DEPOSITION: Pilot Study

Decreasing Postoperative Blood Loss by Topical vs. Intravenous Tranexamic Acid in Open Cardiac Surgery

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TABLE OF CONTENTS

1.0 STUDY SUMMARY 7

2.0 BACKGROUND 7

2.1 Postoperative bleeding 7

2.2 Why is this study needed now? 7

2.3 Conclusions/future direction 8

3.0 PLAN OF INVESTIGATION 8

3.1 Objectives 8

3.2 Study Setting and Design 8

3.3 Sample size 8

3.4 Intervention 9

3.5 Timeline 9

4.0 ELIGIBILITY CRITERIA 10

4.1 Inclusion Criteria 10

4.2 Exclusion Criteria 10

5.0 STUDY PHASES 10

5.1 Phase I: Baseline 10

5.2 Phase II: In-hospital 11

5.3 Phase III: Follow-up 11

6.0 STUDY OUTCOMES 11

6.1 Primary Outcomes 11

6.2 Secondary Outcomes 11

6.3 Reporting and Adjudication of Outcomes 11

7.0 STATISTICAL ANALYSIS 12

7.1 General Considerations 12

7.2 Analysis of the primary objective 12

7.3 Analysis of Secondary Objectives 12

8.0 PROJECT MANAGEMENT 13

9.0 ETHICAL STANDARDS 13

9.1 Good Clinical Practice (GCP) 13

9.2 Informed consent of the patient 13

9.3 Approval of study protocol 13

9.4 Maintenance of records 13
9.5 Confidentiality 13
10.0 REFERENCES 14
11.0 EVENT DEFINITIONS 17

List of Abbreviations

CCU: Coronary Care Unit
CPB: Cardiopulmonary Bypass
HHS: Hamilton Health Sciences
ICU: Intensive Care Unit
I.P.: Intra-Pericardial
I.V.: Intravenous
OR: Operating Room
PHRI: Population Health Research Institute
RCT: Randomized Controlled Trial
TA: Tranexamic Acid

Study Synopsis

Title	DEPOSITION: Pilot Study
Project Office	Population Health Research Institute 237 Barton Street East, Hamilton, Ontario Canada L8L 2X2
Study Size	115 patients
Study Design	Single-center randomized controlled clinical trial
Primary Objectives	We hypothesize that topical intra-pericardial (i.p.) application of Tranexamic Acid (TA) vs. intravenous (i.v.) will reduce postoperative bleeding in patients who have undergone cardiac surgery using cardiopulmonary bypass (CPB) and decrease or eliminate the risk of seizures.
Secondary Objectives	Determine the systemic absorption of topical TA
Primary Outcomes	Postoperative chest tube production 24 hours after surgical procedure
Secondary Outcomes	1. Postoperative Number of Participants developing seizure 2. Number of Participants Requiring Surgical Re-exploration 3. Total Blood Transfusions 4. Length of ICU stay 5. All-cause death 6. Plasma level of TA on arrival in ICU
Inclusion Criteria	1. Male or female ≥ 18 years old 2. Undergoing cardiac surgical procedure with the use of cardiopulmonary bypass and median sternotomy. 3. Provide written informed consent
Exclusion Criteria	1. Poor (English) language comprehension 2. Minimally invasive surgery 3. Off-pump procedures 4. Emergency operations 5. Known history of increased bleeding disorder 6. Thromboembolic disease 7. Allergy to tranexamic acid 8. Severe renal impairment (eGFR <30 mL/min/1.73m^2) 9. Expected circulatory arrest
Interventions	This is a double-blinded trial. Anesthetists and surgeons will deliver TA (i.v. or i.p.) or matching placebo. The interventions are TA i.v. + placebo i.p. versus placebo i.v. + TA i.p. TA and matching placebo will be prepared and blinded in the pharmacy. **TA topical (i.p.):** 5 g (diluted in 50 ml normal saline) are poured into the pericardial cavity in 2 equal doses, 25 ml when the patient comes off-pump (after protamine) and the other 25 ml before sternotomy is closed. **Placebo topical**: as above without TA. **TA intravenous (i.v.)** : as per usual care from anesthetist. The anesthetist will give the dose that he/she usually give (usual care). The dose usually varies from 3 to 6 g per patient. Placebo (i.v.): same as above but without TA.
Study follow up	In-hospital, 30-day

1.0 STUDY SUMMARY

We aim to conduct a double-blinded single-centre randomized controlled clinical trial of application of topical dose of tranexamic acid (TA) versus the usual intravenous TA in patients undergoing cardiac surgery at the Hamilton General Hospital. This pilot study will assess the feasibility to perform a large randomized international trial exploring this objective.

2.0 BACKGROUND

2.1 Postoperative bleeding

Postoperative bleeding related to open cardiac surgery increases the rates of complications and mortality, representing a serious problem. It can result from many factors like acquired platelet dysfunction, thrombocytopenia, free heparin, clotting factors loss, and increased fibrinolysis [1-3]. Extracorporeal circulation can result in significant fibrinolysis, reflected by increased concentrations of plasmin and fibrin degradation products, both of which have deleterious effects on platelet function [4]. Antifibrinolytic therapy has become a mainstay in cardiac surgical procedures for decreasing bleeding and minimizing transfusion requirements [5,6]. Current guidelines make a class I recommendation for intravenous tranexamic acid (TA) use as a blood-conservation strategy during cardiac operations to reduce bleeding [7].

Although intravenous TA is usually well tolerated, its antifibrinolytic effect can theoretically increase the risk of thromboembolic events (e.g. early graft closure in coronary artery bypass grafting, deep vein thrombosis, pulmonary embolism, myocardial and cerebral infarctions), but in practice these adverse events were reported quite rarely [8, 9]. The most significant adverse effect recently reported in small and large studies of cardiac surgery is the risk of postoperative convulsive seizures after administration of different intravenous doses of TA, particularly with high-dose regimens [9-11]. This effect is possibly due to the similarity between TA molecules and the molecules of g-aminobutyric acid, which leads to the occupancy of g-aminobutyric A brain receptors [12].

2.2 Why is this study needed now?

When used topically, TA is effective in controlling bleeding in patients with hemorrhagic diathesis and in patients who are treated with anticoagulants pre-operatively. It is also effective in controlling bleeding in oral, orthopedic, gynaecologic, and otolaryngeal surgeries [13-15]. In addition, the fibrinolytic activity in the pericardial cavity exceeds that in the systemic circulation as human pericardium contains high levels of tissue plasminogen activator, which under normal/physiological conditions prevents the formation of adhesions and maintains the fluidity of the pericardial [16,17]. Furthermore, surgical tissue manipulations may enhance this local fibrinolytic activity. All these findings lead to the rationale for the topical application of TA into the pericardial cavity during cardiac surgery.

Between 2000 to 2016, seven small randomized controlled trials comparing the topical application of **TA vs. placebo** were reported [18–24]. In all of these trials the topical application of TA significantly reduced the 24-hour postoperative blood loss. We performed a meta-analysis (Appendix 1) of these 7 trials and confirmed the substantial reduction in 24-hour blood loss with topical application of TA [25]. In two other reports, the addition of topical application to intravenous TA vs. intravenous TA alone did not added benefit in reducing postoperative 24-hour blood loss compared with intravenous drug alone [26,27] but significantly less products were used [26] or significantly less seizures were seen with intravenous TA plus topical TA [27]due to lower of intravenous TA used. **No** studies comparing the effectiveness of topical application vs. intravenous administration of TA are reported. We hypothesize that topical application of TA can reduce postoperative bleeding in patients who have undergone cardiac surgery without the risk of seizures associated with systemic (intravenous) infusion of TA.

2.3 Conclusions/future direction

This is a single-centre randomized controlled clinical trial of application of topical dose of tranexamic acid (TA) versus the usual intravenous TA in patients undergoing cardiac surgery at the Hamilton General Hospital. This pilot study will assess the feasibility to perform a large trial using a cluster crossover design with blinding of drugs in pharmacy.

3.0 PLAN OF INVESTIGATION

3.1 Objectives

3.1.1. Primary objectives are:

We hypothesize that topical intra-pericardial (i.p.) application of TA vs. intravenous (i.v.) will reduce postoperative bleeding in patients who have undergone cardiac surgery using cardiopulmonary bypass (CPB) and decrease or eliminate the risk of seizures.

3.1.2 Secondary objectives are:

- Postoperative Number of Participants developing seizure
- Number of Participants Requiring Surgical Re-exploration (bleeding/tamponade)
- Total Blood Transfusions and components
- Length of ICU stay
- All-cause death
- Plasma level of TA on arrival in ICU

3.2 Study Setting and Design

This study is a single-center randomized controlled clinical (RCT) trial at the Hamilton General Hospital site. Patients will be recruited before surgery by the research staff.

3.3 Sample size

We will recruit a sample of 115 patients for this pilot study.

3.4 Intervention

The TA comes in bottle of 1g per 10 ml of normal saline or in 5g per 50ml of normal saline. For topical applications, we have selected a dose of 5 g of TA (or matching placebo) for simplicity as it comes in a reasonable volume of saline to allow distribution everywhere in the mediastinum. The topical will be poured into the pericardial mediastinal cavities in 2 equal doses, 25 ml when the patient comes off-pump (after protamine) and the other 25 ml before sternotomy is closed.

The intravenous dose is not standardized at all across the country. Every anesthesiologist has his/her own concoction and a standardization of the dose is very difficult. The ATACAS trial had a lot of difficulty with this and had to cut the dose in half during the trial in order to improve participation and recruitment. Therefore, we will let each anesthesiologist give their usual dose. We will collect the dose on induction and subsequent per-infusion. We will analyze the results according to the dose per kg.

The pharmacy will prepare 1 syringe of 50 ml of topical TA (5 g) or placebo. They will also prepare for the same patient 2 syringes of 50 ml (5 g) for intravenous (i.v.) injection or placebo. TA is similar in all aspects to normal saline. Blinding of both teams will be easy. The syringes will be prepared and randomized in pharmacy before the surgery.

We will collect blood at arrival in ICU to measure the serum level of TA in both groups.

3.5 Timeline

Cardiac surgery is performed on approximately 125-140 patients per month. We plan on recruiting the 115 patients in a 4 month period.

Consented patients will undergo the intervention during the surgery. Blood tests are done in ICU-West within 3 hours. Patients will be seen by research staff daily in hospital until discharge and will be followed up at 30 days as per chart below.

Time period	Screening	Baseline	OR	Post-op	Clinical or Phone Visit (30 days)
Eligibility	X				
Informed Consent	X				
Medical History		X			
Demographics		X			
Medications		X		X	X
Operative Details			X		
Events[a]				X	X

[a] Primary and secondary outcome events.

4.0 ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

1. Male or female ≥ 18 years old
2. Undergoing cardiac surgical procedure with the use of cardiopulmonary bypass and median sternotomy.
3. Provide written informed consent

4.2 Exclusion Criteria

1. Poor (English) language comprehension
2. Minimally invasive surgery
3. Off-pump procedures
4. Emergency operations
5. Known history of increased bleeding disorder
6. Thromboembolic disease
7. Allergy to tranexamic acid
8. Severe renal impairment (eGFR <30 mL/min/1.73m^2)
9. Expected circulatory arrest

5.0 STUDY PHASES

5.1 Phase I: Baseline

Eligible patients will be approached by a trained member of the research team before surgery to obtain consent to participate in the study. When the consent is signed, the randomization will be done at PHRI. The ratio is 1:1 with blocks of 2 and 4 patients.

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

5.2 Phase II: In-hospital

Research staff will prospectively collect relevant intra-operative details from observations in the OR and referring to the anesthesia and OR documentation.

5.3 Phase III: Follow-up

Participants will complete a follow-up (surgeon's office or by phone) that will be scheduled at 30 days post-op.

6.0 STUDY OUTCOMES

6.1 Primary Outcomes

1. Postoperative chest tube production 24 hours after surgical procedure
2. Rate of crossover (need to use both approaches or supplementary dose of TA)
3. Recruitment rate per week
4. Proportion of patients lost to follow-up at 30 days post-operatively

6.2 Secondary Outcomes

1. Postoperative Number of Participants developing seizure
2. Number of Participants Requiring Surgical Re-exploration (bleeding/tamponade)
3. Total Blood Transfusions
4. Length of ICU stay
5. All-cause death
6. Level of TA on arrival in ICU

6.3 Reporting and Adjudication of Outcomes

If it becomes evident from the clinic visit or telephone follow-up that the participant suffered from any event of interest or a hospital-readmission, the institution where the patient was admitted will be contacted by members of the research team to request the patient's chart around this episode.

If the patient is deceased, the death certificate will be requested from the institution where the death took place or from the patient's family physician if the death occurred outside of hospital. This will allow us to collect information about the cause of death.

Available source documents will be adjudicated by two independent reviewers at the central project office. We will adjudicate the following outcomes: mortality, surgical re-exploration and seizures.

All adjudication will be performed by a committee of clinicians independent of the study design and conduct. The clinicians on this committee will be individuals with experience in perioperative outcomes.

7.0 STATISTICAL ANALYSIS

7.1 General Considerations

Standard methods will be used to provide tabular and graphical summaries as appropriate for continuous and categorical variables. Summaries of continuous variables will include the number of subjects (N), mean, standard deviation, median, quartiles 1 and 3, minimum and maximum. Frequency distributions (N and %) will be given for categorical data. Descriptive summaries will be provided overall, and by surgical technique. Baseline characteristics will be compared between patients with and without covert stroke with chi-square tests for categorical variables, and analysis of variance for numerical variables (or Kruskal-Wallis [non-parametric] test, if the assumption of normality of the residuals and/or homoscedasticity do not hold). Analyses will be conducted with SAS version 9.4 or higher, and the significance level will be 0.05.

7.2 Analysis of the primary objective

The primary outcome (blood loss) will be analyzed with a t-test as it is a continuous variable.

7.3 Analysis of Secondary Objectives

The secondary outcomes (death, surgical re-exploration, seizures) will be compared via a Fisher's exact test as their frequency will be low. Transfusions will be analyzed by chi-square. Plasma levels and length of stay will be analyzed with a t-test.

Method Development and Measurement of Tranexamic Acid in Blood - The proposed study aims at developing a method for measurement of antifibrinolytic agent, tranexamic acid, in blood for potential therapeutic monitoring of this drug. The specific objectives of this study are 1) to develop, optimize, and validate an analytical method for measurement of tranexamic acid levels in human plasma and serum; 2) use the in-house developed method for measuring tranexamic acid in patients treated the drug during the open heart surgery, who have been enrolled in the DEPOSITION Study.

The Biochemical Genetics Laboratory, Hamilton Regional Laboratory Medicine Program at McMaster University Medical Centre will be developing and validating the method using liquid

chromatography-mass spectrometry technology. This will be led by Dr. Murray Potter and Dr. Josko Ivica.

8.0 PROJECT MANAGEMENT

The study will be centrally co-ordinated by the Peri-operative and Cardiac Surgery division of the Population Health Research Institute (PHRI) at McMaster University, Hamilton, Canada. The NeuroVISION Cardiac Project Office will be responsible for the day-to-day study management of this pilot.

9.0 ETHICAL STANDARDS

9.1 Good Clinical Practice (GCP)

The procedures set out in this protocol are designed to ensure that the investigator abide by the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines (ICH-GCP) in the latest version, in conduct, evaluation and documentation of the study.

9.2 Informed consent of the patient

Patients who meet all inclusion criteria and none of the exclusion criteria are deemed eligible. Before being registered into the clinical study, all patients, or their proxy decision-makers, will be explained the details of this study protocol, and be asked to sign a consent form for participation after the nature, scope and possible consequences of the study have been explained both orally and in writing.

9.3 Approval of study protocol

Before the start of the study, the study protocol and the informed consent form used at the site and other appropriate documents must be submitted to and approved by Hamilton Health Sciences Research Ethics Board (HIREB) before sites are activated to enroll patients.

9.4 Maintenance of records

The Investigator agrees to obtain a correctly completed informed consent form for each patient included in the study. The investigator will maintain a personal list of patient numbers and patient names to enable records to be found at a later date. The Investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice.

9.5 Confidentiality

All patient names will be kept confidential. Patients will be identified by the patient ID number allotted to them by the study. The patients will be assured that all findings will be stored on computer and handled in the strictest confidence. The Investigator agrees to maintain the confidentiality of the study protocol.

10.0 REFERENCES

1-Kucuk O, Kwaan HC, Frederickson J, Wade L, Green D: Increased fibrinolytic activity in patients undergoing cardiopulmonary bypass operation.Am J Hematol1986; 23:223-9.

2-Harker LA, Malpass TW, Branson HE, Hessel EA II, Slichter SJ: Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: acquired transient platelet dysfunction associated with selective alpha-granule release. Blood 1980; 56:824-34.

3-Depotis GJ, Santoro SA, Spitznagel E, Kater KM, Cox JL, Barnes P: Prospective evaluation and clinical utility of on-site monitoring of coagulation in patients undergoing cardiac operation. J Thorac Cardiovasc Surg. 1994; 107:271-279.

4-Lemmer JH Jr, Stanford W, Bonney SL, Breen JF, Chomka EV, Elderge WJ: Aprotonin for coronary bypass operations: efficacy, safety, and influence on early saphenous graft patency-a multicenter, randomized, double blind, placebo-controlled study. J Thorac Cardiovasc Surg 1994, 107:543-53.

5-Santos AT, Kalil RA, Bauemann C, Pereira JB, Nesralla IA. A randomized double-blind and placebo-controlled study with tranexamic acid of bleeding and fibrinolytic activity after primary coronary bypass grafting. Braz J Med Biol Res 2006; 39:63–69.

6-Pleym H, Stenseth R, Wahba A, Bjella L, Karevold A, Dale O. Single dose tranexamic acid reduces post-operative bleeding after coronary surgery in patients treated with aspirin until surgery. Anesth Analg 2003; 96:923–92 8.

7-Ferraris VA, Brown JR, Despotis GJ, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011; 91:944–98 2.

8-Ross J., Al-Shahi S.R. The frequency of thrombotic events among adults given antifibrinolytic drugs for spontaneous bleeding: systematic review and meta-analysis of observational studies and randomized trials, Current Drug Safety 2012;7: 44–54.

9-Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. N Engl J Med. 2017;376:136-148.

10-Martin K., Wiesner G., Breuer T., et al., The risks of aprotinin and tranexamic acid in cardiac surgery: a one-year follow-up of 1188 consecutive patients, Anesthesia and Analgesia 2008; 107:1783–1790.

11-Kalavrouziotis D., Voisine P., Mohammadi S., et al. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass, Annals of Thoracic Surgery 2012;93:148–153.

12-Furtmu¨ller R., Schlag M.G., Berger M., et al., Tranexamic acid, antifibrinolytic agent, causes convulsions by g-aminobutyric acid A receptor antagonistic effect, Journal of Pharmacology and Experimental Therapeutics 2002; 301:168–173.

13-Versraette M: Clinical application of fibrionolysis. Drugs 1985; 29:236-61.

14-Valsecchi A: Further notes on the topical use of Tranexamic acid in the treatment of gynaecological haemorrhage. Minerva Ginecol 1980; 32:825-30.

15-Sindet-Pedersen S, Ramtro G, Bernvil S, Blomback M: Haemostatic effect of tranexamic acid mouthwash in anticoagulanttreated patients undergoing oral surgery. N Engl J Med 1989; 320:840-3.

16-Henry D, Carless P, Fergusson D, Laupacis A: The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. CMAJ 2009; 180(2):183-93.

17-Alderman EL, Levy JH, Rich JB: Analyses of coronary graft patency after Aprotinin use: results from the International Multicenter Aprotinin Graft Patency Experience study (IMAGE) trial. J Thorac Cardiovasc Surg 1998; 116:716-730.

18-De Bonis M., Cavaliere F., Alessandrini F., et al., Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study, Journal of Thoracic and Cardiovascular Surgery 2000;119:575–580.

19-Abul-Azm A., Abdullah K.M., Effect of topical tranexamic acid in open heart surgery, European Journal of Anaesthesiolgy 23 (2006) 380–384.

20-Baric D., Biocina B., Unic D., et al., Topical use of antifibrinolytic agents reduces postoperative bleeding: a double-blind, prospective, randomized study, European Journal of Cardiothoracic Surgery 2007;31:366–371.

21-Fawzy H., Elmistekawy E., Bonneau D., et al., Can local application of tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial, Journal of Cardiothoracic Surgery 2009;4:25.

22-Aoki M, Okawa Y, Goto Y, Ogawa S, Baba H. Local administration of tranexamic acid in off-pump coronary artery bypass. Asian Cardiovasc Thorac Ann. 2012; 20:658-62.

23-Hosseini H, Rahimianfar AA, Abdollahi MH, Moshtaghiyoon MH, Haddadzadeh M, Fekri A, Barzegar K, Rahimianfar F. Evaluations of topical application of tranexamic acid on post-operative blood loss in off-pump coronary artery bypass surgery. Saudi J Anaesth. 2014; 8:224-8.

24-Ali Shah MU, Asghar MI, Siddiqi R, Chaudhri MS, Janjua AM, Iqbal A. Topical application of tranexamic acid reduces postoperative bleeding in open-heart surgery: myth or fact? J Coll Physicians Surg Pak. 2015; 25:161-5.

25-Habbab LM, Semelhago L, Lamy A. Intrapericardial Use of Tranexamic Acid in Cardiac Surgery: a meta-analysis of seven RCT. (in process).

26-Spegar J., Vanek T., Snircova J., et al., Local and systemic application of tranexamic acid in heart valve surgery: a prospective, randomized, double blind LOST study, Journal of Thrombosis and Thrombolysis 32 (2011) 303–310.

27-Taman HI., Amer GF., Amera SA. Can topical administration of tranexamic acid be a good adjuvant to the intravenous route for decreasing postoperative seizure incidence? A double blinded randomized study. Ain-Shams Journal of Anesthesiology 2015; 08:36–42

11.0 EVENT DEFINITIONS

Chest tube bleeding
The bleeding will be collected from the nurses' charts at 24 hours after arrival in ICU

Seizure
All causes of seizures will be recorded as the secondary outcome. We will define further these seizures as related to a stroke (including acute cerebral ischemia, TIA, covert stroke) or as unknown

Surgical exploration
All causes of return to the operating room for bleeding, tamponade, surgical ischemia or shock. Pacemaker insertion, tracheostomy are sternal dehiscence/mediatinitis are excluded.

Transfusions
All blood products (except albumin) will be recorded and analyzed as a total but also individually by type. Usage of factor VII will be also recorded

Death

Any death regardless of cause. Death will be stratified as cardiac and non-cardiac. All deaths in the first 30 days or before hospital discharge will be considered cardiac deaths.

Cardiac Death - All death related to cardiovascular system or of sudden or unknown cause.

Non-Cardiac Death – Defined as clearly documented death unrelated to cardiovascular system (e.g. trauma, malignancy, suicide).

Clinical stroke
Stroke that is clinically apparent and confirmed by a neurologist and imaging (CT scan or MRI)

Acute cerebral ischemia
Acute cerebral ischemia will be defined as a hyper intense lesion on diffusion-weighted/T2 magnetic resonance imaging

Covert stroke
Covert stroke is defined as acute cerebral ischemia detected on MR testing, but without any new clinical findings of focal neurological deficits.

Overt Stroke
Overt stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours, as diagnosed by a physician involved in the patient's care.

Transient Ischemic Attack

Transient ischemic attack is defined as a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting less than 24 hours, as diagnosed by a physician involved in the patient's care.

Myocardial infarction (MI)

The diagnosis of myocardial infarction requires any one of the following criteria:

1. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism). This criterion also requires that 1 of the following must also exist:
    a. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema)
    b. development of pathologic Q waves present in any two contiguous leads that are > 30 milliseconds
    c. ECG changes indicative of ischemia (i.e., ST segment elevation [> 2 mm in leads V1, V2, or V3 OR > 1 mm in the other leads], ST segment depression [> 1 mm], or symmetric inversion of T waves > 1 mm) in at least two contiguous leads
    d. coronary artery intervention (i.e., PCI or CABG surgery)
    e. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging
2. Pathologic findings of an acute or healing myocardial infarction
3. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event

Renal failure

Patients who require dialysis after surgery (not including peri-operative dialysis)

New delirium

Defined as acute onset of confusion fulfilling the diagnostic criteria of the Cognitive Assessment Method (CAM) for delirium.

1) Acute onset of fluctuating cognitive impairment;
2) Deficits of attention; AND
3) One of:
    a. altered level of consciousness; OR
    b. disorganized thought processes.