Bleeding Reduction in Acute and Chronic KidnEy patienTs having Surgery (BRACKETS) Pilot Trial

Study Protocol Synopsis

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Principal Investigator:
Dr. Pavel Roshanov, MD, MSc, FRCPC
Division of Nephrology, Department of Medicine, Western University, London, ON
339 Windermere Road
Room A10-216
London, Ontario, Canada N6A 5A5
Tel: + 1 519-663-3350
Fax: + 1 519-663-3449
Email: pavel.roshanov@phri.ca

Study Chair:
Dr. PJ Devereaux, MD, PhD, FRCPC
Population Health Research Institute
DBCVSRI, 237 Barton Street East
Hamilton, Ontario, Canada L8L 2X2

Sponsor and Study Coordinating Group:
Hamilton Health Sciences Corporation,
Through its Population Health Research Institute
Hamilton General Hospital
237 Barton Street East
Hamilton, Ontario, Canada L8L 2X2
Email: brackets@phri.ca

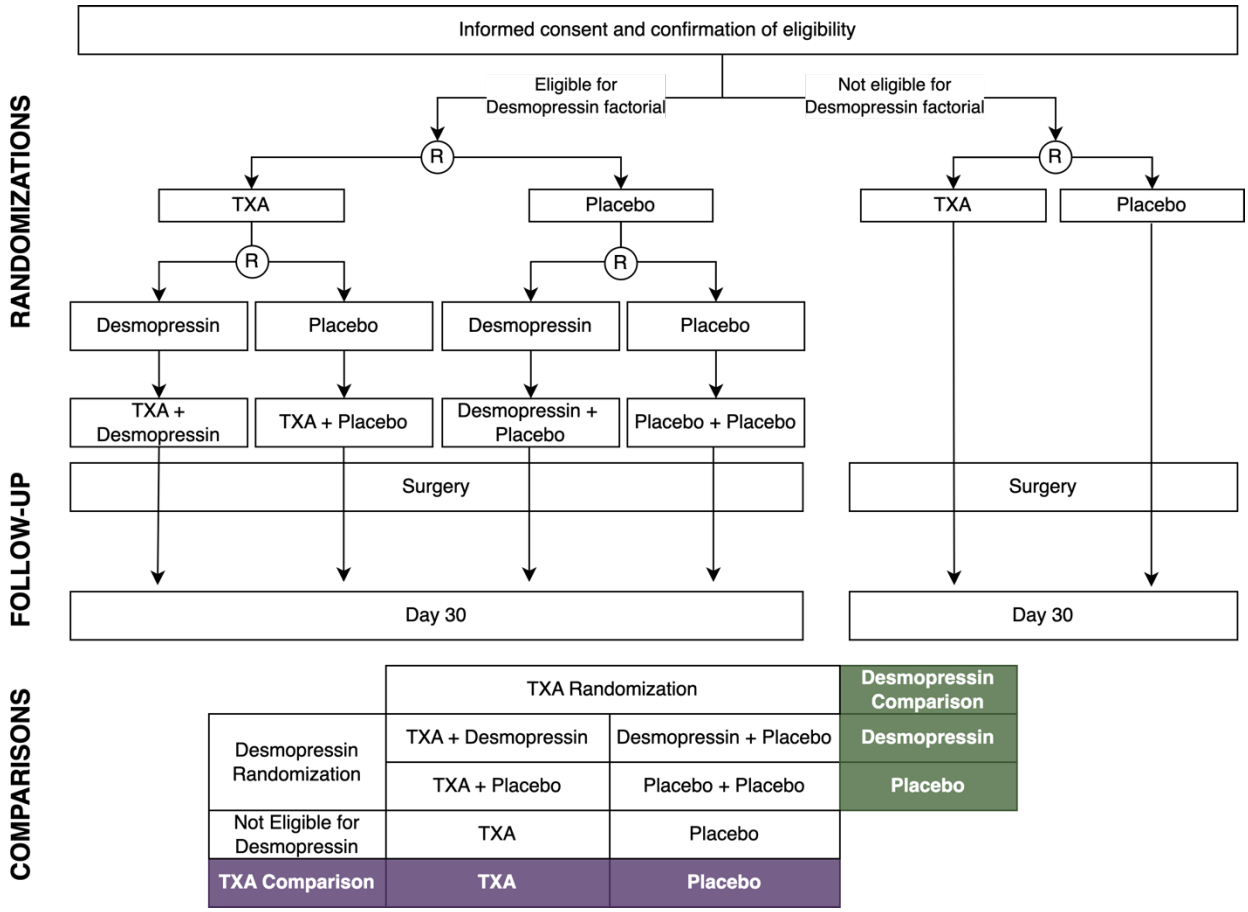
PROTOCOL SYNOPSIS

Title	**B**leeding **R**eduction in **A**cute and **C**hronic **K**idn**E**y patien**T**s having **S**urgery (BRACKETS) Pilot Trial
Project Office	BRACKETS Project Office, Population Health Research Institute Hamilton General Hospital Campus, DBCVSRI 237 Barton Street East, Hamilton, Ontario, Canada L8L 2X2 Email: brackets@phri.ca
Study Design	Multicentre prospective randomized controlled trial of intravenous prophylactic preoperative tranexamic acid (TXA) versus placebo and, using a partial factorial design, of intravenous prophylactic preoperative desmopressin versus placebo.
Study Size	100 patients.
Eligibility Criteria	Patients must fulfill <u>all</u> of the following inclusion criteria to be eligible to participate in the TXA factorial component of the trial and in the desmopressin component of the trial: 1. One of either: a. eGFR <25 ml/min/1.73m^2 estimated using the CKD-Epi 2009 or 2021 creatinine-based equation from the most recent serum creatinine measurement done in the previous 6 months; or b. Receipt of dialysis (including hemodialysis, peritoneal dialysis, hemofiltration, or hemodiafiltration) within the last 7 days; 2. Planned noncardiac surgery (elective, urgent, or emergency surgery); 3. Expected to require at least an overnight hospital admission after surgery; 4. Age ≥18 years; and 5. Informed consent is obtained to participate in the BRACKETS-Pilot Trial. Patients meeting <u>any</u> of the following criteria are excluded from participating in the TXA factorial component of the trial and the desmopressin factorial component of the trial: 1. Undergoing cardiac surgery; 2. Undergoing intracranial neurosurgery; 3. Undergoing surgery for creation or revision of arteriovenous fistula or graft for dialysis access; 4. Planned use of prophylactic systemic TXA or ϵ-aminocaproic acid; 5. Hypersensitivity or known allergy to TXA; 6. History of seizure disorder; 7. Recent (within 90 days) stroke, myocardial infarction, acute arterial thrombosis, deep venous thrombosis, pulmonary embolism, or thrombosis of an arteriovenous fistula or graft; 8. History of thrombotic thrombocytopenic purpura, atypical hemolytic uremic syndrome, or antiphospholipid antibody syndrome; 9. Women who are known to be pregnant, breastfeeding, or who meet both of the following criteria: i) are of childbearing potential and do not have a negative pregnancy test documented in the 7 days before surgery, AND ii) are not using effective contraception; or 10. Previously enrolled in the BRACKETS-Pilot Trial. Patients meeting <u>any</u> of the following criteria are excluded from the desmopressin factorial component of the trial: 1. The hospital does not have access to desmopressin; 2. Planned use of prophylactic desmopressin; 3. Most recent serum sodium concentration < 130 mEq/L; 4. Known or suspected von Willebrand disease (any kind), hemophilia, or platelet function disorder; or

	5. Hypersensitivity or known allergy to desmopressin.
Treatment Regimen	**Preoperative TXA versus placebo:** Patients will be randomized as close to the time of surgery as practically possible. Starting within 20 minutes before the anticipated skin incision, patients allocated to the TXA intervention group will receive preoperative prophylactic intravenous TXA over 10 minutes. The dose of TXA will be 1000 mg for all patients who have an eGFR <25 ml/min/1.73m^2 and did not receive dialysis in the 7 days before randomization and 500 mg for patients who received dialysis in the 7 days before randomization. Patients allocated to the TXA control group will receive intravenous placebo (saline) of the same volume infused over 10 minutes. **Preoperative desmopressin versus placebo:** Starting within 20 minutes preceding the anticipated skin incision, patients allocated to the desmopressin intervention group will receive intravenous desmopressin at a dose of 20 mcg over 30 minutes. Patients allocated to the desmopressin control group will receive intravenous placebo (saline).
Primary Objective	To determine the feasibility of a large international randomized trial to establish the efficacy and safety of TXA and desmopressin in patients with advanced kidney disease having major noncardiac surgery. 1. The primary outcome is the number of participants recruited per study site per week of active recruitment. The recruitment target is 0.25 patients per site per week. Other feasibility outcomes include: 1. receipt of the allocated study drug within 1 hour before the start of surgery for the TXA factorial; 2. receipt of the allocated study drug within 1 hour before the start of surgery for the desmopressin factorial; and 3. completion of 30-day follow-up.
Secondary Objective	To collect data that inform the clinical efficacy and safety of TXA and desmopressin in patients with advanced kidney disease undergoing major noncardiac surgery. These data will only be analyzed at the end of the pilot trial if it is deemed that we will not proceed to the full trial or if the design is modified to an extent that precludes including these data in the full trial. Clinical efficacy and safety data for TXA and desmopressin will be collected at 30 days after randomization, unless stated otherwise: 1. BIMS (bleeding independently associated with mortality in noncardiac surgery); 2. bleeding score; 3. reoperation for reasons of bleeding; 4. number of units of blood (red blood cells or whole blood) transfused; 5. number of units of blood (red blood cells or whole blood) transfused up to and including postoperative day 3; 6. any blood transfusion (red blood cells or whole blood); 7. any blood transfusion (red blood cells or whole blood) up to and including postoperative day 3; 8. calculated blood loss up to postoperative day 5; 9. lowest measured hemoglobin concentration; 10. most recent hemoglobin concentration; 11. death;

	12. major arterial and venous thrombosis (i.e., composite of myocardial injury after noncardiac surgery [MINS], non-hemorrhagic stroke, peripheral arterial thrombosis, thrombosis of arteriovenous fistula or graft, or symptomatic venous thromboembolism); 13. MINS; 14. MINS that meets criteria for myocardial infarction (based on the Fourth Universal Definition of myocardial infarction); 15. MINS that is an isolated ischemic myocardial injury; 16. stroke; 17. non-hemorrhagic stroke; 18. hemorrhagic stroke; 19. peripheral arterial thrombosis; 20. thrombosis of arteriovenous fistula or graft; 21. symptomatic proximal venous thromboembolism; 22. symptomatic pulmonary embolism; 23. symptomatic proximal leg or arm deep venous thrombosis; 24. non-fatal cardiac arrest; 25. coronary revascularization procedure; 26. clinically important atrial fibrillation or flutter; 27. acute heart failure; 28. acute kidney injury (for patients not receiving dialysis before surgery); 29. new start of dialysis; 30. seizure; 31. clinically significant intraoperative hypotension; 32. clinically significant postoperative hypotension up to the end of postoperative day 1; 33. sepsis; 34. duration of surgery; 35. receipt of platelets; 36. receipt of fibrinogen; 37. receipt of fresh frozen plasma; 38. receipt of cryoprecipitate; 39. receipt of recombinant factor VIIa; 40. receipt of prothrombin complex concentrate; 41. weekly dose of erythropoiesis-stimulating agent on prescription active at 30 days; 42. severe hyponatremia (serum sodium <125 meq/L) up to the end of postoperative day 1; 43. duration of hospital stay after surgery; 44. duration of critical care stay after surgery; 45. delayed graft function after kidney transplantation; 46. persistent dialysis dependence; and 47. incisional site pain.
Tertiary Objectives	In a pharmacokinetic substudy: 1. to determine plasma concentrations of TXA achieved with the trial dosing regimen; 2. to validate and update an existing pharmacokinetic model for TXA; and 3. to summarize model-derived estimates of TXA exposure. Centre participation in the pharmacokinetic substudy is optional.
Follow-up	30 days.

Figure 1. Process flow of the BRACKETS-Pilot trial.



Footnote: TXA, tranexamic acid; eGFR, estimated glomerular filtration rate.