

## RENAL FUNCTION IN PATIENTS UNDERGOING SURGERY

RENAL FUNCTION IN PATIENTS UNDERGOING SURGERY

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## **ABSTRACT**

Reduced kidney function around the time of surgery is an important risk factor for postoperative mortality. Despite this there is limited information on how reduced kidney function prior to surgery alters prognosis, what causes sudden decrements in kidney function after surgery (known as acute kidney injury), or how they might be avoided. The studies in this thesis inform these knowledge gaps. Chapter 2 describes the results of a post hoc analysis of the interaction between preoperative estimated glomerular filtration rate, a marker of kidney function, and postoperative cardiac troponin T, a marker of heart damage, for predicting 30-day mortality in a prospective cohort study of patients undergoing noncardiac surgery. Chapter 3 uses administrative and clinical data from a single centre to inform the risk of acute kidney injury after noncardiac surgery by concentrations of preoperative hemoglobin and change in postoperative hemoglobin. Chapter 4 uses the same data to determine a definition of intraoperative hypotension that is prognostic of acute kidney injury, myocardial injury and death. Chapter 5 describes a randomized controlled trial that compares a novel therapeutic procedure called remote ischemic preconditioning to a sham procedure in patients undergoing cardiac surgery.

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## **Contributions by Others**

At the end of each chapter is a full account of author's contributions.

## Table of Contents

|   |             |
|---|-------------|
| <b>Title Page</b> .....   | <b>i</b>    |
| <b>Descriptive Note</b> .....   | <b>ii</b>   |
| <b>Abstract</b> .....   | <b>iii</b>  |
| <b>Acknowledgements</b> .....   | <b>iv</b>   |
| <b>Contributions by Others</b> .....  | <b>vi</b>   |
| <b>Table of Contents</b> .....  | <b>vii</b>  |
| <b>List of Abbreviations</b> .....  | <b>viii</b> |
| <b>Chapter 1: Introduction</b> .....  | <b>1</b>    |
| <b>Chapter 2: The association between postoperative troponin and mortality in patients with and without impaired kidney function</b> .....                                  | <b>36</b>   |
| <b>Chapter 3: Association between perioperative hemoglobin and acute kidney injury in patients having noncardiac surgery</b> .....  | <b>72</b>   |
| <b>Chapter 4: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: towards an empirical definition of hypotension</b> | <b>100</b>  |
| <b>Chapter 5: The effects of remote ischemic preconditioning in high-risk patients undergoing cardiac surgery (Remote IMPACT): a randomized controlled trial</b> .....      | <b>131</b>  |
| <b>Chapter 6: Conclusions and future directions</b> .....   | <b>163</b>  |



## LIST OF ABBREVIATIONS

|          |  |
|----------|--|
| aHR      | Adjusted hazard ratio  |
| AKI      | Acute kidney injury  |
| ASA      | American Society of Anesthesiology                             |
| CABG     | Coronary artery bypass graft                                   |
| CK       | Creatine kinase  |
| CKD      | Chronic kidney disease   |
| cTnT     | Cardiac troponin T   |
| DVT      | Deep venous thrombosis   |
| eGFR     | Estimated glomerular filtration rate                           |
| ERK      | Extracellular signal regulated kinase                          |
| ESRD     | End-stage renal disease  |
| HOST     | Hemodialysis Outcomes and Symptoms assessmentT                 |
| hsTnI    | High sensitivity cardiac troponin I                            |
| IPC      | Ischemic preconditioning                                       |
| JNK      | c-Jun N-terminal kinase  |
| KRESCENT | Kidney Research Scientist Core Education and National Training |
| MAP      | Mean arterial pressure   |
| MI       | Myocardial infarction  |
| NRI      | Net reclassification improvement                               |
| OR       | Odds ratio   |
| PAR      | Population attributable risk                                   |
| PCI      | Percutaneous coronary intervention                             |

|               |  |
|---------------|--|
| PE            | Pulmonary embolism   |
| PHASE         | Pilot trial of Hemodialysis patients undergoing Aldosterone antagoniSm with Eplerenone |
| PHDS          | Perioperative Health Documentation System  |
| POISE         | Perioperative Ischemia Evaluation Trial  |
| Remote IMPACT | Remote IscheMic Preconditioning in cArdiaC surgery Trial                               |
| RIPC          | Remote ischemic preconditioning  |
| RISK          | Reperfusion injury salvage kinase  |
| RRT           | Renal replacement therapy  |
| RSI           | Risk stratification index  |
| SD            | Standard deviation   |
| VIF           | Variance inflation factor  |
| VISION        | Vascular events In noncardiac Surgery patIents cOhort evaluationN                      |

## **CHAPTER 1**

### **Introduction**

#### **1.1 Background**

Worldwide over 200 million adults undergo major surgery annually. Millions of these patients will suffer a major perioperative vascular event (e.g., death, myocardial infarction [MI], cardiac arrest, or stroke). Another complication of surgery is a sudden, post-operative deterioration of renal function known as an acute kidney injury (AKI). Our capacity to predict major vascular complications and AKI is limited. Physicians need simple methods to facilitate the estimation of major vascular complications and AKI after surgery, to allow patients and surgeons to make informed decisions about the appropriateness of surgery and to guide perioperative management and monitoring.

Reduced kidney function is increasingly recognized as an important risk factor for vascular events and all-cause mortality. Both chronic kidney disease (CKD) and AKI are powerful predictors of in-hospital and one year mortality in hospitalized patients. Furthermore, 40% of deaths in patients with advanced CKD are attributed to vascular causes. As such, kidney function around the time of surgery, both CKD and AKI, are important risk factors for death after cardiac surgery.

In this thesis, I explore the interaction between a marker of myocardial injury and kidney function in patients undergoing noncardiac surgery, novel and potentially modifiable risk factors for AKI after noncardiac surgery, and a potential prophylactic treatment to prevent AKI and vascular complications after cardiac surgery

## **1.2 The interaction between kidney function and cardiac troponin T in patients undergoing noncardiac surgery**

CKD, characterized by a reduced estimated glomerular filtration rate (eGFR), affects over 30% of older adults and is a strong independent risk factor for cardiovascular events both in surgical and nonsurgical patients (1-3). Furthermore, an increasing number of patients with chronic kidney disease undergo surgery due to its increasing prevalence, longer survival, and improved surgical and anesthetic safety.

Over 11% of major noncardiac surgeries in patients at least 45 years old are complicated by an abnormal level of cardiac troponin T (cTnT), a commonly used marker of ischemic cardiovascular events (4). Furthermore, an abnormal cTnT is one of the most important risk factors, in terms of population attributable risk, for postoperative all-cause mortality. However, there is uncertainty over how to interpret cTnT in patients with a reduced eGFR. Specifically, elevations in patients with a reduced eGFR are frequently not considered as important as elevations in patients with a normal eGFR. This practice appears largely based on the observation of chronic elevations in patients with dialysis-dependent CKD in the nonoperative setting. Given CKD is common, is strongly associated with vascular events in the nonoperative setting and is strongly associated with postoperative mortality, understanding its relationship to postoperative vascular events is important.

To address the possibility that kidney function modifies the association between postoperative cTnT and all-cause mortality in patients undergoing noncardiac surgery, we analysed the interaction between several strata of preoperative kidney function and an abnormal cTnT in a prospective cohort of patients undergoing noncardiac surgery.

### **1.3 Predicting acute kidney injury**

Severe AKI requiring renal replacement therapy (RRT) is independently associated with high mortality (50 to >60%) in both short-term (5-8), and longer term studies. (9, 10) In the cardiac surgery setting, between 1 and 5% of patients develop severe AKI requiring RRT. In a Veteran's Affairs study of 42,773 patients undergoing cardiac surgery, AKI requiring RRT resulted in an adjusted OR of death of 27 (95% CI 22 to 34).(11) AKI was as strongly associated with death as a cardiac arrest (OR 23) and more strongly associated with death than perioperative myocardial infarction (OR 5.0), or postoperative stroke or coma (OR 4.5) in this study. This strong independent association between severe AKI and death was also seen in several other cohorts. (12-19)

AKI defined by lesser reductions in kidney function is also a significant predictor of all-cause mortality during hospitalization.(20, 21) The association between AKI and mortality is noted in diverse populations from the critically ill to those undergoing non-operative procedures such as percutaneous coronary intervention and in both short and long-term studies and there is a dose-response relationship between severity of AKI and risk of death. (5, 22-30)

There are few studies of AKI in noncardiac surgery. Severe AKI after noncardiac surgery was evaluated in 594,911 Veteran's Affairs patients. In this study AKI, defined as a requirement for RRT, complicated 0.4% of all noncardiac surgeries between 1991 and 1999 and was 50% more common in patients over the age of 80 years. Half of the patients requiring RRT died within 30 days of surgery.(31) An additional 0.4% of this cohort developed AKI defined as a rise in serum creatinine above 265  $\mu\text{mol/L}$  and oliguria.(31) In a substudy of 105,951 of these patients with long term follow-up, AKI by this definition was associated with an OR of death of

1.5 compared to 1.7 for postoperative requirement for RRT.(32) Clearly, severe AKI after noncardiac surgery has major health implications.

It is likely that less severe but still clinically and prognostically important AKI is underestimated in noncardiac surgery since it is often clinically silent and the laboratory tests to detect it are not always routinely done. In prospective single centre cohorts examining rates of AKI in all noncardiac surgeries, 7 and 23% of patients developed at least mild AKI resulting in an increased odds of death with an OR of 2.4 (95% CI 1.1 to 5.4) compared to patients without AKI.(33, 34)

These data demonstrate that AKI, even non-severe AKI, is an important outcome after noncardiac surgery in terms of its association with death. The importance of AKI is underscored by the tremendous burden AKI creates on health care resources. In high risk noncardiac surgery, a diagnosis of AKI was associated with an \$11,308 increase in the median cost compared to all patients who did not experience post-operative AKI.(35) In multi-variable analysis, severe AKI was the single most costly postoperative complication for these patients and resulted in the largest proportion of resource use compared to all other complications. In a sample of 5875 surgical patients from a Veteran's Affairs hospital, AKI requiring dialysis was the second most costly postoperative complication with an estimated mean increase in hospital expenditures of \$28,359 (2005 US Dollars) compared to an uncomplicated postoperative course and resulted in almost twice the excess cost compared to a cardiac arrest.(36)

The impacts of AKI on loss of life and health resource utilization are even more dramatic when one considers that AKI is increasing. Hospital based cohorts in the United States demonstrate an 11% increase per year between 1992 and 2001 (37) while population based community cohorts in the United States demonstrate an increase of 50% in incident cases of AKI

requiring dialysis between 1993 and 2006.(38) Importantly, these increases are not explained by changes to more sensitive definitions of AKI.

Developing a strategy to prevent AKI requires the identification of causal risk factors that can be modified. There are several models to predict the development of severe AKI after cardiac surgery with good predictive ability.(39-42) Furthermore, many risk factors are common to the models suggesting they are truly associated and broadly applicable in cardiac surgery. However, many of these risk factors are specific to cardiac surgery (e.g., type of cardiac surgery being performed, time on cardiopulmonary bypass, etc.) and most are not modifiable (e.g., preoperative comorbidities, emergency surgery). Thus, they have limited applicability to noncardiac surgery and little applicability to identifying potential therapies. Furthermore there are very few studies of risk factors in noncardiac surgery and those that exist identify only non-modifiable risk factors.

Ischemia is a commonly purported mechanism for AKI in the hospital setting. Ischemia results from inadequate oxygen delivery to the highly metabolically active kidneys. From a physiological perspective, inadequate oxygen delivery may develop from reduced blood flow to a tissue or from a reduced oxygen carrying capacity of the blood. Clinically, this may manifest as a reduced blood pressure or reduced hemoglobin. The following two studies utilized a large cohort of patients from the Cleveland Clinic that underwent noncardiac surgery to determine the association between perioperative hemoglobin and AKI and intraoperative blood pressure and AKI (and other outcomes), two potentially modifiable risk factors. In addition, the risk of death associated with AKI seen in the nonoperative setting and cardiac surgery setting is confirmed in the noncardiac surgery setting in these studies.

#### **1.4 Intraoperative blood pressure is a risk factor for postoperative acute kidney injury and other postoperative morbidities**

Intraoperative hypotension, blood pressure too low to adequately perfuse a tissue, has the potential to cause an ischemic injury which may manifest as dysfunction of an organ. Among the most sensitive organs affected in this way are the kidneys and the heart. (43) This theory is supported by a systematic reviews of interventions to prevent perioperative AKI that demonstrates maneuvers to prevent hypotension reduced the incidence of AKI (44) as well as data from the Perioperative Ischemia Evaluation Trial (POISE) which demonstrated hypotension was the most responsible factor for postoperative death (of which, the majority were vascular).

Although avoiding hypotension is an intraoperative goal, the level of intraoperative blood pressure that incurs risk is unclear. A systematic review of intraoperative hypotension identified 140 definitions used in 130 studies.(45) Most of these definitions were not empirically derived and each definition's association with clinical outcomes was explored in relatively few and/or small studies. We therefore studied patients who had noncardiac surgery to determine what durations of various levels of mean arterial pressure (MAP) are associated with AKI and myocardial injury to establish an empirical definition of prognostically important intraoperative hypotension.

#### **1.5 Perioperative hemoglobin is a risk factor for postoperative acute kidney injury**

Preoperative anemia and perioperative transfusions are associated with AKI in cardiac surgery (46). In noncardiac surgery, preoperative anemia is also an important risk factor for mortality (47). Whether preoperative anemia is associated with early postoperative AKI, has not been studied in noncardiac surgery. Furthermore, transfusions may be associated with AKI either



because the transfusions themselves are harmful or because the reasons for transfusion cause AKI. Given both perioperative decrements in hemoglobin concentration and low preoperative hemoglobin concentrations may both trigger transfusion, we examined the independent contributions of each of these risk factors to the development of AKI.

### **1.6 Remote ischemic preconditioning as a prophylactic therapy to prevent ischemia reperfusion injury in patients undergoing cardiac surgery**

Annually, approximately 2 million patients worldwide (30,000 Canadians) undergo cardiac surgery. Although this procedure can prolong life and improve patients' quality of life, 3 to 5% of all patients undergoing cardiac surgery will not survive their hospital stay.(48-50) Ischemia-reperfusion injury (IRI) induced during cardiac surgery is an important mechanism that causes poor patient outcomes. IRI is first induced by hypoxic ischemia during periods of low blood pressure and organ hypoperfusion which is then exacerbated by a systemic inflammatory response upon restoration of cardiac output.(51) The resulting injury can damage the heart (causing MI), the kidneys (causing AKI), and the brain (causing cognitive dysfunction and ischemic stroke), all of which are independently associated with an increased risk of short- and long-term mortality, and high health care costs.(46, 52-56) In addition to the 3 to 5% in-hospital mortality rate (50) associated with cardiac surgery, between 5 and 12% of patients will experience an MI, between 1 and 2% of all patients will require dialysis, and between 1.5 and 5.2% will have a stroke.

Perioperative MI is independently associated with 4 fold increased risk of death by six months after surgery.(52) Further, significant cardiac damage demonstrated by >5 fold increases in CKMB, irrespective of the presence of other markers of MI (e.g. ECG changes or symptoms) are

also independently associated with an increased risk of death.(57) Given the high frequency of these event (>17%) reducing cardiac damage is a major target for improving outcomes in cardiac surgery.(58-60)

Post-operative need for dialysis occurs in 1 to 2% of patients and rises to between 3 and 5% of patients with at least one risk factor.(39, 40) Of patients requiring dialysis, postoperatively 2/3 will die and a quarter of the survivors will require long-term dialysis. (61) This problem is growing worse: levels of comorbidity and the age of patients undergoing cardiac surgery are both increasing resulting in the incidence of patients requiring dialysis following cardiac surgery doubling in the last 20 years.(62-65) Further, less severe AKI defined as a 50% increase in serum creatinine or a 25% decrease in estimated glomerular filtration rate (eGFR) is also independently associated with in-hospital mortality. In a cohort study of 3500 patients undergoing cardiac surgery, 24% suffered mild AKI (>25% decrease in eGFR) which was independently associated with a 4 fold increase in the risk of in-hospital death (adjusted OR 4.0; 95% CI 2.3-6.7).(46) Other studies have demonstrated similar results.(13, 16, 66)

The incidence of clinically apparent stroke after cardiac surgery ranges from 1.5 to 5.2% in prospective studies.(54, 63, 64, 67) Furthermore, small studies suggest up to 18% of patients incur clinically silent ischemic cerebral events on magnetic resonance imaging.(55) At least two-thirds of strokes occur and are discovered within the first two postoperative days and approximately 93% are apparent with in the first 7 days after cardiac surgery.(68, 69) Strokes are associated with a 3-fold increased risk of death (adjusted hazard ratio 3.2; 95% CI 2.8 to 3.7). (70)

MI, AKI and stroke all significantly increase health care costs. Postoperative MI is associated with a 50% increase in intensive care unit days and a 41% increase in total hospital costs (71). Even moderate severity AKI results in significant medical costs. In a case-control study, AKI (defined as only a 50% increase in creatinine or 25% decrease in eGFR) was associated with a 2.2 fold increase in intensive care unit length of stay and a 1.6 fold increase in the in-hospital medical costs (72). Patients with the most severe AKI had a three-fold increase in medical costs and intensive care unit length of stay. Similarly, patients with stroke had a median 30 day hospital stay (IQR 13 – 62 days) compared to 7 days for patients without stroke (IQR 5 – 12;  $p < 0.001$ ).

Perioperative MI, AKI and stroke are significant causes of morbidity and mortality after cardiac surgery and represent a significant health care cost. There is no established intervention that reduces perioperative MI, AKI, stroke and mortality associated with cardiac surgery (73).

Reducing the incidence or severity of these outcomes will significantly benefit patients, society, and the health care systems.

#### *Ischemia-Reperfusion Injury is a Cause of MI, AKI and Stroke in Cardiac Surgery*

Cardiac surgery is associated with a period of relatively low blood flow to the heart and other organs during surgery followed by a sudden increase in blood flow towards the end of the procedure (51). The initial low flow period is associated with an ischemic injury due to reduced energy production, the accumulation of the products of anaerobic metabolism and a reduced cellular pH in highly metabolically active cells such as cardiac myocytes and renal tubular cells (74, 75). Paradoxically, the restoration of blood flow towards the end of surgery results in additional cellular damage known as the reperfusion injury (76). During reperfusion, factors such

as free radical formation (77), leukocyte and platelet aggregation (78, 79), complement activation (80, 81), pro-apoptotic signaling cascades (82-84) and endothelial dysfunction appear to mediate the reperfusion injury (85). The reperfusion injury then results in arrhythmias (86), endothelial cell damage and dysfunction, myocardial stunning and myocardial infarction. In animal data, up to 50% of infarct size may be due to reperfusion rather than ischemia (87).

Studies of patients undergoing cardiac surgery have demonstrated that ischemia-reperfusion injury is common (88) with similar outcomes to animal models causing arrhythmias (89), myocardial stunning, myocardial infarction, wide spread endothelial dysfunction, coagulation activation, and neutrophil dysfunction (90). In a consecutive sample of 190 patients that died within 30 days of cardiac surgery, greater than 25% had gross pathologic evidence of ischemia-reperfusion injury (i.e., contraction band necrosis) as a direct cause of death (91). Due to the extreme nature of the pathologic findings in this series, it is likely this represents an underestimation of the burden of ischemia-reperfusion injury and its contribution to perioperative mortality. Because of its widespread and often severe effects, ischemia-reperfusion injury is a major problem among patients undergoing cardiac surgery and its prevention is likely to improve patient outcomes.

### *Classical Ischemic Preconditioning*

Classical ischemic preconditioning (IPC) may mitigate ischemic reperfusion injury. IPC is accomplished by providing a brief, non-lethal episode of ischemia to a tissue which then activates endogenous cellular mechanisms that may protect the tissue from future ischemic insults. This was first described in animal models in which dogs that received 4 cycles of 5 minutes of cardiac ischemia induced by clamping the left anterior descending (LAD) coronary

artery followed by 5 minutes of reperfusion prior to a 40 minute LAD occlusion to induce a myocardial infarction had their infarct volume reduced to 1/6<sup>th</sup> the size of dogs that did not receive preconditioning (92). Similar findings were subsequently noted in multiple species (93-95) and in animal models of ischemia-reperfusion injury to the brain, skeletal muscle, retina, liver and kidneys (96-100). Furthermore, animal models of cardiac surgery and cardiopulmonary bypass also demonstrated myocardial protection with IPC (101). Support for the presence of IPC effects in humans was evident first in *in vitro* cardiac myocytes and later at the level of multiple organs (102, 103).

### *Mechanisms of Preconditioning*

Insights gained from animal models and *in vivo* studies suggest several different mediators are released from ischemic tissue locally and to the circulation and activate G-proteins and phospholipases in the cells of target organs. These mediators exert their effects by inducing translocation and activation of protein kinase C (PKC) (104-106). Leading candidate mediators of IPC include:

Adenosine accumulates as ischemic cells consume ATP and is then released during reperfusion. Evidence for the potential importance of adenosine in mediating IPC comes from animal studies in which adenosine antagonists reduce the benefits of IPC, and administration of exogenous adenosine replicates some of the benefits of IPC in animal and *in vitro* models(103, 107, 108).

Bradykinin which was first noted to reduce ischemia induced arrhythmia (109). Subsequent animal models demonstrated exogenous bradykinin administration reduced myocardial infarction size and that bradykinin receptor antagonists mitigate the benefits of IPC (107, 110).

Opioids or opioid receptors are also likely involved in IPC signal transduction since administration of exogenous opioids mimics IPC and the blockade of opioid receptors such as naloxone mitigate the benefits of IPC (111, 112).

Oxygen radicals generated during ischemia likely act as a non-receptor mediated signaling pathway for IPC. The administration of N-2 mercaptopyrpyonyl glycine, a cell permeable free radical scavenger, decreased cardioprotection by IPC (113).

Sympathetic nerve stimulation may act as an additional non-humoral mediator of IPC.

Stimulation of afferent nerves in ischemic tissue are hypothesized to trigger the release several signaling molecules (e.g., catecholamine, adenosine, bradykinins, and nitric oxide) via efferent sympathetic nerves (114). This is supported by the observation that administration of hexamethonium prevented IPC effects in an animal model (115).

The activation of PKC by these mediators results in intracellular signaling cascades that include extracellular signal regulated kinase (ERK)/ c-Jun N-terminal kinase (JNK) pathways and result in the opening of mitochondrial  $K_{ATP}$  channel opening and subsequent or concomitant reductions in intracellular energy demands, increased intracellular pH and the induction of stress resistant state for mitochondria (116-127). In addition to PKC signaling, RIPC may activate pro-survival kinases in the reperfusion injury salvage kinase (RISK) pathway. Activation of the RISK pathway results in inhibition of the mitochondrial permeability transition pore. This cascade results in fewer pro-apoptotic signaling molecules released from the mitochondria during periods of oxidative stress.

While many of these adaptations appear to occur almost immediately, those requiring protein synthesis, such as the production of heat shock proteins, nuclear factor kappa B, nitric oxide

synthetase, and superoxide manganese dismutase, may require many hours before conferring significant protection. This combination of immediate but short lived protective effects and delayed but sustained benefits have been termed classic preconditioning and delayed preconditioning respectively (96, 116, 128, 129). Although the period of protection may be more sustained during the delayed preconditioning phase than the classic preconditioning phase, it is likely also to confer a lesser degree of protection (Figure 2) (130).

#### *Remote Ischemic Preconditioning (RIPC)*

The IPC concept was extended to RIPC after the observation that occlusion of one coronary artery reduced the size of infarcts induced in other vascular territories and that IPC of non-cardiac organs reduced infarct size in the heart (131). RIPC is most commonly induced by inflating a pneumatic tourniquet on a limb to stop distal blood flow for a brief period of time and then deflating the tourniquet to allow reperfusion. It appears that several of the mediators of IPC are released systemically (e.g., adenosine, bradykinin, opioids, oxygen radicals) and are able affect distant organs (110, 132-134). As in IPC, the activation of these signaling pathways results in a state of reduced cellular energy demand, reduced glycolysis, reduced ATP consumption, and improved intracellular energy use, which in turn improves ischemia tolerance. Additionally, upon reperfusion, tissues protected by preconditioning exhibit reduced free radical production, maintenance of redox potential, resistance to apoptosis, preservation of mitochondrial integrity, diminution of the “no-reflow” phenomenon, and a reduction of leukocyte activation and cytokine production. These cellular changes also result in reduced endothelial dysfunction, and reduced systemic inflammatory responses to later ischemic stimuli (132, 135).

#### *Clinical Experience with Preconditioning is Promising*

The potential for RIPC to improve patient-important outcomes after cardiac surgery is demonstrated by three lines of evidence. The first is drawn from classical IPC, while the remaining two are drawn from RIPC in percutaneous coronary intervention (PCI) and RIPC in cardiac surgery itself.

A systematic review of 22 RCTs including 933 patients by Walsh et al summarizes the IPC experience in cardiac surgery (136). Of patients that received IPC, 84/289 compared to 157/318 controls required postoperative inotropic support (OR 0.34; 95% CI 0.17-0.68;  $p=0.002$ ) and 28/153 patients treated with IPC compared to 65/182 controls had postoperative ventricular dysrhythmia (OR 0.11; 95% CI 0.04-0.29;  $p=0.001$ ). Although substantially underpowered (there were only 5 deaths), IPC favored a lower risk of in-hospital mortality (OR 0.33; 95% CI 0.07-1.64;  $p=0.17$ ). This meta-analysis failed to show reductions in MI, stroke, and AKI, however, there were few clinical events and lack of effect may also have resulted from the heterogeneity of IPC regimens, some of which may have been ineffective. For example, IPC regimens consisted of a variety of ischemia inducing techniques including aortic cross-clamping with or without rapid epicardial pacing, left anterior descending coronary artery occlusion, and smaller coronary artery occlusion and ischemic times ranged from 1 to 5 minutes and 1 to 3 cycles of ischemia and reperfusion.

Despite the encouraging data from IPC, there are several arguments that suggest RIPC may overcome some of its limitations. The myocardium is a relatively small tissue mass and therefore IPC of the myocardium may generate a limited quantity of signaling molecules. Further, the effects of these limited signals may be attenuated by the presence of cardioplegia which would limit their circulation and thus confine their actions to local tissues. The focus of IPC on cardiac tissue may also neglect important benefits from attempting to protect other vital organs. In



addition to utilizing a large mass of tissue that can release RIPC signaling molecules systemically, RIPC is also more practical than IPC since there is no potential to cause trauma to important blood vessels such as coronary arteries, it requires no special skills to perform, and does not delay surgery (i.e., RIPC can be performed during the normal preparation of the patient in the operating theatre while IPC requires the surgeons to take additional time between opening the chest and putting the patient on bypass).

In PCI, coronary artery occlusion occurs as part of the procedure and can cause myocyte necrosis from ischemia-reperfusion injury, atheromatous embolization, and coronary side-branch occlusion. Post-procedure elevations in cardiac markers, such as Troponin T, are associated with subsequent cardiovascular events. Two trials were recently published in this area. The CRISP study randomized 240 patients to RIPC (by applying 3 cycles of 200 mmHg pressure to an upper limb for 5 minutes) or a sham 1 hour prior to PCI (137). Median troponin I levels at 24 hours post-procedure in the RIPC group were 0.06 ng/mL compared to 0.16 ng/mL in the control group ( $p=0.04$ ). Patients who underwent RIPC experienced fewer (4 versus 13 events;  $p=0.018$ ) major cardiovascular events (MI, cardiac arrest, or stroke), less post-procedure chest discomfort (56 vs 76 events;  $p=0.0006$ ) and fewer ECG ST-segment deviations (37 vs 55 events;  $p=0.005$ ). At 6 months, patients randomized to RIPC also had fewer strokes (4 vs. 13;  $p=0.02$ ). The CRISP trial also noted fewer AKI events ( $>25\%$  rise in creatinine) in the RIPC group compared to controls although this did not reach statistical significance (6/104 RIPC patients compared to 10/98 control patients;  $p=0.30$ ).

Similarly, Botker and colleagues published a trial of 333 patients in Denmark with evolving myocardial infarctions randomized to receive RIPC (4 cycles of 5 minutes ischemia to an upper limb at 200 mmHg) prior to primary percutaneous coronary intervention (138). The primary

outcome was the myocardial salvage index determined by single photon emission computed tomography (SPECT). Although the intention to treat analysis demonstrated no difference between groups, it was limited by significant missing data. In the per protocol analysis, RIPC resulted in a 0.12 improvement in myocardial salvage index (95% CI 0.01 to 0.21;  $p=0.03$ ). However, no secondary endpoints demonstrated significant differences between the groups although Troponin T was lower in the RIPC group (median 1.66  $\mu\text{g/L}$  [interquartile range 0.83 to 3.84] compared to 3.30 [interquartile range 1.64 to 5.49];  $p=0.06$ ).

The third line of evidence comes from small RCTs of RIPC in cardiovascular surgery already completed. A recent meta-analysis included 9 studies with 704 patients. It suggested a small reduction in cardiac troponin (standardized mean difference -0.36, 95% CI -0.62 to -0.09) although there was moderate heterogeneity ( $I^2$  60%) and the largest studies suggested no benefit with RIPC. However, the 6 studies including 703 patients with renal outcomes showed no benefit with RIPC (weighted mean difference in creatinine 0.02 mg/dL (-0.09 to 0.13)).

Although the evidence supporting the potential role for RIPC in cardiac surgery is encouraging it is also limited. While most trials suggest RIPC reduces cardiac damage the trials are small and there is no evidence demonstrating RIPC improves patient-important outcomes in cardiac surgery or any other setting. An adequately powered trial of RIPC in moderate- to high-risk patients would require 3000 to 6000 patients to demonstrate a 30% relative risk reduction in the composite of mortality, myocardial infarction, need for dialysis and stroke. Such a trial would be resource intensive and only worth pursuing if it were demonstrated feasible and the putative biological effects of RIPC (i.e., myocardial protection and renal protection) were substantiated in an adequately powered trial at low risk for bias. We conducted a pilot study to determine the effect of RIPC on markers of MI and AKI and the feasibility of a large international RCT of

RIPC in cardiac surgery. We called this pilot trial the Remote IscheMic Preconditioning in cArdiaC surgery Trial (Remote IMPACT) Pilot. Chapter 6 describes the results of Remote IMPACT.

#### 1.7 Conclusions and future directions

Chapter 7 provides conclusions regarding my thesis work, describes some future work that continues the lines of inquiry started with my thesis work and describes how my thesis work influences my research program moving forward.

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## CHAPTER 2

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**The association between postoperative troponin and mortality in patients with and without impaired kidney function**

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## Abstract

Background: Cardiac troponin T (cTnT) is an important risk factor for 30-day mortality in patients undergoing noncardiac surgery. We previously identified a borderline interaction between kidney function and cTnT; however, whether the risk associated with an abnormal cTnT is the same in patients with and without a reduced kidney function remains uncertain.

Objective: To evaluate the association between an abnormal cTnT after noncardiac surgery at different levels of kidney function.

Design: *Post-hoc* analysis of a prospective cohort study.

Setting: International hospitals.

Patients: At least 45 years old, undergoing noncardiac surgery that required an overnight hospital admission.

Measurements: cTnT measured for three days after surgery and considered abnormal if the peak was  $\geq 0.02$  ng/mL. Kidney function characterized by the estimated glomerular filtration rate (eGFR). Using Cox regression to estimate the risk of 30-day mortality after adjustment for patient characteristics, we examined the interaction between an abnormal cTnT and eGFR.

Results: A total of 14,037 patients were included of which 267 (1.9%) died within 30 days of surgery. 11,266 (80.3%), 1,488 (10.6%), 763 (5.4%), 274 (2.0%) and 246 (1.7%) had an eGFR of  $\geq 60$ , 45 to  $<60$ , 30 to  $<45$ , 15 to  $<30$ , and  $<15$  ml/min/1.73m<sup>2</sup> or on dialysis respectively. The adjusted hazard ratio (aHR) for death with an abnormal cTnT was 4.37, 6.15, 6.30, 1.33 and 1.46 for an eGFR  $\geq 60$ , 45 to  $<60$ , 30 to  $<45$ , 15 to  $<30$ , and  $<15$  ml/min/1.73m<sup>2</sup> or on dialysis respectively. Compared to the  $\geq 60$  ml/min/1.73 m<sup>2</sup> eGFR group, the aHR was

significantly lower for the 15 to <30 eGFR group (interaction p-value=0.02). These results were not affected by redefining an abnormal cTnT as  $\geq 0.03$  or as a change in cTnT of at least 0.02 ng/mL.

Limitations: Few patients with an eGFR <30 ml/min/1.73 m<sup>2</sup> and no preoperative cTnT measurements.

Conclusion: The risk associated with a postoperative cTnT  $\geq 0.02$  ng/mL may be different for patients with severely impaired kidney function but is unlikely affected by mild disease. Further research is required to determine how to interpret perioperative cTnT values for patients with severely impaired kidney function.

## **Introduction**

Over 200 million noncardiac surgeries are performed every year globally.(1) Although these procedures can be life-saving and significantly improve quality of life for patients, more than one million individuals will die each year within 30 days after surgery.(1) Cardiovascular complications are the most important contributor to 30-day mortality in patients undergoing noncardiac surgery.(2)

Chronic kidney disease (CKD), largely characterized by a reduced estimated glomerular filtration rate (eGFR), affects over 30% of older adults and is a strong independent risk factor for cardiovascular events both in surgical and nonsurgical patients.(3-5) Furthermore, an increasing number of patients with chronic kidney disease are undergoing surgery due to its increasing prevalence, longer survival, and improved surgical and anesthetic safety .

We previously identified that over 11% of major noncardiac surgery in patients at least 45 years old are complicated by an important elevation in cardiac troponin T (cTnT), a commonly used marker of ischemic cardiovascular events.(6) In this study, we identified a borderline interaction between kidney function and an abnormal cTnT (overall interaction p-value=0.051). This did not meet our a priori threshold for a statistically significant interaction. However, uncertainty remained whether an elevated cTnT has the same meaning in patients with and without a reduced eGFR, particularly for those with severely reduced eGFR.

To address the possibility that renal function modifies the prognostic properties of postoperative cTnT, we performed a post-hoc analysis exploring the interaction between several strata of preoperative kidney function and previously defined prognostically important postoperative cTnT concentrations.

## **Methods**

### *VISION Cohort methods*

The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION; clinicaltrials.gov identifier NCT00512109) is an international prospective cohort study evaluating major complications after noncardiac surgery. VISION recruited patients undergoing noncardiac surgery from 12 centres in 8 countries between August 2007 and December 2011. Participants were followed during their hospitalization and up to 30 days after surgery.

### *Participants*

Participants in VISION were 45 years or older, were undergoing an operation that required a general or regional anesthetic and required at least an overnight hospital stay. Participants provided consent prior to surgery or, for those whom we could not obtain consent preoperatively due to emergency surgery, consent was obtained within the 24 hours following surgery (i.e., deferred consent). Patients were excluded if they had participated in the VISION for a previous surgery. Potential participants were identified by screening daily patient lists in the preoperative assessment clinics, surgical wards, intensive care units, surgical lists and patients in preoperative holding areas. In centres where the surgical volume exceeded the research staff's capacity to enroll at least 80% of all cases, the centres were assigned random weeks for recruitment of all or randomly selected surgical services.

### *Outcomes and Exposures*

The outcome of interest was mortality from any cause up to 30 days after surgery. Mortality was ascertained through hospital records, contacting the participant or the participant's family and/or

the participant's primary care physician. The main exposures of interest were preoperative kidney function and postoperative cardiac troponin T concentrations. Preoperative kidney function was estimated using the serum creatinine concentration measured most recently prior to surgery as part of routine clinical care. The serum creatinine concentration was converted to an estimated glomerular filtration rate (eGFR) using the CKD-Epi equation.(7) Each participant's eGFR was then categorized as:  $\geq 60$ , 45 to  $<60$ , 30 to  $<45$ , 15 to  $<30$ , and  $<15$  ml/min/1.73m<sup>2</sup> or on dialysis.

Cardiac troponin T was measured prospectively using the Roche 4<sup>th</sup>-generation Elecsys assay at 6 to 12 hours postoperatively then days 1, 2, and 3 postoperatively. Patients enrolled between 12 and 24 hours after surgery had a cTnT measured immediately and then daily up to the third postoperative day. All cTnT measurements were analyzed at the participating centre and were reported to the attending physicians. For our primary analysis, participants were classified by whether their cTnT was  $<0.02$  or  $\geq 0.02$  ng/mL since this was the first threshold shown to have prognostic importance in our previous work.(6) In our secondary analyses, participants were classified as having a cTnT either  $<0.03$  or  $\geq 0.03$  ng/mL or as having a change in cTnT by at least 0.02 ng/mL over the course of the first three postoperative days. For the change in cTnT analysis patients with a lowest cTnT value of  $\leq 0.01$  ng/mL met the abnormal cTnT threshold if the highest cTnT value was at least 0.03 ng/mL while patients with a lowest value  $>0.01$  ng/mL were required to have a value at least 0.02 ng/mL higher to be considered abnormal.

Other potential confounders were assessed prior to surgery or as soon as possible after surgery for patients enrolled using deferred consent (i.e. consented within 24 hours of surgery). A complete list of the potential confounders and their definitions is included Appendix 1.

### *Statistical Analysis*

Patient characteristics are described as mean (SD) or median (25<sup>th</sup> to 75<sup>th</sup> percentile) as appropriate for continuous data and number (%) for frequency data. A two-sided p-value of <0.05 was regarded as statistically significant for all analyses without adjustment for multiple comparisons.

For the primary objective, we performed Cox proportional hazards regression analysis in which the independent variables were the baseline characteristics determined to be of prognostic importance in our previous work.(6) These variables included: age (categorized as 45 to 65 [referent], >65 to 75, and >75 years), history of high risk coronary artery disease, history of peripheral vascular disease, history of stroke, chronic obstructive pulmonary disease, active cancer, urgent or emergent surgery (vs. other surgery), major general surgery, and major neurosurgery. The presence of an abnormal TnT (i.e.  $\geq 0.02$  ng/mL) was used as a dichotomous independent variable. As well, kidney function was included as an independent categorical variable with five levels (i.e.,  $\geq 60$ , 45 to <60, 30 to <45, 15 to <30, and <15 ml/min/1.73m<sup>2</sup> or on dialysis) using the  $\geq 60$  ml/min/1.73 m<sup>2</sup> category as the reference category. Included in the model were the interaction terms between abnormal cTnT and each kidney function category. We calculated the effect estimates from the model calculated as an adjusted Hazard Ratio (aHR) with a corresponding 95% confidence interval computed by bootstrapping the model 500 times. We tested the proportional hazards assumption using a global goodness of fit test of scaled Schoenfeld residuals utilizing rank based methods for both the overall model and each model variable at the same time. We assessed colinearity using the variance inflation factor (VIF) and considered reduction of model parameters for variables with a VIF >10, however, none of the variables had a VIF >10.

We assessed model predictive discrimination through evaluation of the net reclassification improvement (NRI) in patients with severely impaired kidney function (i.e. eGFR <30 ml/min/1.73 m<sup>2</sup>). (8) The NRI is defined as the probability that an event is predicted with a ‘new’ model but not with an ‘old’ model, minus the probability that a non-event is predicted with a ‘new’ model but not with an ‘old’ model. That is, it measures the increase (or decrease) in the proportion of patients with the correct prognosis when based on the ‘new’ model compared to the ‘old’ model. For our analyses, we will consider the model that does not include an abnormal postoperative cTnT as the ‘old’ model. We considered this same model but including the abnormal cTnT variable as the ‘new’ model. We used four categories of predicted 30-day mortality in the calculation of the NRI: <1%, 1-5%, 5.1-10%, and >10%.

Exploratory analyses were conducted to determine if alternative definitions of an abnormal cTnT ameliorated any effect modification of eGFR. The alternative definitions of an abnormal cTnT included a peak cTnT of  $\geq 0.03$  ng/mL or a change in cTnT of  $\geq 0.02$  ng/mL as described above. These alternative definitions replaced the abnormal cTnT variable in the Cox model used for the primary analysis and the interaction terms between an abnormal cTnT and each strata of eGFR were recalculated.

To determine to what extent an abnormal cTnT accounts for death within 30 days of surgery compared to other risk factors, we calculated the population attributable risk (PAR). (9) The PAR is function of both the strength of the association between the exposure and outcome as well as the relative frequency of the exposure and is a general measure of the extent to which an exposure explains the outcome in a model. We separately calculated the PAR for the subgroup with an eGFR <30 ml/min/1.73 m<sup>2</sup> or on dialysis and the subgroup with an eGFR  $\geq 30$  ml/min/1.73 m<sup>2</sup>. Patients with a cTnT elevation associated with sepsis or a pulmonary embolism

(PE) were excluded from these analyses. We developed a Cox Proportional Hazards model where the dependent variable was 30-day mortality. Independent variables included the baseline independent predictors of 30-day mortality used in the primary analysis above. We also included the following postoperative events as independent variables: stroke, arm or leg deep venous thrombosis (DVT), PE not associated with a rise in cTnT, sepsis, pneumonia, and infection. After reviewing the results of the primary analysis, we defined an abnormal cTnT as  $\geq 0.03$  ng/mL given its larger effect size for 30-day mortality compared to 0.02 ng/mL in our previous work. We then calculated the PAR for each independent variable in the model.

All analyses were performed with SAS v9.2 (Cary, USA).

## **Results**

There were 15,133 patients potentially eligible for this analysis. Of these, 1096 were missing a preoperative creatinine leaving 14,037 (92.8%) for analysis. Of these, 26 (0.2%) did not complete 30-day follow-up and were censored at last follow-up (Figure 1).

Table 1 reports the preoperative characteristics of patients by eGFR strata. Patients in lower eGFR strata more frequently had a history of diabetes mellitus, congestive heart failure, and high risk coronary artery disease while malignancy was less common.

A median of 3 (2 to 4) cTnTs were drawn in each patient. The proportion of patients who died within 30 days after surgery was greater for patients with an elevated cTnT than for those without an elevated cTnT in every strata of eGFR (Table 2). For patients with an eGFR  $\geq 30$  ml/min/1.73 m<sup>2</sup>, a cTnT  $\geq 0.02$  was associated with a 4 to 6-fold increase in the adjusted risk of 30-day mortality compared to a 1.3 to 1.5 fold increase in the adjusted risk in patients with an



eGFR <30 or on dialysis (Figure 2) a statistically significant difference in the effect was only seen for the <30 to 15 ml/min/1.73 m<sup>2</sup> group (interaction p-value=0.02).

The addition of postoperative cTnT to the clinical model using preoperative characteristics did not improve risk classification in patients with an eGFR ≤30 ml/min/1.73m<sup>2</sup>. The NRI for a model using cTnT compared to a model without cTnT was 1.5%.

Using an alternative definition of an abnormal cTnT as ≥0.03 did not materially alter these results. The aHR for patients with an eGFR ≥30 ml/min/1.73 m<sup>2</sup> was between 5.1 and 7.2 while the aHR for patients with an eGFR <30 or on dialysis ranged from 1.2 to 1.3 (Supplemental Table 1). Similarly, the alternative definition of an abnormal cTnT as a change of at least 0.02 ng/mL did not materially alter the primary results with an aHR for patients with an eGFR <30 ml/min/1.73 m<sup>2</sup> of 1.86.

In patients with an eGFR ≥30 ml/min/1.73m<sup>2</sup>, a cTnT ≥0.03 postoperatively had the largest PAR (30.8%, 95% CI 25.2 to 36.7%) after age. In patients with an eGFR <30 ml/min/1.73m<sup>2</sup>, a cTnT ≥0.03 postoperatively had a PAR of 2.8% (95% CI -50.8% to 39.7%). Age, urgent/emergency surgery, and history of peripheral vascular disease all increased their PAR substantially and cancer decreased its PAR substantially in patients with an eGFR <30 ml/min/1.73m<sup>2</sup> compared to patients with an eGFR ≥30 ml/min/1.73m<sup>2</sup> (Supplemental Table 2).

## **Discussion**

In patients with an eGFR >30 ml/min/1.73 m<sup>2</sup>, a postoperative cTnT ≥0.02 ng/ml predicts a 4 to 6-fold higher risk of death within 30 days compared to similar patients with postoperative cTnT concentration <0.02 ng/mL. Patients with an eGFR ≤30 ml/min/1.73 m<sup>2</sup> are at substantial risk of death within 30 days of surgery. Although a postoperative cTnT ≥0.02 ng/ml is associated with

an approximate 1.5-fold increased risk of death within 30 days of surgery, it did not significantly improve risk discrimination when added to models including clinical characteristics and did not significantly explain 30-day mortality in models including clinical characteristics and other postoperative complications.

To our knowledge, we are the first to assess the risk associated with postoperative cTnT in patients with severely impaired kidney function. Other studies demonstrated that older generations of cTnT assays were prognostic of short and long-term mortality in asymptomatic patients with a reduced eGFR or ESRD.(10-16) Studies of patients with a reduced eGFR and with an acute coronary syndrome or presenting to an emergency room with chest pain also demonstrated an increased risk of death in those with an elevated cTnT compared to a cTnT below the established necrosis limit.(17-19). Do our results differ from others? A meta-analysis found a 2.6-fold increase in the risk of death in patients with ESRD who had an elevated cTnT (generally defined as  $\geq 0.09$  ng/mL) compared to those that did not. We found an approximate 1.5-fold increase in the risk of death in patients with an eGFR  $< 30$  ml/min/1.73 m<sup>2</sup>. The difference in the magnitude of the effect seen in our study compared to others may be due to the lower cTnT threshold we used to define an abnormal concentration, characteristics of the assay, a truly lesser associated risk in noncardiac surgery patients, or imprecise estimation in either estimate of effect (i.e. random error).

Although there appears to be risk associated with an abnormal cTnT after noncardiac surgery irrespective of eGFR, there are few studies that also compare the risk for those with and without a reduced eGFR. One study that did compare risks in those with versus without an eGFR  $< 60$  ml/min/1.73 m<sup>2</sup> demonstrated that, if anything, an elevated cTnT in patients with a reduced

eGFR was associated with an even higher risk of death than an elevated cTnT and a normal eGFR.(17)

Why is there an apparent attenuation in the risk of death associated with an abnormal cTnT for patients with a reduced eGFR? Perhaps this is a function of the threshold for an abnormal cTnT in our study. Our definition was derived empirically based on the risk of death in a representative sample rather than the measurement characteristics of the assay (i.e. coefficient of variation and 99<sup>th</sup> percentile of a health population) in other studies. Our study also utilized a newer generation of cTnT assay which improves discrimination of lower concentrations of cTnT compared to previous assays. Together these resulted in a substantially lower threshold to define an abnormal cTnT in our study than previous studies. If circulating cTnT is cleared by the kidneys, patients with reduced kidney function may develop measurable elevations with less cardiac injury than patients with normal kidney function. Small increases in cTnT would be expected to have less associated risk in patients with a reduced eGFR in this case. We may also expect studies using older generations of cTnT assays with a threshold of 0.09 ng/mL to find a larger associated risk of death in this scenario.(20)

Also, up to 43% of asymptomatic patients with a reduced eGFR but not requiring dialysis were found to have an abnormal cTnT. The elevated cTnT in patients with poor kidney function in our study may therefore be chronic and not have the same prognostic (or pathophysiologic) implications as an acute rise brought on by surgery. However, in a sub-study of VISION we found that 21% of patients had an elevated high sensitivity cTnT prior to surgery regardless of kidney function or urgency of the surgery suggesting measurable quantities of cTnT are present in many patients without severely impaired kidney function also.(21) Whether this means a substantial number of patients have myocardial injury starting prior to surgery is unclear. Also,

our analysis utilizing a change in cTnT did not differ from analyses utilizing only the peak concentration.

It is also important to remember that patients that undergo surgery are selected to do so. Patients with a reduced eGFR may be more rigorously screened prior to elective surgery and may be more commonly rejected. The population actually operated on may therefore represent a special subgroup of a patients with a reduced eGFR in whom the risk of cardiovascular events is not the primary risk factor for early death after surgery. Some evidence of this is seen by virtue that 24% of the group with an eGFR  $<30$  ml/min/1.73 m<sup>2</sup> underwent urgent/emergent procedures compared to 13% with an eGFR  $\geq 30$  ml/min/1.73 m<sup>2</sup>. It is therefore possible that patients with poor kidney function are either operated on only under more emergent circumstances, in which case their risk of death may be dominated by the urgency of the surgery, and non-vascular complications after surgery are more relevant to them. Also, patients with a low eGFR are at high risk for vascular events while awaiting elective surgery. Patients with a reduced eGFR go on to surgery may either be survivors of cardiovascular disease and therefore resistant to further significant vascular events while those that do not go on to surgery were more fragile.

Finally, we must consider that the number of patients with an eGFR  $<30$  ml/min/1.73 m<sup>2</sup> was small and the apparent difference between those with an eGFR  $<30$  ml/min/1.73 m<sup>2</sup> and those with better kidney function may be due to the play of chance.

It also bears mention that there was a statistically significant interaction for the eGFR strata 15 to  $<30$  ml/min/1.73 m<sup>2</sup> but not for the  $<15$  ml/min/1.73 m<sup>2</sup> or on dialysis strata. This may be due to lack of power to detect the interaction in the lowest kidney function strata which is supported by the consistency of the effect sizes between these two strata. However, dialysis patients may also

be qualitatively different than patients with a low eGFR. They may be more highly selected and therefore represent somewhat better overall health than patients with low eGFR but not on dialysis. Patients already on dialysis are also incapable of developing acute kidney injury, a strong risk factor for postoperative mortality, while patients with low eGFR may be patients with acute kidney injury and therefore represent a higher risk preoperative condition. This is supported by the high rate of urgent/emergent surgery in the low eGFR categories. Our sample was too small, however, to make a valid comparison of urgent/emergent surgeries compared to non-urgent emergent surgeries.

Our study has several notable strengths. The study sample is large, representative of patients undergoing major noncardiac surgery from several hospitals in several countries and is well characterized at baseline. We lost very few patients to follow-up and had excellent adherence to the cTnT measurement in the first 3 days after surgery. Our cTnT threshold was empirically determined using a robust, objective method and was demonstrated to be the most important risk factor for 30-day mortality in patients undergoing noncardiac surgery. Finally there were 269 deaths within 30 days allowing us to fit a stable regression model.

However, our results must also be considered within the context of the study's limitations. Although this is a large prospective study, there were still relatively few patients with very poor kidney function. Thus, only large effects could be reliably detected by a test of interaction. We are unable to determine how stable kidney function was prior to surgery. Patients with a low eGFR may be misclassified due to acute changes in kidney function prior to surgery (i.e., acute kidney injury). Whether the interaction we detected applies equally to patients with acutely deteriorating kidney function and patients with chronically poor kidney function is unclear. Despite this, we still demonstrate statistical significance at the eGFR  $<30$  ml/min/1.73 m<sup>2</sup>. Our

results are based on only one assay, the 4<sup>th</sup> generation cTnT assay. Direct extrapolation of our results to other assays and particularly the newly available high sensitivity assays is problematic. One might expect that highly sensitive assays will only reinforce the issue we identified since they will mostly improve measurement of very low concentrations of troponins. Our results may be all the more important as highly sensitive assays will be even more difficult to interpret in the setting of poor kidney function. Further studies both in the surgical and nonsurgical setting will be needed urgently given patients with a reduced eGFR are at high risk of cardiac events.

Monitoring postoperative cTnT remains an important instrument to identify patients at high risk of a postoperative death. However, the interpretation of postoperative cTnTs in patients with very poor kidney function is unclear. Given the high prevalence of CKD and that over 200 million individuals undergo surgery each year, further studies to determine how to use these important tests for cardiac injury to identify patients at high risk of death and other adverse events are required urgently.

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### **Contributorship Statement**

Michael Walsh contributed significantly to the study's concept and design, data collection, data analysis, and interpretation of the data. He wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

C.Y. Wang contributed to the study's concept, data collection, and interpretation of the data. She provided critical revisions and gave final approval of the submitted manuscript.

G.S.Y. Ong contributed to the study's concept, data collection, and interpretation of the data. She provided critical revisions and gave final approval of the submitted manuscript.

A. S. B. Tan contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

M. Mansor contributed to the study's concept, data collection, and interpretation of the data. She provided critical revisions and gave final approval of the submitted manuscript.

I. I. Shariffuddin contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

N.H.M Hashim contributed to the study's concept, data collection, and interpretation of the data. She provided critical revisions and gave final approval of the submitted manuscript.

H.Y. Lai contributed to the study's concept, data collection, and interpretation of the data. She provided critical revisions and gave final approval of the submitted manuscript.

A. Wahab Undok contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

U.H. Kolandaivel contributed to the study's concept, data collection, and interpretation of the data. She provided critical revisions and gave final approval of the submitted manuscript.

Vasanthan Vajiravelu contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

Amit X. Garg contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

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Lehana Thabane contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

Meaghan Cuerden contributed to the study's concept, data analysis and interpretation of the data. She provided critical revisions and gave final approval of the submitted manuscript.

P.J. Devereaux contributed to the study's concept, data collection, and interpretation of the data.

He provided critical revisions and gave final approval of the submitted manuscript.

Table 1. Preoperative characteristics by estimated glomerular filtration rate (eGFR).

| Characteristics                  | All patients<br>n = 14037 | Estimated GFR *    |                        |                       |                       |                                |
|----------------------------------|---------------------------|--------------------|------------------------|-----------------------|-----------------------|--------------------------------|
|                                  |                           | ≥ 60<br>n = 11,266 | 45 to < 60<br>n = 1488 | 30 to < 45<br>n = 763 | 15 to < 30<br>n = 274 | < 15 or on dialysis<br>n = 246 |
| <b>Age (years)</b>               |                           |                    |                        |                       |                       |                                |
| <b>Median</b>                    | 65.2                      | 62.6               | 74.9                   | 77.7                  | 77.8                  | 66.5                           |
| <b>25th and 75th percentiles</b> | 56.0, 75.1                | 54.4, 72.4         | 67.8, 80.6             | 70.1, 83.6            | 68.9, 84.2            | 55.8, 75.4                     |
| <b>Female, n (%)</b>             | 7169 (51.1%)              | 5735 (50.9%)       | 781 (52.5%)            | 393 (51.5%)           | 148 (54.0%)           | 112 (45.5%)                    |
| <b>Current, n (%)</b>            |                           |                    |                        |                       |                       |                                |
| <b>AF</b>                        | 497 (3.5%)                | 317 (2.8%)         | 71 (4.8%)              | 66 (8.7%)             | 28 (10.2%)            | 15 (6.1%)                      |
| <b>Diabetes</b>                  | 2833 (20.2%)              | 1978 (17.6%)       | 384 (25.8%)            | 266 (34.9%)           | 97 (35.4%)            | 108 (43.9%)                    |
| <b>History of, n (%)</b>         |                           |                    |                        |                       |                       |                                |
| <b>CHF</b>                       | 694 (4.9%)                | 392 (3.5%)         | 100 (6.7%)             | 101 (13.2%)           | 56 (20.4%)            | 45 (18.3%)                     |
| <b>CAD</b>                       | 1766 (12.6%)              | 1133 (10.1%)       | 291 (19.6%)            | 201 (26.3%)           | 76 (27.7%)            | 65 (26.4%)                     |
| <b>High risk CAD</b>             | 172 (1.2%)                | 101 (0.9%)         | 25 (1.7%)              | 24 (3.2%)             | 8 (2.9%)              | 14 (5.7%)                      |
| <b>Cardiac arrest</b>            | 62 (0.4%)                 | 44 (0.4%)          | 8 (0.5%)               | 6 (0.8%)              | 1 (0.4%)              | 3 (1.2%)                       |
| <b>DVT/PE</b>                    | 454 (3.2%)                | 317 (2.8%)         | 65 (4.4%)              | 46 (6.0%)             | 12 (4.4%)             | 14 (5.7%)                      |
| <b>Stroke</b>                    | 670 (4.8%)                | 420 (3.7%)         | 120 (8.1%)             | 81 (10.6%)            | 28 (10.2%)            | 21 (8.5%)                      |
| <b>TIA</b>                       | 361 (2.6%)                | 236 (2.1%)         | 57 (3.8%)              | 39 (5.1%)             | 17 (6.2%)             | 12 (4.9%)                      |
| <b>PVD</b>                       | 788 (5.6%)                | 466 (4.1%)         | 143 (9.6%)             | 89 (11.7%)            | 37 (13.5%)            | 53 (21.5%)                     |

|   |              |              |              |             |             |             |
|---|--------------|--------------|--------------|-------------|-------------|-------------|
| <b>Sleep apnea</b>                          | 734 (5.6%)   | 604 (5.4%)   | 70 (4.7%)    | 39 (5.1%)   | 9 (3.3%)    | 12 (4.9%)   |
| <b>Hypertension</b>                         | 7309 (52.1%) | 5180 (46.0%) | 1073 (72.1%) | 627 (82.2%) | 227 (82.9%) | 202 (82.1%) |
| <b>COPD</b>                                 | 1252 (8.9%)  | 919 (8.2%)   | 165 (11.1%)  | 101 (13.2%) | 43 (15.7%)  | 24 (9.8%)   |
| <b>Active Cancer, n (%)</b>                 | 3865 (27.5%) | 3196 (28.4%) | 381 (25.6%)  | 181 (23.7%) | 69 (25.2%)  | 38 (15.5%)  |
| <b>eGFR (mL/min per 1.73 m<sup>2</sup>)</b> |              |              |              |             |             |             |
| <b>Median ¥</b>                             | 82.6         | 87.3         | 53.8         | 38.3        | 24.7        | 9.4         |
| <b>25th and 75th percentiles</b>            | 66.1, 95.0   | 76.1, 97.3   | 49.7, 57.2   | 34.5, 41.8  | 20.3, 27.6  | 6.7, 12.3   |
| <b>Urgent/emergency surgery, n (%)</b>      | 1902 (13.6%) | 1428 (12.7%) | 205 (13.8%)  | 145 (19.0%) | 69 (25.1%)  | 55 (22.4%)  |
| <b>Type of surgery, n (%)</b>               |              |              |              |             |             |             |
| <b>Vascular</b>                             | 480 (3.4%)   | 295 (2.6%)   | 91 (6.1%)    | 63 (8.3%)   | 15 (5.5%)   | 16 (6.5%)   |
| <b>General</b>                              | 2877 (20.5%) | 2294 (20.4%) | 313 (21.0%)  | 142 (18.6%) | 76 (27.7%)  | 52 (21.1%)  |
| <b>Thoracic</b>                             | 366 (2.6%)   | 326 (2.9%)   | 27 (1.8%)    | 9 (1.2%)    | 1 (0.4%)    | 3 (1.2%)    |
| <b>Major Urology/Gyn</b>                    | 1732 (12.3%) | 1386 (12.3%) | 187 (12.6%)  | 91 (11.9%)  | 27 (9.9%)   | 41 (16.7%)  |
| <b>Major Orthopedic</b>                     | 3013 (21.5%) | 2242 (19.9%) | 405 (27.2%)  | 245 (32.1%) | 69 (25.2%)  | 52 (21.1%)  |
| <b>Major Neurologic</b>                     | 796 (5.7%)   | 710 (6.3%)   | 53 (3.6%)    | 27 (3.5%)   | 3 (1.1%)    | 3 (1.2%)    |
| <b>Low risk surgeries</b>                   | 5374 (38.3%) | 4507 (40.0%) | 476 (32.0%)  | 207 (27.1%) | 96 (35.0%)  | 88 (35.8%)  |

AF=atrial fibrillation; CHF=congestive heart failure; CAD=coronary artery disease; DVT/PE=deep venous thrombosis or pulmonary embolus; TIA= transient ischemic attack; PVD=peripheral vascular disease; COPD=chronic obstructive pulmonary disease; eGFR=estimated glomerular filtration rate;Gyn=gynecologic

\* eGFR calculated using the CKD-EPI equation.

¥ patients on dialysis not included in the median eGFR calculation

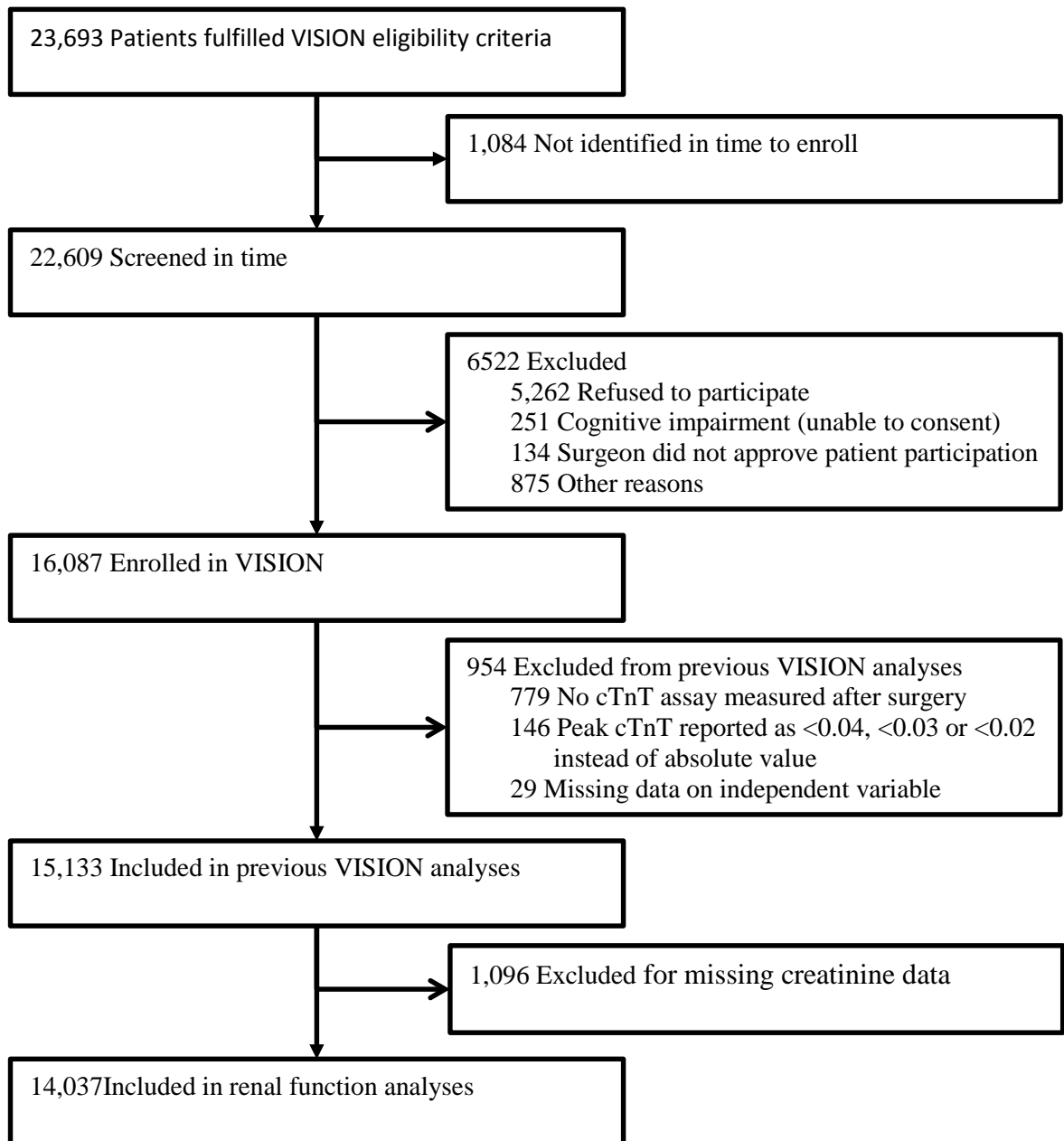


Table 2. Frequency of an abnormal cardiac Troponin T (cTnT) defined as  $\geq 0.02$  ng/mL and 30-day all-cause mortality by estimated glomerular filtration rate (eGFR) strata.

| <b>eGFR Strata</b><br><b>(ml/min/1.73 m<sup>2</sup>)</b> | <b>cTnT value</b><br><b>(ng/mL)</b> | <b>n (%)</b>   | <b>% who died</b><br><b>(95% CI)</b> |
|--|-------------------------------------|----------------|--------------------------------------|
| <b><math>\geq 60</math></b>                              | <0.02                               | 10,418 (92.5%) | 0.9 (0.8, 1.1)                       |
|  | $\geq 0.02$                         | 848 (7.5%)     | 7.3 (5.7, 9.3)                       |
| <b>45 to &lt;60</b>                                      | <0.02                               | 1214 (81.6%)   | 1.0 (0.6, 1.7)                       |
|  | $\geq 0.02$                         | 274 (18.4%)    | 8.4 (5.7, 12.3)                      |
| <b>30 to &lt;45</b>                                      | <0.02                               | 510 (66.8%)    | 1.4 (0.7, 2.8)                       |
|  | $\geq 0.02$                         | 253 (33.2%)    | 10.3 (7.1, 14.6)                     |
| <b>15 to &lt;30</b>                                      | <0.02                               | 127 (46.4%)    | 4.7 (2.2, 9.9)                       |
|  | $\geq 0.02$                         | 147 (53.6%)    | 10.2 (6.3, 16.2)                     |
| <b>&lt;15 or on dialysis</b>                             | <0.02                               | 75 (30.5%)     | 4.0 (1.4, 11.1)                      |
|  | $\geq 0.02$                         | 171 (69.5%)    | 8.8 (5.4, 14.0)                      |

eGFR = estimated glomerular filtration rate; cTnT = cardiac troponin T; n=number of patients with this value of cTnT; CI=confidence interval; aHR = adjusted hazard ratio

Figure 1. Patient flow.



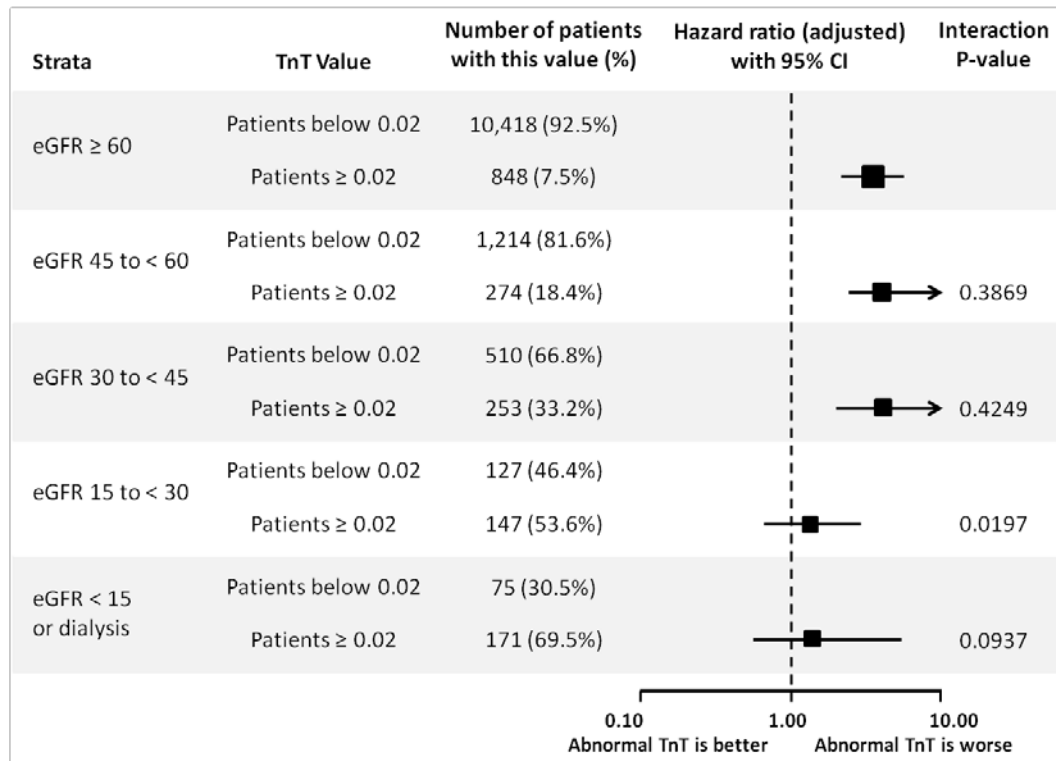


Figure 2. Forest plot of adjusted hazard ratio for 30-day mortality in patients undergoing noncardiac surgery with versus without a postoperative cardiac troponin T (TnT)  $\geq 0.02$  by estimated glomerular filtration rate (eGFR) strata. P-values test the hypothesis that the hazard ratio for an abnormal TnT in an eGFR strata differs from the hazard ratio associated with an abnormal TnT in the eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup>.

Supplemental Material

Appendix 1. Model covariate definitions.

**1. Age** – Patient age in years was recorded and subsequently categorized as 45-64 years of age, 65-74 years of age, and >75 years of age.

**2. Sex** – Male or female.

**3. History of coronary artery disease** – A current or prior history of any one of the following: i. angina; ii. myocardial infarction or acute coronary syndrome; iii. a segmental cardiac wall motion abnormality on echocardiography or a segmental fixed defect on radionuclide imaging; iv. a positive radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test demonstrating cardiac ischemia; v. coronary angiographic or computer tomography (CT) coronary angiographic evidence of atherosclerotic stenosis  $\geq 50\%$  of the diameter of any coronary artery; vi. ECG with pathological Q waves in two contiguous leads.

**4. Recent high-risk coronary artery disease** – A physician diagnosis <6 months prior to noncardiac surgery of: a myocardial infarction, acute coronary syndrome, Canadian Cardiovascular Society Class (CCSC) III angina, or CCSC IV angina CCSC III angina - angina occurring with level walking of 1-2 blocks or climbing <1 flight of stairs at a normal pace CCSC IV angina - inability to carry on any physical activity without the development of angina.

**5. History of cardiac arrest** – A patient with a prior history of a cardiac arrest.

**6. History of congestive heart failure** – A physician diagnosis of a current or prior episode of congestive heart failure or prior radiographic evidence of vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema.

**7. History of peripheral vascular disease** – A physician diagnosis of a current or prior history of: intermittent claudication, vascular surgery for atherosclerotic disease, an ankle/arm systolic blood pressure ratio  $<0.90$  in either leg at rest, or angiographic or doppler study demonstrating  $>70\%$  stenosis in a noncardiac artery.

**8. History of stroke** – A physician diagnosis of a current or prior stroke, or CT or magnetic resonance (MR) evidence of a stroke.

**9. History of a transient ischemic attack (TIA)** – A physician diagnosis of a current or prior TIA.

**10. History of deep venous thrombosis (DVT) or pulmonary embolus (PE)** – A patient with a current or prior history of a DVT or PE.

**11. Diabetes** – Patient stated that they have a diagnosis of diabetes or a physician has previously recorded that the patient has diabetes. This included gestational diabetes at the time of noncardiac surgery, but not past gestational diabetes that had resolved.

**12. Hypertension** – A physician diagnosis of hypertension.

**13. Current atrial fibrillation** – A patient with a current history of atrial fibrillation.

**14. Obstructive sleep apnea** – A physician or sleep study diagnosis of obstructive sleep apnea.

**15. Chronic obstructive pulmonary disease (COPD)** – A physician current or prior diagnosis of chronic bronchitis, emphysema, or COPD, or a patient provided a history of daily production of sputum for at least 3 months in 2 consecutive years.

**16. Active cancer** – A patient was designated as having active cancer if they fulfilled any of the following criteria: i. undergoing surgery for cancer; ii. known metastatic disease; or iii. Patient had received active treatment for their cancer (e.g., chemotherapy, radiation, or surgery) within the 6 months prior to their surgery, but this did not apply to patients with non-melanoma skin cancers or surgery for a biopsy.

**17. Urgent/Emergency surgery** – Emergency surgery was surgery that occurred <24 hours after a patient developed an acute surgical condition, and urgent surgery was surgery that occurred 24-72 hours after a patient developed an acute surgical condition.

**18. Major orthopedic surgery** – A patient undergoing one or more of the following orthopedic surgeries: major hip or pelvis surgery, internal fixation of femur, knee arthroplasty, above knee amputations, or lower leg amputation (amputation below knee but above foot).

**19. Major general surgery** – A patient undergoing one or more of the following general surgeries: complex visceral resection, partial or total colectomy or stomach surgery, other intra-abdominal surgery, or major head and neck resection for non-thyroid tumor.

**20. Major urology or gynecology surgery** – A patient undergoing one or more of the following major urology or gynecology surgeries: nephrectomy, ureterectomy, bladder resection, retroperitoneal tumor resection, exenteration, cytoreduction surgery, hysterectomy, radical prostatectomy, or transurethral prostatectomy.

**21. Major neurosurgery** – A patient undergoing one or more of the following neurosurgeries: craniotomy or major spine surgery (i.e., surgery involving multiple levels of the spine).

**22. Major vascular surgery** – A patient undergoing one or more of the following vascular surgeries: thoracic aorta reconstructive vascular surgery, aorto-iliac reconstructive vascular surgery, peripheral vascular reconstruction without aortic cross-clamping, extracranial cerebrovascular surgery, or endovascular abdominal aortic aneurysm repair.

**23. Major thoracic surgery** – A patient undergoing one or more of the following thoracic surgeries: pneumonectomy, lobectomy, wedge resection of lung, resection of mediastinal tumor, or major chest wall resection.

**24. Low-risk surgeries** – A patient undergoing one or more of the following surgeries: parathyroid, thyroid, breast, hernia, local anorectal procedure, oophorectomy, salpingectomy, endometrial ablation, peripheral nerve surgery, ophthalmology, ears/nose/throat surgery, vertebral disc surgery, hand surgery, cosmetic surgery, arterio-venous access surgery for dialysis, or any other surgery not mentioned above.

Supplemental Table 1. Frequency of an abnormal cardiac Troponin T (cTnT) defined as  $\geq 0.03$  ng/mL and 30-day all-cause mortality by estimated glomerular filtration rate (eGFR) strata.

| <b>eGFR Strata</b><br><b>(ml/min/1.73 m<sup>2</sup>)</b> | <b>cTnT value</b><br><b>(ng/mL)</b> | <b>n (%)</b> | <b>% who died</b><br><b>(95% CI)</b> | <b>aHR for Death</b><br><b>(95% CI)</b> |
|--|-------------------------------------|--------------|--------------------------------------|---|
| <b><math>\geq 60</math></b>                              | <0.03                               | 10682 (95%)  | 1 (0.8, 1.2)                         |   |
|  | $\geq 0.03$                         | 584 (5%)     | 9.6 (7.5, 12.2)                      | 5.14 (3.57, 7.1)                        |
| <b>45 to &lt;60</b>                                      | <0.03                               | 1297 (87%)   | 1.2 (0.8, 2)                         |   |
|  | $\geq 0.03$                         | 191 (13%)    | 9.9 (6.5, 15)                        | 6.02 (3.21, 12.74)                      |
| <b>30 to &lt;45</b>                                      | <0.03                               | 590 (77%)    | 1.5 (0.8, 2.9)                       |   |
|  | $\geq 0.03$                         | 173 (23%)    | 13.9 (9.5, 19.8)                     | 7.23 (3.61, 18.3)                       |
| <b>15 to &lt;30</b>                                      | <0.03                               | 163 (59%)    | 5.5 (2.9, 10.2)                      |   |
|  | $\geq 0.03$                         | 111 (41%)    | 10.8 (6.3, 18)                       | 1.18 (0.44, 3.73)                       |
| <b>&lt;15 or on dialysis</b>                             | <0.03                               | 88 (36%)     | 4.5 (1.8, 11.1)                      |   |
|  | $\geq 0.03$                         | 158 (64%)    | 8.9 (5.4, 14.3)                      | 1.31 (0.47, 8.54)                       |

eGFR = estimated glomerular filtration rate; cTnT = cardiac troponin T; n=number of patients with this value of cTnT; CI=confidence interval; aHR = adjusted hazard ratio



Supplemental Table 2. Population attributable risk for 30-day all-cause mortality of characteristics of patients with an estimated glomerular filtration rate <30 or on dialysis compared to  $\geq 30$  ml/min/1.73 m<sup>2</sup>.

| Characteristic                                | Population Attributable Risk, % |                |
|---|---------------------------------|----------------|
|   | eGFR<30                         | eGFR $\geq$ 30 |
| <b>Peak cTnT <math>\geq</math> 0.03</b>       | 2.8                             | 30.8           |
| <b>Age</b>                                    | 73.9                            | 31.3           |
| <b>Recent high risk CAD</b>                   | 2.9                             | 3.5            |
| <b>History of PVD</b>                         | 25.1                            | 8.7            |
| <b>History of stroke</b>                      | 4.4                             | 7.1            |
| <b>History of COPD</b>                        | 7.6                             | 11.3           |
| <b>Active cancer</b>                          | 2.1                             | 26.9           |
| <b>Urgent or emergent surgery</b>             | 59.0                            | 27.7           |
| <b>General surgery</b>                        | 18.7                            | 14.6           |
| <b>Major neurosurgery</b>                     | -                               | 5.7            |
| <b>Stroke within 30 days after surgery</b>    | -6.4                            | 3.2            |
| <b>Pneumonia within 30 days after surgery</b> | 14.2                            | 8.4            |
| <b>Infection or Sepsis</b>                    | 18.1                            | 19.8           |
| <b>DVT or PE within 30 days after surgery</b> | -                               | 6.8            |

### **CHAPTER 3**

Walsh, Michael, Garg, Amit X., Devereaux, P.J., Argalious, Maged, Honar, Hooman, Sessler, Daniel I. Association between perioperative hemoglobin and acute kidney injury in patients having noncardiac surgery. *Anesthesia and Analgesia*. (Accepted 2013)

**ASSOCIATION BETWEEN PERIOPERATIVE HEMOGLOBIN AND ACUTE KIDNEY  
INJURY IN PATIENTS HAVING NONCARDIAC SURGERY**

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## **ABSTRACT**

**Background:** Acute kidney injury (AKI) is a common complication of noncardiac surgery and is associated with excess morbidity and mortality. Perioperative hemoglobin concentrations are strongly associated with surgical mortality but little is known about their relationship with AKI. We studied hemoglobin before and 24 hours after surgery, and its association with AKI.

**Methods:** We performed a single-centre observational cohort study using clinical and administrative data from the Cleveland Clinic, Ohio, USA. In patients with normal preoperative renal function, we examined the association between the outcome of AKI and the exposures of preoperative hemoglobin concentration and decrements in hemoglobin concentration in the first 24 hours after surgery using logistic regression and controlling for important confounding variables.

**Results:** We included 27,381 patients who had 33,330 non cardiac surgeries. AKI developed in 2478 (7.4%) surgeries. Preoperative hemoglobin concentrations were  $<12.0$  g/dL in 9,566 (29%) patients. Hemoglobin concentrations decreased by  $>4.0$  g/dL in 10,808 (32%) patients. Compared to patients with a preoperative hemoglobin  $>12.0$  g/dL, the adjusted odds ratio (OR) for AKI was 2.01 (95% confidence interval [CI] 1.8 to 2.3) for those with a preoperative hemoglobin between 10.1 and 12.0 g/dL and was 3.7 (95% CI 2.6 to 5.4) for those with a preoperative hemoglobin  $<8.0$  g/dL. Compared to patients who did not have a decrement in postoperative hemoglobin, a decrement of 1.1 to 2.0 g/dL was associated with an adjusted OR of 1.51 (95% CI 1.15 to 1.98), and a decrement  $>4.0$  g/dL a ratio of 4.7 (95% CI 3.6 to 6.2) for AKI.

Conclusions: Low preoperative and early postoperative decrements in hemoglobin concentrations are strongly associated with postoperative AKI in a graded manner. Given the frequency of low perioperative hemoglobin and decrements in hemoglobin concentration, research is needed to determine if safe treatment strategies exist to mitigate the risk of AKI.

## **BACKGROUND**

Acute kidney injury (AKI), a sudden reduction in kidney function, occurs in approximately 7% of hospitalized patients and 7.5% of patients that undergo noncardiac surgery (1, 2). Small changes in serum creatinine, the most common marker of kidney function, are increasingly recognized as strong, independent risk factors for short and long-term mortality (3, 4) and markedly increased health care costs after surgery (2, 5). Severe AKI which requires dialysis, is associated with mortality and hospital costs similar to that of cardiac arrest (5-7).

There is no high-quality evidence demonstrating interventions prevent or reduce the severity of postoperative AKI (8). Identifying risk factors that are common, have a strong association with AKI, and may be modifiable is therefore an important initial step in identifying potential therapeutic targets. Preoperative anemia and perioperative transfusions are associated with AKI in cardiac surgery (9). In noncardiac surgery, preoperative anemia is also an important risk factor for mortality (10). Whether preoperative anemia is associated with early postoperative AKI, has not been studied in noncardiac surgery. Furthermore, transfusions may be associated with AKI either because the transfusions themselves are harmful or because the reasons for transfusion cause AKI. Given both perioperative decrements in hemoglobin concentration and low preoperative hemoglobin concentrations may both trigger transfusion, we examined the independent contributions of each of these risk factors to the development of AKI.

Given that more than 200 million patients undergo noncardiac surgery each year, mitigating the risk of AKI is an important health issue (11). If perioperative hemoglobin is strongly associated with AKI, it may represent a modifiable pathway for ameliorating AKI and therefore reducing perioperative morbidity and mortality. We studied patients who had noncardiac surgery to

determine if preoperative hemoglobin concentrations and early postoperative reductions in hemoglobin concentration are associated with AKI.

## Methods

*Study Design:* We undertook an observational study using data from the Cleveland Clinic Perioperative Health Documentation System (PHDS), an electronic medical record-based registry of noncardiac surgery patients who had surgery between January 6th, 2005 and September 21, 2010 at the Cleveland Clinic, Ohio, USA with additional linkage to hospital based administrative data and death records. Use of this de-identified registry for research was approved by the Cleveland Clinic Institutional Review Board.

*Patients:* Patients who had at least one preoperative and one postoperative creatinine measure within 7 days of surgery as well as a preoperative hemoglobin and at least one postoperative hemoglobin within 1 day of surgery were included. To reduce concerns of confounding related to pre-operative chronic kidney disease (a potent risk factor for AKI), patients who had an estimated glomerular filtration rate  $<60$  ml/min/1.73 m<sup>2</sup> according to the 4-variable Modification of Diet in Renal Disease equation were excluded from study (12). Patients undergoing removal of urinary obstruction, nephrectomy, or renal transplantation were also excluded. Of note, the Cleveland Clinic does not perform obstetrical surgery (i.e. caesarian sections).

*Outcomes and Exposures:* We defined acute kidney injury according to changes in serum creatinine between preoperative and postoperative values. The preoperative creatinine was defined as the concentration measured closest to the time before surgery. The postoperative value used was the highest concentration measured within 7 days of surgery. Consistent with the Acute Kidney Injury Network definition of AKI, patients were considered to have AKI if the highest

postoperative concentration was either >1.5-fold or >0.3 mg/dL greater than the preoperative concentration (4). We further stratified the severity of AKI as mild (1.5 to 2-fold or >0.3 mg/dL increase in creatinine), moderate (>2 to 3-fold increase in creatinine) or severe (>3-fold increase in creatinine).

*Perioperative Hemoglobin:* Both the preoperative hemoglobin level and the change between preoperative hemoglobin and lowest hemoglobin in the 24 hours following surgery were examined for an association with AKI. The preoperative hemoglobin was the value recorded closest to the time preceding the operation.

*Other Exposures:* Patient's age and sex were determined from the registry. The Risk Stratification Index (RSI) for 30 day mortality, a validated score using administrative data codes, was calculated for all patients (13). Intraoperative estimated blood loss, and transfusion of red blood cells (autologous and allogeneic) were recorded in the clinical database. Surgeries were classified according to the Agency for Healthcare Research and Quality descriptors and whether they were emergency or elective procedures using the Clinical Classification Software.

*Statistical Analysis:* Patient characteristics were calculated as mean (standard deviation [SD]), median (25<sup>th</sup> to 75<sup>th</sup> percentile), or frequency (%) as appropriate.

To assess the association between perioperative hemoglobin and AKI we developed a multivariable logistic regression model in which presence or absence of AKI was the outcome (i.e. dependent variable). The main exposures (i.e. independent variables), preoperative hemoglobin concentration and change in hemoglobin concentration were categorized into groups felt to be clinically important. Preoperative hemoglobin concentration was categorized as >12.0 g/dL, 12.0 to 10.1 g/dL, 10.0 to 8.1 g/dL and ≤8.0 g/dL. Change in hemoglobin concentration



was categorized as no decrement (referent group), 0 to 1 g/dL decrement, 1.1 to 2.0 g/dL decrement, 2.1 to 3.0 g/dL decrement, 3.1 to 4.0 g/dL decrement, and >4.0 g/dL decrement.

We adjusted all models for age, sex, the Risk Stratification Index for 30-day mortality, the volume of red cells transfused intraoperatively, and the type of surgery performed. We accommodated the correlation of multiple surgeries within individual patients by calculating estimated standard errors adjusted for intragroup correlations using clustered sandwich estimators (14, 15). We reported adjusted odds ratios (OR) and associated 95% confidence intervals (CI) and p-values. P-values <0.05 without adjustment for multiple testing were considered significant.

We performed sensitivity analyses by constructing logistic regression models similar to the primary analysis, but 1) using alternative definitions of AKI (limited to AKI within 3 days of surgery, moderate AKI and severe AKI), 2) by subgroups of surgeries (elective only, most recent surgery only, abdominal surgery only, orthopedic surgery only, vascular surgery only), and 3) using alternatives to the RSI to control confounding (Charlson comorbidity index and individual comorbidities).

We examined the association between 30-day all-cause mortality and AKI with a logistic regression model adjusted for patient age, sex, RSI score, procedure type, emergency surgery status, estimated blood loss, transfusion volume, change in hemoglobin concentration and preoperative hemoglobin concentration.

All analyses were completed using Stata version 11 MP (College Station, TX).

## Results

Among the 106,122 noncardiac surgeries in the PHDS database, 22,383 were excluded for an estimated GFR < 60 ml/min/1.73 m<sup>2</sup>, 13,169 were excluded for missing preoperative creatinine or hemoglobin concentrations, 28,144 were excluded for missing follow-up laboratory values, 4,715 were excluded because surgery was for removal of urinary obstruction, nephrectomy, or renal transplant procedures and 4,481 were excluded for other missing covariate data (demographics, estimated blood loss, transfusion data, emergency surgery designation) (Figure 1). Among the eligible 33,330 surgeries performed in 27,381 patients AKI occurred in 2,478 (7.4%) surgeries.

Patients who did and did not develop AKI differed significantly; specifically, they were older, more frequently male, had a higher risk of 30-day mortality, more cardiovascular disease, and more often had emergency surgery (Table 1).

In 9,566 (29%) surgeries, patients had a preoperative hemoglobin concentration less than 12.0 g/dL. Patients with lower preoperative hemoglobin concentrations were older, had higher Risk Stratification Index scores, more often had emergency procedures, and were transfused larger volumes of red blood cells (Table 2). Lower preoperative hemoglobin concentrations were associated with a graded risk of postoperative AKI. Each category of lower preoperative hemoglobin below the reference category was associated with a clinically and statistically significant increased risk starting with an OR of 2.0 (95% CI 1.8 to 2.3) for hemoglobin concentrations between 10.1 and 12.0 g/dL and rising to an OR of 3.7 (95% CI 2.6 to 5.4) for hemoglobin concentrations < 8.0 g/dL (Figure 2).

In 17,128 (51%) surgeries patients had a decrement in hemoglobin of > 3.0 g/dL, and 10,808 (32%) a decrement > 4.0 g/dL. Patients with larger decrements in postoperative hemoglobin had

lower RSI scores (i.e. lower risk of 30-day mortality) and were less frequently undergoing emergency surgery and in all but the most extreme category of decrement in hemoglobin, were younger (Table 3). However, larger decrements in hemoglobin also occurred in patients with lower estimated glomerular filtration rates, greater estimated blood losses, and longer case durations. There was no apparent increase in transfusion volumes in those with larger decrements in hemoglobin concentration. Larger decrements in hemoglobin concentration were associated with a graded increase in the risk of AKI. Decrements as small as 1.1 to 2.0 g/dL were significantly associated with AKI with an adjusted OR of 1.5 (95% CI 1.2 to 2.0) and decrements >4.0 g/dL associated with an OR of 4.7 (95% CI 3.6 to 6.2) (Figure 3). In contrast, compared to no transfusion, transfusion with 250 mL of packed red blood cells carried an odds ratio of 1.05 (1.03 to 1.07) while a transfusion of 1000 mL of packed red blood cells carried an odds ratio of 1.20 (1.11 to 1.30).

Sensitivity analyses in which the outcome definition was altered, the type of surgery was restricted, or the method of adjustment was altered were broadly similar to the main analysis (Supplementary Tables 1-3). For example, models in which AKI was defined as a moderate (>2 fold rise in serum creatinine) or severe (>3 fold rise in serum creatinine) also demonstrated a graded increase in the risk of AKI for each lower category of preoperative hemoglobin and each larger category of decrement in postoperative hemoglobin (Supplementary Table 1). AKI defined as by the highest creatinine within 3 days of surgery rather than within 7 days of surgery occurred in 2,043 surgeries (6.1%) and did not change the relationships between preoperative hemoglobin and the postoperative decrement in hemoglobin materially (Supplementary Table 1).

AKI was independently associated with 30-day mortality with an adjusted OR of 2.6 (95% CI 2.0 to 3.3). Increasing severity of AKI was associated with mortality in a graded manner. The

adjusted OR for mild AKI and death was 1.8 (95% CI 1.3 to 2.4), moderate AKI was 3.5 (95% CI 2.3 and 5.4), and severe AKI was 6.9 (95% CI 4.5 to 10.5).

## Discussion

In this large, single-center study we demonstrated that preoperative hemoglobin concentrations and postoperative decrements in hemoglobin are both independently associated with acute kidney injury. Given the graded relationship between the degree of preoperative anemia and odds of acute kidney injury and magnitude of decrement in postoperative hemoglobin, these findings are consistent with an ischemic cause of postoperative AKI (16, 17). The importance of these findings is highlighted by the high proportion of patients undergoing noncardiac surgery who had low preoperative hemoglobin concentrations or substantial postoperative decrements in hemoglobin.

Our finding that preoperative hemoglobin concentrations are strongly associated with AKI is consistent with findings in cardiac surgery (9). Our study extends previous work to noncardiac surgery and shows that low hemoglobin concentration and substantial decrements in hemoglobin are important risk factors for AKI, a finding not previously demonstrated to our knowledge (1, 18, 19). Given that hemoglobin concentrations below 12 g/dL are common in patients undergoing noncardiac surgery, and that the association between lower hemoglobin levels and AKI is strong, risk prediction tools for postoperative AKI may be improved substantially by considering perioperative hemoglobin concentrations.

Our finding that a decrement in postoperative hemoglobin is strongly associated with postoperative AKI is new. The relationship between the number of transfusions required and AKI was described in cardiac surgery and demonstrated less than a 10% increase in risk of AKI

for each unit transfused (9). Even after adjusting estimates for transfusion, which are less numerous in noncardiac than cardiac surgery, even a relatively small decrement in hemoglobin was strongly associated with AKI.

Larger decrements in hemoglobin presumably reduce the oxygen carrying capacity of blood which may be of particular importance to renal tubules which operate under near anaerobic conditions (20, 21). Further, decrements in hemoglobin may represent bleeding (subclinical or overt) which may reduce renal perfusion pressures and result in transfusions which may carry their own risk. Larger decrements in hemoglobin may also result from more extensive surgery resulting in greater systemic inflammation which may compound the risk of AKI. The extent to which decrements in hemoglobin or the precipitating factors are responsible for the observed increase in AKI is unclear. In either case, the measured decrement in hemoglobin is an easily and objectively quantified risk factor (unlike subclinical blood loss, systemic inflammation or renal perfusion pressure) and may serve as a valuable early indicator of postoperative morbidity. Finally, decrements in hemoglobin may precipitate studies with nephrotoxic agents (i.e. contrast) to investigate a source of bleeding. However, it seems unlikely that contrast administration could account for a greater than 4-fold increase in the risk of AKI.

We note, though, that larger decrements in hemoglobin were observed in generally healthier individuals with higher preoperative hemoglobin concentrations. Transfusion practices are often guided by threshold values for at risk groups (22). Larger decrements in hemoglobin/bleeding are presumably tolerated without transfusions when patients are healthier and have relatively higher preoperative hemoglobin values. Our results suggest that hemoglobin decrements might be considered in addition to absolute hemoglobin concentrations when considering when to transfuse surgical patients. That said, transfusions are themselves associated with adverse

outcomes and whether they provide net perioperative benefit remains to be determined in randomized studies that evaluate a constellation of potential adverse outcomes (23-26). An alternative strategy is aggressive prevention of bleeding. The use of agents such as tranexamic acid is currently under study in several areas of noncardiac surgery and may help mitigate decrements in hemoglobin concentration and consequently AKI.

Our study has several notable strengths. We were able to utilize all laboratory data on all patients to define categories of hemoglobin and change in hemoglobin, an approach not available to most administrative databases. Our data also included almost 2,500 events in over 30,000 surgeries allowing us to make precise estimates without the risk of overfitting our statistical models (27). Finally, we were able to characterize patients' comorbidities using the highly predictive Risk Stratification Index which incorporates a large number of administrative codes rather than relying on our limited ability to correctly select coded comorbidities that might be associated with perioperative hemoglobin, changes in hemoglobin, and AKI.

Our results suggest that preoperative hemoglobin in patients having elective surgery may be a rational therapeutic target. However, we cannot make causal inferences from observational data and certainly cannot predict from our analysis whether therapies such as erythropoiesis stimulating agents, autologous donation, or other transfusion strategies will reduce mortality.

Our results are from a single center with a high-acuity population which may limit generalizability. But although the details may vary from center-to-center, it seems likely that our risk-adjusted associations will prove generally applicable across centers, especially given their consistency with studies in patients having cardiac surgery (9).

Only one third of all surgeries were eligible for our study, with many excluded for lack of laboratory data. Patients who did not have hemoglobin or creatinine measured preoperatively or postoperatively (most of whom had ambulatory surgery) were presumably at lower risk of postoperative morbidity than those who had measurements. While it seems likely that the relative associations are largely preserved, they are probably of little practical consequence given the low absolute rate of AKI in patients undergoing ambulatory surgery.

A final limitation is that our study population was restricted to patients with well-preserved preoperative kidney function. However, chronic kidney disease appears to be a risk multiplier for AKI. It is therefore likely that the associations between perioperative hemoglobin and AKI are preserved or even greater in patients with chronic kidney disease.

In summary, even slight reductions in preoperative hemoglobin concentrations and small decrements in hemoglobin are strongly associated with AKI in patients undergoing noncardiac surgery. Whether intervening to improve or maintain perioperative hemoglobin concentration reduces postoperative mortality remains unknown. Furthermore, liberal transfusion strategies and/or the use of erythropoiesis stimulating agents would improve perioperative hemoglobin, but may be associated with net harm (28, 29). Alternatively, strategies to mitigate intraoperative and early postoperative blood loss such as reversal of coagulant deficiencies or changes in preoperative anticoagulant/antiplatelet use may be useful to reduce the early decrement in hemoglobin. Further research targeting perioperative hemoglobin management is clearly needed given the volume of noncardiac surgery globally, the frequency of preoperative anemia, the large decrements in hemoglobin that commonly accompany major surgery, and the frequency of AKI and its serious implications for patient outcomes and health care costs.

## **Contributions**

Michael Walsh originated the study, designed the overall study, conducted the study, analyzed the data, and wrote the first draft of the manuscript and completed subsequent revisions after critical debate with the coauthors.

Amit X. Garg helped design and conduct the study, interpret the data, and write critical revisions of the manuscript.

P.J. Devereaux helped design and conduct the study, interpret the data, and write critical revisions of the manuscript.

Maged Argalious helped interpret the data, and write critical revisions of the manuscript.

Hooman Honar helped interpret the data, and write critical revisions of the manuscript.

Daniel I. Sessler helped design and conduct the study, interpret the data, and write critical revisions of the manuscript.

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Table 1. Characteristics of included patients.

|   | <b>No AKI<br/>N=30,852</b> | <b>AKI<br/>N=2,478</b> | <b>Standardized<br/>Difference</b> |
|---|----------------------------|------------------------|------------------------------------|
| <b>Age, mean years (SD)</b>   | 55.6 (15.6)                | 59.7 (14.6)            | 27.0                               |
| <b>Female, n (%)</b>  | 15,924 (51.6%)             | 912 (36.8%)            | -30.1                              |
| <b>ASA Class, n (%)</b>   |                            |                        |                                    |
| <b>I</b>  | 607 (2.0)                  | 16 (0.6)               | 12.3                               |
| <b>II</b>   | 12,673 (41.1)              | 575 (23.2)             | 39.0                               |
| <b>III</b>  | 15,426 (50.0)              | 1,343 (54.2)           | -8.0                               |
| <b>IV</b>   | 2,074 (6.7)                | 529 (21.4)             | -43.3                              |
| <b>V</b>  | 53 (0.2)                   | 14 (0.6)               | -6.3                               |
| <b>30-Day Mortality RSI, mean<br/>score (SD)</b>  | -0.3 (1.15)                | 0.83 (1.42)            | 66.1                               |
| <b>Diabetes Mellitus, n (%)</b>   | 474 (1.5%)                 | 60 (2.4%)              | -6.5                               |
| <b>History of MI, n (%)</b>   | 1231 (4.0%)                | 129 (5.2%)             | -5.7                               |
| <b>History of CHF, n (%)</b>  | 916 (3.0%)                 | 185 (7.5%)             | -20.3                              |
| <b>History of PVD, n (%)</b>  | 1135 (3.7%)                | 219 (8.8%)             | -21.2                              |
| <b>History of Stroke, n (%)</b>   | 1519 (4.9%)                | 94 (3.8%)              | 5.4                                |
| <b>Preoperative Hemoglobin, mean<br/>g/dL (SD)</b>  | 13.1 (2.0)                 | 12.3 (2.3)             | -36.0                              |
| <b>Estimated GFR, median<br/>ml/min/1.73m<sup>2</sup> (25<sup>th</sup> to 75<sup>th</sup><br/>percentile)</b> | 87 (75 to 103)             | 85 (72 to 103)         | -5.0                               |
| <b>Emergency Procedure, n (%)</b>   | 1802 (5.8%)                | 365 (14.7%)            | 29.7                               |
| <b>Estimated Blood Loss, median<br/>mL (25<sup>th</sup> to 75<sup>th</sup> percentile)</b>                    | 200 (100 to 400)           | 390 (150 to 900)       | 45.0                               |
| <b>Amount Transfused, median mL<br/>(25<sup>th</sup> to 75<sup>th</sup> percentile)</b>                       | 0 (0 to 0)                 | 0 (0 to 320)           | 44.8                               |
| <b>Case Duration, median hours<br/>(25<sup>th</sup> to 75<sup>th</sup> percentile)</b>                        | 4.0 (2.8 to 5.3)           | 4.5 (3.0 to 6.6)       | 25.4                               |

Table 2. Patient characteristics for each preoperative hemoglobin range.

|  | <b>Preoperative Hemoglobin (g/dL)</b> |                      |                     |                     |
|--|---------------------------------------|----------------------|---------------------|---------------------|
|  | <b>&gt;12.0</b>                       | <b>10.1 to 12.0</b>  | <b>8.1 to 10.0</b>  | <b>&lt;8.1</b>      |
|  | <b>N=23,764</b>                       | <b>N=6,173</b>       | <b>N=2,997</b>      | <b>N=396</b>        |
| <b>Age, mean years (SD)</b>  | 55.7 (15.0)                           | 56.4 (16.8)          | 56.4 (16.8)         | 53.5 (16.4)         |
| <b>Female, n (%)</b>   | 11,072 (46.6%)                        | 3935 (63.7%)         | 1632 (54.4%)        | 197 (49.7%)         |
| <b>RSI, median score<br/>(25<sup>th</sup> to 75<sup>th</sup> percentile)</b>                 | -0.09 (-0.72 to 0.28)                 | 0.26 (-0.21 to 1.12) | 0.85 (0.19 to 1.79) | 1.14 (0.48 to 2.05) |
| <b>Emergency Procedure, n (%)</b>  | 849 (3.6%)                            | 621 (10.1%)          | 540 (18.0%)         | 157 (39.6%)         |
| <b>EBL, median mL<br/>(25<sup>th</sup> to 75<sup>th</sup> percentile)</b>                    | 200 (100 to 450)                      | 200 (100 to 500)     | 200 (50 to 400)     | 200 (75 to 850)     |
| <b>Volume of Transfusions, median mL<br/>(25<sup>th</sup> to 75<sup>th</sup> percentile)</b> | 0 (0 to 0)                            | 0 (0 to 0)           | 0 (0 to 360)        | 320 (0 to 885)      |

Table 3. Patient characteristics for each degree of decrement in hemoglobin.

|  | <b>Decrement in Hemoglobin in 24 hours Postoperatively (g/dL)</b> |                         |                         |                        |                         |                          |
|--|---|-------------------------|-------------------------|------------------------|-------------------------|--------------------------|
|  | <b>None</b>   | <b>0.1 to 1</b>         | <b>1.1 to 2.0</b>       | <b>2.1 to 3.0</b>      | <b>3.1 to 4.0</b>       | <b>&gt;4.0</b>           |
|  | <b>N=1,144</b>  | <b>N=2,809</b>          | <b>N=5,372</b>          | <b>N=6,877</b>         | <b>N=6,320</b>          | <b>N=10,808</b>          |
| <b>Age, mean years (SD)</b>  | 56.1 (16.8)   | 55.4 (16.7)             | 54.2 (16.2)             | 54.6 (16.0)            | 55.9 (15.4)             | 57.6 (14.3)              |
| <b>Female, n (%)</b>   | 569 (49.7%)   | 1451 (51.7%)            | 2827 (52.6%)            | 3796 (55.2%)           | 3404 (53.9%)            | 4789 (44.3%)             |
| <b>RSI, median score (25<sup>th</sup> to 75<sup>th</sup> percentile)</b>                 | 0.81<br>(0.05 to 1.79)  | 0.40<br>(-0.01 to 1.26) | 0.05<br>(-0.19 to 0.83) | 0.0<br>(-0.40 to 0.50) | 0.00<br>(-0.63 to 0.35) | -0.18<br>(-1.07 to 0.34) |
| <b>Emergency Procedure, n (%)</b>  | 264 (23.1%)   | 345 (12.3%)             | 492 (9.2%)              | 434 (6.3%)             | 288 (4.6%)              | 344 (3.2%)               |
| <b>Preoperative Hemoglobin (g/dL)</b>  | 9.4 (2.0)   | 10.9 (2.0)              | 12.1 (2.0)              | 13.0 (1.8)             | 13.4 (1.6)              | 14.2 (1.4)               |
| <b>EBL, median mL (25<sup>th</sup> to 75<sup>th</sup> percentile)</b>                    | 100<br>(50 to 400)  | 100<br>(50 to 200)      | 100<br>(50 to 200)      | 150<br>(75 to 300)     | 200<br>(100 to 400)     | 400<br>(200 to 800)      |
| <b>Volume of Transfusions, median mL (25<sup>th</sup> to 75<sup>th</sup> percentile)</b> | 0 (0 to 630)  | 0 (0 to 0)              | 0 (0 to 0)              | 0 (0 to 0)             | 0 (0 to 0)              | 0 (0 to 0)               |

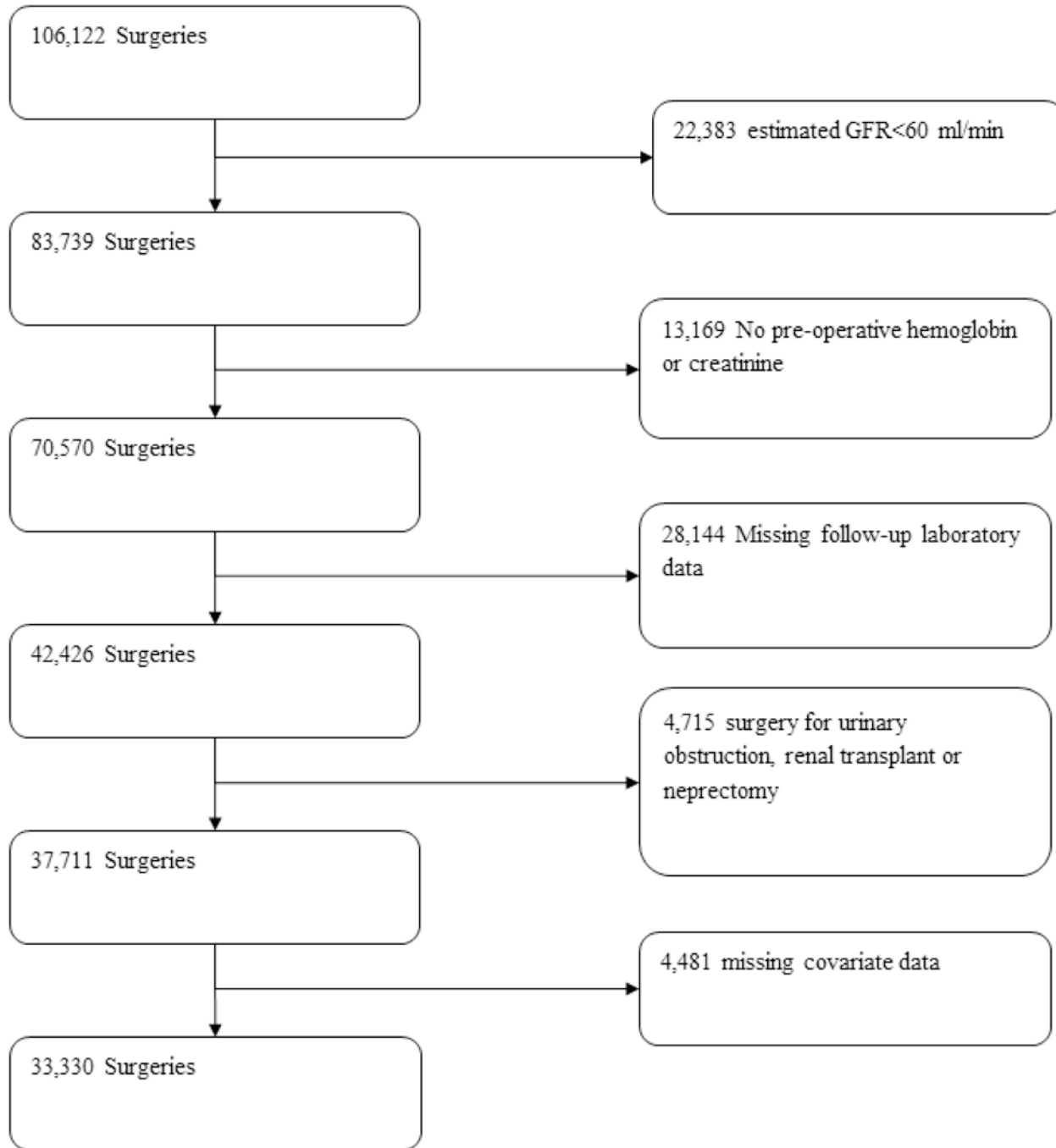


Figure 1. Flow of patients in study.



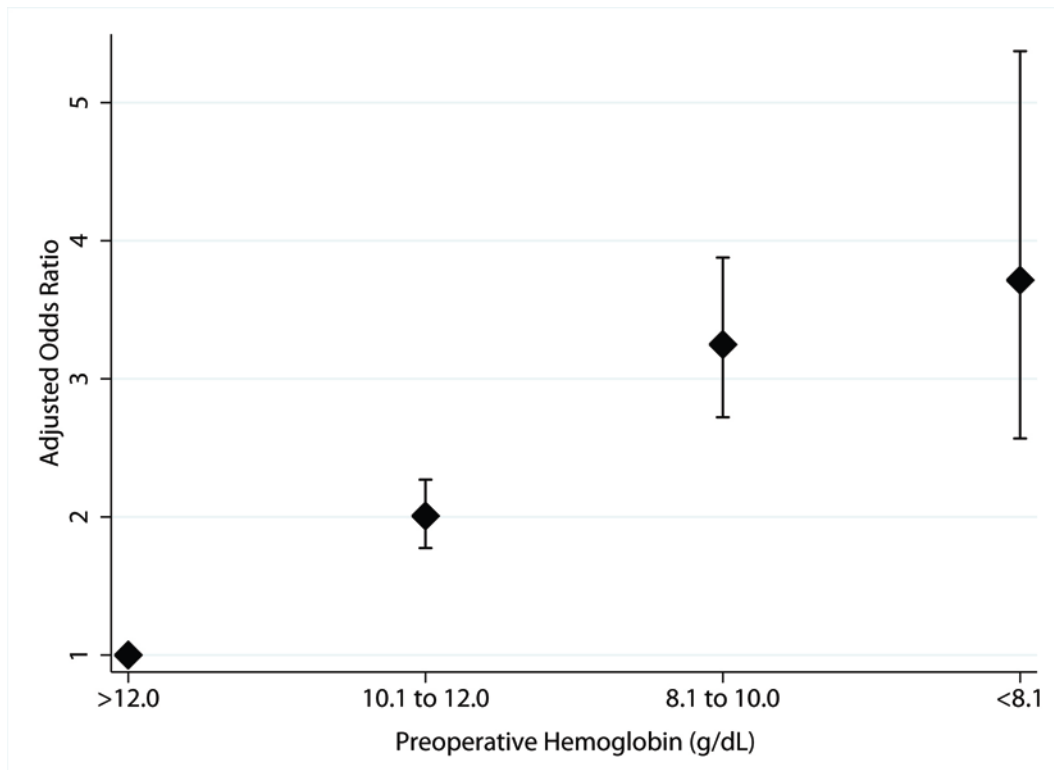


Figure 2. Adjusted odds ratio for each category of preoperative hemoglobin in patients undergoing noncardiac surgery. Estimates were adjusted for age, sex, Risk Stratification Index for 30 day mortality, type of surgery, estimated blood loss, red cell transfusion volume, and postoperative decrement in hemoglobin.

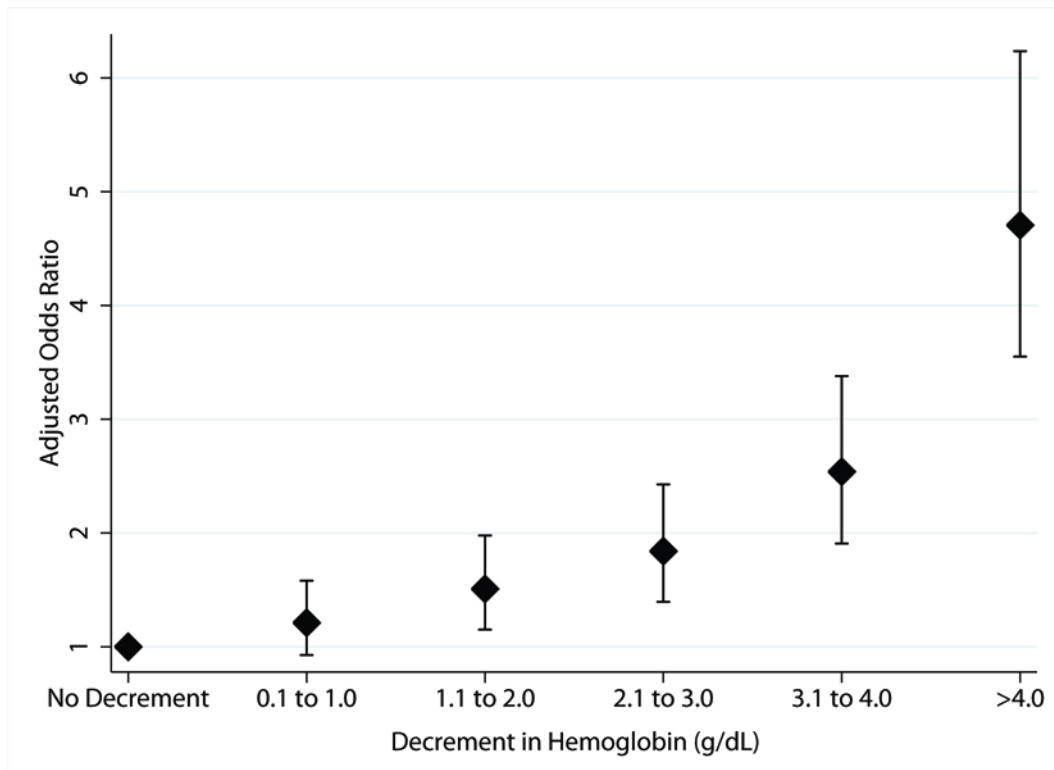


Figure 3. Adjusted odds ratio for each category of decrement in hemoglobin within 24 hours after noncardiac surgery. Estimates were adjusted for age, sex, Risk Stratification Index for 30 day mortality, type of surgery, estimated blood loss, red cell transfusion volume, and preoperative hemoglobin.

Supplementary Table 1. Estimates of association between preoperative hemoglobin concentration and change in hemoglobin concentration with acute kidney injury in sensitivity analyses in which the endpoint is alternatively defined.

|                                       | <b>Adjusted OR (95% CI)</b> |                      |                                     |
|---------------------------------------|-----------------------------|----------------------|-------------------------------------|
|                                       | <b>Moderate AKI</b>         | <b>Severe AKI</b>    | <b>AKI within 3 Days of Surgery</b> |
| <b>Preoperative Hemoglobin (g/dL)</b> |                             |                      |                                     |
| >12.0                                 | Referent                    | Referent             | Referent                            |
| 10.1 to 12.0                          | 2.00 (1.59 to 2.52)         | 1.84 (1.26 to 2.69)  | 2.03 (1.78 to 2.32)                 |
| 8.1 to 10.0                           | 2.87 (2.07 to 3.96)         | 2.93 (1.76 to 4.87)  | 3.03 (2.49 to 3.68)                 |
| <8.1                                  | 3.52 (1.89 to 6.54)         | 2.24 (0.62 to 8.08)  | 2.80 (1.85 to 4.22)                 |
| <b>Change in Hemoglobin (g/dL)</b>    |                             |                      |                                     |
| No Decrement                          | Referent                    | Referent             | Referent                            |
| 0.1 to 1.0                            | 0.97 (0.60 to 1.55)         | 1.60 (0.65 to 3.94)  | 1.03 (0.77 to 1.40)                 |
| 1.1 to 2.0                            | 1.72 (1.10 to 2.68)         | 2.06 (0.82 to 5.18)  | 1.44 (1.07 to 1.93)                 |
| 2.1 to 3.0                            | 2.44 (1.55 to 3.84)         | 3.94 (1.60 to 9.73)  | 1.73 (1.27 to 2.35)                 |
| 3.1 to 4.0                            | 2.72 (1.68 to 4.38)         | 4.03 (1.57 to 10.31) | 2.49 (1.82 to 3.41)                 |
| >4.0                                  | 5.22 (3.30 to 8.26)         | 7.32 (2.95 to 18.19) | 4.79 (3.52 to 6.52)                 |

Supplementary Table 2. Estimates of association between preoperative hemoglobin concentration and change in hemoglobin concentration with acute kidney injury in sensitivity analyses in which the type of surgery is restricted.

|                                       | <b>Adjusted OR (95% CI)</b> |                                 |                             |                                |                              |
|---------------------------------------|-----------------------------|---------------------------------|-----------------------------|--------------------------------|------------------------------|
|                                       | <b>Last Operation Only</b>  | <b>Elective Procedures Only</b> | <b>General Surgery Only</b> | <b>Orthopedic Surgery Only</b> | <b>Vascular Surgery Only</b> |
| <b>Preoperative Hemoglobin (g/dL)</b> |                             |                                 |                             |                                |                              |
| >12.0                                 | Referent                    | Referent                        | Referent                    | Referent                       | Referent                     |
| 10.1 to 12.0                          | 2.03 (1.74 to 2.38)         | 2.41 (2.14 to 2.72)             | 1.99 (1.63 to 2.42)         | 1.81 (1.39 to 2.35)            | 1.63 (1.12 to 2.38)          |
| 8.1 to 10.0                           | 3.15 (2.50 to 3.97)         | 4.62 (3.88 to 5.51)             | 3.92 (2.96 to 5.19)         | 3.09 (2.08 to 4.58)            | 2.41 (1.44 to 4.02)          |
| <8.1                                  | 4.12 (2.54 to 6.70)         | 5.45 (3.74 to 7.93)             | 4.50 (2.45 to 8.28)         | 4.24 (1.73 to 10.4)            | 1.50 (0.53 to 4.22)          |
| <b>Change in Hemoglobin (g/dL)</b>    |                             |                                 |                             |                                |                              |
| No Decrement                          | Referent                    | Referent                        | Referent                    | Referent                       | Referent                     |
| 0.1 to 1.0                            | 1.09 (0.78 to 1.54)         | 1.22 (0.94 to 1.60)             | 1.62 (1.01 to 2.61)         | 1.32 (0.67 to 2.60)            | 1.03 (0.52 to 2.04)          |
| 1.1 to 2.0                            | 1.34 (0.95 to 1.90)         | 1.51 (1.15 to 1.98)             | 2.41 (1.50 to 3.85)         | 1.30 (0.62 to 2.70)            | 0.89 (0.44 to 1.80)          |
| 2.1 to 3.0                            | 1.59 (1.11 to 2.27)         | 1.82 (1.37 to 2.41)             | 2.49 (1.53 to 4.05)         | 2.12 (1.04 to 4.37)            | 1.58 (0.78 to 3.23)          |
| 3.1 to 4.0                            | 2.10 (1.46 to 3.02)         | 2.49 (1.86 to 3.33)             | 4.00 (2.43 to 6.57)         | 2.65 (1.27 to 5.53)            | 1.81 (0.85 to 3.82)          |
| >4.0                                  | 3.92 (2.74 to 5.62)         | 4.60 (3.45 to 6.12)             | 7.74 (4.75 to 12.6)         | 4.11 (1.98 to 8.56)            | 3.23 (1.54 to 6.78)          |

Supplementary Table 3. Estimates of association between preoperative hemoglobin concentration and change in hemoglobin concentration with acute kidney injury in sensitivity analyses in which the method of adjustment is altered.

|                                       | <b>Adjusted OR (95% CI)</b>            |  |
|---------------------------------------|--|--|
|                                       | <b>Individual Comorbidity Adjusted</b> | <b>Charlson Comorbidity Score Adjusted</b> |
| <b>Preoperative Hemoglobin (g/dL)</b> |  |  |
| >12.0                                 | Referent                               | Referent                                   |
| 10.1 to 12.0                          | 2.41 (2.14 to 2.72)                    | 2.48 (2.20 to 2.80)                        |
| 8.1 to 10.0                           | 4.62 (3.88 to 5.51)                    | 4.78 (4.03 to 5.68)                        |
| <8.1                                  | 5.45 (3.74 to 7.93)                    | 5.52 (3.80 to 8.03)                        |
| <b>Change in Hemoglobin (g/dL)</b>    |  |  |
| No Decrement                          | Referent                               | Referent                                   |
| 0.1 to 1.0                            | 1.22 (0.94 to 1.60)                    | 1.25 (0.95 to 1.63)                        |
| 1.1 to 2.0                            | 1.51 (1.15 to 1.98)                    | 1.51 (1.15 to 1.99)                        |
| 2.1 to 3.0                            | 1.82 (1.37 to 2.41)                    | 1.82 (1.38 to 2.41)                        |
| 3.1 to 4.0                            | 2.49 (1.86 to 3.33)                    | 2.48 (1.87 to 3.31)                        |
| >4.0                                  | 4.60 (3.45 to 6.12)                    | 4.56 (3.44 to 6.04)                        |

## CHAPTER 4

Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: towards an empirical definition of hypotension. *Anesthesiology*. 2013. 119 (Accepted)

**RELATIONSHIP BETWEEN INTRAOPERATIVE MEAN ARTERIAL PRESSURE  
AND CLINICAL OUTCOMES AFTER NONCARDIAC SURGERY: TOWARDS AN  
EMPIRICAL DEFINITION OF HYPOTENSION**

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## **Abstract**

**Background:** Intraoperative hypotension may contribute to postoperative acute kidney injury (AKI) and myocardial injury but what blood pressures are unsafe is unclear. We evaluated the association between the intraoperative mean arterial pressure (MAP) and the risk of AKI and myocardial injury.

**Methods:** We obtained perioperative data for 33,330 noncardiac surgeries at the Cleveland Clinic, Ohio, USA. We evaluated the association between intraoperative MAP from <55 to 75 mmHg and postoperative AKI and myocardial injury to determine the threshold of MAP where risk is increased. We then evaluated the association between the duration below this threshold and our outcomes adjusting for potential confounding variables.

**Results:** AKI and myocardial injury developed in 2,478 (7.4%) and 770 (2.3%) surgeries, respectively. The MAP threshold where the risk for both outcomes increased was below 55 mmHg. Compared to never developing a MAP <55 mmHg, those with a MAP < 55 mmHg for 1 to 5, 6 to 10, 11 to 20 and >20 minutes had graded increases in their risk of the two outcomes [AKI: 1.18 (95% confidence interval [CI] 1.06 to 1.31), 1.19 (1.03 to 1.39), 1.32 (1.11 to 1.56) and 1.51 (1.24 to 1.84), respectively. Myocardial injury: 1.30 (1.06 to 1.58), 1.47 (1.13 to 1.93), 1.79 (1.33 to 2.39) and 1.82 (1.31 to 2.55), respectively].

**Conclusions:** Even short durations of an intraoperative MAP <55 mmHg are associated with AKI and myocardial injury. Randomized trials are required to determine whether outcomes improve with interventions that maintain an intraoperative MAP of at least 55 mmHg.



## **Introduction**

Intraoperative hypotension has the potential to cause an ischemia-reperfusion injury which may manifest as dysfunction of any vital organ. Among the most sensitive organs to be affected in this way are the kidneys and the heart. However, blood pressures that constitute hypotension and provoke acute kidney and myocardial injury remain unclear.

Acute kidney injury (AKI), a sudden reduction in kidney function, occurs in approximately 7% of hospitalized patients and 7.5% of patients that undergo noncardiac surgery.(1, 2) Small changes in serum creatinine, the most commonly used marker of kidney function, are increasingly recognized as strong independent risk factors for short- and long-term mortality (3, 4) and more costly health care after surgery.(2, 5) Similarly, myocardial injury after noncardiac surgery manifests as an acute elevation in the concentration of cardiac biomarkers and occurs in 11.6% of noncardiac surgeries.(6) Myocardial injury after noncardiac surgery is also associated with a strong, independent risk of death after surgery, even with only small biomarker elevations.(6)

Ischemia reperfusion injury due to hypotension may substantially contribute to postoperative AKI and myocardial injury.(7) As such, optimizing intraoperative hemodynamics may mitigate or prevent both complications. This theory is supported by a systematic reviews of interventions to prevent perioperative AKI that demonstrates maneuvers to prevent hypotension reduced the incidence of AKI (8) as well as data from the Perioperative Ischemia Evaluation Trial (POISE) which demonstrated hypotension was the most responsible factor for postoperative death (of which, the majority were vascular).

Although hypotension is recognized as an important factor in the development of postoperative complications, there is uncertainty as to how to optimally define intraoperative hypotension. A systematic review of intraoperative hypotension identified 140 definitions used in 130 studies.<sup>(9)</sup> Most of these definitions were not empirically derived and each definition's association with clinical outcomes was explored in relatively few and/or small studies. We therefore studied patients who had noncardiac surgery to determine what durations of various levels of mean arterial pressure (MAP) are associated with AKI and myocardial injury to establish an empirical definition of prognostically important intraoperative hypotension.

## **Materials and Methods**

*Study Design:* We undertook an observational study using data from the Cleveland Clinic Perioperative Health Documentation System, an electronic medical record-based registry of noncardiac surgery patients who had surgery between January 6th, 2005 and September 21, 2010 at the Cleveland Clinic, Ohio, USA. Use of this de-identified registry for research was approved by the Cleveland Clinic Institutional Review Board.

*Patients:* Eligible patients had noncardiac surgery, stayed at least one night in hospital, and had a preoperative creatinine concentration measured and at least one postoperative creatinine. As chronic kidney disease may affect the interpretation and prognostic significance of absolute changes in serum creatinine and cardiac biomarkers, we excluded patients with chronic kidney disease, defined as an estimated preoperative glomerular filtration rate  $< 60 \text{ ml/min/1.73m}^2$ . Patients having urological procedures such as the relief of urinary obstruction, nephrectomy, or renal transplantation were also excluded due to their association with changes in creatinine independent of renal injury.

*Outcomes and Exposures:* We defined AKI according to changes in serum creatinine between preoperative and postoperative values. The preoperative creatinine was considered to be the concentration measured closest to the time of surgery. The postoperative value used was the highest concentration measured within 7 days after surgery. Consistent with the Acute Kidney Injury Network threshold, patients were considered to have AKI if the highest postoperative concentration was either >1.5-fold or >0.3 mg/dL greater than the preoperative concentration.(4) The small changes in creatinine utilized by this definition is independently associated with mortality in numerous studies.(10-13)

We defined myocardial injury as a postoperative cardiac enzyme concentration within 7 days of surgery that was greater than or equal to the suggested necrosis limit for troponin T and greater than the upper limit of normal for creatinine kinase MB. For a 4<sup>th</sup> generation troponin T assay (Roche Diagnostics, Mannheim, Germany) this was  $\geq 0.04 \mu\text{g/L}$  and for creatine kinase-MB  $\geq 8.8 \text{ ng/mL}$ . These definitions are consistent with the universal definition of myocardial infarction and data from a large international study of perioperative myocardial infarction. (6, 14) Rather than exclude patients who were otherwise eligible but did not have any cardiac enzymes measured, we assumed these patients did not have a myocardial injury and included them in all analyses.

As a secondary outcome we also examined the association between intraoperative blood pressure and the outcome of a postoperative cardiac complication as defined by the Agency for Healthcare Research and Quality using administrative codes for complications of surgical

procedures\*. This definition includes intraoperative and postoperative acute myocardial infarctions, heart failure and cardiac arrest.

*Intraoperative Blood Pressure:* The intraoperative mean arterial pressure (MAP) was recorded electronically for all cases directly into an electronic medical record. When an arterial catheter was used (44.5% of cases), MAP was recorded every one-to-two minutes. When non-invasive blood pressure monitoring was used, MAP was recorded from every two-to-five minutes. During minutes when no blood pressure was recorded or when a reading was marked as artifact by the attending anesthesiologist, the last non-artifact blood pressure was carried forward.

For each case we calculated the total number of minutes spent with a MAP <55 mmHg, <60 mmHg, <65 mmHg, <70 mmHg, and <75 mmHg. For each case we also calculated the number of minutes during which the MAP was <55 mmHg, 55 to 59 mmHg, 60 to 64 mmHg, 65 to 69 mmHg, 70 to 74 mmHg and  $\geq 75$  mmHg

*Other Exposures:* Patient's age and sex were determined from the registry. The Charlson Comorbidity Index and Risk Stratification Index for 30 day mortality, validated risk scores using administrative data codes, were calculated for all patients.(15, 16) Preoperative kidney function was characterized according to patient's estimated glomerular filtration rate using the 4-variable Modification of Diet in Renal Disease equation.(17) Preoperative hemoglobin was categorized according to the hemoglobin concentration taken closest to the time before surgery.

Intraoperative estimated blood loss, and transfusion of red blood cells (autologous and allogeneic) were recorded in the clinical database. We previously demonstrated that decrements in hemoglobin concentration in the first 24 hours after surgery are strongly associated with AKI

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\* <http://www.hcup-us.ahrq.gov/toolsoftware/ccs/> last accessed 28/10/2011.

so this parameter was also included in the model. Surgeries were classified according to the Agency for Healthcare Research and Quality descriptors and whether they were emergency or elective procedures.

### *Statistics*

Patient characteristics were calculated as mean (standard deviation [SD]), median (25<sup>th</sup> to 75<sup>th</sup> percentile), or frequency (%) as appropriate. Comparisons of patient characteristics between groups were made using analysis of variance for continuous data and the  $\chi^2$  test for frequency data.

We visually assessed the relationship between the total amount of time under each MAP threshold (<55 mmHg, <60 mmHg, <65 mmHg, <70 mmHg, and <75 mmHg) and each outcome using restricted cubic splines in a logistic regression model. For each threshold, risk appeared to initially substantially increase rapidly for each minute under the threshold for about ten minutes, followed by a less rapid risk increase thereafter. We therefore categorized patients as having spent 0 minutes, 1 to 5 minutes, 6 to 10 minutes, 11 to 20 minutes, or >20 minutes in each strata. We were concerned that the association between time spent under each threshold may be due to time spent well beneath that threshold rather than just under the threshold value (i.e. an association between time under a MAP of 65 mmHg may be due to time spent with a map <55 mmHg rather than the time spent with a MAP between 55 and 65 mmHg). We therefore conducted several further analyses to more accurately determine the blood pressure threshold that was most clinically relevant.

Using logistic regression we next explored whether the risk for each category was in fact driven by the lowest MAPs by: 1) calculating the risk of AKI and separately myocardial injury

associated with the amount of time each patient spent with a MAP in each strata (i.e. <55 mmHg, 55 to 59 mmHg, 60 to 64 mmHg, 65 to 69 mmHg, and 70 to 74 mmHg) while excluding patients with any time spent in lower blood pressure strata (i.e. only patients with a lowest blood pressure in a given strata or higher strata remained in the analysis); 2) calculating the risk of AKI and separately myocardial injury for the time spent in each blood pressure strata while adjusting for time spent in the other strata; and, 3) calculating separately the risk of AKI and myocardial injury by the lowest MAP during surgery irrespective of the amount of time at that blood pressure.

Based on these models, we then constructed final logistic models using the amount of time spent with a MAP below the highest threshold MAP that was predictive of one of the outcomes categorized as 0 minutes, 1 to 5 minutes, 6 to 10 minutes, 11 to 20 minutes or >20 minutes below that threshold. The final model was adjusted for age, sex, the Charlson Comorbidity Index, the volume of red cells transfused intraoperatively, estimated blood loss, preoperative hemoglobin, decrement in hemoglobin within 24 hours of surgery and the type of surgery performed. We *a priori* tested for interactions between duration of a MAP below threshold and emergency surgery status and decrement in hemoglobin concentration and dropped these interaction terms when they were found to be non-significant. We accommodated the correlation of multiple surgeries at different times for an individual by calculating estimated standard errors adjusted for intragroup correlations using clustered sandwich estimators.(18, 19) We reported adjusted odds ratios (OR) and associated 95% confidence intervals (CI) and p-values. We tested the trend of increasing risk with increasing time with a MAP <55 mmHg using the Cochran-Armitage test for trend. We set the criterion for statistical significance at  $p < 0.05$  for all tests.

We performed sensitivity analyses to assess the robustness of our findings. Sensitivity models were constructed as logistic regression identical to the final model above, except: 1) with the primary outcome AKI redefined on the basis of postoperative creatinine concentrations only up to 3 days postoperatively; 2) using severe AKI (3 fold rise in creatinine) as the outcome; 3) using the Risk Stratification Index rather than the Charlson Comorbidity Index; 4) restricting the analysis of myocardial injury to only those patients with a troponin T measured; 5) adjusting for systolic blood pressure recorded in the Preoperative Clinic for patients in whom this was recorded; 6) adjusting for the duration of the surgery; 7) using multiple imputation of missing covariate data, and; 8) utilizing only one surgery per patient (the most recent surgery).

We completed all analyses using Stata version 11 MP (College Station, TX).

## **Results**

Figure 1 reports the patient flow chart. In total, we included 33,330 surgeries performed in 27,381 patients in the analysis. Compared to patients in excluded surgeries, the included patients were younger, had lower American Society of Anesthesiology Status Scores and less comorbidity but had longer operations and postoperative lengths of stay (data not shown). Acute kidney injury occurred after 2,477 surgeries (7.4%) of which 2,043 (82.4%) occurred within 3 days of surgery. Myocardial injury was documented in 770 surgeries (2.3%) and 926 (2.8%) had a cardiac complication after surgery. Five-hundred and six patients (1.5%) died within 30 days of surgery.

*Defining Hypotension:* Point estimates for the risk of AKI and myocardial injury minimally increased with the amount of time spent under each MAP threshold, and was pronounced for any time spent with a MAP <60 mmHg (Figure 2). The risks appeared non-linear in each model

( $p < 0.001$  in every model) with risk increasing markedly during the first 10 minutes, but at a slower rate thereafter. In multivariable spline models in which we controlled for the amount of time spent in each MAP category, the risk of AKI appeared greater for time spent with a MAP  $< 60$  mmHg and the risk of myocardial injury appeared greater only for a MAP  $< 55$  mmHg (Figure 3).

We then performed analyses in which we excluded patients who had any time in the lowest MAP category (i.e. MAP  $< 55$  mmHg for any duration). These analyses were performed to ensure that correlations between time below a MAP of 55 mmHg and time spent in other blood pressure strata did not cause us to miss significant associations between a MAP  $> 55$  mmHg and our outcomes. In the 18,989 eligible surgeries, there was a modest but statistically significant risk of AKI for a MAP of 55 to 59 mmHg lasting longer than 5 minutes (adjusted OR 1.65, 95% CI 1.21 to 2.25;  $p = 0.002$ ). However, there was no additional risk in the time categories  $> 10$  minutes for a MAP of 55 to 59 mmHg and there was no risk of AKI in higher MAP categories (i.e. MAP  $\geq 60$  mmHg). There was no risk of myocardial injury associated with any MAP range or duration once periods of MAP  $< 55$  mmHg were excluded.

Finally, we performed univariable spline analyses in which the lowest MAP for the surgery was the predictor of AKI and myocardial injury. The risk of both AKI and myocardial injury appeared to increase substantially at MAPs below 55 to 60 mmHg (Figure 4).

Based on these analyses, for the final models we categorized patients by the amount of time they spent with a MAP  $< 55$  mmHg as 0 minutes, 1 to 5 minutes, 6 to 10 minutes, 11 to 20 minutes, and  $> 20$  minutes.



Patients with different amounts of time with a MAP <55 mmHg differed significantly with respect to most characteristics (Table 1). However, only emergency procedures, preoperative hemoglobin and intraoperative estimated blood loss appeared to have a clear progression as time with a MAP < 55 mmHg increased (i.e. more emergency procedures, lower hemoglobin and larger estimated blood loss).

*Risk of AKI, Myocardial Injury, cardiac complications and 30-day mortality with Hypotension:*

In our fully adjusted model, we observed an independent, graded relationship between the length of time spent with a MAP <55 mmHg and AKI, and cardiac complications (Table 2 and Figure 4). A similar magnitude of association was seen for myocardial injury although the relationship was less graded as time with a MAP < 55 mmHg increased. Compared to patients who spent no time with a MAP <55 mmHg, those with the longest periods of a MAP <55 mmHg had approximately a 1.5-fold increased risk of AKI or myocardial injury and an almost 2-fold increased risk of a cardiac complication. The test for trend across durations of MAP <55 mmHg was  $p < 0.001$  for all three outcomes. These relationships were qualitatively preserved across sensitivity analyses (Tables 3 and 4). Of note, although the absolute risk of AKI and myocardial injury was increased in patients in the highest quartile of preoperative clinic blood pressures, the relative effect of each period of time spent with a MAP under 55 mmHg was preserved across all baseline blood pressures and there was no evidence of interaction between preoperative blood pressure and time with a MAP <55 mmHg ( $p > 0.1$  for all interaction groups).

As time increased with a MAP <55 mmHg there was a trend to a higher risk of death by 30 days after surgery (test for trend  $p < 0.001$ ). However, 30-day mortality was only significantly associated with >20 minutes of MAP <55 mmHg (Table 2).

## Discussion

In this large cohort with detailed intraoperative blood pressures, we found that MAP <55 mmHg was associated with the development of AKI, myocardial injury, and cardiac complications. Furthermore, we found that risk escalates rapidly and there does not appear to be any safe duration of a MAP <55 mmHg. This finding is important because AKI and myocardial injury are common, strongly associated with morbidity and mortality, and costly. Unlike baseline patient characteristics which are rarely modifiable, intraoperative MAP can usually be controlled and may thus be an important therapeutic target. Understanding what arterial pressures are associated with ischemic damage will help guide interventional studies.

Our study differs from many others in that we account for each minute spent with a MAP <55 mmHg which appears to be an especially sensitive method of determining the effect of MAP on the kidneys and heart. Our findings that a MAP <55 mmHg is strongly associated with renal and cardiac risk are nonetheless broadly consistent with previous work. Classic physiology experiments, for example, suggested that renal blood flow is maintained (autoregulated) down to a MAP of 50-60 mmHg.(20, 21) However, this inference is extrapolated from experiments in healthy animals.

In critically ill patients, one study of 217 patients found a MAP of up to 82 mmHg may be required to prevent AKI.(22) Similarly, a study of 31 critically ill patients, demonstrated periods with a systolic blood pressure < 90 mmHg for at least 30 minutes were associated with higher levels of cardiac enzymes. However, critically ill patients may have more confounding influences than the generally healthier population we studied. One study of patients undergoing noncardiac surgery found that in those that were at high risk for AKI, periods of a MAP

<60 mmHg were more common in those that developed AKI than those who did not.(23)

Further, using classification and regression tree analysis, Bijker and colleagues, found a MAP <50 mmHg had the largest independent association with death in their study of 1,705 patients undergoing noncardiac surgery.(24) However, there were only 88 deaths in the study and it was therefore likely underpowered to show an association between a low intraoperative MAP and death at 1-year. Another study found that periods of clinically significant hypotension corresponding to a systolic blood pressure <90 mmHg requiring treatment were a strong determinant of postoperative death; however, this study did not assess the association between hypotension and myocardial injury or hypotension and AKI.(7) Our study extends previous work and informs the degree and duration of low MAP that is clinically important, and suggests that hypotension is independent of other risk factors in a diverse cohort of noncardiac surgical patients. Further, our cohort is among the largest and therefore capable of detecting modest effects of low blood pressure on clinical events that occur close to the time of surgery.

Most studies examining risk factors for postoperative complications such as myocardial events and AKI concentrate on preoperative morbidity. Although preoperative patient characteristics allow us to appropriately stratify the risk of myocardial events and AKI, they provide few risk factors that are potentially modifiable. Intraoperative and early postoperative risk factors may improve risk stratification and provide important therapeutic targets. By understanding at what level of MAP ischemia-reperfusion injury becomes likely, it is possible to focus interventions on patients most likely to benefit. This is a promising target for intervention as shown in small trials of hemodynamic optimization.(8)

Our study has several notable strengths. We used electronically recorded blood pressures which were available on a minute-by-minute basis in 14,828 patients and every 2 to 5 minutes in the

remaining patients. These detailed records allowed us to characterize intraoperative hemodynamics in considerable detail. Our large sample size provided sufficient statistical power to fit a stable model despite numerous covariates, and thus detect even moderate associations between intraoperative blood pressures and AKI and myocardial injury. Our sample included a broad spectrum of patients in terms of surgical types and comorbidities, thereby making our findings generalizable. And finally, our results were consistent across numerous sensitivity analyses testing important assumptions related to our primary analysis.

An important limitation of our analysis is that observed associations could result from residual confounding. For example, we were not able to incorporate perioperative medication effects such as angiotensin converting enzyme inhibitors or angiotensin receptor antagonists which may be important in the pathogenesis of both intraoperative hypotension and AKI.(25, 26) While the observed association may not be causal, and the treatments used for low MAP may account for some of the observed associations, there is a strong biologic plausibility for the effect we saw and it was consistent across all analyses. The association between time spent with a MAP <55 mmHg and both AKI and myocardial injury were of moderate size. While it is probable that residual confounding accounts for at least part of the observed associations, the fact that our findings were consistent across outcomes and sensitivity analyses suggests an underlying biologic effect. Our study was only from a single centre, which may reduce the generalizability, although we would expect that a physiologic parameter like MAP should have consistent effects across centres. We also need to be cautious applying our findings to groups of patients and to outcomes not included in our study. As we excluded patients with abnormal renal function preoperatively and patients that did not have postoperative serum creatinine measurements (and who were therefore likely healthier and/or underwent less complicated procedures) our empiric

definition of hypotension needs to be studied in these patients. Similarly, we lack data on stroke outcomes. Importantly, our results provide information on what the average tolerated MAP may be in patients having noncardiac surgery. Individuals tolerated limits will vary. But currently, there are not specific data indicating how thresholds may vary or that would allow clinicians to determine the threshold in a specific patient. Finally, we have not yet validated our finding in an independent cohort.

In summary, we found that time spent with a MAP <55 mmHg during noncardiac surgery is independently associated with an increased risk of AKI and myocardial injury. Notably, any amount of time at a MAP <55 mmHg was associated with adverse outcomes. Further research is required to determine whether interventions to prevent and rapidly treat intraoperative hypotension ameliorate the risk of AKI and myocardial injury in patients having noncardiac surgery.

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### **Contributorship Statement**

Michael Walsh contributed significantly to the study's concept and design, data analysis, and interpretation of the data. He wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

PJ Devereaux contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

Amit X. Garg contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

Andrea Kurz contributed to the study's concept, data collection, and interpretation of the data. She provided critical revisions and gave final approval of the submitted manuscript.

Alparslan Turan contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

Reitze N. Rodseth contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

Jacek Cywinski contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

Lehana Thabane contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

Daniel I. Sessler contributed to the study's concept, data collection, and interpretation of the data. He provided critical revisions and gave final approval of the submitted manuscript.

Table 1. Patient characteristics by operative time spent with a Mean Arterial Pressure (MAP) &lt; 55 mmHg.

|                                     | MAP < 55 mmHg     |                           |                            |                             |                        | p-value |
|-------------------------------------|-------------------|---------------------------|----------------------------|-----------------------------|------------------------|---------|
|                                     | Never<br>n=18,989 | 1 to 5 minutes<br>n=8,266 | 6 to 10 minutes<br>n=2,856 | 11 to 20 minutes<br>n=1,987 | >20 minutes<br>n=1,232 |         |
| <b>Age, years *</b>                 | 54.8 (15.3)       | 57.3 (15.5)               | 57.9 (15.6)                | 56.1 (16.6)                 | 55.7 (16.7)            | <0.001  |
| <b>Female, n (%)</b>                | 9,519 (50.0)      | 4,102 (49.6)              | 1,516 (53.1)               | 1,064 (53.5)                | 635 (51.5)             | <0.001  |
| <b>Emergency Procedure, n (%)</b>   | 1063 (5.6)        | 579 (7.0)                 | 193 (6.8)                  | 188 (9.5)                   | 144 (11.7)             | <0.001  |
| <b>ASA Score, n (%)</b>             |                   |                           |                            |                             |                        |         |
| <b>I</b>                            | 418 (2.2)         | 121 (1.4)                 | 42 (1.5)                   | 26 (1.3)                    | 16 (1.3)               | <0.001  |
| <b>II</b>                           | 8,262 (43.6)      | 2,965 (35.9)              | 1,022 (35.8)               | 652 (32.8)                  | 347 (28.2)             |         |
| <b>III</b>                          | 9,120 (48.1)      | 4,387 (53.1)              | 1,521 (53.3)               | 1,087 (54.7)                | 654 (53.1)             |         |
| <b>IV</b>                           | 1,143 (6.0)       | 767 (9.3)                 | 264 (9.2)                  | 218 (11.0)                  | 211 (17.1)             |         |
| <b>V</b>                            | 28 (0.1)          | 24 (0.3)                  | 7 (0.2)                    | 4 (0.2)                     | 4 (0.3)                |         |
| <b>Charlson Index †</b>             | 0 (0 to 2)        | 1 (0 to 2)                | 1 (0 to 2)                 | 1 (0 to 2)                  | 1 (0 to 2)             | <0.001  |
| <b>Diabetes Mellitus, n (%)</b>     | 2,424 (12.8)      | 1,056 (12.8)              | 384 (13.4)                 | 246 (12.4)                  | 156 (12.7)             | 0.71    |
| <b>Myocardial Infarction, n (%)</b> | 699 (3.7)         | 387 (4.7)                 | 143 (5.0)                  | 88 (4.4)                    | 43 (3.5)               | <0.001  |

|  |                    |                     |                     |                  |                      |        |
|--|--------------------|---------------------|---------------------|------------------|----------------------|--------|
| <b>Congestive Heart Failure, n (%)</b>           | 581 (3.1)          | 302 (3.7)           | 90 (3.2)            | 85 (4.3)         | 43 (3.5)             | <0.001 |
| <b>Peripheral Vascular Disease, n (%)</b>        | 576 (3.0)          | 474 (5.7)           | 150 (5.3)           | 97 (4.9)         | 57 (4.6)             | <0.001 |
| <b>Stroke, n (%)</b>                             | 796 (4.2)          | 495 (6.0)           | 150 (5.2)           | 88 (4.4)         | 84 (6.8)             | <0.001 |
| <b>Estimated GFR, ml/min/1.73m<sup>2</sup> *</b> | 92.3 (26.3)        | 91.7 (26.7)         | 93.2 (29.6)         | 94.9 (32.2)      | 96.6 (33.8)          | <0.001 |
| <b>Hemoglobin, g/dL *</b>                        | 13.1 (2.0)         | 13.0 (2.0)          | 12.8 (2.1)          | 12.6 (2.1)       | 12.3 (2.1)           | <0.001 |
| <b>Intraoperative RBC transfusions, mL †</b>     | 0 (0 to 0)         | 0 (0 to 0)          | 0 (0 to 0)          | 0 (0 to 320)     | 0 (0 to 690)         | <0.001 |
| <b>Estimated Blood Loss, mL †</b>                | 200 (80 to<br>350) | 250 (100 to<br>550) | 250 (100 to<br>600) | 300 (100 to 700) | 400 (163 to<br>1000) | <0.001 |

\* mean (SD), † median (1<sup>st</sup> to 3<sup>rd</sup> quarter), p-values for continuous data computed by analysis of variance, p-values for frequency data computed by  $\chi^2$  test, MAP= mean arterial pressure, ASA=American Society of Anesthesiology

Table 2. Adjusted odds ratios for acute kidney injury, myocardial injury and cardiac complications for intraoperative time spent with a mean arterial pressure less than 55 mmHg. Estimates adjusted for patient age, sex, Charlson comorbidity index, emergency procedure status, type of surgery, preoperative hemoglobin, decrement in hemoglobin concentration, estimated blood loss and volume of red blood cell transfusions.

| <b>Adjusted Odds Ratio (95% Confidence Interval)</b> |                                |                          |                                 |                         |
|--|--------------------------------|--------------------------|---------------------------------|-------------------------|
| <b>Time MAP &lt;55<br/>mmHg (minutes)</b>            | <b>Acute Kidney<br/>Injury</b> | <b>Myocardial Injury</b> | <b>Cardiac<br/>Complication</b> | <b>30 Day Mortality</b> |
| <b>0</b>   | <b>Referent</b>                |                          |                                 |                         |
| <b>1 to 5</b>  | 1.18 (1.06 to 1.31)            | 1.30 (1.06 to 1.58)      | 1.35 (1.15 to 1.58)             | 1.16 (0.91 to 1.46)     |
| <b>6 to 10</b>                                       | 1.19 (1.03 to 1.39)            | 1.47 (1.13 to 1.93)      | 1.46 (1.17 to 1.83)             | 1.16 (0.84 to 1.60)     |
| <b>11 to 20</b>                                      | 1.32 (1.11 to 1.56)            | 1.79 (1.33 to 2.39)      | 1.50 (1.16 to 1.94)             | 1.26 (0.89 to 1.80)     |
| <b>&gt;20</b>  | 1.51 (1.24 to 1.84)            | 1.82 (1.31 to 2.55)      | 1.95 (1.46 to 2.60)             | 1.79 (1.21 to 2.65)     |

Table 3. Comparison of results for primary analysis of acute kidney injury outcome compared to sensitivity analyses

|  |          | <b>Time Mean Arterial Pressure &lt;55 mmHg (minutes)</b> |                     |                     |                     |               |
|--|----------|--|---------------------|---------------------|---------------------|---------------|
|  |          | <b>0</b>   | <b>1 to 5</b>       | <b>6 to 10</b>      | <b>11 to 20</b>     | <b>&gt;20</b> |
| Primary  | Referent | 1.18 (1.06 to 1.31)                                      | 1.19 (1.03 to 1.39) | 1.32 (1.11 to 1.56) | 1.51 (1.24 to 1.84) |               |
| AKI within 3 days                                    | Referent | 1.15 (1.02 to 1.29)                                      | 1.15 (1.00 to 1.35) | 1.30 (1.09 to 1.56) | 1.45 (1.17 to 1.80) |               |
| Severe AKI   | Referent | 1.05 (0.77 to 1.50)                                      | 1.70 (1.16 to 2.63) | 1.20 (0.70 to 2.11) | 1.31 (0.72 to 2.37) |               |
| Adjusted for RSI                                     | Referent | 1.12 (1.01 to 1.25)                                      | 1.13 (1.00 to 1.32) | 1.23 (1.04 to 1.46) | 1.36 (1.12 to 1.66) |               |
| Adjusted for Preoperative Systolic<br>Blood Pressure | Referent | 1.19 (1.07 to 1.33)                                      | 1.17 (1.00 to 1.38) | 1.30 (1.10 to 1.56) | 1.55 (1.26 to 1.91) |               |
| Adjusted for case duration                           | Referent | 1.11 (1.00 to 1.24)                                      | 1.12 (0.97 to 1.30) | 1.22 (1.03 to 1.45) | 1.33 (1.09 to 1.62) |               |
| Multiple Imputation of Missing<br>Covariates         | Referent | 1.24 (1.12 to 1.37)                                      | 1.25 (1.09 to 1.45) | 1.38 (1.18 to 1.63) | 1.58 (1.31 to 1.91) |               |
| Most Recent Surgery Only                             | Referent | 1.10 (0.99 to 1.26)                                      | 1.07 (0.90 to 1.29) | 1.36 (1.10 to 1.68) | 1.33 (1.03 to 1.71) |               |

Note: All models are adjusted for patient age, sex, preoperative hemoglobin, Charlson Comorbidity score (except RSI model), preoperative hemoglobin, estimated blood loss, transfusions, emergency surgery, and type of surgery.

AKI= acute kidney injury; RSI = risk stratification index

Table 4. Comparison of results for primary analysis of myocardial injury outcome compared to sensitivity analyses

|  | <b>Time Mean Arterial Pressure &lt;55 mmHg (minutes)</b> |                     |                     |                     |                     |
|--|--|---------------------|---------------------|---------------------|---------------------|
|  | <b>0</b>   | <b>1 to 5</b>       | <b>6 to 10</b>      | <b>11 to 20</b>     | <b>&gt;20</b>       |
| <b>Primary</b>   | Referent   | 1.30 (1.06 to 1.58) | 1.47 (1.13 to 1.93) | 1.79 (1.34 to 2.39) | 1.82 (1.31 to 2.55) |
| <b>Restricted to Patients with Troponin T Measured (n= 4533)</b> | Referent   | 0.99 (0.80 to 1.20) | 1.12 (0.84 to 1.50) | 1.32 (1.00 to 1.79) | 1.35 (0.99 to 1.90) |
| <b>Adjusted for RSI</b>  | Referent   | 1.21 (0.99 to 1.48) | 1.35 (1.03 to 1.78) | 1.60 (1.22 to 2.10) | 1.67 (1.23 to 2.25) |
| <b>Adjusted for Preoperative Systolic Blood Pressure</b>         | Referent   | 1.15 (0.95 to 1.43) | 1.26 (0.96 to 1.70) | 1.54 (1.15 to 2.08) | 1.56 (1.11 to 2.17) |
| <b>Adjusted for case duration</b>                                | Referent   | 1.27 (1.05 to 1.53) | 1.44 (1.12 to 1.86) | 1.72 (1.30 to 2.26) | 1.89 (1.39 to 2.58) |
| <b>Multiple Imputation of Missing Covariates</b>                 | Referent   | 1.31 (1.10 to 1.57) | 1.48 (1.16 to 1.89) | 1.85 (1.42 to 2.40) | 2.03 (1.51 to 2.72) |
| <b>Most Recent Surgery Only</b>                                  | Referent   | 1.21 (0.97 to 1.52) | 1.05 (0.75 to 1.47) | 1.51 (1.08 to 2.13) | 1.58 (1.07 to 2.32) |

Note: All models are adjusted for patient age, sex, preoperative hemoglobin, Charlson Comorbidity score (except RSI model), preoperative hemoglobin, estimated blood loss, transfusions, emergency surgery, and type of surgery.

RSI = risk stratification index



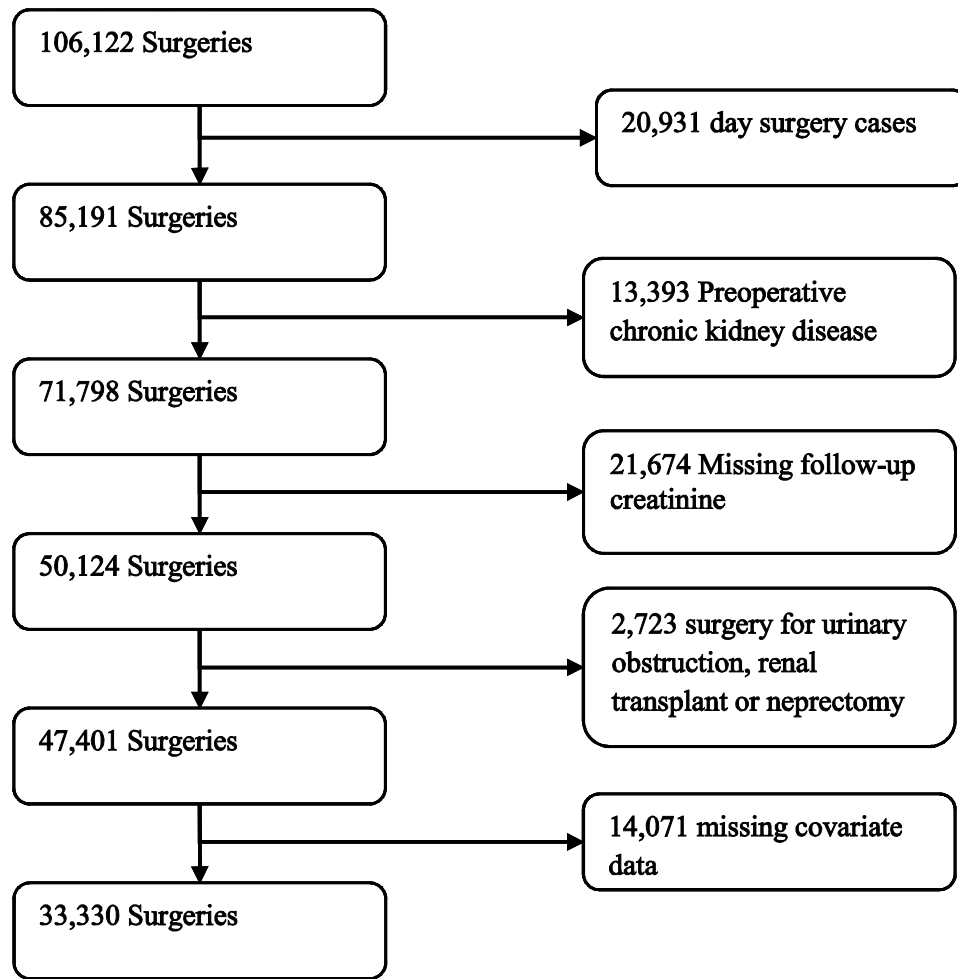


Figure 1. Patient selection

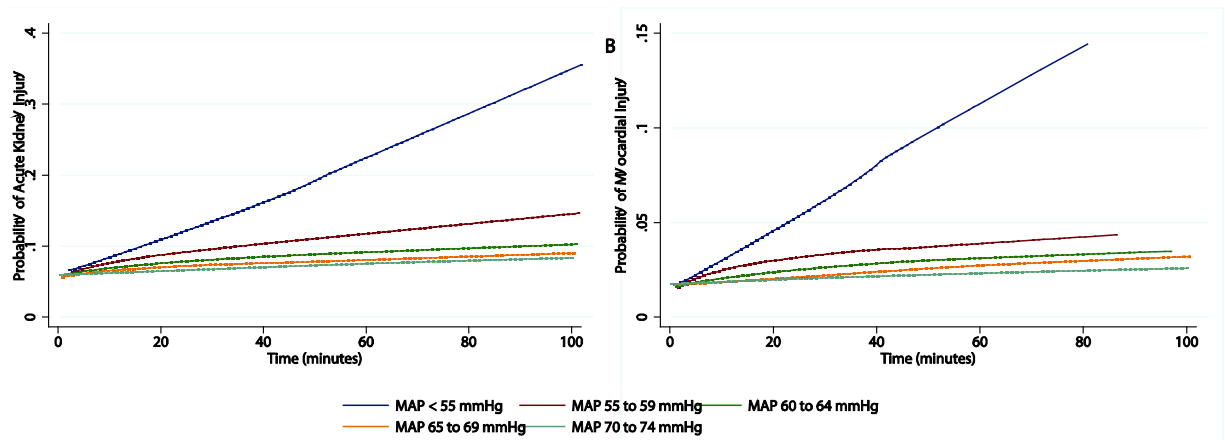


Figure 2. Predicted risk of (A) acute kidney injury and (B) myocardial injury for each minute the mean arterial pressure (MAP) is under 55 mmHg, between 55 and 59 mmHg, between 60 and 64 mmHg, between 65 and 69 mmHg and between 70 and 74 mmHg during noncardiac surgery. The risk for time in each blood pressure strata is adjusted for time in all other blood pressure strata.

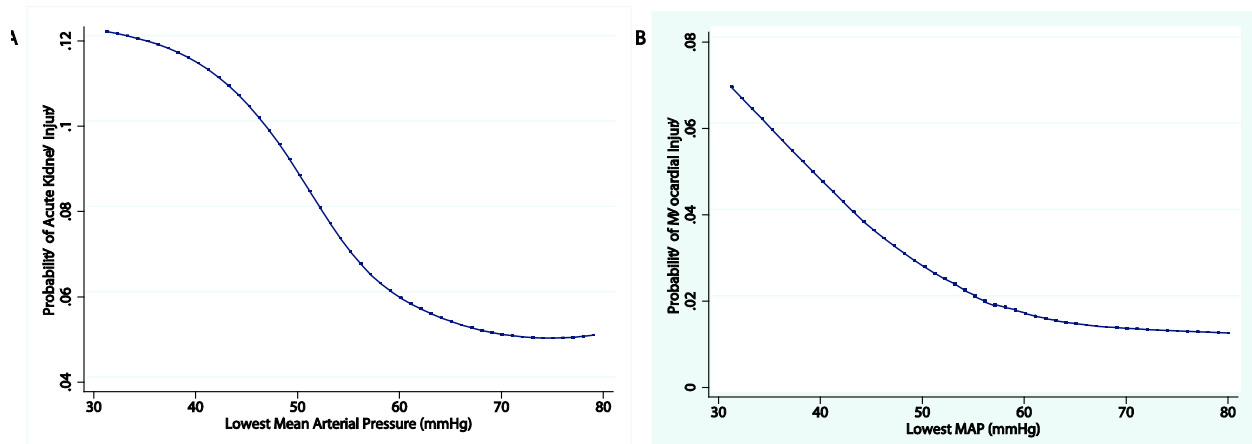


Figure 3. Predicted probability of (A) acute kidney injury and (B) myocardial injury by lowest mean arterial pressure (MAP) experienced during surgery.

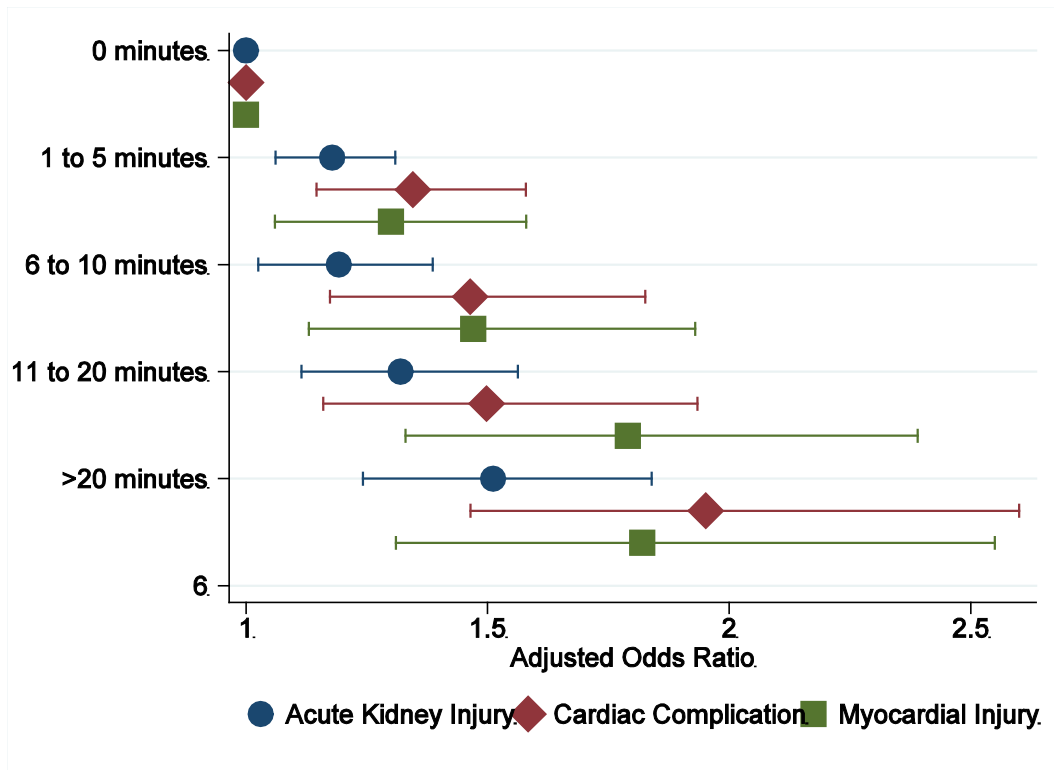


Figure 4. Adjusted odds ratios for acute kidney injury, cardiac complications and myocardial injury by time spent with a mean arterial pressure under 55 mmHg.

## CHAPTER 5

Walsh M, Whitlock R, Garg AX, Legare JF, Duncan AE, Zimmerman R, Miller S, Fremes S, Kieser T, Karthikeyan G, Chan M, Ho A, Nasr V, Vincent J, Chrolavicius S, Teoh K, Ali I, Lavi R, Sessler DI, Kramer R, Gardner J, Syed S, VanHelder T, Guyatt G, Rao-Melacini P, Thabane L, Devereaux PJ. The effects of remote ischemic preconditioning in high-risk patients undergoing cardiac surgery (Remote IMPACT): a randomized controlled trial. (Submitted 2013).

**The effects of remote ischemic preconditioning in high-risk patients undergoing cardiac surgery (Remote IMPACT): a randomized controlled trial**

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**Background:** Cardiac surgery is frequently complicated by ischemia-reperfusion injury which can lead to kidney and myocardial injury. Preoperative Remote Ischemic Preconditioning (RIPC), cycles of brief ischemia to a limb alternating with reperfusion, may reduce the frequency or severity of organ injury after cardiac surgery.

**Methods:** We performed a randomized controlled trial comparing RIPC to a sham procedure in patients undergoing cardiac surgery. Either RIPC or sham was started after induction of anesthesia. RIPC consisted of three cycles of thigh tourniquet inflation to 300 mmHg for five minutes followed by five minutes deflated. The sham procedure was identical to RIPC except that inflation was to 15 mmHg. Patients, care providers, and outcome adjudicators were blinded to treatment allocation. The main outcomes were log-transformed peak CK-MB within 24 hours of surgery and log-transformed change in creatinine within 4 days of surgery compared to preoperative. Other outcomes were assessed up to six months after randomization.

**Findings:** We randomized 128 patients to RIPC and 130 to sham. There were no significant between group differences in postoperative log-transformed CK-MB (0.15 multiples of the upper limit of normal, 95% confidence interval [CI] -0.07 to 0.36) or log-transformed change in creatinine (0.06  $\mu\text{mol/L}$ , 95% CI -0.10 to 0.23). Clinical outcomes did not differ significantly between groups: myocardial infarction 25.0% vs 18.5% (relative risk [RR] 1.35, 95% CI 0.85 to 2.17), acute kidney injury 22.2% vs 20.2% (RR 1.10, 95% CI 0.68 to 1.78), stroke 4.7% vs 4.6% (RR 1.02, 95% CI 0.34 to 3.07) or mortality (RR 1.47, 95% CI 0.65 to 3.31) at six months after randomization.



**Interpretation:** RIPC did not affect markers of myocardial or kidney injury in patients at high risk of death after cardiac surgery. These results suggest that RIPC may not impact outcomes important to patients in this setting.

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**Clinical Trial Registration:** NCT01071265

Annually, two million patients worldwide undergo cardiac surgery. Many patients' cardiac surgery is complicated by myocardial infarction (MI) and/or acute kidney injury (AKI), both of which are strongly associated with morbidity and mortality. (1-6) Preventing MI and AKI after cardiac surgery would likely improve patient survival, reduce the burden of care required for these patients, and may result in substantial cost savings.

An important cause of MI and AKI in patients undergoing cardiac surgery is ischemia-reperfusion injury. (7, 8) This injury is caused first by ischemia during periods of low organ perfusion which is exacerbated by a systemic inflammatory response upon restoration of organ perfusion.(9) Remote ischemic preconditioning (RIPC) is a promising intervention that may mitigate ischemia-reperfusion damage. RIPC is accomplished by inducing one or more brief episodes of ischemia to a limb prior to surgery. These ischemic episodes lead to widespread activation of endogenous cellular systems, including those in the heart and kidney, which may protect organs from subsequent severe ischemia and reperfusion. (10, 11)

Small randomized controlled trials evaluated the efficacy of RIPC with mixed results. (12-19) Some trials demonstrated substantial reductions in postoperative cardiac enzymes or markers of kidney injury in patients who received RIPC compared to control patients.(17, 19) Others failed to demonstrate any benefits.(20, 21) The interpretation of these data are difficult due to small sample sizes and heterogeneity in the RIPC procedures and patient populations (i.e., few trials evaluated patients at high risk of organ injury and postoperative death).

RIPC is an appealing therapy because it has no known risks, requires no special equipment, and costs very little. However, whether RIPC effectively mitigates ischemia-reperfusion injury is uncertain. We undertook the Remote IscheMic Preconditioning in cArdiaC surgery Trial (Remote IMPACT) to determine if RIPC reduces myocardial and kidney injury.

We proposed that a large trial to determine the effect of RIPC on clinically important outcomes would only be worthwhile if a substantial effect on myocardial and/or kidney injury were observed.

## **Methods**

We conducted a two-parallel-group randomized controlled trial of RIPC compared to a sham procedure in patients undergoing cardiac surgery from 11 centres in 4 countries. The research ethics board at each participating institution reviewed and accepted the protocol and all participants provided informed consent.

### *Patients*

Recruitment for Remote IMPACT took place between 2011 and 2012. Patients were eligible if they were undergoing cardiac surgery, were aged 18 or older, were at high risk of post-operative mortality determined by an additive EuroScore  $\geq 6$  or  $\geq 4$  and undergoing valve surgery in India and China, and provided informed consent. (22) Patients were excluded if they required an intra-aortic balloon pump prior to surgery. All participating sites obtained ethical approval from institutional ethics review boards prior to recruiting patients. All participants provided written informed consent.

### *Randomization and blinding*

After obtaining written informed consent, research personnel randomized patients via a computerized World Wide Web-based randomization system maintained by the coordinating centre at the Population Health Research Institution (PHRI), which is part of the Hamilton

Health Sciences and McMaster University, Hamilton, Ontario, Canada. The randomization process used block randomization, with randomly varying block sizes, stratified by centre and whether the patient required dialysis prior to surgery. Study centre personnel were not aware of the block sizes. Participants, health care providers (surgeons, anesthetists, and operating room staff), and outcome adjudicators were masked to treatment allocation.

### *Procedures*

After induction of anesthesia and prior to commencing bypass, research staff applied a pneumatic tourniquet to the thigh of the participant and draped the tourniquet system to prevent operating room staff from seeing whether or not the cuff was inflated. Patients allocated to receive RIPC had three cycles of tourniquet inflation to 300 mmHg for 5 minutes then deflated for 5 minutes. Patients allocated to receive the sham procedure had three cycles of tourniquet inflation to 15 mmHg for 5 minutes then deflated for 5 minutes.

CK-MB was measured 8 and 24 hours post-operatively and serum creatinine was measured before surgery and daily for 4 days starting the day after surgery. Patients were followed for postoperative events during their hospitalization and up to 6 months after surgery.

### *Outcomes*

The main proof-of-concept outcomes of this trial were the highest recorded CK-MB level within the first 24 hours after surgery and change between the preoperative creatinine measurement and the peak creatinine measurement during the first 4 days after surgery. Patients that required dialysis prior to surgery were not included in the change in creatinine analysis. Secondary outcomes included MI, AKI, stroke and all-cause mortality up to 6 months after

randomization. Within the first 72 hours after surgery MI was defined as a CK-MB measurement  $\geq 8$  times the upper limit of normal ( $\geq 5$  times for an isolated CABG procedure), angiographic evidence of vessel occlusion, or imaging evidence of new loss of myocardium. Starting 72 hours after surgery the diagnosis of MI required an elevation of a cardiac enzyme above the upper reference limit and ischemic electrocardiography changes. Acute kidney injury was defined as at least a 1.5-fold or 26.4  $\mu\text{mol/L}$  (0.3 mg/dL) increase in serum creatinine compared to the preoperative value, or the initiation of dialysis. Patients that required dialysis prior to surgery were excluded from this analysis. Stroke was defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or resulting in death.

### *Statistical Analysis*

The sample size was based on the change in serum creatinine as it required a larger sample size than the peak CK-MB outcome. We assumed a mean change in serum creatinine (highest postoperative value minus preoperative value) of 36  $\mu\text{mol/L}$ . Using log transformed values to normalize these data, we expected a mean change of 2.5 (1.5) with a coefficient of variation of 0.9. We considered a 25% reduction in peak serum creatinine or greater would be required to result in an improvement in clinically important outcomes. We therefore require 114 participants per arm (228 total) to detect at least a 25% reduction with 80% power and a two-sided alpha of 0.05 using analysis of covariance. This sample size allowed us a power of at least 95% to detect a between group difference of 0.4 log-transformed multiples of the upper limit of normal (equivalent to a between group difference of approximately 10 U/L) assuming a standard deviation of 0.8 log-transformed units. Calculations were performed with PASS version 8.08 (Kaysville, Utah). (23) We inflated the recruitment goal to 250 patients to account for potential

missing data, and the fact that patients enrolled with end-stage renal disease would not be eligible for an assessment of change in creatinine.

Patients were analyzed in the treatment group to which they were allocated according to the intention-to-treat principle. Data are presented as mean (SD), median (25<sup>th</sup> to 75<sup>th</sup> percentile) or n (%) as appropriate. Results are expressed as the RIPC group relative to the Sham group. CK-MB was analyzed as multiples of the upper limit of normal to account for between-centre differences in assays. Differences between groups were calculated by comparing the log transformed concentrations to account for the right skewed distribution. Patients that did not have a post-operative CK-MB measurement were excluded from the primary CK-MB analysis but included in a sensitivity analysis utilizing multiple imputation of the peak concentration. (24) Change in serum creatinine was computed by analysis of covariance with the preoperative creatinine and treatment group as covariates and the highest recorded serum creatinine within 4 days of surgery as the outcome. Patients who required preoperative dialysis were excluded from all analyses of kidney function. A sensitivity analysis utilizing multiple imputation of missing serum creatinine values was also performed. (24)

#### *Role of the Funding Source*

The Population Health Research Institute coordinated the study, managed the data, and undertook analyses under the supervision of the Principal Investigators. The study was funded by peer reviewed grants from the Hamilton Health Sciences New Investigator Fund and the Canadian Network and Centre for Trials Internationally (CANNeCTIN). None of the funders had

a role in trial design, conduct, data collection analyses, data interpretation, or writing of this manuscript. The corresponding author had full access to all trial data.

## Results

Figure 1 shows the trial flow. One hundred twenty-eight patients were assigned to the RIPC group and 130 patients were assigned the Sham group. No patients were lost to follow-up. The RIPC group and Sham group were similar at randomization and had similar operative characteristics (Table 1) although there were more patients with a history of congestive heart failure, prior cardiac surgery, and previous myocardial infarction in the RIPC group and fewer patients in the RIPC group underwent an isolated CABG procedure. Of the 258 patients randomized, 124 (96.9%) in the RIPC group and 124 (95.4%) in the Sham group received the intended treatment as assigned (Figure 1).

Postoperative CK-MB data was available in 251 patients (125 RIPC group and 127 Sham group). Figure 2 shows the CK-MB concentrations in the first 24 hours after surgery for the RIPC and Sham groups. The median peak was 3.5 (2.3 to 6.7) times the upper limit of normal for the RIPC group and 3.3 (2.0 to 5.6) times the upper limit of normal in the Sham group which, when comparing the mean difference in log-transformed values, was not statistically significant (mean difference 0.15  $\mu\text{mol/L}$ , 95% CI -0.07 to 0.36). Sensitivity analyses utilizing multiple imputations to account for the 7 patients with missing CK-MB data did not alter the results (mean difference in log-transformed values 0.14  $\mu\text{mol/L}$ , 95% CI -0.06 to 0.35).

Of the 248 patients that did not require dialysis at baseline, change in creatinine data was available in 246 (122 RIPC and 124 Sham). The postoperative serum creatinine concentrations during the first 4 days after surgery for the RIPC and Sham groups are shown in Figure 3. The

median peak change in creatinine was 16.9  $\mu\text{mol/L}$  in the RIPC group and 14.6  $\mu\text{mol/L}$  in the Sham group which was not statistically significant when comparing the log-transformed concentrations (mean difference 0.06, 95% CI -0.10 to 0.23). Sensitivity analyses utilizing multiple imputations to account for the 2 patients with missing creatinine data did not alter the results (mean difference 0.06, 95% CI -0.09 to 0.22).

The groups did not significantly differ with respect to the risk of MI, AKI, stroke, or all-cause mortality within six months of randomization (Table 2). In the RIPC group, 33 (25.8%) experience a serious adverse event compared to 30 (23.1%) in the Sham group at six months after randomization ( $p=0.61$ ). One venous thrombosis occurred in the Sham group compared to none in the RIPC group and no nerve compression injuries were identified.

## **Discussion**

In our trial of 258 patients at high risk of postoperative MI and AKI, RIPC did not reduce the peak CK-MB in the first 24 hours or creatinine in the first 4 days after surgery. Although RIPC appears safe and it was feasible to conduct a trial in which RIPC was performed after induction of anesthesia but before patients went underwent surgery, there was no demonstrable benefit to RIPC in this trial. Given the lack of an effect on these surrogate outcomes, the need for large trials in this population is questionable.

Our trial is among the largest evaluating RIPC in patients undergoing cardiac surgery. While we found no effect of RIPC on cardiac enzyme release or kidney function, other, smaller trials reported a benefit.(13, 17-19) It is unclear why these differences exist. We can hypothesize that some differences may be due to differences in the preconditioning regimen. However, recent meta-analyses summarizing previous trials show reductions in cardiac enzymes irrespective of



the preconditioning regimen.(25, 26) Furthermore, our regimen was demonstrated to have biological effects compared to regimens that used fewer cycles on arms.(27)

It is also possible that some patient populations do not derive a benefit. Patients with chronic intermittent ischemia may be preconditioned prior to surgery (e.g., approximately one-third of our patients had a history of prior coronary artery disease). Similarly, patients undergoing very long or high risk procedures may have such a strong stimulus for adverse events that RIPC may be insufficiently potent to influence those events. In fact, our patients were higher risk than those in prior studies (e.g., two-thirds of our patients had more complicated surgery than isolated coronary artery bypass grafting).

Further, there is evidence suggesting volatile anesthetics provide preconditioning.(28) Given 84.4% of our patients received a volatile anesthetic in both groups, there may be no additional benefit to RIPC.

Finally, it is also possible that RIPC is not an effective therapy and results from several prior trials simply represent false positive findings. Indeed, the most recent meta-analyses of RIPC in cardiac surgery suggested the reduction in cardiac enzyme release was small with a standardized mean difference ranging from -0.28 and -0.3.(25, 26) By updating these meta-analyses with our trial results the suggested benefit in terms of cardiac enzyme release after cardiac surgery becomes non-significant and the peak serum creatinine concentration remains non-significant (Online Supplements 1 and 2).

Our trial has several strengths. It is one of the largest to compare RIPC to a sham procedure in cardiac surgery and had sufficient power to detect modest benefits in biomarkers. We applied the intervention to a group at high risk for poor outcomes and therefore one of the most important to potentially treat. Our trial was multicentre and international and therefore

perhaps more generalizable and may provide a more realistic estimate of effect than other prior, single-centre, trials.(29) Finally, our trial had a low risk of bias (i.e., we had concealment of randomization, blinding of patients, care providers and outcome adjudicators, and no patient was lost to follow-up).

The results of our trial must also be considered in the context of their limitations. Our trial is not large and may be underpowered to reliably detect a difference in CK-MB or creatinine. However, although the change and distribution in creatinine we observed was smaller than anticipated, the change and distribution of CK-MB was as predicted and provided adequate power to detect a modest treatment effect. There is also the possibility that imbalances in baseline risk exist due to random chance and may have confounded our results. For example, there were a larger number of isolated CABG procedures and fewer patients with a history of heart failure in the sham group which may have resulted in a lower mean change in CK-MB and creatinine compared to the RIPC group. However, such an imbalance in baseline risk would have to be large in order to reduce any true effect of RIPC to the level that we observed (i.e., to the point that the mean CK-MB was actually higher in the RIPC group). The imbalance would either have to be very large, or the effect of RIPC would have to be very small.(30) Moreover, the EuroScore, an overall marker of prognosis, was reasonably balanced between groups.

In conclusion, in patients at high risk of complications after cardiac surgery, our results suggest RIPC is unlikely to have an important biological effect on myocardial or kidney injury. Although our results do not preclude the possibility that RIPC improves outcomes important to patients, particularly in those at lower risk, current data provides very limited support for this hypothesis.

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### **Contributorship Statement**

Michael Walsh contributed significantly to the study's concept and design, data collection, data analysis, and interpretation of the data. He wrote the first draft of the manuscript, provided critical revisions, and gave final approval of the submitted manuscript.

Richard Whitlock contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Amit X. Garg contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

J. F. Legare contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Andra E. Duncan contributed significantly to the study's concept and design, data collection, and interpretation of the data. She provided critical revisions, and gave final approval of the submitted manuscript.



Robert Zimmerman contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Scott Miller contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Stephen Fremes contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Teresa Kieser contributed significantly to the study's concept and design, data collection, and interpretation of the data. She provided critical revisions, and gave final approval of the submitted manuscript.

Ganesan Karthikeyan contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Matthew Chan contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Anthony Ho contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Vivian Nasr contributed significantly to the study's concept and design, data collection, and interpretation of the data. She provided critical revisions, and gave final approval of the submitted manuscript.

Jessica Vincent contributed significantly to the study's concept and design, data collection, and interpretation of the data. She provided critical revisions, and gave final approval of the submitted manuscript.

Susan Chrolavicius contributed significantly to the study's concept and design, data collection, and interpretation of the data. She provided critical revisions, and gave final approval of the submitted manuscript.

Kevin Teoh contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Imtiaz Ali contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Ronit Lavi contributed significantly to the study's concept and design, data collection, and interpretation of the data. She provided critical revisions, and gave final approval of the submitted manuscript.

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Robert Kramer contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Jeff Gardner contributed significantly to the study's concept and design, data collection, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Summer Syed contributed significantly to the study's concept and design, data collection, and interpretation of the data. She provided critical revisions, and gave final approval of the submitted manuscript.

Tomas VanHelder contributed significantly to the study's concept and design, data collection, and interpretation of the data. She provided critical revisions, and gave final approval of the submitted manuscript.

Gordon Guyatt contributed significantly to the study's concept and design, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Purnima Rao-Melacini contributed significantly to the data analysis, and interpretation of the data. She provided critical revisions, and gave final approval of the submitted manuscript.

Lehana Thabane contributed significantly to the study's concept and design, data analysis, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

PJ Devereaux contributed significantly to the study's concept and design, and interpretation of the data. He provided critical revisions, and gave final approval of the submitted manuscript.

Table 1. Baseline and operative characteristics

|  | <b>RIPC Group</b> | <b>Sham Group</b> |
|--|-------------------|-------------------|
|  | <b>n=128</b>      | <b>n=130</b>      |
| <b>Age, years (SD)</b>   | 72.1 (12.0)       | 72.3 (13.0)       |
| <b>Male, n (%)</b>   | 72 (56.3)         | 79 (60.8)         |
| <b>EuroScore, median (IQR)</b>                                     | 7.5 (6.0 to 9.0)  | 7.0 (6.0 to 9.0)  |
| <b>Comorbidities, n (%)</b>  |                   |                   |
| <b>Congestive heart failure</b>                                    | 45 (35.2)         | 30 (23.1)         |
| <b>Previous MI</b>   | 41 (32.0)         | 35 (26.9)         |
| <b>Atrial fibrillation</b>   | 36 (28.1)         | 29 (22.3)         |
| <b>Previous Cardiac Surgery</b>                                    | 29 (22.7)         | 21 (16.2)         |
| <b>Stroke</b>  | 10 (7.8)          | 12 (9.2)          |
| <b>Peripheral Vascular Disease</b>                                 | 17 (13.3)         | 15 (11.5)         |
| <b>Diabetes mellitus</b>   | 39 (30.5)         | 40 (30.8)         |
| <b>Dialysis dependent</b>  | 5 (3.9)           | 5 (3.8)           |
| <b>Preoperative creatinine, <math>\mu\text{mol/L}</math> (SD)*</b> | 101 (33)          | 102 (37)          |
| <b>Procedure, n (%)</b>  |                   |                   |
| <b>Isolated CABG</b>   | 26 (20.3)         | 38 (29.2)         |
| <b>Isolated valve surgery</b>                                      | 35 (27.3)         | 33 (25.4)         |
| <b>CABG + valve or other</b>                                       | 45 (35.2)         | 38 (29.2)         |
| <b>Other</b>   | 22 (17.2)         | 21 (16.1)         |
| <b>Bypass Time, minutes (SD)</b>                                   | 142.6 (86.9)      | 132.7 (63.7)      |
| <b>Cross clamp time, minutes (SD)</b>                              | 100.3 (48.0)      | 97.9 (51.2)       |

|   |                  |                  |
|---|------------------|------------------|
| <b>Number of grafts, median (IQR)<sup>†</sup></b> | 2.0 (1.0 to 3.0) | 3.0 (2.0 to 3.0) |
| <b>Hypothermic arrest, n (%)</b>                  | 11 (8.6)         | 9 (7.0)          |
| <b>Volatile gas anesthesia, n (%)</b>             | 107 (83.6)       | 109 (85.2)       |

\* excluding patients that required dialysis preoperatively

<sup>†</sup> in patients that had CABG

RIPC = remote ischemic preconditioning; SD = standard deviation; IQR = 25<sup>th</sup> to 75<sup>th</sup> percentile;

MI = myocardial infarction; CABG = coronary artery bypass graft.

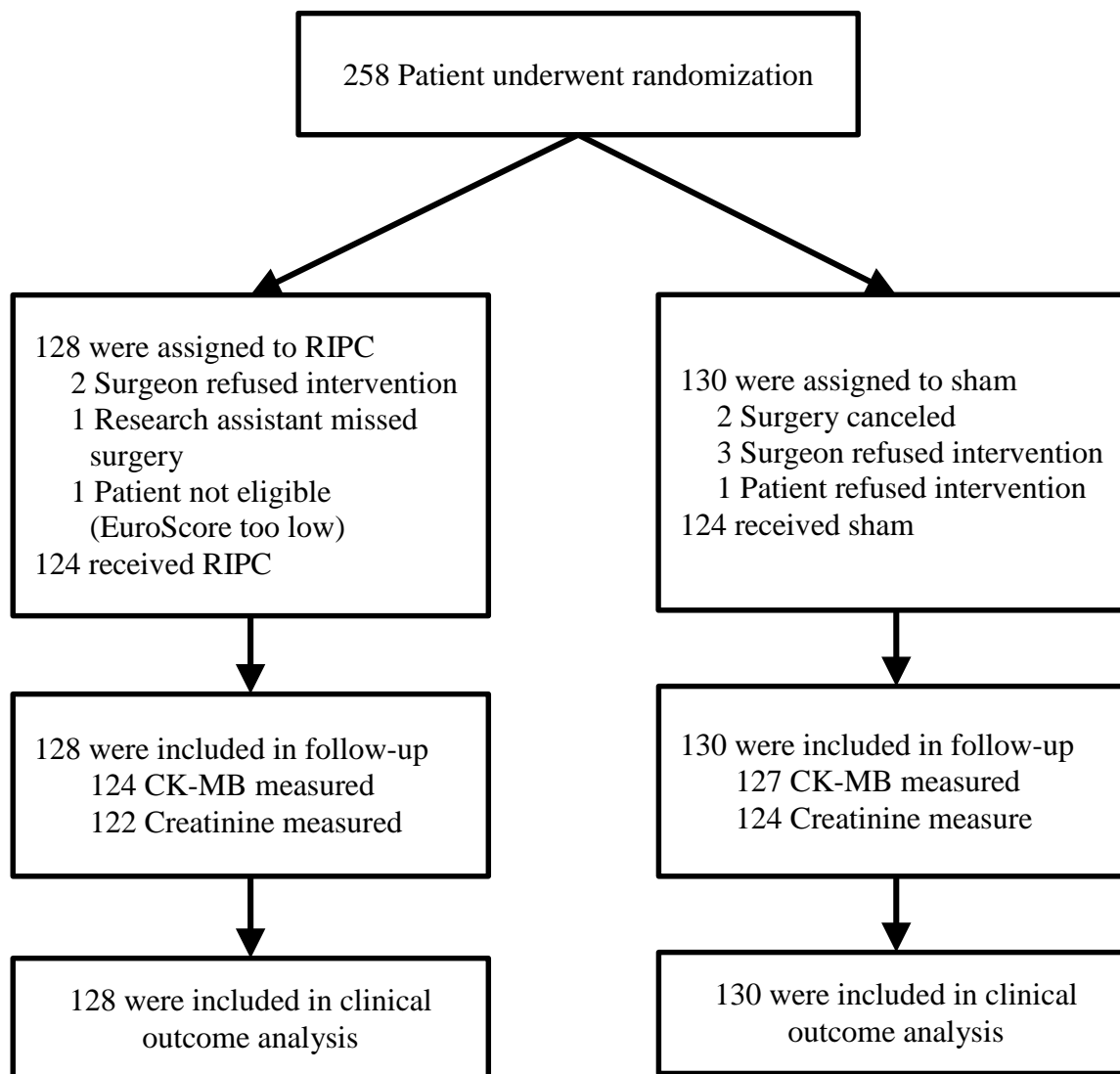
Table 2. Clinical outcomes of patients in the remote ischemic preconditioning group compared to the sham group up to 6 months.

| <b>Outcome</b>                      | <b>RIPC<br/>n=128</b> | <b>Sham<br/>n=130</b> | <b>Relative Risk (95%<br/>Confidence Interval)</b> |
|-------------------------------------|-----------------------|-----------------------|--|
| <b>Myocardial Infarction, n (%)</b> | 32 (25.0)             | 24 (18.5)             | 1.35 (0.85 to 2.17)                                |
| <b>Acute Kidney Injury, n (%)*</b>  |                       |                       |  |
| <b>Any</b>                          | 27 (22.2)             | 25 (20.2)             | 1.10 (0.68 to 1.78)                                |
| <b>Mild</b>                         | 11 (9.0)              | 15 (12.1)             |  |
| <b>Moderate</b>                     | 8 (6.6)               | 8 (6.5)               |  |
| <b>Severe</b>                       | 8 (6.6)               | 2 (1.6)               |  |
| <b>Stroke, n (%)</b>                | 6 (4.7)               | 6 (4.6)               | 1.02 (0.34 to 3.07)                                |
| <b>Death, n (%)</b>                 | 13 (10.2)             | 9 (6.9)               | 1.47 (0.65 to 3.31)                                |

\* excludes patients that required preoperative dialysis

RIPC = remote ischemic preconditioning; Mild = at least a 150% to 200% rise in serum creatinine or at least a 26.4  $\mu\text{mol/L}$  rise; Moderate = greater than 200% to 300% rise in serum creatinine; Severe = greater than 300% rise in serum creatinine or a rise to greater than 354  $\mu\text{mol/L}$  with an increase of at least 44  $\mu\text{mol/L}$  or need for acute dialysis.

Figure 1. Trial flow





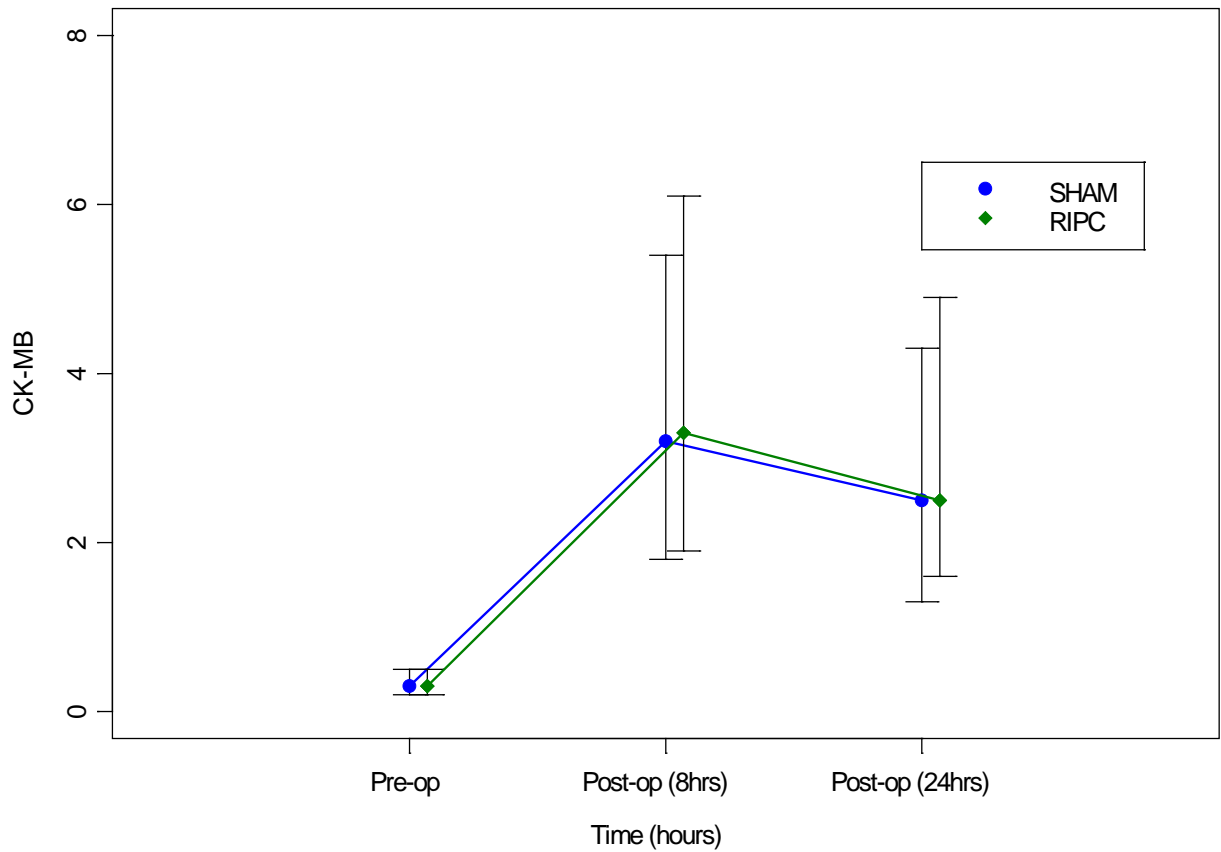


Figure 2. Serum CK-MB in multiples of the upper limit of normal in patient in the RIPC and sham group. Points represent median and lower and upper whiskers represent 25<sup>th</sup> and 75<sup>th</sup> percentile respectively.

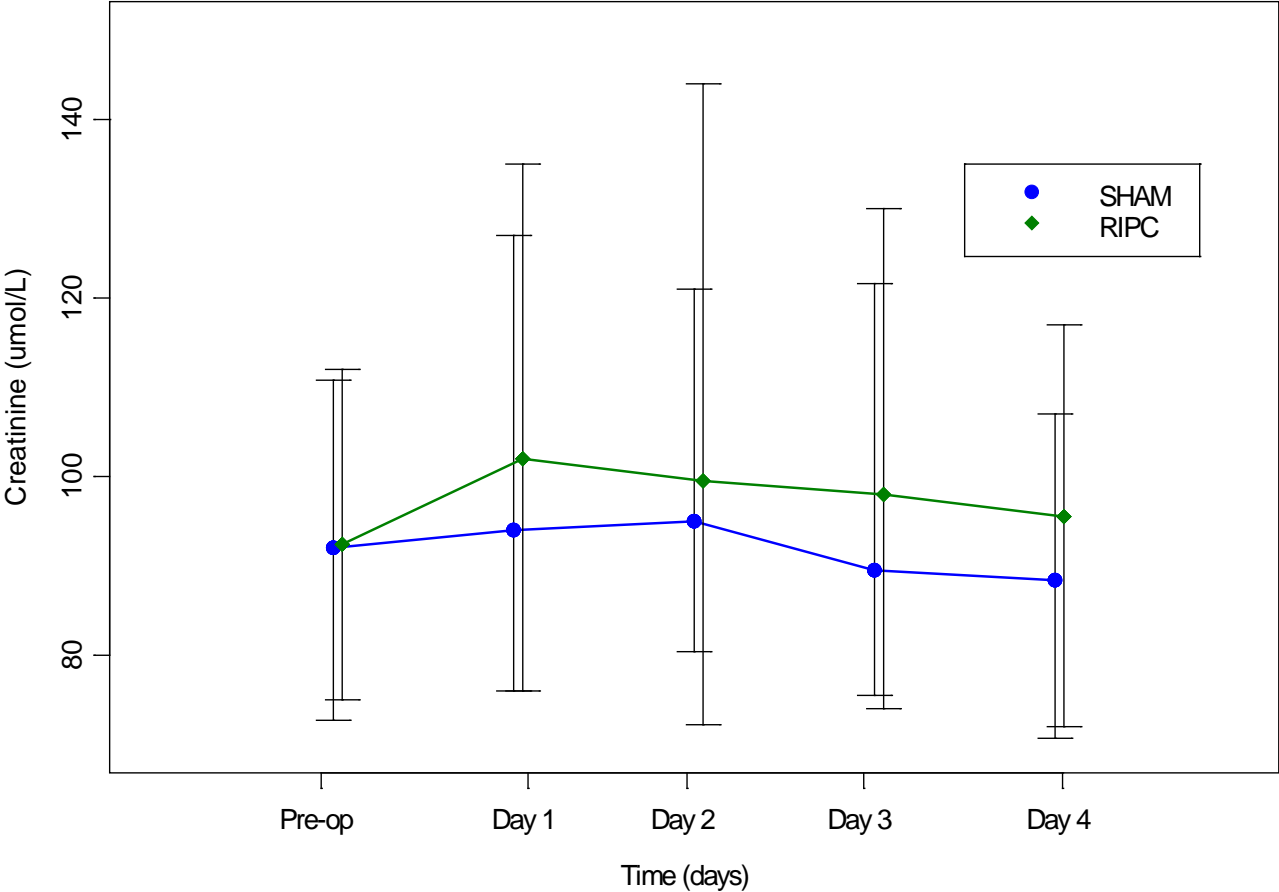
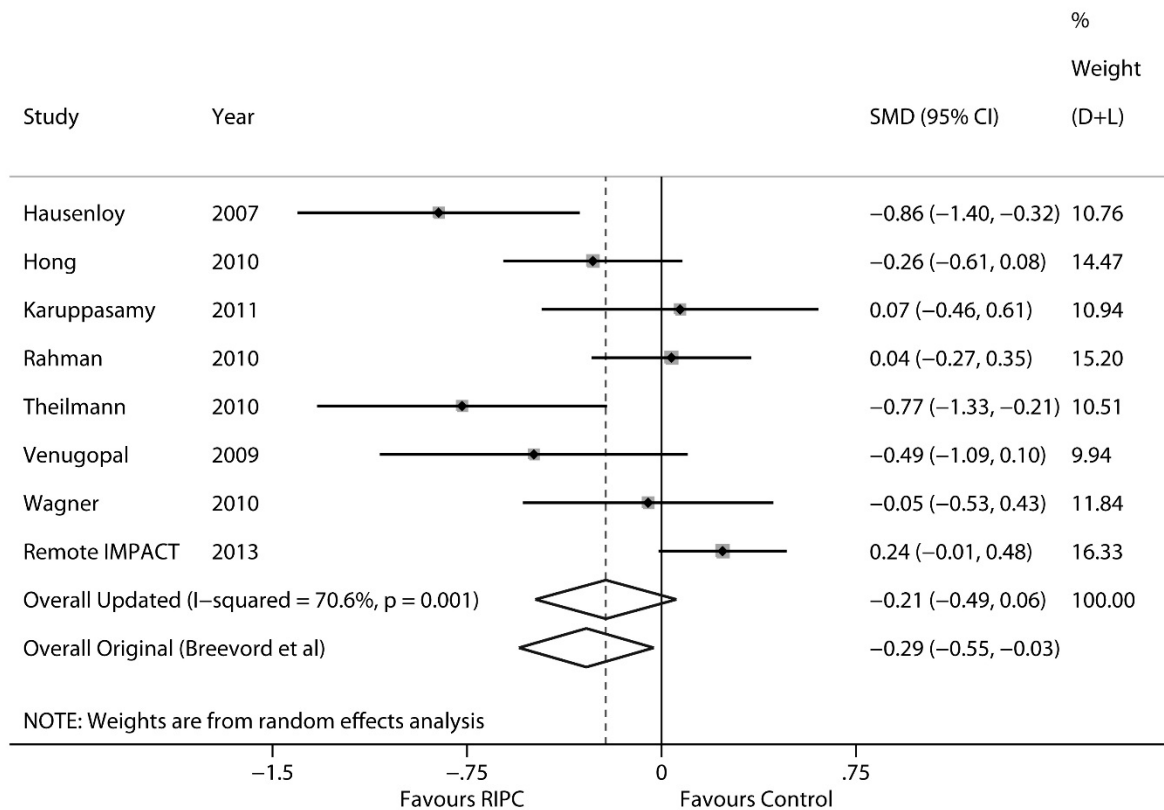
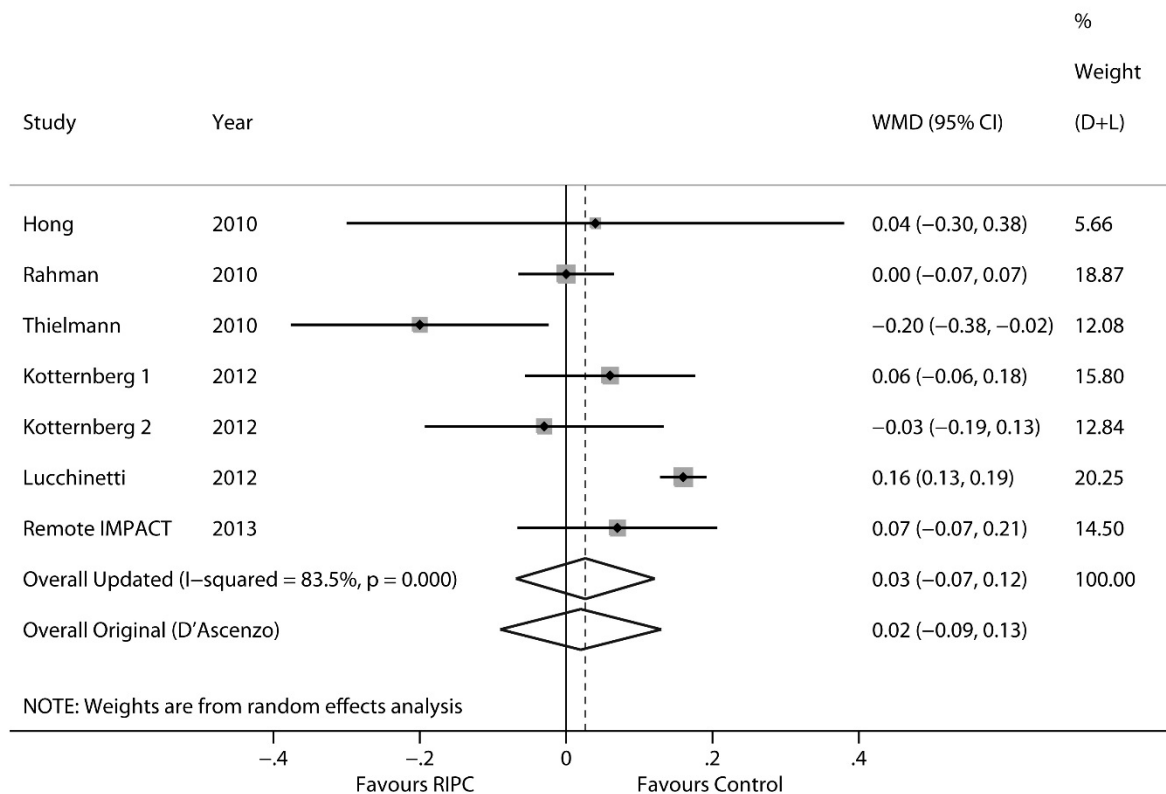


Figure 3. Serum creatinine in the RIPC and sham group. Points represent median and lower and upper whiskers represent 25<sup>th</sup> and 75<sup>th</sup> percentile respectively.

Online Supplements



Online Supplement 1. Results of Breevord et al meta-analysis of cardiac enzymes in patients that undergo cardiac surgery and remote ischemic preconditioning compared to controls updated for Remote IMPACT results. The updated pooled effect size is a standardized mean difference of -0.22 (95% confidence interval -0.49 to 0.06) compared to the original -0.29 (95% confidence interval -0.55 to -0.03).



Online Supplement 2. Results of D'Ascenzo et al meta-analysis of creatinine in patients that undergo cardiac surgery and remote ischemic preconditioning compared to controls updated for Remote IMPACT results. The updated pooled effect size is a weighted mean difference of 0.03 mg/dL (95% confidence interval -0.07 to 0.12) compared to the original 0.02 mg/dL (95% confidence interval -0.09 to 0.13).

## CHAPTER 7

### Conclusions and future directions

#### 8.1. Background

This thesis explored issues related to kidney function in patient undergoing surgery. The included original studies informed the relationship between preoperative kidney function and perioperative risk prediction, the relationship between perioperative hemoglobin and intraoperative hypotension and the risk of acute kidney injury after noncardiac surgery, and remote ischemic preconditioning as a potential prophylactic therapy for acute kidney injury and myocardial infarction in patients undergoing cardiac surgery.

#### 8.2. The interaction between kidney function and cardiac troponin T in patients undergoing noncardiac surgery

In Chapter 2, data from a prospective cohort study, VISION, was used to inform the how risk for postoperative death associated with postoperative cardiac troponin T (cTnT) varies by preoperative kidney function. cTnT concentrations  $\geq 0.02$  ng/mL, a prognostically relevant threshold in patients with an eGFR  $\geq 30$  ml/min/1.73 m<sup>2</sup>, were common in patients with an eGFR  $< 30$  ml/min/1.73 m<sup>2</sup>. However, the risk of death within 30 days of surgery associated with a cTnT concentrations above the threshold values was not as large in patients with an eGFR  $< 30$  ml/min/1.73 m<sup>2</sup> as in the subgroup with an eGFR  $\geq 30$  ml/min/1.73 m<sup>2</sup>. These results were consistent when redefining the cTnT threshold as  $\geq 0.03$  ng/mL or as a rise in cTnT of at least 0.02 ng/mL.

It is unclear whether a different cTnT threshold would alter the risk associated death in patients with an eGFR  $<30$  ml/min/1.73 m<sup>2</sup> or if the results would be similar with other assays. Moving forward, this study has informed the design of a second study examining the interaction between high sensitivity cTnT in an additional 25,000 patients in the VISION cohort that also includes preoperative cTnT samples. This study will allow the examination of change in cTnT (preoperatively to postoperatively) in greater detail and will add a larger number of patients with an eGFR  $<30$  ml/min/1.73 m<sup>2</sup>. Furthermore, the study included in this thesis informs a substudy from the VISION Biobank study that contains 4,400 patients in which we can determine if a similar interaction between cTnT and eGFR exists with other cardiac markers (e.g., high sensitivity cardiac troponin I).

### **8.3. Association between perioperative hemoglobin and acute kidney injury in patients having noncardiac surgery**

In Chapter 3, clinical and administrative data from a noncardiac surgery registry informed the relationship between preoperative and postoperative hemoglobin concentrations and the risk of AKI. Preoperative anemia is strongly associated with AKI, as expected from other work demonstrating preoperative anemia is associated with death. However, the finding that an acute decrement in hemoglobin concentration, independent of transfusions, was also strongly associated with AKI is a novel finding. Furthermore, this study demonstrated that such decrements are common and that they occur primarily in patients with higher preoperative hemoglobin concentrations. This is important as it suggests that an absolute hemoglobin threshold may be less important than the change in hemoglobin.

The results of Chapter 3 inform several ongoing and planned studies. First the results may be replicated in part in the VISION study. Second, a meta-analysis of the risks and benefits of preoperative erythropoiesis stimulating agents, a method of increasing preoperative hemoglobin concentration, is underway. This is particularly important given the chronic use of these agents is associated with significant harm but in the preoperative setting where they are used for a short period of time and potentially in lower doses than in chronic disease they may have fewer adverse events. Third, there are ongoing studies planned to prevent decrements in hemoglobin concentration (e.g., perioperative tranexamic acid).

#### **8.4. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: towards an empirical definition of hypotension**

In Chapter 4, an empiric definition of intraoperative hypotension was empirically derived. This study represents an important advance in the methodology of defining hypotension since it takes into account both the magnitude of blood pressure and the duration of that magnitude and their association with clinical outcomes. In the past, hypotension definitions were often arbitrary, or based on assumptions from animal models and physiologic experiments in small numbers of individuals. As a result, over one hundred definitions exist in the literature.

The results of this study will be used in several ways. The methodology informs parallel studies in the VISION cohort and other studies that seek to define hypotension. The definition also be verified in other perioperative cohorts. Future studies may also use this empiric definition of hypotension as the point at which interventions are started. Our definition of hypotension will be particularly important for these studies as interventions that elevate blood pressure carry a certain amount of risk. Widely applied strategies that include substantial numbers of patients with a

MAP not in our hypotensive range may have a low probability of deriving benefit from elevating their blood pressure compared to their probability of suffer adverse effects from the treatment.

#### 8.5. The effects of remote ischemic preconditioning in high-risk patients undergoing cardiac surgery

In Remote IMPACT we randomized 258 patients undergoing high risk cardiac surgery to receive RIPC or a sham procedure. We demonstrated that a large trial of RIPC in high risk cardiac surgery is possible with a recruitment rate of over 2 patients per centre per month. To demonstrate a large benefit of RIPC (i.e., 30% relative risk reduction in patient-important outcomes) between 3000 and 6000 patients would need to be randomized depending on their baseline risk. A more realistic benefit (i.e., 15 to 20% relative risk reduction) would require between 6000 and 12000 patients. Such a trial would be a major undertaking and require enormous resources. Given there is, at most, a small biological effect on cardiac enzymes and serum creatinine, even a small to moderate effect on patient-important outcomes is unlikely in this clinical setting. As there are limited resources to devote to large clinical trials, more promising potential treatments likely merit examination in a large RCT over RIPC.

This realization has important implications. First there are several moderate size trials of RIPC underway. Remote IMPACT suggests that such trials are extremely underpowered and unlikely to detect any benefit to RIPC. Second, it is possible that the benefits of RIPC may be seen in different populations (i.e., healthier patients) or on different outcomes (e.g., pain). These scenarios are not addressed by our pilot trial. Third, although Remote IMPACT is one of the largest RIPC trials conducted, there was a relative imbalance in some baseline characteristics.



This finding reinforces the doubt one should have in the ability of randomization to produce balanced groups when small numbers of patients are randomized.

## 8.6. Future directions

The studies included in this thesis have influenced my research program substantially. I will extend the research on the interaction between cTnT and eGFR in the next wave of VISION. Moreover, I will apply the concepts that the threshold concentration of cardiac enzymes that is clinically important in patients with advanced kidney disease is unclear and that a prospective cohort is a suitable research paradigm to inform this issue. Recently I initiated the Hemodialysis Outcomes and Symptoms assessment (HOST) pilot study in which I am examining the change in a high sensitivity troponin I (hsTnI) concentration over a short period of time in hemodialysis patients. This study will help determine if there is a threshold concentration in hsTnI or change in hsTnI in hemodialysis patients that is associated with dialysis symptoms and overt cardiovascular events. The HOST study will also provide a platform to examine the relationship between intradialytic blood pressure and postdialysis symptoms and other clinical events. The study design and analytical methods for this are directly informed by the work done on perioperative hemoglobin and intraoperative hypotension. Although a trial of RIPC is not planned, Remote IMPACT greatly enhanced my knowledge of RCT methods and logistics. The experience informed the design and conduct of a pilot RCT I am now leading, the Pilot trial of Hemodialysis patients undergoing Aldosterone antagonism with Eplerenone (PHASE). PHASE has recruited over 120 patients in four months from 5 Canadian sites and it will inform the safety of eplerenone in the special population of patients that require dialysis. PHASE will also inform the design of a large trial, powered to detect a difference in patient-important outcomes, in the dialysis population.