%) and 1,653 (12%) were performed in Ottawa and Winnipeg, respectively. The overall prophylactic TXA administration rate in the cohort was 17%, ranging from 0% to 68% among individual types of surgery. Prophylactic TXA administration was more common in Ottawa (n=2,317/12,647; 18%) than in Winnipeg (n=74/1,653; 4%; p<0.0001). TXA use was more common in orthopedic surgeries (n=2,043/4,942; 41%) and spine surgery (n=239/1,322; 18%) compared to other surgical domains (n=109/8,036; 1%). The surgical distribution between cities was comparable. Those undergoing urgent surgery were less likely to receive prophylactic TXA compared to elective surgical patients (11% vs. 21%; p <0.0001). This is primarily influenced by the high use of TXA in total hip arthroplasty (an elective surgery). Patients undergoing urgent surgery had more pre-operative anemia (mean hemoglobin 117 g/L vs. 131 g/L; p<0001) and perioperative RBC transfusions (57% vs. 43%; p <0.0001) compared to elective surgical patients. Surgery-specific demographics and TXA administration in the top 10 surgeries with the highest percentage of TXA utilization is included in **Table 3.**

**Table 3.** Surgery-specific baseline demographics and TXA utilization. Includes the top 10 surgeries with the highest percentage of TXA utilization.

| **Surgery** | **Surgical volume (# surgeries / year)** | **Urgency (% elective)** | **Age (mean, SD)** | **Sex (% female)** | **Pre-op Hb (g/L)** | **% transfused** | **% TXA use** |
|---|---|---|---|---|---|---|---|
| Open pelvic osteoplasty/osteotomy | 41 | 92.7 | 35 (17) | 71 | 129 (19) | 17.1 | 68.3 |
| Open hip arthroplasty | 2,648 | 67.2 | 68 (15) | 54 | 130 (17) | 10.0 | 67.3 |
| Pelvic ORIF | 106 | 14.2 | 51 (20) | 28 | 120 (19) | 26.4 | 34.9 |
| Femur ostectomy | 52 | 57.7 | 52 (20) | 50 | 125 (19) | 21.2 | 23.1 |
| Spinal fusion | 855 | 73.8 | 58 (15) | 44 | 134 (18) | 13.2 | 22.2 |
| Scalp resection | 17 | 94.1 | 70 (16) | 12 | 125 (22) | 5.9 | 17.7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Diskectomy with insertion of spacer | 136 | 87.5 | 54 (13) | 38 | 139 (15) | 4.4 | 16.2 |
| Endoscopic femur fixation | 90 | 2.2 | 78 (17) | 61 | 116 (17) | 33.3 | 13.3 |
| Femur ORIF | 1,019 | 3.7 | 72 (18) | 71 | 116 (18) | 34.8 | 12.8 |
| Open splenectomy | 50 | 44.0 | 49 (18) | 56 | 102 (24) | 46.0 | 12.0 |

The mean time from the start of the surgery to TXA administration was 28 minutes (SD 16 minutes). TXA was administered as an isolated bolus in 88% of administrations (n=2,097/2,391), as an infusion only in 3% of administrations (n=78/2,391), and as a combined bolus followed by an infusion in 9% of administrations (n=214/2,391). Overall, the median (Q1, Q3) total TXA dose was 1,000 mg (1,000, 1,000 mg).

### 4.3 STUDY 3: VARIATION IN PROPHYLACTIC TXA ADMINISTRATION AMONG ANESTHESIOLOGISTS AND SURGEONS IN ORTHOPEDIC SURGERY

Houston BL, Fergusson DA, Falk J, Ariano R, Houston DS, Krupka E, Blankstein A, Perelman I, Breau RH, McIsaac DI, Rimmer E, Garland A, Tinmouth A, Turgeon AF, Jacobsohn E, Bohm E, Zarychanski R. Variation in prophylactic tranexamic acid administration among anethesiologists and surgeons in orthopedic surgery: a retrospective cohort study. Can J Anaesth. 2021 Feb 16. Doi: 10.1007/s12630-01939-x. Online ahead of print. PMID: 33594597.

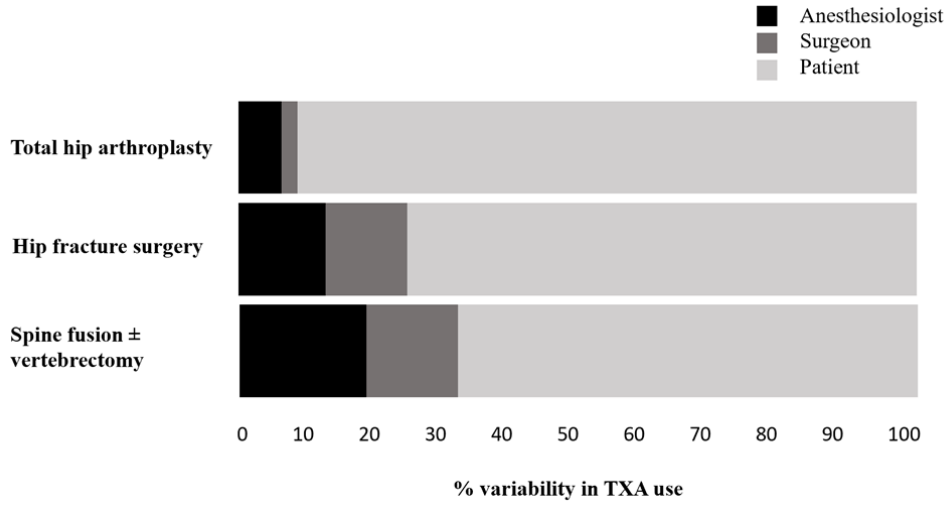
In two hospitals we identified 3,900 patients undergoing primary THA, hip fracture surgery or spine fusion ± vertebrectomy. Surgical urgency varied by surgery type; most THAs (98%) and spine fusion ± vertebrectomies (74%) were elective, whereas all hip fracture surgeries were urgent/emergent.

Overall, there were 121 anesthesiologists and 45 surgeons. The overall rate of prophylactic TXA administration was 48% (n=1,872/3,900). TXA was administered intra-operatively in 98% of patients (n=1,828/1,872), with a mean administration time of 28 minutes (SD 14 minutes) after surgery start. In our multivariable mixed-effects logistic regression models, anesthesiologists and surgeons added significant variability to the odds of receiving TXA in hip fracture surgery and spine fusion ± vertebrectomy, but not THA. In THA where TXA use is high, the variability of TXA use among anesthesiologists and surgeons was low.

Conversely, in hip fracture surgery and spine fusion ± vertebrectomy where TXA use is lower, the variability in TXA use among anesthesiologists and surgeons was higher.

Among patients undergoing THA, most of the variation could be attributed to patient and other factors (variance partition coefficient 92%), with some to anesthesiologists (6%), and less to surgeons (2%) **(Figure 3)**. The median OR for TXA administration among anesthesiologists and surgeons was 1.6 and 1.3, respectively. This means that for a given patient, their median odds of receiving TXA would differ by 1.6-fold depending on the anesthesiologist they receive care from, and by approximately 1.3-fold depending on the surgeon who performs their surgery. Among patients undergoing hip fracture surgery, 12% of the variation in TXA use was attributable to the anesthesiologist, 10% to the surgeon, and 78% to patient and other factors. The median OR for TXA administration among anesthesiologists and surgeons performing hip fracture surgery was 2.0 and 1.8, respectively. Lastly, among patients undergoing spinal fusion ± vertebrectomy, 19% of the variation in TXA use was attributable to the anesthesiologist, 13% to the surgeon and 68% to patient-specific factors. The median OR for TXA use among anesthesiologists and surgeons performing spinal fusion ± vertebrectomy was 2.5 and 2.1, respectively.

**Figure 3.** The partition of variability in TXA use amongst patient specific factors, the anesthesiologist, and surgeon for a given patient undergoing primary total hip arthroplasty, hip fracture surgery and spine fusion ± vertebrectomy.



### 4.4 STUDY 4: ASSOCIATION BETWEEN PERIOPERATIVE TXA USE AND RBC TRANSFUSION IN ORTHOPEDIC SURGERY

In two hospitals we identified 3,900 patients undergoing primary THA, hip fracture surgery or spine fusion ± vertebrectomy. The overall rate of prophylactic TXA administration was 48% (n=1,872/3,900). The baseline standardized difference exceeded 0.1 in 9 of 17 variables in the total hip arthroplasty cohort, 11 of 17 variables in the hip fracture surgery cohort, and 9 of 17 variables in the spine fusion cohort. Following stabilized inverse probability weighting (IPTW), in total hip arthroplasty, the mean stabilized weight was 1.00 (SD 0.29) with a stabilized weight range from 0.21 to 2.39. In hip fracture surgery, the mean stabilized weight was 1.02 (SD 0.46) with a stabilized weight range from 0.27 to 4.73. In spine fusion ± vertebrectomy, the mean stabilized weight was 1.01 (SD 0.26) with a stabilized weight range from 0.29 to 3.20. In all 3 surgeries, as the mean stabilized weights were close to 1, and range of stabilized weights were all <10, there was no concrete evidence of non-positivity or mis-specification of the propensity score. The median (IQR) standardized differences of the variables were less than 0.1 in nearly all three surgeries.

Among patients undergoing total hip arthroplasty, TXA administration was associated with a trend towards reduced odds of perioperative RBC transfusion (OR 0.77; 95% CI 0.34 to 1.77). The relative risk of perioperative RBC transfusion in treated patients compared to untreated patients was 0.61 (95% CI 0.37 to 0.99). The represents an absolute risk reduction of 9% (95% CI 2% to 21%). These effect estimates were consistent among the different analytic strategies. Among patients undergoing hip fracture surgery, TXA administration was associated with reduced odds of perioperative RBC transfusion (OR 0.60; 95% CI 0.41 to 0.87). The relative risk of perioperative RBC transfusion in treated patients compared to untreated patients was 0.90 (95% CI 0.83 to 0.96). This represents an absolute risk reduction of 9% (95% CI 3% to 14%). These effect estimates were consistent among the different analytic strategies. Among patients undergoing spine fusion ± vertebrectomy, TXA administration was associated with increased odds of perioperative RBC transfusion (OR 1.33; 95% CI 0.72 to 2.45). The relative risk of perioperative RBC transfusion in treated patients compared to untreated patients was 1.07 (95% CI 0.91 to 1.27). This represents an absolute risk increase of 5% (95% CI -7% to 17%). These effect estimates were consistent among the different analytic strategies.

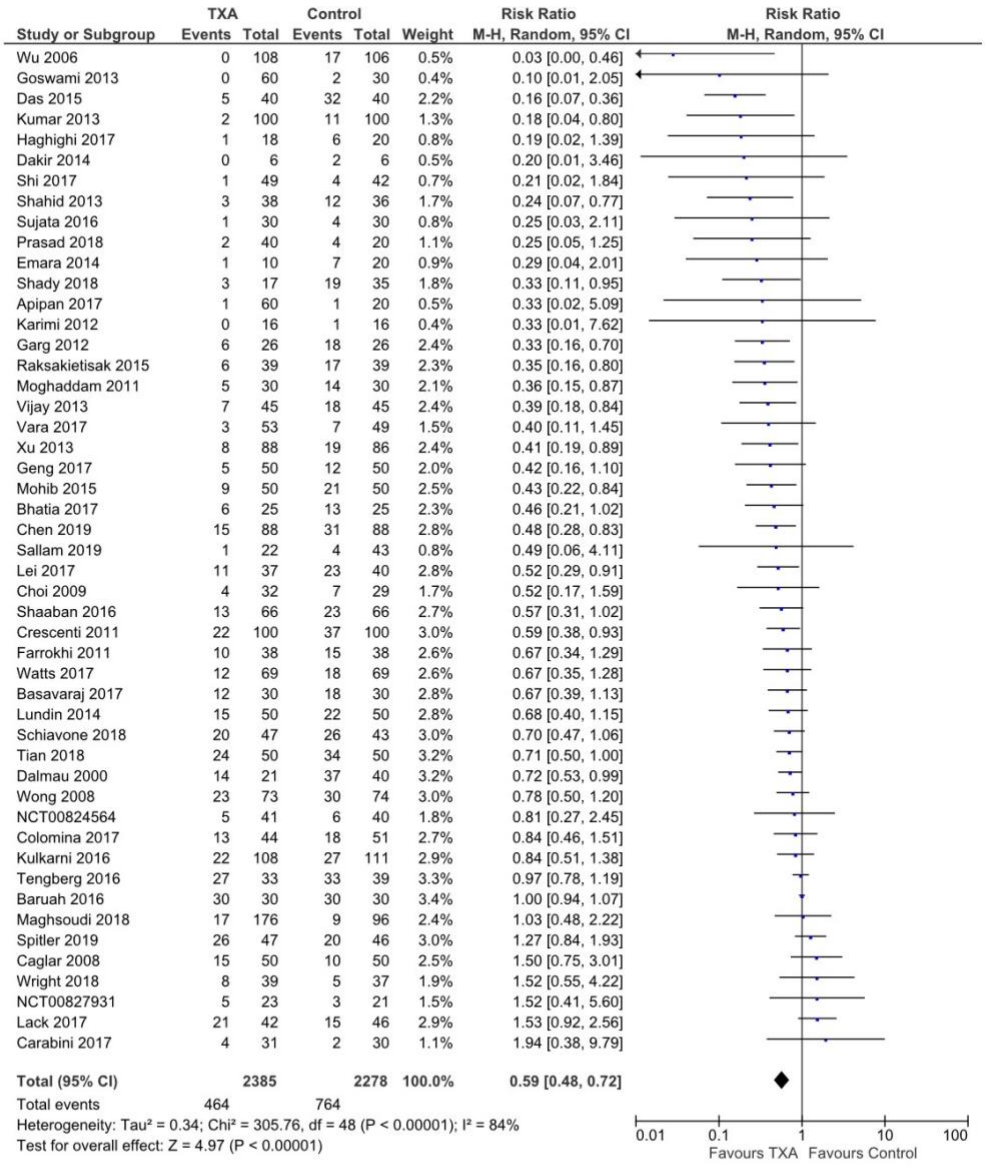
### 4.5 STUDY 5: EFFICACY AND SAFETY OF TXA IN NON-CARDIAC SURGERIES AT HIGH RISK OF TRANSFUSION

Houston BL, Uminski K, Mutter T, Rimmer E, Houston DS, Menard CE, Garland A, Ariano R, Tinmouth A, Abou-Setta AM, Rabbani R, Neilson C, Rochwerg B, Turgeon AF, Falk J, Breau RH, Fergusson DA, Zarychanski R. Efficacy and Safety of Tranexamic Acid in Major Non-Cardiac Surgeries at High Risk for Transfusion: A Systematic Review and Meta-Analysis. Transfus Med Rev. 2020 Jan;34(1):51-62. doi: 10.1016/j.tmrv.2019.10.001. Epub 2019 Oct 23. PMID: 31982293.

Of the 8565 citations identified, we included 69 RCTs enrolling 6157 patients. Forty-three trials (3844 patients) evaluated elective surgical procedures and 20 trials (1584 patients) evaluated urgent/emergent procedures; the urgency of the remaining 6 trials was mixed or unclear. Patients with active malignancy were enrolled in 13 trials. Most trials (45/69; 65%) were of unclear risk of bias. The most common TXA dosing was calculated based on patient weight (57 trials; 4837 patients). Of these, 27 trials (2126 patients) administered TXA as a bolus followed by an infusion; 26 trials (2383 patients) administered TXA exclusively as a bolus; four trials (328 patients) administered TXA exclusively as an infusion.

Compared to placebo or usual care, TXA reduced the proportion of patients transfused red blood cells (relative risk (RR) 0.59; 95% confidence interval (CI) 0.48 to 0.72; $I^2$ 84%; 49 trials; 4663 patients) **(Figure 4)**. This represents an absolute risk reduction of 12% (95% CI 9% to 16% reduction) and a number needed to treat (NNT) of 9 (95% CI 6 to 11) patients to prevent at least one red blood cell transfusion. Subgroup and sensitivity analyses did not detect differences in treatment effect, nor did they resolve sources of statistical heterogeneity. Based on the relative risk reduction of 0.41 and accounting for the heterogeneity ($I^2$ = 84%) in our sample, the trial sequential boundary for superiority was reached, indicating that TXA reduces the proportion of patients transfused RBCs.

**Figure 4.** The proportion of patients exposed to RBC transfusion at longest follow-up




TXA = tranexamic acid; CI = confidence interval; M-H = Mantel Haenszel; *Control = placebo or usual care

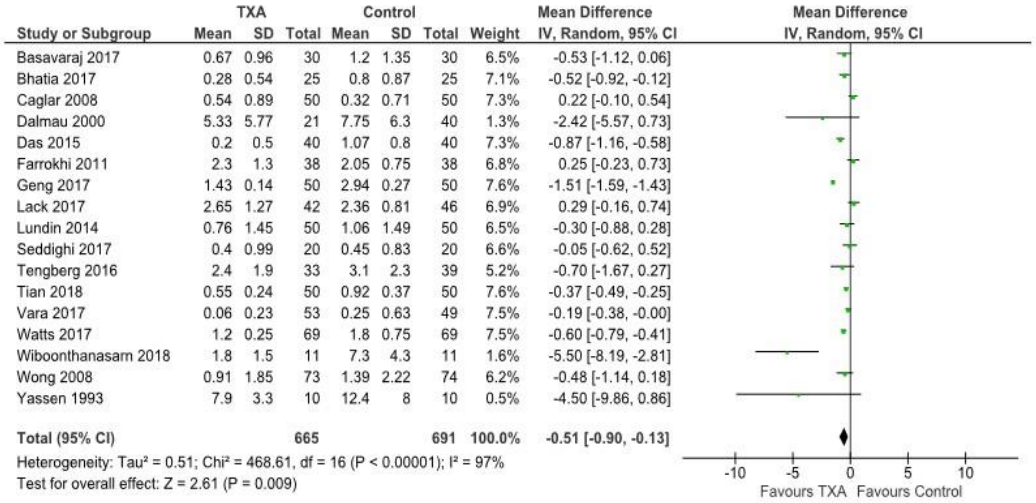
In the context of substantial between-study heterogeneity, funnel plot analysis suggested the absence of small to moderate-size studies favoring placebo or usual care. Given that the majority of trials were considered to be of unclear or high risk of bias and due to significant

between-study heterogeneity, we graded the overall strength of evidence as low. No active comparators reduced the proportion of patients transfused RBCs compared to TXA.

Compared to placebo or usual care, TXA reduced the volume of RBCs transfused (mean difference of 0.51 RBC units; 95% CI 0.13 to 0.9 units; $I^2$ 97%; 17 trials; 1356 patients) **(Figure 5)**. Statistically significant subgroup differences were detected when analyzed by funding source (non-industry funded vs. industry funded. vs not reported; p = 0.01), with larger reductions in volume of transfused RBCs in the TXA arm of trials that did not report funding source. Subgroup differences were also noted when analyzed by surgery type (p = 0.01), as hepatobiliary trials reported larger reductions in volume of transfused RBCs in the TXA group relative to other surgical domains. Statistical heterogeneity was not substantially resolved by subgroup analyses. A trial sequential analysis was performed for number of RBC units transfused based on a mean change of -0.51 units. Accounting for the heterogeneity ($I^2$ 97%) in our sample, the trial sequential boundary for superiority was reached, indicating that TXA reduces the number of RBC units transfused.

In the context of substantial between-study heterogeneity, funnel plot analysis suggested the absence of small to moderate-size studies favoring placebo or usual care. Given that the majority of trials were considered to be of unclear or high risk of bias and due to significant between-study heterogeneity, we graded the overall strength of evidence as low. No active comparators reduced the number of RBC units transfused compared to TXA.

**Figure 5.** The number of RBC units transfused at longest follow-up




TXA = tranexamic acid; SD = standard deviation; CI = confidence interval; *Control = placebo or usual care

### 4.6 STUDY 6: EVALUATION OF AGREEMENT BETWEEN RBC TRANSFUSION VARIABLES

*Comparison of TraceLine to the patient record*

A manual review of the patient record was performed in 1554 randomly selected patients undergoing non-cardiac surgery at high-risk for RBC transfusion to confirm the accuracy of TraceLine. Manual review of the patient record identified 86 patients (n=86/1554; 5.5%) who received an RBC transfusion within 7 days of their surgery (n=192 RBC units transfused). TraceLine documented 84 patients (n=84/1554; 5.4%) who received an RBC transfusion (n=212 RBC units transfused). There was near perfect agreement between the patient record and TraceLine for documentation of RBC exposure (n=1552/1554; kappa=0.99; 95% CI 0.97 to 1).

There was also near perfect agreement between the patient record and TraceLine for number of RBC units transfused (n=1525/1554 patients; kappa=0.82; 95% CI 0.76 to 0.87). Of

these patients, 1468 patients (n=96%) were not transfused, 28 patients (n=2%) received 1 RBC unit, 16 patients (n=1%) received 2 RBC units, and 13 patients received >2 RBC units (n=1%).

When we limited the analysis to transfused patients, there was moderate agreement between the patient record and TraceLine for documentation of the number of RBC units (kappa=0.53; 95% CI 0.40 to 0.66). Of those who received <5 RBC units, agreement remained moderate (53/72 patients; kappa=0.59; 95% CI 0.43 to 0.75). Agreement decreased substantially among patients who received ≥ 5 RBC units (4/12 patients; kappa=0.11; 95%CI -0.1 to 0.3). In most instances (n=23/29; 79%), discrepancies in the number of RBC units transfused were limited to a single unit.

*Comparison of the DAD to electronic transfusion databases*

We compared the transfusion status in the DAD to the electronic transfusion databases in 25,607 patient admissions for non-cardiac surgery at ≥ 5% risk for transfusion across 5 centres. We found near perfect agreement between the two data sources for documentation of RBC transfusion during hospital admission (n=24,740/25,607 patient admissions; kappa=0.88; 95% CI 0.87 to 0.89).

Assuming the electronic transfusion records are the 'gold standard', the sensitivity of the DAD for identifying patients exposed to an RBC transfusion during their hospitalization was 84% (95% CI 83% to 85%). The specificity of the DAD for ruling out receipt of an RBC transfusion during hospital admission was 99% (95% CI 99% to 99%). The positive predictive value and negative predictive value were both 97% (95% CI 96% to 97%). The sensitivity of the DAD increased marginally to 86% among patients who received >1 RBC unit.

# 5.0 DISCUSSION

## 5.1 PRINCIPAL FINDINGS

In this thesis, we have completed the preparatory work needed to comprehensively inform the design and conduct of the TRACTION trial, a pragmatic RCT of TXA use in non-cardiac surgeries at high risk for RBC transfusion. In Study 1, we identified 85 unique non-cardiac surgeries associated with an RBC transfusion rate ≥ 5%. We focused on both the percentage of patients transfused RBCs as well as the total number of RBCs transfused annually, as these measures have differing implications for patients and the health care system.

In Study 2, we observed that the prophylactic use of TXA varies widely according to surgical subtype, with limited use outside the specialties of orthopedic and spine surgery. We also noted that TXA was most commonly administered as a bolus, with a median total dose of 1 gram.

In Study 3, we evaluated 3 common orthopedic surgeries with >10% TXA use and found that in total hip arthroplasty, where TXA use is highest, the variability of TXA use among anesthesiologists and surgeons was low. Conversely, in hip fracture surgery and spine fusion ± vertebrectomy where TXA use is lower, the variability in TXA use among anesthesiologists and surgeons was higher.

In Study 4 we used propensity score analysis to evaluate the effectiveness of TXA to reduce RBC transfusion in 3 common orthopedic surgeries. We found a trend towards reduced odds of perioperative RBC transfusion with TXA use in total hip arthroplasty and hip fracture surgery, but an increased odds of perioperative RBC transfusion with TXA use in spine fusion surgery. Unfortunately, methodologic limitations precluded robust interpretation of study results.

In Study 5 we meta-analyzed 69 randomized trials of TXA use in non-cardiac surgeries at increased risk for RBC transfusion. We found that TXA reduces both the proportion of patients transfused RBC perioperatively as well as the volume of RBCs transfused. TXA was not associated with differences in deep vein thrombosis or pulmonary embolism, although summary effect estimates were limited by lack of systemic screening and short duration of follow-up.

Lastly, in Study 6 we evaluated the agreement between RBC transfusion documentation in the patient record, transfusion databases and the DAD. When we compared manual review of the patient record to TraceLine, there was excellent agreement for documentation of RBC

exposure, but agreement decreased with increasing number of RBC units transfused. When we compared the DAD to electronic transfusion databases, we found near-perfect agreement between the two data sources for documentation of transfusion exposure during hospital admission. The DAD had very high specificity for ruling out receipt of RBC transfusion.

## 5.2 CURRENT EVIDENCE AND IMPLICATIONS

### *5.2.1 RBC transfusion in non-cardiac surgery*

In the era of blood conservation initiatives, we have described transfusion practices in major non-cardiac surgeries at high risk (≥5%) for red blood cell transfusion. We focused on both the proportion of patients transfused RBCs as well as the number of RBC units transfused annually, as these measures have differing implications. Transfusion exposure is a patient prioritized outcome that informs patient consent discussions and perioperative surgical planning. Transfusion burden considers both the percentage of patients transfused as well as surgical frequency, with systemic implications for the health care system and blood banking, as blood products are a costly but finite resource[2].

Prior studies evaluating the frequency and distribution of real-world perioperative transfusion in non-cardiac surgery do not reflect recent efforts to mitigate blood transfusion, such as pre-operative anemia correction, intraoperative cell salvage, variation in surgical technique, use of more restrictive transfusion thresholds, single-unit transfusion policies and the increasing use of medications such as TXA [16-18, 77-79]. Reflective of this, a patient blood management initiative in Ontario, Canada demonstrated that the implementation of blood conservation efforts substantially reduces perioperative transfusion in select patient populations such as coronary artery bypass grafting (CABG), radical prostatectomy and hip and knee arthroplasty[8]. Our study builds on these findings by providing a comprehensive and updated description of transfusion practices in non-cardiac surgery in the era of blood conservation prioritization.

We preselected a higher risk surgical population by limiting cohort inclusion to hospitalized patients undergoing a surgery with a transfusion rate ≥ 5%, a threshold felt to be meaningful to both patient partners and stakeholders. As expected, patients undergoing open surgery experienced increased RBC transfusion exposure. This could possibly relate to the more invasive nature of the surgery, a pre-selection for higher risk surgeries that may not be amenable

to a minimally invasive approach or reduced venous blood loss in minimally invasive surgeries from venous collapse due to pneumoperitoneum-related pressure increases. Non-elective surgeries were also associated with increased RBC transfusion exposure, likely due to the inability to correct pre-operative anemia and increased illness acuity and severity.

*5.2.2 TXA use in non-cardiac surgery*

Perioperative TXA use has been shown to reduce RBC transfusion in large randomized trials[26, 56], yet real-world reports of TXA utilization are limited[80, 81]. Higher TXA use in orthopedic and spine surgery aligns with a substantive body of literature supporting its efficacy and cost-effectiveness in these surgical populations[32, 82-87]. Low TXA utilization in other surgeries is inconsistent with Study 5 (a meta-analysis that included 69 RCTs enrolling 6157 patients) that demonstrates the ability of TXA to reduce RBC transfusion across a broad range of major non-cardiac surgeries[56]. While the perceived lack of uptake of TXA into routine practice could reflect the time-period evaluated in our study (2014 to 2016) relative to publication date of individual trials, 64% (21/33 trials) of the trials in this surgical population were published prior to 2016. Possible barriers to TXA uptake may reflect low confidence in the published trials, which are relatively small (median size 80 patients (IQR 60-100 patients)) with most at unclear or high risk of bias (97%; 32/33 trials). Concern regarding the perceived risk of thrombotic complications may further decrease use[56, 88].

The high utilization (85%) and low variability of TXA use in THA reflects the substantial evidence supporting TXA efficacy and cost-effectiveness in this surgery[32, 87, 89]. As most of the variability in TXA use was related to patient and other factors, this could appropriately reflect risk-adapted clinical decision-making based on differing patient characteristics. Overall, this suggests the supportive recommendations for routine TXA use from multiple American orthopedic society guidelines have been effectively translated into clinical practice and incorporated into standard of care[82].

In hip fracture and spine fusion surgeries, lower utilization and substantial variability in TXA use among surgical team members could reflect explicit anesthesiologist or surgeon preference for TXA administration, variations in surgical technique between surgeons, or the surgeon-specific case composition. Recently, randomized data have been published supporting the ability of TXA to reduce RBC transfusion in hip fracture[31, 90-92] and complex spine

surgeries[56, 93, 94], although the certainty surrounding safety (i.e. thrombosis) is less clear. The underreporting of thrombotic complications and limited durations of follow-up in trials may have underestimated the true incidence of thromboembolic complications in an elderly population at particularly increased risk[56]. Future randomized trials powered for important safety endpoints are needed prior to routine adoption.

The dosing of TXA observed in Study 2 aligns with prior trials evaluating intravenous prophylactic TXA, although standard dosing of perioperative TXA does not exist, and a wide dosing ranges and dosing schedules have been reported[26, 56]. In keeping with practice trends of reduced TXA doses over time[95], Study 5 demonstrated that less than 2 grams of TXA was used in 31/49 trials (n = 2,775 patients) of patients undergoing non-cardiac surgeries at high-risk for RBC transfusion[56]. While detailed pharmacokinetic and pharmacodynamic data in this population are lacking, studies in healthy volunteers have shown that a bolus of 1 gram maintained therapeutic plasma concentrations for 3 hours, with an elimination half-life of approximately 2 hours[24, 25]. The PORTO trial evaluated variations in TXA dosing (1-gram intravenous bolus followed by 1 gram infusion versus 1 gram intravenous bolus followed by placebo) in total hip arthroplasty, and found no difference in perioperative blood loss between these two groups[96]. Based on our pharmacokinetic model, we estimate that therapeutic concentrations are maintained for approximately 240 minutes. Given the median surgical duration in our study was 190 minutes (IQR 133 to 286 minutes), it is likely that a 1-gram bolus dose would be adequate to maintain therapeutic concentrations for the duration of surgery in the majority of cases[59].

*5.3.3 TXA effectiveness in non-cardiac surgery*

In Study 4, the trend towards reduced RBC transfusion with perioperative TXA use in primary total hip arthroplasty and hip fracture surgery is consistent with a substantive body of literature supporting its efficacy[31, 82, 83, 89-91, 97]. This is consistent with supportive recommendations for routine TXA use from multiple American orthopedic society guidelines[82].

The increase in RBC transfusion associated with TXA use in spine fusion ± vertebrectomy contradicts prior evidence syntheses which suggest TXA reduces RBC transfusion in this surgical population[56, 85]. This may reflect the grouping of procedures within a single

category of spine fusion ± vertebrectomy which may have obscured much greater variability in complexity, invasiveness, tissue trauma and hemorrhage than the more homogeneous categories of THA and hip fracture surgery. This is supported by the wide range of operative time within this grouping (median surgical duration 6 hours; range 1 to 16 hours). This single grouping may therefore not account for differing RBC transfusion risk. Within spine surgery, differences RBC transfusion rate have been reported with increasing age, female sex, varying surgical approaches, multilevel surgery, instrumented fusion, preoperative anemia and duration of surgery[98-102]. This degree of granularity was not available using CCI procedure codes from the DAD, and therefore we were not able to adjust for these variables. It is possible that patients who received TXA did so because of a perceived increased risk of transfusion that was otherwise not captured with our study variables. The increased duration of surgery among patients who received TXA versus those who did not (6.2 vs 5.5 hours; $p < 0.001$) supports this hypothesis. Duration of surgery was intentionally not included in our propensity score model as this would not have been known at the time of TXA administration.

While the same limitation of unmeasured variability in surgical invasiveness may have impacted total hip arthroplasty and hip fracture surgery analyses, this is less likely given there was less operative time variability among these groupings. The mean surgical duration in patients who underwent hip fracture and spine fusion surgery was 2 hours (standard deviation 0.8 hours) and 1.6 hours (SD 0.7 hours), respectively. It seems mechanistically implausible that TXA actually increases RBC transfusion, and this has not been reported in systematic reviews synthesizing data from more than 60 randomized trials[26, 56].

Propensity methods utilize a quasi-experimental approach to control for measured confounding using the balancing property of the propensity score. Compared to randomized studies, propensity scores are efficient, cost-effective and can more easily evaluate rare outcomes due to their observational design. However, an intrinsic limitation of the propensity score is its inability to balance unmeasured confounders. Investigators are limited to covariates present in the dataset, which can lack sufficient granularity. If the assumption of exchangeability is violated, then biased treatment effects will result despite perfect balance of measured confounders. For these reasons, with comprehensive, high-fidelity datasets, propensity analyses can certainly be beneficial to supplement trial data with supportive observational real-world evidence of effectiveness. Propensity scores are a helpful tool to study rare outcomes and clinical

circumstances where randomized trials are infeasible or unethical, although careful scrutiny of the included covariates and balance diagnostics are absolutely essential. In circumstances where RCTs are feasible and precise evaluation of safety and efficacy are needed, then RCTs should remain the gold standard.

*5.3.4 TXA efficacy and safety in non-cardiac surgery*

TXA has been consistently shown to reduce RBC transfusion in cardiac surgery, trauma, and hip and knee arthroplasty, where it is now routinely incorporated into standard of care[28, 31-34, 77]. Perioperative TXA use is supported by the American Society of Anesthesiologists (ASA) Practice Guidelines for Perioperative Blood Management to reduce transfusion for patients at increased risk for bleeding[103]. The supporting evidence base for these specific surgical populations parallels TXA use. In a recent study of TXA use at five academic institutions, TXA use was high in hip (75%) and knee arthroplasty (85%), and low (16%) in other non-cardiac surgeries with comparable risks for transfusion[54].

Our systematic review builds on targeted evidence syntheses evaluating TXA in discrete surgeries such as spine[104] and hip fracture surgery[105, 106]. Prior to our study, the most recent comprehensive evaluation of TXA and its impact on perioperative transfusion in non-cardiac surgery was a 2011 Cochrane systematic review[26]. The included study population of this review comprised primarily cardiac surgery and hip and knee arthroplasty; non-cardiac surgical patients made up 455 of 4842 (9%) of included patients. Fifty-two (75%) of our included trials were published in the interim.

While the broad inclusion of all non-cardiac surgeries with a baseline transfusion rate ≥5% serves to highlight the universal benefits of TXA, summary estimates are associated with significant heterogeneity. Despite comprehensive subgroup analyses, causes of the heterogeneity could not be fully resolved. Effect estimates, however, consistently favor TXA, and thus unresolved heterogeneity reflect uncertainty in the precise magnitude of TXA efficacy rather than the presence or absence of efficacy. Variability may be plausibly related to yet to be identified patient- or procedure-, or operator-dependent characteristics.

The incidence of post-operative DVT was low in our study (2.2%); however, widespread underreporting, and limited trial duration of follow-up are likely to underestimate the true incidence. The risk of post-operative venous thromboembolic disease is substantially increased

in the three months post-operatively,[107] yet only 14/50 (28%) and 6/50 (12%) of the trials reporting DVT events had a follow-up duration of one and three months, respectively. Follow-up limited to hospital discharge is known to inadequately capture VTE events, as highlighted by two recent studies where VTE events occurred following hospital discharge in 34-100% of affected individuals[108, 109]. While the low incidence of thrombotic complications appears favorable, studies evaluating TXA safety with extended duration of follow-up would be required to generate precise estimates of postoperative venous thromboembolism.

#### *5.3.5 Evaluation of agreement between RBC variables*

TraceLine is the electronic transfusion database that will be used to ascertain transfusion status in the TRACTION trial. When we compared manual review of the patient record to TraceLine, there was excellent agreement for documentation of RBC exposure, although agreement decreased with increasing number of RBC units transfused. This could relate to the acuity of the circumstances in which large volume transfusions are administered in the operative and perioperative setting, as well as the multiple transfers of care involving the operating room, post-operative recovery and ward or intensive care.

## 5.3 STRENGTHS AND LIMITATIONS

*Strengths*

The main strength of this thesis is the systematic and multi-faceted approach used to achieve the stated objectives and ultimately inform the TRACTION trial. By creating a structured research program whereby each study sequentially informs the next, we were able to comprehensively evaluate RBC transfusion, TXA use, TXA efficacy and safety across major non-cardiac surgeries at increased risk for transfusion, while simultaneously informing key elements of the TRACTION trial.

For the retrospective cohort studies, we utilized high fidelity datasets to reliably capture patient demographics, surgical information, transfusion practices and TXA administration across a health care system that cares for more than 1 million people. This data linkage and data manipulation provided invaluable experience with the exact data sources and formats that will be used to capture patient demographics and clinical outcomes in the TRACTION trial.

All individual studies were designed to address existing knowledge gaps in the literature. In Study 1, we described real-world transfusion practices across a range of higher-risk non-cardiac surgeries. In Study 2, we demonstrated low utilization outside the orthopedic and spine domains, which is otherwise not apparent in the literature, and inconsistent with current perioperative guidelines[103]. We furthered the study of TXA variation by describing not only the rates of TXA use across different orthopedic surgeries, but also how the use varies across surgical team members. To the best of our knowledge, this has never been previously reported. In Study 5, rather than updating or repeating systematic reviews in populations where TXA is known to be efficacious, our review focused on surgeries where TXA is not routinely used as standard of care. In Study 6, we evaluated the agreement in reporting of transfusion data across differing source data, which remains critical to the validity of the TRACTION trial.

Throughout this thesis, we consistently aimed to evaluate outcomes meaningful to patients. Rather than focusing on volume of intra-operative or post-operative bleeding, which is known to suffer methodologic concerns regarding reliability of capture[110, 111], we focused on exposure to RBC and TXA safety. By studying RBC transfusion and TXA use in all non-cardiac surgeries at ≥5% risk of RBC transfusion, the results of this thesis are generalizable to a large population of perioperative patients.

Individual studies were executed from an *a priori* protocol to minimize bias and increase transparency. In Study 4, we used a comprehensive analytic approach including stabilized inverse probability weighting, matching, stratification, and logistic regression with and without propensity score adjustment. Analyses were separated *a priori* between the three surgeries to facilitate evaluation of populations as homogenous as possible. In Study 5, we used an *a priori* published protocol, and followed established methodological guidelines concerning the conduct and reporting of this review.

*Limitations*

While we used high fidelity data sets within our retrospective studies, the retrospective nature of the studies resulted in limitations related to variable capture. Perhaps most importantly, surgical information was obtained from the DAD and, while standardized, the CCI codes do not directly reflect surgical descriptions in clinical practice. We tried to mitigate this limitation by involving surgical content experts, and by using both administrative CCI code definitions as well

as governmental descriptions to finalize our surgical cohort. Despite this, our databases lacked granularity regarding specifics of the surgical procedures, particularly with respect to spine surgery. This substantially affected the interpretation of Study 4, where we were unable to control for all relevant surgical factors that influence whether a patient receives TXA. While we were able to balance measured covariates, we were unable to control for key unmeasured covariates[69, 112]. This critical methodologic flaw ultimately resulted in the decision to forego publication in a peer-review journal.

Ascertainment of TXA administration in Manitoba required a manual chart review, and therefore TXA administration data was largely informed by two centers in Ottawa, Ontario and logistic regression models were limited to two Ottawa hospitals. We evaluated variability in TXA use among care providers from 2014 to 2016, which may not reflect recent TXA utilization practices. We were unable to evaluate the impact of practitioner characteristics and training, nor the potential impact of trainees on TXA administration. Topical TXA was not explicitly captured, although this reflects institutional practice as topical administration was uncommonly used, if at all during the study period. An updated evaluation of TXA utilization in additional centers may provide an even more comprehensive evaluation of how centers have implemented international anesthesiology guidelines.

Institutional differences in surgical practice and transfusion rates may impact generalizability, particularly in resource limited settings where perioperative practice may vary. We described transfusion practices from 2014 to 2016, which may not reflect present day blood conservation initiatives and may therefore overestimate contemporary transfusion rates[19]. We were unable to evaluate other blood conservation strategies such as topical TXA, pre-operative anemia correction, or iron replacement, which could have affected operative or postoperative RBC transfusion.

The relationship between preoperative anemia and perioperative transfusion was difficult to ascertain as preoperative hemoglobin values were limited to 67% of our cohort, with reduced capture in elective surgeries. This was most relevant in Study 3 and 4 when we evaluated predictors of TXA administration. This absence of data likely relates to perioperative guidelines which discourage routine bloodwork prior to surgery [113]. To further understand the impact of these missing data, sensitivity analyses were planned *a priori* and performed with various imputation techniques, none of which significantly altered the results.

In Study 5, we were unable to resolve sources of heterogeneity in our meta-analysis despite extensive subgroup analysis. However, the observed heterogeneity is similar to what was reported in the Cochrane review[26] despite their narrow inclusion of only 3 dominant surgeries. The heterogeneity may be related to patient co-morbidities or prior medication administration, operative factors (anesthetic variability, transfusion thresholds, surgeon factors), which were not comprehensively addressed by the primary trials. The duration of follow-up was relatively short (and often not reported), which limits our evaluation of TXA safety.

### 5.4 INFORMING THE TRACTION TRIAL

We have achieved our stated objective of comprehensively informing the design and conduct of the TRACTION trial, which is a multi-centre registry-based RCT evaluating TXA in non-cardiac surgeries at increased risk for RBC transfusion.

#### *5.4.1 Inclusion criteria*

In Study 1, we identified a surgical population at increased (≥5%) risk of RBC transfusion, which has directly informed the trial's inclusion criteria. A 1 in 20 risk of RBC transfusion was felt by key patient partners and stakeholders to optimize the balance between enrolling a broad range of surgeries with sufficient generalizability while considering the patient's likelihood of benefit.

#### *5.4.2 Exclusion criteria*

Exclusion criteria for the TRACTION criteria were informed by Study 2, where we have excluded hip and knee arthroplasty on the basis of TXA utilization data. As TXA utilization was >75% in these surgeries, it was felt there was insufficient equipoise to randomize these patients as TXA is considered to be standard of care.

#### *5.4.3 TXA dosing*

Pragmatic TXA dosing was informed by both Study 2 and Study 5. In Study 2, we found that TXA was most commonly administered as a bolus (88%), with a median TXA dose was 1g (IQR 1g to 1g). In Study 5, TXA doses of less than 2g were administered in 31/49 trials (n=2,775

patients). In response, TXA dosing in the TRACTION trial is a 1g bolus (2g if patient >100kg) intravenously administered within 10 minutes of surgical incision, followed by an additional 1g given intravenously prior to skin close, at the discretion of the anesthesiologist. This was designed to approximate dosing used in routine process and studied in trials, while providing contextual flexibility for the anesthesiologists.

*5.4.4 Study outcomes*

The TRACTION trial has been designed with co-primary outcomes that evaluate effectiveness in the context of safety. The co-primary outcomes include the proportion of patients transfused RBCs (during hospitalization), and the incidence of DVT or VTE at 3 months. These outcomes inform surgeons' and anethesiologists' decision to use TXA by placing the expected benefits in the context of potential harm. The prioritization of safety occurred in large part due to a knowledge gap identified in Study 5, whereby safety estimates were inconsistently captured and were limited by short duration of follow-up. Given the low event rate of VTE, this markedly increased the sample size needed, but this was felt necessary to truly provide the evidence needed to define future perioperative practice.

*5.4.5 Sample size calculations*

The sample size calculations were directly informed by this thesis work because we: a) captured the mean number of eligible patients per site per month; b) evaluated RBC transfusion 'event rates' which powered the sample size calculations for RBC transfusion effectiveness; and c) identified a knowledge gap with our systematic review and meta-analysis prioritizing the need for safety as a co-primary outcome. Ultimately, a total sample size of 8320 patients reflects the power needed to inform the safety outcome of VTE.

*5.4.6 Pairing of sites for cluster-cross over*

TRACTION is designed as a cluster crossover trial whereby sites will be paired with comparable sites, and the pair will then be randomized to TXA or placebo monthly. Based on the number of eligible patients identified in Study 1, we have identified that 8 sites will be needed to complete the trial in approximately 8 months. The pairing of sites was informed by the surgical volume and caseload identified in Study 1.

*5.4.7 Transfusion data*

In Study 6 we evaluated the agreement between the patient record, the DAD and the TraceLine transfusion database. We confirmed that there is excellent agreement for ascertainment of transfusion exposure between the data sources, which is critical as this is one of the co-primary outcomes of the TRACTION trial. TRACTION is intended to be a pragmatic RCT that relies on existing databases to capture outcomes. Following completion of Study 6, TRACTION will ascertain RBC transfusion in Manitoba using both the RBC transfusion flag within the DAD, and transfusion records from TraceLine.

*5.4.8 Patient engagement*

From conception, the proposed design and conduct of TRACTION was informed by the active involvement of patient partners. In March 2018, we established a patient-partner committee that meets quarterly. The committee is comprised of patients or family members of patients who required major non-cardiac surgery and received a blood transfusion. The RBC transfusion data (Study 1), TXA utilization data (Study 2) and TXA safety data (Study 5) were all discussed at these patient partner meetings, and informed the inclusion / exclusion criteria, timing and methods of consent, and development of informational study materials. With safety in mind, the patient voice was essential when selecting our co-primary outcomes that prioritize safety. With this information, patients were able to provide critical input into the trial design, processes and outcomes.

## 6.0 CONCLUSION

In the course of this thesis, the preparatory work to comprehensively inform the design and conduct of the TRACTION trial was effectively planned and executed. We identified 85 non-cardiac surgeries at increased (≥5%) risk of RBC transfusion, which have directly informed the trial's inclusion criteria and sample size calculations. We evaluated TXA dosing and utilization patterns, and identified that contemporary TXA use is predominantly limited to orthopedic and spine surgeries, with little routine use among other non-cardiac surgical populations. When used, TXA is commonly administered as a 1 gram bolus. Based on results of these studies, we excluded surgeries where TXA usage was high (>50%) and considered standard of care. These studies also informed TXA dosing for the TRACTION trial. We evaluated TXA efficacy and safety by completing a systematic review and meta-analysis of TXA in non-cardiac surgeries at ≥5% risk of RBC transfusion, which established that TXA is associated with both reduced RBC exposure and RBC transfusion volume perioperatively, but identified critical limitations in VTE safety data. The results of this meta-analysis have directly informed the trial's primary outcomes and sample size.

Notably, we have identified a large surgical population who remain at significant risk of perioperative RBC transfusion. While TXA use is common in cardiac and orthopedic surgery, its application in other major surgeries at increased transfusion risk is low. Whether TXA should be universally administered to patients undergoing high risk non-cardiac surgeries is unknown - a randomized controlled trial is needed to inform best practice. If TXA reduces transfusion in this broad surgical population, it is expected that this inexpensive and widely available agent would be adopted as part of routine surgical care in a variety of health care settings. My thesis evaluated the key clinical questions needed to inform such a trial, a trial which has potential to change the standard of care in perioperative medicine in Manitoba and around the world.

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# 8.0 SUPPLEMENTARY MATERIALS

## 8.1 REGULATORY APPROVALS

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada, R3E 0W3
Telephone : 204-789-3255
Fax: 204-789-3414

UNIVERSITY OF MANITOBA | Research Ethics - Bannatyne
Office of the Vice-President (Research and International)

**HEALTH RESEARCH ETHICS BOARD (HREB)**
**CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES**
**Delegated Review**

| PRINCIPAL INVESTIGATOR: | INSTITUTION/DEPARTMENT: | ETHICS #: |
|---|---|---|
| Dr. Brett Houston | U of M and CCMB/Medicine/Internal/ Hematology/Medical Oncology | HS20577 (H2017:088) |
| **APPROVAL DATE:** March 31, 2017 | **EXPIRY DATE:** March 31, 2018 | |
| **STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):** Dr. Ryan Zarychanski | | |

| PROTOCOL NUMBER: | PROJECT OR PROTOCOL TITLE; |
|---|---|
| N/A | Evaluation of transfusion rates and tranexamic acid administration in high-risk non-cardiac surgeries |
| **SPONSORING AGENCIES AND/OR COORDINATING GROUPS:** N/A | |

| Submission Date of Investigator Documents: | HREB Receipt Date of Documents: |
|---|---|
| February 7 and March 23, 2017 | February 9 and March 23, 2017 |

**THE FOLLOWING ARE APPROVED FOR USE:**

| Document Name | Version(if applicable) | Date |
|---|---|---|
| **Protocol:** | | |
| Protocol<br>Clarification Letter dated March 23, 2017<br>Revised REB Submission Form signed March 21, 2017 | V. 1 | February 7, 2017 |
| **Consent and Assent Form(s):** | | |
| **Other:** | | |
| Master List | V. 1 | February 7, 2017 |
| Case Report Form | V. 1 | February 7, 2017 |

**CERTIFICATION**
The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

**HREB ATTESTATION**
The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5

of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

**QUALITY ASSURANCE**
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

**CONDITIONS OF APPROVAL:**

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus



**Please quote the above Human Ethics Number on all correspondence.**
Inquiries should be directed to the REB Secretary **Telephone:** (204) 789-3255/ **Fax:** (204) 789-3414

Winnipeg Regional Health Authority / Office régional de la santé de Winnipeg
Caring for Health / À l'écoute de notre santé

George and Fay Yee Centre for Healthcare Innovation
4th Floor, Chown Building
753 McDermot Avenue, Winnipeg, Manitoba, R3E 0T6

April 18, 2017

Dr. Brett Houston
Hematology Resident
Department of Hematology and Medical Oncology, CancerCare Manitoba
Department of Community Health Sciences, University of Manitoba
ON2056 – 675 McDermot Avenue
Winnipeg, MB R3E 0V9

Dear Dr. Houston:

**Re: Letter of Approval – "Evaluation of transfusion rates and tranexamic acid administration in high-risk non-cardiac surgeries"**

**Reference No: RAAC 2017-019** **UofM REB: HS20577(H2017:088)**

**We are pleased to inform you that your request for the above-named study has been approved by the Winnipeg Regional Health Authority (WRHA) Research Access and Approval Committee (RAAC).**

Access and approval are pending confirmation that the following conditions are met or agreed to:

1. In compliance with the *Personal Health Information Act, [Sec 24(4)],* we receive a duly executed Researcher Agreement (attached for your signature) between yourself (the PI), CancerCare Manitoba (CCMB) and the WRHA;

    - This letter of approval, along with the 'Data Capture Sheet' and the 'WRHA Data Access and Disclosure Plan' constitutes Schedule 'B' of the Researcher Agreement.
    - Once signed, please return the Researcher Agreement to Judy Dyrland, Research Coordinator, George and Fay Yee Centre for Healthcare Innovation, 4th Floor, Chown Building, 753 McDermot Avenue, Winnipeg, MB R3E 0T6.
    - The WRHA RAAC office will forward a duly executed copy of the Researcher Agreement once signed by all parties.

2. Submit any significant changes in your proposal prior to implementation, or any significant changes during the course of the study;
3. You agree to be accountable for the appropriate storage, disposal and/or destruction of material, as stipulated in the Researcher Agreement;
4. Appropriately acknowledge the role of the WRHA and/or affiliated organizations in any peer-reviewed publications resulting from this study;
5. Submit a summary of the final results of the study to the WRHA and provide the RAAC with a copy of any publications arising from the study;
6. Give the WRHA a minimum of five working days advance notice of the publication or presentation of results with policy implications, in order for the WRHA to be prepared for a public response.

Thank you for selecting the Winnipeg Regional Health Authority as the site to conduct your research. Please let us know should you encounter any site-related difficulties during the course of your study.

We extend best wishes for successful completion of your study.

Yours sincerely,

Dr. Paul Beaudin, MSc-SLP, PhD
Researcher, Evaluation Platform, George and Fay Yee Centre for Healthcare Innovation
Chair, Research Access and Approval Committee, WRHA

cc. Mr. Milton Sussman, President and CEO, WRHA
Ms. Christina Von Schindler, Chief Privacy Officer, WRHA
Dr. John Arnett, Chair, HREB

Attachment – Researcher Agreement & Appendices

Canadian Blood Services
Société canadienne du sang

1800 Alta Vista Drive
Ottawa, ON K1G 4J5
T 613.739.2300 F 613.731.1411
www.blood.ca www.sang.ca

PROTOCOL REFERENCE # **2017.015** June 27, 2017

Dr. Bret Houston
University of Manitoba
675 McDermot Ave
Winnipeg, MB R3E 0V9

Dear Dr. Houston,

Re: **Evaluation of transfusion rates and tranexamic acid administration in high-risk non-cardiac surgeries**

| **ETHICS APPROVAL** | **Annual Renewal Date** | **2018-06-27** |
|---|---|---|

We are writing to advise you that the CBS Research Ethics Board has granted approval to the above-named research study, for a period of ***one year.***

The REB's decision to approve the ethical aspect of a research proposal depends on the initial information submitted. The REB must be informed about any changes/amendments to the project. No change can be made without prior permission, except in an emergency when subject safety is in question.

Best wishes for the successful completion of your project.

Yours sincerely,

Francis Rolleston, DPhil
Chair, Canadian Blood Services, Research Ethics Board

CancerCare
MANITOBA
ActionCancerManitoba

675 McDermot Avenue
Winnipeg, Manitoba
Canada R3E 0V9

409 Taché Avenue
Winnipeg, Manitoba
Canada R2H 2A6

www.cancercare.mb.ca

May 24, 2017

Brett Houston
ON2084 - 675 McDermot Ave.
Winnipeg MB R3E 0V9

**Re: RRIC #2017-024: Evaluation of transfusion rates and tranexamic acid utilization and effectiveness in high-risk non-cardiac surgeries**

The above-named study has been approved by the CancerCare Manitoba (CCMB) Research Resource Impact Committee (RRIC).

This RRIC approval is valid for 2 years from the date at the top of this letter. An amendment form needs to be completed before the expiration date to extend the study period if more time is required.

The following departments at CCMB have signed off on this study: Privacy Officer

According to the CCMB RRIC submission form that you completed, NO CCMB paper charts will be required for this study.

A copy of the signed CCMB PHIA form for research is appended to this letter.

ANY SIGNIFICANT CHANGES TO THIS RESEARCH PROJECT MUST BE REPORTED TO THE RRIC BY SUBMITTING A "REQUEST FOR AMENDMENT FORM" FOR CONSIDERATION IN ADVANCE OF IMPLEMENTATION OF SUCH CHANGES. Significant changes include (but are not limited to): a change in the study design or in the data to be collected; a change in the study duration, the patient cohort to be studied, or the number of participants to be studied; the need to review CCMB paper charts (when not originally planned) or the need to review significantly more CCMB paper charts than originally planned; the addition of other trainees or co-investigators to the project; or the inclusion of additional individuals who will have access to the data or database.

Please cite the RRIC number for this study in all future correspondence with the RRIC about it. Please note that annual approval is not required if there are no changes to the project (as outlined above).

This approval is for RRIC use only. For ethics of human use and/or regulatory bodies, approval should be sought from the relevant parties as required.

Yours sincerely,

Paul Penner, B.COMM (HONS), CPA, CMA
Chief of Clinical Operations, CancerCare Manitoba
In place of Chair of CCMB Research Resource Impact Committee

Enclosure: Signed CCMB PHIA Form for Research

cc: Janice Osondu Iheke – Privacy Officer
Maureen Crump – Paper Charts
File copy

## 8.2 TRACTION RCT PROTOCOL

**Trial Title:**

**A Phase IV trial of a hospital policy of Tranexamic acid to reduce transfusion in major non-cardiac surgery (TRACTION)**

**Protocol: TXA-51231**

**Version Number and Date**: Version 5, October 20, 2021


**Nominated Principal Investigator:** Ryan Zarychanski, MD MSc FRCPC
University of Manitoba
ON4005C - 675 McDermot Avenue
Winnipeg, Manitoba, Canada, R3E 0V9
Tel: 204-787-8641
Fax: 204-235-3309
Email: rzarychanski@cancercare.mb.ca

**Principal Investigators:** Dr. Dean Fergusson, Dr. Brett Houston, Dr. Daniel McIssac Dr. Rodney Breau, Dr. Thomas Mutter

**Coordinating Sponsor:** The University of Manitoba
540 Machray Hall
Winnipeg, Manitoba, R3T 2N2



**Financial Sponsor:** The Canadian Institutes of Health Research (CIHR)
160 Elgin Street, 10th Floor
Address Locator 4809A
Ottawa, Ontario, K1A 0W9


**Nominated Principal Investigator** _____

**Signature:** _____

**Date:** _____

LOCAL SITE QI / PI SIGNATURE PAGE

Investigator's Statement and Signature:

I have read and understand this protocol and concur with the study design. I agree to participate as Qualified / Principal Investigator and to follow the protocol as outlined.

**Printed name**:

_____

**Signature:**

_____ **Date:** __ __ / __ __ __ / __ __ __ __

Day - Month - Year

## 1.0 KEY TRIAL CONTACTS

| | |
|---|---|
| **Nominated Principal Investigator** | Dr. Ryan Zarychanski<br>Department of Internal Medicine<br>Sections of Hematology/Medical Oncology and Critical Care<br>University of Manitoba<br>ON4005C-675 McDermot Avenue<br>Winnipeg, Manitoba, R3E 0V9<br>Tel: 204-787-1992<br>Email: rzarychanski@cancercare.mb.ca |
| **Trial Coordinator** | Dayna Solvason<br>Centre for Healthcare Innovation<br>753 McDermot Avenue<br>Winnipeg, Manitoba, R3E 0T6<br>Tel: 204-792-3372<br>Email: dsolvason@wrha.mb.ca |
| **Coordinating Sponsor** | The University of Manitoba<br>540 Machray Hall<br>Winnipeg, Manitoba, R3T 2N2 |
| **Financial Sponsors** | The Canadian Institutes of Health Research (CIHR)<br>160 Elgin Street, 10th Floor<br>Address Locator 4809A<br>Ottawa, Ontario, K1A 0W9 |

## 2.0 SYNOPSIS

| | |
|---|---|
| Title | **A Phase IV trial of a hospital policy of** Tranexamic acid use to reduce transfusion in major non-cardiac surgery (TRACTION): A pragmatic randomized cluster crossover trial |
| Short Title | Tranexamic acid to reduce transfusion in major surgery |
| Trial Design | A pragmatic, randomized cluster-crossover trial |
| Planned Sample Size of Trial Participants | Approximately 8320 patients 18 years of age and with Increased local fibrinolysis undergoing surgeries known to have a baseline transfusion rate of 5% or greater. |
| Investigational Medicinal Product(s) | Tranexamic acid (TXA) |
| Formulation, Dose, Route of Administration | TXA 1 gram intravenous bolus followed by 1 additional gram prior to skin closure |
| Treatment Duration | From first surgical incision until skin closure (or 8h) |
| Follow Up Duration | 90 day |
| Planned Trial Period | 1 year |
| Primary Outcomes | Co-primary outcomes include: a) the proportion of patients transfused red blood cells (RBCs); and b) the incidence of deep vein thrombosis or pulmonary embolus within 3 months of surgery. |
| Secondary Outcomes | (1) Transfusion: The number of RBC units transfused, both at an individual-level and at a cluster-level; (2) Safety: *In-hospital* diagnosis of myocardial infarction, stroke, deep vein thrombosis or pulmonary embolus**;** (3) Clinical: Hospital length of stay, ICU admission, hospital survival, 3-month survival, and the number of days at home to day 30 ($DAH_{30}$); 4) Compliance: proportion of eligible patients who receive the policy intervention, and the policy compliance in enrolled patients. |

## 3.0 ABBREVIATIONS

| | |
|---|---|
| CCI | Canadian Classification of Health Interventions |
| CHI | George & Fay Yee Centre for Healthcare Innovation |
| CIHR | Canadian Institutes of Health Research |
| Co-I | Co-investigators |
| CRF | Case report form |
| DAD | Discharge Abstract Database |
| DSMB | Data Safety Monitoring Board |
| DVT | Deep vein thrombosis |
| hr | Hour |
| ICES | Institute for Clinical Evaluative Sciences |
| ICH GCP | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use- Good Clinical Practice: Consolidated Guideline |
| IP | Investigational product |
| IPP | Investigational product packs |
| IU | International units |
| IV | Intravenous |
| Kg | Kilograms |
| LIS | Laboratory Information System |
| mcg | Micrograms |
| MCHP | Manitoba Centre for Health Policy |
| mL | Millilitres |
| MI | Myocardial infarction |
| OHRI | Ottawa Hospital Research Institute |
| PE | Pulmonary embolus |
| QI/PI | Qualified investigator/Principal investigator |
| RBC | Red blood cells |
| REB | Research ethics board |
| RC | Research coordinator |
| RCT | Randomized control trial |
| SIMS | Surgical Information Management System |

| | |
|---|---|
| SOP | Standard operating procedure |
| TCPS | Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans |
| TXA | Tranexamic acid |
| VTE | Venous thromboembolism |

## 4.0 BACKGROUND AND RATIONALE

Perioperative bleeding is a major indication for red blood cell (RBC) transfusion and the third most common reason for transfusion among hospitalized patients[1,2]. Approximately 50% of patients undergoing major cardiac and revision orthopedic surgery require RBC transfusions[3,4]. The rates of transfusion in other major, and more commonly performed, non-cardiac surgeries can approach or exceed these estimates[5]. RBC transfusions are a scarce and costly resource associated with adverse patient outcomes[6,7]. Approximately 700,000 RBC transfusions are administered each year in Canada, and while the need remains stable, the eligible donor pool is declining[7].

Administration of each RBC unit (product plus hospital and nursing costs) is estimated to cost $600, resulting in over $1 billion in Canadian health care expenditure each year[8]. While transfusions can be life-saving, they are not without harm[7,9]. Transfusions are associated with both allergic and non-allergic transfusion reactions, infection, immune dysregulation, prolonged post-operative length of stay, and increased morbidity[7,10-14]. Considerable enthusiasm exists to reduce transfusion need in the perioperative setting[15,16]. Strategies to mitigate perioperative RBC transfusion include pre-operative anemia correction, variation in surgical technique, acute normovolemic hemodilution, autologous blood donations, intraoperative blood salvage, and medications[11,16,17].

Tranexamic acid (TXA) is an inexpensive (~$5-10 per surgery) and widely available drug given broadly to patients who have increased local fibrinolysis, and hyperfibrinolysis such as during hemorrhage, trauma, and surgery. TXA is standard of care in cardiac surgery and hip and knee arthroplasty, and given to >90% of patients[18]. The clinical effectiveness and safety of TXA in other major surgeries with comparable transfusion rates has been confirmed in our recently published meta-analysis, but effect estimates are heterogenous. Demonstrating that a hospital policy of TXA can safely reduce transfusion in a broad patient population undergoing major non-cardiac surgery will forward a new standard of care, reduce costs, and promote the sustainability of Canada's blood supply.

### 4.1 Investigational Product: Tranexamic acid (TXA)

The study drug will be Canadian-sourced TXA. TXA is an antifibrinolytic agent that decreases blood loss by preventing blood clot breakdown.

In Canada, TXA is now routinely incorporated as standard of care in cardiac surgery and hip and knee arthroplasty[17,19-21]. We recently published a meta-analysis of TXA use in our trial target population of patients undergoing major non-cardiac / non-orthopedic surgery at high risk for red blood cell transfusion (≥5% transfusion rate). Consistent with prior systematic

reviews, tranexamic acid reduced the risk of transfusion by 41% (RR 0.59, 95%CI 0.48 to 0.72; 49 trials; n=6663)[18,22]. TXA was also associated with a mean reduction of 0.51 RBC units (95%CI 0.13 to 0.90) transfused per patient. Tranexamic acid has consistently proven efficacious in large meta-analyses of typically small randomized trials. Real-world evaluation of tranexamic effectiveness is required before TXA is adopted as routine policy.

### 4.2 Summary of known and potential risks to participants

Given that TXA inhibits clot breakdown, its thrombosis potential has impeded its routine uptake, especially for cancer patients who are at particularly increased risk[23,24]. In a Cochrane meta-analysis that was primarily driven by cardiac and orthopedic trials, TXA was not associated with increased adverse events, including myocardial infarction (RR 0.79, 95%CI 0.41 to 1.52; 21 trials; n = 2186), stroke (RR 1.23, 95%CI 0.49 to 3.07; 18 trials; n = 2027), deep vein thrombosis (RR 0.71, 95%CI 0.35 to 1.43, 23 trials; n = 1472), pulmonary embolism (PE) (RR 0.67, 95%CI 0.23 to 1.99; 14 trials; n = 1006) or renal failure (RR 0.89, 95%CI 0.33 to 2.37; 9 trials; n = 912)[18]. In cardiac surgery, rare reports of self-limiting postoperative seizure activity upon re-emergence from anesthesia have been reported[25]. These seizures were felt to be multifactorial, related to historically high doses of TXA, and provoked by cardiopulmonary bypass associated cerebral hypoperfusion. Seizure has not been reported in non-cardiac surgery. In cancer surgery, a patient population at increased risk for thromboembolism, we recently reported that in 11 trials (n=1117), TXA decreased RBC transfusion (RR 0.52, 95%CI 0.34-0.80; 7 trials; n = 955) without increasing venous thromboembolism (Peto OR 0.58; 95%CI 0.26 to 1.28; 9 trials; n = 1075)[26]. In our recently completed meta-analysis of TXA in high risk non-cardiac/non-orthopedic surgeries, TXA was again not associated with differences in deep vein thrombosis (RR 1.03, 95%CI 0.72 to 1.48; 29 trials; n = 3333) or pulmonary embolism (RR 1.00, 95%CI 0.54 to 1.84; 29 trials; 2469)[22]. Furthermore, in our trial sequential analysis, the sample size reached futility indicating no increased risk of DVT in patients randomized to receive TXA.

### 4.3 Why is the TRACTION trial needed now

TXA has been consistently shown to reduce RBC transfusion in cardiac surgery, and in hip and knee arthroplasty, where it is now routinely incorporated into standard of care[16,20,21]. Clinical trials and meta-analyses consistently demonstrate that TXA also reduces transfusion in trauma, post-partum hemorrhage and in other non-cardiac surgeries. Clinical trials and meta-analyses of TXA in all populations studied consistently show that TXA is safe and not associated with adverse thrombotic events.

When administered to highly selected groups of patients undergoing major non-cardiac surgery, and in the context of explanatory (vs. pragmatic) trials, TXA consistently reduces transfusion without evidence of increased thrombotic risk. While the efficacy and safety data are compelling, the impact of a universal policy of TXA administered to patients undergoing major non-cardiac surgery procedures must be quantified prior to the routine adoption as policy. The generation of such evidence will necessitate inclusion of patient populations not well represented in previous trials, and a design that mimics a policy-level change to practice.

TRACTION has been designed as a pragmatic trial. The traditional process of developing and conducting randomized trials is inefficient and expensive, and novel trial methodologies

are needed. One important innovation is the development of pragmatic trials. These trials are intentionally designed to emulate everyday clinical practices to maximize trial feasibility and allow results to be more easily incorporated into clinical care.

## 5.0 THE TRACTION RESEARCH PROGRAM

**5.1 Overall hypothesis:** We hypothesize that hospital-level implementation of routine tranexamic acid use in patients undergoing major non-cardiac surgery will reduce RBC transfusion without increasing thrombotic risk.

### 5.2 Foundational studies to support TRACTION

#### 5.2.1 Identification of surgeries at high risk of red blood cell transfusion

To identify surgeries at high risk of RBC transfusion, we evaluated contemporary perioperative transfusion practices in five academic centres in Canada (The Ottawa Hospital (General and Civic campuses), and at three hospitals in Winnipeg, Manitoba (Health Sciences Centre, St. Boniface General Hospital, and Concordia Hospital)), as well as from a large international administrative data set (ACS-NSQIP).

From 2014 to 2016 we identified 82,971 patient admissions with a surgery in the main operating room. We next identified 85 open (ie. laparotomy) non-cardiac surgeries associated with a transfusion rate of ≥5%[27]. In these surgeries, the mean baseline transfusion rate was 16% (range 5% to 49%). Thirty-nine percent of patients received 1 RBC unit, 36% received 2 RBC units, and 8% were transfused ≥5 units. The surgeries with a transfusion rate ≥ 5% are included in **Appendix 1.**

To supplement our Canadian transfusion data, we queried the American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) *Participant Use File* from 2005 to 2014, a large surgical database which captures patient demographics, baseline comorbidities, operative information, and 30-day postoperative morbidity and mortality from >500 hospitals worldwide[28]. We identified 1949 different CPT (Current Procedural Terminology) codes accounting for 3,243,369 patients, of whom 191,721 received at least one RBC transfusion. The non-cardiac surgeries at highest risk for transfusion paralleled that of our Canadian retrospective evaluation.

#### 5.2.2 Tranexamic acid use in high-risk non-cardiac surgeries

While TXA use in cardiac surgery and total hip and knee arthroplasty is considered best-practice, its use in other major non-cardiac surgeries was largely unknown but thought to be variable. To inform the TRACTION trial, following the identification of the high-risk non-cardiac surgeries identified in section 5.2.1, we evaluated contemporary tranexamic use in these patients[29].
Of the 82,971 high-risk surgeries performed from 2014 to 2016, tranexamic acid was used in only 17% of surgeries (range 0% to 68%). TXA usage was highest in orthopedic and spine surgeries, including open hip arthroplasty (n=1,799/2,648; 68%), open pelvis osteoplasty/ostectomy (n=28/41; 68%), pelvic open reduction internal fixation (ORIF) (n=37/106; 35%), femur ostectomy (n=15/52; 29%) and spinal fusion (n=198/855; 23%)[29]**.**

#### 5.2.3 Systematic reviews and meta-analyses informing TRACTION

*1) RCTs in major surgery*: The Cochrane meta-analysis conducted by Fergusson (PI) *et al*, convincingly demonstrated the utility of TXA to reduce RBC transfusion in cardiac and orthopedic surgery[18]. The use of TXA was not associated with an increased risk of arterial (stroke, myocardial infarction) or venous (deep vein thrombosis, pulmonary embolus) thrombotic events (see section 4.2).

*2) RCTs evaluating TXA in patients with cancer:* Cancer surgeries comprise a unique subset of high-risk surgery, where patients frequently require RBC transfusions and are at increased risk for thrombosis[23,24]. We performed a meta-analysis to evaluate whether lysine analogues safely reduce transfusion in cancer patients[26]. We included 11 trials (n = 1177), of which 8 trials (n = 1063) evaluated perioperative TXA use. Consistent with our prior meta-analysis, we found that lysine analogues decreased RBC transfusion (RR 0.52, 95%CI 0.34-0.80; 7 trials; n = 955) compared to placebo or standard of care, without increasing venous thromboembolism (Peto OR 0.58; 95%CI 0.26 to 1.28; 9 trials; n = 1075). While the body of evidence evaluating TXA in patients with cancer is relatively sparse, we did not find evidence to support increased risk of VTE in this population, despite their elevated baseline risk.

*3) RCTs in major non-cardiac surgeries at high risk of transfusion:* Our meta-analysis builds on the above Cochrane review, and focused specifically on high-risk non-cardiac surgeries, for which TXA use is standard of care. We included 69 RCTs (n = 6157 patients), of which 52 trials (75%) were published since the Cochrane review[30]. In patients undergoing high-risk surgery (baseline transfusion rate ≥5%), we found that TXA was associated with a reduction in the proportion of patients transfused RBCs (RR 0.59, 95%CI 0.48 to 0.72; 49 trials; n = 4663). This represents an absolute risk reduction of 12% (95% CI 9% to 16% reduction) and a number needed to treat (NNT) of 9 (95% CI 6 to 11) patients to prevent at least one red blood cell transfusion. TXA was associated with a mean reduction of 0.51 (95%CI 0.13 to 0.90; 17 trials; n = 1356) RBC units transfused per patient, when compared to placebo or standard of care. TXA use was not associated with significant differences in deep vein thrombosis (RR 1.03, 95%CI 0.72 to 1.48; 39 trials; n = 3333) or pulmonary embolism (RR 1.00, 95%CI 0.54 to 1.84; 29 trials; n = 2469). The incidence of DVT was low (2.2%).

These evidence syntheses consistently demonstrate that TXA is associated with reduced transfusion without increased thrombosis. Significant between-study heterogeneity and the potential for bias among the included trials translates into low certainty of evidence and a need to conduct an adequately powered trial to inform best-practice.

### 5.2.4 Stakeholder and patient engagement

Clinical stakeholders: We conducted a survey exploring the use of TXA in major surgeries at high risk for transfusion at the Ottawa Hospital[28]. The objectives of the study were to: a) evaluate surgeons' estimation of perioperative transfusion rates; b) evaluate self-reported TXA use and perceived barriers to use; c) characterize the degree of uncertainty regarding the benefits and harms of TXA in patients undergoing high-risk surgery; d) assess the willingness of physicians to consider a future clinical trial of TXA in this patient population. Our survey response rate was 82% (23/28 invited participants). The surgeons underestimated the perioperative transfusion rate in 93% of surgeries when compared with our retrospective evaluation of a large international perioperative database (NSQIP)[28]. The most common reason for not using TXA was

unfamiliarity with the benefits or harms. Seventy one percent (71%) of surgeons felt a trial is needed to demonstrate the efficacy of TXA and 61% felt a trial is needed to demonstrate safety.

Patient Partners: The proposed design and conduct of TRACTION has been informed by the active involvement of patient partners. In March 2018, we established a patient partner committee that meets quarterly. The committee is comprised of patients or family members of patients who required major non-cardiac surgery and received a blood transfusion. Through our patient partner committee, in the context of 3 committee meetings, surveys, and electronic communications, we've finalized the trial design (patient vs. cluster randomized), planned the timing and methods of consent, and developed informational study materials. Patients and caregivers have provided critical input into the trial design, processes, and outcomes. With safety in mind, the patient voice was essential when selecting our co-primary outcome that prioritizes safety. Secondary outcomes were also finalized through shared dialogue and it was our patient committee that specifically forwarded days alive at home as a secondary outcome. One representative (MH) from the patient advisory committee sits as a member of the TRACTION steering committee and serves as the liaison to the patient partner committee. A summary of patient input and how this shaped the TRACTION trial is included in **Appendix 1**; the patient information poster and brochure are included in **Appendix 2.**

## 6.0 THE TRIAL

### 6.1 Trial design

TRACTION is a pragmatic, multicenter, randomized, registry-based cluster-crossover trial

#### 6.1.1 Rationale for a cluster trial

In all patient cohorts and surgical populations where TXA has been evaluated, its use is associated with reduced transfusion. In trauma and postpartum hemorrhage, TXA reduces the proportion of patients who receive blood. In cardiac and orthopedic surgery, TXA consistently reduces transfusion. Furthermore, these trials are not associated with increased thrombosis. While individual patient randomized trials are useful to prove efficacy of an intervention in a specific population, they do not adequately address questions of effectiveness, particularly at an institutional level.

To maximize successful outcomes and minimize risk in major surgery, many effective perioperative practices such as preoperative surgical safety checklists, peri-operative use of antibiotics, and surgical sponge counts have been standardized and introduced as policy at an institutional level. When administered to highly selected groups of patients undergoing major non-cardiac surgery, and in the context of explanatory (vs. pragmatic) trials, TXA consistently reduces transfusion without evidence of increased thrombotic risk. Given the large numbers of patients undergoing major non-cardiac surgery, generalizable evidence that TXA is safe and effective is required. The generation of such evidence will necessitate inclusion of patient populations not well represented in previous trials, and a design that mimics a policy-level change to practice. Cluster trials are appropriate trial designs to inform such an important policy decision. To minimize loss of statistical power that arises in cluster trials due to the intra-cluster correlation (where patients within a cluster are more similar than patients across clusters), we will use a cluster-crossover trial design. In this type of trial, clusters will randomly, and without

their knowledge, crossover from the intervention to placebo groups multiple times over the duration of the trial.

## 6.2 Trial interventions

### 6.2.1 Intervention group

**Tranexamic acid.** TXA 1 gram bolus (2 grams for patients over 100 kg) intravenously (IV) administered within 10 minutes of the first surgical incision, followed by 1 additional gram given intravenously prior to skin closure, at the discretion of the anesthesiologist (e.g. IV bolus at 2-4 hours of surgery, at skin closure, or the 1 additional gram given as a continuous infusion throughout the surgical procedure).

### 6.2.2 Control group

**Placebo**. Matching placebo bolus and infusion

### 6.2.3 Rationale for tranexamic dosing

Standard dosing of perioperative TXA does not exist. Despite the wide variety of doses and dosing schedules in clinical trials, TXA has been shown to be more effective than placebo at reducing perioperative RBC transfusion[18,22].

The TXA dose and dosing schedule in TRACTION is pragmatic, supported by the existing literature, and emulates the variable dosing strategies used in current practice as evidenced by our preparatory studies. In a recently published trial of TXA in major trauma, a 1 gram TXA bolus followed by a 1 gram infusion over 8 hours reduced RBC transfusion and improved survival[19]. In large trial of TXA to treat post-partum hemorrhage, a 1 gram TXA bolus, with an option to administer an additional bolus if bleeding continued, reduced bleeding and death due to bleeding[31]. In a Canadian led trial of TXA in patients undergoing hepatectomy, 1 gram TXA bolus followed by 1 gram infusion over 8 hours is being evaluated. The 1 gram bolus proposed will be sufficient to achieve therapeutic plasma TXA concentrations (37+/-17 mcg/mL after a 10 mg/kg loading dose, unless the patient weighs over 100 kg)[32-34]. Given the mean surgery duration in our eligible population is 3.5 (SD 2.1) hours[35], our proposed dosing will maintain therapeutic plasma TXA concentration for the duration of the surgery. In formal stakeholder engagement interviews, the schedule chosen is feasible in the setting of a trial, and will facilitate global adoption in the context of a positive result. Further details of informative preparatory studies and pharmacokinetic and pharmacodynamic analyses to justify the TRACTION dosing are included in **Appendix 3.**

### 6.2.4 Rationale for placebo

Although designed as a pragmatic trial, a placebo arm is required to preserve the validity of our trial outcomes. Given the hypothesized reduction in bleeding and transfusion, the use of an open-label design with usual care as the comparator would increase the risk of contamination (i.e. use of TXA) due to changes in practice over time. For our superiority outcome of transfusion, contamination would appear to decrease the effectiveness of a policy to universally adopt TXA. With regards to our non-inferiority safety outcome of venous thromboembolism, contamination could bias the trial towards concluding non-inferiority. Furthermore, no other agent or antifibrinolytic exists in Canada for which TXA could be compared against.

### 6.3 Co-interventions

Given the pragmatic nature of the trial, perioperative co-interventions, including but not limited to, cell-salvage, autologous transfusion, acute normovolemic hemodilution, use of aprotinin or topical TXA use will be documented but not protocolized. The decision to transfuse blood products will be entirely at the discretion of the treating physicians. Any drugs, or procedures thought to be required as 'rescue' therapies are permitted and at the discretion of the surgical team. Additional doses of study drug beyond what is outlined in the protocol is not permitted unless the treating anesthesiologist requests the patient be unblinded.

### 6.4 Inclusion criteria

Cluster-level inclusion criteria:
Hospital sites will be included in the trial if anesthesia and hospital leadership agree to manage patients as per the policy being implemented and evaluated in the trial.

Patient-level inclusion criteria:

- Patients >/= 18 years of age undergoing major non-cardiac surgery (a state of hyperfibrinolysis)
- Inpatient surgeries with an estimated >/= 5% risk of RBC transfusion, including open surgeries or laparoscopic surgeries with an estimated duration of >/= 3 hours

Examples of eligible surgeries could include (but are not limited to):

1. General surgery (esophagectomy, gastrectomy, gastric repair, small bowel repair or resection, ostomy formation, colon/rectum repair or resection, colostomy, splenectomy, hepatectomy, pancreatectomy, resection of abdominal mass)
2. Orthopedics (hip fracture repair, pelvic fixation, femur repair / fixation, shoulder / humerus open reduction internal fixation, lower extremity amputation)
3. Spine (vertebrectomy, surgery involving >/= 3 levels)
4. Otolaryngology (glossectomy, mandibulectomy, radical laryngectomy)
5. Thoracic (lung resection or decortication)
6. Vascular (arterial bypass / endarterectomy / aneurysmorrhaphy involving the aorta or proximal vessels off the aorta)
7. Gynecology (hysterectomy)
8. Urology (nephrectomy, cystectomy, prostatectomy, pelvic exenteration)
9. Plastic surgery (large neoplasm resections, burns or debridements)
   Surgeries anticipated to be associated with 5% or greater risk of RBC transfusion in hospital as per the surgical team.

### 6.5 Exclusion criteria

The following groups of patients will be excluded from the TRACTION trial:

- Active thromboembolic disease (ie, patient is anticoagulated for thromboembolic disease prior to admission)
- Pregnancy
- Cardiac surgery and hip and knee arthroplasty where TXA is standard-of-care.
- Surgeries with free flap reconstruction
- Trauma surgeries where TXA has been administered within the previous 3 hours

## 6.6 Outcome measures

### 6.6.1 Primary outcomes

As our pragmatic trial is designed to define practice, we have selected co-primary outcomes that evaluate effectiveness in the context of safety. Our co-primary outcomes are the:
Proportion of patients transfused RBCs
Incidence of DVT or PE (collectively called venous thromboembolism (VTE)) within 3 months of surgery.

*Outcome justification:* Our primary outcomes inform a patient's, surgeon's and anesthestist's decision to use TXA whereby the expected benefits are placed in the context potential harm. These outcomes reflect the specific views and input of clinician knowledge users and our patient committee.

### 6.6.2 Secondary outcomes

Transfusion: The number of RBC units transfused (both at cluster level and patient level)
Safety: Secondary safety outcomes include the *in-hospital* diagnosis of myocardial infarction, stroke, deep vein thrombosis or pulmonary embolus
Clinical: Hospital length of stay, ICU admission, hospital survival, 3-month survival, and the number of days at home to day 30 ($DAH_{30}$). $DAH_{30}$ is a validated, patient-centered outcome, that integrates length of stay, readmission, discharge destination and early deaths after surgery into a single outcome metric[36].
Compliance: Proportion of eligible patients who receive the policy intervention, and the policy compliance in enrolled patients.

## 6.7 Randomization, allocation concealment and study duration.

Over the duration of the study, participating centres will be centrally and randomly allocated to receive either TXA or matching placebo at 1-month intervals for a total of 8 months. Intervention assignment will only be known to the research pharmacy staff who will prepare the study drug specific to the interval assignment. To minimize sources of selection and ascertainment biases, anaesthesiologists, surgeons, investigators, research staff, and members of the Data Safety and Monitoring Board will all be blinded to randomization schemes and treatments administered; only the trial statistician will have access to randomization schemes for all sites. The research site's Pharmacy staff will not have contact with the study team or the patient and will be expressly forbidden to discuss individual treatment allocation with the study team, the patient, the operating room and clinical care team unless emergency un-blinding is warranted. Clinical teams will be permitted to unmask treatment allocation only under exceptional circumstances.

## 6.8 Premature Withdrawal / Discontinuation Criteria

*Individual Discontinuation criteria:*
Individual patients have the right to withdraw from the study at any time without any impact to their current and future care. If an eligible elective patient communicates their wish to *not* participate in the trial, they will not be enrolled. For emergent patients who wish to not have their data included in TRACTION, their data will be removed from all analyses and reports provided

the analyses have not been published. Participation could be discontinued by the study doctor or study sponsor for the following reasons: a) the study doctor feels it is in the patient's best interest, or b) if the funding agency (Canadian Institutes of Health Research) or Health Canada stops the study.

*Part of trial/entire trial Discontinuation Criteria.*
Given the short enrollment period (8 months), low rate of VTE reported in published trials, and need for 3 month follow-up for VTE rates to mature, formal interim analyses are not planned as this could not occur until the final month of enrolment. While effectiveness could be ascertained after 25% or 50% of patients have been enrolled, a decision to adopt a policy of TXA could not be made until the rate of 90-day VTE is known for all patients enrolled.

Regarding the type and timing of the data to be collected for withdrawn subjects:
In the setting of emergency unblinding, all data will be collected as if unblinding did not occur. If a patient withdraws their consent to participate in the trial prior to being anesthetized, then study drug will not be administered, and patient data will not be collected. In the situation that a patient withdraws consent following the elective or emergency surgery, then all patient data will be removed from the trial database and will not be included in analyses. The number of patients who opt-out of the trial prior or following surgery will tabulated and presented in aggregate.

## 6.9 Blinding

The investigational drug (either TXA or placebo), will be supplied as 2 identical investigational product packs (IPP). The IPP will either contain 1 gram of TXA diluted in normal saline (intervention), or normal saline (control). TXA is clear, colourless and indistinguishable from normal saline (placebo) both at rest and when vigorously agitated[23]**.**
In accordance with Division 5 (Health Canada) section C.05.011, all TRACTION study drug (both tranexamic acid and placebo) will bear a label indicating:
The drug is an investigational drug to be used only by a qualified investigator
The name, number or identifying mark of the drug
The expiration date of the drug
The recommended storage conditions for the drug
An assigned lot number; the name and address of the sponsor
The protocol code or identification

## 6.10 Confirmation of TXA administration and emergency unblinding

*Confirmation of TXA administration*

In the event of life-threatening hemorrhage, if the surgical team believes that it's absolutely necessary to confirm the patient received TXA (rather than placebo) then, to preserve blinded site allocation assignment, blinded emergency IPP will be available upon request. The emergency IPP will contain the opposite of what the site is current randomized to - either placebo or TXA, contingent on whether the hospital is randomized to TXA or placebo. By administering both 1 mini-bag of the assigned IPP and 1 mini-bag of the emergency IPP, it ensures that, a patient has received 1 gram of TXA. If confirmation of the second protocolized gram of TXA is required, then this procedure can be repeated (ie, giving both the assigned and emergency IPP mini-bags). Given the cluster trial design, this procedure abrogates the need for emergency unblinding which could compromise the site for the randomization period.

Regardless of cluster treatment assignment, off-protocol and unblinded TXA can be administered by the anesthesiologist if the they or the surgeon feel it's absolutely required.

*Emergency unblinding*

Given the established safety profile of TXA, and the confirmation of dosing procedure outlined in section 6.10, the need for emergency blinding is likely to be rare or not required. In the event of anaphylaxis or seizure following the first dose of IPP, the second protocolized dose of IPP should be withheld and documented on the CRF. Anaphylaxis or seizure should be treated at the discretion of the surgical team.

If the surgical team or patient feels knowledge of treatment assignment is essential, then:

a.) If emergent knowledge of treatment assignment is felt to be necessary to provide care to a given patient, the anesthesiologist or surgeon can call the primary investigator or delegate.

b.) If knowledge of treatment assignment is felt to be required but is not urgent, then the trial coordinator can be emailed at dsolvason@wrha.ca

## 6.11 Assessment of safety and adverse event reporting

TXA is not known to be associated with adverse events when used in non-cardiac surgery. In cardiac surgery, rare events of seizure activity have been described up re-emergence from anesthesia. Though not expected, out of an abundance of caution, incidence of perioperative seizure activity or immediate allergic reaction to the study drug will be ascertained and reported. Serious adverse events will constitute seizure activity or allergic reactions that result in death, are life-threatening, prolong hospitalization, cause significant disability or incapacity, or cause another condition judged as serious. Serious adverse events will be reported to the coordinating centre within 24 hours and likewise will be promptly reported to Health Canada.

*The occurrence of VTE (venous thromboembolism) at 3 months is our primary safety outcome and a co-primary outcome for the TRACTION trial. This outcome will be ascertained at the end of the trial using administrative billing, prescribing and physician reimbursement data. The TRACTION trial is a minimal risk registry-based trial - in over 50,000 patients randomized to receive TXA or placebo in trauma, post-partum hemorrhage, head injury, cardiac surgery, or non-cardiac surgery, there was no evidence of increased thrombosis or other events to suggest increased harm.*

## 7.0 PHARMACY PREPARATION AND DISPENSING PROCEDURES

The research site's Pharmacy staff will prepare batches of the study drug or placebo according to a site-specific allocation table provided by the trial statistician. The intervention drug (TXA) will be prepared by withdrawing the appropriate dose of TXA from a glass vial. TXA will be administered either via syringe or minibag as per institutional protocol. If a syringe is used, 1 gram of TXA at 100 mg/ml = 10 ml undiluted into a 10 ml syringe. The stability of the undiluted syringes will be 24h stored at room temperature. If a minibag is used, TXA will be diluted to 1% tranexamic acid (i.e. 1 gram in 100 mL or 10 mg/mL). The stability of the minibags will be 7 days stored at room temperature[48,49]. The TXA will be diluted using 0.9% NaCl solution (saline).

This procedure will be repeated to produce two (2) IPPs that each contain 1 gram of TXA. The placebo IPP will be prepared in the same way with the same volume. Once labelled (see 6.8), investigational product packs will be sent to the operating room for use in the trial.
Each site is to maintain pharmacy accountability logs/records. These logs/records will include dates, quantities, batch/serial numbers, expiration dates, as applicable, and the unique code numbers assigned to the investigational product(s) and trial site.

## 8.0 ORDERING STUDY DRUG

According to the needs of participating sites, the TRACTION Coordinator/ Research Assistant at each site will be responsible for locally ordering appropriate quantities study drug from their site's Pharmacy. Each site pharmacy will be responsible for ordering their own stock of tranexamic acid for the study.

## 9.0 SAMPLE SIZE AND STATISTICAL ANALYSIS

### 9.1 Sample size

The TRACTION trial has been designed with 2 co-primary outcomes that incorporate clinical effectiveness and safety respectively. The total sample size of 8320 patients reflects the power needed to inform the safety outcome of VTE.

Transfusion (effectiveness; superiority): Informed by our large observational study, the average cluster-period size is predicted to be 130 patients. Estimating a within-period intraclass correlation (ICC) of 0.005 and a cluster autocorrelation (CAC) of 0.85 in the TRACTION trial, with 8 clusters randomly assigned to 8 monthly study intervals, we will have 99.9% power to detect an 6% absolute risk difference in the proportion of patients transfused RBCs from a baseline transfusion rate of 18%.

VTE (safety; non-inferiority): Informed by previously published estimates of DVT and PE following major surgery where TXA had been used, with an average cluster period size of 130 patients, an ICC of 0.005 and a CAC of 0.85, in 8 clusters randomly assigned to 8 monthly study intervals, we will have 83% power to exclude a 1% or greater increase in VTE at 3 months from a predicted baseline rate of 2.2%.

Placing effectiveness in the context of safety, TRACTION will be overpowered to evaluate the superiority of our co-primary transfusion effectiveness outcome, but adequately powered to detect a clinically relevant increase in thrombosis. Since each of the two co-primary hypotheses must be satisfied to deem TXA beneficial, the type I error rate is preserved without the need for multiplicity adjustments[37].

### 9.2 Analysis of primary outcomes

We will analyze our primary superiority outcome (proportion transfused) using an intent-to-treat analysis (ITT). Since ITT can bias to the null and lead to false claims of non-inferiority, we will analyze our non-inferiority outcome (VTE at 3-months) using both per-protocol (primary analysis for this outcome) and ITT populations. Robust conclusion will require both analyses to yield consistent results. The ITT population will include all randomized patients, as we expect that virtually all outcomes will be available from routinely collected data. The per-protocol

population will include all patients, with the exception of those allocated to the TXA arm who did not receive TXA. All analyses will be at an individual patient level.
Between-group event rates will be estimated using a hierarchical mixed model for binary outcomes adjusted for cluster and cluster-by-period as random effect terms, and reported as odds ratios with 95% confidence intervals. Carry-over effects will be assessed for the primary outcomes using tests for interactions between periods and treatment effects using hierarchical mixed models.

Our primary non-inferiority analysis will test the absolute difference in VTE events at 3 months between groups using a one-sided chi-square test with an alpha = 0.025. The risk difference and its 97.5% confidence interval will be computed as the proportion in the TXA group minus the proportion in the placebo group. If the upper limit of the 97.5% confidence interval excludes the non-inferiority margin of 1%, non-inferiority will have been established at the 2.5% significance level. Our primary analysis will be unadjusted. In a secondary analysis we will compare VTE occurrence between the study arms after adjusting for age, sex, center, surgical urgency and pre-operative hemoglobin concentration using hierarchical logistic regression analysis.
The difference in our primary effectiveness outcome, the proportion transfused RBCs, will be tested using a two-sided chi square at alpha=0.05, with 95% confidence intervals. Additional analyses will adjust for the factors and covariates using hierarchical logistic regression as specified for the primary non-inferiority outcome.

### 9.3 Analysis of secondary outcomes

The absolute differences in the dichotomous secondary outcomes (in-hospital diagnosis of MI, stroke, DVT or PE and need for ICU admission) will be analyzed as described for the primary effectiveness outcome above. The continuous secondary outcome (number of RBC units transfused) will be analyzed using linear regression analysis adjusting for age, sex, center, surgical urgency and pre-operative hemoglobin concentration. Number of days at home to day 30 will be analyzed using negative binomial regression analysis. Hospital length of stay, hospital survival and 3-month survival will be analyzed using Cox proportional hazards regression analysis adjusting for the factors and covariates as specified for the primary outcome. The assumption of proportional hazards will be assessed using Schoenfeld residuals. Results will be expressed as hazard ratios with 95% confidence intervals.

### 9.4 Subgroup and sensitivity analyses

We will explore differences by age, sex, surgery type, surgical urgency, pre-operative hemoglobin, and baseline transfusion rate for our co-primary outcomes, proportion transfused and VTE. These analyses will be conducted using the Cochran-Mantel-Haenszel approach, and by including interactions between each subgroup variable and treatment indicators in analytical models for adjusted analyses. Differences across centers will be explored using random effects models with center and center by treatment interaction specified as random terms.

### 9.5 Interim analyses

Given the short enrollment period (8 months), low rates of VTE reported in published trials, and need for 3-month follow-up for rates of VTE to mature, no formal interim analyses are planned. While effectiveness could be ascertained after 50% of patients are enrolled, even if TXA is found

to be superior to placebo after enrolment of 50% of patients, a complete clinical decision to adopt a policy of TXA could not be made until the rate of VTE is known for all patients enrolled. The trial DSMB will receive all reports of serious adverse events related to perioperative seizure or allergic reaction related to the administration of TXA. Serious adverse events will be reported within 24 hours of their occurrence. On a monthly basis and for the duration of the trial the DSMB will receive aggregate by-group adverse event and serious adverse event reports.

## 10.0 IDENTIFICATION OF ELIGIBLE POPULATION

Patients undergoing major non-cardiac surgery that meet study inclusion criteria will be electronically identified pre-operatively using an external surgical slate summary generated from the Surgical Information Management System (SIMS) database. Using the Patient Access Registry Tool (PART), surgical offices will complete the online booking card, which is submitted to the surgical slating office. From here, patients are entered into the SIMS database and slated for their operation. The external slate summary provides select de-identified information including surgery name, surgery date/time, location (hospital, operating room), surgeon, and anesthesiologist. Review of the external slate, devoid of patient identifiers, restricts the review of personal health information to potential study participants. The research coordinator will regularly review the external surgical slate to identify and enrol patients undergoing high-risk non-cardiac surgery.

Eligible patients will be enrolled by study coordinator using a secure web-based portal, at which point each participant will be assigned a unique study identifier. The research coordinator will provide the site research pharmacist with the patient's name, study identifier, hospital identification number, weight, surgery name, and date, time and location of the surgery to facilitate preparation of dispensing of the study drug.

### 10.1 Patient consent

Our altered consent model was informed through extensive discussions with patients and caregivers (Appendix 1), and was endorsed as appropriate by our patient-partners. The patients/caregivers preferred that information about the trial be publicly visible in the pre-anesthesia clinic (Appendix 1). Our patient-partners further suggested that, to increase the effective disclosure of the study to potentially eligible elective patients, study information be integrated into the pre-operative information packages routinely provided to patients seen in the clinic. In the setting of virtual care clinics, sites will have the option to disseminate the trial information to patients through their institution's adapted method for delivery of pre-operative information. All patients and/or families will be provided with study information via a study poster (in PAC) as well as a study brochure. These materials will include contact information for the research coordinator and information on how an individual could opt-out of the trial if they wish to do so. Patients who did not receive a study brochure preoperatively will be provided with the study brochure postoperatively while admitted to hospital (preferred) or via mail. This is in keeping with feedback from our patient-partners who voiced a preference to receive study information while in hospital post-operatively in the event they were unable to be informed pre-operatively.

As our study involves altered consent; if patients wish to withdraw their data from the study, they can do so by contacting the research coordinator within 90 days of their surgery.

## 11.0 DATA ACQUISITION

To enable TRACTION, we have proven our ability to identify and link all required data from robust, and validated data sources to facilitate trial monitoring and reliable outcome capture. In the context of our preparatory observational cohort studies, we identified accessible and linkable high-quality and high-fidelity databases. Using the Surgical Management Information System (SIMS) and Discharge Abstract Database (DAD) at each hospital, regional or national transfusion databases, and provincial administrative data, we electronically captured patient demographics and comorbidities, surgery specifics, transfusion, clinical, and safety outcomes.

We will ascertain patient demographics and comorbidities and hospital outcomes from the DAD. The DAD at each hospital utilizes standard International Classification of Diseases (ICD) coding for diagnoses, comorbidities and procedures and undergoes a continual process of data quality assurance and data validation[38,39]. High-fidelity transfusion data will be obtained from TraceLine, which has been extensively validated as part of the Canadian Blood System's 'vein-to-vein' accountability platform[40-43]. Laboratory data will be obtained from the Laboratory Information System (LIS). We will obtain in-hospital VTE rates from the DAD, and out-of-hospital VTE rates by linking to provincial health administrative databases available at the Manitoba Centre for Health Policy (MCHP), including the Drug Program Information Network (DPIN), Radiology Information System (RIS), and medical claims. Previous studies conducted at our sites have validated the use of administrative data to identify acute VTE (95% sensitivity; 86% specificity)[44-46].

A half-page case report form will be used to capture the administration of the study drug (Winnipeg sites do not presently capture intraoperative medication administration in their SIMS system). We will obtain 3-month VTE outcomes from both hospital and provincial administrative sources (MCHP) using a combination of billing and imaging codes[44,45].
At time of enrollment, a master list will be generated to link patient identifiers to their unique study identifier and allow data linkage. This list will be stored on a secure shared drive/access point created in collaboration by Digital Health and the Government of Manitoba. In Winnipeg, manually collected data from the operative case report form will be added to the dataset. This data repository is part of a larger provincial initiative to create a near real-time integrated clinical health data platform in Manitoba, an initiative that represents a partnership between Manitoba Health, Shared Health and several other provincial or regional partners. At approximately 3-monthly intervals (a 3-month delay is unavoidable as the DAD information takes on average 3 months to populate, and our longest study outcome occurs at 3-months), Digital Health will link the data sources outlined above to create a complete study record for enrolled patients. Datasets will initially be linked based on personal health identification number. All linked datasets will be immediately de-identified with removal of all patient identifiers (with the exception of age and sex). If a link to MCHP is required to obtain VTE outcomes, this will occur using scrambled PHINs in the usual methods and procedures required to obtain MHCP data; however, at this time, it is our understanding that these may be simply incorporated into the study dataset given that Manitoba Health are partners in this project. A process map outlining the database linkages is included in **Appendix 4**.

## 12.0 MONITORING

The trial data and compliance will be rigorously monitored using both remote and on-site methods of surveillance. This ensures that trial-related data are accurate, complete and verifiable from source documents and that participant rights and safety are protected. The monitor will verify compliance with the regulatory requirements, protocol, GCP, study-specific procedures and participant eligibility. The monitor will identify any trends in data that may be indicative of insufficient documentation or protocol deviations. Discrepancies noted in the data will be recorded and the site will be informed of all observations in the subsequent monitoring report. The monitor will address deficiencies to the appropriate study team member in order to implement corrective actions or to recommend follow-up procedures. All observations noted during the monitoring visit will appear in the monitoring report. The monitor will assess study files and documentation against ICH-GCP, regulatory requirements, protocol, OHRI study operating procedures (SOP) and any study-specific SOPs.

## 13.0 PATIENT CONFIDENTIALITY AND RECORD MANAGEMENT

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to the sponsor.
Subjects are to be identified by a unique subject identification number.
Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
For serious adverse events reported to the sponsor, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).

Documents that are not submitted to the sponsor are to be kept in confidence by the Investigator, except as described below.
In compliance with Federal regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the Sponsor, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access

includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

Complete records of the work performed in connection with the study in accordance with the protocol will be maintained by the Sponsor and clinical trial sites for a period of 25 years.

## 14.0 TRIAL MANAGEMENT

The overall management of the TRACTION trial will be coordinated at the George & Fay Yee Centre for Healthcare Innovation (CHI) (Winnipeg, MB). The Ottawa Methods Centre located at the Ottawa Hospital Research Institute (OHRI) (Ottawa, ON) will be responsible for generating the randomization scheme, hosting web-based enrolment, data management, data validation, and statistical analyses. Individual site Principal Investigators are responsible for ensuring trial conduct at their respective sites.

### 14.1 Strategies to enhance participant enrolment and protocol adherence

TRACTION'S primary investigators (PIs) and co-investigators (Co-I) are local scientific and thought-leaders at their respectful institutions. With their leadership, and with committed support from the Departments of Surgery and Anesthesia, the stakeholders are collectively engaged and committed to the success of the trial (see letters of support in **Appendix 5**). Prior to individual site activation, TRACTION study personnel will conduct a start-up meeting to review study procedures. To encourage protocol adherence, centres will use pre-printed study orders to facilitate study drug administration and monitoring. Email correspondence and quarterly teleconferences will facilitate regular communication between the coordinating site and individual site personnel.

### 14.2 How will knowledge from the TRACTION trial be transferred, translated and exchanged?

All aspects of the TRACTION research program have integrated core components of the knowledge-to-action cycle to facilitate incorporation into current evidence and ensure widespread uptake of new knowledge generated[47]. We have identified an important clinical problem and justified our trial with observational research and knowledge syntheses manuscripts. Stakeholders have been surveyed to assess the relevancy of the research question, identify barriers to knowledge use and investigate clinical equipoise. Our randomized trial has been developed with input and active engagement from knowledge users, decision- makers, and patients. Following completion of the trial, a plain-language summary of the trial results will be posted to the trial website and distributed in the lay press. Leadership at participating clusters (hospitals) will be forwarded a summary/interpretation of the trial. At the completion of the trial we will work with our patient-partners, decision-, and policy-makers to create a knowledge translation strategy so the results of the study effectively impacts perioperative surgical policy in participating hospitals, and around the world.

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## APPENDIX 1: SUMMARY OF PATIENT PERSPECTIVES AND RECOMMENDATIONS

TRACTION

Tranexamic acid use to reduce transfusion in major non-cardiac surgery (TRACTION): A pragmatic randomized cluster crossover trial

November 1, 2019

The Hematology and Critical Care Patient/Caregiver Partner Team consists of six (adult) patients and caregivers who have lived experiences with both the Intensive Care setting and transfusion. Some of our team members have experiences as participants in other research initiatives. Together, we are a diverse team who have been recruited without restrictions placed on gender, age, race, ethnicity, Indigeneity, geographical location, ability, socioeconomic or immigrant status.

Our team's objectives are to convey perspectives and experiences as recipients of health care or a caregivers on topics and issues of priority and relevance to the Hematology and Critical Care Research Program; provide guidance and share in decision-making for research project design, processes, and materials; contribute to the dissemination process of project results to educate the public, influence policy, and affect the practice of healthcare.

Patients and caregivers of the Hematology & Critical Care Patient/Caregiver Partner Team have been involved in the design of the TRACTION trial for the last 18 months. At our meetings the topics discussed and contributed to include the proposal, study purpose, study outcomes, and more intensely the study design and model of consent. At our recent October meeting we discussed the differences between individual patient vs cluster randomized clinical trials and the various models of consent relevant to these trial designs. For example, we talked about "traditional" informed consent, waived consent and our proposal of "altered consent" or "altered waived consent" and explored optimal consent models for TRACTION.

The corresponding documents are details from our October 24th, 2019 meeting and have been reviewed and approved by the committee chair. As patients, our voice has been authentically incorporated into TRACTION and is reflected in the finaly study design, outcomes, and method/materials pertaining to consent.

Mac Horsburgh
The Hematology and Critical Care Patient/Caregiver Partner Team Committee
Chair

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## Summary of Patient and Caregiver Input and Feedback on the TRACTION Trial consent model

*We discussed and have summarized the following advantages/disadvantages to various models of consent:*

| | Traditional informed consent | Traditional waived consent | Altered waived consent |
|---|---|---|---|
| Uses and potential advantages | • Most commonly used<br>• Intended to protect the rights and welfare of participants<br>• Essential for a "study drug", intervention, procedure or device with unknown side effects<br>• Moderate/high risk interventions<br>• Knowledge of study before hand<br>• Ability to opt-out | • Involves well known, previously studied drugs, interventions, procedures or devices with known side effects<br>• When informed consent is impractical; ie. cluster randomized control trials<br>• All eligible patients are studied<br>• Results are widely generalizable<br>• Risk adapted to low risk interventions | • Involves well known, previously studied drugs, interventions, procedures or devices with known side effects<br>• When traditional informed consent is impractical (ie. cluster randomized control trials) and more information is felt to be necessary<br>• All eligble patients are studied<br>• Results are widely generalizable<br>• Risk adapted to low risk interventions<br>• Trial information provided to patients<br>• Ability to opt-out |
| Potential disadvantages | • Not always understandable<br>• Can be lengthy<br>• Many patients (75-90%) ultimately excluded<br>  ○ Lower enrollment rates<br>  ○ Selection bias<br>• Resource intensive (↑ resources required, time and cost) | • Patients may not have prior knowledge of the study<br>• Individuals may not be given a choice to participate or have the opportunity to withdrawal their information<br>• No opportunity to ask questions | • Communication may not reach all patients, although can be adapted based on circumstance<br>• In-person contact not the same as with traditional informed consent, although the study coordinator can be contacted |

***The following are questions and responses presented to the patient partner group following an evening of discussion. This was preceded by distribution of pre-meeting reading materials***

1. Do you support a **traditional waived consent** model for TRACTION?
   ☐Yes – 3
   ☐No – 2
   ☐Undecided
   ☐Other (specify): _____
2. Do you support an **altered** waived consent model for TRACTION?
   ☐Yes – 5
   ☐No
   ☐Undecided
   ☐Other (specify): _____

**Rationale:** Patients fully agreed with the need for a cluster-level trial given the policy-level intervention being tested at a hospital level. Though a minimal-risk intervention in the context of a trial where individual traditional informed consent is impractical, patients preferred the use of both posters and brochures to convey study information with the ability to contact a coordinator if they had questions or if they wished not to participate.

3. In an **altered** waived consent model, what would be your preferred method to receive information about the study? **Select all that apply.**
   ☐Study poster in pre-operative waiting and clinic rooms – 4
   ☐Patient brochure provided at pre-operative clinic appointment – 5
   ☐Study brochure attached to patient chart for patients to receive while in hospital – 2
   ☐Given the low-risk intervention (of which patients aren't routinely informed of at present), a patient information brochure isn't required
   ☐Other (specify):

***Action taken**: A poster was created that will be put up in the pre-anesthetic clinic (PAC). Brochures will be added to the pre-operative surgical package provided to patients in PAC. Urgent/Emergent surgical patients included will be provided the informational brochure on the hospital ward following surgery.*

4. Is there anything in the patient information poster / brochure that you would like to see changed (added or removed)?
   ☐Yes (specify): - 2

   *Comment: Explain how it could benefit them and cost savings*
   *Comment: Re work some of the language*

   ☐No – 3

***Recommendation:** Poster and brochures have been developed and edited to reflect the voice of our patient partners.*

5. Do you have any suggestions for different ways of communicating the trial to patients?
   ☐Yes (specify): - 1

   *Comment: Use social media/website*

   ☐No – 4

7. In your opinion, is there a benefit to having a study website available for patients to access study information, progress, updates, and final results? Keeping in mind that study results could be years later.

   ☐Yes - 3
   ☐No -1
   ☐Other (specify): - 1

   *Comment:* it may be difficult years later, engagement may be weakened

The outcome of the meeting was unanimous support from our patient partners for the use of an *altered waived consent* model for the TRACTION trial. They fully supported our strategy to disclose study information in the pre- anesthetic clinic by way of posters in the clinic waiting rooms and further suggested individual patient information brochures, which have been prepared in collaboration with our patient partners.

For patients undergoing urgent/emergent surgeries (who would not be seen in the pre-anesthetic clinic), our patient partners felt it would be most appropriate to provide study information after their surgery, but still while the patient is still in hospital. They proposed that either a member of the health care team or a research coordinator provide the information brochure, which includes the study coordinator contact information for participants to call for more information and/or to remove their data from the analysis.

## APPENDIX 2. PATIENT INFORMATION POSTER AND BROCHURE

# TRACTION

A Phase IV trial of a hospital policy of Tranexamic acid use to reduce transfusion in major non-cardiac surgery

**A research study, led by Dr. Thomas Mutter and Dr. Ryan Zarychanski at the University of Manitoba, is currently underway at this Hospital to assess the use of tranexamic acid (TXA) during major non-cardiac surgery. The purpose of this study is to evaluate whether the hospital-level policy of routinely administering tranexamic acid to patients undergoing major non-cardiac surgery will reduce RBC transfusion without increasing thrombotic risk".**

**WHY?**
"Tranexamic is an inexpensive drug that has been shown to reduce the need for blood transfusion during some surgeries. The universal policy of giving TXA to patients undergoing major non-cardiac surgery has the potential to reduce exposure and risks associated with blood transfusion and ensure enough blood is available for those who need it.

**WHO?**
We are conducting this research study at eight Canadian hospitals. Approximately 8000 patients undergoing major non-cardiac surgeries associated with a risk of blood transfusion of 5% or more will be included.

**WHAT?**
A computer will assign each hospital to a 4 week policy to administer either TXA or placebo (a salt water solution). Your anesthesiologist (the doctor administering your anesthetic) will *not* know which drug you are receiving, but always has the option to use TXA if they feel it's in your best interest.

**WHEN/WHERE?**
Patients will receive TXA or placebo intravenously (in a vein) in the operating room at the start of the operation.

**What are the potential risks associated with a blood transfusion?**
Blood transfusions are generally safe, and the most common risks—fever and allergic reaction (hives) —occur in fewer than 1 in 10 patients. While very rare, serious risks associated with blood transfusions include heart failure from too much fluid, major allergic reactions and major infections (<1/million risk of viral transmission).

**What are the potential risks associated with receiving TXA?**
TXA has been used in patients undergoing surgery for decades, and shown to be safe in clinical trials. Because it stops the body from breaking up blood clots, there is a *theoretical* risk of blood clot formation in areas they should not be (for example, in the legs – called a deep vein thrombosis; or in the lungs – called a pulmonary embolism). TXA has not been extensively studied in patients undergoing your planned surgery, but has been given to thousands of patients undergoing other kinds of surgeries where it has ***not*** increased the risk of blood clots.

**What are the potential risks associated with this study?**
The only intervention in this study whether or not you will receive TXA. All other aspects of your care will not be affected.
We are not collecting additional information beyond what is routinely collected while patients are admitted to hospital. While we do plan to share the results of this study with patients and the medical community, the results will not and cannot identify individual patients.

**WHAT INFORMATION IS BEING COLLECTED?**
Using existing electronic databases, we will obtain routine information on your health before, during and after surgery. The information collected will comprise medical and surgical details relevant to your hospital admission and surgical procedure. This health information is already collected as part of routine care. Electronic health information that contains your identify will be treated as confidential in accordance with the Personal Health Information Act of Manitoba.

**HOW WILL THE INFORMATION BE USED?**
After collecting the information, we will remove details that can identify patients personally (de- identified). Study results will be reported in group form, so no individuals can be identified. Information will be stored in a secure location in order to protect patient privacy. The University of Manitoba Research Ethics Board and this Hospital may review research-related records for quality assurance purposes.

**WHO CAN YOU CONTACT IF YOU HAVE QUESTIONS?**
If you wish **not** to be included in the research study or have any questions please contact the Study Coordinator at (204) XXX-XXXX. If you have any questions regarding your rights as a research participant, you may contact the University of Manitoba Research Ethics Board at 204-789-3389.

**CAN YOU REQUEST TO HAVE YOUR INFORMATION REMOVED FROM THE STUDY?**
You can request to have your information removed from the study. This request can be made to the Study Coordinator listed below. Requesting your information to be removed will not affect your care.

A complete description of the research study and research team can be found online at the following internet address: www.tractiontrials.org

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Version 3 dated June 3, 2020

# TRACTION

## A Phase IV trial of a hospital policy of Tranexamic acid use to reduce transfusion in major non-cardiac surgery

**A research study, led by Dr. Brett Houston, Dr. Thomas Mutter and Dr. Ryan Zarychanski at the University of Manitoba, is currently underway at this Hospital to assess the use of tranexamic acid during major non-cardiac surgery. The purpose of this study is to evaluate whether the hospital-level policy of routinely administering tranexamic acid to patients undergoing major non-cardiac (heart) surgery will reduce red blood cell transfusion without increasing thrombotic risk (blood clot).**

### WHY

Tranexamic is an inexpensive drug that is routinely given to reduce the need for blood transfusion during some heart and joint replacement surgeries. However, for many other surgeries, including the type of surgery you had, tranexamic acid is not routinely given. This study will help us determine if routinely giving tranexamic acid will also help reduce blood transfusions in these other surgeries.

### WHO

We are conducting this re- search study at eight Canadian hospitals. Approximately 8000 patients undergoing major surgeries associated with a risk of blood transfusion of 5% or more will be included. Eligible patients will receive a brochure about the study when discharged from hospital.

### WHAT

A computer will assign each hospital to a 4 week policy to administer either TXA tranexamic acid or placebo (a salt water solution). Your anesthesiologist (the doctor administering your anesthetic) will know if you are eligible for the study but not know which drug you are receiving. They, but always has have the option to use tranexamic acid if they feel it's in your best interest.

### WHEN/WHERE

Patients will receive TXA or placebo intravenously (in a vein) in the operating room at the start of the operation.

### What are the potential risks associated with a blood transfusion?

Blood transfusions are generally safe, and the most common risks—fever and allergic reaction (hives) —occur in fewer than 1 in 10 patients. While very rare, serious risks associated with blood transfusions include heart failure from too much fluid, major allergic reactions and major infections (<1/million risk of viral transmission).

### What are the potential risks associated with receiving tranexamic acid?

Tranexamic acid has been used in patients undergoing surgery for decades and shown to be safe in clinical trials. Because it stops the body from breaking up blood clots, there is a theoretical risk of blood clot formation in areas they should not be (for example, in the legs – called a deep vein thrombosis; or in the lungs – called a pulmonary embolism). Tranexamic acid has not been extensively studied in many types of (non-cardiac) surgery. However, it has been given to many thousands of patients undergoing joint replacement or cardiac surgery, where it has not been associated with increased risk of blood clots.

### What are the potential risks associated with this study?

The only intervention in this study whether or not you will receive tranexamic acid during your surgery. All other aspects of your care will not be affected. We are not collecting additional information beyond what is routinely collected while patients are admitted to hospital. While we do plan to share the results of this study with patients and the medical community, the results will not and cannot identify individual patients.

### WHAT INFORMATION IS BEING COLLECTED?

Using existing electronic databases, we will obtain routine information on eligible patients' health before, during and after surgery. The information collected will comprise medical and surgical details relevant to their hospital admission and surgical procedure. This health information is already collected as part of routine care. Electronic health information that contains your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba.

### HOW WILL THE INFORMATION BE USED?

After collecting the information, we will remove details that can identify patients personally (de- identified). Study results will be reported in group form, so no individuals can be identified. Information will be stored in a secure location in order to protect patient privacy. The University of Manitoba Research Ethics Board and this Hospital may review research-related records for quality assurance purposes.

### WHO CAN YOU CONTACT IF YOU HAVE QUESTIONS?

If you wish not to be included in the research study or have any questions please contact the Study Coordinator at (204) 430-9815. If you have any questions regarding your rights as a research participant, you may contact the University of Manitoba Research Ethics Board at 204-789-3389.

### CAN YOU REQUEST TO HAVE YOUR INFORMATION REMOVED FROM THE STUDY?

You can request to have your information removed from the study. This request can be made to the Study Coordinator listed above requesting your information to be removed will not affect your care.

**A complete description of the research study and research team can be found online at the following internet address: www.tractiontrials.org**

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Version 4, dated October 1, 2021

## What are the potential risks associated with this study?

The only protocolized intervention in this study is whether or not you will receive tranexamic acid during your surgery.. All other aspects of your care will not be affected.

We are not collecting additional information beyond what is routinely collected while patients are admitted to hospital. While we do plan to share the results of this study with patients and the medical community, the results will not and cannot identify individual patients.

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## WHO CAN YOU CONTACT IF YOU HAVE QUESTIONS?

If you have any questions about your participation in the research study please contact the Study Coordinator at (204) 430-9815.

If you have any questions regarding your rights as a research participant, you may contact the University of Manitoba Research Ethics Board at (204) 789-3389.

## CAN YOU REQUEST TO HAVE YOUR INFORMATION REMOVED FROM THE STUDY?

You can request to have your information removed from the study. This request can be made to the Study Coordinator listed above. Requesting your information to be removed will not affect your care.

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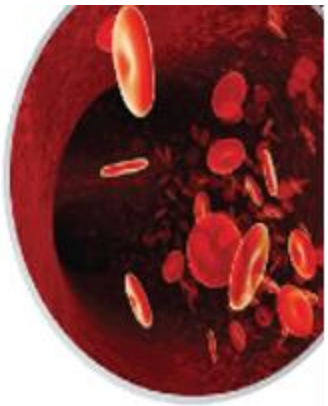

# TRACTION

**A Phase IV trial of a hospital policy of Tranexamic acid use to reduce transfusion in major non-cardiac surgery**

You have participated in a research study, led by Dr. Brett Houston, Dr. Thomas Mutter, and Dr. Ryan Zarychanski at the University of Manitoba, This study is currently underway at this Hospital to assess the ability of tranexamic acid to reduce blood transfusion in major non-cardiac/heart surgery where the risk of blood transfusion is more than 5%..

The purpose of this study is to evaluate whether the hospital-level policy of routinely administering tranexamic acid to patients undergoing major non-cardiac surgery will reduce red blood cell transfusion without increasing thrombotic risk (blood clots)[a].

**WHAT INFORMATION IS BEING COLLECTED?**

Using existing electronic databases, we will obtain routine information on your health before, during and after surgery. The information collected will comprise medical and surgical details relevant to your hospital admission and surgical procedure. This health information is already collected as part of routine care. Electronic health information that contains your identify will be treated as confidential in accordance with the Personal Health Information Act of Manitoba.

**HOW WILL THE INFORMATION BE USED?**

After collecting the information, we will remove details that can identify patients personally (de- identified). Study results will be reported in group form, so no individuals can be identified. Information will be stored in a secure location (password-protected file on secure server) in order to protect patient privacy. The University of Manitoba Research Ethics Board and this Hospital may review research-related records for quality assurance purposes.

**WHO CAN YOU CONTACT IF YOU HAVE QUESTIONS?**

If you wish not to be included in the research study or have any questions please contact the Study Coordinator at (204) XXX-XXXX. If you have any questions regarding your rights as a research participant, you may contact the University of Manitoba Research Ethics Board at 204-789-3389.

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Version 3, June 3, 2020

# TRACTION

## A Phase IV trial of a hospital policy of Tranexamic acid use to reduce transfusion in major non-cardiac surgery

A research study, led by Dr. Thomas Mutter and Dr. Ryan Zarychanski at the University of Manitoba, is currently underway at this Hospital to assess the use of tranexamic acid (TXA) during major non-cardiac surgery. The purpose of this study is to evaluate whether the hospital-level policy of routinely administering tranexamic acid to patients undergoing major non-cardiac surgery will reduce RBC transfusion without increasing thrombotic risk".

## APPENDIX 3. SUPPLEMENTAL TXA DOSING JUSTIFICATION

*Systematic reviews evaluating TXA dosing:* Substantial variability in TXA dosing exists, yet despite this, TXA consistently reduces transfusion compared to placebo. In 34 cardiac surgery trials investigating the efficacy of TXA, loading doses ranged from 2.5 to 100 mg/kg and commonly used maintenance infusions ranged from 0.25 to 40 mg/kg/hr delivered over 1 to 12 hrs[1]. Similar variation exists in orthopedic surgery. In our meta-analysis of TXA in major non-cardiac/non-orthopedic surgeries, the dosing schedule varied considerably. Boluses alone were used in 47 % of trials and estimated doses ranged from 5 to 80 mg/kg. The remaining trials used a combination of boluses and infusion (43%) or infusions alone (10%). Infusion doses ranged from 0.1 to 40 mg/kg/hr for wide-ranging durations of time[2]. The relative reduction in the proportion of patients transfused RBCs were similar if a weight-based (RR 0.56, 95%CI 0.42 to 0.77) or a fixed-dose (RR 0.57, 95%CI 0.31 to 1.02) strategy was employed. Neither efficacy (transfusion) nor safety (DVT/PE) were associated with total dose administered and did not vary significantly according to dosing schedule (ie. bolus, infusion or a composite of bolus and infusion)[2].

*Evaluation of real-life TXA use:* In our large retrospective cohort study of 28,116 high-risk non-cardiac surgeries, TXA was largely administered to patients undergoing orthopedic or spinal surgery (98% of TXA use). An initial bolus was administered in 91% of cases (median dose of 1 gram); infusion doses and durations varied considerably[3].

*Pharmacokinetic and pharmacodynamic studies of TXA:* In the absence of trials comparing dosing strategies, pharmacokinetic and pharmacodynamic studies are used to justify the proposed dosing in the TRACTION trial. The elimination half-life of TXA is 120 minutes[4]. This means that steady state serum concentrations are not expected to be realized for up to 10 hours of an infusion justifying the need for a loading dose to rapidly achieve therapeutic serum concentrations at the onset of surgery. In vitro data suggest that the plasma TXA concentration required to inhibit fibrinolysis (i.e. 80% inhibition of tissue plasminogen activity) is **10** mcg/mL. In a pharmacokinetic study in (n=61) of patients undergoing cardiopulmonary bypass, a low-dose group consisted of 10 mg/kg of TXA followed by 1 mg/kg/h resulted in a plasma TXA concentration of **28-55** mcg/mL[5]. They found no association between CPB and pharmacokinetic parameters. The main covariate explaining between-subject variability in pharmacokinetic parameters was body weight. Unfortunately, they did not included patients with various degrees of renal dysfunction and thus could not confirm other significant influences on TXA pharmacokinetic parameters (e.g. creatinine clearance). Note that the half-life of TXA can increase from 2 hours up to 38 hours in severe renal disease[6]. From the work of Dowd and others, it is estimated that cardiopulmonary bypass increases the volume of distribution by 15% meaning that in non-cardiac surgery, plasma TXA concentrations would be expected to be up to 15% higher at the same dose of 10 mg/kg[7]. Thus, the 1 gram bolus proposed would be sufficient to achieve therapeutic plasma TXA concentrations (37+/-17 mcg/mL after a 10 mg/kg loading dose unless the patient weighs over 100 kg)[8-10]. In these instances, the 2 gram load will achieve target plasma TXA levels. Given the 120- minute half-life of TXA, plasma concentrations drop by 50% 2 hours after the loading dose and potentially leading to sub-therapeutic plasma concentrations in surgeries lasting greater than 2 hours. This risk will be accentuated in patients with significant blood loss and transfusion or volume shifts. The mean duration of surgery in our eligible study population is 3.5 (SD 2.1) hours[3]. For this reason, a maintenance infusion was chosen to ensure therapeutic plasma concentrations throughout the surgery. Infusions of 1

mg/kg/hr after a 10 mg/kg load are associated with plasma TXA levels that range from 28 to 31 mcg/mL in cardiac surgery despite the use of cardiopulmonary bypass[7].

## DOSING JUSTIFICATION REFERENCES:


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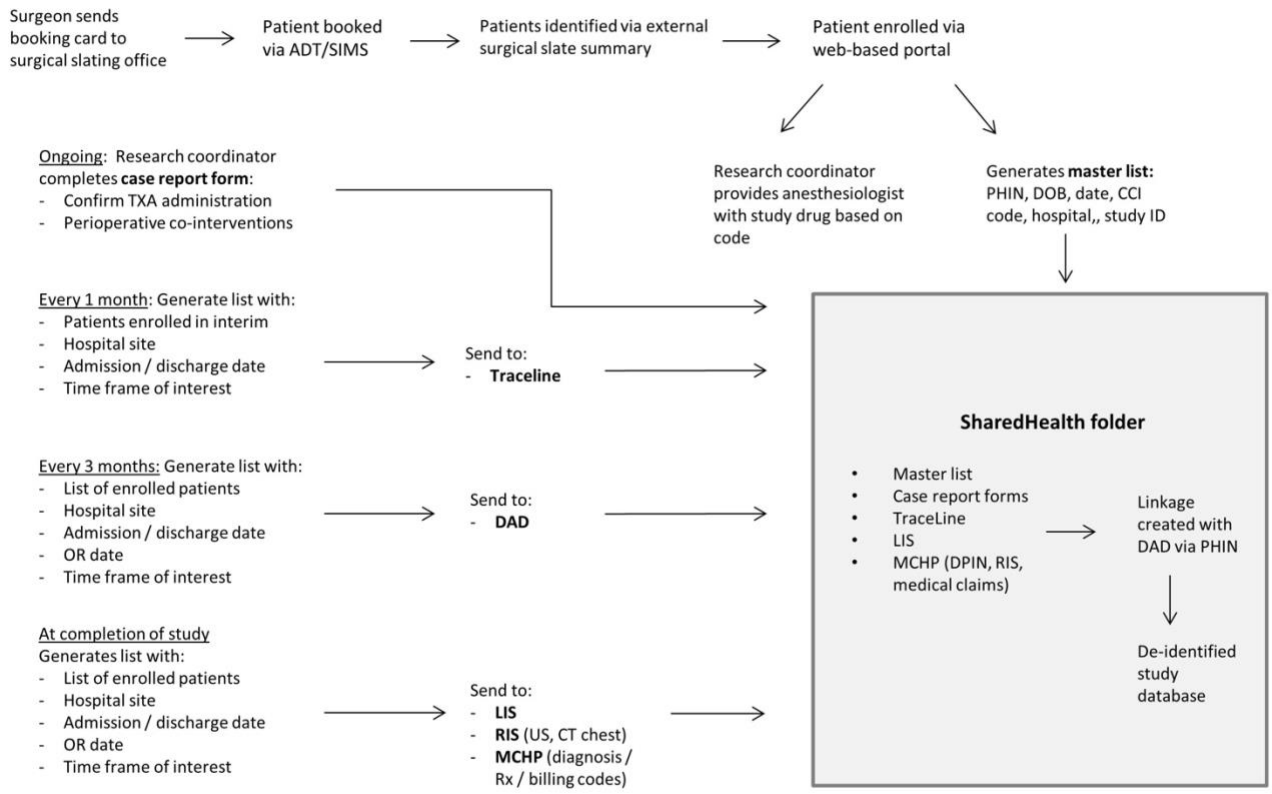
## APPENDIX 4: TRACTION PROCESS MAP




CAPTION: APPENDIX 4 - Potentially eligible patients will be identified using the external surgical slate, which is generated by the Surgical Management Information System (SIMS) database. All patients will be enrolled using an electronic portal, and assigned a unique study identification. Tranexamic acid (TXA) administration will be ascertained electronically (through SIMS) at the Ottawa site, and using a half page case report form at the Winnipeg site (the Winnipeg site does not presently capture intraoperative medications in their SIMS system). We will ascertain patient demographics and comorbidities and hospital outcomes from the Discharge Abstract Database (DAD). High-fidelity transfusion data will be obtained from TraceLine (through Canadian Blood Services), and laboratory data from the Laboratory Information System (LIS). We will obtain in-hospital VTE rates from the DAD, and out-of-hospital VTE rates by linking to provincial health administrative databases available at the Manitoba Centre for Health Policy (MCHP). Datasets will be linked using unique personal health identification numbers (PHINs), which is a high-fidelity patient-specific identifier captured in each of the datasets. Once the data has been linked, all personal identifiers will be removed and replaced with the assigned unique study identification. ADT, Admission Discharge Transfer; DOB, date of birth; CCI, Canadian Classification of Health Interventions; ID, identification; OR, operating room; RIS, Radiology Information System; DPIN, Drug Program Information Network; Rx, prescription

## APPENDIX 5. INSTITUTIONAL LETTERS SUPPORTING THE TRACTION TRIAL

PACT | Canadian Perioperative Anesthesia Clinical Trials

November 1, 2019

Letter of Support

**Re: University of Manitoba REB Application: TRACTION Trial**

The executive of the Canadian Perioperative Anesthesia Clinical Trials (PACT) Group provides their full support to Dr. Zarychanski and the TRACTION investigative team. The TRACTION trial is an extremely needed and timely trial of TXA in non-cardiac surgery. The trial is well justified and meticulously planned. The results of the trial will inform practice throughout the world.

The PACT Group is committed to promoting practice-changing research in perioperative medicine. As such, we the support research, provide mentorship and networking opportunities to Canadian investigators in the fields of anesthesia and perioperative medicine.

The TRACTION trial is a tremendous priority for PACT. Our members have contributed intellectually to the design of the trial and feel the study will generate essential knowledge. Our members, national leaders in perioperative medicine, will use the knowledge of the trial to inform practice at their centre and beyond.

Given the expense and potential for adverse events known to be associated with transfusion, the TRACTION trial has never been so relevant. Confirming that TXA will safely reduce the need for perioperative trial will establish a new standard of care in perioperative medicine, help rationalize our use of blood, and foster the sustainability of our National blood system.

We look forward to collaborating with the TRACTION investigators and look forward to the results of the trial.

Sincerely,

Linda Girling
PACT Secretariat
Research Manager, Anesthesia Research Office
Department of Anesthesiology, Perioperative and Pain Medicine
University of Manitoba

**PACT SECRETARIAT,** c/o Department of Anesthesiology, Perioperative and Pain Medicine, University of Manitoba
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Winnipeg Regional Health Authority / Office régional de la santé de Winnipeg
Caring for Health / À l'écoute de notre santé

University of Manitoba
Rady Faculty of Health Sciences

September 14, 2019

Dr. Zarychanski
2056-675 McDermot Ave
Winnipeg, MB R3E 0V9

**RE: Tranexamic Acid to Reduce Red Cell Transfusion in Major Non-Cardiac Surgery (TRACTION) Trial**

Dear Dr. Zarychanski,

This letter is being written in support of the **Tranexamic acid to reduce red cell transfusion in major non-cardiac surgery (TRACTION) trial.** Three hospitals in the Winnipeg Regional Health Authority that are affiliated with the University of Manitoba will be participating in the trial. Site based co-investigators from my department have ensured that trial logistics are feasible at these three sites. This is facilitated by the registry based data collection, and risk-adapted models of consent informed by patients and by members of our Department. Recruitment targets are reasonable based on the volume of eligible surgeries seen at these sites.

A significant fraction of all blood transfusions are given by anesthesiologists. Optimizing hospital policy to safely reduce blood transfusion rates, both in the operating room and while recovering from surgery, is of interest to anesthesiologists broadly. In that regard, the trial outcomes are relevant to anesthesiologists and the patients that they share with other members of the surgical team. The trial results will be immediately applicable to all hospitals performing major surgical procedures and anesthesiologists practicing in our health region and beyond.

This trial has my full support and I look forward to my department's participation.

Best Wishes,

Chris Christodoulou, MBChB, Cum Laude DA (UK), FRCPC
Head, Department of Anesthesiology, Perioperative and Pain Medicine
Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba
Medical Director, Winnipeg Regional Health Authority Anesthesia Program
Winnipeg, Canada

Dorothy Miller, Executive Assistant to Dr. Christodoulou, Department Head and Reid McMurchy, Administrative Director
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Winnipeg Regional Health Authority / Office régional de la santé de Winnipeg
Caring for Health / À l'écoute de notre santé

University of Manitoba
Rady Faculty of Health Sciences

1 November 2019

To: University of Manitoba Biomedical Research Ethics Board Members

From: Thomas Mutter MD FRCPC MSc, Associate Head Research and Academic Affairs, Department of Anesthesiology, Perioperative and Pain Medicine, Rady Faculty of Health Sciences, Rady College of Medicine

Re: Tranexamic acid use to reduce transfusion in major non-cardiac surgery (TRACTION): A pragmatic randomized cluster crossover trial

Dear committee Members,

I am writing this letter in support of the TRACTION trial in my role as Associate Head Research and Academic Affairs and a co-principal investigator for the trial. As evidenced by the preliminary work done in the TRACTION research program, there is a need to determine if perioperative administration of tranexamic acid should become a standard of care for the broad surgical population in the trial. Answering this research question with this trial will have far reaching implications for perioperative care, and a pragmatic hospital-based cluster trial is the only feasible way to answer this question. As outlined in the protocol, the evidence strongly suggests that tranexamic acid given to bleeding patients reduces the need for transfusion with no increase in the risk of arterial or venous thromboembolism. At a hospital policy level, we are anticipating that the universal administration of tranexamic acid to non-cardiac surgical patients at high risk of transfusion will safely reduce red blood cell transfusion and that a become standard policy/practice similar to perioperative policies to give preoperative antibiotics or prescribe venous thromboembolism prophylaxis perioperatively.

The TRACTION trial leadership has engaged with patients and with anesthesia leadership in Ottawa and locally in the Winnipeg Health Region. Support for the trial and the altered consent mechanism is unanimous; both among clinicians, policy-makers, and patients. The local anesthesia site medical directors for the Health Sciences Centre (Dr. Craig Haberman) and the Grace General Hospital (Dr. Jayesh Daya) as well as St. Boniface General Hospital anesthesiologists Drs. Hema Bagry and Eric Jacobsohn have joined the study team. They have been involved with the study design including the altered consent mechanism. Our department is already familiar with altered waived consent from the recently completed B-FREE pilot trial and the soon to start B-FREE main trial.

On behalf of our University of Manitoba department of Anesthesiology, I look forward to your review of the TRACTION study.

Sincerely,

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## 9.0 MANUSCRIPTS

1. Houston BL, Fergusson DA, Falk J, Krupka E, Perelman I, Breau RH, McIsaac DI, Rimmer E, Houston DS, Garland A, Ariano RE, Tinmouth A, Balshaw R, Turgeon AF, Jacobsohn E, Park J, Buduhan G, Johnson M, Koulack J, Zarychanski R. Evaluation of Transfusion Practices in Noncardiac Surgeries at High Risk for Red Blood Cell Transfusion: A Retrospective Cohort Study. Transfus Med Rev. 2021 Jan;35(1):16-21. doi: 10.1016/j.tmrv.2020.08.001. PMID: 32994103.

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# Evaluation of transfusion practices in non-cardiac surgeries at high risk for red blood cell transfusion: a retrospective cohort study

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# Evaluation of Transfusion Practices in Noncardiac Surgeries at High Risk for Red Blood Cell Transfusion: A Retrospective Cohort Study

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Noncardiac surgery
Red blood cell

ABSTRACT

Perioperative bleeding is a major indication for red blood cell (RBC) transfusion, yet transfusion data in many major noncardiac surgeries are lacking and do not reflect recent blood conservation efforts. We aim to describe transfusion practices in noncardiac surgeries at high risk for RBC transfusion. We completed a retrospective cohort study to evaluate adult patients undergoing major noncardiac surgery at 5 Canadian hospitals between January 2014 and December 2016. We used Canadian Classification of Health Interventions procedure codes within the Discharge Abstract Database, which we linked to transfusion and laboratory databases. We studied all patients undergoing a major noncardiac surgery at ≥5% risk of perioperative RBC transfusion. For each surgery, we characterized the percentage of patients exposed to an RBC transfusion, the mean/median number of RBC units transfused, and platelet and plasma exposure. We identified 85 noncardiac surgeries with an RBC transfusion rate ≥5%, representing 25,607 patient admissions. The baseline RBC transfusion rate was 16%, ranging from 5% to 49% among individual surgeries. Of those transfused, the median (Q1, Q3) number of RBCs transfused was 2 U (1, 3 U); 39% received 1 U RBC, 36% received 2 U RBC, and 8% were transfused ≥5 U RBC. Platelet and plasma transfusions were overall low. In the era of blood conservation, we described transfusion practices in major noncardiac surgeries at high risk for RBC transfusion, which has implications for patient consent, preoperative surgical planning, and blood bank inventory management.

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Approximately 700,000 red blood cell (RBC) transfusions are administered annually in Canada, with an estimated cost of $600 per unit and approximately $1 billion in Canadian health care expenditure each year [1-3]. Although transfusions can be life-saving, they are not without harm [4]. Transfusions are associated with both allergic and nonallergic transfusion reactions, infection, immune dysregulation, prolonged postoperative length of stay, and increased morbidity [5-10].

Perioperative bleeding is a major indication for allogeneic RBC transfusion and is the third most common indication for transfusion in US hospital inpatients [11,12]. Approximately 50% of patients undergoing major cardiac and orthopedic surgery receive a perioperative transfusion [13-15]. Data are lacking in other major noncardiac surgeries and do not reflect recent efforts to minimize perioperative transfusion [7,16-19]. The objective of our study is to describe transfusion practices in noncardiac surgeries at high risk for RBC transfusion to inform patient consent discussions, preoperative planning, and blood bank utilization by health care practitioners and health system administrators.

## 1. Materials and Methods

### 1.1. Study Design

We completed a retrospective cohort study to evaluate all patients (≥18 years of age) undergoing noncardiac surgery at 3 hospitals in Winnipeg, Manitoba (Health Sciences Centre, St. Boniface General Hospital, and Concordia Hospital), and 2 hospitals in Ottawa, Ontario (Ottawa Hospital, Civic and General Campuses), between January 1, 2014 and December 31, 2016. These are tertiary care centers that provide health service to approximately 2 million people.

### 1.2. Data Sources

We obtained patient demographics and clinical and administrative hospitalization data from the Discharge Abstract Database (DAD), a national database which captures patient hospitalizations. The DAD at each hospital undergoes a continual process of data quality assurance and data validation, and uses standard International Classification of Diseases coding for diagnoses and comorbidities and Canadian Classification of Health Interventions (CCI) coding for surgical procedures [20]. Manitoba transfusion data were obtained from a provincial transfusion database (TraceLine) dually governed by Diagnostic Services Manitoba and Canadian Blood Services. Supplementary laboratory data in Manitoba were obtained from the hospital Laboratory Information System. Ontario transfusion and laboratory data were obtained from the Ottawa Hospital Data Warehouse, a repository of clinical and health administrative data that are routinely validated to ensure accuracy.

### 1.3. Study Population

We evaluated all patients undergoing a major noncardiac surgery at high risk of perioperative RBC transfusion. *High risk* of RBC transfusion was a priori defined as 5% or greater. This transfusion threshold was chosen because clinicians and patient partners identified that a 1 in 20 chance of transfusion was both substantive and allowed inclusion of a broad patient population. We included all patients with an inpatient visit and a CCI code. To focus on a surgical population at high risk for RBC transfusion, we removed lower-risk day surgeries by exclusively evaluating inpatient surgeries. We isolated surgeries to those conducted in the main operating room to remove low-risk procedures performed in the emergency department, radiology suite, and hospital ward. We excluded all patients with >1 surgery during their hospitalization, as this could confound the surgery-specific transfusion rates. If a patient was readmitted for another surgery during the study period (2014-2016), we evaluated only their initial hospital admission.

We stratified the CCI codes by surgical approach, which allowed distinction between open and minimally invasive surgeries, as this has clinically significant bleeding implications [21,22]. Using the letters in the sixth and seventh positions of the CCI codes, letters *AA* to *KS* were assigned as "minimally invasive," whereas letters *KZ* to *XY* were assigned as "open." As the granularity of CCI codes can make the clinical interpretation challenging (n = 2863 unique codes), we renamed and reclassified the CCI codes to reflect clinically relevant surgeries using both the Canadian Classification of Health Interventions alphabetical index [23,24] and the Winnipeg Regional Health Authority Surgical Information Management System Procedure Catalog [25]. A list of the CCI codes along with their corresponding surgical descriptions is included in Appendix A. We further refined the surgical population by removing all uncommon procedures (absolute number <30 over the 3-year period), low-risk procedures (transfusion rate <5%), procedures outside of our surgical scope (cardiac, obstetrics), and procedures not associated with bleeding (ie, intubation, biopsies) (Fig 1).

### 1.4. Study Variables

We obtained patient demographics including age, sex, baseline comorbidities, admission diagnosis, and preoperative hemoglobin. Baseline comorbidities were evaluated using the Charlson comorbidity index [26]. For preoperative hemoglobin, we obtained the value drawn closest to the start of surgery, within the preceding 4 weeks. *Preoperative anemia* was defined as a hemoglobin value less than 140 g/L in men and 130 g/L in women [27]. Surgical information, including surgery name, date/time, and urgency (eg, elective, urgent/emergent), was obtained from the DAD using standardized CCI procedure codes [23,24]. To evaluate transfusions related to perioperative bleeding, we included all transfusions from the start of surgery to 7 days postoperatively or hospital discharge, whichever occurred first.

### 1.5. Outcomes

For each surgical domain and individual surgery, we characterized the percentage of patients exposed to RBC transfusion and the mean/median number of RBC units transfused. We summarized the distribution of RBC

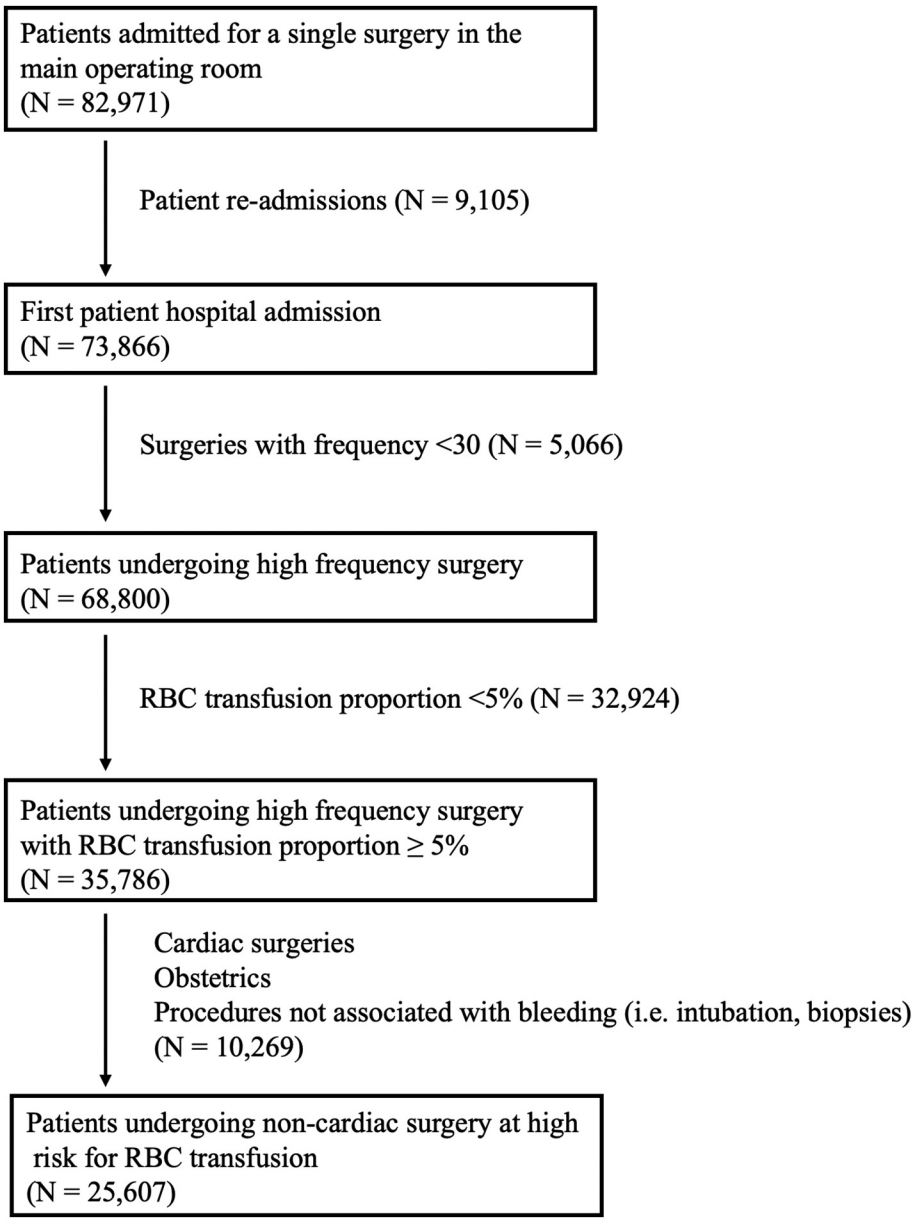


**Fig 1.** Flow diagram depicting the derivation of our surgical cohort.

transfusions by describing the noncardiac surgeries with the highest risk of transfusion, as well as those with the highest annual number of RBC units transfused (ie, transfusion burden). This identifies common surgeries where a high percentage of patients are transfused a low number of RBC units and lower-frequency surgeries where patients receive larger numbers of RBC units. For each individual surgery, we evaluated the percentage of patients requiring ≥5 U RBC and the timing of RBC transfusion in relation to the surgery. Lastly, we evaluated the percentage of patients exposed to platelets and plasma.

### *1.6. Subgroup Analyses*

A priori subgroup analyses included the study of differences in RBC transfusion according to surgical urgency (elective vs urgent/emergent) and surgical approach (open vs minimally invasive).

### *1.7. Analysis*

Baseline characteristics were summarized as means (standard deviation [SD]), medians (interquartile range), or frequency (percentage), as appropriate. We analyzed group differences in categorical or continuous data using $\chi^2$ and *t* tests, as appropriate. *P* values less than .5 were considered significant. Sample size calculations were not performed because the primary intent of this analysis was descriptive and the cohort was derived by convenience sampling. Missing data were evaluated and summarized. We conducted all analyses using SAS/STAT software (SAS version 9.4 for Windows; SAS Institute Inc, Cary, NC).

## 2. Results

### *2.1. Baseline Characteristics*

In our 5 centers, we captured 82,971 patient admissions with a single surgery performed in hospital operating rooms and 85 noncardiac surgeries with an RBC transfusion rate ≥5%, which represented 25,607 patient admissions (Fig 1). The surgical distribution between cities was comparable. Most surgeries were elective (n = 16,383; 64%) and performed using an open surgical approach (69/85; 81%). The mean patient age was 63 years (SD 17 years), and 55% were female. Preoperative

**Table 1**
Baseline demographics categorized by surgical domain

| Surgical domain | Surgical volume (# surgeries/y) | Urgency (% elective) | Mean age (SD) | Sex (% female) | Mean Charlson CI (SD) | Mean preop Hb (g/L) (SD) | % Transfused | Mean # RBC units[a] (SD) | RBC burden (# U/y) |
|---|---|---|---|---|---|---|---|---|---|
| General surgery | 4907 | 57 | 62.1 (16.3) | 48 | 2.1 (2.8) | 121 (23) | 17.5 | 2.5 (2.7) | 719 |
| Gynecology | 3792 | 96 | 52.3 (13.2) | 100 | 1.2 (2.1) | 125 (18) | 9.5 | 2.4 (1.7) | 285 |
| Neurosurgery | 296 | 61 | 56.7 (12.1) | 71.0 | 0.9 (1.0) | 133 (17) | 11.6 | 2.2 (1.6) | 25 |
| Orthopedic surgery | 8515 | 47 | 70.0 (17.1) | 56.7 | 0.6 (1.5) | 121 (20) | 17.2 | 1.9 (1.2) | 929 |
| Otolaryngology | 187 | 97 | 61.2 (13.9) | 44.4 | 3.2 (3.0) | 130 (15) | 8.1 | 2.0 (0.8) | 10 |
| Plastic surgery | 416 | 63 | 56.5 (16.8) | 44.7 | 1.2 (1.8) | 118 (24) | 9.4 | 2.2 (1.1) | 28 |
| Spine surgery | 2233 | 66 | 56.6 (15.3) | 43.1 | 0.3 (1.3) | 133 (19) | 16.6 | 2.9 (2.2) | 352 |
| Thoracic surgery | 736 | 73 | 59.5 (16.5) | 43.2 | 2.1 (2.6) | 124 (22) | 17.3 | 2.4 (2.6) | 103 |
| Urology | 1775 | 81 | 63.2 (14.3) | 25.4 | 2.2 (1.8) | 121 (22) | 16.2 | 2.8 (2.5) | 272 |
| Vascular surgery | 2750 | 69 | 70.1 (11.9) | 30.3 | 1.1 (1.2) | 128 (21) | 22.2 | 3.1 (3.8) | 636 |

CI, comorbidity index; Hb, hemoglobin; Preop, preoperative; U, units; Y, year; SD, standard deviation.
[a] Mean number of RBC transfusions in those patients who received a RBC transfusion.

hemoglobin values were available in 67% of the cohort, with more complete capture among patients undergoing urgent/emergent surgeries (95%). Other study variables had near complete (>99%) capture. Baseline demographics classified by surgical domain and individual surgery type are included in Table 1 and Appendix B, respectively.

### 2.2. Description of RBC Transfusion Among the Individual Surgeries

In our surgical cohort, the baseline RBC transfusion rate was 16% and ranged from 5% to 49% among individual surgeries. Of those transfused, the median (Q1, Q3) number of RBCs transfused was 2 U (1, 3 U); 39% received 1 U RBC, 36% received 2 U RBC, and 8% were transfused ≥5 U RBC. The 10 surgeries with the highest RBC transfusion risks were open cystectomy (49%), open abdominal aortic repair (46%), open splenectomy (46%), spinal fusion with vertebrectomy (38%), open abdominal aortic bypass (38%), open gastroplasty (36%), femur open reduction internal fixation (35%), above-knee amputation (32%), open gastrectomy (30%), and endoscopic femur fixation (30%) (Table 2, Fig 2, Appendix C). The surgeries that led to the largest annual numbers of RBC units transfused included femur open reduction internal fixation (558 surgeries; 1094 U RBC), open hip arthroplasty (1577 surgeries; 896 U RBC), hysterectomy (1127 surgeries; 773 U RBC), abdominal aortic repair (112 surgeries; 720 U RBC), and spinal fusion (531 surgeries; 677 U RBC).

Of those who received a RBC transfusion, 27% were transfused intraoperatively, 60% were transfused postoperatively, and 13% were transfused both intraoperatively and postoperatively. Overall, 40% of the RBC units were transfused intraoperatively, and 60% were transfused postoperatively. Postoperative transfusions were administered a median of 50 hours (28, 77 hours) after surgery completion. Platelet and plasma transfusions were overall low, with 4% (3/85) and 12% (10/85) of surgeries associated with a platelet and plasma transfusion rate ≥5%, respectively (Appendix C).

### 2.3. Subgroup Analyses

Compared to elective surgical patients, those admitted for an urgent/emergent surgery were more likely to have preoperative anemia (hemoglobin 118g/L [95% confidence interval 118-119 g/L] vs 130 g/L [95% confidence interval 129-130 g/L]) and were more likely to receive an RBC transfusion (26% vs 11%; $P < .001$). RBC transfusion was higher among patients undergoing open surgeries compared to minimally invasive surgeries (17% vs 11%; $P < .001$).

## 3. Discussion

In the era of blood conservation initiatives, we have described transfusion practices in major noncardiac surgeries at high risk (≥5%) for RBC transfusion. We focused on both the percentage of patients transfused

**Table 2**
Surgery-specific transfusion outcomes

| Surgery | # Surgeries/y | Mean age (SD) | Sex (% female) | Mean Charlson CI (SD) | Mean preop Hb (g/L) (SD) | % Transfused | Mean # U RBC[a] (SD) | Transfusion burden (# U RBC/y) |
|---|---|---|---|---|---|---|---|---|
| *Surgeries with the highest percentage of patients transfused* | | | | | | | | |
| Open cystectomy | 53 | 65.6 (11.5) | 28 | 2.8 (2.6) | 125.9 (18.3) | **49.1** | 78.0 (3.1) | 239 |
| Open abdominal aortic repair | 112 | 70.8 (8.6) | 23 | 1.2 (1.1) | 131.2 (21.9) | **46.3** | 156.0 (4.6) | 720 |
| Open splenectomy | 17 | 49.1 (17.5) | 56 | 0.6 (1.5) | 107.1 (26.4) | **46.0** | 23.0 (4.8) | 111 |
| Spinal fusion with vertebrectomy | 57 | 56.8 (13.6) | 49 | 0.8 (2.1) | 126.7 (20.7) | **38.4** | 66.0 (3.5) | 233 |
| Open abdominal aortic bypass | 63 | 65.8 (9.4) | 30 | 1.0 (0.9) | 135.6 (19.6) | **38.3** | 72.0 (2.9) | 210 |
| *Surgeries with the highest transfusion burden* | | | | | | | | |
| Femur open reduction internal fixation | 558 | 74.5 (18.6) | 69 | 0.9 (1.8) | 115.1 (18.5) | 34.8 | 583.0 (1.9) | **1094** |
| Open hip arthroplasty | 1577 | 68.1 (14.4) | 55 | 0.4 (1.2) | 128.7 (17.7) | 10.1 | 480.0 (1.9) | **896** |
| Open hysterectomy | 1127 | 52.6 (12.8) | 100 | 1.2 (2.1) | 124.9 (18.2) | 9.5 | 320.0 (2.4) | **773** |
| Open abdominal aortic repair | 112 | 70.8 (8.6) | 23 | 1.2 (1.1) | 131.2 (21.9) | 46.3 | 156.0 (4.6) | **720** |
| Spinal fusion | 531 | 57 (15.4) | 41 | 0.2 (1.0) | 132.4 (19.1) | 16.1 | 257.0 (2.6) | **677** |

Includes the top 5 surgeries with the highest percentage of patients transfused RBCs, as well as the top 5 surgeries with the highest annual transfusion burden (# U RBC transfused per year).
[a] Mean number of RBC transfusions in those patients who received an RBC transfusion.

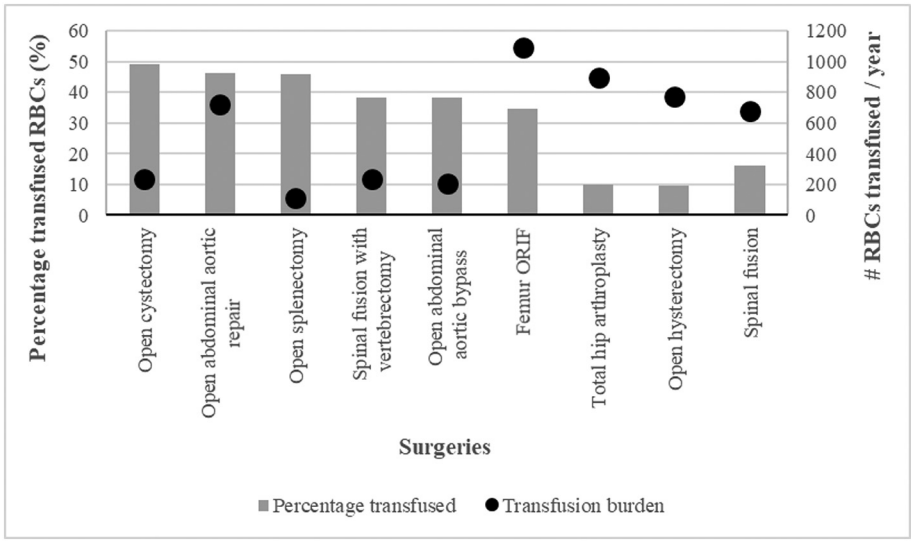


**Fig 2.** The top 5 surgeries ranked according to the percentage of patients transfused RBCs (%) and the number of RBC units transfused annually. This captures distinct surgical populations with differential impact on patients and the health care system.

RBCs as well as the number of RBCs transfused annually, as these measures have differing implications. Transfusion exposure is a patient prioritized outcome, which informs patient consent discussions and perioperative surgical planning. Transfusion burden considers both the percentage of patients transfused as well as surgical frequency, with systemic implications for the health care system and blood banking, as blood products are a costly but finite resource [1]. Except for open abdominal aortic artery repair, surgeries with a high percentage of RBC transfusion were distinct from those with the highest RBC transfusion burden, highlighting that both of these factors should be considered when evaluating perioperative transfusion practices.

Prior studies evaluating the frequency and distribution of real-world perioperative transfusion in noncardiac surgery are outdated and do not reflect recent efforts to mitigate blood transfusion, such as preoperative anemia correction, intraoperative cell salvage, variation in surgical technique, use of more restrictive transfusion thresholds, single-unit transfusion policies, and the increasing use of medications such as tranexamic acid [16-18,28-30]. Reflective of this, a patient blood management initiative in Ontario, Canada, demonstrated that the implementation of blood conservation efforts substantially reduces perioperative transfusion in select patient populations such as coronary artery bypass grafting, radical prostatectomy, and hip and knee arthroplasty [7]. Our study builds on these findings by providing a comprehensive and updated description of transfusion practices in noncardiac surgery in the era of blood conservation prioritization.

We preselected a higher-risk surgical population by limiting cohort inclusion to hospitalized patients undergoing a surgery with a transfusion rate ≥5%, a threshold felt to be meaningful to both patient partners and stakeholders. As expected, patients undergoing open surgery experienced increased RBC transfusion exposure, possibly related to the more invasive nature of the surgery, a preselection for higher-risk surgeries that may not be amenable to a minimally invasive approach, and the reduced venous blood loss in minimally invasive surgeries from venous collapse due to pneumoperitoneum-related pressure increases. Nonelective surgeries were also associated with increased RBC transfusion, likely due to the inability to correct preoperative anemia and increased illness acuity and severity.

Using a large multicenter cohort, we used high-fidelity datasets to reliably capture patient demographics, surgical information, and transfusion practices. We comprehensively described the transfusion practices in 85 noncardiac surgeries at high risk for RBC transfusion, involving approximately 25,000 patients. In doing so, we have addressed a knowledge gap by describing real-world transfusion practices in high-risk noncardiac surgery.

Our study describes transfusion practices in 5 Canadian centers; however, institutional differences in surgical practice and transfusion rates may impact generalizability, particularly in resource-limited settings where perioperative practice may vary. We described transfusion practices from 2014 to 2016, which may not reflect recent blood conservation initiatives and may therefore overestimate contemporary transfusion rates [19]. Surgical information was obtained from the DAD, and although standardized, the CCI codes do not directly reflect surgical descriptions in clinical practice. We tried to mitigate this potential limitation by involving surgical content experts and by using both administrative CCI code definitions as well as governmental descriptions to finalize our surgical cohort. The relationship between preoperative anemia and transfusion was difficult to ascertain because preoperative hemoglobin values were limited to 67% of our cohort, with reduced capture in elective surgeries. This likely relates to perioperative guidelines which discourage routine blood work prior to surgery [31]. Furthermore, it is possible that receipt of transfusion may not reflect true transfusion demand.

In the era of blood conservation, we have described the transfusion practices in major noncardiac surgeries at high risk for RBC transfusion. This has implications for patient consent discussions, preoperative surgical planning, and blood bank inventory management.

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## Conflicts of interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmrv.2020.08.001.

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**Appendix A.** Canadian Classification of Health Interventions (CCI) codes and their respective surgical descriptions. Using the Canadian Classification of Health Interventions alphabetical index(21, 22), Winnipeg Regional Health Authority SIMS Procedure Catalog(23), and with input from surgeons and anesthesiologists with content expertise, the CCI codes were reviewed and amalgamated (as needed) to reflect the clinical description of the surgery performed. The CCI codes were stratified by surgical approach to allow distinction between open and minimally invasive surgeries. Using the letters in the 6$^{th}$ and 7$^{th}$ positions of the CCI codes, letters AA to KS were assigned as 'minimally invasive'; letters KZ to XY were assigned as 'open.'

| **Surgery name** | **CCI codes** |
|---|---|
| Abdominal aortic bypass | 1.ID.76, 1.ID.89, 1.ID.86, 1.ID.87, I.KA.76 |
| Abdominal aortic repair | 1.KA.80 |
| Abdominal artery dilation | 1.KE.50 |
| Abdominal artery repair | 1.KE.80 |
| Abdominopelvic neoplasm resection | 1.OT.91 |
| Above knee amputation | 1.VC.93 |
| Below knee amputation | 1.VQ.93 |
| Bile duct excision | 1.OE.87, 1.OE.89 |
| Bladder diverticulectomy (endoscopic) | 1.PM.87 |
| Cholecystectomy | 1.OD.57, 1.OD.89 |
| Colectomy | 1.NM.87, 1.NM.89, 1.NM.91 |
| Colonic anastomosis | 1.NM.82 |
| Colostomy | 1.NM.77 |
| Craniotomy/craniectomy | 1.EA.72, 1.EA.87, 1.AJ.87, 1.AN.87 |
| Cystectomy | 1.PM.87, 1.PM.91, 1.PM.92 |
| Cystectomy (partial) | 1.PM.59 |
| Decortication, pleurectomy, pleurodesis | 1.GV.87, 1.GV.89 |
| Diaphragmatic herniorrhaphy | 1.GX.80 |
| Diskectomy with insertion of spacer | 1.SE.53 |
| Elbow arthroplasty | 1.TM.53 |
| Enterectomy | 1.NK.87 |
| Enterostomy | 1.NK.76, 1.NK.77 |
| Esophageal diverticulectomy (endoscopic) | 1.NA.87 |
| Esophagectomy | 1.NA.87, 1.NA.88, 1.NA.89, 1.NA.90, 1.NA.91 |
| Femur fixation | 1.VC.74 |
| Femur ostectomy | 1.VC.87 |
| Foot amputation | 1.WI.93, 1.WJ.93, 1.WL.93, 1.WN.93 |

| | |
|---|---|
| Gastrectomy | 1.NF.87, 1.NF.89, 1.NF.90, 1.NF.91 |
| Gastroplasty | 1.NF.80 |
| Glossectomy | 1.FJ.87, 1.FJ.91 |
| Hip arthroplasty | 1.VA.53 |
| Hip joint fixation | 1.VA.74 |
| Humerus ORIF | 1.TK.74 |
| Hysterectomy | 1.RM.87, 1.RM.89, 1.RM.91 |
| Intervertebral disk resection | 1.SE.89 |
| Intra-abdominal wound repair | 1.OT.80 |
| Intracranial vessel embolization | 1.JW.51 |
| Knee arthroscopy | 1.VG.87 |
| Knee debridement/repair (open) | 1.VG.87 |
| Large vessel aneurysmorrhaphy | 1.JM.80, 1.KE.80, 1.KG.80, 1.KT.80 |
| Large vessel arterial bypass | 1.JM.76, 1.KE.76, 1.KG.76, 1.KT.76 |
| Large vessel endarterectomy/thrombectomy | 1.KA.57, 1.KE.57, 1.KG.57, 1.KT.57 |
| Leg amputation stump revision | 1.VX.59 |
| Lobectomy | 1.GR.87, 1.GR.89, 1.GR.91 |
| Lower limb soft tissue resection | 1.VX.87 |
| Lower limb endarterectomy with resection | 1.KG.87 |
| Lower limb arterial bypass | 1.KR.76 |
| Lower limb dilation NEC | 1.KG.50 |
| Lysis of adhesions | 1.OT.72, 1.NP.72 |
| Mandibulectomy | 1.EE.87, 1.EE.91 |
| Meningectomy | 1.AA.87 |
| Nephrectomy | 1.PC.87, 1.PC.89, 1.PC.90, 1.PC.91 |
| Omentectomy | 1.OT.87 |
| Oopherectomy | 1.RB.87, 1.RB.89 |
| Mesh implant removal of chest/abdomen | 1.SY.55 |
| Pancreatic resection | 1.OJ.76, 1.OJ.87, 1.OJ.89, 1.OK.87, 1.OK.89, 1.OK.91 |
| Partial hepatectomy | 1.OA.87 |
| Pelvic ORIF | 1.SQ.74, 1.SQ.53 |
| Pelvic osteoplasty/osteotomy | 1.SQ.80, 1.SQ.87 |
| Pneumonectomy | 1.GT.89, 1.GT.91 |
| Proctectomy | 1.NQ.87, 1.NQ.89 |
| Prostatectomy | 1.QT.89, 1.QT.91 |

| | |
|---|---|
| Renal transplant | 1.PC.85 |
| Repair skin of leg | 1.YV.80 |
| Resection of skin on abdomen/trunk | 1.YS.87 |
| Resection of soft tissue of chest/abdomen | 1.SZ.87 |
| Scalp resection | 1.YA.87 |
| Shoulder ORIF | 1.TA.74 |
| Skull base resection | 1.EA.92 |
| Small intestine repair | 1.NK.80 |
| Spinal decompression | 1.AW.72 |
| Spinal cord resection | 1.AW.87 |
| Spinal decompression with instrumentation | 1.SC.74 |
| Spinal fusion | 1.SC.75 |
| Spinal fusion with vertebrectomy | 1.SC.89 |
| Splenectomy | 1.OB.89 |
| Total salpingooopherectomy | 1.RD.89 |
| Foot and ankle soft tissue debridement | 1.WV.59 |

ORIF = open reduction internal fixation; NEC = not elsewhere classified

**Appendix B.** Surgery-specific description of baseline demographics

| Surgical domain | Surgery | Surgical approach | # surgeries / year | Mean age (SD) | Sex (% female) | Mean Charlson CI (SD) | Mean pre-op Hb (g/L) (SD) | % transfused | Mean # RBC units* (SD) | Transfusion burden (# units / year) |
|---|---|---|---|---|---|---|---|---|---|---|
| General surgery | Abdominopelvic neoplasm resection | O | 17 | 55.5 (14.6) | 67 | 2.7 (2.6) | 122.4 (19.1) | 25.0 | 5.8 (6.8) | 75 |
| | Bile duct excision | O | 12 | 63.2 (15) | 43 | 1.6 (2.8) | 124.7 (19.5) | 20.0 | 7.0 (2.0) | 14 |
| | Cholecystectomy | O | 70 | 60 (16.5) | 50 | 0.6 (1.7) | 122.8 (20) | 9.1 | 19.0 (2.5) | 47 |
| | Colectomy | MI | 202 | 64.4 (15) | 48 | 2.1 (2.7) | 119.2 (22.4) | 11.1 | 67.0 (1.9) | 129 |
| | Colectomy | O | 345 | 64.7 (16.4) | 51 | 2.2 (2.9) | 114.9 (22.7) | 25.0 | 259.0 (2.3) | 603 |
| | Colonic anastomosis | O | 19 | 56.1 (13.7) | 52 | 0.3 (1.1) | 129 (16.3) | 7.1 | 4.0 (2.0) | 8 |
| | Colostomy | MI | 20 | 58.2 (15.1) | 48 | 2.6 (2.8) | 109.8 (21.3) | 5.0 | 3.0 (2.3) | 7 |
| | Colostomy | O | 54 | 64.5 (15.8) | 49 | 3.5 (3.4) | 111 (23.8) | 16.8 | 18.0 (2.3) | 41 |
| | Enterectomy | MI | 32 | 53.5 (19.3) | 58 | 0.9 (2.1) | 127.1 (20.3) | 7.4 | 7.0 (1.9) | 13 |
| | Enterectomy | O | 165 | 60.6 (19.4) | 55 | 0.9 (2.0) | 123.3 (22.5) | 17.0 | 84.0 (2.8) | 233 |
| | Enterostomy | MI | 14 | 61 (17.1) | 40 | 3.0 (3.4) | 112.7 (21.8) | 7.0 | 3.0 (3.0) | 9 |
| | Enterostomy | O | 37 | 61.6 (16.1) | 38 | 3.4 (3.4) | 113.1 (22.9) | 14.3 | 16.0 (2.3) | 37 |
| | Esophageal diverticulectomy | MI | 18 | 63.2 (11.6) | 21 | 3.0 (3.1) | 128.9 (18.6) | 15.1 | 8.0 (1.3) | 10 |
| | Esophagectomy | O | 23 | 64.6 (11) | 32 | 2.1 (2.8) | 128.2 (11.7) | 19.1 | 13.0 (2.2) | 28 |
| | Gastrectomy | O | 46 | 64.4 (13.5) | 38 | 1.6 (2.3) | 115.7 (24.9) | 30.2 | 42.0 (2.7) | 112 |
| | Gastroplasty | O | 11 | 51.3 (21.1) | 39 | 0.8 (1.6) | 125.7 (29.8) | 36.4 | 12.0 (2.3) | 27 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Intra-abdominal wound repair | O | 17 | 44.8 (13.5) | 74 | 0.1 (0.3) | 127 (17.8) | 6.0 | 3.0 (2.3) | 7 |
| | Lysis of adhesions | O | 71 | 64.8 (18.6) | 57 | 0.7 (1.6) | 126.9 (22.1) | 5.6 | 12.0 (2.5) | 30 |
| | Omentectomy | O | 26 | 57 (13.4) | 66 | 2.8 (3.2) | 122 (21.9) | 23.4 | 18.0 (3.8) | 68 |
| | Pancreatic resection | O | 96 | 63.2 (12.9) | 51 | 2.8 (3.0) | 125 (20.1) | 19.8 | 57.0 (2.9) | 165 |
| | Partial hepatectomy | O | 94 | 61.4 (12.3) | 44 | 4.4 (3.0) | 132.2 (17.2) | 15.3 | 43.0 (2.6) | 113 |
| | Proctectomy | O | 206 | 63 (14.2) | 40 | 2.4 (2.6) | 125.6 (20) | 16.7 | 103.0 (2.0) | 203 |
| | Small intestine repair | MI | 22 | 50.4 (18.4) | 44 | 1.0 (1.4) | 129.7 (27) | 9.3 | 4.0 (3.0) | 12 |
| | Small intestine repair | O | 29 | 55.6 (19.9) | 46 | 1.3 (1.9) | 129.3 (29) | 25.3 | 22.0 (2.5) | 56 |
| | Splenectomy | O | 17 | 49.1 (17.5) | 56 | 0.6 (1.5) | 107.1 (26.4) | 46.0 | 23.0 (4.8) | 111 |
| Gynecology | Hysterectomy | O | 1127 | 52.6 (12.8) | 100 | 1.2 (2.1) | 124.9 (18.2) | 9.5 | 320.0 (2.4) | 773 |
| | Total salpingoopherectomy | O | 137 | 49.8 (15.8) | 100 | 1.2 (2.3) | 122.8 (16.8) | 9.5 | 39.0 (2.1) | 81 |
| Neurosurgery | Intracranial vessel embolization | O | 63 | 55 (11.1) | 77 | 1.1 (0.5) | 130.6 (16.3) | 11.6 | 22.0 (2.0) | 43 |
| | Meningectomy | O | 36 | 59.7 (13.3) | 61 | 0.5 (1.4) | 138.2 (18.2) | 11.2 | 12.0 (2.6) | 31 |
| Orthopedic Surgery | Above knee amputation | O | 49 | 72.4 (15.3) | 49 | 1.6 (2.1) | 104.1 (19.5) | 32.4 | 48.0 (2.0) | 94 |
| | Below knee amputation | O | 102 | 62.1 (13.2) | 28 | 0.9 (1.3) | 101.9 (19.4) | 30.0 | 92.0 (1.9) | 177 |
| | Elbow arthroplasty | O | 28 | 59 (15.9) | 76 | 0.4 (0.7) | 126.5 (14.7) | 6.0 | 5.0 (1.8) | 9 |
| | Femur fixation | MI | 50 | 75.2 (17.8) | 58 | 1.2 (2.1) | 115.6 (18.9) | 30.0 | 45.0 (1.7) | 76 |
| | Femur ORIF | O | 558 | 74.5 (18.6) | 69 | 0.9 (1.8) | 115.1 (18.5) | 34.8 | 583.0 (1.9) | 1094 |
| | Femur ostectomy | O | 22 | 52.4 (19.9) | 48 | 2.4 (3.3) | 122.9 (20.9) | 23.9 | 16.0 (2.6) | 42 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Foot amputation | O | 63 | 64 (15.2) | 34 | 2.0 (1.7) | 105.9 (18) | 12.2 | 23.0 (2.1) | 48 |
| | Hip arthroplasty | O | 1577 | 68.1 (14.4) | 55 | 0.4 (1.2) | 128.7 (17.7) | 10.1 | 480.0 (1.9) | 896 |
| | Hip joint fixation | MI | 17 | 74.5 (18.3) | 70 | 1.0 (1.6) | 118.7 (15.9) | 8.0 | 4.0 (1.8) | 7 |
| | Hip ORIF | O | 122 | 73.1 (18.1) | 64 | 0.7 (1.4) | 120 (17.8) | 21.9 | 80.0 (1.8) | 141 |
| | Humerus ORIF | O | 106 | 54.4 (18.4) | 57 | 0.7 (1.9) | 122.5 (19) | 7.5 | 24.0 (1.7) | 40 |
| | Knee arthroscopy | MI | 21 | 49 (18.5) | 44 | 0.3 (0.8) | 115.2 (23.6) | 7.8 | 5.0 (3.0) | 15 |
| | Knee debridement/repair | O | 13 | 62.5 (19.1) | 39 | 0.4 (0.8) | 116 (21) | 13.2 | 5.0 (1.6) | 8 |
| | Leg amputation stump revision | O | 19 | 52.6 (17.5) | 36 | 0.7 (1.4) | 114.6 (22) | 12.1 | 7.0 (3.3) | 23 |
| | Pelvic ORIF | O | 37 | 52 (20) | 30 | 0.2 (0.8) | 117.6 (18.8) | 26.4 | 29.0 (2.6) | 75 |
| | Pelvic osteoplasty/ osteotomy | O | 17 | 36.7 (17.5) | 67 | 1.0 (2.6) | 128 (19.1) | 15.4 | 8.0 (2.0) | 16 |
| | Shoulder ORIF | O | 35 | 58.3 (15.7) | 66 | 0.1 (0.3) | 121.6 (20.2) | 12.3 | 13.0 (1.9) | 25 |
| Otolaryngology | Glossectomy | O | 46 | 60.5 (13.3) | 43 | 3.5 (2.9) | 131.7 (14.7) | 8.8 | 12.0 (1.9) | 23 |
| | Mandibulectomy | O | 17 | 63.3 (15.5) | 48 | 2.4 (3.0) | 125.1 (15.9) | 6.0 | 3.0 (2.3) | 7 |
| Plastic surgery | Foot and ankle soft tissue debridement | O | 11 | 52.6 (12.7) | 29 | 1.3 (1.4) | 112.9 (20.1) | 5.9 | 2.0 (2.0) | 4 |
| | Lower extremity soft tissue resection | O | 35 | 60.1 (15.6) | 46 | 1.7 (2.0) | 128.9 (18.7) | 14.2 | 15.0 (2.2) | 33 |
| | Mesh implant removal of chest/abdomen | O | 24 | 57.9 (14.8) | 41 | 1.5 (1.6) | 96.5 (18.1) | 5.5 | 4.0 (2.0) | 8 |
| | Repair – leg skin | O | 16 | 51.7 (19) | 47 | 0.2 (0.8) | 112.6 (19.4) | 12.2 | 6.0 (2.2) | 13 |
| | Resection – skin on abdomen/trunk | O | 18 | 52 (16.1) | 46 | 0.4 (0.8) | 130.1 (26.2) | 11.1 | 6.0 (2.0) | 12 |
| | Resection – soft issue on abdomen/trunk | O | 23 | 52.9 (18.3) | 62 | 1.2 (2.2) | 129.6 (19.3) | 5.8 | 4.0 (2.8) | 11 |

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|---|---|---|---|---|---|---|---|---|---|---|
| | Scalp resection | O | 10 | 68.2 (15.7) | 19 | 1.9 (2.4) | 123.2 (22.2) | 6.5 | 2.0 (1.5) | 3 |
| Spine surgery | Diskectomy with insertion of spacer | O | 50 | 54 (13) | 37 | 0.2 (1.0) | 138.6 (15.1) | 6.0 | 9.0 (2.4) | 22 |
| | Intervertebral disk resection | O | 14 | 47.1 (17.1) | 57 | 0.1 (0.3) | 137.7 (18.8) | 7.1 | 3.0 (4.3) | 13 |
| | Skull base resection | O | 19 | 57.3 (15.3) | 66 | 1.3 (2.3) | 136 (13.8) | 17.9 | 10.0 (2.6) | 26 |
| | Spinal decompression | O | 18 | 62.4 (13.8) | 36 | 0.2 (1.0) | 128.6 (24.1) | 16.4 | 9.0 (3.1) | 28 |
| | Spinal cord resection | O | 15 | 47.8 (17.8) | 58 | 0.8 (1.9) | 137.3 (14.2) | 8.9 | 4.0 (2.8) | 11 |
| | Spinal decompression with instrumentation | O | 40 | 56.7 (15.8) | 45 | 0.6 (1.6) | 131.9 (20.3) | 9.9 | 12.0 (3.9) | 47 |
| | Spinal fusion | O | 531 | 57 (15.4) | 41 | 0.2 (1.0) | 132.4 (19.1) | 16.1 | 257.0 (2.6) | 677 |
| | Spinal fusion with vertebrectomy | O | 57 | 56.8 (13.6) | 49 | 0.8 (2.1) | 126.7 (20.7) | 38.4 | 66.0 (3.5) | 233 |
| Thoracic surgery | Decortication, pleurectomy and pleurodesis | MI | 33 | 48.3 (19.6) | 28 | 0.6 (1.6) | 120.7 (25) | 17.2 | 17.0 (2.0) | 34 |
| | Decortication, pleurectomy and pleurodesis | O | 29 | 54.1 (16.6) | 26 | 0.5 (1.8) | 107 (19.8) | 26.4 | 23.0 (2.0) | 46 |
| | Diaphragmatic herniorrhaphy | O | 17 | 51.9 (21.2) | 41 | 0.1 (0.2) | 134 (19.9) | 17.7 | 9.0 (2.1) | 19 |
| | Lobectomy | O | 148 | 63.6 (13.6) | 50 | 2.9 (2.6) | 128.8 (19.5) | 14.8 | 66.0 (2.7) | 181 |
| | Pneumonectomy | O | 18 | 62.8 (12.6) | 43 | 3.4 (3.0) | 131 (18) | 22.2 | 12.0 (2.3) | 28 |
| Urology | Bladder diverticulectomy | MI | 154 | 73.2 (13.5) | 27 | 2.2 (1.7) | 116.4 (23.8) | 5.4 | 25.0 (1.9) | 47 |
| | Cystectomy | O | 53 | 65.6 (11.5) | 28 | 2.8 (2.6) | 125.9 (18.3) | 49.1 | 78.0 (3.1) | 239 |
| | Cystectomy (partial) | MI | 26 | 66.8 (17.2) | 17 | 0.9 (1.8) | 117.6 (25.8) | 7.7 | 6.0 (2.8) | 17 |
| | Nephrectomy | O | 144 | 60.1 (11.8) | 34 | 2.2 (2.0) | 128.9 (21.7) | 19.0 | 82.0 (3.9) | 319 |

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|---|---|---|---|---|---|---|---|---|---|---|
| | Prostatectomy | O | 98 | 63.1 (5.5) | 0 | 2.5 (2.0) | 147.1 (13.3) | 9.2 | 27.0 (1.9) | 52 |
| | Renal transplant | O | 117 | 52.1 (14.1) | 37 | 1.9 (0.9) | 109.9 (13.4) | 19.9 | 70.0 (2.0) | 142 |
| Vascular surgery | Abdominal aortic bypass | O | 63 | 65.8 (9.4) | 30 | 1.0 (0.9) | 135.6 (19.6) | 38.3 | 72.0 (2.9) | 210 |
| | Abdominal aortic repair | MI | 156 | 76.5 (8.2) | 26 | 1.3 (0.8) | 132.2 (18.2) | 12.6 | 59.0 (2.8) | 165 |
| | Abdominal aortic repair | O | 112 | 70.8 (8.6) | 23 | 1.2 (1.1) | 131.2 (21.9) | 46.3 | 156.0 (4.6) | 720 |
| | Abdominal artery dilation | MI | 10 | 68.2 (10.8) | 45 | 1.7 (1.6) | 121.7 (18.7) | 19.4 | 6.0 (1.7) | 10 |
| | Abdominal artery repair | MI | 11 | 72.9 (14.2) | 6 | 0.6 (0.8) | 130.4 (20.9) | 15.6 | 5.0 (1.2) | 6 |
| | Large vessel aneurysmorrhaphy | O | 42 | 59.1 (19.9) | 29 | 0.6 (1.1) | 122.6 (22.1) | 24.8 | 31.0 (3.4) | 105 |
| | Large vessel arterial bypass | O | 340 | 68.5 (11.4) | 34 | 1.0 (1.3) | 126.2 (21.9) | 20.2 | 206.0 (2.4) | 493 |
| | Large vessel endarterectomy/ thrombectomy | O | 139 | 72.3 (11.8) | 31 | 1.1 (1.2) | 127.7 (21.1) | 13.9 | 58.0 (2.6) | 148 |
| | Lower limb endarterectomy with resection | O | 18 | 65.4 (14.3) | 37 | 1.0 (1.5) | 129.2 (18.7) | 14.8 | 8.0 (2.9) | 23 |
| | Lower limb arterial bypass | O | 14 | 69 (12) | 32 | 0.7 (0.9) | 129.5 (25) | 14.6 | 6.0 (4.5) | 27 |
| | Lower limb arterial dilation (NEC) | MI | 12 | 71 (12.3) | 36 | 2.3 (1.1) | 118.7 (22.7) | 8.3 | 3.0 (1.0) | 3 |

*Mean # of RBC transfusions in those patients who received a RBC transfusion; O = open; MI = minimally invasive; SD=standard deviation; CI = comorbidity index; Pre-op = pre-operative; Hb = hemoglobin; RBC = red blood cells; ORIF = open reduction internal fixation; NEC = not elsewhere classified

**Appendix C.** Surgery-specific transfusion outcomes

| Surgical domain | Surgery name | Surgical approach | # surgeries / year | % transfused RBCs | | | Mean # RBC units transfused (SD) | | % ≥5 RBC units | RBC burden (# units / year) | % tranfused Platelets | % tranfused Plasma |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total | I | P | All patients | Transfused patients | | | | |
| General surgery | Abdominopelvic neoplasm resection | O | 17 | 25 | 17.3 | 17.3 | 1.4 (4.2) | 5.8 (6.8) | 9.6 | 75 | 5.8 | 7.7 |
| | Bile duct excision | O | 12 | 20 | 5.7 | 14.3 | 0.4 (0.9) | 2 (0.8) | 0 | 14 | 0 | 0 |
| | Cholecystectomy | O | 70 | 9.1 | 2.4 | 7.6 | 0.2 (1.1) | 2.5 (2.7) | 1.0 | 47 | 1.0 | 1.4 |
| | Colectomy | MI | 202 | 11.1 | 4.6 | 8.3 | 0.2 (0.7) | 1.9 (1.1) | 0.3 | 129 | 0.5 | 1.2 |
| | Colectomy | O | 345 | 25 | 13.2 | 15.9 | 0.6 (1.3) | 2.3 (1.8) | 2.4 | 603 | 1.6 | 4.7 |
| | Colonic anastomosis | O | 19 | 7.1 | 0 | 7.1 | 0.1 (0.5) | 2 (0) | 0 | 8 | 0 | 0 |
| | Colostomy | MI | 20 | 5 | 0 | 5 | 0.1 (0.6) | 2.3 (1.5) | 0 | 7 | 0 | 0 |
| | Colostomy | O | 54 | 16.8 | 6.5 | 12.1 | 0.4 (1.2) | 2.3 (2.1) | 0.9 | 41 | 1.9 | 5.6 |
| | Enterectomy | MI | 32 | 7.4 | 4.2 | 3.2 | 0.1 (0.6) | 1.9 (1.1) | 0 | 13 | 1.1 | 3.2 |
| | Enterectomy | O | 165 | 17 | 5.5 | 14.2 | 0.5 (2.0) | 2.8 (4.1) | 0.4 | 233 | 1.6 | 4.7 |
| | Enterostomy | MI | 14 | 7 | 0 | 7 | 0.2 (1.0) | 3 (2.6) | 2.3 | 9 | 0 | 0 |
| | Enterostomy | O | 37 | 14.3 | 8.0 | 9.8 | 0.3 (1.0) | 2.3 (1.7) | 1.8 | 37 | 0.9 | 3.6 |
| | Esophageal diverticulectomy | MI | 18 | 15.1 | 5.7 | 9.4 | 0.2 (0.5) | 1.3 (0.5) | 0 | 10 | 0 | 0 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Esophagectomy | O | 23 | 19.1 | 2.9 | 19.1 | 0.4 (1.0) | 2.2 (1.1) | 0 | 28 | 0 | 1.5 |
| | Gastrectomy | O | 46 | 30.2 | 18.7 | 18.7 | 0.8 (1.7) | 2.7 (2.2) | 3.6 | 112 | 1.4 | 4.3 |
| | Gastroplasty | O | 11 | 36.4 | 9.1 | 36.4 | 0.8 (1.4) | 2.3 (1.4) | 3.0 | 27 | 3.0 | 12.1 |
| | Intra-abdominal wound repair | O | 17 | 6 | 6 | 2 | 0.1 (0.6) | 2.3 (0.6) | 0 | 7 | 2.0 | 4.0 |
| | Lysis of adhesions | O | 71 | 5.6 | 2.3 | 5.2 | 0.1 (0.7) | 2.5 (1.6) | 0.5 | 30 | 0.9 | 3.3 |
| | Omentectomy | O | 26 | 23.4 | 10.4 | 18.2 | 0.9 (3.1) | 3.8 (5.6) | 5.2 | 68 | 2.6 | 2.6 |
| | Pancreatic resection | O | 96 | 19.8 | 10.4 | 14.2 | 0.6 (2.0) | 2.9 (3.8) | 2.4 | 165 | 1.0 | 3.1 |
| | Partial hepatectomy | O | 94 | 15.3 | 9.2 | 10.3 | 0.4 (1.2) | 2.6 (1.9) | 1.8 | 113 | 1.4 | 4.3 |
| | Proctectomy | O | 206 | 16.7 | 8.6 | 10 | 0.3 (0.9) | 2 (1.3) | 0.8 | 203 | 0.3 | 1.8 |
| | Small intestine repair | MI | 22 | 9.3 | 7 | 7 | 0.3 (1.0) | 3 (1.8) | 2.3 | 12 | 2.3 | 4.7 |
| | Small intestine repair | O | 29 | 25.3 | 12.6 | 18.4 | 0.6 (1.4) | 2.5 (1.6) | 4.6 | 56 | 2.3 | 11.5 |
| | Splenectomy | O | 17 | 46 | 36 | 26 | 2.2 (4.7) | 4.8 (6.1) | 12.0 | 111 | 18.0 | 12.0 |
| Gynecology | Hysterectomy | O | 1127 | 9.5 | 2.9 | 7.8 | 0.2 (0.9) | 2.4 (1.7) | 0.8 | 773 | 0.4 | 0.6 |
| | Total salpingoopherectomy | O | 137 | 9.5 | 2.7 | 8.3 | 0.2 (0.7) | 2.1 (1.1) | 0.5 | 81 | 0 | 0.5 |
| Neurosurgery | Intracranial vessel embolization | O | 63 | 11.6 | 5.3 | 7.9 | 0.2 (0.9) | 2 (1.7) | 1.1 | 43 | 1.1 | 0.5 |
| | Meningectomy | O | 36 | 11.2 | 9.3 | 3.7 | 0.3 (0.9) | 2.6 (1.2) | 0.9 | 31 | 0 | 0.9 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Orthopedic Surgery | Above knee amputation | O | 49 | 32.4 | 8.1 | 27.7 | 0.6 (1.2) | 2 (1.4) | 2.0 | 94 | 2.7 | 1.4 |
| | Below knee amputation | O | 102 | 30 | 5.9 | 28 | 0.6 (1.0) | 1.9 (1) | 1.0 | 177 | 0 | 0.7 |
| | Elbow arthroplasty | O | 28 | 6 | 1.2 | 4.8 | 0.1 (0.4) | 1.8 (0.4) | 0 | 9 | 0 | 0 |
| | Femur fixation | MI | 50 | 30 | 4.0 | 27.3 | 0.5 (0.9) | 1.7 (0.8) | 0 | 76 | 0 | 1.3 |
| | Femur ORIF | O | 558 | 34.8 | 8.5 | 30.1 | 0.7 (1.1) | 1.9 (1.2) | 1.0 | 1094 | 0.9 | 0.7 |
| | Femur ostectomy | O | 22 | 23.9 | 9.0 | 19.4 | 0.6 (1.4) | 2.6 (1.7) | 3.0 | 42 | 0 | 0 |
| | Foot amputation | O | 63 | 12.2 | 0.5 | 12.2 | 0.3 (0.9) | 2.1 (1.5) | 1.1 | 48 | 0.5 | 0.5 |
| | Hip arthroplasty | O | 1577 | 10.1 | 2.9 | 8.4 | 0.2 (0.7) | 1.9 (1.2) | 0.4 | 896 | 0.4 | 0.2 |
| | Hip joint fixation | MI | 17 | 8 | 0 | 8 | 0.1 (0.5) | 1.8 (0.5) | 0 | 7 | 0 | 0 |
| | Hip ORIF | O | 122 | 21.9 | 3.8 | 19.9 | 0.4 (0.9) | 1.8 (1) | 0.5 | 141 | 0 | 0.5 |
| | Humerus ORIF | O | 106 | 7.5 | 2.5 | 5 | 0.1 (0.5) | 1.7 (1) | 0.3 | 40 | 0 | 0.6 |
| | Knee arthroscopy | MI | 21 | 7.8 | 1.6 | 7.8 | 0.2 (0.9) | 3 (1.9) | 1.6 | 15 | 1.6 | 1.6 |
| | Knee debridement/repair | O | 13 | 13.2 | 2.6 | 10.5 | 0.2 (0.6) | 1.6 (0.5) | 0 | 8 | 0 | 2.6 |
| | Leg amputation stump revision | O | 19 | 12.1 | 5.2 | 8.6 | 0.4 (1.4) | 3.3 (2.9) | 3.4 | 23 | 1.7 | 5.2 |
| | Pelvic ORIF | O | 37 | 26.4 | 19.1 | 13.6 | 0.7 (1.6) | 2.6 (2.1) | 4.5 | 75 | 2.7 | 1.8 |
| | Pelvic osteoplasty/ osteotomy | O | 17 | 15.4 | 7.7 | 9.6 | 0.3 (0.8) | 2 (0.8) | 0 | 16 | 0 | 1.9 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Shoulder ORIF | O | 35 | 12.3 | 3.8 | 11.3 | 0.2 (0.7) | 1.9 (1) | 0 | 25 | 0 | 0 |
| Otolaryngology | Glossectomy | O | 46 | 8.8 | 5.1 | 5.1 | 0.2 (0.6) | 1.9 (0.7) | 0 | 23 | 0 | 0 |
| | Mandibulectomy | O | 17 | 6 | 2 | 4 | 0.1 (0.6) | 2.3 (1.5) | 0 | 7 | 0 | 0 |
| Plastic surgery | Foot and ankle soft tissue debridement | O | 11 | 5.9 | 0 | 5.9 | 0.1 (0.5) | 2 (0) | 0 | 4 | 0 | 0 |
| | Lower extremity soft tissue resection | O | 35 | 14.2 | 8.5 | 7.5 | 0.3 (0.9) | 2.2 (1.3) | 0.9 | 33 | 0 | 0 |
| | Mesh implant removal of chest/abdomen | O | 24 | 5.5 | 0 | 5.5 | 0.1 (0.5) | 2 (0.8) | 0 | 8 | 0 | 1.4 |
| | Repair – leg skin | O | 16 | 12.2 | 2 | 12.2 | 0.3 (0.8) | 2.2 (1) | 0 | 13 | 2.0 | 0 |
| | Resection – skin on abdomen/trunk | O | 18 | 11.1 | 0 | 11.1 | 0.2 (0.7) | 2 (0.9) | 0 | 12 | 0 | 0 |
| | Resection – soft issue on abdomen/trunk | O | 23 | 5.8 | 2.9 | 5.8 | 0.2 (0.7) | 2.8 (1.7) | 1.4 | 11 | 0 | 1.4 |
| | Scalp resection | O | 10 | 6.5 | 3.2 | 3.2 | 0.1 (0.4) | 1.5 (0.7) | 0 | 3 | 3.2 | 0 |
| Spine surgery | Diskectomy with insertion of spacer | O | 50 | 6 | 3.4 | 4.7 | 0.1 (0.7) | 2.4 (1.3) | 0.7 | 22 | 0.7 | 0 |
| | Intervertebral disk resection | O | 14 | 7.1 | 7.1 | 4.8 | 0.3 (1.2) | 4.3 (1.5) | 2.4 | 13 | 0 | 2.4 |
| | Skull base resection | O | 19 | 17.9 | 16.1 | 1.8 | 0.5 (1.2) | 2.6 (1.5) | 3.6 | 26 | 0 | 1.8 |
| | Spinal decompression | O | 18 | 16.4 | 10.9 | 14.5 | 0.5 (1.5) | 3.1 (2.4) | 3.6 | 28 | 1.8 | 3.6 |
| | Spinal cord resection | O | 15 | 8.9 | 6.7 | 6.7 | 0.2 (0.9) | 2.8 (1.5) | 2.2 | 11 | 0 | 0 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Spinal decompression with instrumentation | O | 40 | 9.9 | 8.3 | 6.6 | 0.4 (1.3) | 3.9 (1.7) | 2.5 | 47 | 1.7 | 3.3 |
| | Spinal fusion | O | 531 | 16.1 | 8.5 | 12.1 | 0.4 (1.2) | 2.6 (1.8) | 2.3 | 677 | 0.5 | 1.3 |
| | Spinal fusion with vertebrectomy | O | 57 | 38.4 | 20.3 | 29.7 | 1.4 (2.7) | 3.5 (3.5) | 8.7 | 233 | 4.1 | 7.6 |
| Thoracic surgery | Decortication, pleurectomy and pleurodesis | MI | 33 | 17.2 | 9.1 | 11.1 | 0.3 (0.9) | 2 (1.3) | 1.0 | 34 | 1.0 | 0 |
| | Decortication, pleurectomy and pleurodesis | O | 29 | 26.4 | 9.2 | 23 | 0.5 (1.2) | 2 (1.5) | 2.3 | 46 | 1.1 | 4.6 |
| | Diaphragmatic herniorrhaphy | O | 17 | 17.7 | 7.8 | 11.8 | 0.4 (1.0) | 2.1 (1.3) | 2.0 | 19 | 0 | 2.0 |
| | Lobectomy | O | 148 | 14.8 | 5.8 | 10.8 | 0.4 (1.6) | 2.7 (3.3) | 1.6 | 181 | 1.8 | 2.9 |
| | Pneumonectomy | O | 18 | 22.2 | 11.1 | 18.5 | 0.5 (1.2) | 2.3 (1.4) | 1.9 | 28 | 0 | 0 |
| Urology | Bladder diverticulectomy | MI | 154 | 5.4 | 1.5 | 4.1 | 0.1 (0.5) | 1.9 (0.8) | 0 | 47 | 0.2 | 0.2 |
| | Cystectomy | O | 53 | 49.1 | 42.1 | 20.1 | 1.5 (2.0) | 3.1 (1.8) | 6.3 | 239 | 0.6 | 4.4 |
| | Cystectomy (partial) | MI | 26 | 7.7 | 3.8 | 5.1 | 0.2 (1.0) | 2.8 (2.8) | 1.3 | 17 | 0 | 0 |
| | Nephrectomy | O | 144 | 19 | 13.7 | 10.9 | 0.7 (2.2) | 3.9 (3.8) | 4.6 | 319 | 2.8 | 5.3 |
| | Prostatectomy | O | 98 | 9.2 | 3.4 | 7.5 | 0.2 (0.6) | 1.9 (0.8) | 0 | 52 | 0.3 | 0 |
| | Renal transplant | O | 117 | 19.9 | 2.3 | 18.2 | 0.4 (1.0) | 2 (1.2) | 0.6 | 142 | 0.6 | 1.4 |
| Vascular surgery | Abdominal aortic bypass | O | 63 | 38.3 | 26.1 | 20.7 | 1.1 (2.5) | 2.9 (3.4) | 4.8 | 210 | 4.3 | 10.6 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Abdominal aortic repair | MI | 156 | 12.6 | 8.8 | 6.4 | 0.4 (1.3) | 2.8 (2.7) | 1.7 | 165 | 1.3 | 1.7 |
| | Abdominal aortic repair | O | 112 | 46.3 | 33.8 | 25.2 | 2.1 (4.6) | 4.6 (5.8) | 14.8 | 720 | 11.3 | 18.7 |
| | Abdominal artery dilation | MI | 10 | 19.4 | 9.7 | 12.9 | 0.3 (0.7) | 1.7 (0.5) | 0 | 10 | 0 | 0 |
| | Abdominal artery repair | MI | 11 | 15.6 | 15.6 | 0 | 0.2 (0.5) | 1.2 (0.4) | 0 | 6 | 0 | 0 |
| | Large vessel aneurysmorrhaphy | O | 42 | 24.8 | 11.2 | 16 | 0.8 (2.2) | 3.4 (3.2) | 4.0 | 105 | 4.0 | 5.6 |
| | Large vessel arterial bypass | O | 340 | 20.2 | 7.4 | 16.2 | 0.5 (1.3) | 2.4 (1.9) | 2.3 | 493 | 0.8 | 1.5 |
| | Large vessel endarterectomy/thrombectomy | O | 139 | 13.9 | 4.1 | 12 | 0.4 (1.2) | 2.6 (2.3) | 2.4 | 148 | 1.7 | 2.2 |
| | Lower limb endarterectomy with resection | O | 18 | 14.8 | 5.6 | 11.1 | 0.4 (1.3) | 2.9 (2.2) | 1.9 | 23 | 1.9 | 5.6 |
| | Lower limb arterial bypass | O | 14 | 14.6 | 4.9 | 14.6 | 0.7 (2.6) | 4.5 (5.7) | 2.4 | 27 | 2.4 | 2.4 |
| | Lower limb arterial dilation (NEC) | MI | 12 | 8.3 | 2.8 | 5.6 | 0.1 (0.3) | 1 (0) | 0 | 3 | 0 | 0 |

O = open; MI = minimally invasive; I = intra-operative; P = post-operative; RBC = red blood cell; SD = standard deviation; ORIF =open reduction internal fixation; NEC = not elsewhere classified

# Prophylactic tranexamic acid use in non-cardiac surgeries at high-risk for transfusion

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ORIGINAL ARTICLE

TRANSFUSION MEDICINE WILEY

# Prophylactic tranexamic acid use in non-cardiac surgeries at high risk for transfusion

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## Abstract

**Background:** Tranexamic acid (TXA) reduces transfusion in a wide range of surgical populations, although its real-world use in non-cardiac surgeries has not been well described. The objective of this study was to describe prophylactic TXA use in non-cardiac surgeries at high risk for transfusion.

**Methods:** This is a retrospective cohort study of all adult patients undergoing major non-cardiac surgery at ≥5% risk of perioperative transfusion at five Canadian hospitals between January 2014 and December 2016. Canadian Classification of Health Interventions procedure codes within the Discharge Abstract Database were linked to transfusion and laboratory databases. TXA use was ascertained electronically from The Ottawa Hospital Data Warehouse and via manual chart review for Winnipeg hospitals. For each surgery, we evaluated the percentage of patients who received TXA as well as the specifics of TXA dosing and administration.

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**Results:** TXA use was evaluable in 14 300 patients. Overall, 17% of surgeries received TXA, ranging from 0% to 68% among individual surgeries. TXA use was more common in orthopaedic ($n$ = 2043/4942; 41%) and spine surgeries (n = 239/1322; 18%) compared to other surgical domains (n = 109/8036; 1%). TXA was commonly administered as a bolus (n = 2097/2391; 88%). The median TXA dose was 1000 mg (IQR 1000–1000 mg).

**Conclusion:** TXA is predominantly used in orthopaedic and spine surgeries, with little uptake in other non-cardiac surgeries at high risk for red blood cell transfusion. Further studies are needed to evaluate the effectiveness and safety of TXA and to understand the barriers to TXA administration in a broad range of non-cardiac surgeries.

**KEYWORDS**
blood conservation, perioperative, surgery, tranexamic acid, transfusion

## 1 | INTRODUCTION

Perioperative bleeding is a major indication for red blood cell (RBC) transfusion and is the second most common indication for transfusion in hospitalised patients.[1,2] Surgery-specific transfusion rates in patients undergoing major non-cardiac surgery vary widely, ranging from approximately 5% to 50%.[3-6] Strategies to mitigate perioperative transfusion include pre-operative correction of anaemia, variation in surgical technique, intraoperative blood salvage, restrictive transfusion thresholds and medications such as tranexamic acid (TXA).[7-9]

TXA is an inexpensive and widely available medication that reversibly blocks lysine binding sites on plasminogen inhibiting plasmin formation and consequent fibrinolysis.[10] TXA has been shown to consistently reduce RBC transfusion in cardiac surgery, orthopaedic surgery and trauma, where it is now incorporated into usual care.[7,11-15] In a meta-analysis of randomised trials that enrolled patients undergoing non-cardiac surgeries at high risk for RBC transfusion, TXA reduced both the percentage of patients transfused RBC cells and the volume of RBCs transfused compared to placebo or usual care.[16]

Guidelines support TXA use in surgeries at increased risk for bleeding, although its use in this broad patient population has not been previously described.[17] To evaluate clinical equipoise and inform clinical studies evaluating perioperative TXA use, we described prophylactic TXA use in patients undergoing non-cardiac surgeries at high risk for RBC transfusion.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design, setting and population

We completed a retrospective cohort study to evaluate all adult patients (≥18 years of age) undergoing major non-cardiac surgery at high risk for RBC transfusion at three hospitals in Winnipeg, Manitoba (Health Sciences Centre, St. Boniface General Hospital and Concordia Hospital) and two hospitals in Ottawa, Ontario (Ottawa Hospital, Civic and General Campuses) between 1 January 2014 and 31 December 2016. All hospitals are tertiary care centres providing health services to approximately 2 million people. Surgeries were defined as 'high risk' if they were associated with a ≥5% incidence of perioperative RBC transfusion, using previously described methodology[3] (Figure 1).

### 2.2 | Data sources

We obtained patient demographics, clinical and administrative hospitalisation data from the Discharge Abstract Database (DAD), which uses standard International Classification of Diseases coding for diagnoses and comorbidities, and Canadian Classification of Health Interventions (CCI) coding for surgical procedures. The DAD undergoes a continual process of data quality assurance and data validation.[18] In Manitoba, transfusion data were obtained from a provincial transfusion database (TraceLine) dually governed by Diagnostic Services Manitoba and the Canadian Blood Services. Laboratory data were obtained from the hospital Laboratory Information System. As intraoperative TXA administration is not electronically captured in Manitoba, we performed a manual chart review of a randomly selected subset (n = 1653/12 960) of patients who underwent a major non-cardiac surgery at high risk for transfusion. In Ottawa, transfusion, laboratory and TXA data are electronically captured and were obtained from The Ottawa Hospital Data Warehouse, a repository of clinical and health administrative data that is routinely validated to ensure accuracy.

### 2.3 | Study variables

We obtained patient demographics including age, sex, weight, baseline comorbidities, admission diagnosis and preoperative haemoglobin. Baseline comorbidities were evaluated using the Charlson comorbidity index.[19] For the pre-operative haemoglobin, we obtained the value drawn closest to the start of surgery, within the preceding 4 weeks. Pre-operative anaemia was defined as a haemoglobin value of less than

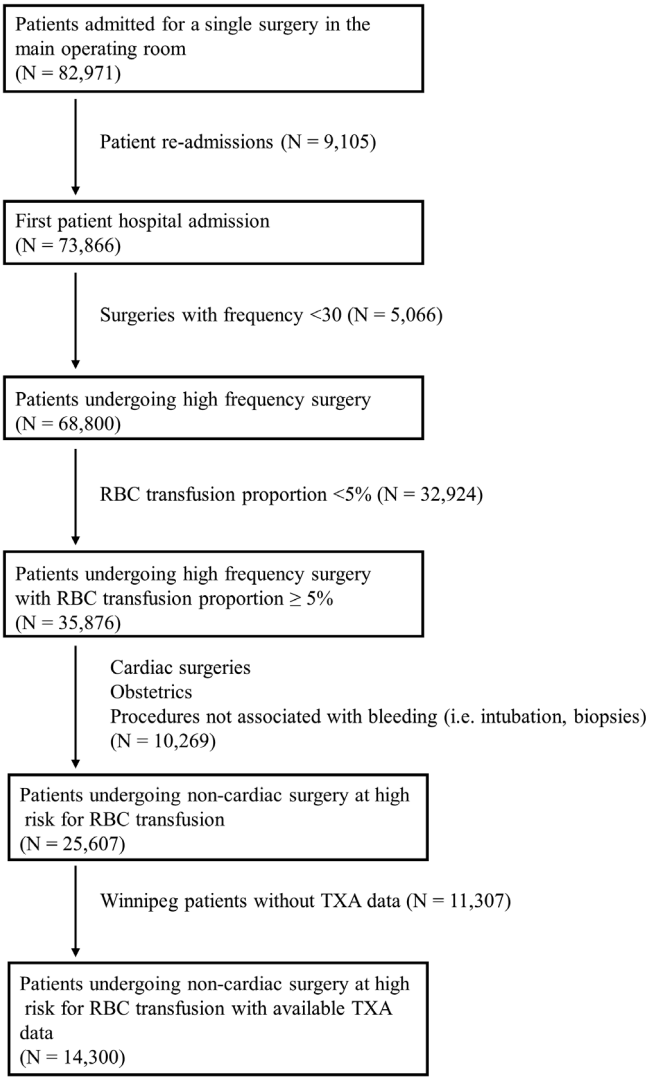


**FIGURE 1** Flow diagram: Derivation of surgical cohort

140 g/L in males and 120 g/L in females. Surgical information, including surgery name, date/time and surgical urgency (ie, elective, urgent/emergent) was obtained from the DAD using standardised CCI procedure codes.[20,21] CCI codes were modified to reflect clinically relevant surgeries (Table S1).[3] To reflect transfusions attributable to perioperative bleeding, surgery-specific transfusion rates were defined based on RBC transfusions from the start of the surgery to 7 days post-operative or hospital discharge, whichever occurred first. Prophylactic TXA administration was defined as intravenous TXA initiated within 1 h before or after the start of surgery, with the intent to exclude cases where TXA was administered later in response to surgical bleeding. Only prophylactic TXA use is considered in this study.

### 2.4 | Descriptive analysis of prophylactic TXA use

We described the percentage of patients who received intraoperative TXA by surgical domain and individual surgery, as well as specifics of TXA dosing (mg/kg/h and mg/h) and administration. We used pharmacokinetic modelling to examine the ability of a bolus dose to maintain TXA concentrations above the reported threshold concentration of 10 mg/L necessary to achieve antifibrinolysis.[22,23] We estimated the concentration–time profile after administration of a single 1000 mg intravenous TXA bolus over 30 min in a 70 kg patient with normal renal function. We chose a one-compartment open model of drug distribution as the distributional phase of a two-compartment model ends before 30 min,[22] and would therefore be insignificant in the surgical setting after the first few hours.

Baseline characteristics were summarised as means (SD), median (interquartile range [IQR]) or frequency (%), as appropriate. We analysed group differences in categorical or continuous data using Chi-square and *t*-tests, as appropriate. *p*-values <0.05 were considered significant. Sample size calculations were not performed as the primary intent of this analysis was descriptive, and the cohort was derived by convenience sampling. Missing data were evaluated and summarised. We conducted all analyses using SAS/STAT software (SAS version 9.4 for Windows; SAS Institute Inc., Cary, NC).

## 3 | RESULTS

### 3.1 | Baseline characteristics

In five hospitals, we identified 14 300 patients undergoing non-cardiac surgeries with an RBC transfusion rate ≥5%, for which TXA use was evaluable. Of these, 12 647 (88%) and 1653 (12%) were performed in Ottawa and Winnipeg, respectively. The Winnipeg TXA data were ascertained in a subset of the total population by manual chart review. Most surgeries were elective (n = 8773; 61%) and were performed using an open surgical approach (n = 12 932; 90%). The median duration of surgery was 190 min (IQR 133–286 min). The mean patient age was 64 years (SD 17 years), and 52% were female. The median patient weight was 81 kg (SD 20 kg). Pre-operative haemoglobin values were available in 81% of the cohort. Other study variables had near complete (>99%) capture. Baseline demographics classified by surgical domain and individual surgery are included in Table 1 and Table S2, respectively.

### 3.2 | Descriptive analysis of prophylactic TXA use

The overall prophylactic TXA administration rate in the cohort was 17%, ranging from 0% to 68% among individual types of surgery. Prophylactic TXA administration was more common in Ottawa (n = 2317/12 647; 18%) than in Winnipeg (n = 74/1653; 4%; $p < 0.0001$). TXA use was more common in orthopaedic surgeries (n = 2043/4942; 41%) and spine surgery (n = 239/1322; 18%) compared to other surgical domains (n = 109/8036; 1%). Compared to elective surgical patients, those undergoing urgent surgery were less likely to receive prophylactic TXA (11% vs. 21%; $p < 0.0001$), despite more pre-operative anaemia (haemoglobin 117 g/L vs. 131 g/L;

**TABLE 1** Description of baseline demographics categorised by surgical domain

| Surgical domain | Surgical volume (# surgeries/year) | Urgency (% elective) | Age (mean, SD) | Sex (% female) | Charlson CI (mean, SD) | Pre-op Hb (g/L) | % transfused | % TXA use |
|---|---|---|---|---|---|---|---|---|
| General surgery | 2997 | 59 | 62 (16) | 48 | 2.5 (2.9) | 122 (22) | 18.1 | 1.4 |
| Gynaecology | 1509 | 95 | 54 (14) | 100 | 1.7 (2.4) | 126 (17) | 12.7 | 1.3 |
| Neurosurgery | 139 | 64 | 56 (11) | 73 | 1.0 (1.1) | 134 (17) | 18.0 | 0.7 |
| Orthopaedic surgery | 4942 | 42 | 69 (17) | 57 | 0.8 (1.6) | 123 (20) | 18.1 | 41.3 |
| Otolaryngology | 91 | 98 | 62 (13) | 45 | 3.6 (2.9) | 131 (15) | 11.0 | 0 |
| Plastic surgery | 202 | 65 | 60 (16) | 41 | 1.8 (2.1) | 121 (22) | 9.4 | 5.0 |
| Spine surgery | 1322 | 73 | 58 (15) | 45 | 0.5 (1.4) | 134 (17) | 14.4 | 18.1 |
| Thoracic surgery | 330 | 85 | 60 (16) | 48 | 2.6 (2.6) | 129 (20) | 17.6 | 1.2 |
| Urology | 1184 | 74 | 63 (15) | 27 | 2.3 (1.8) | 121 (22) | 18.7 | 1.8 |
| Vascular surgery | 1584 | 67 | 71 (12) | 28 | 1.4 (1.3) | 130 (21) | 25.3 | 1.2 |

Abbreviations: Charlson CI, Charlson comorbidity index; Hb, haemoglobin; Pre-op, preoperative; TXA, tranexamic acid.

**TABLE 2** Surgery-specific baseline demographics and TXA utilisation

| Surgery | Surgical volume (# surgeries/year) | Urgency (% elective) | Age (mean, SD) | Sex (% female) | Charlson CI (mean, SD) | Pre-op Hb (g/L) | % transfused | % TXA use |
|---|---|---|---|---|---|---|---|---|
| Open pelvic osteoplasty/osteotomy | 41 | 92.7 | 35 (17) | 71 | 1.0 (2.7) | 129 (19) | 17.1 | 68.3 |
| Open hip arthroplasty | 2648 | 67.2 | 68 (15) | 54 | 0.5 (1.3) | 130 (17) | 10.0 | 67.3 |
| Pelvic ORIF | 106 | 14.2 | 51 (20) | 28 | 0.3 (0.8) | 120 (19) | 26.4 | 34.9 |
| Femur ostectomy | 52 | 57.7 | 52 (20) | 50 | 2.8 (3.5) | 125 (19) | 21.2 | 23.1 |
| Spinal fusion | 855 | 73.8 | 58 (15) | 44 | 0.4 (1.2) | 134 (18) | 13.2 | 22.2 |
| Scalp resection | 17 | 94.1 | 70 (16) | 12 | 1.8 (2.3) | 125 (22) | 5.9 | 17.7 |
| Diskectomy with insertion of spacer | 136 | 87.5 | 54 (13) | 38 | 0.3 (1.0) | 139 (15) | 4.4 | 16.2 |
| Endoscopic femur fixation | 90 | 2.2 | 78 (17) | 61 | 1.1 (1.8) | 116 (17) | 33.3 | 13.3 |
| Femur ORIF | 1019 | 3.7 | 72 (18) | 71 | 1.0 (1.9) | 116 (18) | 34.8 | 12.8 |
| Open splenectomy | 50 | 44.0 | 49 (18) | 56 | 0.6 (1.5) | 102 (24) | 46.0 | 12.0 |

*Note:* Includes the top 10 surgeries with the highest percentage of TXA utilisation.
Abbreviations: Charlson CI, Charlson comorbidity index; Hb, haemoglobin; ORIF, open reduction internal fixation; Pre-op, preoperative; TXA, tranexamic acid.

$p < 0.0001$) and perioperative RBC transfusions (57% vs. 43%; $p < 0.0001$).

The surgeries with the highest prophylactic TXA use included open hip arthroplasty (n = 1799/2648; 68%), open pelvis osteoplasty/ostectomy (n = 28/41; 68%), pelvic open reduction internal fixation (n = 37/106; 35%), femur ostectomy (n = 15/52; 29%) and spinal fusion (n = 198/855; 23%) (Table 2).

The mean time from the start of surgery to TXA administration was 28 min (SD 16 min). TXA was administered as an isolated bolus in 88% (n = 2097/2391), as an infusion in 3% (n = 78/2391) and as a combined bolus followed by an infusion in 9% (n = 214/2391). Overall, the median total TXA dose was 1000 mg (IQR 1000–1000 mg). The median TXA bolus dose was 1000 mg (IQR 1000–1000 mg), and the median total TXA infusion was 716 mg (IQR 260–2000 mg), with a median TXA infusion rate of 144 mg/h (IQR 68–1302 mg/h). Accounting for patient weight, the median TXA bolus was 11.5 mg/kg (IQR 10.1–13.8 mg/kg) and the median infusion rate was 1.9 mg/kg/h (IQR 0.9–16 mg/kg/h). The estimated concentration–time profile after administration of a 1000 mg intravenous bolus of TXA in a 70 kg patient with normal renal function is included in Figure 2.

## 4 | DISCUSSION

In this historical cohort study, we observed that the prophylactic use of TXA varies widely by surgical subtype, with limited use outside of orthopaedic and spine surgery. TXA was most commonly administered as a bolus, with a median total dose of 1 g.

Perioperative TXA use has been shown to reduce RBC transfusion in large randomised trials,[16,24] yet real-world reports of TXA utilisation are limited.[25,26] Higher TXA use in orthopaedic and spine surgery aligns with a substantive body of literature supporting its

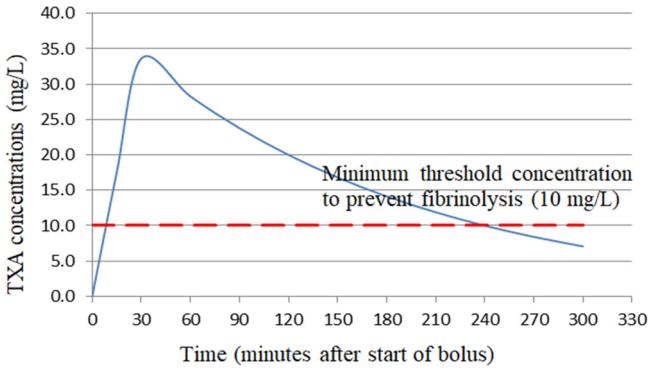


**FIGURE 2** Estimated concentration–time profile after administration of a 1000 mg intravenous bolus of tranexamic acid over 30 min in a 70 kg patient with normal renal function. The assumed elimination rate was based on a 2-h half-life and a drug distribution space of 0.39 L/kg.[39] The minimum threshold concentration to prevent fibrinolysis (10 mg/L) was ascertained from Picetti et al[23] [Color figure can be viewed at wileyonlinelibrary.com]

efficacy and cost-effectiveness in these surgical populations.[12,27-32] Low TXA utilisation in other surgeries is inconsistent with the results of a recently published systematic review that demonstrates the ability of TXA to reduce RBC transfusion across a broad range of major non-cardiac surgeries.[16] While the perceived lack of uptake of TXA into routine practice could reflect the time period evaluated in our study (2014–2016) relative to publication date of individual trials, 64% (21/33 trials) of the trials in this surgical population were published prior to 2016. Possible barriers to TXA uptake may reflect low confidence in the published trials, which are relatively small (mean size 97 patients [64 patients]) with most at unclear or high risk of bias (97%; 32/33 trials). Concern regarding the perceived risk of thrombotic complications may further decrease use.[16,33]

The dosing of TXA observed in our study aligns with prior trials evaluating intravenous prophylactic TXA, although standard dosing of perioperative TXA does not exist, and a wide dosing ranges and dosing schedules have been reported.[16,24] In keeping with practice trends of reduced TXA doses over time,[34] we recently published a systematic review demonstrating that less than 2 g of TXA was used in 31/49 trials (n = 2775 patients) of patients undergoing non-cardiac surgeries at high risk for RBC transfusion.[16] Although detailed pharmacokinetic and pharmacodynamic data in this population is lacking, studies in healthy volunteers have shown that a bolus of 1 g maintained therapeutic plasma concentrations for 3 h, with an elimination half-life of approximately 2 h.[35,36] The perioperative tranexamic acid in hip arthroplasty trial recently evaluated variations in TXA dosing (1 g intravenous bolus followed by 1 g infusion versus 1 g intravenous bolus followed by placebo) in total hip arthroplasty and found no difference in perioperative blood loss between these two groups.[37] Based on our pharmacokinetic model, we estimate that therapeutic concentrations are maintained for approximately 240 min. Given the median surgical duration in our study was 190 min (IQR 133–286 min), it is likely that a 1 g bolus dose would be adequate to maintain therapeutic concentrations for the duration of surgery in the majority of cases.[23]

Strengths of our study include the use of high-fidelity data sets to reliably capture patient demographics, surgical information and TXA administration within our multicentre cohort. By evaluating TXA utilisation rates in all non-cardiac surgeries with a baseline transfusion rate of ≥5%, the broad surgical population makes our results generalisable to a large population of perioperative patients. We have addressed a knowledge gap by demonstrating low utilisation outside the orthopaedic and spine surgery, which is otherwise not apparent in the literature, and inconsistent with current perioperative guidelines.[17]

Limitations of our study include the less than complete ascertainment of pre-operative haemoglobin, which could be related to perioperative guidelines advocating for reductions in routine blood work prior to surgery.[38] Additionally, as ascertainment of TXA administration in Manitoba required a manual chart review, TXA administration data were largely informed by two centres in Ottawa, ON. An updated evaluation of TXA utilisation in additional centres may provide an even more comprehensive evaluation of how centres have implemented international anaesthesiology guidelines.

Prophylactic use of TXA is primarily limited to orthopaedic and spine surgeries, with limited uptake in other surgical domains. Randomised trials are needed to comprehensively evaluate the effectiveness and safety of TXA in a broad range of non-cardiac surgeries. Further study is warranted to understand the barriers to TXA implementation in non-cardiac surgical patients.

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## CONFLICT OF INTEREST

The authors have no competing interests.

## AUTHOR CONTRIBUTIONS

Brett L. Houston, Dean A. Fergusson, Jamie Falk, Emily Rimmer, Donald S. Houston, Allan Garland, Robert E. Ariano, Robert Balshaw, Ryan Zarychanski were involved in study design. Brett L. Houston and Emily Krupka completed the manual chart review. Iris Perelman, led the database linkage(s). All authors made material contributions to the manuscript, wrote and reviewed the manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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**Appendix 1.** Canadian Classification of Health Interventions (CCI) codes and their respective surgical descriptions. CCI codes were classified based on the Canadian Classification of Health Interventions alphabetical index(20), Winnipeg Regional Health Authority SIMS Procedure Catalog(41), and with input from surgeons and anesthesiologists with content expertise.

| **Surgery name** | **CCI codes** |
|---|---|
| Abdominal aortic bypass | 1.ID.76, 1.ID.89, 1.ID.86, 1.ID.87, I.KA.76 |
| Abdominal aortic repair | 1.KA.80 |
| Abdominal artery dilation | 1.KE.50 |
| Abdominal artery repair | 1.KE.80 |
| Abdominopelvic neoplasm resection | 1.OT.91 |
| Above knee amputation | 1.VC.93 |
| Below knee amputation | 1.VQ.93 |
| Bile duct excision | 1.OE.87, 1.OE.89 |
| Bladder diverticulectomy (endoscopic) | 1.PM.87 |
| Cholecystectomy | 1.OD.57, 1.OD.89 |
| Colectomy | 1.NM.87, 1.NM.89, 1.NM.91 |
| Colonic anastomosis | 1.NM.82 |
| Colostomy | 1.NM.77 |
| Craniotomy/craniectomy | 1.EA.72, 1.EA.87, 1.AJ.87, 1.AN.87 |
| Cystectomy | 1.PM.87, 1.PM.91, 1.PM.92 |
| Cystectomy (partial) | 1.PM.59 |
| Decortication, pleurectomy, pleurodesis | 1.GV.87, 1.GV.89 |
| Diaphragmatic herniorrhaphy | 1.GX.80 |
| Diskectomy with insertion of spacer | 1.SE.53 |
| Elbow arthroplasty | 1.TM.53 |
| Enterectomy | 1.NK.87 |
| Enterostomy | 1.NK.76, 1.NK.77 |
| Esophageal diverticulectomy (endoscopic) | 1.NA.87 |
| Esophagectomy | 1.NA.87, 1.NA.88, 1.NA.89, 1.NA.90, 1.NA.91 |
| Femur fixation | 1.VC.74 |
| Femur ostectomy | 1.VC.87 |
| Foot amputation | 1.WI.93, 1.WJ.93, 1.WL.93, 1.WN.93 |
| Gastrectomy | 1.NF.87, 1.NF.89, 1.NF.90, 1.NF.91 |
| Gastroplasty | 1.NF.80 |
| Glossectomy | 1.FJ.87, 1.FJ.91 |
| Hip arthroplasty | 1.VA.53 |
| Hip joint fixation | 1.VA.74 |
| Humerus ORIF | 1.TK.74 |
| Hysterectomy | 1.RM.87, 1.RM.89, 1.RM.91 |
| Intervertebral disk resection | 1.SE.89 |
| Intra-abdominal wound repair | 1.OT.80 |
| Intracranial vessel embolization | 1.JW.51 |
| Knee arthroscopy | 1.VG.87 |
| Knee debridement/repair (open) | 1.VG.87 |
| Large vessel aneurysmorrhaphy | 1.JM.80, 1.KE.80, 1.KG.80, 1.KT.80 |
| Large vessel arterial bypass | 1.JM.76, 1.KE.76, 1.KG.76, 1.KT.76 |
| Large vessel endarterectomy/thrombectomy | 1.KA.57, 1.KE.57, 1.KG.57, 1.KT.57 |
| Leg amputation stump revision | 1.VX.59 |

| | |
|---|---|
| Lobectomy | 1.GR.87, 1.GR.89, 1.GR.91 |
| Lower limb soft tissue resection | 1.VX.87 |
| Lower limb endarterectomy with resection | 1.KG.87 |
| Lower limb arterial bypass | 1.KR.76 |
| Lower limb dilation NEC | 1.KG.50 |
| Lysis of adhesions | 1.OT.72, 1.NP.72 |
| Mandibulectomy | 1.EE.87, 1.EE.91 |
| Meningectomy | 1.AA.87 |
| Nephrectomy | 1.PC.87, 1.PC.89, 1.PC.90, 1.PC.91 |
| Omentectomy | 1.OT.87 |
| Oopherectomy | 1.RB.87, 1.RB.89 |
| Mesh implant removal of chest/abdomen | 1.SY.55 |
| Pancreatic resection | 1.OJ.76, 1.OJ.87, 1.OJ.89, 1.OK.87, 1.OK.89, 1.OK.91 |
| Partial hepatectomy | 1.OA.87 |
| Pelvic ORIF | 1.SQ.74, 1.SQ.53 |
| Pelvic osteoplasty/osteotomy | 1.SQ.80, 1.SQ.87 |
| Pneumonectomy | 1.GT.89, 1.GT.91 |
| Proctectomy | 1.NQ.87, 1.NQ.89 |
| Prostatectomy | 1.QT.89, 1.QT.91 |
| Renal transplant | 1.PC.85 |
| Repair skin of leg | 1.YV.80 |
| Resection of skin on abdomen/trunk | 1.YS.87 |
| Resection of soft tissue of chest/abdomen | 1.SZ.87 |
| Scalp resection | 1.YA.87 |
| Shoulder ORIF | 1.TA.74 |
| Skull base resection | 1.EA.92 |
| Small intestine repair | 1.NK.80 |
| Spinal decompression | 1.AW.72 |
| Spinal cord resection | 1.AW.87 |
| Spinal decompression with instrumentation | 1.SC.74 |
| Spinal fusion | 1.SC.75 |
| Spinal fusion with vertebrectomy | 1.SC.89 |
| Splenectomy | 1.OB.89 |
| Total salpingooopherectomy | 1.RD.89 |
| Foot and ankle soft tissue debridement | 1.WV.59 |

ORIF = open reduction internal fixation; NEC = not elsewhere classified

**Appendix 2.** Surgery-specific baseline demographics and TXA administration

| Surgical domain | Surgery | Surgical approach | # surgeries | Age (mean, SD) | Sex (% female) | Charlson CI (mean, SD) | Pre-op Hb (g/L) | % transfused RBCs | % TXA administration |
|---|---|---|---|---|---|---|---|---|---|
| General surgery | Abdominopelvic neoplasm resection | O | 52 | 55.5 (14.6) | 67 | 2.7 (2.6) | 121 (20) | 25.0 | 3.9 |
| | Bile duct excision | O | 9 | 65.2 (17.4) | 56 | 1.1 (2.7) | 132 (21) | 22.2 | 0 |
| | Cholecystectomy | O | 82 | 59.1 (15.3) | 38 | 0.9 (2.1) | 128 (18) | 6.1 | 2.4 |
| | Colectomy | MI | 288 | 65.8 (14.2) | 53 | 3.0 (2.9) | 122 (21) | 11.1 | 0.7 |
| | Colectomy | O | 566 | 64.8 (16.6) | 51 | 2.7 (3.1) | 115 (23) | 24.9 | 0.7 |
| | Colonic anastomosis | O | 24 | 55.0 (15.4) | 42 | 0.6 (1.7) | 132 (14) | 8.3 | 0 |
| | Colostomy | MI | 34 | 56.5 (16.4) | 53 | 2.0 (2.3) | 111 (23) | 5.9 | 0 |
| | Colostomy | O | 43 | 64.8 (15.9) | 58 | 4.1 (3.5) | 107 (21) | 25.6 | 2.3 |
| | Enterectomy | MI | 53 | 49.9 (20.1) | 60 | 1.1 (2.2) | 126 (22) | 11.3 | 0 |
| | Enterectomy | O | 308 | 60.5 (19.3) | 49 | 1.1 (2.2) | 124 (22) | 16.2 | 0 |
| | Enterostomy | MI | 16 | 58.4 (18.7) | 38 | 3.0 (3.4) | 115 (25) | 12.5 | 0 |
| | Enterostomy | O | 73 | 61.2 (15) | 38 | 3.4 (3.4) | 116 (22) | 11.0 | 0 |
| | Esophageal diverticulectomy | MI | 43 | 62.8 (10.5) | 16 | 3.4 (3.1) | 130 (19) | 18.6 | 0 |
| | Esophagectomy | O | 31 | 63.1 (10.2) | 29 | 2.7 (3.0) | 127 (9) | 19.4 | 0 |
| | Gastrectomy | O | 113 | 64.3 (13.4) | 42 | 1.8 (2.4) | 114 (26) | 23.0 | 0.9 |
| | Gastroplasty | O | 32 | 50.8 (21.2) | 38 | 0.8 (1.7) | 118 (36) | 34.4 | 6.3 |
| | Intra-abdominal wound repair | O | 42 | 44.6 (12.3) | 79 | 0.1 (0.4) | 126 (17) | 2.4 | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Lysis of adhesions | O | 120 | 66.2 (18.7) | 53 | 0.9 (1.6) | 128 (23) | 5.8 | 0.8 |
| | Omentectomy | O | 77 | 56.9 (13.4) | 66 | 2.8 (3.2) | 121 (22) | 23.4 | 0 |
| | Pancreatic resection | O | 234 | 63.8 (12.7) | 50 | 3.0 (3.1) | 124 (20) | 19.7 | 0.9 |
| | Partial hepatectomy | O | 240 | 61.3 (12.4) | 44 | 4.5 (3.0) | 132 (17) | 15.4 | 6.3 |
| | Proctectomy | O | 410 | 63.5 (14.2) | 42 | 2.6 (2.8) | 125 (20) | 17.1 | 0.7 |
| | Small intestine repair | MI | 12 | 43.4 (13.4) | 33 | 0.8 (0.7) | 127 (24) | 8.3 | 0 |
| | Small intestine repair | O | 45 | 60.5 (19.5) | 56 | 1.7 (2.1) | 128 (28) | 31.1 | 0 |
| | Splenectomy | O | 50 | 49.1 (17.5) | 56 | 0.6 (1.5) | 102 (24) | 46.0 | 12 |
| Gynecology | Hysterectomy | O | 1363 | 53.6 (13.6) | 100 | 1.6 (2.4) | 126 (17) | 12.6 | 1.39 |
| | Total salpingoopherectomy | O | 146 | 53.5 (15.4) | 100 | 2.2 (2.8) | 125 (16) | 13.7 | 0 |
| Neurosurgery | Intracranial vessel embolization | O | 91 | 55.3 (10.3) | 78 | 1.2 (0.6) | 131 (17) | 17.6 | 1.1 |
| | Meningectomy | O | 48 | 57.8 (12.5) | 63 | 0.6 (1.6) | 138 (18) | 18.8 | 0 |
| Orthopedic Surgery | Above knee amputation | O | 145 | 72.6 (15.2) | 49 | 1.6 (2.1) | 104 (20) | 32.4 | 2.1 |
| | Below knee amputation | O | 153 | 62.8 (13.6) | 30 | 1.5 (1.6) | 101 (21) | 32.0 | 2.6 |
| | Elbow arthroplasty | O | 34 | 62.6 (15.5) | 76 | 0.5 (0.7) | 122 (15) | 11.8 | 0 |
| | Femur fixation | MI | 90 | 78.3 (16.6) | 61 | 1.1 (1.8) | 116 (17) | 33.3 | 13.3 |
| | Femur ORIF | O | 1019 | 76.3 (17.8) | 71 | 1.0 (1.9) | 116 (18) | 34.8 | 13.3 |
| | Femur ostectomy | O | 52 | 52.1 (20) | 50 | 2.8 (3.5) | 125 (19) | 21.2 | 28.9 |
| | Foot amputation | O | 128 | 67.2 (14.2) | 33 | 2.8 (1.3) | 106 (17) | 11.7 | 0 |
| | Hip arthroplasty | O | 2648 | 68.2 (15) | 55 | 0.5 (1.3) | 130 (17) | 10.0 | 67.9 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Hip joint fixation | MI | 18 | 78.8 (14.1) | 83 | 1.6 (2.3) | 118 (14) | 11.1 | 5.6 |
| | Hip ORIF | O | 256 | 74.2 (17.8) | 64 | 0.7 (1.4) | 119 (18) | 22.7 | 8.6 |
| | Humerus ORIF | O | 113 | 55.6 (19.1) | 60 | 0.8 (2.1) | 126 (19) | 9.7 | 9.7 |
| | Knee arthroscopy | MI | 34 | 51.9 (20.2) | 44 | 0.6 (1.0) | 119 (20) | 11.8 | 0 |
| | Knee debridement/repair | O | 22 | 64.0 (17.1) | 32 | 0.5 (0.9) | 121 (23) | 13.6 | 9.1 |
| | Leg amputation stump revision | O | 40 | 51.7 (16.1) | 35 | 0.8 (1.1) | 118 (22) | 7.5 | 0 |
| | Pelvic ORIF | O | 106 | 51.3 (19.3) | 28 | 0.3 (0.8) | 120 (19) | 26.4 | 34.9 |
| | Pelvic osteoplasty/ osteotomy | O | 41 | 35.3 (16.8) | 71 | 1.0 (2.7) | 129 (19) | 17.1 | 68.3 |
| | Shoulder ORIF | O | 43 | 59.9 (13.2) | 70 | 0.2 (0.4) | 125 (16) | 4.7 | 4.7 |
| Otolaryngology | Glossectomy | O | 71 | 61.5 (12.5) | 45 | 3.8 (2.9) | 132 (15) | 12.7 | 0 |
| | Mandibulectomy | O | 20 | 62.3 (14.2) | 45 | 3.1 (3.1) | 130 (12) | 5.0 | 0 |
| Plastic surgery | Foot and ankle soft tissue debridement | O | 25 | 53.8 (11.5) | 24 | 1.8 (1.4) | 115 (19) | 4.0 | 0 |
| | Lower extremity soft tissue resection | O | 67 | 60.7 (15.6) | 49 | 2.0 (2.1) | 130 (19) | 13.4 | 10.5 |
| | Mesh implant removal of chest/abdomen | O | 30 | 60.9 (15.8) | 33 | 2.5 (1.7) | 95 (14) | 10.0 | 0 |
| | Repair – leg skin | O | 8 | 61.4 (15.8) | 37 | 0.6 (1.1) | 112 (14) | 25.0 | 0 |
| | Resection – skin on abdomen/trunk | O | 15 | 61.5 (16.8) | 33 | 0.9 (1.1) | 136 (20) | 6.7 | 0 |
| | Resection – soft issue on abdomen/trunk | O | 40 | 54.7 (19) | 58 | 1.7 (2.7) | 132 (16) | 5.0 | 0 |
| | Scalp resection | O | 12 | 70.3 (16) | 19 | 1.8 (2.3) | 124 (22) | 5.9 | 17.7 |
| Spine surgery | Diskectomy with insertion of spacer | O | 136 | 54.1 (12.8) | 38 | 0.3 (1.0) | 139 (15) | 4.4 | 16.2 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Intervertebral disk resection | O | 35 | 45.9 (16.6) | 60 | 0.1 (0.4) | 140 (14) | 2.9 | 2.9 |
| | Skull base resection | O | 42 | 56.7 (15.9) | 64 | 1.1 (2.0) | 134 (12.7) | 23.8 | 7.1 |
| | Spinal decompression | O | 18 | 62.0 (12.3) | 22 | 0.6 (1.7) | 137 (22) | 0 | 11.1 |
| | Spinal cord resection | O | 23 | 47.6 (15.4) | 57 | 1.0 (2.2) | 137 (11) | 8.7 | 8.7 |
| | Spinal decompression with instrumentation | O | 81 | 61.2 (14.5) | 48 | 0.7 (1.6) | 135 (19) | 9.9 | 7.4 |
| | Spinal fusion | O | 855 | 58.4 (15.1) | 44 | 0.4 (1.2) | 134 (18) | 13.2 | 23.2 |
| | Spinal fusion with vertebrectomy | O | 132 | 57.2 (13.5) | 53 | 1.0 (2.4) | 126 (19) | 37.9 | 10.6 |
| Thoracic surgery | Decortication, pleurectomy and pleurodesis | MI | 44 | 38.8 (18.6) | 32 | 0.5 (1.3) | 132 (23) | 13.6 | 0 |
| | Decortication, pleurectomy and pleurodesis | O | 6 | 57.7 (8.3) | 17 | 5.0 (3.9) | 120 (22) | 0 | 0 |
| | Diaphragmatic herniorrhaphy | O | 21 | 60.0 (18.7) | 43 | 0.1 (0.4) | 137 (16) | 14.3 | 0 |
| | Lobectomy | O | 217 | 63.6 (13.1) | 54 | 3.2 (2.5) | 129 (19) | 17.1 | 1.8 |
| | Pneumonectomy | O | 42 | 62.8 (12.5) | 40 | 3.0 (2.8) | 124 (18) | 28.6 | 0 |
| Urology | Bladder diverticulectomy | MI | 267 | 75.5 (12.4) | 22 | 2.4 (1.9) | 115 (24) | 7.1 | 1.1 |
| | Cystectomy | O | 142 | 66.7 (10.7) | 29 | 3.0 (2.5) | 126 (18) | 50.0 | 2.1 |
| | Cystectomy (partial) | MI | 54 | 66.5 (17.6) | 17 | 0.8 (1.6) | 119 (25) | 9.3 | 0 |
| | Nephrectomy | O | 359 | 60.3 (11.9) | 38 | 2.4 (2.1) | 129 (21) | 19.5 | 2.2 |
| | Prostatectomy | O | 102 | 64.8 (6.1) | 0 | 2.3 (1.1) | 147 (12) | 9.8 | 6.9 |
| | Renal transplant | O | 260 | 52.5 (14.2) | 38 | 2.2 (0.6) | 111 (13) | 17.7 | 0 |

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|---|---|---|---|---|---|---|---|---|---|
| Vascular surgery | Abdominal aortic bypass | O | 166 | 65.7 (8.5) | 30 | 1.0 (0.9) | 135 (18) | 38.6 | 1.2 |
| | Abdominal aortic repair | MI | 324 | 76.9 (7.9) | 20 | 1.4 (0.9) | 133 (18) | 15.7 | 0.3 |
| | Abdominal aortic repair | O | 283 | 70.7 (8.6) | 23 | 1.3 (1.1) | 132 (22) | 46.6 | 2.5 |
| | Abdominal artery dilation | MI | 28 | 68.2 (11) | 46 | 1.8 (1.6) | 122 (19) | 21.4 | 0 |
| | Abdominal artery repair | MI | 28 | 72.4 (15.1) | 0 | 0.5 (0.8) | 130 (21) | 17.9 | 0 |
| | Large vessel aneurysmorrhaphy | O | 57 | 50.8 (18.5) | 30 | 1.2 (1.4) | 128 (19) | 21.1 | 1.8 |
| | Large vessel arterial bypass | O | 403 | 68.2 (12.1) | 29 | 1.7 (1.6) | 128 (22) | 24.1 | 1.2 |
| | Large vessel endarterectomy/ thrombectomy | O | 215 | 72.3 (11.6) | 37 | 1.6 (1.2) | 128 (20) | 9.8 | 0.5 |
| | Lower limb endarterectomy with resection | O | 31 | 64.4 (13.9) | 42 | 1.4 (1.8) | 128 (20) | 16.1 | 3.2 |
| | Lower limb arterial bypass | O | 14 | 74.7 (12.1) | 43 | 1.4 (1.2) | 125 (25) | 28.6 | 7.1 |
| | Lower limb arterial dilation (NEC) | MI | 35 | 71.3 (12.3) | 34 | 2.3 (1.1) | 119 (23) | 8.6 | 0 |

O = open; MI = minimally invasive; SD=standard deviation; CI = comorbidity index; Pre-op = pre-operative; Hb = hemoglobin; RBC = red blood cells; ORIF = open reduction internal fixation; NEC = not elsewhere classified

# Variation in prophylactic tranexamic acid administration among anesthesiologists and surgeons in orthopedic surgery: a retrospective cohort study

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REPORTS OF ORIGINAL INVESTIGATIONS

# Variation in prophylactic tranexamic acid administration among anesthesiologists and surgeons in orthopedic surgery: a retrospective cohort study

# Variation dans l'administration prophylactique d'acide tranexamique selon les anesthésiologistes et les chirurgiens en chirurgie orthopédique : une étude de cohorte rétrospective

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## Abstract

**Purpose** *Tranexamic acid (TXA) reduces red blood cell transfusion in various orthopedic surgeries, yet the degree of practice variation in its use among anesthesiologists and surgeons has not been described. To target future knowledge transfer and implementation strategies, and to better understand determinants of variability in prophylactic TXA use, our primary objective was to evaluate the influence of surgical team members on the variability of prophylactic TXA administration.*

**Methods** *This was a retrospective cohort study of all adult patients undergoing primary total hip arthroplasty (THA), hip fracture surgery, and spine fusion ± vertebrectomy at two Canadian hospitals between January 2014 and December 2016. We used Canadian Classification of Health Interventions procedure codes within the*

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*Discharge Abstract Database which we linked to the Ottawa Data Warehouse. We described the percentage of patients that received TXA by individual surgery, the specifics of TXA dosing, and estimated the effect of anesthesiologists and surgeons on prophylactic TXA using multivariable mixed-effects logistic regression analyses.*

**Results** *In the 3,900 patients studied, TXA was most commonly used in primary THA (85%; n = 1,344/1,582), with lower use in hip fracture (23%; n = 342/1,506) and spine fusion surgery (23%; n = 186/812). The median [interquartile range] total TXA dose was 1,000 [1,000–1,000] mg, given as a bolus in 92% of cases. Anesthesiologists and surgeons added significant variability to the odds of receiving TXA in hip fracture surgery and spine fusion, but not primary THA. Most of the variability in TXA use was attributed to patient and other factors.*

**Conclusion** *We confirmed the routine use of TXA in primary THA, while observing lower utilization with more variability in hip fracture and spine fusion surgery. Further study is warranted to understand variations in use and the barriers to TXA implementation in a broader population of orthopedic surgical patients at high risk for transfusion.*

**Résumé**

**Objectif** *L'acide tranexamique (ATX) réduit la transfusion d'érythrocytes dans diverses chirurgies orthopédiques. Cependant, les variations de pratique quant à son utilisation parmi les anesthésiologistes et les chirurgiens n'ont pas été décrites. Afin de cibler les stratégies futures de transfert des connaissances et de mise en œuvre, et pour mieux comprendre les déterminants de la variabilité dans l'utilisation prophylactique d'ATX, notre objectif principal était d'évaluer l'influence des membres de l'équipe chirurgicale sur la variabilité de l'administration prophylactique d'ATX.*

**Méthode** *Il s'agissait d'une étude de cohorte rétrospective de tous les patients adultes subissant une arthroplastie totale primaire de la hanche (ATH), une chirurgie de fracture de la hanche et une fusion intervertébrale ± vertébrectomie dans deux hôpitaux canadiens entre janvier 2014 et décembre 2016. Nous avons utilisé les codes de procédure de la Classification canadienne des interventions en santé dans la Base de données sur les congés des patients, que nous avons liée à la banque de données d'Ottawa. Nous avons décrit le pourcentage de patients qui ont reçu de l'ATX par chirurgie individuelle, les détails du dosage de l'ATX, et avons estimé l'effet des anesthésiologistes et des chirurgiens sur l'ATX prophylactique en réalisant des analyses de régression logistique multivariées à effets mixtes.*

**Résultats** *Parmi les 3900 patients étudiés, l'ATX était le plus fréquemment utilisé lors d'une ATH primaire (85 %; n = 1344/1582), avec une utilisation plus faible lors de chirurgie de fracture de la hanche (23 %; n = 342/1506) et de chirurgie de fusion intervertébrale (23 %; n = 186/812). La dose totale médiane [écart interquartile] d'ATX était de 1000 mg [1000 à 1000], administrés dans 92 % des cas sous forme de bolus. Les anesthésiologistes et les chirurgiens ont ajouté une variabilité significative aux probabilités de recevoir de l'ATX lors d'une chirurgie de fracture de la hanche et de fusion, mais pas lors d'ATH primaire. La majeure partie de la variabilité dans l'utilisation d'ATX était attribuable aux facteurs liés au patient et à d'autres facteurs.*

**Conclusion** *Nous avons confirmé l'utilisation de routine de l'ATX dans l'ATH primaire, tout en observant une utilisation moins répandue et plus variable lors de chirurgie de fracture de la hanche et de fusion*

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*intervertébrale. Une étude plus approfondie est nécessaire pour comprendre les variations d'utilisation et les obstacles à la mise en œuvre de l'ATX dans une population plus étendue de patients de chirurgie orthopédique à haut risque de transfusion.*

**Keywords** tranexamic acid · orthopedic surgery · blood conservation · retrospective cohort study

Red blood cell (RBC) transfusion rates among orthopedic surgeries vary widely, with lower rates among hip arthroplasty and higher rates in hip fracture and complex spine surgery.[1-4] Strategies to mitigate perioperative RBC transfusion include preoperative correction of anemia, variation in surgical technique, intraoperative blood salvage, restrictive transfusion thresholds, and medications such as tranexamic acid (TXA).[5-7]

Tranexamic acid is an inexpensive and widely available medication that reversibly blocks lysine binding sites on plasminogen inhibiting plasmin formation and consequent fibrinolysis.[8] Tranexamic acid has been shown to consistently reduce RBC transfusion in cardiac surgery, hip and knee arthroplasty, and trauma, where it is now incorporated into standard of care.[5,9-12] Recent evidence syntheses suggest that TXA is effective in reducing transfusion in hip fracture surgery[13-15] and spine surgery.[16,17] In a recent meta-analysis evaluating a broader surgical population at high risk for RBC transfusion, TXA reduced the percentage of patients receiving transfused RBCs as well as the volume of transfused RBCs compared with placebo or usual care.[18]

Despite guidelines supporting the utilization of TXA to reduce transfusion in surgeries at increased risk for bleeding, real-world TXA use in orthopedic surgery has not been well described nor has the degree of practice variation in its use between anesthesiologists and surgeons.[6] We studied how TXA use varies across orthopedic surgeries, and the influence of surgical team members on this variability. Understanding these determinants of practice variability will help inform and target future knowledge transfer and implementation strategies.

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## Methods

### Study design, setting, and population

We completed a retrospective cohort study of all adult patients (≥ 18 yr of age) undergoing primary total hip arthroplasty (THA), hip fracture surgery, and spine fusion ± vertebrectomy at two hospitals in Ottawa, Ontario (Ottawa Hospital, Civic and General Campuses) between 1 January 2014 and 31 December 2016. These hospitals are tertiary care centres providing health services to approximately 1 million people. A formal policy or institutional guideline specific to TXA administration did not exist during the study period, nor was TXA stocked in the operating rooms. These orthopedic surgeries were chosen because they are high frequency surgeries ($n > 150$ per year) with higher rates of RBC transfusion (> 5%) and TXA utilization (> 10%) within the cohort.[19] To prevent misclassification of surgery-specific rates of TXA utilization, we excluded patients with more than one surgery during their hospitalization. If a patient was re-admitted for another surgery during the study period (2014–2016), we evaluated only their initial hospital admission (Fig. 1).

### Data sources

We obtained patient demographics, clinical, and administrative hospitalization data from the Discharge Abstract Database (DAD). The DAD uses standard International Classification of Diseases (ICD) coding for diagnoses and comorbidities, and Canadian Classification of Health Interventions (CCI) coding for surgical procedures. The DAD undergoes a continual process of data quality assurance and data validation.[20] Transfusion, laboratory, and TXA data were obtained from the Ottawa Hospital Data Warehouse, which is a repository of clinical, laboratory, and health services information collected from the hospital's information systems from both study institutions. Within the Ottawa Hospital Data Warehouse, TXA data were sourced from the Surgical Information Management System, a perioperative medical record which represents the medicolegal record for all surgical cases and is the gold standard for perioperative medication administration.

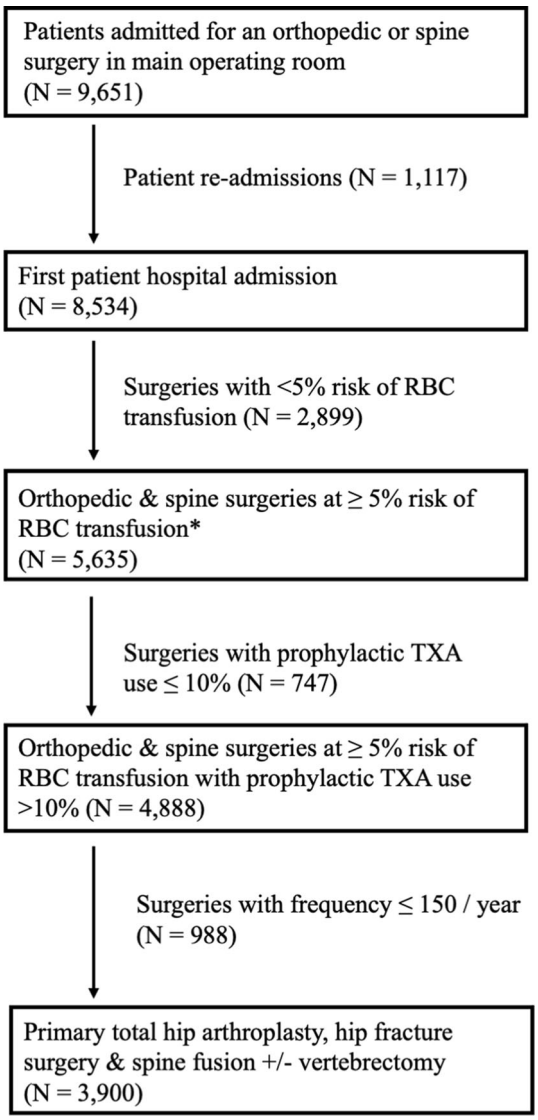


**Fig. 1** Flow diagram. Derivation of orthopedic cohort. *RBC transfusion rate based on retrospective cohort study evaluating non-cardiac surgeries at five Canadian academic institutions.[20] RBC = red blood cell; TXA = tranexamic acid

## Study variables

We obtained patient demographics including age, sex, baseline comorbidities, most responsible diagnosis, and preoperative hemoglobin. Baseline comorbidities were evaluated using the Charlson comorbidity index.[21] For the preoperative hemoglobin, we obtained the value drawn closest to the start of surgery, within the preceding four weeks. Surgical information, including type of procedure, date/time, surgical urgency (i.e., elective, urgent/emergent), and surgical team members (anesthesiologist, surgeon), was obtained from the DAD using standardized CCI procedure codes.[22,23] The most responsible anesthesiologist was the anesthesiologist who started the surgical case. CCI procedure codes and ICD-10 diagnosis codes were used to define the orthopedic surgeries (eAppendix 1, Electronic Supplementary Material [ESM]).[19] Total hip arthroplasty for osteoarthritis was evaluated separately, whereas THA for hip fracture was included in the hip fracture surgery group. Hip fracture surgery comprised THA (for hip fracture), hip hemiarthroplasty, and hip open reduction internal fixation (ORIF). To reflect transfusions attributable to perioperative bleeding, surgery-specific transfusion rates were defined based on RBC transfusions from the start of the surgery to seven days postoperative or hospital discharge, whichever occurred first. Prophylactic TXA administration was defined as intravenous TXA initiated within one hour before or after the start of surgery, with the intent to exclude cases where TXA was administered in response to surgical bleeding. Only prophylactic intravenous TXA use is considered in this paper.

## Descriptive analysis of prophylactic TXA use

We described the percentage of patients who received intraoperative TXA by individual surgery, as well as specifics of TXA dosing ($mg \cdot kg^{-1} \cdot hr^{-1}$ and $mg \cdot hr^{-1}$) and administration. Baseline characteristics were summarized as means (standard deviation [SD]), medians [interquartile range (IQR)], or frequency (percent). We analyzed group differences in categorical or continuous data using Chi square and $t$ tests. $P$ values $< 0.05$ were considered significant. Sample sizes were not calculated as the primary intent of this analysis was descriptive, and the cohort was derived by convenience sampling. A data analysis and statistical plan was written and filed with our institutional review board before data were accessed.

## Statistical analysis: evaluating the impact of surgical team members on variability of TXA administration

To estimate the effect of anesthesiologists and surgeons on prophylactic TXA utilization, we performed separate multivariable mixed-effects logistic regression analyses for primary THA, hip fracture surgery, and spinal fusion ± vertebrectomy. Our exposure of interest was the anesthesiologist and surgeon; the outcome was the administration of TXA. To account for patient and surgical risk, we adjusted for patient age, sex, comorbidities, preoperative hemoglobin, surgical urgency, hospital, and year. Patient age and preoperative hemoglobin were modelled using restricted cubic splines with five knots to allow for possible non-linear associations.[24,25] For hip fracture surgery, the model was adjusted for the specific surgery subtypes, including THA (in patients with a diagnosis of hip fracture), hip

hemiarthroplasty, and hip ORIF. Models were restricted to patients with data available for all covariates.

The exposures of interest, the anesthesiologist and surgeon, were included as random effects.[26] The specific anesthesiologists and surgeons were considered randomly chosen exemplars from a hypothetical and infinite population of such practitioners. Rather than having a separate coefficient representing the association of TXA use with each specific individual (fixed effects), our mixed-effects model computes the spread, separately, across the hypothetical population of anesthesiologists and surgeons. Thus, the variance components express how widely TXA use ranges across anesthesiologists and across surgeons. To assess which of the two groups of practitioners account for more variation in TXA use, their variance components can be directly compared in magnitude.

To characterize the relative contributions of anesthesiologists, surgeons, and patient-level factors on variation in TXA administration, we used the random intercepts to calculate the variance partition coefficient (VPC) and the median odds ratio (OR) for the receipt of TXA.[27] The VPC characterizes the proportion of variation attributable to the anesthesiologists, surgeons, patient factors, and other factors, and was calculated using the linear threshold model method. We used modified Wald *P* values to test if the variance was significantly different from zero.[28] The median OR is a standardized measure of the variability in the odds of TXA use among surgeons or anesthesiologists. It represents the median amount by which the odds of TXA administration would change given two different anesthesiologists (or surgeons), one with a higher probability of TXA use, and one with a lower probability of TXA use. For example, a median OR of 1.75 suggests that the odds of TXA use is increased 1.75-fold (75% increase) when comparing two anesthesiologists on the same surgical case (same patient, same surgeon). Similarly, a median OR of 1.15 for anesthesiologists would mean that changing the anesthesiologist would typically result in a 15% increase in the odds of receiving TXA (same patient, same surgeon).

To more clearly illustrate how widely TXA use varies by anesthesiologist and surgeon, we plotted practitioner-specific estimated rates of TXA use for a hypothetical but typical patient, whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population. To examine anesthesiologists, we set the surgeon to the surgeon with the median predicted likelihood of TXA use; for surgeons, we used the median anesthesiologist. We then plotted these predicted likelihoods using a box-and-whisker plot.

### Sensitivity analyses

As missing data were primarily limited to preoperative hemoglobin, the logistic regression models were performed using both single and multiple imputation for missing preoperative hemoglobin values. We performed single imputations assuming the missing hemoglobin values were: (a) the population mean, and (b) normal (120 $g{\cdot}L^{-1}$ for females, and 140 $g{\cdot}L^{-1}$ for males). To increase the generalizability of our findings, we conducted a separate logistic regression analysis that included all orthopedic and spine surgeries with TXA administration $> 10\%$.

We conducted all analyses using SAS/STAT software (SAS version 9.4 for Windows; SAS Institute Inc., Cary, NC, USA). Multilevel models were specified and analyzed using the SAS command PROC GLIMMIX (SAS version 9.4 for Windows; SAS Institute Inc., Cary, NC, USA).

## Results

### Baseline characteristics

In two hospitals, we identified 3,900 patients undergoing primary THA, hip fracture surgery, or spine fusion ± vertebrectomy. Surgical urgency varied by surgery type; most THAs (98%) and spine fusion ± vertebrectomies (74%) were elective, whereas all hip fracture surgeries were urgent/emergent. The mean (SD) patient age was 68 (16) yr and 55% of patients were female. Preoperative hemoglobin values were available in 89% of the cohort; other study variables had near complete (> 99%) capture. Baseline demographics classified by surgery type are included in Table 1.

Overall, there were 121 anesthesiologists and 45 surgeons. Most physicians worked exclusively at one hospital (72% of anesthesiologists; 67% of surgeons). Among the primary THAs, there were 105 anesthesiologists and 16 surgeons. Among the hip fracture surgeries, there were 107 anesthesiologists and 37 surgeons. Among the spine fusion ± vertebrectomies, there were 72 anesthesiologists and 14 surgeons.

### Description of prophylactic TXA use

The overall rate of prophylactic TXA administration was 48% ($n$ = 1,872/3,900). Prophylactic TXA was administered preoperatively in 2% of patients ($n$ = 44/1,872), with a mean (SD) administration time of 10 (12) min prior to surgery start. Tranexamic acid was administered intraoperatively in 98% of patients ($n$ = 1,828/1,872), with a mean (SD) administration time of 28 (14) min after surgery start. Tranexamic acid was

**Table 1** Description of baseline demographics categorized by surgery type

| Surgery | Surgery subgroup | Surgical volume (No. surgeries/ year) | Urgency (% elective) | Age, mean (SD) years | Sex (% female) | Charlson CI, mean (SD) | Pre-op Hb ($g \cdot L^{-1}$) | % transfused | % TXA use |
|---|---|---|---|---|---|---|---|---|---|
| Total hip arthroplasty | | 528 | 98 | 62 (13) | 47 | 0.2 (1.0) | 136 (15) | 3 | 85 |
| Hip fracture surgery | Total hip arthroplasty | 72 | 0 | 78 (12) | 65 | 0.8 (1.3) | 122 (15) | 14 | 45 |
| | Hip hemi-arthroplasty | 160 | 0 | 83 (9) | 69 | 0.8 (1.3) | 122 (16) | 14 | 29 |
| | Hip ORIF | 269 | 1 | 80 (14) | 70 | 0.8 (1.4) | 116 (18) | 31 | 13 |
| Spine fusion ± vertebrectomy | | 271 | 74 | 59 (15) | 45 | 0.5 (1.4) | 135 (17) | 14 | 23 |

CI = comorbidity index; Hb = hemoglobin; ORIF = open reduction internal fixation; SD = standard deviation; pre-op = preoperative; TXA = tranexamic acid

administered as an isolated bolus in 92% ($n$ = 1,714/1,872), as an infusion in 2% ($n$ = 31/1,872), and as a combined bolus and infusion in 7% ($n$ = 127/1,872) of cases. Overall, the median [IQR] cumulative TXA dose was 1,000 [1,000–1,000] mg. Tranexamic acid use was most common in primary THA ($n$ = 1,344/1,582; 85%), with lower utilization in hip fracture surgery ($n$ = 342/1,506; 23%) and spine fusion ± vertebrectomy (n=186/812; 23%) (Table 1). Surgery-specific patient demographics are included in eAppendix 2 (ESM).

## Evaluation of variability in prophylactic TXA administration by surgical team members

In our multivariable mixed-effects logistic regression models, anesthesiologists and surgeons added significant variability to the odds of receiving TXA in hip fracture surgery and spine fusion ± vertebrectomy, but not THA (eAppendices 3–6 [ESM]). In THA where TXA use is high, the variability of TXA use among anesthesiologists and surgeons was low. Conversely, in hip fracture surgery and spine fusion ± vertebrectomy where TXA use is lower, the variability in TXA use among anesthesiologists and surgeons was higher.

Among patients undergoing THA, most of the variation could be attributed to patient and other factors (VPC 92%), with some to anesthesiologists (6%), and less to surgeons (2%) (Fig. 2). The median OR for TXA administration was 1.6 among anesthesiologists and 1.3 among surgeons (Fig. 3). This means that for a given patient, their median odds of receiving TXA would differ by 1.6-fold depending on the anesthesiologist they receive care from, and by approximately 1.3-fold depending on the surgeon who performs their surgery. Among patients undergoing hip fracture surgery, 12% of the variation in TXA use was attributable to the anesthesiologist, 10% to the surgeon, and 78% to patient and other factors. The median OR for TXA administration was 2.0 among anesthesiologists and 1.8 among surgeons performing hip fracture surgery. Lastly, among patients undergoing spinal fusion ± vertebrectomy, 19% of the variation in TXA use was attributable to the anesthesiologist, 13% to the surgeon, and 68% to patient-specific factors. The median OR for TXA use was 2.5 among anesthesiologists and 2.1 among surgeons performing spinal fusion ± vertebrectomy.

Practitioner-specific estimated rates of TXA use for a hypothetical but typical patient undergoing each of the three surgeries are included in Fig. 4. For a typical THA patient, the likelihood of TXA use varied by anesthesiologist with a median [IQR] predicted probability of 0.84 [0.82–0.85], and by surgeon with a median [IQR] predicted probability of 0.85 [0.84–0.85] (Fig. 4). For a typical hip fracture surgery patient, the likelihood of TXA use varied by anesthesiologist with a median [IQR] predicted probability of 0.30 [0.26-0.37], and by surgeon with a median [IQR] predicted probability of 0.30 [0.27–0.36]. Lastly, for a typical spine fusion patient, the likelihood of TXA use varied by anesthesiologist with a median [IQR] predicted probability of 0.16 [0.13–0.24], whereas the likelihood of TXA use varied by surgeon with a median [IQR] predicted probability of 0.14 [0.12–0.20].

The variability among surgical team members was consistent when the models were run with imputation of preoperative hemoglobin, and when the impact of anesthesiologist and surgeon were evaluated in a broader population of orthopedic and spine surgeries. As a post-hoc sensitivity analysis, model estimates did not appreciably

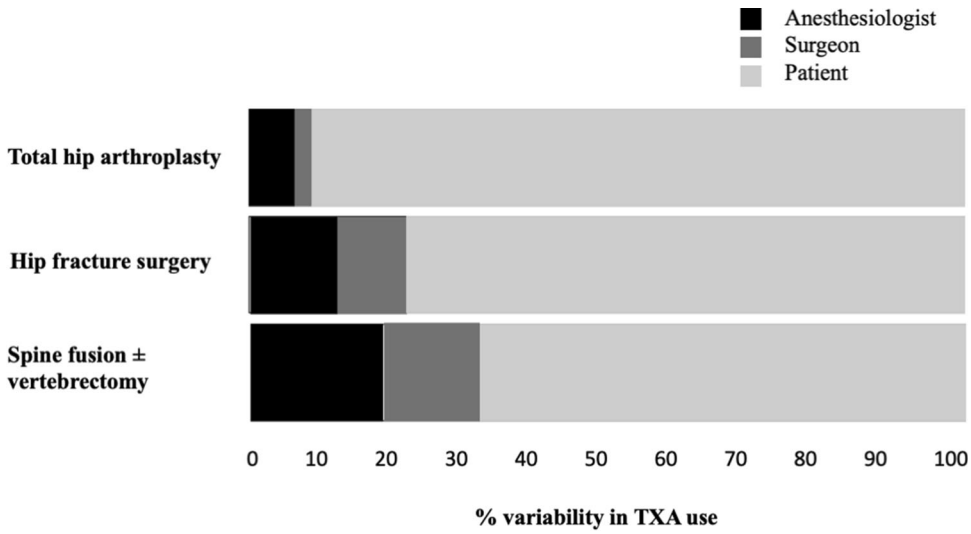


**Fig. 2** The partition of variability in TXA use among patient specific factors, the anesthesiologist, and surgeon for a given patient undergoing primary THA and spine fusion ± vertebrectomy. THA = total hip arthroplasty; TXA = tranexamic acid

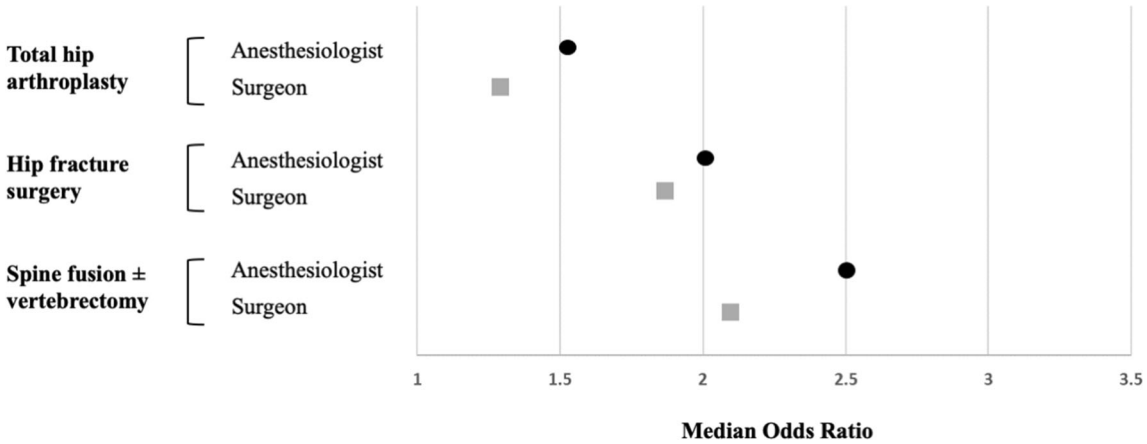


**Fig. 3** Median odds ratios (OR) of TXA administration for primary THA, hip fracture surgery and spine fusion ± vertebrectomy. The median OR is a standardized measure of the variability in the odds of TXA use among surgeons or anesthesiologists. It represents the median amount by which the odds of TXA administration would change given two different anesthesiologists (or surgeons), one with a higher probability of TXA use, and one with a lower probability of TXA use. TXA = tranexamic acid

change when we excluded care providers who worked at both the General and Civic campuses.

## Discussion

In our cohort, TXA use was highest in primary THA, with lower utilization in hip fracture surgery and spine fusion ± vertebrectomy. Most of the variability was related to patient and other factors. There was little variability in TXA use among anesthesiologists and surgeons in primary THA, with more substantial practice variability in the other two surgeries.

The high utilization (85%) and low variability of TXA use in THA reflects the substantial evidence supporting TXA efficacy and cost-effectiveness in this surgery.[9,29,30] As most of the variability in TXA use was related to patient and other factors, this could appropriately reflect risk-adapted clinical decision-making based on differing patient characteristics. Overall, this suggests the supportive recommendations for routine TXA use from multiple American orthopedic society guidelines have been effectively translated into clinical practice and incorporated into standard of care.[31]

In hip fracture and spine fusion surgeries, lower utilization and substantial variability in TXA use among surgical team members could reflect explicit anesthesiologist or surgeon preference for TXA administration, variations in surgical technique between surgeons, or the surgeon-specific case composition. Recently, randomized data have been published supporting the ability of TXA to reduce RBC transfusion

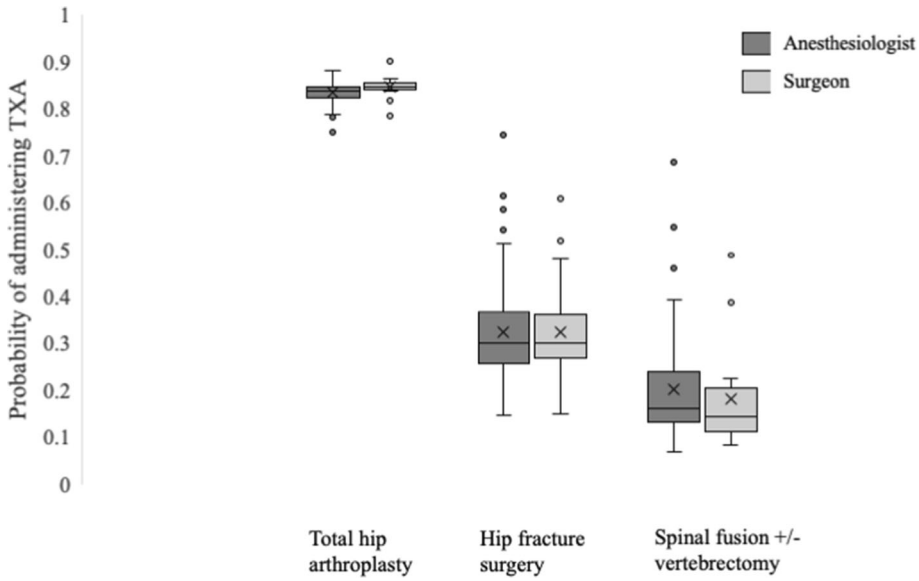


**Fig. 4** Practitioner-specific estimated rates of TXA use for a hypothetical, but typical patient, whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population. To examine anesthesiologists, we set the surgeon to the surgeon with the median predicted probability of TXA use; for surgeons, we used the median anesthesiologist. TXA = tranexamic acid

in hip fracture[13-15,32] and complex spine surgeries,[18,33,34] although the certainty surrounding safety (i.e., thrombosis) is less clear. The underreporting of thrombotic complications and limited durations of follow-up in trials may have underestimated the true incidence of thromboembolic complications in an elderly population at particularly increased risk.[18] Future randomized trials powered for important safety endpoints are needed prior to routine adoption.

Strengths of our study include the use of high-fidelity data sets that reliably capture patient demographics, surgical information, and TXA administration across a healthcare system that cares for more than 1 million people. We have addressed a knowledge gap by describing not only the rates of TXA use across different orthopedic surgeries but also how the use varies across surgical team members. To the best of our knowledge, this has never been previously reported.

Limitations of this study include the incomplete ascertainment of preoperative hemoglobin, which could be related to perioperative guidelines that advocate for reduced routine bloodwork prior to surgery.[35] To further understand the impact of this missing data, sensitivity analyses were planned *a priori* and performed with various imputation techniques, none of which significantly altered the results. We evaluated variability in TXA use among care providers from 2014 to 2016, which may not reflect recent TXA utilization practices. We were unable to evaluate the impact practitioner characteristics and training, nor the potential impact of trainees on TXA administration. Topical TXA was not explicitly captured, although this reflects institutional practice as topical administration was uncommonly used, if at all, during the study period. Though representative of a large referral population, our logistic regression models were limited to two Ottawa hospitals; an expanded evaluation of TXA utilization in additional centres could be beneficial.

In our cohort, prophylactic TXA was routinely used in primary THA, with little variation in use by anesthesiologists and surgeons. In hip fracture surgery and spine fusion, the prophylactic use of TXA was lower and more variable. Further study is warranted to understand the determinants of TXA practice variation and barriers to TXA implementation in a broader population of orthopedic surgical patients at high risk for RBC transfusion.

**Author contributions** All authors contributed to the conception and design of the manuscript. *Brett L. Houston*, *Emily Krupka*, *Iris Perelman*, *Alan Tinmouth*, and *Anna Blankstein* contributed to data acquisition. *Brett L. Houston*, *Allan Garland*, *Robert Balshaw*, and *Ryan Zarychanski* contributed to data analysis. *Brett L. Houston* drafted the manuscript, and all authors contributed to manuscript review.

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**Appendix 1.** Surgery names with their respective International Classification of Diseases (ICD-10) diagnosis codes and Canadian Classification of Health Interventions (CCI) codes. Codes were reviewed and amalgamated (as needed) to reflect the clinical description of the surgery performed.

| **Surgery** | **Surgery sub-type** | **CCI codes** | **ICD codes** |
|---|---|---|---|
| Total hip arthroplasty* | | 1VA53LAPN, 1VA53LLPN | C, M13, M16, M17, M19, M87, M841, M009, M06, M08, M45, M46, M844, Q, T8413 |
| Hip fracture surgery | THA | 1VA53LAPN, 1VA53LLPN | S72010, S72080, S72081, S72090, S72091, S72100, S72101, S72190, S72200, S72900 |
| | Hemi-arthroplasty | 1VA53LAPM, 1VA53LLPM | S72010, S72080, S72081, S72090, S72091, S72100, S72101, S72190, S72200, S72900 |
| | ORIF | 1VA74 | |
| | | 1VC74 | S72100, S72190 |
| Spine fusion ± vertebrectomy | | 1SC75, 1SC89 | |

*Primary total hip arthroplasty for arthritis; THA = total hip arthroplasty; ORIF = open reduction internal fixation

**Appendix 2.** Description of baseline characteristics by surgery and TXA status

| **Surgery** | **Surgery subgroup** | **Age (mean, SD)** | | **Sex (% female)** | | **Pre-op Hb (g/L)** | | **% transfused** | |
|---|---|---|---|---|---|---|---|---|---|
| | | **TXA** | **No TXA** | **TXA** | **No TXA** | **TXA** | **No TXA** | **TXA** | **No TXA** |
| Total hip arthroplasty | | 62 (13) | 64 (14) | 47 | 50 | 136 (14) | 133 (17) | 3 | 7 |
| Hip fracture surgery | Total hip arthroplasty | 73 (12) | 82 (10) | 67 | 64 | 123 (14) | 121 (16) | 9 | 18 |
| | Hip hemi-arthroplasty | 81 (10) | 83 (9) | 65 | 71 | 123 (15) | 121 (16) | 8 | 17 |
| | Hip ORIF | 79 (15) | 80 (14) | 75 | 69 | 113 (19) | 117 (18) | 32 | 31 |
| Spine fusion ± vertebrectomy | | 59 (15) | 58 (15) | 45 | 45 | 135 (18) | 134 (17) | 15 | 14 |

SD = standard deviation; pre-op = preoperative; Hb = hemoglobin; TXA = tranexamic acid; ORIF = open reduction internal fixation

**Appendix 3.** Summary of the variability between surgical team members and TXA use among the different surgeries

| Model | Surgical team member | Variance | Standard error | p-value |
|---|---|---|---|---|
| Total hip arthroplasty | Anesthesiologist | 0.23 | 0.19 | 0.11 |
| | Surgeon | 0.08 | 0.07 | 0.14 |
| Hip fracture surgery | Anesthesiologist | 0.51 | 0.17 | <0.01 |
| | Surgeon | 0.41 | 0.17 | <0.01 |
| Spine fusion ± vertebrectomy | Anesthesiologist | 0.90 | 0.31 | <0.01 |
| | Surgeon | 0.65 | 0.40 | 0.05 |

**Appendix 4.** Summary of fixed effects estimates from the multivariate logistic regression model of total hip arthroplasty. The area under the curve (AUC) was 0.74.

| Effect | | Estimate | Standard Error | Degrees of freedom | t Value | Pr > \|t\| | Pr > F |
|---|---|---|---|---|---|---|---|
| **Sex** | F | -0.07125 | 0.1757 | 1252 | -0.41 | 0.6852 | 0.6852 |
| **Surgical urgency (ref = urgent)** | Elective | 1.5766 | 0.4934 | 1252 | 3.20 | 0.0014 | 0.0014 |
| **Charlson comorbidity index** | 1 | 0.07871 | 0.3418 | 1252 | 0.23 | 0.8179 | 0.8179 |
| | 2 | -0.5432 | 0.4455 | 1252 | -1.22 | 0.2230 | 0.2230 |
| | ≥ 3 | -0.7452 | 0.4664 | 1252 | -1.63 | 0.1031 | 0.1031 |
| **Hospital (ref = General)** | Civic Hospital | -0.1196 | 0.2991 | 1252 | -0.40 | 0.6893 | 0.6893 |
| **Year** | 2014 | -0.2764 | 0.2162 | 1252 | -1.28 | 0.2012 | 0.2977 |
| | 2015 | -0.3102 | 0.2137 | 1252 | -1.45 | 0.1470 | |
| **Age** | Spline 1 | 0.03948 | 0.01743 | 1252 | 2.27 | 0.0237 | 0.0840 |
| | Spline 2 | -0.01499 | 0.01048 | 1252 | -1.43 | 0.1528 | |
| | Spline 3 | 0.02853 | 0.02779 | 1252 | 1.03 | 0.3048 | |
| | Spline 4 | -0.01439 | 0.02508 | 1252 | -0.57 | 0.5662 | |
| **Hemoglobin** | Spline 1 | -0.00764 | 0.01557 | 1252 | -0.49 | 0.6239 | 0.0809 |
| | Spline 2 | 0.01326 | 0.008972 | 1252 | 1.48 | 0.1396 | |
| | Spline 3 | -0.02948 | 0.02573 | 1252 | -1.15 | 0.2520 | |
| | Spline 4 | 0.07125 | 0.02859 | 1252 | 0.61 | 0.5393 | |

Ref = reference

**Appendix 5.** Summary of fixed effects estimates from the multivariate logistic regression model of hip fracture surgery. The area under the curve (AUC) was 0.74.

| Effect | | Estimate | Standard Error | Degrees of freedom | t Value | Pr > \|t\| | Pr > F |
|---|---|---|---|---|---|---|---|
| **Sex** | F | 0.2276 | 0.1777 | 1477 | 1.28 | 0.2005 | 0.2005 |
| **Surgical urgency (ref = urgent)** | Elective | 1.6669 | 0.9526 | 1477 | 1.75 | 0.0804 | 0.0804 |
| **Charlson comorbidity index** | 1 | -0.1222 | 0.2476 | 1477 | -0.49 | 0.6218 | 0.6218 |
| | 2 | 0.1885 | 0.1979 | 1477 | 0.95 | 0.3408 | 0.3408 |
| | ≥ 3 | 0.07621 | 0.2710 | 1477 | 0.28 | 0.7786 | 0.7786 |
| **Hospital (ref = General)** | Civic Hospital | -0.7174 | 0.3306 | 1477 | -2.17 | 0.0302 | 0.0302 |
| **Year** | 2014 | -0.6221 | 0.1884 | 1477 | -3.30 | 0.0010 | 0.0009 |
| | 2015 | -0.5751 | 0.1835 | 1477 | -3.13 | 0.0018 | |
| **Surgery type (ref = THA)** | Hip ORIF | -1.6655 | 0.2057 | 1477 | -8.10 | <.0001 | <.0001 |
| | Hip hemi-arthroplasty | -0.3529 | 0.2018 | 1477 | -1.75 | 0.0806 | |
| **Age** | Spline 1 | -0.01563 | 0.01163 | 1477 | -1.34 | 0.1792 | 0.0109 |
| | Spline 2 | -0.00416 | 0.00418 | 1477 | -0.99 | 0.3199 | |
| | Spline 3 | 0.02035 | 0.02106 | 1477 | 0.97 | 0.3340 | |
| | Spline 4 | -0.02758 | 0.03237 | 1477 | -0.85 | 0.3942 | |
| **Hemoglobin** | Spline 1 | 0.005283 | 0.01187 | 1477 | 0.45 | 0.6564 | 0.7674 |
| | Spline 2 | -0.00056 | 0.002960 | 1477 | -0.19 | 0.8506 | |
| | Spline 3 | -0.00004 | 0.01021 | 1477 | -0.00 | 0.9969 | |
| | Spline 4 | 0.001480 | 0.01155 | 1477 | 0.13 | 0.8981 | |

Ref = reference

**Appendix 6.** Summary of fixed effects estimates from the multivariate logistic regression model of spine fusion ± vertebrectomy. The area under the curve (AUC) was 0.84.

| Effect | | Estimate | Standard Error | Degrees of freedom | t Value | Pr > \|t\| | Pr > F |
|---|---|---|---|---|---|---|---|
| **Sex** | F | -0.1462 | 0.2207 | 679 | -0.66 | 0.5078 | 0.5078 |
| **Surgical urgency (ref = urgent)** | Elective | 0.4591 | 0.2704 | 679 | 1.70 | 0.0900 | 0.0900 |
| **Charlson comorbidity index** | 1 | -0.1075 | 0.3384 | 679 | -0.32 | 0.7510 | 0.7510 |
| | 2 | -0.6967 | 0.5546 | 679 | -1.26 | 0.2095 | 0.2095 |
| | ≥ 3 | -0.4157 | 0.6137 | 679 | -0.68 | 0.4984 | 0.4984 |
| **Year** | 2014 | -0.05634 | 0.2723 | 679 | -0.21 | 0.8362 | 0.8090 |
| | 2015 | -0.2394 | -0.1796 | 0.2848 | 679 | -0.63 | |
| **Age** | Spline 1 | -0.01131 | 0.02023 | 679 | -0.56 | 0.5765 | 0.9773 |
| | Spline 2 | 0.001800 | 0.005887 | 679 | 0.31 | 0.7599 | |
| | Spline 3 | -0.00411 | 0.02303 | 679 | -0.18 | 0.8585 | |
| | Spline 4 | 0.002398 | 0.02475 | 679 | 0.10 | 0.9228 | |
| **Hemoglobin** | Spline 1 | -0.01631 | 0.01448 | 679 | -1.13 | 0.2603 | 0.4395 |
| | Spline 2 | 0.002478 | 0.005908 | 679 | 0.42 | 0.6751 | |
| | Spline 3 | -0.00570 | 0.02338 | 679 | -0.24 | 0.8073 | |
| | Spline 4 | 0.005408 | 0.02842 | 679 | 0.19 | 0.8491 | |

Ref = reference

# The association between perioperative tranexamic acid use and red blood cell transfusion in orthopedic surgery: a retrospective cohort study

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# The association between perioperative tranexamic acid use and red blood cell transfusion in orthopedic surgery: a retrospective cohort study

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**Conflicts of interest:** None

**ABSTRACT**

BACKGROUND: Tranexamic acid (TXA) has been shown to reduce perioperative red blood cell (RBC) transfusion in a variety of surgeries. We aim to evaluate the real-world effectiveness of prophylactic intravenous TXA in 3 high frequency orthopedic surgeries: primary total hip arthroplasty (THA), hip fracture surgery and spine fusion ± vertebrectomy.

METHODS: We completed a retrospective cohort study of all adult patients undergoing primary total hip arthroplasty, hip fracture surgery and spine fusion ± vertebrectomy at two Canadian hospitals between January 2014 and December 2016. We used Canadian Classification of Health Interventions procedure codes within the Discharge Abstract Database, which we linked to the Ottawa Data Warehouse. To evaluate the effectiveness of TXA to reduce RBC transfusion, we completed a propensity analysis using stabilized inverse probability of treatment weighting.

RESULTS: We identified 3,900 patients undergoing primary THA, hip fracture surgery or spine fusion ± vertebrectomy. TXA use was most common in primary THA (85%; n=1,344/1,582), with lower use in hip fracture surgery (23%; n=342/1,506) and spine fusion (23%; n=186/812). In primary THA, TXA use was associated with a trend towards the reduced odds of perioperative RBC transfusion (OR 0.77; 95% CI 0.34 to 1.77). In hip fracture surgery, TXA administration was associated with reduced odds of perioperative RBC transfusion (OR 0.60; 95% CI 0.41 to 0.87), whereas in spine fusion TXA use was associated with increased the odds of perioperative RBC transfusion (OR 1.33; 95% CI 0.72 to 2.45).

CONCLUSION: Perioperative TXA was associated with variable impact on perioperative RBC transfusion. Further study with detailed surgery-specific data is needed to adequately capture all relevant patient and surgery-specific covariates.

## INTRODUCTION:

Orthopedic surgeries are commonly associated with perioperative red blood cell (RBC) transfusion.[1] TXA is an inexpensive and widely available antifibrinolytic medication that has consistently been shown to reduce RBC transfusion in cardiac surgery, hip and knee arthroplasty and trauma, where it is now incorporated into standard of care.[2-7] Recent evidence syntheses support the efficacy of TXA in reducing transfusion in hip fracture surgery[8-10] and spine surgery.[11,12] Despite this, TXA is not routinely used perioperatively in this patient population. Real-world data on TXA effectiveness will supplement clinical trial findings and inform the perioperative management patients. We aim to provide a real-world evaluation of TXA effectiveness in three high frequency orthopedic surgeries: primary total hip arthroplasty, hip fracture surgery and spine fusion ± vertebrectomy.

## METHODS:

*Study design, setting and population*

We completed a retrospective cohort study of all adult patients (≥ 18 years of age) undergoing primary total hip arthroplasty, hip fracture surgery and spine fusion ± vertebrectomy at two hospitals in Ottawa, Ontario (Ottawa Hospital, Civic and General Campuses) between January 1, 2014 and December 31, 2016. These hospitals are tertiary care centers providing health services to approximately 1 million people. These orthopedic surgeries were chosen because they are high frequency surgeries (n >150 per year) with higher (>10%) rates of TXA utilization[13,14]. To prevent misclassification of surgery-specific rates of prophylactic TXA use, we excluded patients with more than one surgery during their hospitalization. If a patient was re-admitted for another surgery during the study period (2014-2016), we evaluated only their initial hospital admission (**Figure 1)**.

*Data sources*

We obtained patient demographics, clinical, and administrative hospitalization data from the Discharge Abstract Database (DAD). The DAD uses standard International Classification of Diseases (ICD) coding for diagnoses and comorbidities, and Canadian Classification of Health Interventions (CCI) coding for surgical procedures[15]. The DAD undergoes a continual process of data quality assurance and data validation.[16] Transfusion, laboratory and TXA data were

obtained from The Ottawa Hospital Data Warehouse, which is a data repository of clinical, laboratory and health services information collected from the hospital's information systems. Within the Ottawa Hospital Data Warehouse, TXA data was sourced from the Surgical Information Management System (SIMS), a perioperative electronic medical record which represents the medicolegal record for all surgical cases and the gold standard for perioperative medication administration.

*Study variables*

We obtained patient demographics including age, sex, baseline comorbidities, most responsible diagnosis and preoperative hemoglobin. Baseline comorbidities were evaluated using the Charlson comorbidity index.[17] For the pre-operative hemoglobin, we obtained the prior value drawn closest to the start of surgery, within the preceding 4 weeks. Surgical information, including type of procedure, date/time and surgical urgency (ie, elective, urgent/emergent) and surgical staff (ie, anethesiologist, surgeon) was obtained from the DAD using standardized CCI procedure codes.[15,18] CCI procedure codes and ICD-10 diagnosis codes were used to define the orthopedic surgeries **(Appendix 1).**[13] Total hip arthroplasty (THA) for osteoarthritis was evaluated separately, whereas THA performed for hip fracture was included as part of the hip fracture surgery grouping. Hip fracture surgery was comprised of THA (for hip fracture), hip hemiarthroplasty and hip open reduction internal fixation (ORIF). To reflect transfusions attributable to perioperative bleeding, surgery-specific transfusion rates were defined based on RBC transfusions from the start of the surgery to 7 days post-operative or hospital discharge, whichever occurred first. Prophylactic TXA administration was defined as intravenous TXA initiated within 1 hour before or after the start of surgery, with the intent to exclude cases where TXA was administered in response to surgical bleeding. Only prophylactic intravenous TXA use is considered in this paper.

*Baseline comparisons of treatment groups*

Baseline characteristics were summarized as mean and standard deviation for continuous variables, and proportions for categorical variables. Standardized differences were used to compare baseline characteristics between the two treatment groups.[19]

*Propensity score estimation*

The propensity score estimates the patient's likelihood of receiving TXA given their characteristics. We estimated the propensity score using a logistic regression model in which TXA status (receipt of prophylactic TXA versus no prophylactic TXA) was regressed on 17 baseline covariates included in Table 1 **(Appendices 2-4)**.[20] Age was categorized as <50 years, 50 to 69 years, and ≥70 years. Preoperative hemoglobin was included as normal (≥120g/L in females; ≥130g/L in males), mild anemia (≤20g/L below normal) or more significant anemia (>20g/L below normal). With input from content experts, variables were included if they affected either the outcome (possible confounder), or both the treatment and outcome (confounder).[21-23] The propensity score model was restricted to patients with data available for all covariates.

*Methods to achieve balance between treatment groups*

The success of a propensity score is determined by its ability to balance measured covariates between treatment groups. Prior to performing the analysis, we conducted a feasibility assessment to evaluate the overlap of the propensity score distribution between treated and untreated individuals **(Appendices 5-7)**. For each surgery, we used 3 distinct analytic approaches to assess the relationship between TXA use and perioperative RBC transfusion: (1) stabilized inverse probability weighting (IPTW); (2) propensity matching; and (3) stratification based on propensity score. We considered IPTW the primary analysis, as it estimates the average treatment effect, which more closely approximates that of a trial, resulted in the best overall covariate balance between treatment groups, and used most of the patient data. This was determined prior to estimation of the treatment effect. The remaining analyses were secondary analyses.

*Stabilized inverse probability of treatment weighting*

Weighting attempts to use weights to create a pseudo-sample in which the distribution of measured covariates is independent of treatment assignment. Each patient is assigned a weight

equal to the inverse of the probability of receiving the treatment that the patient received. As such, treated patients with very small propensity scores (i.e., close to 0), and untreated patients with large propensity scores (i.e., close to 1) can be assigned large weights with significant influence. To minimize disproportionate weighting on patients with extreme propensity score values, we weighted our study population using the stabilized inverse probability of treatment weights derived from the propensity score[27]. To assess for potential concerns regarding non-positivity of mis-specification of the propensity score, we calculated the mean stabilized weight as well as the range of stabilized weights.

To evaluate the ability of the propensity score to balance observed covariates across treatment groups, we compared the differences in means or prevalence in continuous and dichotomous covariates between treatment groups. Standardized differences were calculated to quantify the differences in means or prevalences between the treatment groups. An absolute standardized difference <0.1 and variance ratio between 0.5 and 2 were used as thresholds for adequate covariate balance[25].The distribution of continuous covariates were compared by side-by-side plots, quantile-quantile plots and cumulative density plots.

*Sensitivity analyses*

As missing data was primarily limited to preoperative hemoglobin, the logistic regression model used to derive the propensity score was performed using both single and multiple imputation for missing preoperative hemoglobin values. We performed single imputations assuming the missing hemoglobin values were: (a) the population mean, and (b) normal (120 g/L for females, and 130 g/L for males).

*Statistical analysis*

Baseline characteristics were summarized as means (standard deviation [SD]), medians (interquartile range [IQR]) or frequency (percent). We analyzed group differences in categorical or continuous data using Chi-square and t-tests. P-values <0.05 were considered significant. Effect comparisons were presented as odds ratios (OR), relative risk (RR), and absolute risk reduction. Sample size calculations were not performed as the primary intent of this analysis was

descriptive, and the cohort was derived by convenience sampling. We conducted all analyses using SAS/STAT software (SAS version 9.4 for Windows; SAS Institute Inc., Cary, NC, USA).

## RESULTS:

*Baseline characteristics*

In two hospitals we identified 3,900 patients undergoing primary THA, hip fracture surgery or spine fusion ± vertebrectomy **(Figure 1)**. The overall rate of prophylactic TXA administration was 48% (n=1,872/3,900). TXA use was most common in primary THA (n=1,344/1,582; 85%), with lower utilization in hip fracture surgery (n=342/1,506; 23%) and spine fusion ± vertebrectomy (n=185/812; 23%). Surgical urgency varied by surgery type; most THAs (98%) and spine fusion ± vertebrectomies (74%) were elective, whereas all hip fracture surgeries were urgent/emergent. The mean patient age was 68 years (SD 16 years); 55% were female. Preoperative hemoglobin values were available in 89% of the cohort; other study variables had near complete (>99%) capture. The baseline standardized difference exceeded 0.1 in 9 of 17 variables in the total hip arthroplasty cohort, 11 of 17 variables in the hip fracture surgery cohort, and 9 of 17 variables in the spine fusion cohort. Baseline demographics classified by surgery type are included in **Tables 1a-c**.

*Propensity score weighting balance diagnostics*

Among patients undergoing total hip arthroplasty, the mean stabilized weight was 1.00 (SD 0.29) with a stabilized weight range from 0.21 to 2.39 **(Appendix 8)**. The absolute standardized differences ranged from 0.001 to 0.141, with a median of 0.028 (IQR 0.012 to 0.049) **(Appendix 9**). Among patients undergoing hip fracture surgery, the mean stabilized weight was 1.02 (SD 0.46) with a stabilized weight range from 0.27 to 4.73 **(Appendix 10)**. The absolute standardized differences ranged from 0.001 to 0.122, with a median of 0.028 (IQR 0.015 to 0.046) **(Appendix 11)**. Lastly, among patients undergoing spine fusion ± vertebrectomy, the mean stabilized weight was 1.01 (SD 0.26) with a stabilized weight range from 0.29 to 3.20 (**Appendix 12)**. The absolute standardized differences ranged from 0.004 to 0.111, with a median of 0.038 (IQR 0.017 to 0.060) **(Appendix 13)**. The standardized

differences and variance ratios for matching and stratification analyses are included in **Appendices 14-19**.

*Estimation of treatment effects*

Among patients undergoing total hip arthroplasty, TXA administration was associated with a trend towards the reduced odds of perioperative RBC transfusion (OR 0.77; 95% CI 0.34 to 1.77) **(Figure 2)**. The relative risk of perioperative RBC transfusion in treated patients compared to untreated patients was 0.61 (95% CI 0.37 to 0.99). The represents an absolute risk reduction of 9% (95% CI 2% to 21%). These effect estimates were consistent among the different analytic strategies.

Among patients undergoing hip fracture surgery, TXA administration was associated with reduced odds of perioperative RBC transfusion (OR 0.60; 95% CI 0.41 to 0.87). The relative risk of perioperative RBC transfusion in treated patients compared to untreated patients was 0.90 (95% CI 0.83 to 0.96). This represents an absolute risk reduction of 9% (95% CI 3% to 14%). These effect estimates were consistent among the different analytic strategies.

Among patients undergoing spine fusion ± vertebrectomy, TXA administration was associated with increased the odds of perioperative RBC transfusion (OR 1.33; 95% CI 0.72 to 2.45). The relative risk of perioperative RBC transfusion in treated patients compared to untreated patients was 1.07 (95% CI 0.91 to 1.27). This represents an absolute risk increase of 5% (95% CI -7% to 17%). These effect estimates were consistent among the different analytic strategies.

**DISCUSSION:**

In primary total hip arthroplasty and hip fracture surgery, prophylactic intravenous TXA administration was associated with a trend to reduced RBC transfusion. Conversely, among patients undergoing spinal fusion ± vertebrectomy, TXA was associated with an increased likelihood of RBC transfusion. The surgery-specific differences in the association between TXA use and RBC transfusion were consistent across the different analyses.

The trend towards reduced RBC transfusion with perioperative TXA use in primary total hip arthroplasty and hip fracture surgery is consistent with a substantive body of literature

supporting its efficacy.[8,10,28-32] This is consistent with supportive recommendations for routine TXA use from multiple American orthopedic society guidelines.[28]

The increase in RBC transfusion associated with TXA use in spine fusion ± vertebrectomy is discrepant to prior evidence syntheses which suggest TXA benefit.[11,13] This may reflect the grouping of procedures within the categorization of spine fusion ± vertebrectomy, which may vary in complexity, invasiveness, tissue trauma and hemorrhage. This is supported by the wide range of operative time within this grouping (median surgical duration 6 hours; range 1 to 16 hours). This single grouping may therefore not account for differing RBC transfusion risk. Within spine surgery, differences RBC transfusion rate have been reported with increasing age, female sex, varying surgical approaches, multilevel surgery, instrumented fusion, preoperative anemia and duration of surgery[33-37]. This degree of granularity was not available using CCI procedure codes from the DAD, and therefore we were not able to adjust for these variables. It is possible that patients who received TXA did so because of a perceived increased risk of transfusion that was otherwise not captured with our study variables. The increased duration of surgery among patients who received TXA versus those who did not (6.2 vs 5.5 hours; $p < 0.001$) supports this hypothesis. Duration of surgery was intentionally not included in our propensity score model as this would not have been known at the time of TXA administration.

While the same limitation of unmeasured variability in surgical invasiveness may have impacted total hip arthroplasty and hip fracture surgery analyses, this is less likely given there was less operative time variability among these groupings. The mean surgical duration in patients who underwent hip fracture and spine fusion surgery was 2 hours (standard deviation 0.8 hours) and 1.6 hours (SD 0.7 hours), respectively. It seems mechanistically implausible that TXA actually increases RBC transfusion, and this has not been reported in systematic reviews synthesizing data from more than 60 randomized trials[38,39].

Strengths of our study include the use of high-fidelity datasets that reliably capture patient demographics, surgical information, and TXA administration across a health care system that cares for more than 1 million people. We used a comprehensive analytic approach including stabilized inverse probability weighting, matching, stratification, and logistic regression with and without propensity score adjustment. The consistency of the effect estimates within each surgery

subtype supports the adequacy of covariate balance between the measured covariates. Analyses were separated *a priori* between the three surgeries to facilitate evaluation of populations as homogenous as possible. These propensity analyses support trial data by providing a real-world evaluation of TXA use and RBC transfusion among consecutive patients undergoing high-frequency orthopedic surgeries over a three-year period.

The major limitation of our study was our inability to control for all relevant factors that influence whether a patient receives TXA. While we were able to balance measured covariates, we were unable to control for unmeasured covariates[25,40]. Our databases lacked granularity regarding specifics of the surgical procedures, particularly with respect to spine surgery. Additionally, we defined prophylactic TXA use as TXA administered within one hour of surgery start, yet this could conceivably encompass patients who received TXA in response to surgical bleeding. Lastly, we were unable to evaluate other blood conservation strategies such as topical TXA administration, which could have affected RBC transfusion.

Using propensity methods, we have evaluated the association between prophylactic TXA administration and RBC transfusion in three high frequency orthopedic surgeries. Further study with detailed surgery-specific data is needed to adequately capture all relevant patient and surgery-specific covariates.

**Figure 1**. Flow diagram

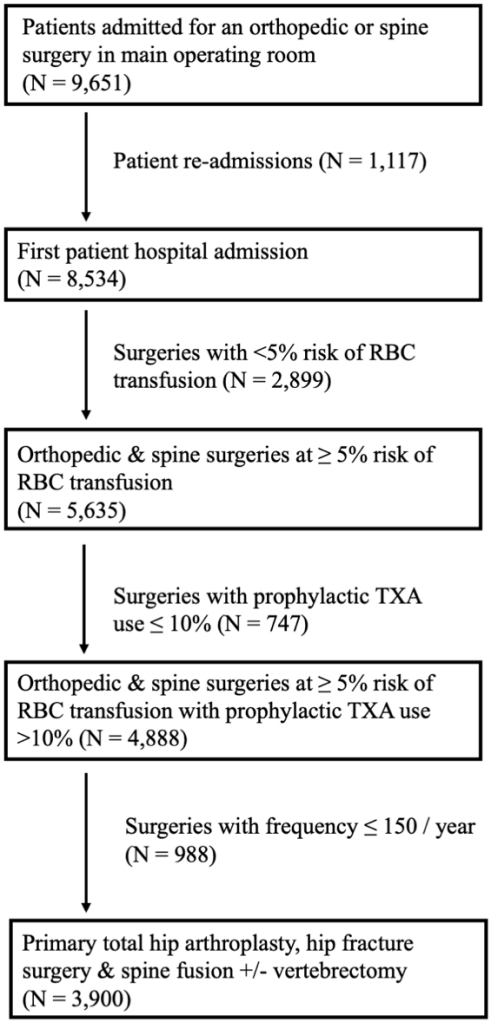
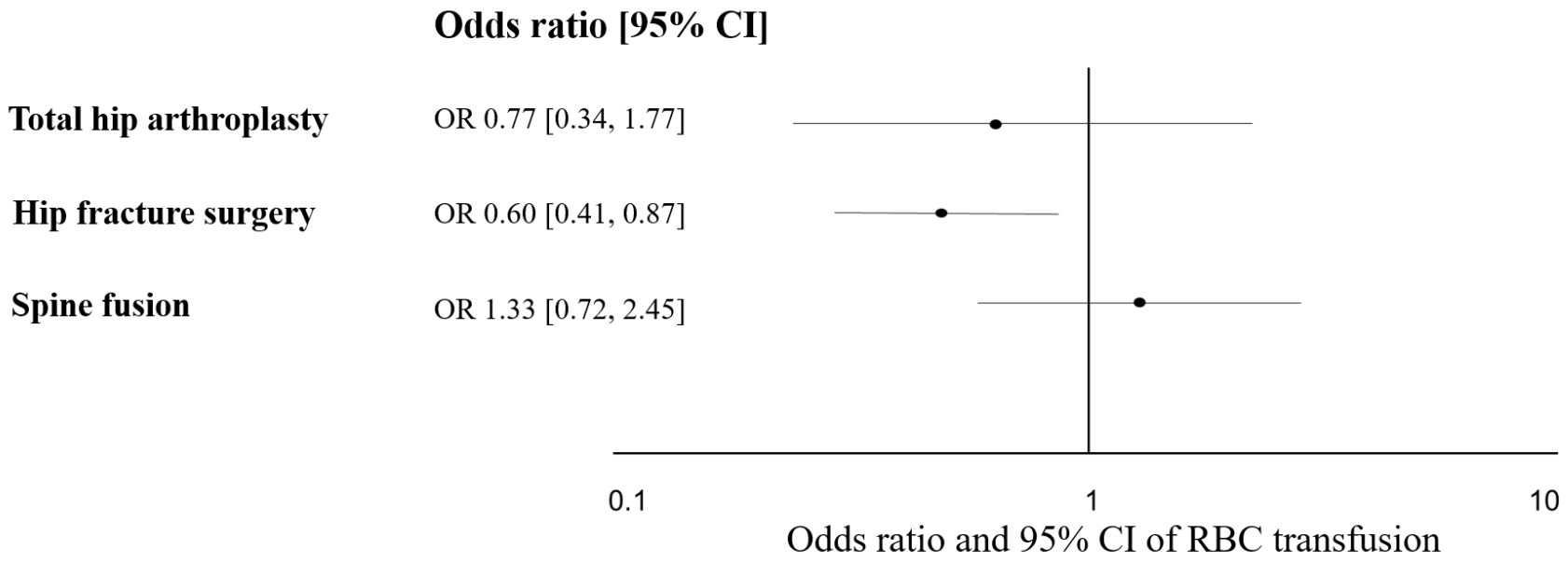


**Figure 2.** Odds ratios (95% CIs) for RBC transfusion associated with TXA use




CI = confidence interval; RBC = red blood cell; TXA = tranexamic acid

**Table 1a.** Baseline characteristics of treated and untreated patients undergoing total hip arthroplasty surgery before and after stabilized inverse probability weighting

| | Entire cohort | | | Post stabilized IPTW | | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | TXA (n=1068) | No TXA (n=201) | SD | TXA (n=589) | No TXA (n=169) | SD | % reduction | Variance ratio |
| Age (years) | 62 (13) | 64 (15) | -0.174 | 63 (13) | 65 (14) | -0.055 | 68 | 0.84 |
| % Female | 47 | 50 | -0.080 | 49 | 53 | 0.048 | 40 | |
| No comorbidities | 91 | 84 | 0.219 | 86 | 80 | 0.005 | 98 | |
| Preoperative hemoglobin (g/L) | 137 (14) | 133 (17) | 0.247 | 135 (15) | 131 (17) | 0.044 | 82 | 0.82 |
| Year | | | | | | | | |
| 2014 | 34 | 38 | 0.088 | 38 | 41 | -0.060 | 32 | |
| 2015 | 32 | 35 | 0.052 | 34 | 35 | 0.036 | 30 | |
| 2016 | 34 | 27 | -0.147 | 28 | 24 | 0.026 | 82 | |
| Anesthesiologist | | | | | | | | |
| Q1 | 16 | 39 | 0.599 | 30 | 51 | 0.012 | 97 | |
| Q2 | 27 | 29 | 0.035 | 42 | 31 | -0.001 | 96 | |
| Q3 | 15 | 13 | -0.066 | 14 | 9 | 0.066 | 1 | |
| Q4 | 21 | 14 | -0.197 | 13 | 9 | 0.028 | 86 | |
| Q5 | 21 | 5 | -0.572 | 1 | 1 | 0.023 | 96 | |
| Surgeon | | | | | | | | |
| Q1 | 12 | 26 | 0.346 | 18 | 30 | 0.019 | 94 | |
| Q2 | 2 | 3 | 0.068 | 4 | 2 | -0.141 | 0 | |
| Q3 | 0 | 1 | 0.090 | 1 | 1 | -0.009 | 89 | |
| Q4 | 28 | 24 | -0.068 | 27 | 24 | 0.011 | 84 | |
| Q5 | 58 | 46 | -0.252 | 51 | 43 | 0.025 | 91 | |

*Continuous variables are represented by mean (standard deviation); dichotomous variables are presented as %. SD = standardized difference; IPTW = inverse probability of treatment weighting; TXA = tranexamic acid; Q = quintile. Q1 to Q5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population.

**Table 1b**. Baseline characteristics of treated and untreated patients undergoing hip fracture surgery before and after stabilized inverse probability weighting

| | Entire cohort | | | Post stabilized IPTW | | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | TXA (n=340) | No TXA (n=1161) | SD | TXA (n=319) | No TXA (n=672) | SD | % reduction | Variance ratio |
| Age (years) | 78 (13) | 81 (13) | -0.223 | 78 (13) | 80 (13) | -0.094 | 58 | 0.99 |
| % Female | 69 | 69 | -0.008 | 69 | 68 | 0.025 | 0 | |
| No comorbidities | 61 | 64 | -0.052 | 62 | 61 | 0.071 | 0 | |
| Preoperative hemoglobin (g/L) | 120 (17) | 119 (17) | 0.060 | 120 (17) | 119 (17) | 0.025 | 58 | 1.00 |
| Year | | | | | | | | |
| 2014 | 27 | 35 | 0.182 | 30 | 33 | -0.001 | 99 | |
| 2015 | 29 | 33 | 0.077 | 34 | 32 | -0.021 | 72 | |
| 2016 | 44 | 32 | -0.248 | 36 | 35 | 0.022 | 91 | |
| Anesthesiologist | | | | | | | | |
| Q1 | 8 | 27 | 0.527 | 7 | 14 | -0.122 | 77 | |
| Q2 | 11 | 21 | 0.274 | 10 | 15 | 0.012 | 95 | |
| Q3 | 10 | 12 | 0.069 | 9 | 13 | 0.030 | 56 | |
| Q4 | 30 | 24 | -0.135 | 29 | 31 | 0.043 | 68 | |
| Q5 | 41 | 16 | -0.586 | 44 | 28 | 0.028 | 95 | |
| Surgeon | | | | | | | | |
| Q1 | 15 | 41 | 0.608 | 12 | 21 | -0.013 | 98 | |
| Q2 | 6 | 12 | 0.211 | 6 | 9 | -0.050 | 76 | |
| Q3 | 6 | 7 | 0.031 | 5 | 8 | 0.049 | 0 | |
| Q4 | 17 | 13 | -0.100 | 18 | 19 | 0.036 | 64 | |
| Q5 | 56 | 27 | -0.628 | 60 | 44 | -0.010 | 98 | |

*Continuous variables are represented by mean (standard deviation); dichotomous variables are presented as %. SD = standardized difference; IPTW = inverse probability of treatment weighting; TXA = tranexamic acid; Q = quintile. Q1 to Q5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population.

**Table 1c.** Baseline characteristics of treated and untreated patients undergoing spine fusion surgery before and after stabilized inverse probability weighting

| | Entire cohort | | | Post stabilized IPTW | | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | TXA (n=159) | No TXA (n=536) | SD | TXA (n=146) | No TXA (n=272) | SD | % reduction | Variance ratio |
| Age (years) | 59 (15) | 58 (15) | 0.058 | 59 (15) | 58 (16) | 0.046 | 20 | 0.83 |
| % Female | 45 | 45 | 0.020 | 45 | 45 | 0.020 | 0 | |
| No comorbidities | 83 | 79 | 0.087 | 83 | 81 | -0.061 | 30 | |
| Preoperative hemoglobin (g/L) | 135 (18) | 134 (17) | 0.019 | 135 (18) | 134 (17) | -0.024 | 0 | 1.10 |
| Year | | | | | | | | |
| 2014 | 36 | 36 | 0.021 | 39 | 40 | 0.005 | 77 | |
| 2015 | 30 | 32 | 0.040 | 27 | 31 | -0.106 | 0 | |
| 2016 | 34 | 32 | -0.062 | 34 | 29 | 0.099 | 0 | |
| Anesthesiologist | | | | | | | | |
| Q1 | 6 | 34 | 0.784 | 1 | 0 | -0.162 | 79 | |
| Q2 | 17 | 23 | 0.245 | 15 | 29 | 0.087 | 64 | |
| Q3 | 11 | 13 | 0.104 | 10 | 17 | 0.063 | 39 | |
| Q4 | 22 | 16 | -0.203 | 24 | 28 | -0.054 | 73 | |
| Q5 | 44 | 14 | -0.798 | 51 | 25 | 0.064 | 92 | |
| Surgeon | | | | | | | | |
| Q1 | 5 | 15 | 0.365 | 3 | 8 | -0.078 | 79 | |
| Q2 | 5 | 13 | 0.283 | 5 | 7 | 0.087 | 69 | |
| Q3 | 15 | 22 | 0.201 | 14 | 21 | -0.074 | 63 | |
| Q4 | 13 | 18 | 0.084 | 14 | 22 | -0.034 | 60 | |
| Q5 | 62 | 32 | -0.628 | 64 | 42 | 0.083 | 87 | |

*Continuous variables are represented by mean (standard deviation); dichotomous variables are presented as %. SD = standardized difference; IPTW = inverse probability of treatment weighting; TXA = tranexamic acid; Q = quintile. Q1 to Q5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population.

**Appendix 1.** Surgery names with their respective International Classification of Diseases (ICD-10) diagnosis codes and Canadian Classification of Health Interventions (CCI) codes. Codes were reviewed and amalgamated (as needed) to reflect the clinical description of the surgery performed.

| **Surgery** | **Surgery sub-type** | **CCI codes** | **ICD codes** |
|---|---|---|---|
| Total hip arthroplasty* | | 1VA53LAPN, 1VA53LLPN | C, M13, M16, M17, M19, M87, M841, M009, M06, M08, M45, M46, M844, Q, T8413 |
| Hip fracture surgery | THA | 1VA53LAPN, 1VA53LLPN | S72010, S72080, S72081, S72090, S72091, S72100, S72101, S72190, S72200, S72900 |
| | Hemi-arthroplasty | 1VA53LAPM, 1VA53LLPM | S72010, S72080, S72081, S72090, S72091, S72100, S72101, S72190, S72200, S72900 |
| | ORIF | 1VA74 | |
| | | 1VC74 | S72100, S72190 |
| Spine fusion ± vertebrectomy | | 1SC75, 1SC89 | |

*Primary total hip arthroplasty for arthritis; THA = total hip arthroplasty; ORIF = open reduction internal fixation

**Appendix 2.** Logistic regression propensity score model for TXA use in patients undergoing primary total hip arthroplasty

| Covariate | Description | Odds Ratio | 95% CI |
|---|---|---|---|
| Age | <50 years | Reference | |
| | 50 – 69 years | 0.98 | 0.62 to 1.53 |
| | ≥ 70 years | 0.72 | 0.44 to 1.18 |
| Sex | Male | Reference | |
| | Female | 0.93 | 0.69 to 1.26 |
| Comorbidities | Absent | Reference | |
| | Present | 0.85 | 0.55 to 1.32 |
| Preoperative hemoglobin | Normal* | Reference | |
| | ≤20 g/L below normal | 0.63 | 0.43 to 0.91 |
| | >20 g/L below normal | 0.86 | 0.59 to 1.26 |
| Anesthesiologist | Quintile 1 | Reference | |
| | Quintile 2 | 2.29 | 1.59 to 3.30 |
| | Quintile 3 | 3.27 | 2.04 to 5.25 |
| | Quintile 4 | 4.31 | 2.72 to 6.82 |
| | Quintile 5 | 11.50 | 6.06 to 21.79 |
| 3.50 | Quintile 1 | Reference | |
| | Quintile 2 | 1.67 | 0.64 to 4.40 |
| | Quintile 3 | 1.37 | 0.22 to 8.47 |
| | Quintile 4 | 2.17 | 1.35 to 3.50 |
| | Quintile 5 | 2.46 | 1.66 to 3.65 |
| 0.71 | 2014 | 0.72 | 0.49 to 1.08 |
| | 2015 | 0.80 | 0.55 to 1.18 |
| | 2016 | Reference | |

*Normal defined as hemoglobin ≥120g/L in females and ≥130g/L in males; Quintile 1 to quintile 5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population; TXA = tranexamic acid; CI = confidence interval

**Appendix 3.** Logistic regression propensity score model for TXA use in patients undergoing hip fracture surgery

| Covariate | Description | Odds Ratio | 95% CI |
|---|---|---|---|
| Age | <50 years | Reference | |
| | 50 – 69 years | 1.78 | 0.68 to 4.68 |
| | ≥ 70 years | 0.95 | 0.37 to 2.42 |
| Sex | Male | Reference | |
| | Female | 0.94 | 0.68 to 1.29 |
| Comorbidities | Absent | Reference | |
| | Present | 1.15 | 0.86 to 1.53 |
| Preoperative hemoglobin | Normal* | Reference | |
| | ≤20 g/L below normal | 1.11 | 0.81 to 1.52 |
| | >20 g/L below normal | 0.72 | 0.48 to 1.08 |
| Anesthesiologist | Quintile 1 | Reference | |
| | Quintile 2 | 1.99 | 1.15 to 3.46 |
| | Quintile 3 | 3.06 | 1.72 to 5.43 |
| | Quintile 4 | 4.13 | 2.55 to 6.69 |
| | Quintile 5 | 10.68 | 6.59 to 17.32 |
| 17.32 | Quintile 1 | Reference | |
| | Quintile 2 | 1.31 | 0.74 to 2.30 |
| | Quintile 3 | 2.12 | 1.20 to 4.07 |
| | Quintile 4 | 3.42 | 2.19 to 5.34 |
| | Quintile 5 | 6.40 | 4.44 to 9.23 |
| 0.71 | 2014 | 0.51 | 0.36 to 0.71 |
| | 2015 | 0.59 | 0.43 to 0.82 |
| | 2016 | Reference | |

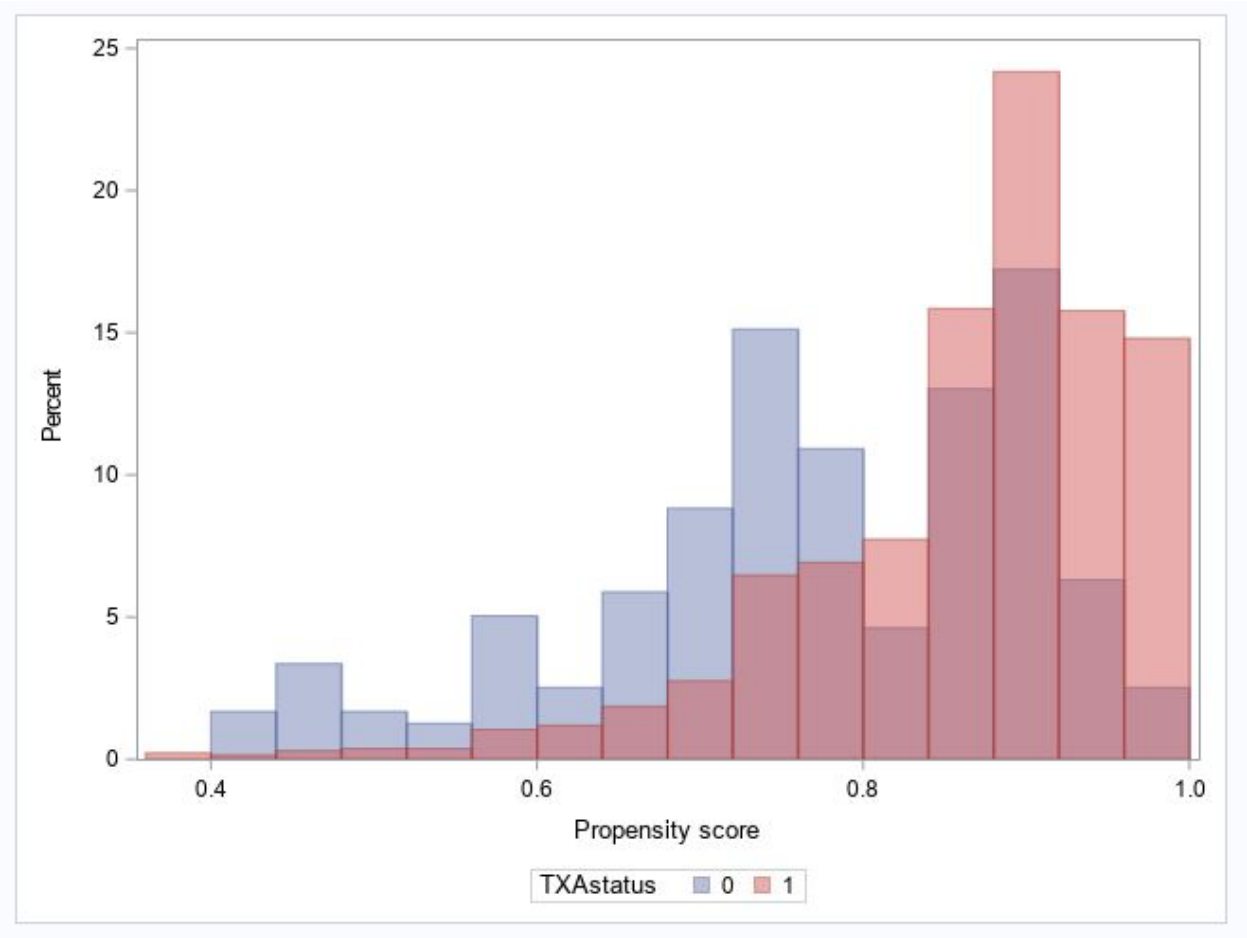
*Normal defined as hemoglobin ≥120g/L in females and ≥130g/L in males; Quintile 1 to quintile 5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population; TXA = tranexamic acid; CI = confidence interval

**Appendix 4.** Logistic regression propensity score model for TXA use in patients undergoing spine fusion ± vertebrectomy

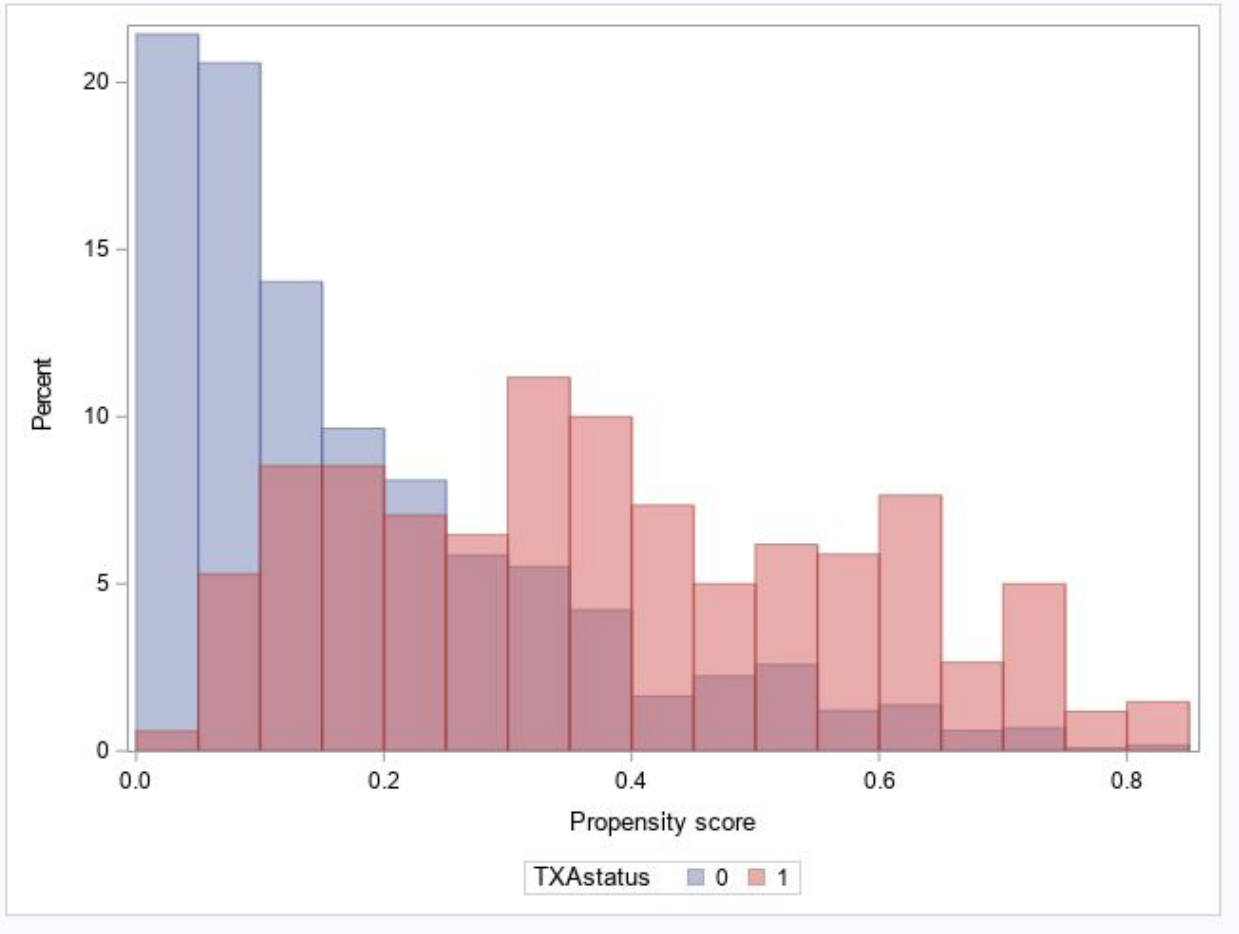
| Covariate | Description | Odds Ratio | 95% CI |
|---|---|---|---|
| Age | <50 years | Reference | |
| | 50 – 69 years | 0.91 | 0.56 to 1.45 |
| | ≥ 70 years | 0.98 | 0.57 to 1.68 |
| Sex | Male | Reference | |
| | Female | 0.99 | 0.68 to 1.44 |
| Comorbidities | Absent | Reference | |
| | Present | 0.71 | 0.44 to 1.16 |
| Preoperative hemoglobin | Normal* | Reference | |
| | ≤20 g/L below normal | 0.85 | 0.52 to 1.39 |
| | >20 g/L below normal | 0.91 | 0.56 to 1.48 |
| Anesthesiologist | Quintile 1 | Reference | |
| | Quintile 2 | 3.51 | 1.72 to 7.18 |
| | Quintile 3 | 4.49 | 2.07 to 9.74 |
| | Quintile 4 | 7.27 | 3.59 to 14.73 |
| | Quintile 5 | 18.65 | 9.43 to 36.89 |
| 17.32 | Quintile 1 | Reference | |
| | Quintile 2 | 1.19 | 0.43 to 3.30 |
| | Quintile 3 | 2.33 | 0.00 to 5.42 |
| | Quintile 4 | 2.91 | 1.23 to 6.89 |
| | Quintile 5 | 7.11 | 3.29 to 15.36 |
| 0.71 | 2014 | 1.20 | 0.76 to 1.91 |
| | 2015 | 1.09 | 0.67 to 1.75 |
| | 2016 | Reference | |

*Normal defined as hemoglobin ≥120g/L in females and ≥130g/L in males; Quintile 1 to quintile 5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population; TXA = tranexamic acid; CI = confidence interval

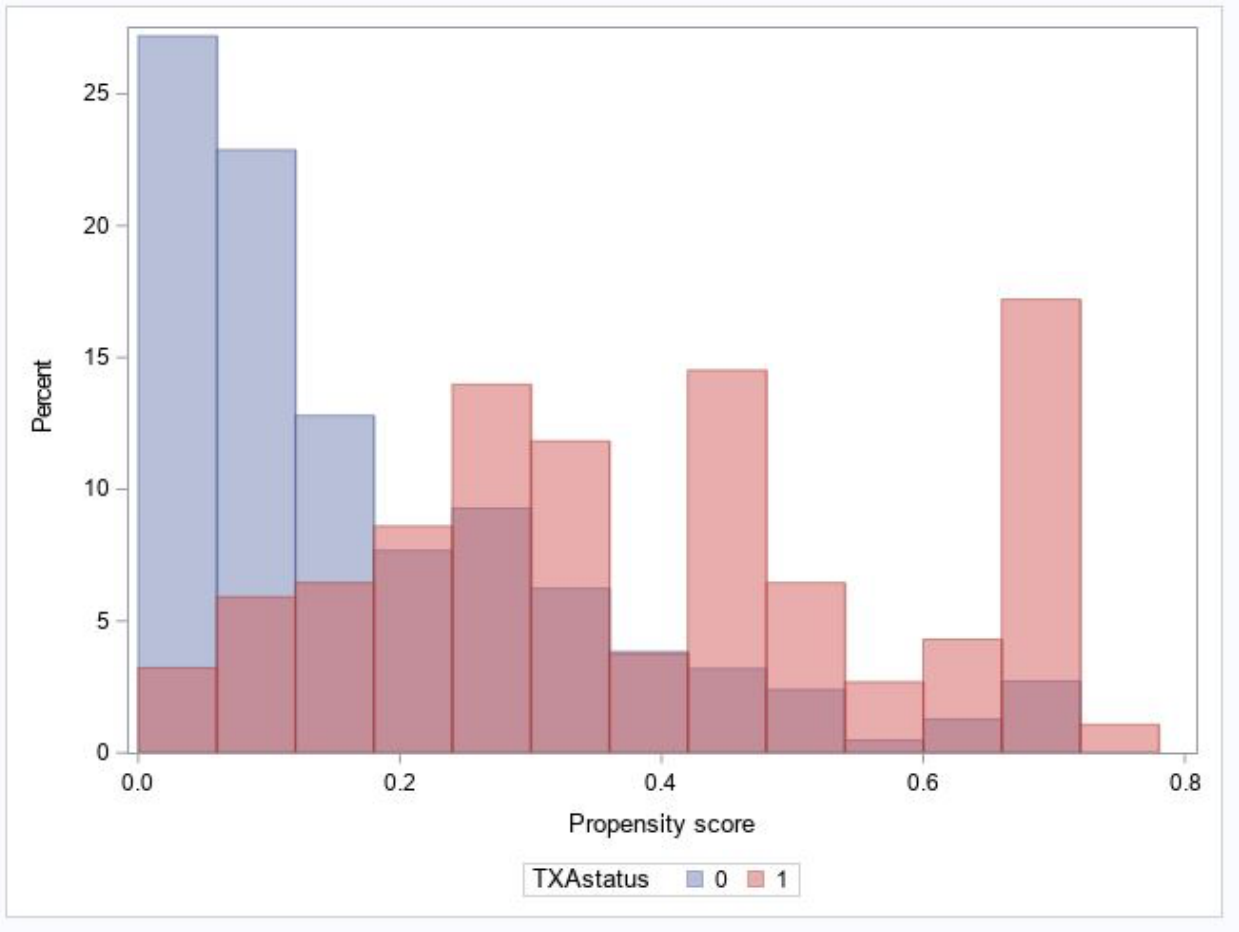
**Appendix 5.** Distribution of propensity scores between treated (TXAstatus = 1) and untreated patients (TXAstatus = 0) undergoing total hip arthroplasty.



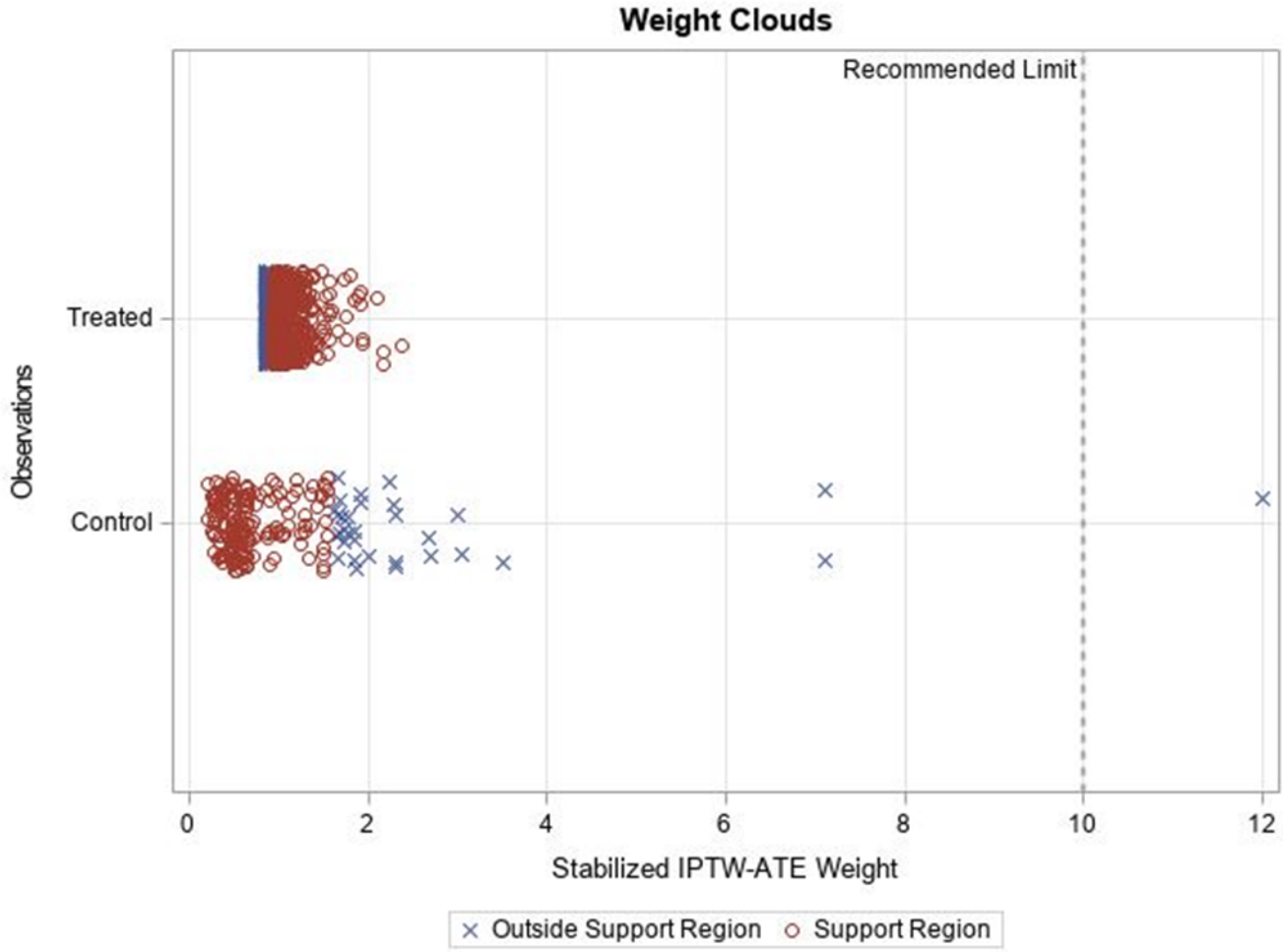
**Appendix 6.** Distribution of propensity scores between treated (TXAstatus = 1) and untreated patients (TXAstatus = 0) undergoing hip fracture surgery.



**Appendix 7.** Distribution of propensity scores between treated (TXAstatus = 1) and untreated patients (TXAstatus = 0) undergoing spine fusion ± vertebrectomy.

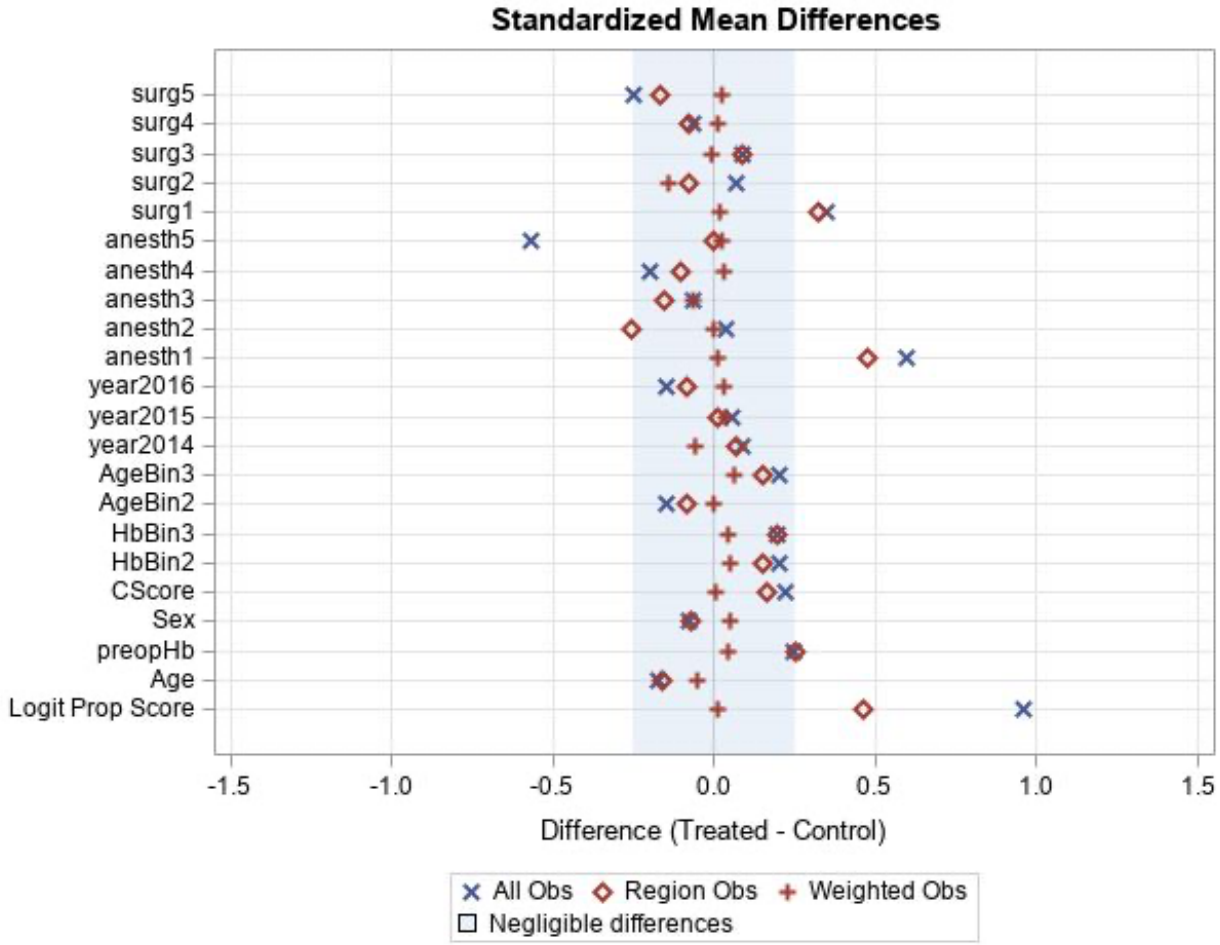


**Appendix 8.** Cloud plot depicting the distribution of stabilized weights among TXA treated and untreated patients undergoing total hip arthroplasty



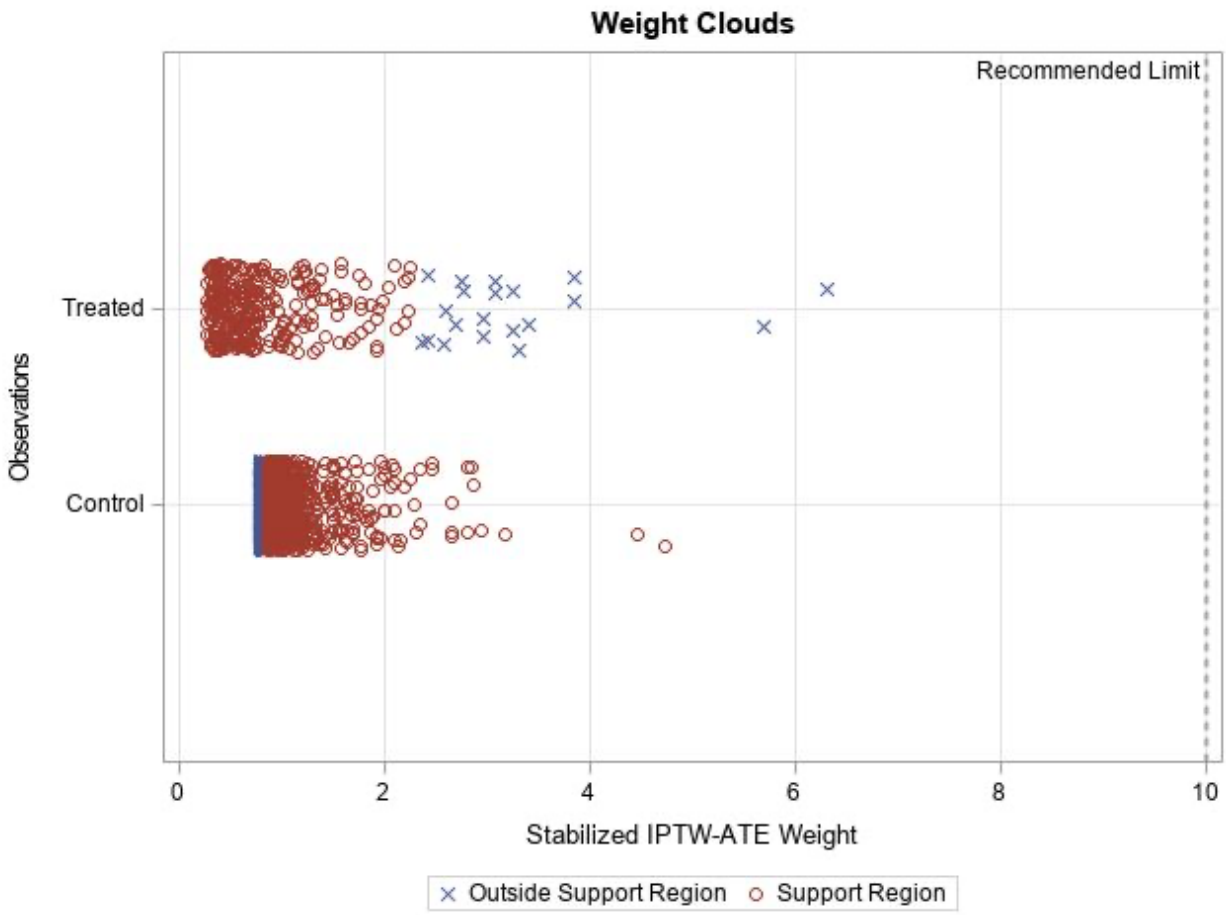

IPTW = inverse probability treatment weighting; ATE = absolute treatment effect; TXA = tranexamic acid

**Appendix 9.** Plot depicting standardized mean differences in overall cohort, restricted to common support region, and after stabilized IPTW weighting in total hip arthroplasty



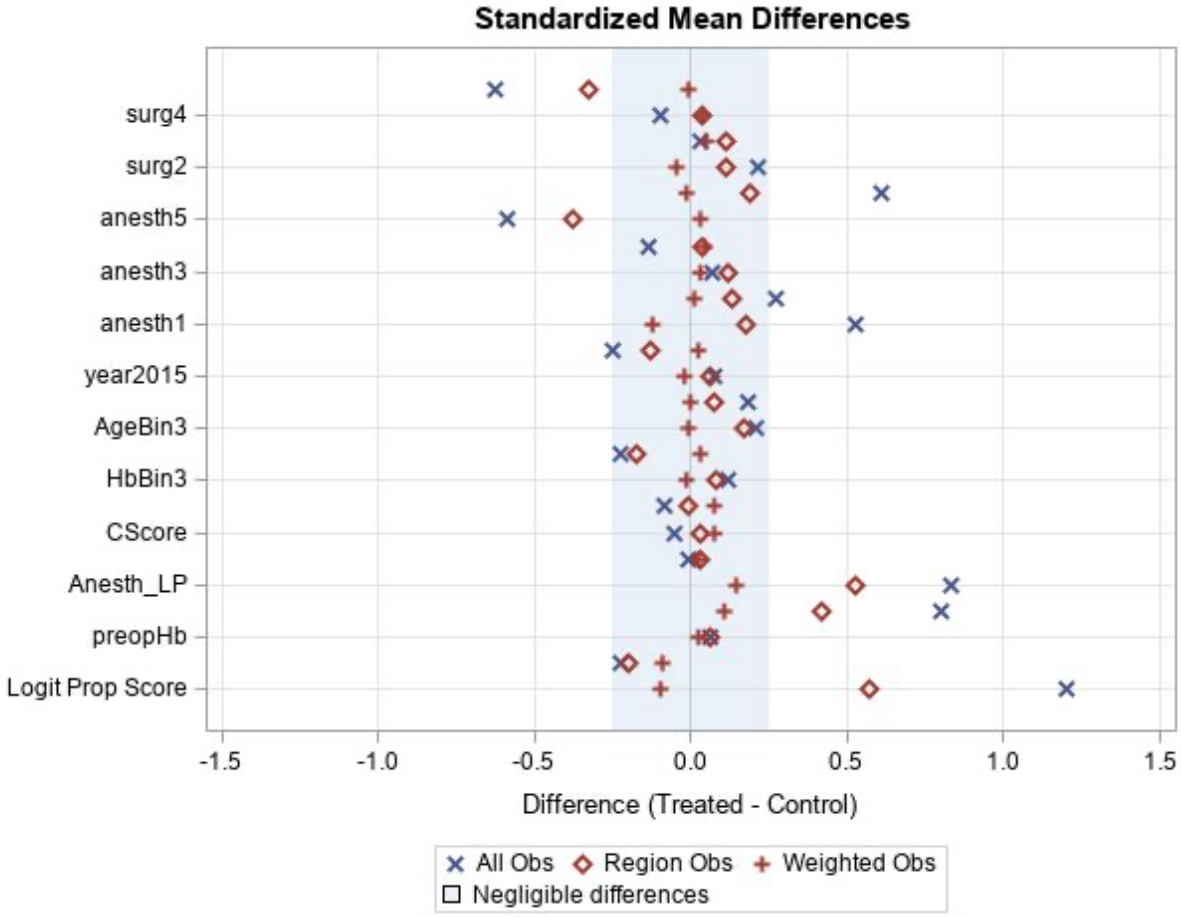

Obs = observations; Surg = surgeon; Anesth = anesthesiologist; CScore = Charlson comorbidity score; preopHb = preoperative hemoglobin; Prop score = propensity score

**Appendix 10.** Cloud plot depicting the distribution of stabilized weights among TXA treated and untreated patients undergoing hip fracture surgery




IPTW = inverse probability treatment weighting; ATE = absolute treatment effect; TXA = tranexamic acid

**Appendix 11.** Plot depicting standardized mean differences in overall cohort, restricted to common support region, and after stabilized IPTW weighting in hip fracture surgery

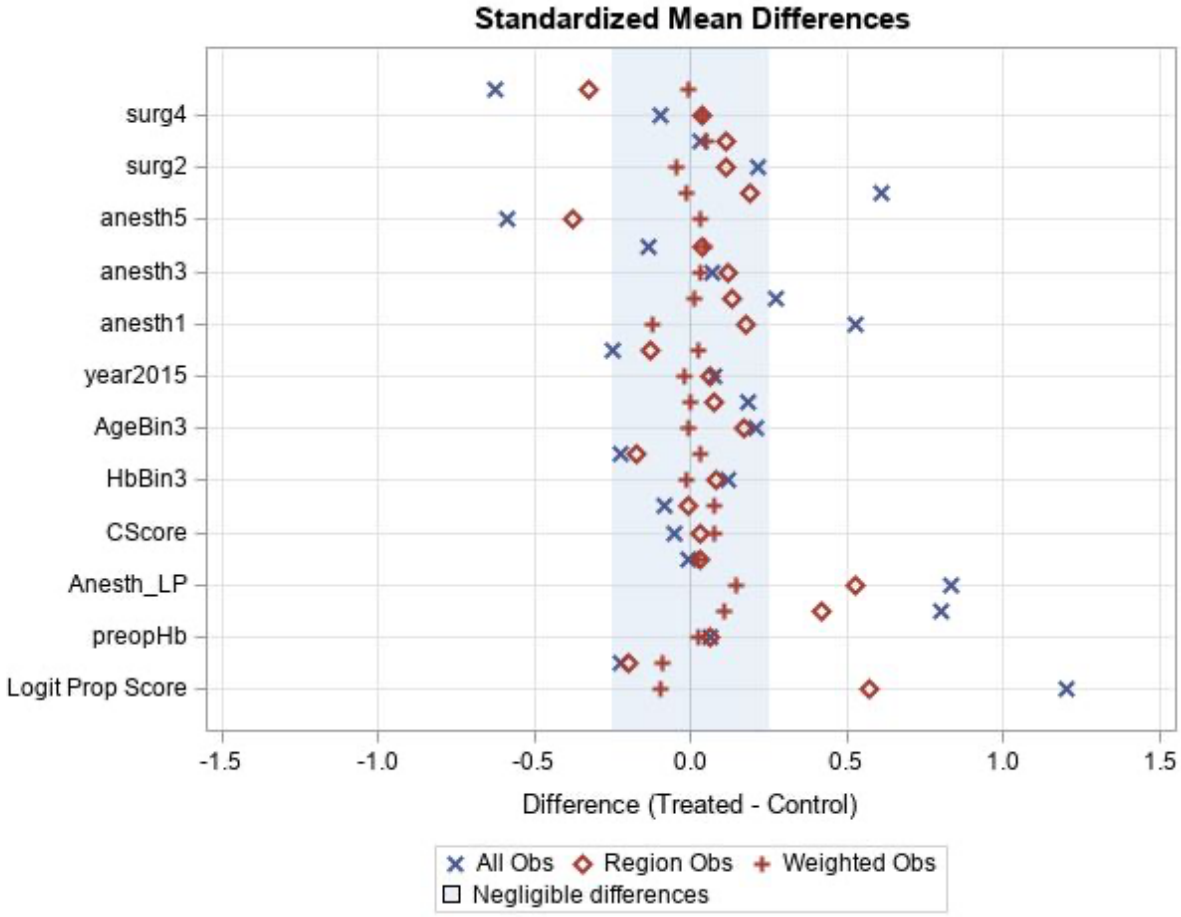



Obs = observations; Surg = surgeon; Anesth = anesthesiologist; CScore = Charlson comorbidity score; preopHb = preoperative hemoglobin; Prop score = propensity score

**Appendix 12.** Cloud plot depicting the distribution of stabilized weights among TXA treated and untreated patients undergoing spine fusion ± vertebrectomy

IPTW = inverse probability treatment weighting; ATE = absolute treatment effect; TXA = tranexamic acid

**Appendix 13.** Plot depicting standardized mean differences in overall cohort, restricted to common support region, and after stabilized IPTW weighting in spine fusion ± vertebrectomy




Obs = observations; Surg = surgeon; Anesth = anesthesiologist; CScore = Charlson comorbidity score; preopHb = preoperative hemoglobin; Prop score = propensity score

**Appendix 14.** Baseline characteristics of treated and untreated patients undergoing total hip arthroplasty surgery before and after matching

| | Entire cohort | | | Post matching | | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | TXA (n=1068) | No TXA (n=201) | SD | TXA (n=199) | No TXA (n=199) | SD | % reduction | Variance ratio |
| Age (years) | 62 (13) | 64 (15) | -0.174 | 64 (13) | 64 (15) | 0.017 | 91 | 0.82 |
| % Female | 47 | 50 | -0.080 | 50 | 51 | -0.030 | 62 | |
| No comorbidities | 91 | 84 | 0.219 | 86 | 83 | 0.088 | 60 | |
| Preoperative hemoglobin (g/L) | 137 (14) | 133 (17) | 0.247 | 135 (16) | 133 (16) | 0.097 | 61 | 0.93 |
| Year | | | | | | | | |
| 2014 | 34 | 38 | 0.088 | 35 | 40 | 0.104 | 0 | |
| 2015 | 32 | 35 | 0.052 | 35 | 34 | -0.022 | 59 | |
| 2016 | 34 | 27 | -0.147 | 30 | 26 | -0.088 | 40 | |
| Anesthesiologist | | | | | | | | |
| Q1 | 16 | 39 | 0.599 | 39 | 42 | 0.069 | 89 | |
| Q2 | 27 | 29 | 0.035 | 26 | 29 | 0.056 | 0 | |
| Q3 | 15 | 13 | -0.066 | 13 | 13 | -0.015 | 78 | |
| Q4 | 21 | 14 | -0.197 | 15 | 13 | -0.054 | 72 | |
| Q5 | 21 | 5 | -0.572 | 7 | 3 | -0.094 | 83 | |
| Surgeon | | | | | | | | |
| Q1 | 12 | 26 | 0.346 | 24 | 26 | 0.039 | 89 | |
| Q2 | 2 | 3 | 0.068 | 3 | 4 | 0.060 | 12 | |
| Q3 | 0 | 1 | 0.090 | 0 | 0 | 0.063 | 30 | |
| Q4 | 28 | 24 | -0.068 | 22 | 24 | 0.035 | 49 | |
| Q5 | 58 | 46 | -0.252 | 51 | 46 | -0.091 | 64 | |

*Continuous variables are represented by mean (standard deviation); dichotomous variables are presented as %. SD = standardized difference; IPTW = inverse probability of treatment weighting; TXA = tranexamic acid; Q = quintile. Q1 to Q5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population.

**Appendix 15.** Baseline characteristics of treated and untreated patients undergoing hip fracture surgery before and after matching

| | Entire cohort | | | Post matching | | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | TXA (n=1068) | No TXA (n=201) | SD | TXA (n=329) | No TXA (n=329) | SD | % reduction | Variance ratio |
| Age (years) | 62 (13) | 64 (15) | -0.174 | 78 (13) | 79 (14) | -0.023 | 90 | 0.84 |
| % Female | 47 | 50 | -0.080 | 68 | 68 | -0.007 | 16 | |
| No comorbidities | 91 | 84 | 0.219 | 62 | 60 | 0.025 | 54 | |
| Preoperative hemoglobin (g/L) | 137 (14) | 133 (17) | 0.247 | 119 (17) | 119 (18) | 0.037 | 39 | 0.95 |
| Year | | | | | | | | |
| 2014 | 34 | 38 | 0.088 | 28 | 27 | -0.026 | 86 | |
| 2015 | 32 | 35 | 0.052 | 29 | 29 | -0.007 | 91 | |
| 2016 | 34 | 27 | -0.147 | 43 | 44 | -0.032 | 87 | |
| Anesthesiologist | | | | | | | | |
| Q1 | 16 | 39 | 0.599 | 8 | 6 | 0.042 | 92 | |
| Q2 | 27 | 29 | 0.035 | 11 | 13 | 0.034 | 88 | |
| Q3 | 15 | 13 | -0.066 | 10 | 11 | 0.029 | 58 | |
| Q4 | 21 | 14 | -0.197 | 31 | 35 | 0.096 | 29 | |
| Q5 | 21 | 5 | -0.572 | 40 | 35 | -0.112 | 81 | |
| Surgeon | | | | | | | | |
| Q1 | 12 | 26 | 0.346 | 16 | 15 | 0.021 | 97 | |
| Q2 | 2 | 3 | 0.068 | 6 | 8 | 0.063 | 70 | |
| Q3 | 0 | 1 | 0.090 | 6 | 6 | 0.013 | 60 | |
| Q4 | 28 | 24 | -0.068 | 17 | 18 | 0.017 | 83 | |
| Q5 | 58 | 46 | -0.252 | 55 | 53 | -0.039 | 94 | |

*Continuous variables are represented by mean (standard deviation); dichotomous variables are presented as %. SD = standardized difference; IPTW = inverse probability of treatment weighting; TXA = tranexamic acid; Q = quintile. Q1 to Q5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population.

**Appendix 16.** Baseline characteristics of treated and untreated patients undergoing spine fusion ± vertebrectomy before and after matching

| | Entire cohort | | | Post matching | | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | TXA (n=1068) | No TXA (n=201) | SD | TXA (n=133) | No TXA (n=133) | SD | % reduction | Variance ratio |
| Age (years) | 62 (13) | 64 (15) | -0.174 | 60 (15) | 57 (16) | 0.163 | 0 | 0.90 |
| % Female | 47 | 50 | -0.080 | 44 | 44 | 0 | 100 | |
| No comorbidities | 91 | 84 | 0.219 | 81 | 83 | -0.038 | 57 | |
| Preoperative hemoglobin (g/L) | 137 (14) | 133 (17) | 0.247 | 135 (19) | 135 (17) | -0.024 | 0 | 1.12 |
| Year | | | | | | | | |
| 2014 | 34 | 38 | 0.088 | 41 | 45 | 0.093 | 0 | |
| 2015 | 32 | 35 | 0.052 | 26 | 28 | 0.033 | 19 | |
| 2016 | 34 | 27 | -0.147 | 33 | 27 | 0.130 | 0 | |
| Anesthesiologist | | | | | | | | |
| Q1 | 16 | 39 | 0.599 | 6 | 7 | -0.020 | 98 | |
| Q2 | 27 | 29 | 0.035 | 18 | 20 | 0.038 | 85 | |
| Q3 | 15 | 13 | -0.066 | 11 | 12 | 0.024 | 77 | |
| Q4 | 21 | 14 | -0.197 | 29 | 27 | -0.038 | 81 | |
| Q5 | 21 | 5 | -0.572 | 36 | 34 | -0.035 | 96 | |
| Surgeon | | | | | | | | |
| Q1 | 12 | 26 | 0.346 | 6 | 5 | 0.050 | 86 | |
| Q2 | 2 | 3 | 0.068 | 6 | 6 | 0 | 100 | |
| Q3 | 0 | 1 | 0.090 | 17 | 20 | 0.078 | 61 | |
| Q4 | 28 | 24 | -0.068 | 14 | 12 | -0.062 | 27 | |
| Q5 | 58 | 46 | -0.252 | 57 | 57 | 0.016 | 97 | |

*Continuous variables are represented by mean (standard deviation); dichotomous variables are presented as %. SD = standardized difference; IPTW = inverse probability of treatment weighting; TXA = tranexamic acid; Q = quintile. Q1 to Q5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population.

**Appendix 17**. Baseline characteristics of treated and untreated patients undergoing total hip arthroplasty surgery before and after stratification

| | Entire cohort | | | Post stratification | | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | TXA (n=1068) | No TXA (n=201) | SD | TXA (n=1029) | No TXA (n=199) | SD | % reduction | Variance ratio |
| Age (years) | 62 (13) | 64 (15) | -0.174 | 62 (13) | 64 (15) | 0.021 | 88 | 0.86 |
| % Female | 47 | 50 | -0.080 | 48 | 51 | 0.029 | 64 | |
| No comorbidities | 91 | 84 | 0.219 | 90 | 83 | -0.01 | 93 | |
| Preoperative hemoglobin (g/L) | 137 (14) | 133 (17) | 0.247 | 137 (14) | 133 (16) | -0.063 | 75 | 0.84 |
| Year | | | | | | | | |
| 2014 | 34 | 38 | 0.088 | 37 | 40 | -0.085 | 3 | |
| 2015 | 32 | 35 | 0.052 | 31 | 34 | -0.020 | 63 | |
| 2016 | 34 | 27 | -0.147 | 32 | 26 | 0.110 | 25 | |
| Anesthesiologist | | | | | | | | |
| Q1 | 16 | 39 | 0.599 | 17 | 42 | -0.030 | 95 | |
| Q2 | 27 | 29 | 0.035 | 28 | 28 | -0.131 | 0 | |
| Q3 | 15 | 13 | -0.066 | 15 | 13 | -0.044 | 33 | |
| Q4 | 21 | 14 | -0.197 | 21 | 13 | -0.006 | 97 | |
| Q5 | 21 | 5 | -0.572 | 19 | 4 | 0.278 | 51 | |
| Surgeon | | | | | | | | |
| Q1 | 12 | 26 | 0.346 | 13 | 26 | 0.003 | 99 | |
| Q2 | 2 | 3 | 0.068 | 3 | 3 | -0.029 | 57 | |
| Q3 | 0 | 1 | 0.090 | 0 | 1 | 0.005 | 95 | |
| Q4 | 28 | 24 | -0.068 | 27 | 24 | 0.065 | 4 | |
| Q5 | 58 | 46 | -0.252 | 57 | 46 | -0.050 | 80 | |

*Continuous variables are represented by mean (standard deviation); dichotomous variables are presented as %. SD = standardized difference; IPTW = inverse probability of treatment weighting; TXA = tranexamic acid; Q = quintile. Q1 to Q5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population.

**Appendix 18.** Baseline characteristics of treated and untreated patients undergoing hip fracture surgery before and after stratification

| | Entire cohort | | | Post stratification | | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | TXA (n=1068) | No TXA (n=201) | SD | TXA (n=339) | No TXA (n=953) | SD | % reduction | Variance ratio |
| Age (years) | 62 (13) | 64 (15) | -0.174 | 78 (13) | 80 (13) | 0.064 | 72 | 0.71 |
| % Female | 47 | 50 | -0.080 | 68 | 69 | -0.041 | 0 | |
| No comorbidities | 91 | 84 | 0.219 | 61 | 64 | 0.098 | 0 | |
| Preoperative hemoglobin (g/L) | 137 (14) | 133 (17) | 0.247 | 120 (17) | 119 (17) | 0.050 | 16 | 0.99 |
| Year | | | | | | | | |
| 2014 | 34 | 38 | 0.088 | 27 | 34 | 0.017 | 91 | |
| 2015 | 32 | 35 | 0.052 | 29 | 32 | -0.005 | 93 | |
| 2016 | 34 | 27 | -0.147 | 44 | 34 | 0.011 | 96 | |
| Anesthesiologist | | | | | | | | |
| Q1 | 16 | 39 | 0.599 | 8 | 16 | 0.023 | 96 | |
| Q2 | 27 | 29 | 0.035 | 11 | 21 | 0.098 | 64 | |
| Q3 | 15 | 13 | -0.066 | 10 | 15 | 0.013 | 81 | |
| Q4 | 21 | 14 | -0.197 | 30 | 29 | -0.024 | 82 | |
| Q5 | 21 | 5 | -0.572 | 41 | 19 | -0.047 | 92 | |
| Surgeon | | | | | | | | |
| Q1 | 12 | 26 | 0.346 | 15 | 33 | 0.024 | 96 | |
| Q2 | 2 | 3 | 0.068 | 6 | 12 | 0.049 | 77 | |
| Q3 | 0 | 1 | 0.090 | 6 | 7 | -0.096 | 0 | |
| Q4 | 28 | 24 | -0.068 | 17 | 16 | 0.070 | 31 | |
| Q5 | 58 | 46 | -0.252 | 56 | 32 | -0.011 | 98 | |

*Continuous variables are represented by mean (standard deviation); dichotomous variables are presented as %. SD = standardized difference; IPTW = inverse probability of treatment weighting; TXA = tranexamic acid; Q = quintile. Q1 to Q5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population.

**Appendix 19.** Baseline characteristics of treated and untreated patients undergoing spine fusion ± vertebrectomy before and after stratification

| | Entire cohort | | | Post stratification | | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | TXA (n=1068) | No TXA (n=201) | SD | TXA (n=156) | No TXA (n=435) | SD | % reduction | Variance ratio |
| Age (years) | 62 (13) | 64 (15) | -0.174 | 59 (15) | 58 (15) | 0.023 | 60 | 0.94 |
| % Female | 47 | 50 | -0.080 | 44 | 45 | 0.043 | 0 | |
| No comorbidities | 91 | 84 | 0.219 | 82 | 81 | -0.069 | 21 | |
| Preoperative hemoglobin (g/L) | 137 (14) | 133 (17) | 0.247 | 134 (18) | 135 (17) | -0.129 | 0 | 1.24 |
| Year | | | | | | | | |
| 2014 | 34 | 38 | 0.088 | 37 | 40 | 0.019 | 7 | |
| 2015 | 32 | 35 | 0.052 | 30 | 31 | -0.078 | 0 | |
| 2016 | 34 | 27 | -0.147 | 33 | 29 | -0.057 | 7 | |
| Anesthesiologist | | | | | | | | |
| Q1 | 16 | 39 | 0.599 | 5 | 21 | -0.002 | 100 | |
| Q2 | 27 | 29 | 0.035 | 15 | 28 | 0.062 | 75 | |
| Q3 | 15 | 13 | -0.066 | 10 | 16 | 0.053 | 49 | |
| Q4 | 21 | 14 | -0.197 | 24 | 19 | -0.057 | 72 | |
| Q5 | 21 | 5 | -0.572 | 46 | 16 | -0.046 | 94 | |
| Surgeon | | | | | | | | |
| Q1 | 12 | 26 | 0.346 | 5 | 11 | 0.025 | 93 | |
| Q2 | 2 | 3 | 0.068 | 5 | 11 | 0.084 | 70 | |
| Q3 | 0 | 1 | 0.090 | 15 | 19 | -0.040 | 80 | |
| Q4 | 28 | 24 | -0.068 | 15 | 21 | 0.044 | 47 | |
| Q5 | 58 | 46 | -0.252 | 60 | 38 | -0.036 | 94 | |

*Continuous variables are represented by mean (standard deviation); dichotomous variables are presented as %. SD = standardized difference; IPTW = inverse probability of treatment weighting; TXA = tranexamic acid; Q = quintile. Q1 to Q5 represent the aggregated practitioner-specific estimated rates of TXA use for a hypothetical but typical patient whose fixed effects covariate values were set to the mean or mode (for continuous or categorical variables) over the surgery-specific population.

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# Efficacy and safety of tranexamic acid in major non-cardiac surgeries at high risk of transfusion: a systematic review and meta-analysis

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# Efficacy and Safety of Tranexamic Acid in Major Non-Cardiac Surgeries at High Risk for Transfusion: A Systematic Review and Meta-Analysis

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ABSTRACT

Tranexamic acid (TXA) reduces transfusion requirements in cardiac surgery and total hip and knee arthroplasty, where it has become standard of care. Our objective is to determine the efficacy and safety of TXA in other surgeries associated with a high risk for red blood cell (RBC) transfusion. We identified randomized controlled trials in Medline, Embase, CENTRAL, and CAB abstracts from inception to June 2019. We included trials evaluating intraoperative IV TXA in adult patients undergoing a non-cardiac and non-hip and knee arthroplasty surgeries at high-risk for RBC transfusion, defined as a baseline transfusion rate ≥5% in comparator arm. We assessed risk of bias using the Cochrane Risk of Bias tool. We used GRADE methodology to assess certainty of evidence. From 8565 citations identified, we included 69 unique trials, enrolling 6157 patients. TXA reduces both the proportion of patients transfused RBCs (relative risk (RR) 0.59; 95% confidence interval (CI) 0.48 to 0.72; low certainty evidence) and the volume of RBC transfused (MD −0.51 RBC units; 95%CI −0.13 to −0.9 units; low certainty evidence) when compared to placebo or usual care. TXA was not associated with differences in deep vein thrombosis, pulmonary embolism, all-cause mortality, hospital length of stay, need for re-operation due to hemorrhage, myocardial infarction, stroke or seizure. In patients undergoing a broad range of non-cardiac and non-hip and knee arthroplasty surgeries at high risk for RBC transfusion, perioperative TXA reduced exposure to RBC transfusion. No differences in thrombotic outcomes were identified; however, summary effect estimates were limited by lack of systemic screening and short duration of follow-up.

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Perioperative bleeding is a major indication for red blood cell (RBC) transfusion and is the second most common indication for transfusion among hospitalized patients [1,2]. Approximately 50% of patients undergoing major cardiac and orthopedic surgery require perioperative transfusion [3,4]. The rates of transfusion in other, and more commonly performed, non-cardiac surgeries can approach or exceed these estimates [5]. RBC transfusion is a scarce and costly resource that can be life-saving, although they are not without harm [6,7]. Transfusions are known to be associated with allergic and non-allergic transfusion reactions, infection, immune dysregulation, prolonged post-operative length of stay, and increased morbidity and mortality [8-13]. In 2015, an estimated 11 million RBC transfusions were administered in US acute care hospitals, with an estimated RBC unit cost of $211 USD [14].

Tranexamic acid (TXA) is an inexpensive and widely available compound that blocks lysine binding sites on plasminogen and inhibits fibrinolysis [15]. TXA has been consistently shown to reduce RBC transfusion in cardiac surgery, orthopedic surgery and trauma, where it is now routinely incorporated into standard of care [16,17]. In a 2011 Cochrane review (65 trials; n = 4842 patients), composed primarily of cardiac (n = 3006 patients) and orthopedic surgical trials (n = 1381 patients), TXA reduced RBC transfusion (RR 0.61, 95% CI 0.53-0.70) without an increase in adverse events [18]. However, this systematic review does not reflect interval studies evaluating TXA use in other surgical domains at high-risk for RBC transfusion. The objective of our systematic review is to determine the efficacy and safety of TXA in surgeries with a high risk for RBC transfusion where TXA is not currently standard of care.

## Materials and Methods

Using an a priori published protocol (CRD42018094409; available at https://www.crd.york.ac.uk/PROSPERO), we conducted a systematic review using methodologic approaches outlined in the *Cochrane Handbook for Systematic Reviewers* and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria [19,20]. A panel of experts in multiple fields formulated the review question, reviewed search strategies and methods, and provided input throughout the review process. The roles of the systematic review team members are included as **Appendix A.**

### *Populations, Interventions, Comparators, Outcome Measures Setting and Study Designs*

Our research question was "In surgeries at high risk for RBC transfusion where TXA is not standard of care, does TXA safely reduce red blood cell transfusion?" We included randomized controlled trials (RCTs) of adults (age ≥18 years) undergoing surgeries at high risk for RBC transfusion (≥5% baseline transfusion rate), for which TXA use is not standard of care. This transfusion threshold was chosen because clinicians and patient partners identified that a 1 in 20 chance of transfusion was substantive, and allowed inclusion of a broad patient population [5]. To determine trial eligibility (≥5% transfusion rate), we preferentially obtained the baseline transfusion rates from the placebo/usual care arm of each trial, as transfusion risk depends on both patient and surgical factors. However, if an individual trial did not report the transfusion rate in the control arm, we utilized surgery-specific transfusion rates obtained from a multicenter retrospective study of contemporary transfusion rates in non-cardiac surgeries **(Appendix B)** [5]. To identify surgeries where TXA is not standard of care, we excluded surgeries with TXA utilization rates ≥50%, which included total hip and knee arthroplasty **(Appendix C)**. This data was obtained from a multicenter retrospective study evaluating current TXA utilization rates, and is further supported by international consensus guidelines [16,21-24]. Our intervention included intravenous prophylactic perioperative (within 1 hour of start of surgery) TXA regardless of dose, frequency and duration. Comparators included placebo, usual care (ie. open-label), or active comparators **(Appendix D)**.

Our primary outcome measures were the proportion of patients transfused at least one RBC transfusion, and the number of allogeneic RBC units transfused. Our main safety outcome was incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). Other secondary outcomes included all-cause mortality, hospital length of stay, re-operation due to hemorrhage, myocardial infarction (MI), stroke and seizure. All outcomes were obtained for the longest duration of follow-up reported in each study.

### *Search Strategy for Identification of Studies*

We searched Medline (Ovid), Embase (Ovid), CENTRAL (Cochrane Library - Wiley) and CAB Abstracts (CAB International) from inception to June 2019 to identify relevant citations of published trials. The Medline search was peer reviewed by an independent information professional as per the PRESS guidelines, and formed the basis for subsequent individualized systematic database-specific search strategies [25]. Our MEDLINE strategy is presented in **Appendix E**. We searched the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP), clinicaltrials.gov and conference proceedings (American Society of Hematology and American Society of Anesthesiology from 2015–2018) to identify planned, ongoing, or recently completed but unpublished trials. We performed forward searches of included trials and relevant reviews in Web of Science to identify additional citations, and contacted study authors to request pertinent unpublished data or provide clarifications on study methods or results. Reference lists of narrative and systematic reviews and of the included trials were searched for additional citations. We performed reference management in EndNote™ (Version X8, Thomson Reuters, Philadelphia, PA, USA).

### *Study Selection, Data Extraction and Risk of Bias Assessments*

We screened citations in two stages, selected studies and extracted data in duplicate using standardized and piloted screening and data

extraction forms. A list of excluded full-text studies with the reason for exclusion is included in **Appendix F.** The following data were extracted from each trial: author identification, publication year, publication language, trial location, source of funding, patient characteristics (age, sex, weight, malignancy status, American Society of Anesthesiologists Classification (ASA) score), procedure information (procedure name, type of procedure (e.g. gynecologic, urologic, spine etc.), procedure urgency (elective, urgent/emergent), intervention/comparator characteristics (tranexamic acid dose, mode of administration, timing, duration, and comparator), duration of follow-up, as well as the results for the primary and secondary outcomes. We assessed the internal validity of included trials using the Cochrane Collaboration Risk of Bias tool [19]. Discrepancies between the two reviewers were resolved by consensus or by a third reviewer (RZ), as required. Data extraction and descriptive statistics were performed using Microsoft Excel 2016 (version 15, Microsoft Corporation, Redmond, WA, USA).

### *Statistical Analysis*

Data analysis were performed using Review Manager (RevMan v5.3.5, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) and Stata/IC 14.2 (StataCorp, College Station, TX). Study level summary effect comparisons of dichotomous outcomes were presented as risk ratios (RR) and risk difference (RD) with 95% confidence intervals (CI) using a Mantel–Haenszel random-effects model with constant continuity correction of 0.5 for zero events [26]. Summary effect-estimates for continuous data were expressed as the mean difference (MD) with 95% CIs. Statistical heterogeneity was quantified using the $I^2$ statistic and visual inspection of the forest plot [27]. Statistical heterogeneity, if detected ($I^2 > 50\%$), was explored using sensitivity analyses. For the primary outcomes, we evaluated potential publication bias using funnel plot analysis [28]. All tests of statistical inference reflect a 2-sided $\alpha$ of .05.

### *Subgroup Analyses, Meta-regression, and Trial Sequential Methods*

To determine summary effect estimates of TXA in specific patient populations, we performed several a priori subgroup analyses. For our primary outcomes subgroup analyses included funding source (industry funded vs non-industry funded vs not reported), risk of bias (low risk vs unclear/high risk), type of surgery, surgical urgency, baseline risk of perioperative transfusion, intervention characteristics (TXA dose, and dosing schedule (weight-based vs fixed dose; bolus vs infusion vs composite), timing of TXA administration (intra-operative vs intra-operative and post-operative)), trial size (<50 patients, 50-99 patients, ≥100 patients), and duration of trial follow-up (<28 days vs ≥28 days). Subgroup differences were evaluated using the Chi-squared test.

We conducted univariable random-effects meta-regression as a sensitivity analysis to evaluate the impact of moderator variables on the pooled estimate of receiving a RBC transfusion (Stata/IC 14.2 (StataCorp. College Station, TX). Moderating variables of interest included tranexamic dose, RBC transfusion rate in the control arm, and duration of follow-up.

To mitigate the potential for type I or type II error in meta-analyses and to understand if the required information size was attained, we conducted a trial sequential analysis for our primary RBC transfusion outcomes and DVT outcome, as both outcomes inform the decision to use TXA. We used TSA software (v.0.9.5.5 beta Copenhagen Trial Unit Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark (www.ctu.dk/tsa)), and followed the methods outlined by Wetterslev et al [29,30]. We used a random effects model with a conventional test boundary of $p < .05$ and calculated the required information size for efficacy (proportion transfused RBCs) based on the summary effect estimate. For safety (incidence of DVT), the required information size was based on a minimally clinically important effect size (relative risk increase of 0.5). Information size calculations assumed two-sided tests of significance, a power level of 80%, $\alpha < .05$, and were adjusted by between-study heterogeneity.

### *Grading the evidence*

We assessed the certainty of the evidence for our primary outcomes using the GRADE methodology [31]. GRADE methodology assesses the evidence according to the following domains: study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. This approach classifies the certainty of evidence as *high, moderate, low,* or *very low*.

## Results

### *Trial Characteristics and Study Population*

Of the 8565 citations identified, we included 69 RCTs enrolling 6157 patients **(Appendix G & H)**. Trials were published between 1993 and 2019; all trials published prior to 2006 evaluated TXA use in the context of liver transplantation [32-37]. The majority of trials 63/69, (92%) were published in peer reviewed journals; 6 trials [37-42] were English-language abstracts from conference proceedings. Eleven trials were from North America [34,35,40,41,43-49], 11 were from Europe [32,33,36,37,50-56], 17 were from the Middle East [39,42,57-71], 28 were from Asia [38,72-98].

The mean age of study patients within each study ranged from 23 to 84 years, and the average study level proportion of males was 41%. Trials included procedures from the following surgical specialties: neurosurgery [86], otolaryngology [62,73,83-85,89], general surgery [41,98,99], hepatobiliary [32-37,55,74], urology [42,53,79], gynecology [50,51,66,67,69,71], obstetrics [57,70,78,82,91], non-hip or knee arthroplasty orthopedics [39,45-47,49,54,56,58,59,63,68,77,80,81,92,95-97,100], plastic surgery [75] and spine surgery [38,40,43,44,48,52,60,61,64,65,72,76,87,88,90,93,94]. Forty-three trials (3844 patients) evaluated elective surgical procedures and 20 trials (1584 patients) evaluated urgent/emergent procedures; the urgency of the remaining 6 trials was mixed or unclear. Patients with active malignancy were enrolled in 13 trials (1454 patients) [32,33,41,51,53,72,74,84-86,96,98,99].

Most trials (45/69; 65%) were of unclear risk of bias. In 35 trials (51%), we considered the blinding of patients and personnel to be adequate **(Appendix I)**. Likewise, 27 trials (39%) adequately incorporated blinded outcome assessment. Five were considered to have a low risk of bias [35,45,72,76,90]. The remainder of the trials were considered unclear or high risk for bias, due to reporting unclear processes of randomization (24 trials) or allocation concealment (43 trials). Three trials [61,99,100] were reported as industry funded.

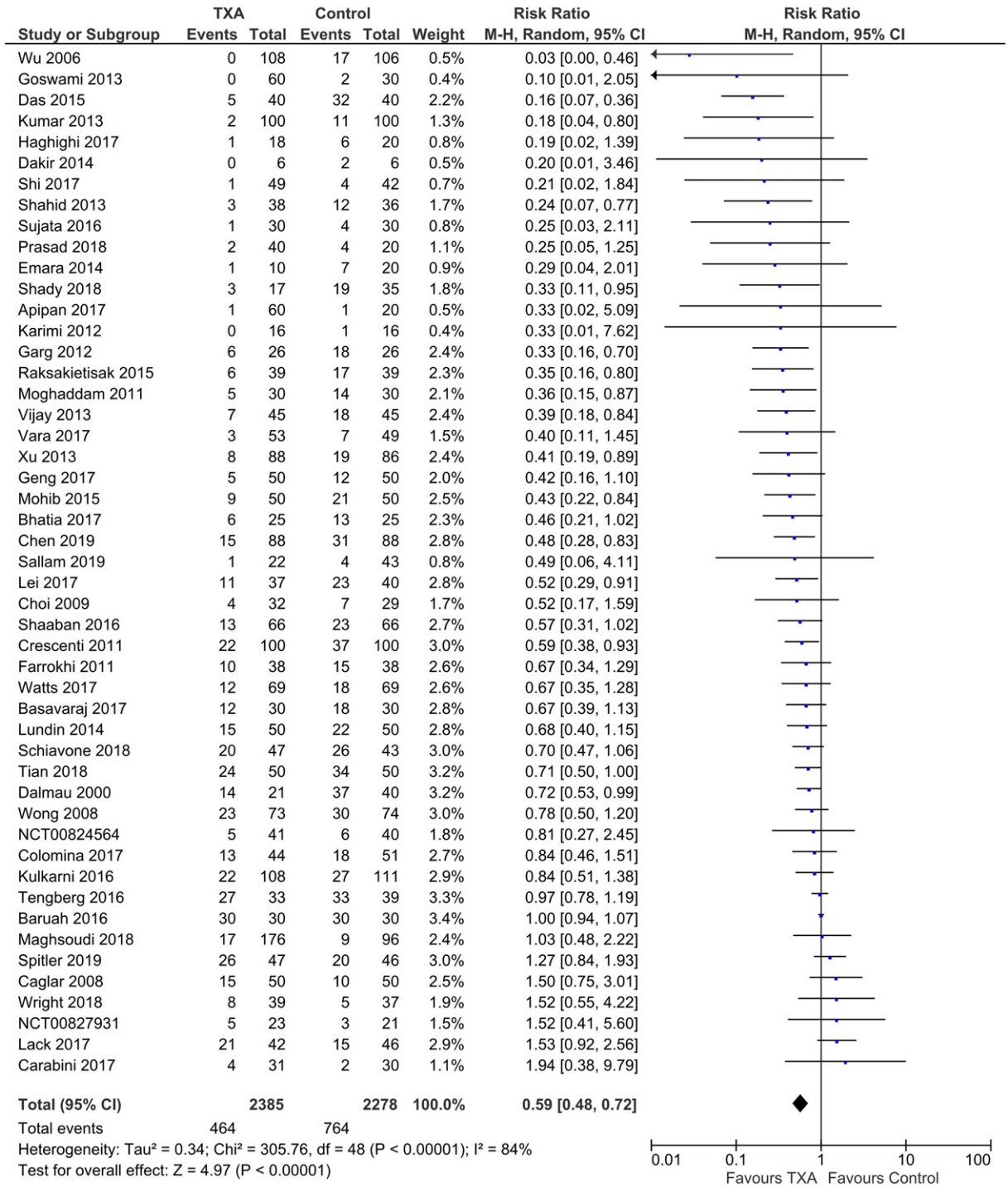
### *Interventions*

The most common TXA dosing was calculated based on patient weight (57 trials; 4837 patients). Of these, 27 trials (2126 patients) administered TXA as a bolus followed by an infusion; 26 trials (2383 patients) administered TXA exclusively as a bolus; four trials (328 patients) administered TXA exclusively as an infusion. TXA was compared to placebo in 54 (78%) trials, and usual care in 8 (12%) trials [36,42,60,67,79,97,99,100]. Active comparators in the remaining 10 trials included aprotinin [32,37,55], epsilon-aminocaproid acid [33,48,77], oral tranexamic acid [40], topical tranexamic acid [68,69,71,94], activated recombinant factor VII [65], and batroxobin [87] **(Appendix H).**

### *Primary Outcomes*

#### *Proportion of patients transfused red blood cells*

Compared to placebo or usual care, TXA reduces the proportion of patients transfused red blood cells (relative risk (RR) 0.59; 95%




TXA = tranexamic acid; CI = confidence interval; M-H = Mantel Haenszel; *Control = placebo or usual care

**Fig. 1.** The proportion of patients exposed to red blood cell transfusion at longest follow-up. TXA, tranexamic acid; CI, confidence interval; M-H, Mantel Haenszel; *Control, placebo or usual care.

confidence interval (CI) 0.48 to 0.72; $I^2$ 84%; 49 trials; 4663 patients). This represents an absolute risk reduction of 12% (95% CI 9%-16% reduction) and a number needed to treat (NNT) of 8 (95% CI 6-11) patients to prevent at least one red blood cell transfusion (Fig. 1; Table 1).

Subgroup analyses according to funding source, risk of bias, type of surgery, surgical urgency, baseline risk of perioperative transfusion, intervention characteristics (TXA dose, and dosing schedule (weight-based vs fixed dose; bolus vs infusion vs composite), timing of TXA administration (intra-operative vs intra-operative and post-operative)), trial size, and duration of trial follow-up were not associated with significant differences in treatment effect and did not substantially resolve sources of statistical heterogeneity (Fig. 2). By meta-regression, TXA dose **(Appendix J)**, baseline transfusion rate **(Appendix K)**, or surgical urgency were not associated with RBC transfusion. Based on the relative risk reduction of 0.41 and accounting for the heterogeneity ($I^2 = 84\%$) in our sample, the trial sequential boundary for superiority

**Table 1**
Summary of findings table including absolute effect measure, relative effect measure, number of participants and certainty of evidence (GRADE)

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo/ usual care | Risk with TXA | | | | |
| Proportion of patients transfused RBCs | 335 per 1000 | **198 per 1000** (161 to 241) | **RR 0.59** (0.48 to 0.72) | 4663 (49 RCTs) | ⨁⨁◯◯ LOW [a,b] LOW [a,b] | |
| # RBC units transfused | The mean # RBC units transfused ranged from **0.23–12** units | The mean # RBC units transfused in the intervention group was 0.51 units lower (0.9 lower to 0.13 lower) | - | 1356 (17 RCTs) | ⨁⨁◯◯ LOW [a,c] LOW [a,c] | |
| Deep vein thrombosis | 22 per 1000 | **23 per 1000** (16 to 33) | **RR 1.03** (0.72 to 1.48) | 3333 (39 RCTs) | ⨁⨁◯◯ LOW [a,d] LOW [a,d] | |
| Pulmonary embolism | 8 per 1000 | **8 per 1000** (4 to 15) | **RR 1.00** (0.54 to 1.84) | 2469 (29 RCTs) | ⨁⨁◯◯ LOW [a,d] LOW [a,d] | |
| Mortality | 35 per 1000 | **40 per 1000** (26 to 62) | **RR 1.14** (0.73 to 1.76) | 1915 (17 RCTs) | ⨁⨁◯◯ LOW [a,d] LOW [a,d] | |
| Hospital LOS | The mean hospital LOS ranged from **2–13** days | The mean hospital LOS in the intervention group was 0.69 days lower (1.16 lower to 0.22 lower) | - | 1055 (12 RCTs) | ⨁◯◯◯ VERY LOW [a,e] VERY LOW [a,e] | |
| Reoperation due to hemorrhage | 33 per 1000 | **14 per 1000** (3 to 56) | **RR 0.41** (0.10 to 1.68) | 400 (4 RCTs) | ⨁⨁◯◯ LOW [a,f] LOW [a,f] | |
| Myocardial infarction | 7 per 1000 | **7 per 1000** (3 to 16) | **RR 1.07** (0.46 to 2.47) | 1509 (15 RCTs) | ⨁⨁◯◯ LOW [a,f] LOW [a,f] | |
| Stroke | 2 per 1000 | **3 per 1000** (1 to 10) | **RR 1.45** (0.48 to 4.44) | 920 (10 RCTs) | ⨁⨁◯◯ LOW [a,f] LOW [a,f] | |
| Seizure | 8 per 1000 | **6 per 1000** (1 to 23) | **RR 0.73** (0.18 to 2.95) | 530 (6 RCTs) | ⨁◯◯◯ VERY LOW [a,f] VERY LOW [a,f] | |

CI, confidence interval; TXA, tranexamic acid; RCT, randomized controlled trial; RBC, red blood cells; RR, relative risk; LOS, length of stay.
**Explanations:**
a. Majority of included studies at unclear or high risk for bias leading to lower certainty in effect estimate.
b. Heterogeneity: $\tau^2 = 0.34$; $\chi^2 = 305.76$; $df = 48$ ($P < .00001$); $I^2 = 84\%$.
c. Heterogeneity: $\tau^2 = 0.51$; $\chi^2 = 468.61$, $df = 16$ ($P < .00001$); $I^2 = 97\%$.
d. Although point estimate suggests no effect, confidence intervals do not exclude clinically important benefit or harm.
e. Heterogeneity: $\tau^2 = 0.50$; $\chi^2 = 61.59$, $df = 11$ ($P < .00001$); $I^2 = 82\%$.
f. Optimal information size not met with small sample size and low event rate.

was reached, indicating that TXA reduces the proportion of patients transfused RBCs **(Appendix L).**

In the context of substantial between-study heterogeneity, funnel plot analysis suggested the absence of small to moderate-size studies favoring placebo or usual care **(Appendix M)**. Given that the majority of trials were considered to be of unclear or high risk for bias and due to significant between-study heterogeneity, we graded the overall strength of evidence as low. No active comparators reduced the proportion of patients transfused RBCs compared to TXA **(Appendix N).**

*Number of RBC units transfused*

Compared to placebo or usual care, tranexamic acid reduces the volume of RBCs transfused (mean difference of 0.51 RBC units; 95% CI 0.13-0.9 units; $I^2$ 97%; 17 trials; 1356 patients) **(**Fig. 3**;** Table 1**).**

Statistically significant subgroup differences were detected when analyzed by funding source (non-industry funded vs industry funded. vs not reported; $P = .01$) and surgery type ($P = .01$) **(**Fig. 4**).** Otherwise, we did not detect subgroup differences for risk of bias, surgical urgency, baseline risk of perioperative transfusion, intervention characteristics (TXA dose, and dosing schedule (weight-based vs fixed dose; bolus vs infusion vs composite), timing of TXA administration (intra-operative vs intra-operative and post-operative)), trial size, or duration of trial follow-up **(**Fig. 4**).** Statistical heterogeneity was not substantially resolved by subgroup analyses. There was no subgroup difference detected in a post-hoc sensitivity analysis of the transfusion rate data source that informed the inclusion criteria (either derived from the RCT control arm or retrospective study).

A trial sequential analysis was performed for number of RBC units transfused based on a mean change of −0.51 units. Accounting for the heterogeneity ($I^2$ 97%) in our sample, the trial sequential boundary for superiority was reached, indicating that TXA reduces the number of RBC units transfused **(Appendix O).** In the context of substantial between-study heterogeneity, funnel plot analysis suggested the absence of small to moderate-size studies favoring placebo or usual care **(Appendix P)**. Given that the majority of trials were considered to be of unclear or high risk for bias and due to significant between-study heterogeneity, we graded the overall strength of evidence as low **(**Table 1**).** No active comparators reduced the number of RBC units transfused compared to TXA **(Appendix Q).**

*Secondary Outcomes*

TXA was not associated with an increase in incidence of deep vein thrombosis (RR 1.03; 95% CI 0.72-1.48; $I^2$ 0%; 39 trials; 3333 patients) or pulmonary embolism (RR 1.0; 95% CI 0.54-1.84; $I^2$ 0%; 29 trials; 2469 patients) **(Appendix R & S;** Table 1**).** TXA use was not associated

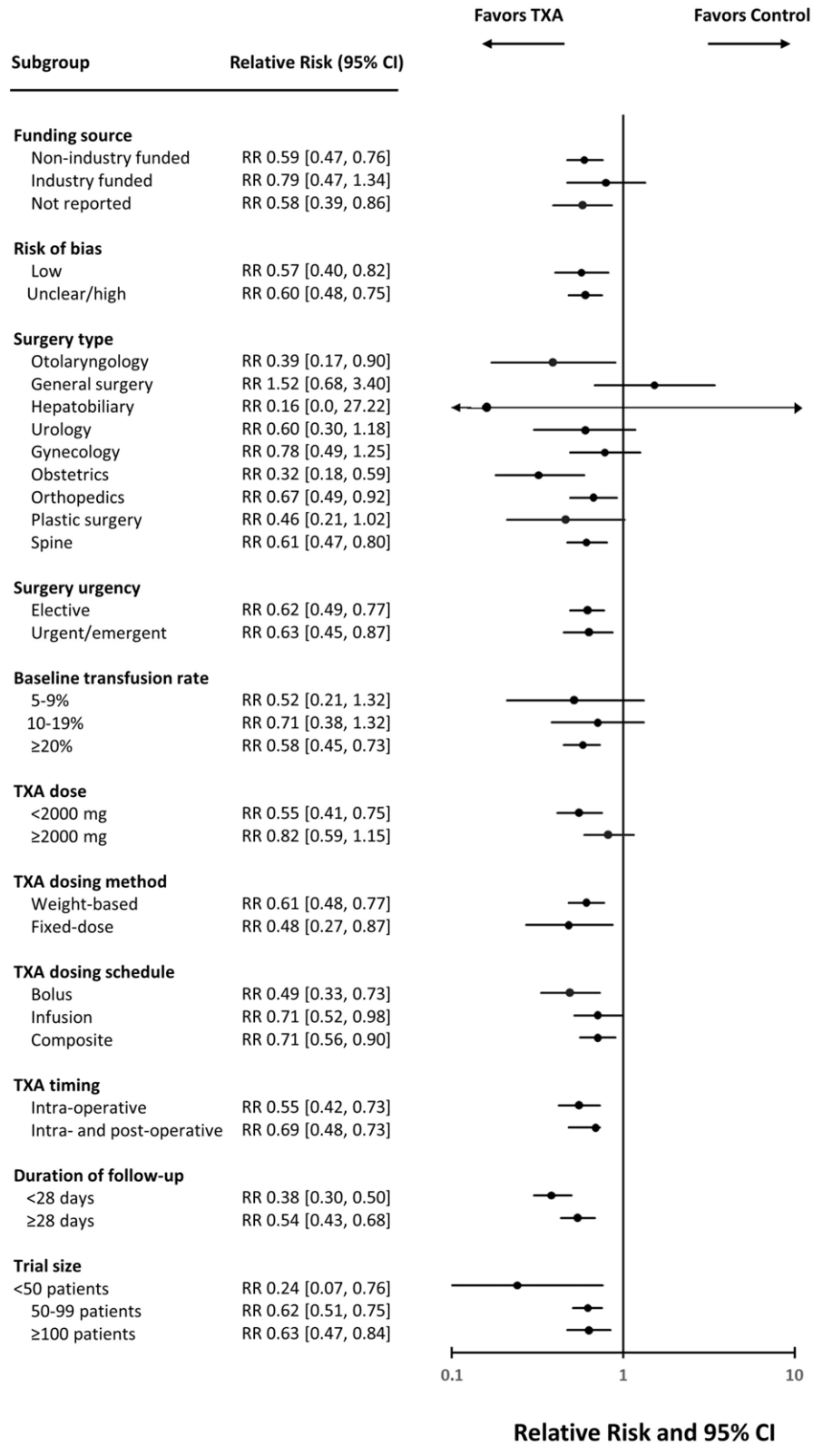
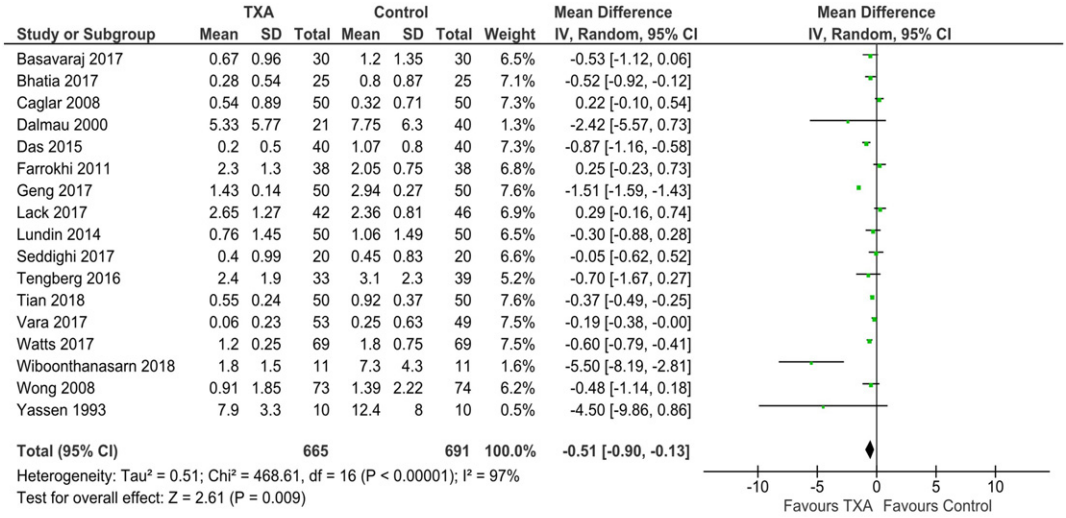



**Fig. 2.** Subgroup analyses of the proportion of patients tranfused red blood cells. TXA, tranexamic acid; CI, confidence interval; RR, relative risk; mg, milligrams; *Control, placebo or usual care.




TXA = tranexamic acid; SD = standard deviation; CI = confidence interval; *Control = placebo or usual care

**Fig. 3.** The number of RBC units transfused at longest follow-up. TXA, tranexamic acid; SD, standard deviation; CI, confidence interval; *Control, placebo or usual care.

with all-cause mortality (RR 1.14; 95% CI 0.73-1.76; $I^2$ 0%; 17 trials; 1915 patients), hospital length of stay (MD -0.69; 95% CI −1.16 to −0.22; $I^2$ 82%; 12 trials; 1055 patients), re-operation due to hemorrhage (RR 0.41; 95% CI 0.10-1.68; $I^2$ 0%; 4 trials; 400 patients), or the incidence of adverse outcomes, including myocardial infarction (RR 1.07; 95% CI 0.46-2.47; $I^2$ 0%; 15 trials; 1509 patients), stroke (RR 1.45; 95% CI 0.48-4.44; $I^2$ 0%; 10 trials; 920 patients) and seizure (RR 0.73; 95% CI 0.18-2.95; $I^2$ 0%; 6 trials; 530 patients) **(Appendix T-Y;** Table 1**)**. A table summarizing the deep vein thrombosis rates in relation to duration of follow-up is included in **Appendix Z**; 14/39 trials (36%) reported a follow-up of at least 28 days.

To assess the robustness of our most clinically relevant safety outcome, that is, venous thrombosis, a trial sequential analysis was performed. Based on the summary baseline DVT rates (2.2%), a relative risk increase of 0.5, and our sample heterogeneity (0%), the sample size reached the futile area concluding TXA is not associated with a clinically significant increase in DVT **(Appendix AA)**.

## Discussion

In patients undergoing non-cardiac surgery at high risk for transfusion, we found that perioperative intravenous TXA, compared to placebo or usual care was associated with a 41% reduction in the proportion of patients transfused at least one unit of RBCs, and a mean reduction of 0.51 units of red blood cells transfused per patient. We did not identify a significant increased risk of venous thrombosis, although summary effect estimates were limited by lack of systemic screening and a relatively short duration of follow-up.

TXA has been consistently shown to reduce RBC transfusion in cardiac surgery, trauma, and hip and knee arthroplasty, where it is now routinely incorporated into standard of care [16,23,101-104]. Perioperative TXA use is supported by the American Society of Anesthesiologists (ASA) Practice Guidelines for Perioperative Blood Management to reduce transfusion for patients at increased risk for bleeding [105]. The supporting evidence base for these specific surgical populations parallels TXA use. In a recent study of TXA use at five academic institutions, TXA use was high in hip (75%) and knee arthroplasty (85%), and low (16%) in other non-cardiac surgeries with comparable risks for transfusion [21].

Our systematic review builds on targeted evidence syntheses evaluating TXA in discrete surgeries such as spine [106] and hip fracture surgery [107,108]. Prior to our study, the most recent comprehensive evaluation of TXA and its impact on perioperative transfusion in non-cardiac surgery was a 2011 Cochrane systematic review [18]. The included study population of this review comprised primarily cardiac surgery and hip and knee arthroplasty; non-cardiac surgical patients made up 455 of 4842 (9%) of included patients. Fifty-two (75%) of our included trials were published in the interim.

While the broad inclusion of all non-cardiac surgeries with a baseline transfusion rate ≥ 5% serves to highlight the universal benefits of TXA, summary estimates are associated with significant heterogeneity. Despite comprehensive subgroup analyses, causes of the heterogeneity could not be fully resolved. Effect estimates, however, consistently favor TXA, and thus unresolved heterogeneity reflect uncertainty in the precise magnitude of TXA efficacy rather than the presence or absence of efficacy. Variability may be plausibly related to yet to be identified patient- or procedure-, or operator-dependent characteristics.

The incidence of post-operative DVT was low in our study (2.2%); however, widespread underreporting, and limited trial duration of follow-up are likely to significantly underestimate the true incidence. The risk of post-operative venous thromboembolic disease is substantially increased in the 3 months post-operatively [109], yet only 14/50 (28%) and 6/50 (12%) of the trials reporting DVT events had a follow-up duration of one and 3 months, respectively. Follow-up limited to hospital discharge is known to inadequately capture VTE events, as highlighted by two recent studies where VTE events occurred following hospital discharge in 34–100% of affected individuals [110,111]. While the low incidence of thrombotic complications appears favorable, studies evaluating TXA safety with extended duration of follow-up would be required to generate precise estimates of postoperative venous thromboembolism.

Rather than updating or repeating systematic reviews in populations where tranexamic acid is known to be efficacious, our review addressed important knowledge gaps by the use of a comprehensive search strategy, which included electronic databases, trial registries, and forward searches. We used an a priori published protocol, and followed established methodological guidelines concerning the conduct and reporting of this review. Rather than focusing on volume of intra-operative or post-operative bleeding, which is known to suffer methodologic concerns regarding reliability of capture [112,113], we focused on patient-centered outcomes (presence of transfusion, safety) and system-specific outcomes (units of RBC transfusion). This allowed the evaluation of efficacy outcomes that are relevant to both the patient and healthcare system, in the context of relevant safety outcomes and

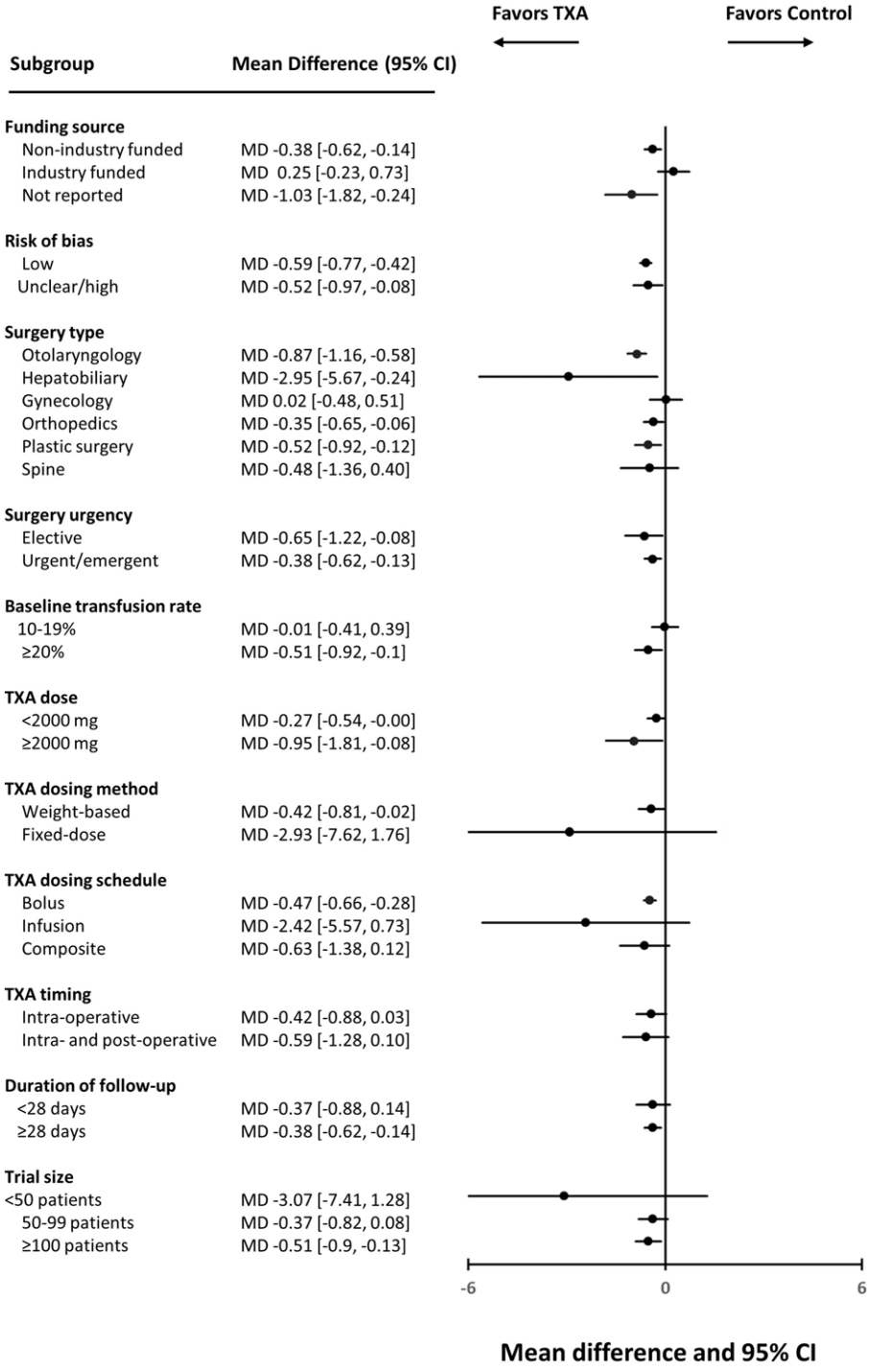



**Fig. 4.** Subgroup analysis of the number of red blood cell units transfused. TXA, tranexamic acid; CI, confidence interval; MD, mean difference; mg, milligram; *Control, placebo or usual care.

adverse events. The broad inclusion criteria and the consistency of effect estimates favoring TXA make our review generalizable to a large population of perioperative patients.

A potential weakness of our systematic review is the use of a retrospective study of surgery-specific transfusion rates to inform the inclusion criteria, as it is possible there are institutional differences in transfusion rates. To mitigate this, we preferentially included trials based on the published transfusion rate of an individual trial's control arm which circumvents this concern. The duration of follow-up was relatively short (and often not reported), which limits our evaluation of TXA safety. Lastly, we were unable to resolve sources of heterogeneity despite extensive subgroup analysis. However, the observed

heterogeneity is similar to what was reported in the Cochrane review [18] despite their narrow inclusion of only 3 dominant surgeries. The heterogeneity may be related to patient co-morbidities or prior medication administration, operative factors (anesthetic variability, transfusion thresholds, surgeon factors), which were not comprehensively addressed by the primary trials.

In patients undergoing a broad range of non-cardiac and non-hip and knee arthroplasty surgeries at high risk for RBC transfusion, perioperative TXA is associated with reduced exposure to RBC transfusion. No differences in thrombotic outcomes were identified, however, summary effect estimates are limited by lack of systemic screening and short duration of follow-up.

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## Competing Interests

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, no other relationships or activities that could appear to have influenced the submitted work.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmrv.2019.10.001.

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**Appendix A.** Systematic review team members

One reviewer (BLH) with hematology and research training coordinated all components of the review, including development of the literature search strategy, screening of relevant material, data extraction and analysis, and preparation of the final manuscript. A second reviewer (KU) with internal medicine training screened citations, and extracted trial level data in duplicate. A panel of experts from multiple fields (e.g. hematology (ER, DSH, CM, RZ), anesthesiology (TM, AFT), surgery (RB), critical care medicine (AFT, RZ, BR, ML) transfusion medicine (DAF, AT), and health research methodology (DAF, AG, SM, JF, BR, RZ) provided content expertise. One librarian (CN) with expertise in systematic review search methodology developed the database search strategies and performed the literature search. Statistical analysis was overseen by a senior statistician with specific expertise in meta-analysis (RR). One clinician/researcher with systematic review expertise (AMAS) provided statistical and methodological support. One clinician scientist / hematologist (RZ) provided content expertise, methodologic advice, resolution of disagreement among reviewers, and project oversight.

**Appendix B.** Surgeries with a red blood cell transfusion rate ≥5%[5]. Data obtained from a retrospective cohort study evaluating surgeries (n = 74,906) performed at five academic institutions located in two Canadian cities (Winnipeg, MB; Ottawa, ON) between 2014 and 2016.

GENERAL SURGERY
Fundoplication
Esophagectomy
Gastric banding, sleeve and bypass
Gastroplasty
Gastrectomy
Enterostomy
Enteroplasty
Enterectomy
Colostomy
Colonic repair
Colonic take-down
Colectomy
Proctectomy
Partial hepatectomy
Splenectomy
Cholecystectomy
Hepatojejunostomy
Bile duct excision
Pancreatic resection
Lysis of adhesions
Omentectomy
Abdominal tumor resection
Mesh removal
Skin repair with graft/flap
Hernia repair (epigastric, umbilical, femoral, inguinal, ventral)

ORTHOPEDIC
Hip open reduction internal fixation
Hip partial excision
Femur hardware removal
Femur open reduction internal fixation
Femur osteotomy
Femur resection (cancer)
Pelvic open reduction internal fixation
Pelvic osteoplasty/osteotomy
Hemipelvectomy
Shoulder open reduction internal fixation
Humerus open reduction internal fixation
Humerus ostectomy
Tibia/fibula hardware removal

Tibia/fibula ostectomy
Above knee amputation
Below knee amputation
Foot amputation

SPINE
Spinal cord release
Spinal cord partial excision
Drainage spinal abscess/hematoma
Hardware removal
Vertebral fixation with instrumentation
Vertebral fusion
Vertebral debridement
Vertebrectomy
Diskectomy

OTOLARYNGOLOGY
Mandibulectomy
Glossectomy
Floor of mouth resection
Radical laryngectomy

THORACIC
Lobectomy
Pneumonectomy
Decortication/pleurectomy/pleurodesis
Diaphragmatic repair

VASCULAR
Abdominal aortic bypass
AAA repair
Carotid artery bypass
Large vessel arterial bypass
Large vessel aneurysmorrhaphy
Large vessel endarterectomy/thrombectomy
Lower extremity arterial resection
Lower extremity venous bypass

GYNECOLOGIC
Oopherectomy
Salpingo-oopherectomy
Salpingectomy
Hysterectomy

UROLOGIC

Nephrectomy
Cystectomy
Orchiectomy
Prostatectomy

PLASTIC SURGERY
Scalp skin resection
Neoplasm resection (back)
Soft tissue debridement (chest/abdomen)
Abscess/hematoma drainage (chest/abdomen)
Abdomen skin resection
Leg skin graft
Leg skin resection
Leg cyst marsupialization/drainage of abscess/hematoma
Leg soft tissue resection
Lower extremity neoplasm ablation/debridement/amputation

**Appendix C**. Surgeries with a red blood cell transfusion rate ≥5%[21]. Data obtained from a retrospective cohort study evaluating surgeries (n = 74,906) performed at five academic institutions located in two Canadian cities (Winnipeg, MB; Ottawa, ON) between 2014 and 2016.

SURGERY NAME:
Total hip arthroplasty
Total knee arthroplasty

**Appendix D.** Inclusion and exclusion criteria

*Inclusion criteria:*

- Adults (≥ 18 years; at least 80% of the study population) undergoing a surgical procedure in the operating room
- Intraoperative (defined as no more than one hour prior to or during surgery) prophylactic intravenous tranexamic acid administration
- Surgical procedures with a transfusion rate ≥ 5% (at least 80% of the study population); defined based on the transfusion rate of the trial control group, or if unavailable we utilized surgery-specific transfusion rates obtained from a multi-centre retrospective study of contemporary transfusion rates in non-cardiac surgeries[5]
- Randomized controlled trials reporting at least one of our outcomes of interest

*Exclusion criteria:*

- Animal studies
- Observational study designs, quasi-randomized, cross-over or cluster randomized trials
- Surgeries where TXA is standard of care (utilization ≥ 50%), as identified from a multicenter retrospective study evaluating current TXA utilization rates[21]
- Multi-organ trauma patients (≥ 20% of patient population)
- Cardiac surgery (≥ 20% of patient population)

**Appendix E.** Medline search strategy

| # | Searches | Results |
|---|---|---|
| 1 | Tranexamic Acid/ | 3001 |
| 2 | tranexamic acid.rn. | 3001 |
| 3 | ("(aminomethyl)cyclohexane 1 carboxylic acid" or "(aminomethyl)cyclohexane carbonic acid" or "(aminomethyl)cyclohexanecarboxylic acid" or "4aminomethylcyclohexanecarboxylic acid" or "amino methylcyclohexane carboxylate" or "aminomethyl cyclohexane carboxylic acid" or "aminomethyl cyclohexanecarboxylic acid" or "aminomethyl-1alpha-cyclohexanecarboxylic acid" or "aminomethyl-1-cyclohexane carboxylic acid" or "aminomethyl-1-cyclohexanecarboxylic acid" or "aminomethylcyclohexane 1 carboxylic acid" or "aminomethylcyclohexane 4 carboxylic acid" or "aminomethylcyclohexane carbonic acid" or "aminomethylcyclohexane carboxylic acid" or "aminomethylcyclohexane-1-carboxylic acid" or "aminomethylcyclohexane-4-carboxylic acid" or "aminomethylcyclohexanecarbonic acid" or "aminomethylcyclohexanecarboxylic acid" or "aminomethyl-cyclohexanecarboxylic acid" or "aminomethylcyclohexanocarboxylic acid" or "aminomethylcyclohexanoic acid" or "Cyclohexanecarboxylic Acid").ti,ab,kf,kw. | 264 |
| 4 | "acide tranexamique".ti,ab,kf,kw. | 4 |
| 5 | "acido tranexamico".ti,ab,kf,kw. | 22 |
| 6 | "acidum tranexamicum".ti,ab,kf,kw. | 0 |
| 7 | "Cyclo-F".ti,ab,kf,kw. | 9 |
| 8 | "FMOC-R-2-aminobutyric acid".ti,ab,kf,kw. | 0 |

| | | |
|---|---|---|
| 9 | "kabi 2161".ti,ab,kf,kw. | 3 |
| 10 | "Tranesamic acid".ti,ab,kf,kw. | 0 |
| 11 | "Tranexamsaeure".ti,ab,kf,kw. | 0 |
| 12 | "tranexanic acid".ti,ab,kf,kw. | 6 |
| 13 | "Tranhexamic acid".ti,ab,kf,kw. | 2 |
| 14 | "transexamic acid".ti,ab,kf,kw. | 18 |
| 15 | ("cl 65336" or cl65336).ti,ab,kf,kw. | 0 |
| 16 | (AMCA or AMCHA or ACHMA).ti,ab,kf,kw. | 426 |
| 17 | (antivoff or anvitoff).ti,ab,kf,kw. | 1 |
| 18 | (cyclocapron or cyclokapron).ti,ab,kf,kw. | 18 |
| 19 | (cyklocapron or cyklokapron).ti,ab,kf,kw. | 33 |
| 20 | (hexacapron or hexakapron).ti,ab,kf,kw. | 0 |
| 21 | (Tranexamic adj4 acid*).ti,ab,kf,kw. | 3647 |
| 22 | amchafibrin.ti,ab,kf,kw. | 0 |
| 23 | amikapron.ti,ab,kf,kw. | 1 |
| 24 | amstat.ti,ab,kf,kw. | 0 |
| 25 | anexan.ti,ab,kf,kw. | 0 |
| 26 | caprilon.ti,ab,kf,kw. | 0 |
| 27 | carxamin.ti,ab,kf,kw. | 0 |
| 28 | Emorhalt.ti,ab,kf,kw. | 0 |
| 29 | exacyl.ti,ab,kf,kw. | 12 |
| 30 | Femstrual.ti,ab,kf,kw. | 0 |
| 31 | fibrinon.ti,ab,kf,kw. | 0 |
| 32 | Frenolyse.ti,ab,kf,kw. | 1 |
| 33 | HAKU.ti,ab,kf,kw. | 4 |
| 34 | hemostan.ti,ab,kf,kw. | 0 |
| 35 | hexapromin.ti,ab,kf,kw. | 0 |
| 36 | Hexatron.ti,ab,kf,kw. | 1 |

| | | |
|---|---|---|
| 37 | kalnex.ti,ab,kf,kw. | 0 |
| 38 | Lysteda.ti,ab,kf,kw. | 6 |
| 39 | Mastop.ti,ab,kf,kw. | 1 |
| 40 | micranex.ti,ab,kf,kw. | 0 |
| 41 | retavase.ti,ab,kf,kw. | 12 |
| 42 | rikaparin.ti,ab,kf,kw. | 0 |
| 43 | Rikavarin.ti,ab,kf,kw. | 0 |
| 44 | ronex.ti,ab,kf,kw. | 0 |
| 45 | spiramin.ti,ab,kf,kw. | 0 |
| 46 | spotof.ti,ab,kf,kw. | 0 |
| 47 | TAMCHA.ti,ab,kf,kw. | 1 |
| 48 | theranex.ti,ab,kf,kw. | 0 |
| 49 | tramic.ti,ab,kf,kw. | 0 |
| 50 | tranex.ti,ab,kf,kw. | 1 |
| 51 | tranexam.ti,ab,kf,kw. | 10 |
| 52 | tranexamate.ti,ab,kf,kw. | 3 |
| 53 | tranexan.ti,ab,kf,kw. | 0 |
| 54 | tranexic.ti,ab,kf,kw. | 0 |
| 55 | tranol.ti,ab,kf,kw. | 0 |
| 56 | Transamin.ti,ab,kf,kw. | 20 |
| 57 | Trasamlon.ti,ab,kf,kw. | 0 |
| 58 | traxamic.ti,ab,kf,kw. | 0 |
| 59 | trenaxin.ti,ab,kf,kw. | 0 |
| 60 | TXA.ti,ab,kf,kw. | 1534 |
| 61 | Ugurol.ti,ab,kf,kw. | 5 |
| 62 | zataranax.ti,ab,kf,kw. | 0 |
| 63 | or/1-62 | 5748 |
| 64 | exp Randomized Controlled Trials as Topic/ | 130921 |

| | | |
|---|---|---|
| 65 | exp randomized controlled trial/ | 516550 |
| 66 | Random Allocation/ | 103232 |
| 67 | Double Blind Method/ | 162625 |
| 68 | Single Blind Method/ | 27815 |
| 69 | clinical trial/ | 561721 |
| 70 | clinical trial, phase i.pt. | 21244 |
| 71 | clinical trial, phase ii.pt. | 34212 |
| 72 | clinical trial, phase iii.pt. | 16183 |
| 73 | clinical trial, phase iv.pt. | 1740 |
| 74 | controlled clinical trial.pt. | 101755 |
| 75 | randomized controlled trial.pt. | 516249 |
| 76 | multicenter study.pt. | 261743 |
| 77 | exp Clinical Trials as topic/ | 346830 |
| 78 | trial*.ti. | 272128 |
| 79 | (clinical adj trial*).ti,ab. | 337979 |
| 80 | (controlled adj trial*).ti,ab. | 203359 |
| 81 | (blind*3 or mask*3).ti,ab. | 338053 |
| 82 | PLACEBOS/ | 37130 |
| 83 | placebo*.ti,ab. | 217037 |
| 84 | "control group".ti,ab. | 374266 |
| 85 | RCT.ti. | 1208 |
| 86 | RCTs.ti. | 419 |
| 87 | random*.ti,ab. | 1059994 |
| 88 | or/64-87 | 2479407 |
| 89 | Comment/ | 761090 |
| 90 | Editorial/ | 479795 |
| 91 | News/ | 191427 |
| 92 | (letter not (letter and randomized controlled trial)).pt. | 1050673 |

| | | |
|---|---|---|
| 93 | historical article/ | 361677 |
| 94 | or/89-93 | 2240529 |
| 95 | 88 not 94 | 2403737 |
| 96 | 63 and 95 | 1669 |
| 97 | 96 not (exp animals/ not humans/) | 1608 |
| 98 | remove duplicates from 97 | 1417 |

**Appendix F.** A list of studies excluded during full-text review, grouped by the reason for their exclusion

Excluded based on patient population:

[1] H. Abbasi, S. Behdad, V. Ayatollahi, N. Nazemian, P. Mirshamsi. Comparison of two doses of tranexamic acid on bleeding and surgery site quality during sinus endoscopy surgery, *Adv* 2012; 21:773-780.
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[3] ACTRN12612000313831. The use of tranexamic acid to reduce blood loss during and after cesarean section. *ICTRP*: 2012.
[4] ACTRN12615000312549. Efficiency and safety of preoperative Tranexamic acid in reducing perioperative blood loss in elective cesarean section. *ICTRP*: 2015.
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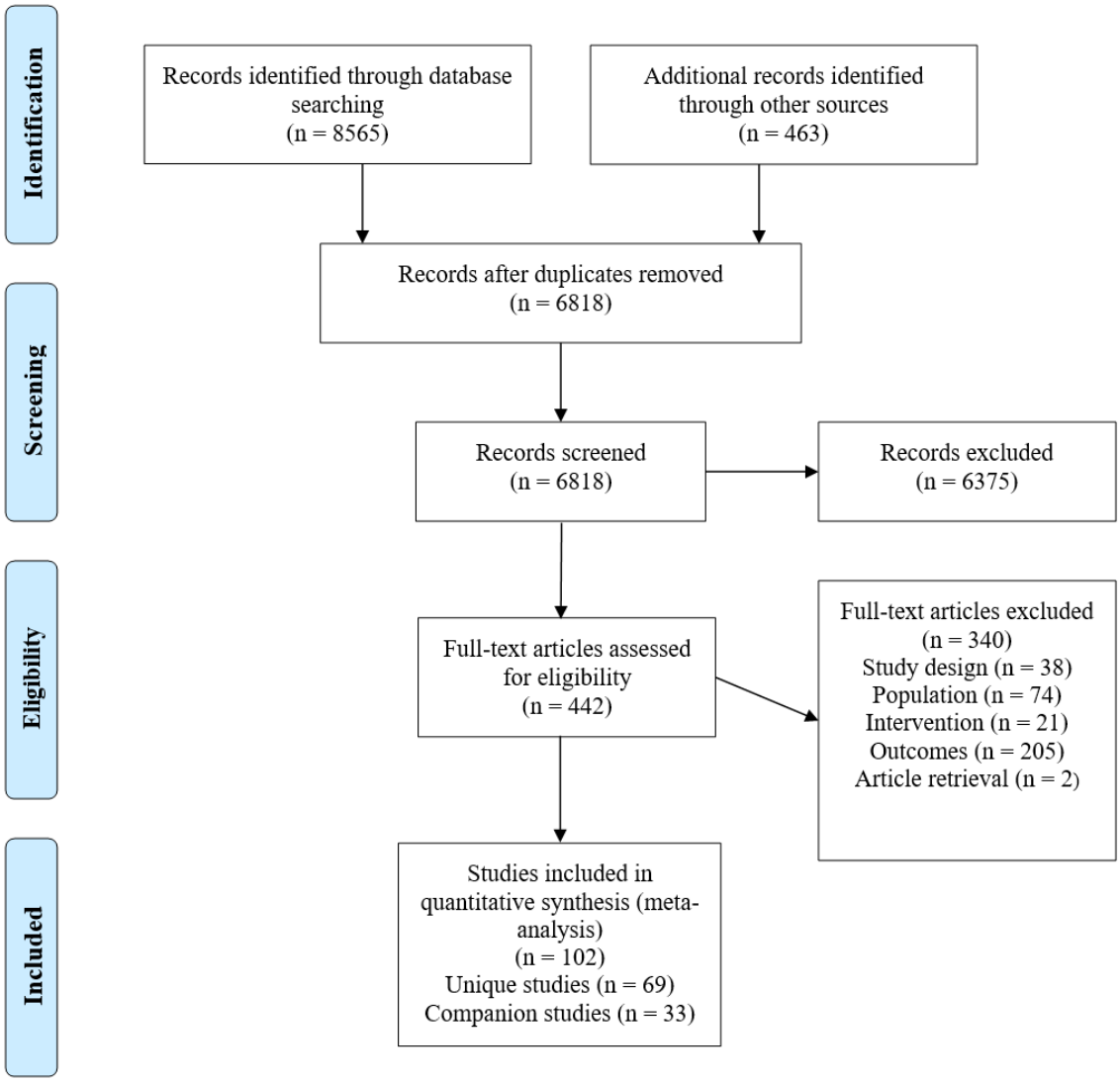
**Appendix G.** Study flow diagram following the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA)[20] with modifications



**Appendix H.** Characteristics of individual trials, patient populations and interventions

| Source | No. of patients (TXA/ Control) | Age, Mean (SD) | Procedure type | Procedure name | TXA administration (IV) | Comparator | Duration of follow-up |
|---|---|---|---|---|---|---|---|
| Apipan, 2018[73] | 60/20 | 25.7 (3.1) | Orolaryngology | Bimaxillary osteotomy | 10/15/20 mg/kg bolus* | Placebo | 1 month |
| Choi, 2009[89] | 32/29 | 23.4 (5.4) | Otolaryngology | Bimaxillary osteotomy | 20 mg/kg bolus | Placebo | Hospital discharge |
| Dakir, 2014[83] | 6/6 | Range 20-40 | Otolaryngology | Maxillofacial trauma surgery | 10 mg/kg bolus | Placebo | Hospital discharge |
| Das, 2015[84] | 40/40 | 44 (10.5) | Otolaryngology | Head and neck cancer surgery | 20 mg/kg bolus | Placebo | Post-op day 1 |
| Karimi, 2012[62] | 16/16 | 23.4 (12.3) | Otolaryngology | Bimaxillary osteotomy | 20 mg/kg bolus | Placebo | Hospital discharge |
| Kulkarni, 2016[85, 114] | 108/111 | 51 (11.5) | Otolaryngology | Squamous cell carcinoma resection and reconstruction | 10 mg/kg bolus; repeat if OR >3hr | Placebo | Hospital discharge |
| NCT00827931, 2009[99] | 49/45 | /^ | General surgery | Major abdominal surgery | 15 mg/kg bolus q3h x3 doses | Usual care | Not reported |
| Prasad, 2018[98] | 40/20 | 47.5 (9.5) | General surgery | Abdominal oncologic surgery | 10 mg/kg bolus +/- 1 mg/kg/hr until 4hr post-op* | Placebo | Hospital discharge |
| Wright, 2018[41, 115, 116] | 17/19 | /^ | General surgery | Major oncologic surgery | 1000 mg bolus | Placebo | Not reported |
| Crescenti, 2011[53, 117-119] | 100/100 | 64 (7.6) | Urology | Radical retropubic prostatectomy | 500 mg bolus, then 250 mg/hr | Placebo | 6 months |
| Kumar, 2013[79] | 100/100 | 38.9 (11.6) | Urology | Percutaneous nephrolithotomy | 1000 mg bolus, then 500 mg PO q8hr x3 doses | Usual care | 1 month |
| Maghsoudi, 2018[42] | 176/96 | 46.1^^ | Urology | Percutaneous nephrolithotomy | 10/15 mg/kg bolus q12hr x2 doses, then 250/500mg bolus q8hr x3 doses* | Usual care | Not reported |
| Caglar, 2008[50] | 50/50 | 35.5 (5.1) | Gynecology | Myomectomy | 10 mg/kg bolus, then 1mg/kg/hr x10 hrs | Placebo | Hospital discharge |
| Lundin, 2014[51, 120, 121] | 50/50 | 63.8 (11.6) | Gynecology | Ovarian cancer debulking | 15 mg/kg bolus | Placebo | Post-op day 35 |
| Mousa, 2012[66] | 23/24 | 34.7 (5.8) | Gynecology | Hysteroscopic myomectomy | 15 mg/kg bolus, then 10 mg/kg/hr | Placebo | Not reported |
| Sallam, 2019[69] | 43/86 | 47.6 (4.2) | Gynecology | Abdominal hysterectomy | 600 mg/hr (total 1g) | Placebo / topical TXA | Hospital discharge |
| Shaaban, 2016[67] | 66/66 | 34.8 (5.2) | Gynecology | Abdominal myomectomy | 10mg/kg bolus, then 1mg/kg/hr | Usual care | Post-op day 7 |

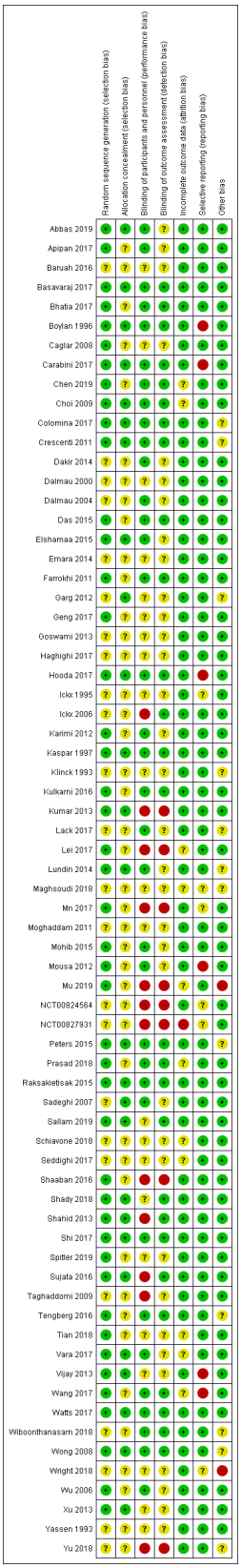
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Shady, 2018[71] | 35/70 | 35.6 (4.4) | Gynecology | Open myomectomy | 1000 mg bolus | Placebo / topical TXA | Hospital discharge |
| Boylan, 1996[34, 122] | 25/20 | 49.2 (9.2) | Hepatobiliary | Liver transplantation | 40 mg/kg/hr until portal vein unclamped | Placebo | 30 days |
| Dalmau, 2000[33, 123] | 42/82 | 58 (7.3) | Hepatobiliary | Liver transplantation | 10 mg/kg/hr until portal vein unclamped | Placebo/ EACA | 5 months |
| Dalmau, 2004[32] | 64/63 | 53.5 (9.5) | Hepatobiliary | Liver transplantation | 10 mg/kg/hr until 2hr after portal vein unclamped | Aprotinin | 3 months |
| Ickx, 1995[37] | 10/10 | /^ | Hepatobiliary | Liver transplantation | 80 mg/kg bolus, then 40 mg/kg/hr | Aprotinin | Unclear |
| Ickx, 2006[55] | 27/24 | 51.6 (8.6) | Hepatobiliary | Liver transplantation | 40 mg/kg bolus (during anhepatic phase), then 40 mg/kg/hr until 2 hr after reperfusion | Aprotinin | Hospital discharge |
| Kaspar, 1997[35] | 16/16 | /^ | Hepatobiliary | Liver transplantation | 2 mg/kg/hr | Placebo | 6-12 months |
| Wu, 2006[74] | 108/106 | 59.5 (10.5) | Hepatobiliary | Liver tumor resection | 500 mg bolus, then 250 mg q6h x3 days | Placebo | Hospital discharge |
| Yassen, 1993[36] | 10/10 | 47.2 (13.1) | Hepatobiliary | Liver transplantation | 10 mg/kg bolus, then 3 mg/kg/hr | Usual care | Not reported |
| Hooda, 2017[86, 124] | 30/30 | 40.5 (11.3) | Neurosurgery | Meningioma resection | 20 mg/kg bolus, then 1 mg/kg/hr | Placebo | Hospital discharge |
| Abbas, 2019[70] | 31/31 | 30.7 (2.6) | Obstetrics | Cesarean section | 1000 mg bolus | Usual care | Hospital discharge |
| Goswami, 2013[82] | 60/30 | 23.6 (2) | Obstetrics | Cesarean section | 10/15 mg/kg bolus[#] | Placebo | Post-op day 1 |
| Shahid, 2013[57] | 38/36 | 24.5 (4) | Obstetrics | Cesarean section | 1000 mg bolus | Placebo | Not reported |
| Sujata, 2016[78, 125] | 30/30 | 29.8 (4.2) | Obstetrics | Cesarean section | 10 mg/kg bolus | Placebo | Not reported |
| Xu, 2013[91] | 88/86 | 26.9 (3.9) | Obstetrics | Cesarean section | 10 mg/kg bolus | Placebo | Not reported |
| Baruah, 2016[80] | 30/30 | 56.5 (14.8) | Orthopedics | Dynamic hip screw plate fixation | 15 mg/kg bolus | Placebo | Not reported |
| Chen 2019[95] | 88/88 | 77.1 (6.9) | Orthopedics | Trochanteric fracture surgery | 15 mg/kg bolus, then 15mg/kg infusion for OR duration, and 15 mg/kg bolus 3hr post-op | Placebo | 6 months |
| Emara, 2014[68] | 20/40 | 55.8 (2.9) | Orthopedics | Hemi-arthroplasty | 10 mg/kg bolus, then 5 mg/kg/hr | Placebo / topical TXA | 4 weeks |
| Haghighi, 2017[63, 126] | 18/20 | 65.7 (7) | Orthopedics | Femoral fracture repair with | 15 mg/kg bolus | Placebo | Hospital discharge |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | intramedullary nailing | | | |
| Lack, 2017[46, 127] | 42/46 | 40.7 (15.8) | Orthopedics | Acetabular fracture surgery | 10 mg/kg bolus, then 10 mg/kg/hr x 4hrs | Placebo | 1 year |
| Lei, 2017[92] | 37/40 | 78.5 (8.2) | Orthopedics | Intertrochanteric fracture surgery | 1000 mg bolus | Placebo | Post-op day 30 |
| Moghaddam, 2011[39, 128] | 30/30 | /^ | Orthopedics | Hip fracture surgery | 10 mg/kg bolus, then 1 mg/kg/hr | Placebo | Not reported |
| Mohib, 2015[58] | 50/50 | 69.5 (9.7) | Orthopedics | Intertrochanteric fracture surgery | 15mg/kg bolus, repeated after 3hr | Placebo | Not reported |
| Mukherjee, 2016[77] | 29/30 | 41.8 (10.9) | Orthopedics | Femoral surgery | 5.4 mg/kg bolus, then 1 mg/kg/hr | EACA | Not reported |
| NCT, 2009[100, 129] | 41/40 | 35.1 (14.9) | Orthopedics | Long bone fracture surgery | 15 mg/kg/hr q3hr x 3 doses | Usual care | Not reported |
| Sadeghi, 2006[59] | 32/35 | 47.9 (26) | Orthopedics | Hip fracture surgery | 15 mg/kg bolus | Placebo | Hospital discharge |
| Schiavone, 2018[56] | 47/43 | 84.3 (8.3) | Orthopedics | Osteosynthesis with Supernail GT | 15 mg/kg bolus | Placebo | 8 weeks |
| Spitler, 2019[49] | 47/46 | 45^^ | Orthopedics | ORIF pelvis, acetabulum and proximal femur | 15 mg/kg bolus q3hr x2 doses | Usual care | 30 days |
| Tengberg, 2016[54, 130] | 33/39 | 77.2 (12.3) | Orthopedics | Hip fracture surgery | 1000 mg bolus, then 125 mg/kg/hr until 24h post-op | Placebo | Post-op day 90 |
| Tian, 2018[97] | 50/50 | 78.5^^ | Orthopedics | Intertrochaneric fracture PFNA | 10 mg/kg bolus, repeated 5hr post-op | Usual care | 1 week |
| Vara, 2017[47, 131] | 53/51 | 66.5 (9) | Orthopedics | Reverse total shoulder arthroplasty | 10 mg/kg bolus, repeated at skin closure | Placebo | 6 weeks |
| Vijay, 2013[81] | 45/45 | 49.1 (17.8) | Orthopedics | Hip and femoral surgery | 10 mg/kg bolus | Placebo | Hospital discharge |
| Watts, 2017[45, 132] | 69/69 | 81.6 (10) | Orthopedics | Hemi-arthroplasty | 15 mg/kg bolus, repeated at skin closure | Placebo | 6 months |
| Wiboonthanasarn, 2018[96] | 11/11 | 52.7 (23.4) | Orthopedics | Malignant musculoskeletal tumor surgery | 2000 mg bolus, then 1000 mg infusion over 8 hr post-op | Usual care | Post-op day 3 |
| Bhatia, 2017[75] | 25/25 | 35.6 (8.9) | Plastics | Burn debridement | 15 mg/kg bolus | Placebo | Not reported |
| Basavaraj, 2017[76] | 30/30 | 54.5 (5.7) | Spine | Thoracic spine fusion | 15 mg/kg bolus, then 1 mg/kg/hr | Placebo | Not reported |
| Carabini, 2017[44, 133, 134] | 31/30 | /^ | Spine | Complex multi-level spine surgery | 10 mg/kg bolus, then 1 mg/kg/hr | Placebo | Hospital discharge |

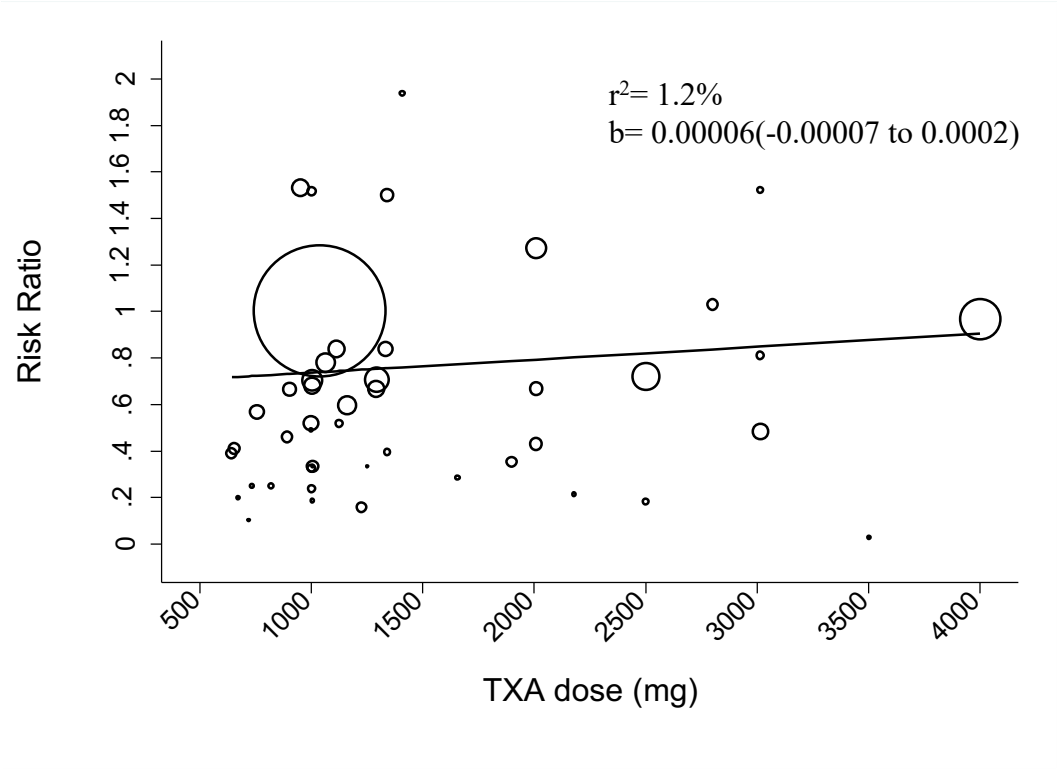
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Colomina, 2017[52, 135, 136] | 44/51 | /^ | Spine | Major spine surgery | 10 mg/kg bolus, then 2 mg/kg/hr | Placebo | Post-op day 14 |
| ElShamma, 2015[65] | 25/25 | 42.5 (3.7) | Spine | Spine surgery | 1 mg/kg/hr | Activated recombinant factor VII | Not reported |
| Farrokhi, 2011[61, 137] | 38/38 | 48.5 (11.9) | Spine | Spinal fixation surgery | 10 mg/kg bolus, then 1 mg/kg/hr | Placebo | Not reported |
| Garg, 2012[38] | 26/26 | /^ | Spine | Thoracolumbar trauma surgery | 15 mg/kg bolus | Placebo | 10 days |
| Geng, 2017[88] | 50/50 | 48.7 (4) | Spine | Spinal tuberculosis surgery | 15 mg/kg bolus, then 2 mg/kg/hr | Placebo | Not reported |
| Mn, 2018[87] | 25/75 | 49.1 (5.6) | Spine | Spinal fusion surgery | 10 mg/kg bolus, then 1 mg/kg/hr | Placebo, batroxobin, TXA/ batroxobin | Not reported |
| Mu, 2019[94] | 45/81 | 52.9 (7.4) | Spine | Double-segment posterior lumbar interbody fusion | 15 mg/kg bolus, then 1mg/kg/hr | Placebo / topical TXA | 1 month |
| Peters, 2015[48, 138] | 19/32 | 53.5^^ | Spine | Spine deformity surgery | 10 mg/kg, then 1 mg/kg/hr | Placebo/ EACA | Hospital discharge |
| Raksakietisak, 2015[72, 139] | 39/39 | 52.9 (12.2) | Spine | Complex laminectomy | 15 mg/kg bolus, repeated after 3 hr | Placebo | Post-op day 1 |
| Seddighi, 2017[64] | 20/20 | 46.8 (11.6) | Spine | Major spine surgery | 10 mg/kg bolus, then 0.5 mg/kg/hr | Placebo | 1 month |
| Shi, 2017[90, 140] | 50/46 | 54.8 (12.6) | Spine | Posterior lumbar surgery | 30 mg/kg bolus, then 2 mg/kg/hr | Placebo | Post-op day 35 |
| Taghaddomi, 2009[60] | 40/41 | 40.5 (3.5) | Spine | Lumbar hernial disc repair | 15 mg/kg bolus, then 0.1 mg/kg/hr | Usual care | Not reported |
| Wang, 2018[93] | 39/41 | 41.9 (9.9) | Spine | Transforaminal thoracic interbody fusion | 10 mg/kg bolus, then 1 mg/kg/hr | Placebo | 12 weeks |
| Wong, 2008[43, 141, 142] | 73/74 | 53.4 (16.5) | Spine | Spine fusion surgery | 10 mg/kg bolus, then 1 mg/kg/hr | Placebo | 3 months |
| Yu, 2018[40, 143] | 4445 | /^ | Spine | Thoracolumbar spine fusion | 1000 mg bolus, repeated at skin closure | Oral TXA | 4 weeks |

*Three aggregated TXA treatment arms; #Two aggregated TXA treatment arms; ^Mean/median age not reported in extractable format; ^^Standard deviation not reported; All infusions were continued for the duration of OR unless otherwise specified; No. =number; TXA = tranexamic acid; IV = intravenous; mg = milligrams; kg = kilograms; hr = hour; EACA = epsilon-aminocaproic acid; PO = oral; OR = operation; post-op = post-operative; PFNA = proximal femoral nail antirotation

## **Appendix I.** Cochrane Risk of Bias Summary

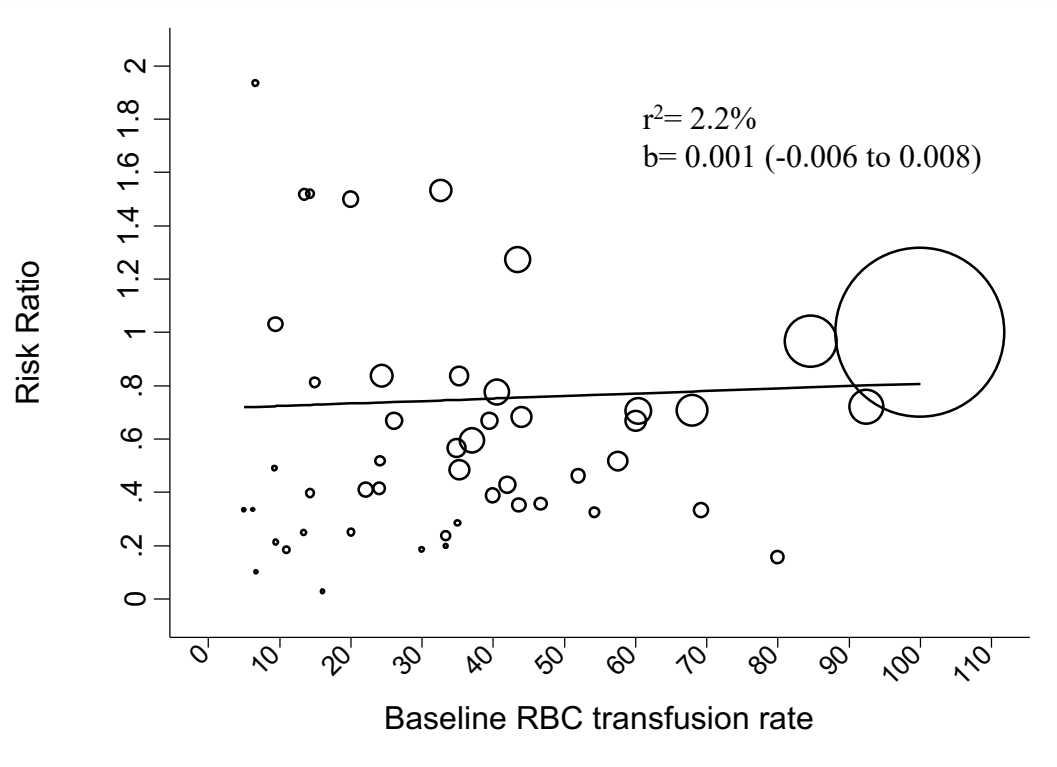


**Appendix J.** Meta-regression of TXA dose (mg) on the risk ratio for the proportion of patients transfused RBCs. Each circle represents a study and the size of the circle represents the influence of that study on the model. The regression prediction is represented by the solid line.



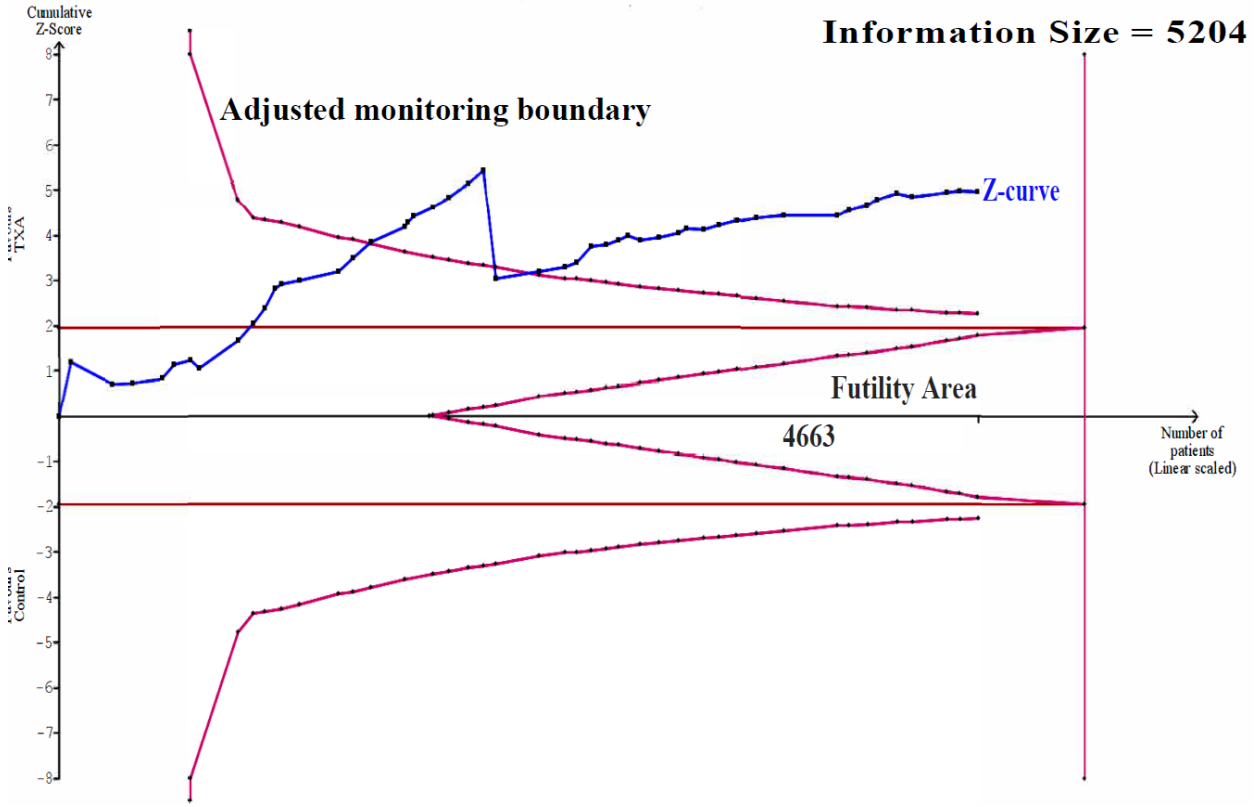

Note: $r^2$ = coefficient of variation explained by transfusion rate; b= regression coefficient (95% confidence interval)

**Appendix K.** Meta-regression of baseline transfusion rate (%) on the risk ratio for the proportion of patients transfused RBCs. Each circle represents a study and the size of the circle represents the influence of that study on the model. The regression prediction is represented by the solid line.



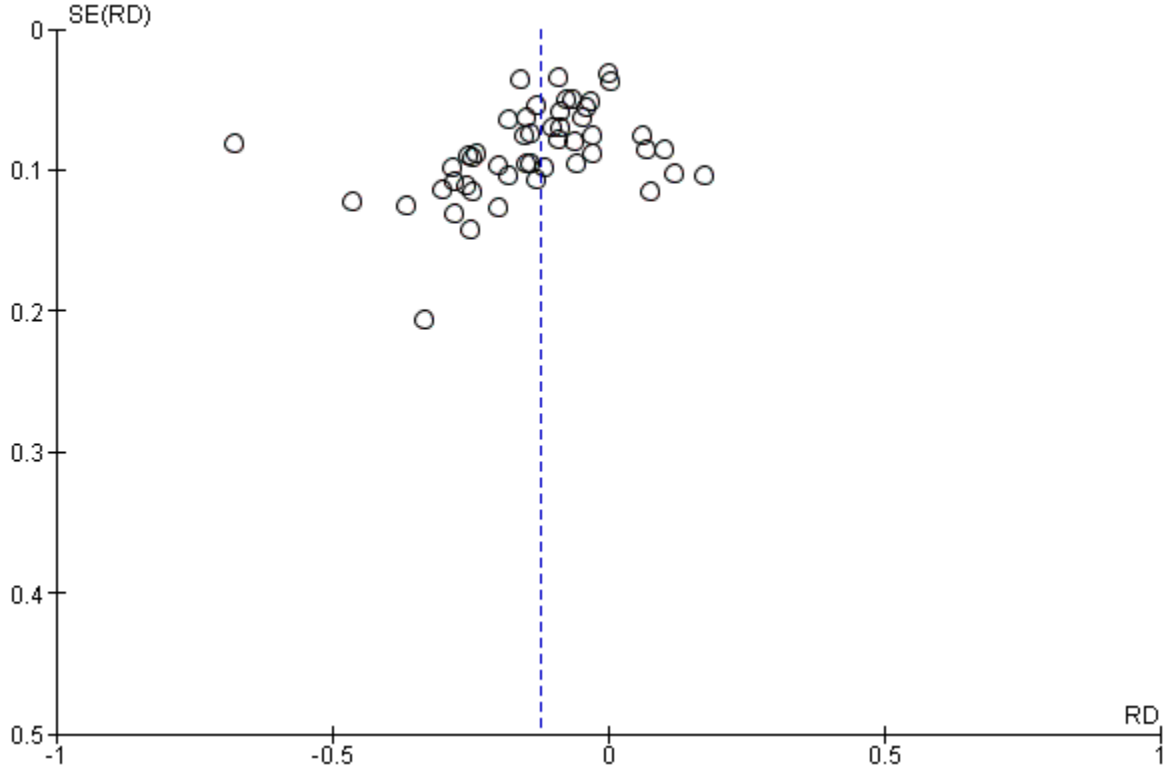

Note: $r^2$ = coefficient of variation explained by transfusion rate; b= regression coefficient (95% confidence interval)

**Appendix L.** Trial sequential analysis (TSA) of the proportion of patients transfused RBCs, based on a relative risk reduction of 0.41. When we account for the heterogeneity ($I^2$ = 84%) in our sample, the trial sequential boundary for superiority was was reached, indicating that TXA reduces the proportion of patients transfused RBCs.




TXA = tranexamic acid

**Appendix M.** Funnel plot for trials reporting proportion of patients transfused RBCs. In trials comparing TXA to placebo or standard of care (n = 49 trials), given the substantial between-study heterogeneity, funnel plot analysis suggested the absence of small to moderate-sized studies favoring placebo or usual care.



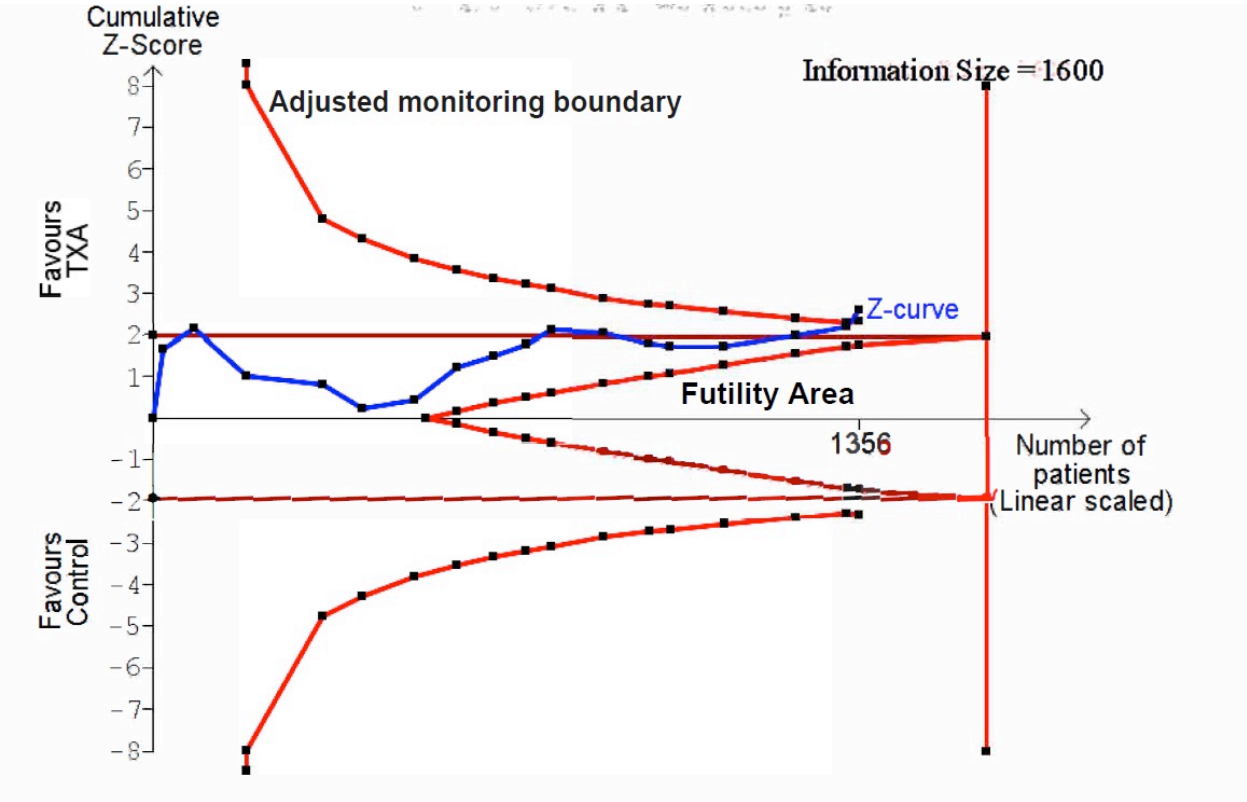

SE = standard error; RD = risk difference

**Appendix N.** Table summarizing active comparators for trials reporting the proportion of patients transfused red blood cells

| Study | TXA | | Comparator | | | Summary effect estimate (95% CI) | $I^2$ |
|---|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | Comparator type | | |
| Dalmau, 2004[32] | 38 | 64 | 30 | 63 | Aprotinin | RR 1.11 [0.63, 1.93] | 91% |
| Ickx, 2006[55] | 27 | 27 | 24 | 24 | Aprotinin | | |
| Dalmau, 2000[33, 123] | 15 | 21 | 36 | 42 | EACA | RR 0.83 [0.62, 1.12] | |
| ElShamaa, 2015[65] | 18 | 25 | 25 | 25 | rFVIIa | RR 0.73 [0.56, 0.93] | |
| Mousa, 2012[66] | 5 | 23 | 1 | 24 | Oxytocin | RR 5.22 [0.66, 41.32] | |
| Emara, 2014[68] | 0 | 10 | 1 | 20 | Topical TXA | RR 0.74 [0.25,2.14] | |
| Sallam 2019[69] | 0 | 21 | 2 | 43 | Topical TXA | | |
| Shady 2018[71] | 3 | 18 | 7 | 35 | Topical TXA | | |
| Yu, 2018[40, 143] | 8 | 44 | 6 | 45 | Oral TXA | RR 1.36 [0.52, 3.61] | |

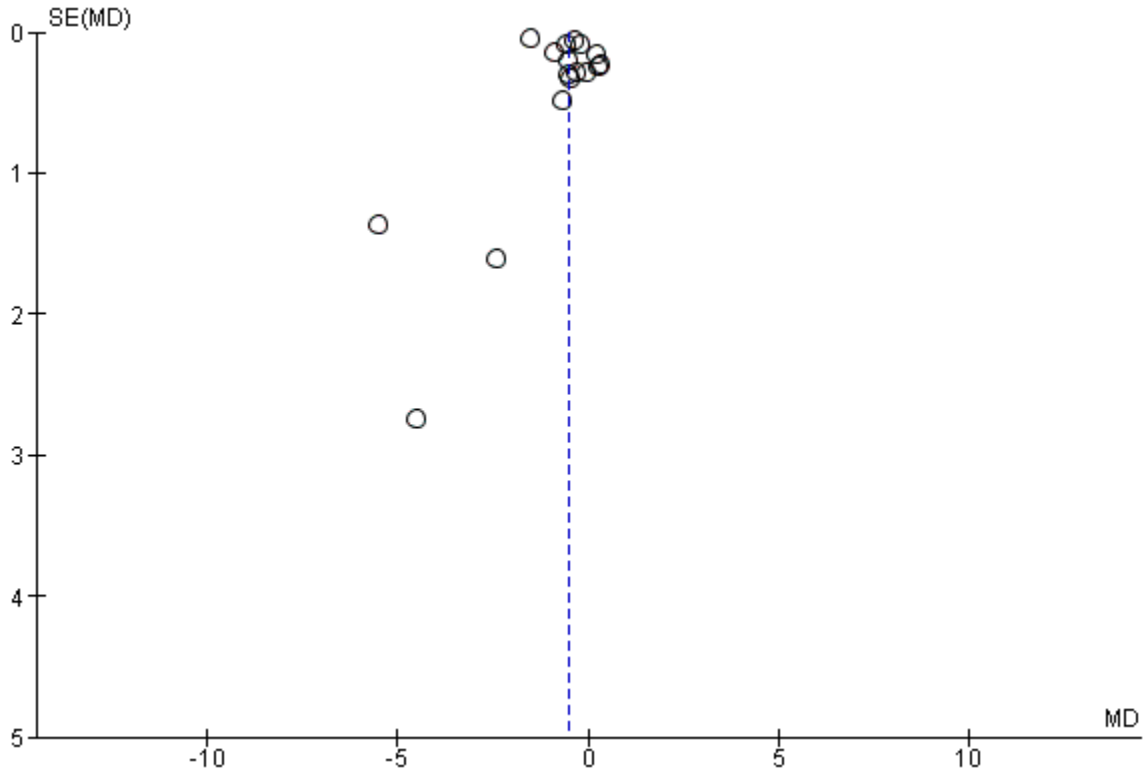
TXA = tranexamic acid; CI = confidence interval; RR = relative risk; EACA = epsilon-aminocaproic acid; rFVIIa = recombinant factor VIIa

**Appendix O.** Trial sequential analysis (TSA) for the number of RBC units transfused. The TSA is based on a mean change of -0.51, and variance change of 0.28 RBC units transfused. Accounting for the heterogeneity ($I^2$ = 97%) in our sample, the trial sequential boundary for superiority was reached, indicating that TXA reduces the number of RBC units transfused.




TXA = tranexamic acid

**Appendix P.** A funnel plot showing the number of RBC units transfused. In trials comparing TXA to placebo or standard of care (n = 17 trials), given the substantial between-study heterogeneity, funnel plot analysis suggested the absence of small to moderate-sized studies favoring placebo or usual care.



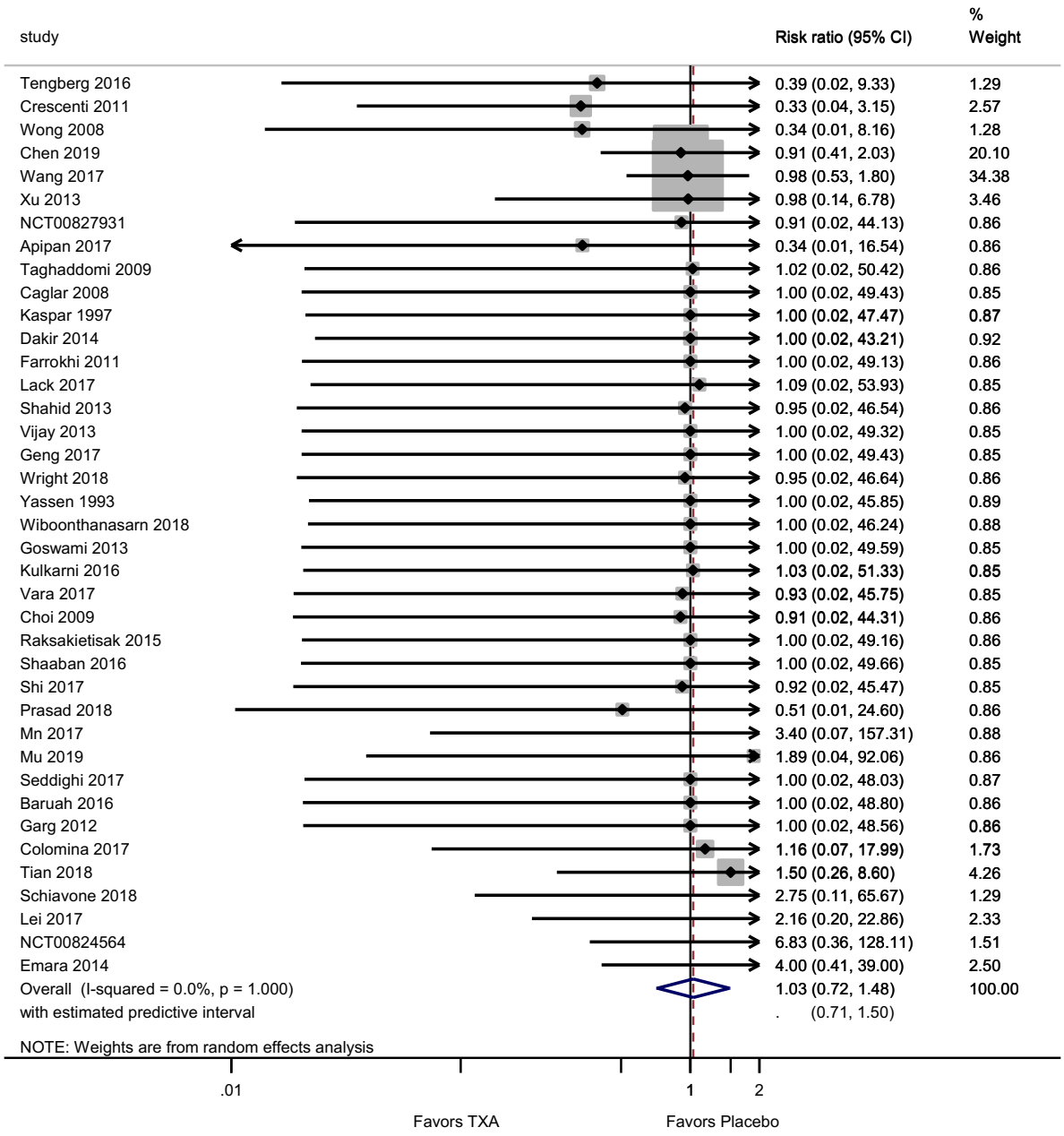

SE = standard error; MD = mean difference

**Appendix Q.** Table summarizing active comparators for trials reporting the number of RBC units transfused

| Study | TXA | | | Comparator | | | | Summary effect estimate (95% CI) | $I^2$ |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Total | Mean | SD | Total | Comparator Type | | |
| Dalmau, 2004[32] | 3.02 | 3.79 | 64 | 3.3 | 4.16 | 63 | Aprotinin | MD -0.49 [-1.74, 0.76] | 0% |
| Ickx, 1995 | 5.1 | 3 | 10 | 6.5 | 3.6 | 10 | Aprotinin | | |
| Dalmau, 2000[33, 123] | 5.33 | 5.77 | 21 | 6.69 | 5.92 | 42 | EACA | MD -1.36 [-4.41, 1.69] | |

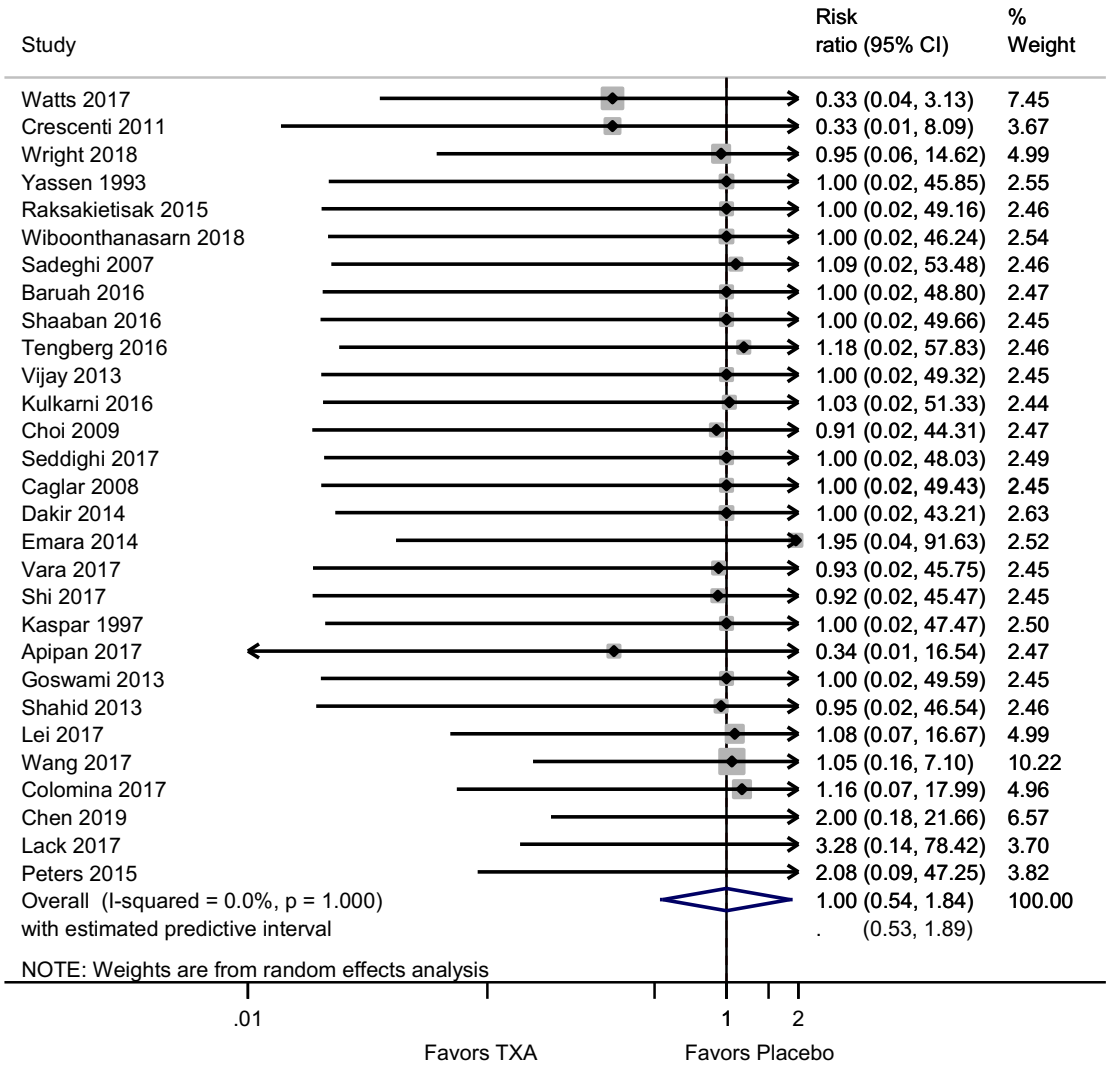
TXA = tranexamic acid; SD = standard deviation; CI = confidence interval; EACA = epsilon-aminocaproic acid; MD = mean difference

## **Appendix R.** Deep vein thrombosis



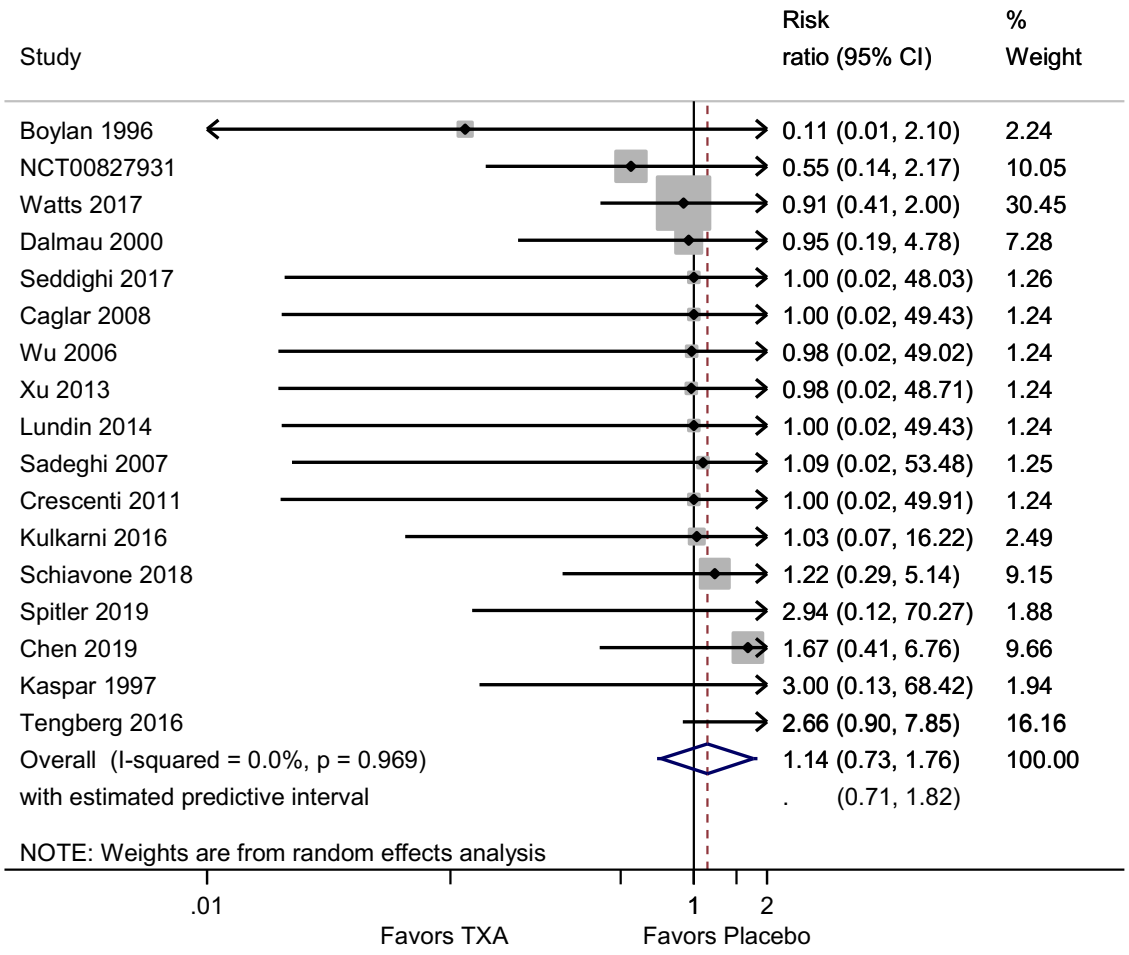

TXA = tranexamic acid; CI = confidence interval

**Appendix S.** Pulmonary embolism



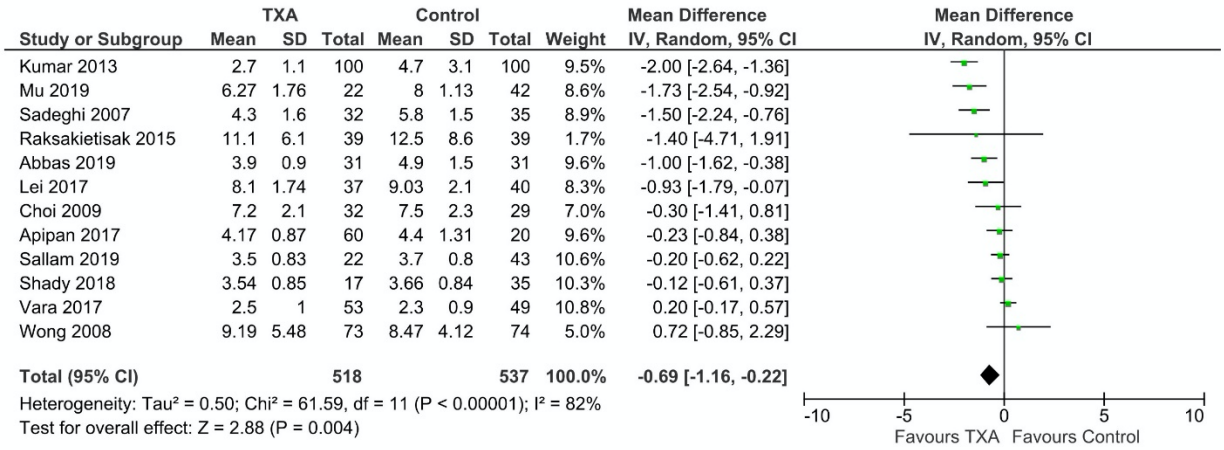

TXA = tranexamic acid; CI = confidence interval

**Appendix T.** All-cause mortality



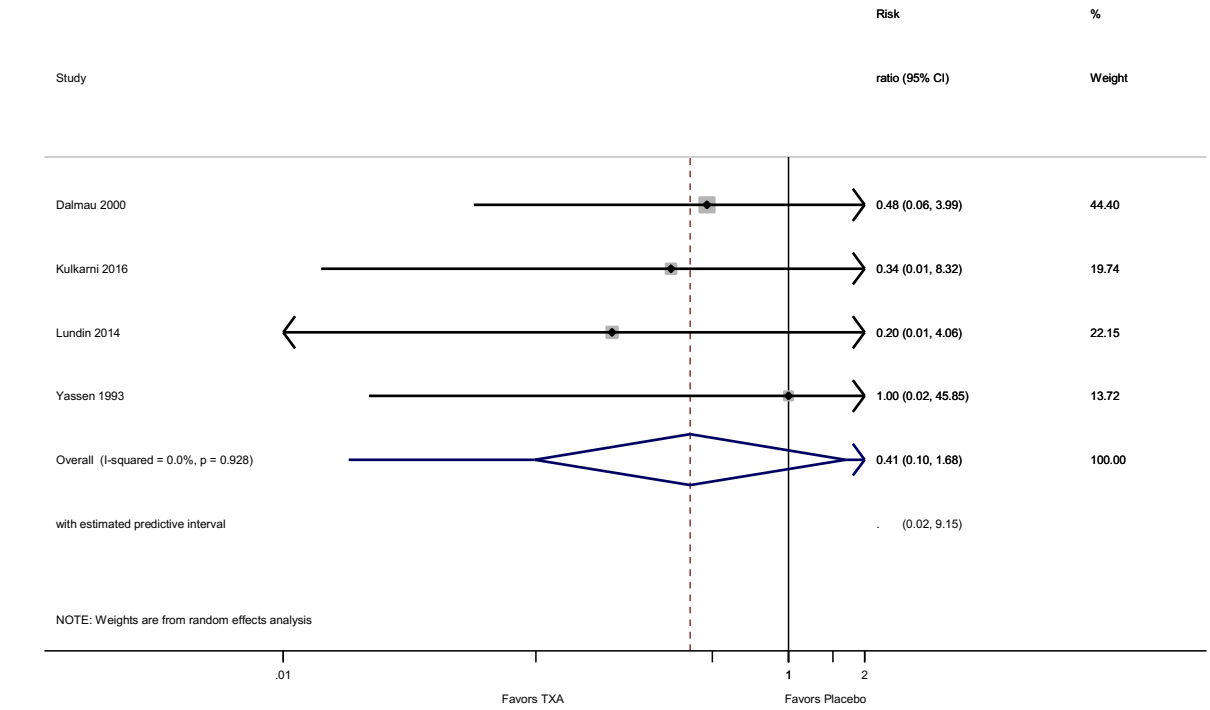

TXA = tranexamic acid; CI = confidence interval;

**Appendix U.** Hospital length of stay (days)



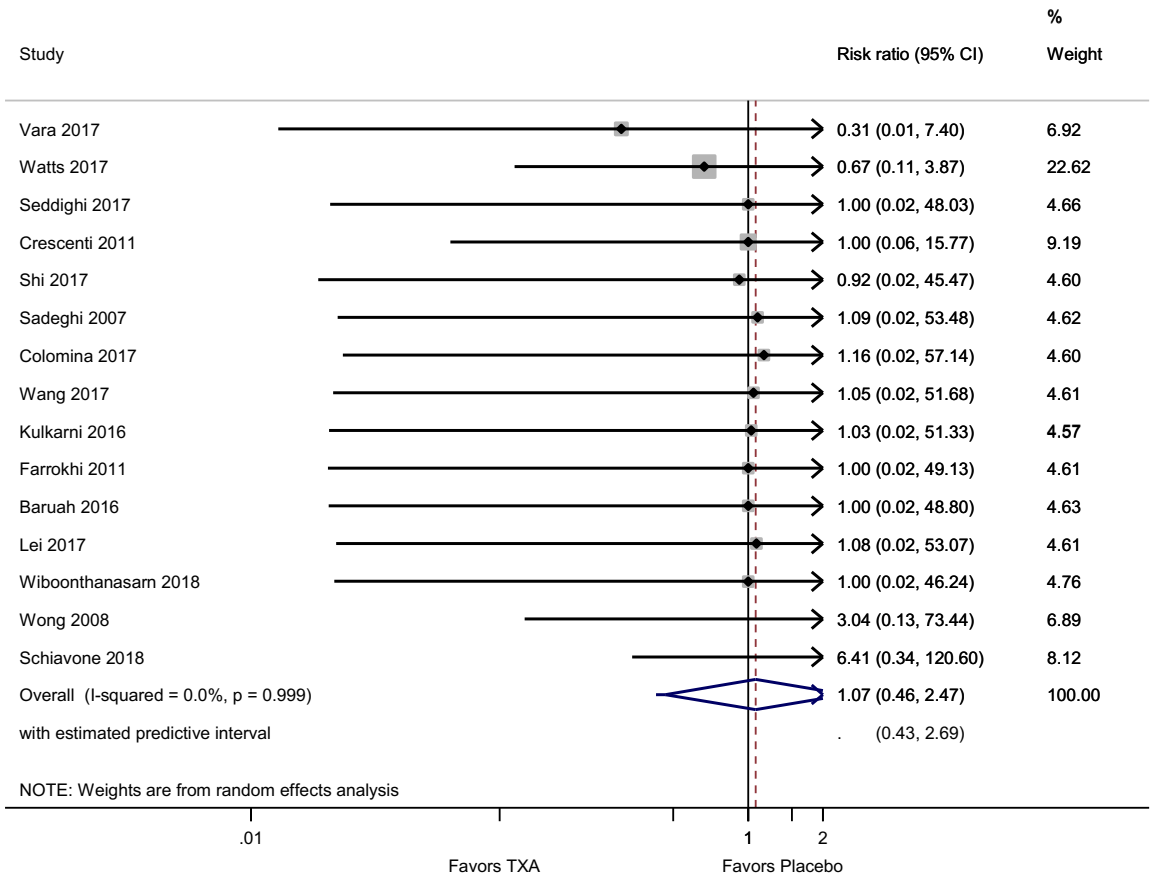

TXA = tranexamic acid; SD = standard deviation; CI = confidence interval

**Appendix V.** Re-operation due to hemorrhage



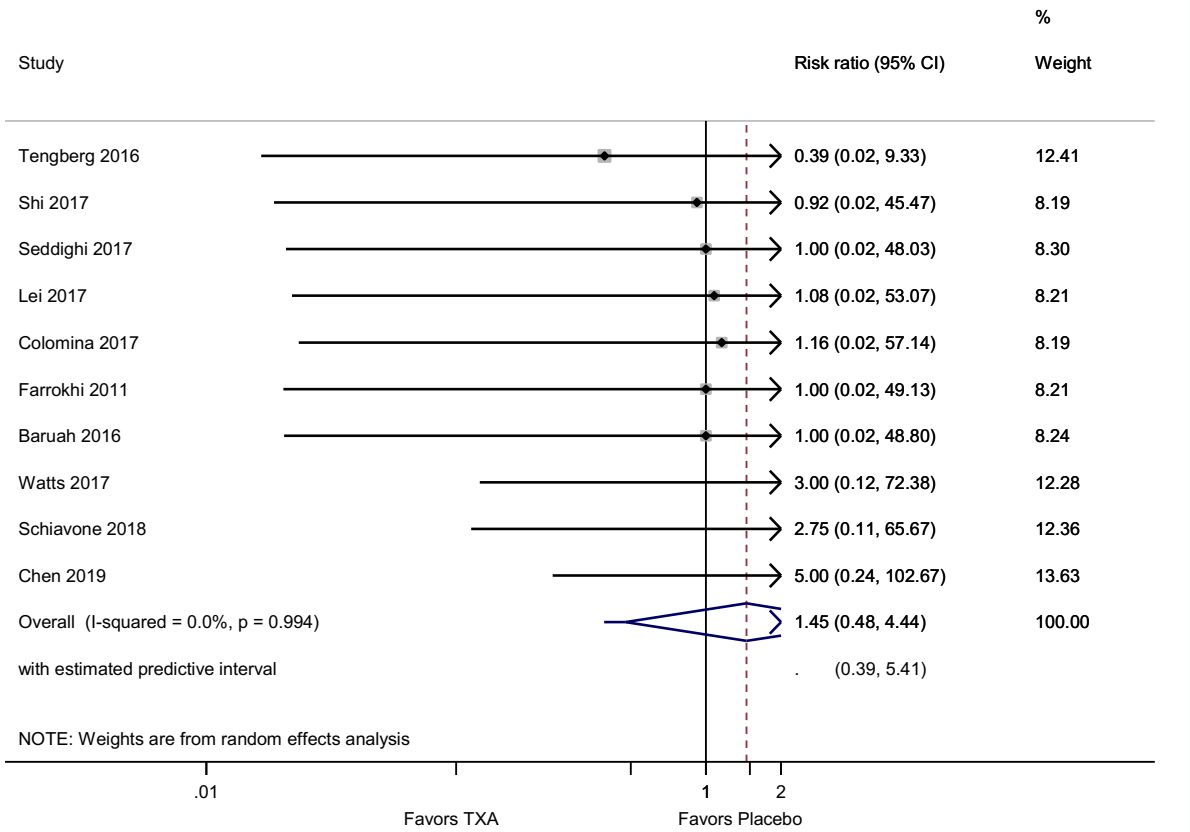

TXA = tranexamic acid; CI = confidence interval;

**Appendix W.** Myocardial infarction



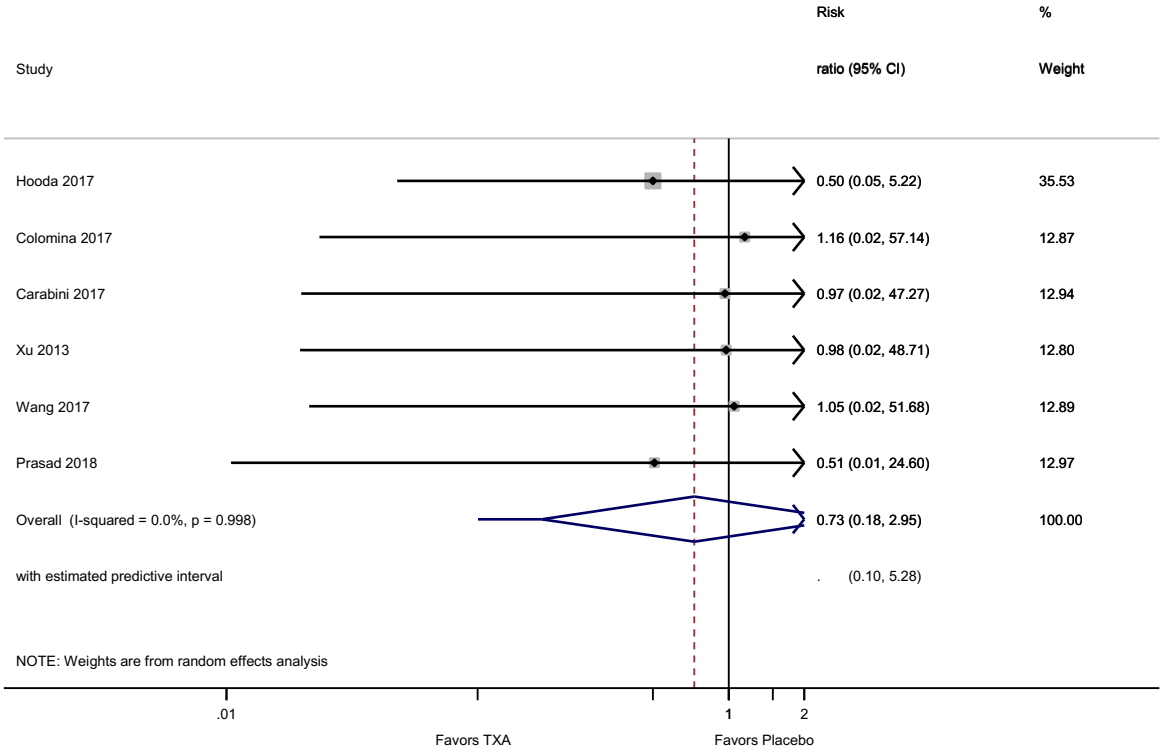

TXA = tranexamic acid; CI = confidence interval;

## **Appendix X.** Stroke




TXA = tranexamic acid; CI = confidence interval

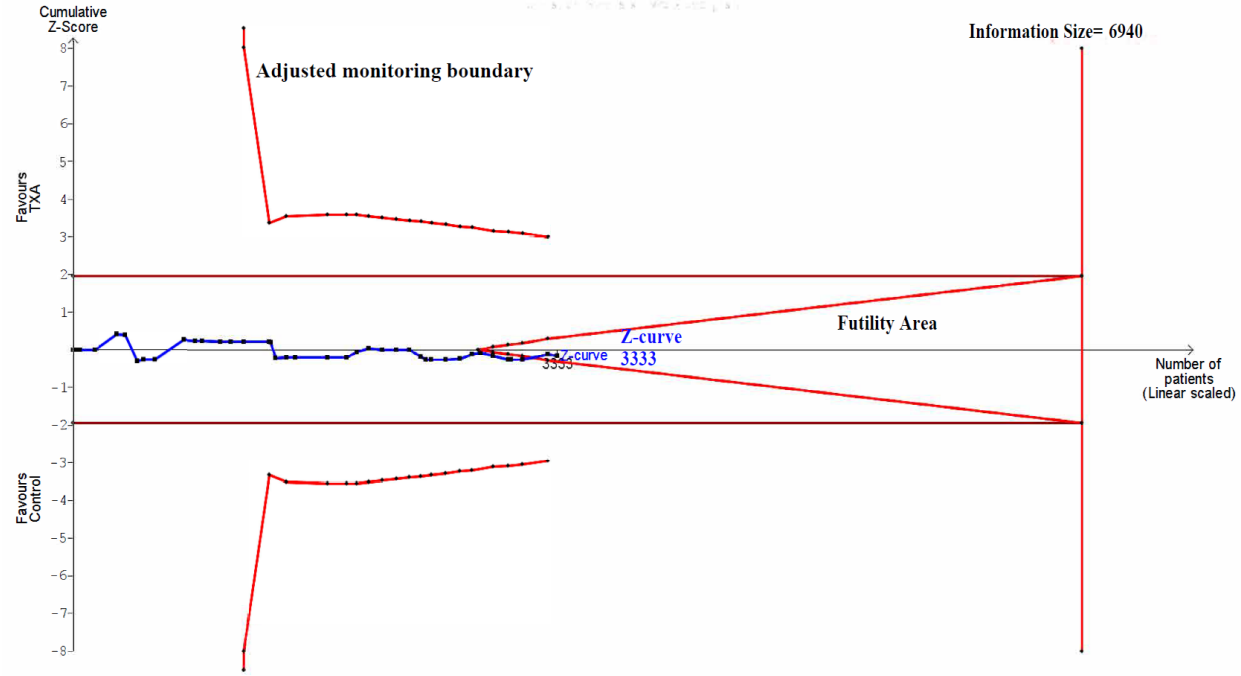
## **Appendix Y.** Seizure




TXA = tranexamic acid; CI = confidence interval

**Appendix Z.** Summary of trials reporting DVT outcome, with duration of follow-up

| Trial | # DVT events | # patients | Duration of follow-up |
|---|---|---|---|
| Goswami, 2013 | 0 | 120 | 1 day |
| Raksakietisak, 2015 | 0 | 78 | 1 day |
| Wiboonthanasarn, 2018 | 0 | 22 | 3 days |
| Shaaban, 2016 | 0 | 132 | 7 days |
| Tian, 2018 | 5 | 100 | 7 days |
| Garg, 2012 | 0 | 52 | 10 days |
| Colomina, 2017 | 2 | 95 | 14 days |
| Apipan, 2017 | 0 | 80 | 1 month |
| Emara, 2014 | 3 | 40 | 1 month |
| Lei, 2017 | 3 | 77 | 1 month |
| Mu, 2019 | 0 | 126 | 1 month |
| Lundin, 2014 | 2 | 100 | 35 days |
| Shi, 2017 | 0 | 96 | 35 days |
| Vara, 2017 | 0 | 102 | 6 weeks |
| Schiavone, 2018 | 1 | 90 | 2 months |
| Tengberg, 2016 | 1 | 72 | 3 months |
| Wang, 2017 | 27 | 80 | 3 months |
| Wong, 2008 | 1 | 147 | 3 months |
| Crescenti, 2011 | 4 | 200 | 6 months |
| Chen, 2019 | 21 | 176 | 6 months |
| Kaspar, 1997 | 0 | 32 | 6-12 months |
| Caglar, 2008 | 0 | 100 | Hospital discharge |
| Choi, 2009 | 0 | 61 | Hospital discharge |
| Dakir, 2014 | 0 | 12 | Hospital discharge |
| Kulkarni, 2016 | 0 | 219 | Hospital discharge |
| Prasad, 2019 | 0 | 60 | Hospital discharge |
| Seddighi, 2017 | 0 | 40 | Hospital discharge |
| Vijay, 2013 | 0 | 90 | Hospital discharge |
| Farrokhi, 2011 | 0 | 76 | Unclear |
| Geng, 2017 | 0 | 100 | Unclear |
| Lack, 2017 | 0 | 88 | Unclear |
| Mn, 2017 | 0 | 32 | Unclear |
| NCT00824564 | 3 | 81 | Unclear |
| NCT00827931 | 0 | 44 | Unclear |
| Baruah, 2017 | 0 | 60 | Unclear |
| Shahid, 2013 | 0 | 74 | Unclear |
| Taghaddomi, 2009 | 0 | 45 | Unclear |
| Wright, 2018 | 0 | 76 | Unclear |
| Xu, 2013 | 4 | 174 | Unclear |
| Yassen, 1993 | 0 | 20 | Unclear |
| **TOTAL:** | **77** | **3469** | |

DVT = deep vein thrombosis

**Appendix AA.** Trial sequential analysis for the incidence of deep vein thrombosis (DVT). TSA based on relative risk increase of 50%, a baseline DVT rate of 2.2%, and sample heterogeneity of $I^2 = 0\%$. Z-curve shows further testing is futile, and that TXA is not associated with a clinically significant increase in DVT.