PERIOPERATIVE BLEEDING IN GENERAL SURGERY

IDENTIFYING AND ADDRESSING THE PROBLEM OF PERIOPERATIVE BLEEDING IN GENERAL SURGERY: A MULTI-METHODS APPROACH

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LAY ABSTRACT

Every surgery carries the risk of unfavourable outcomes that could lead to worse quality of life or in severe cases, death. It is important to understand the factors that are associated with death to know where to best direct future research and resources. In the first two parts of this work, we identify the most common unfavourable outcomes that happen after general surgery and orthopedic surgery and explore which ones can lead to death. By conducting the same study on two different surgery populations, we demonstrate that different surgical fields may have differing areas of focus to improve outcomes after surgery. Upon identifying major bleeding to be the largest contributor for death in the general surgery cohort, the last part of the thesis looked at the use of a medication called tranexamic acid to safely reduce the risk of bleeding among general surgery patients.

ABSTRACT

Background: The contemporary causes of perioperative mortality in general surgery is not well described. It is likely that major bleeding is underestimated in current literature, which may have contributed to the lack of progress made in reducing perioperative bleeding in general surgery. Existing noncardiac surgery data has been instrumental in the identification of common post-operative complications and evaluating promising interventions to address them. However, context-specific evidence is required for uptake of research findings into clinical practice. The present work distilled the existing noncardiac surgery data to focus on the field of general surgery. In doing so, we identified perioperative bleeding to be a common complication in general surgery and attempted to address this issue.

Chapter 1 provides the background information and scientific framework that lay the foundation and justification for conducting the studies included in this work.

Chapter 2 presents the results of a large international prospective cohort study describing the epidemiology of post-operative complications in a cohort of contemporary general surgery patients and identify the complications associated with 30-day mortality.

Chapter 3 presents a study that was conducted with similar methodology as Chapter 2 but in the population of orthopedic surgery patients. The differences in the results as compared to the general surgery cohort highlights the importance of specialty-specific data to supplement noncardiac surgery data.

Chapter 4 presents the results of the PeriOperative ISchemic Evaluation-3 (POISE-3) trial substudy to provide general surgery specific evidence on the safety and efficacy of prophylactic TXA to reduce perioperative bleeding.

Chapter 5 summarizes the major findings of the thesis work and offer areas for future research.

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To my friends and family who were there for me through it all, I hope you read this thesis from beginning to end because I will test you, and because all of this is just as much your accomplishment as it is mine.

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LIST OF ABBREVIATIONS

VISION: Vascular Events in Noncardiac Surgery Patients Cohort

POISE-3: Perioperative Ischemic Evaluation-3

RCT: Randomized controlled trial

IQR: Interquartile range

TXA: Tranexamic acid

CAD: Canadian Dollars

MINS: Myocardial injury after noncardiac surgery

HR: Hazard Ratio

CI: Confidence Interval

AF: attributable fraction

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

PE: Pulmonary embolism

DVT: Deep vein thrombosis

AKI: Acute kidney injury

CHF: Congestive heart failure

hs-TnT: High-sensitivity troponin T

pRBC: Packed red blood cell

RBC: Red blood cell

COPD: Chronic obstructive pulmonary disease

ACS-NSQIP: American College of Surgeons' National Surgical Quality Improvement Program database

EPV: Events per variable

PAD: Peripheral arterial disease

aHR: Adjusted Hazards Ratio

URL: Upper reference limit

LBBB: new left bundle branch block

PCI: Percutaneous coronary intervention

ECG: Electrocardiogram

CABG: Coronary artery bypass grafting

CCSC: Candian Cardiovascular Society Class

GS: General surgery

SD: Standard Deviation

ISTH: International Society of Thrombosis and Haemostasis

BMS: Bare metal stent

DES: Drug eluting stent

NT-proBNP= N-terminal pro–B-type natriuretic peptide

HPB: Hepatopancreaticobiliary

GI: Gastrointestinal

BIMS: bleeding independently associated with mortality in noncardiac surgery

KT: Knowledge Translation

EMR-FO: Electronic medical record-facilitated order

DECLARATION OF ACADEMIC ACHIEVEMENT

I, Lily J Park, declare this thesis to be my own work, designed and conducted in collaboration with my Master's degree supervisor Dr. PJ Devereaux and committee members, Dr. Flavia Borges and Dr. Pablo Serrano. This is a mixed methods study reported as a sandwich thesis, considering two or more components of this work has been submitted or will be submitted for publication in peer reviewed journals. As the primary author of all components of this thesis, my contributions included: leading the conception and design of the study as well as the analysis plan, statistical analyses with support from statisticians, data interpretation, drafting of the manuscripts, and revising the manuscripts based on feedback from co-authors and committee members.

CHAPTER 1: INTRODUCTION

1.1 Background

Worldwide, over 100 million adult patients undergo noncardiac surgery every year.[1,2] Whether the surgery is conducted with curative or palliative intent, the goal remains to improve the overall quantity and or quality of survival. However, to undergo surgery also subjects the patient to potential risk for unfavourable outcomes including a large host of major complications, that may, in turn, lead to accelerated death. There have been great strides to minimize risk while optimizing benefits of surgery such that perioperative mortality rates have dramatically decreased in the last few decades.[3,4] Still, contemporary epidemiologic work describe 30-day mortality to be around 1.8%.[5] Assuming that 100 million adults undergo noncardiac surgery every year, this suggests that around 1.8 million adults die within 30 days from noncardiac surgery annually.[1,2,6] This highlights substantial opportunities to improve outcomes for noncardiac surgery patients.

Although the population of noncardiac surgery is invaluable for the combined sample size and power they provide, particularly in answering perioperative research questions, this thesis work will aim to distill specialty-specific data with a focus on general surgery. The two large bodies of work from which substudies of this thesis are derived, namely the Vascular Events in Noncardiac Surgery Patients Cohort (VISION) study and the PeriOperative ISchemic Evaluation-3 (POISE-3) trial, include noncardiac surgery populations.[6,7] These include general, orthopedic, vascular, urologic, spine, gynecologic, thoracic, plastics, neurologic, and other low-risk surgeries. The foundations

of surgery have remained and will likely continue to remain common denominators across these surgical specialties. However, with increasing specialization of each surgical field and the ever-evolving demographics of patients deemed eligible for different types of surgery, perioperative practices have begun to diverge across specialties, with research needing to adapt to these changes. [8]

The main challenge for specialty-specific data in surgery lies in attaining adequate sample sizes. A systematic review evaluating surgical randomized controlled trials (RCT) from 2008 to 2020 including 388 RCTs demonstrated a median sample size of 122 patients (interquartile range [IQR] 70-245 patients) with median fragility index for primary outcomes of 3.0 (IQR 1.0-6.0).[9] Thus, in the pursuit of enrolling homogenous populations from specific surgical specialties, studies may often be underpowered to adequately answer their primary research questions.[10,11] With the inclusion of noncardiac populations, we can achieve larger sample population sizes that are conducive to achieving precision and accuracy in answering research questions. However, this must be balanced with the external validity of the findings. With rapid expansion of surgical technology and science, there has been increasing acceptance for present day surgeons to limit their pursuit of mastery to specific clinical areas.[8] This shift toward prioritizing specialization in surgical practice has likely contributed to surgeons being less inclined to apply research evidence derived from populations that they have not or will not frequently encounter in their careers. For example, general surgeons may be less inclined to apply evidence derived from a population that included patients undergoing orthopedic surgery. Altogether, there is significant value in both large noncardiac surgery data to

demonstrate reliable effect sizes supported by distilled evidence according to surgical specialty.

For instance, the VISION study was a large international prospective cohort study including 40,004 noncardiac surgery patients that demonstrated that most perioperative deaths occur in the post-operative period.[6] They identified major bleeding, myocardial injury after noncardiac surgery, and sepsis to be the top three complications that are most associated with 30-day mortality.[6] Although this highlights important complications to be considered by all surgeons, the amalgamation of all specialties under one large umbrella of noncardiac surgery render application of these research findings in clinical settings to be a challenge. The patient population, risk profile, propensity for bleeding, surgical techniques, risks differ greatly across surgical specialties. Therefore, Chapters 2 and 3 will focus on distilling this data by the two largest surgical specialties, namely general and orthopedic surgery, to report specialty-specific evidence on the epidemiology of post-operative complications and their association with mortality. General surgery and orthopedic surgery were selected for the substudy evaluations because they comprised the largest populations in the VISION study and represent distinct surgical specialties without overlapping procedures.

The POISE-3 trial was an international double-blinded parallel RCT that investigated the safety and efficacy of two prophylactic 1g boluses of tranexamic acid (TXA) versus placebo in noncardiac surgery patients. This remains the largest RCT to date exploring the use of TXA, an antifibrinolytic agent, in surgery patients. However, there has been variations in the uptake of TXA use in clinical practice.[12,13] Based on a

cross-sectional survey study of oncologic surgeons, more than half voiced the need for evidence in their respective fields to be convinced to change practice.[13] Following the demonstration of major bleeding as the largest contributor of 30-day mortality in general surgery in the preceding chapter, Chapter 4 will discuss the generation of general surgery specific evidence for the prophylactic administration of TXA to reduce perioperative bleeding.

1.2 The Problem with Perioperative Bleeding

Perioperative bleeding is a feared complication by surgeons for many reasons.[14] Bleeding can be difficult to control both surgically and medically, leading to rapid clinical decompensation, impacting visibility of the surgical field, and increasing the technical challenge of the procedure. [15,16]

Perioperative bleeding can also lead to a cascade of physiologic derangements that may lead to further complications and death.[17–19] For instance, although a common treatment for clinically important bleeding includes blood transfusions, emerging evidence has repeatedly demonstrated the negative short- and long-term effects of this intervention consistently across various surgical contexts.[20–26] In addition to the challenge of blood donor economy with demand outpacing supply, there has been evidence to suggest that immunomodulatory effects from transfusion may be associated with immunocompromise and increased risk for cancer recurrence, particularly in colorectal surgery. [27,28]

From a research standpoint, a challenge surrounding perioperative bleeding is that it is a difficult outcome to define and capture.[29] Across studies, perioperative bleeding is

measured inconsistently, and often through methods that are known to be imprecise.[30] Some may measure units of blood transfused, and others may measure estimated blood loss, or changes in hemoglobin from pre-operative to post-operative phases of care.[29,30] Within each of these strategies to quantify perioperative bleeding, there are further methodologic variations.[29,30] Individual studies as well as surgical databases may report the number of blood products transfused but vary in the threshold of transfusion units required to be considered a major bleeding event.[31,32] This is further complicated by differing transfusion triggers that can vary by institution or surgeon practice.[33] Estimation of intraoperative blood loss is also often reported with several different formulae studied, many of which have been demonstrated to be inaccurate.[34] Change in hemoglobin measurements rarely account for preoperative anemia or perioperative hemodilution or hemoconcentration.[30] In all, no method of quantifying perioperative bleeding is without its flaws, leading to inconsistencies in how perioperative blood loss is reported in literature. [30]

As will be discussed in Chapter 2, the challenges of reliably measuring blood loss may have led to the underrepresentation of major bleeding in current literature. Among the few studies that investigated perioperative bleeding in general surgery, there is consistent demonstration of its association with mortality, but rate of occurrence is reported to be low.[31] This thesis work demonstrates the high incidence of perioperative bleeding that is captured when definition for the outcome is changed according to internal prognostic investigations that identified bleeding episodes associated with increased mortality risk.

Our findings for the high incidence of perioperative bleeding and its association with post-operative mortality provides strong rationale for the exploration of various methods to address this issue. There are several junctures throughout the perioperative phases of care that provide opportunity for meaningful intervention. Pre-operatively, there is opportunity for improved anemia detection and optimization.[35,36] Current evidence has consistently demonstrated poor clinical outcomes associated with pre-operative anemia including increased bleeding risk and need for transfusion.[37,38] However, high costs associated with the development of patient blood management (PBM) strategies have been a barrier to changes needed to address pre-operative anemia.[39,40] A recent population-based cohort study, led by the primary author, demonstrated an approximate $2,671 CAD additional cost that is attributable to anemia for each patient that undergoes colorectal surgery in Ontario, Canada.[41] This understanding of the resource use burden from a health systems perspective may help prioritize the development of effective PBM and anemia management strategies. Similarly, there is tremendous opportunity to reduce perioperative bleeding in the intraoperative phase of care through the use of prophylactic TXA, which has demonstrated its efficacy and safety in noncardiac surgery settings. This will be further detailed in Chapter 4.

1.3 Research Questions and Objectives

In the context of the above, the research questions for this thesis work were as follows:

1) Is bleeding an important predictor of mortality in 2 major surgery areas, namely general surgery and orthopedic surgery?
2) Is the use of tranexamic acid effective and safe in general surgery patients?

To address these research questions, 3 studies were conducted. The first two were prospective cohort studies utilizing general surgery and orthopedic surgery cohorts from the VISION study. The general surgery substudy demonstrated major bleeding to be largest contributor of 30-day mortality with the highest attributable fraction for death (i.e., the proportion of deaths that would not have occurred had bleeding not occurred, if causality were to be assumed). The orthopedic surgery study demonstrated myocardial injury after noncardiac surgery (MINS) to be the largest contributor of 30-day mortality, highlighting the differences in the epidemiology of post-operative complications and their impact on mortality by surgical specialty. In Chapter 4, we present a substudy of the POISE-3 trial where we develop general surgery specific evidence for the safety and efficacy of prophylactic TXA use with subgroup analyses across cancer status and subcategories of general surgery. These three studies add novel evidence on the contemporary risk factors for perioperative mortality in general surgery and orthopedic surgery, inform the need for specialty-specific data distilled from noncardiac surgery data, and investigate a promising intervention to reduce perioperative bleeding in general surgery. Altogether, we lay the groundwork for our future work in knowledge translation to facilitate adoption of perioperative research into clinical practice to reduce perioperative bleeding in general surgery.

CHAPTER 2: ASSOCIATION BETWEEN COMPLICATIONS AND DEATH WITHIN 30 DAYS AFTER GENERAL SURGERY: A VASCULAR EVENTS IN

NONCARDIAC SURGERY PATIENTS COHORT EVALUATION (VISION)

SUBSTUDY

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2.1 Abstract

Objective: To determine the epidemiology of post-operative complications among general surgery patients, inform their relationships with 30-day mortality, and determine the attributable fraction of death of each postoperative complication.

Background: The contemporary causes of post-operative mortality among general surgery patients are not well characterized.

Methods: VISION is a prospective cohort study of adult noncardiac surgery patients across 28 centres in 14 countries, who were followed for 30 days after surgery. For the subset of general surgery patients, a cox proportional hazards model was used to determine associations between various surgical complications and post-operative mortality. The analyses were adjusted for preoperative and surgical variables. Results were reported in adjusted hazard ratios (HR) with 95% confidence intervals (CI).

Results: Among 7950 patients included in the study, 240 (3.0%) patients died within 30 days of surgery. Five post-operative complications (myocardial injury after noncardiac surgery [MINS], major bleeding, sepsis, stroke, and acute kidney injury resulting in dialysis) were independently associated with death. Complications associated with the largest attributable fraction (AF) of post-operative mortality (i.e., percentage of deaths in the cohort that can be attributed to each complication, if causality were established) were major bleeding (n=1454, 18.3%, HR 2.49 95%CI 1.87-3.33, p<0.001, AF 21.1%), sepsis (n=783, 9.9%, HR 6.52, 95%CI 4.72-9.01, p<0.001, AF 15.6%), and MINS (n=980, 12.3%, HR 2.00, 95%CI 1.50-2.67, p<0.001, AF 14.4%).

Conclusion: The complications most associated with 30-day mortality following general surgery are major bleeding, sepsis, and MINS. These findings may guide the development of mitigating strategies, including prophylaxis for perioperative bleeding.

2.2 Introduction

Worldwide, over 70 million general surgery procedures are performed annually. [42] With advancements in surgical technology and techniques, there has been significant reductions in perioperative mortality in the last few decades, particularly in the developed nations where a large North American database reported contemporary mortality rates ranging from 0.4-3.7.[3] However, post-operative deaths continue to represent a significant health burden and is still considered the third greatest contributor to deaths globally, after ischemic heart disease and stroke. [4] The epidemiology of post-operative mortality and the perioperative complications associated with mortality are not well reported in the contemporary context. This may be especially important to demarcate considering the increased median age and comorbidity burden among current surgical populations compared to those considered to be eligible surgical candidates in the past. [43,44]

We have previously described the associations of postoperative complications and 30-day mortality in noncardiac surgery.[5] We found that major general surgeries were among the most common surgeries (19.9%) and demonstrated higher mortality rates (3%) compared to other noncardiac surgeries.[5] However, this study included various noncardiac surgical specialties including orthopedic surgery, urologic and gynecologic surgeries, vascular surgeries, and thoracic surgeries, which differ significantly in risk profiles to major general surgery procedures. Specialty-specific epidemiologic data are important to identify and target complications and risk factors in the surgical context of interest. Currently, there is a paucity of data on the epidemiology of postoperative

complications and their relationship with 30-day mortality, specifically among patients undergoing general surgery.

Our objective was to determine the incidence of common postoperative complications within 30 days after a major general surgery procedure, inform the time-dependent relationship between these complications and post-operative death, and determine the attributable fraction of each postoperative complication to post-operative mortality. Consistent with previous VISION analyses, we hypothesize that major bleeding, MINS, and Sepsis will be associated with 30-day mortality.

2.3 Methods

Study design

The design and methods for the VISION study has been previously described.[5] In summary, VISION was a large international, prospective cohort study of a representative sample of surgical patients at participating sites and included 40,004 noncardiac surgery patients. Data were collected across 28 centres in 14 countries in North and South America, Asia, Europe, Africa, and Australia from August 2007 to November 2013. Eligible patients included those aged 45 years or older, had undergone noncardiac surgery (emergency or scheduled), received general or regional anesthesia and remained in hospital for at least 1 night after surgery. Patients that underwent multiple surgeries during the recruitment period were only enrolled once. The Research Ethics Board at each participating site approved the protocol before patient recruitment. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was followed.

Analysis Population

All patients who were enrolled in the VISION study and underwent a major general surgery procedure were included in this substudy. As per the original VISION definitions, major general surgery was defined as complex visceral resection involving multiple organs, hollow viscus resections (i.e., bowel or stomach), other intra-abdominal surgeries, and major head and neck resections. Definitions of surgical procedures are provided in Appendix 2-1.

Follow up

Patients were followed for 30 days after surgery. If patients did not complete the 30-day follow-up, they were censored at the time of their last assessment.

Variable definitions

The primary outcome was all-cause mortality. We investigated the following post-operative complications during the first 30 days after surgery: myocardial injury after noncardiac surgery (MINS), any venous thromboembolism (i.e., pulmonary embolism [PE], deep vein thrombosis [DVT]) stroke, bleeding, acute kidney injury (AKI) requiring dialysis, sepsis, infection without sepsis, new atrial fibrillation, and congestive heart failure (CHF). These variables were selected for clinical relevance while being parsimonious to preserve model stability. Post-operative complications collected in the VISION study, which involved an intervention (percutaneous coronary intervention, coronary artery bypass graft, amputations etc.,) were excluded. Sepsis and infection without sepsis were two separate binary variables (i.e., not ordinal).

MINS was defined as a postoperative troponin elevation within 30 days of surgery that was judged to be due to an underlying ischemic insult. [45–47] A troponin elevation was

defined as the following: a non-high-sensitivity troponin T ≥30 ng/L; a high-sensitivity troponin T (hs-TnT) of 20 to <65 ng/L with an absolute change ≥5 ng/L or a hs-TnT ≥65 ng/L. For patients with both a non-high -sensitivity troponin T and a hs-TnT assays measured, the hs-TnT troponin was used in the MINS definition.

Patients were considered to have experienced major post-operative bleeding if they had an established bleeding event that 1) required transfusion of at least one unit of packed red blood cells (pRBC), 2) resulted in a hemoglobin drop to <70g/L, 3) required re-operation, or 4) was thought to be the cause of death. Definitions for other variables are provided in Appendix 2-2.

Statistical analysis

A statistical analysis plan was finalized and approved on January 18, 2023. The incidence of each of the postoperative complications as well as the proportion of deaths that occurred in-hospital versus after discharge were reported using descriptive statistics. Our sample size of 7950 patients provided 15 events per variable included in our model, which supports stability of the model.[48]

To determine the time-dependent risk of postoperative complications on 30-day mortality, we built a cox regression model where the dependent variable was time to mortality, censored at 30 days. Post-operative complications were included in the model as time-dependent variables. We adjusted for preoperative and surgical variables that were previously associated with mortality in VISION analyses.[49,50] These variables included in the adjusted analyses are age (65-75 years vs 45-65, and age ≥75 vs 45-65), recent high risk coronary artery disease, history of stroke, peripheral vascular disease,

chronic obstructive pulmonary disease (COPD), urgent or emergent surgery, and active cancer. All variables included in the model were selected a priori. Model performance was evaluated using the optimism-corrected concordance index. [51]

Given that all preoperative and surgical variables were already assessed for collinearity in the development of previous VISION analyses, we did not assess for collinearity and instead forced all variables into the model.[50,52] Adjusted hazard ratios and associated 95% CI and p-values for each predictor variable were reported. The attributable risk of death associated with each postoperative complication that was identified as a risk factor for mortality was then calculated based on an established method. [53] The attributable fraction of death is the proportion of deaths in our cohort, that can be attributable to each corresponding complication, if causality were to be established. This could only be calculated for risk factors that were significantly associated with 30-day mortality and therefore were considered to be a risk factor for death. An adjusted comparison by classification of surgery urgency to 30-day mortality was also performed. For all tests, we used alpha <0.05 as the level of significance. Analyses were performed using R Statistical Software (version 4.2.2; R Core Team 2022) using the "survival", "epiR", "ggplot2" packages.

2.4 Results

Patient characteristics

Among 40,004 patients enrolled in the VISION study, 7950 participants were identified to have undergone a major general surgery. Preoperative characteristics included in the models were available for all patients, thus 7950 patients were included in

the mortality analyses. Figure 1 demonstrates the flow of patient identification and inclusion. Appendix 1-1 demonstrates recruitment of patient by geography.

Table 1 demonstrates the preoperative characteristics, subcategories of general surgery, urgency status, and surgical technique (i.e., open, laparoscopic). Among 7950 patients, 48.7% were female patients. Over half (56.4%) of all patients were within the age range of 45-64 years, 25.1% were between the ages of 65-74, and 18.5% of patients were 75 years of age or older. Around half the patients (45%) had active cancer at the time of their surgery. The most common comorbidities included hypertension 46.5%, diabetes 18.9%, and coronary artery disease 10.5%. Within 24 hours prior to surgery, 0.2% had taken oral anticoagulation, 20.3% had received prophylactic subcutaneous anticoagulation, and 1.0% had received therapeutic subcutaneous or intravenous anticoagulation.

Within the subcategories of general surgery, 27.9% underwent gastric or colon surgery, 14.5% underwent a complex visceral resection, 8.2% underwent a major head and neck resection, and 52.8% of patients underwent a procedure that was categorized as other intra-abdominal surgery. Across all 7950 surgeries, 227 (2.9%) procedures were deemed to be low risk surgery. Most patients (69.0%) underwent general anesthesia as a sole anesthetic. There were 289 (3.6%) patients who underwent surgery on an emergency basis (i.e., surgery within 24 of presentation), 825 (10.4%) who underwent surgery on an urgent basis (i.e., surgery within 24-72 hours of presentation), and 6835 (86.0%) patients who underwent surgery on an elective basis. There were 67.0% patients who underwent

an open surgical procedure and 37.2% of patients who underwent a laparoscopic procedure.

Incidence of Death and Post-operative complications

Among 7950 participants, there were 240 deaths (3.0%, 95% CI 2.7-3.4) within 30 days. The median number of days to death following surgery was 11 days (interquartile range [IQR] 6-19). No deaths occurred intraoperatively, 186 (77.5%) of deaths occurred in hospital, and 54 (22.5%) of deaths occurred after the index hospital discharge. Mortality rates by continent are demonstrated in Appendix 1-2.

The risk of death varied by surgical urgency. Among patients who underwent emergent surgery 7.8% (95% CI 4.9-11.7) died, urgent surgery 9.0% (95% CI 7.0-11.2) died, and elective surgery 2.3% died (95% CI 1.9-2.6). Compared to those who underwent elective surgery, there was a significantly greater risk of death in emergent ($p<0.001$) and urgent surgery ($p<0.001$).

Table 2 summarizes the incidence of post-operative complications in the overall general surgery cohort and by subcategories of general surgery. The most common complications were major bleeding (N=1454, 18.3%), MINS (N=980, 12.3%), sepsis (N=783, 9.9%), and infection without sepsis (N=634, 8.0%). Following surgery, the median time to major bleeding was 1 day [IQR 1-3]. The median time to MINS was 2 days [IQR 1-3], sepsis was 7 days [IQR 4-11], and infection without sepsis was 9 days [IQR 6-13].

Relationship between perioperative complications and 30-day mortality

Table 3a demonstrates the relationship between the evaluated perioperative complications and 30-day mortality, while Table 3b demonstrates results for the adjusted variables included in the cox-regression model. Among the post-operative complications included in our model, 6 complications were significantly associated with 30-day mortality. These complications included major bleeding (HR 2.49 [1.87-3.33]), MINS (HR 2.00 [1.50-2.67]), sepsis (HR 6.52 [4.72-9.01]), infection without sepsis (HR 2.12 [1.26-3.58]), AKI resulting in dialysis (HR 3.55 [2.06-6.14]), and stroke (HR 12.78 [6.83-23.90]). This model had an optimism-corrected concordance index (C-index) of 0.85. The attributable fraction from highest to lowest for the six complications were 21.2% for major bleeding, 15.6% for sepsis, 14.4% for MINS, 3.2% for AKI requiring dialysis, 1.1% for stroke, and 0.05% for infection without sepsis. Figure 2 is a cumulative hazard curve that demonstrates the cumulative risk of death as well as the top 3 complications associated with death over the 30-day observation period in our cohort.

A post-hoc analysis including preoperative hemoglobin levels and estimated glomerular filtration rate in our mortality models demonstrated similar results, except that infection without sepsis was no longer significantly associated with 30-day mortality (HR 1.67 [0.97-2.87], p=0.06). The c-index of this model with the additional variables was 0.87. The recalculated attributable fraction for the five complications associated with mortality, that is, with the exclusion of infection without sepsis, resulted in similar values.

Separate post-hoc analyses were conducted in an exploratory analysis according to elective or non-elective surgeries, where the number of death events were 151 and 89, respectively. In the elective group, the 30-day post-operative complications associated

with death included major bleeding, MINS, sepsis, AKI resulting in dialysis, and stroke, with attributable risk percentages of 20.2%, 16.2%, 15.2%, 3.3%, and 2.2%, respectively. In the non-elective group, the complications associated with death included major bleeding, sepsis, and any venous thromboembolism, with attributable risk percentages of 30.1%, 17.7%, and 0.7%, respectively. Further details are provided in Appendix 1-3 and 1-4.

2.5 Discussion

In this prospective cohort study including 7950 general surgery patients, there were 240 deaths (3%) within 30-days of surgery. There were 6 post-operative complications that were significantly associated with 30-day mortality including major bleeding, MINS, sepsis, infection without sepsis, AKI requiring dialysis, and stroke. Of these complications, bleeding, MINS, and sepsis occurred most, and accounted for the top three highest attributable fraction of death in our cohort.

This is the first study to investigate the association of complications with mortality among an international contemporary general surgery prospective cohort. Previous studies are confined to single-institutional datasets or are retrospective analyses of databases, often limited by predefined variables.[3,31,54,55] Notably, sepsis and surgical site infections were consistently reported as commonly occurring complications associated with mortality. [3,54–56] This is consistent with our findings, especially considering that sepsis was among the top three complications that was highly attributable for death in our cohort. The study by Jacka *et al.* was based on the same VISION database but restricted the population only to major general surgery procedures.[45] This work demonstrated that 1

in 6 patients experience MINS with a near 5-fold increase in 30-day mortality. In the present study, around 1 in 8 patients experience MINS with a 2-fold increase in mortality. This is plausible considering the inclusion of lower risk general surgery procedures, that would incur less cardiovascular stress on patients. [45–47] Nonetheless, both studies demonstrate the importance of post-operative troponin measurement to detect MINS in general surgery patients.

Contrary to existing literature, our study identified major bleeding to be the most common complication associated with mortality that also accounted for the greatest attributable fraction of death. [3,31,54,55] These results were unchanged in sensitivity analyses adjusting for pre-operative hemoglobin levels, suggesting pre-operative anemia status likely did not impact our findings. Previous studies investigating post-operative complications do not commonly identify perioperative bleeding as a frequent complication, which may be a consequence of limitations in outcome definition and reporting. The VISION investigators undertook analyses to identify prognostically relevant diagnostic criteria for major bleeding based upon their impact on 30-day mortality.[57] Prior studies have failed to appreciate that bleeding can lead to death without a patient bleeding to death. Bleeding as a causal factor of death may result from numerous pathways such as organ ischemia from supply demand mismatch, thrombotic events due to withdrawal of antiplatelet and anticoagulation therapy, or infection from loss of key cells involved in mitigating sepsis. Prior studies have underestimated the impact of bleeding due to the use of definitions that were not empirically determined based upon prognostic relevance.

Furthermore, several studies reporting epidemiology of post-operative complications in general surgery, even those utilizing large databases, define bleeding incidents solely based on the need for transfusion. [3,31,54,55] A study investigating post-operative complications and their association with mortality using the American College of Surgeons' National Surgical Quality Improvement Program database (ACS-NSQIP) database defined major bleeding to be the need for >5 units of packed red blood cells within 72 hours of operation.[31] This study found that major bleeding showed a strong association with mortality (HR 5.18, 95% CI 3.69-7.27) but that it did not occur as frequently as infectious complications (3.2% versus 6.7%).[31] In contrast, our study found major bleeding occurred most commonly (18.3%, 95% CI 17.4-19.2) followed by MINS (12.3%, 95% CI 11.6-13.1), then sepsis (9.8%, 95% CI 9.2-10.5), then infection without sepsis (8.0%, 95% CI 7.4-8.6). A meaningful investigation of risk factors for mortality must involve the identification of complications before they reach critical stages such that intervention to prevent death is possible. Once a patient necessitates >5 units of packed red blood cells, we are increasingly limited in our options for meaningful interventions, as risk for death has been shown to be dose-dependent in its relationship with transfusion requirement.[58,59] Therefore, our study deliberately adopted a more inclusive definition of major bleeding to encompass less severe episodes that are still associated with mortality but have opportunity for meaningful intervention.[57] Similar to the recent adoption of a new AKI definition that led to a 1700% increase in the rate of reported AKIs in the NSQIP database, our study suggests consideration of adopting more inclusive bleeding

definitions to enhance precision of identifying risk factors with potential for intervention and improving patient outcomes.[60]

Although infection, sepsis, and bleeding were associated with 30-day mortality, we did not find an association of any venous thromboembolism (including pulmonary emboli or leg or arm DVT) with mortality. Post-hoc analyses by non-elective surgeries, which suggested a possible association was based on 3 of 10 venous thromboembolism events that lead to death, and interpretation was limited by the high likelihood of overfitting. Altogether, our results demonstrate that among general surgery patients, significant rates of post-operative bleeding persist and are associated with post-operative mortality, while such correlations are not seen with VTE. This difference may be partly attributed to the routine administration of anticoagulants for DVT prevention, as recommended by the World Health Organization's preoperative checklist.[61] In contrast, there is no requirement for the routine consideration of bleeding prophylaxis. Despite the low rate of prophylactic subcutaneous anticoagulant administration in our cohort at 28.0%, venous thromboembolic event rates were low at 0.9%.

Emerging evidence has demonstrated safety and efficacy of prophylactic tranexamic acid administration in reducing perioperative bleeding.[7,62] A large international trial and a large meta-analysis including 191 RCTs and 40,621 patients have demonstrated a clear benefit in perioperative bleeding reduction with TXA use without increased risk of thromboembolic events.[7,62] This supports routine consideration of prophylactic TXA use as the standard of care, which may help reduce perioperative mortality in general surgery patients. [63]

Limitations of the study

There are a few limitations to consider. Adjudications for some of the outcomes were based on site reports that relied on local physicians to have appropriately diagnosed the outcomes of interest. However, to reduce bias, clear parameters to diagnose each outcome was provided and our large and diverse sample allowed for acceptably precise estimates. The timing of transfusion, hemoglobin drop, or re-operation, around the time of a post-operative bleeding episode was not recorded. Transfusion triggers, which can vary by institutional and surgeon practices, were also not collected.[64,65] Instead, we relied on the judgement of local investigators that these were associated with clinically significant bleeding episodes, to be deemed a major bleeding outcome. Furthermore, this study looked at the short-term follow up of patients 30-days. Therefore, the associations of complications like sepsis or venous thromboembolism that may lead to eventual death but take a longer time to evolve, may have been underestimated. Finally, the sample size may be inadequate for the degrees of freedom in our model. The suggested adequate sample size in cox regression models range from 10-20 events per variable (EPV). Our sample size provided 15 EPV, which falls in the middle range of the least and most conservative suggested EPVs. Thus, there is a small risk of model overfitting.

This is the first study in general surgery to describe associations of complications and mortality. As a large, prospective study with time-dependent data, we were able to create a more dynamic and realistic model of the data, which considers the changes in risk factors for survival that occurs with time. We also had no missing data. Furthermore, the

inclusion of participants from 28 centres across 14 countries, increases generalizability of our results.

2.6 Conclusion

In this large international prospective cohort study of 7950 general surgery patients, the 30-day mortality rate was 3.0%. The post-operative complications significantly associated with 30-day mortality were major bleeding, sepsis, MINS, AKI requiring dialysis, infection without sepsis, and stroke. Among these, major bleeding, sepsis, and MINS accounted for the greatest attributable fraction of death in our cohort. This highlights areas for further study to identify potential interventions to reduce perioperative mortality. Importantly, with major bleeding accounting for a large percentage of mortality, our findings prompt routine consideration of bleeding prophylaxis before major general surgery procedures.

Table 1: Patient baseline characteristics for general surgery cohort

Characteristic	Participants with Characteristic, No. (%)
Age, years	
45–64	4483 (56.4)
65–74	1998 (25.1)
≥ 75	1469 (18.5)
Sex, female	3871 (48.7)
History of	
Hypertension	3696 (46.5) n= 7947
Diabetes	1506 (18.9) N=7947
Coronary artery disease	799 (10.5) n=7942
Peripheral vascular disease	216 (3.0)
Chronic obstructive pulmonary disease	535 (6.7)
Coronary revascularization	374 (4.7) n=7934
Stroke	245 (3.1)
Congestive heart failure	254 (3.2) n=7944
High-risk coronary artery disease	69 (0.9)
Cardiac arrest	37 (0.5) n=7944
Coronary revascularization within 6 mo	23 (0.3) n=7938
Active cancer	3581 (45)
Atrial fibrillation just before surgery	218 (2.7) n=7945
Preoperative estimated glomerular filtration rate (mL/min/1.73 m^2)	n=7444
< 30	275 (3.5)
30–44	293 (3.7)
45–59	677 (8.5)
> 60	6199 (78.0)
Subtypes of general surgery*	
Complex visceral resection	1155 (14.5)
Gastric or colon surgery	2222 (27.9)
Other intra-abdominal surgery	4197 (52.8)

Major head and neck resection for non-thyroid tumour	648 (8.2)
Subcategory of surgery	
Elective	6836 (86.0)
Urgent	825 (10.4)
Emergent	289 (3.6)
Type of anesthesia	
General only	5485 (69.0)
Neuraxial (spinal or epidural) only	228 (2.9)
General with nitrous oxide only	786 (9.9)
General and thoracic epidural only	967 (12.2)
General and nerve block only	88 (1.1)
Other	396 (5.0)
Oncologic status	
Active cancer	3581 (45.0)
No active cancer	4369 (55.0)
Surgical Technique*	
Laparoscopic	2957 (37.2)
Open	5326 (67.0)
Oral Anticoagulation	
≤ 24 hours from surgery	15 (0.2)
>24 hours to 7 days from surgery	220 (2.8)
Prophylactic SC anticoagulation	
≤ 24 hours from surgery	1611 (20.3)
>24 hours to 7 days from surgery	614 (7.7)
Therapeutic SC or IV anticoagulation	
≤ 24 hours from surgery	78 (1.0%)
>24 hours to 7 days from surgery	107 (1.3%)

*Not mutually exclusive data.

No.=number; mL=millilitre; min=minute; m=metre; SC=subcutaneous, IV=intravenous

Table 2: Thirty–day perioperative complications overall and by subtypes of general surgery

Outcome	No. (%, 95% CI) of patients				
		Subtypes of general surgery			
	All general surgery n=7950	**Complex visceral resection n=1155**	**Gastric and Colon Surgery n=2222**	**Other intra-abdominal surgery n=4197**	**Major head and neck resection for non-thyroid tumour n=648**
Major bleeding	1454 (18.3, 17.4-19.2)	386 (33.4, 30.7-36.2)	547 (24.6, 22.8-26.5)	484 (11.5, 10.6-12.5)	132 (20.4, 17.3-23.7)
MINS	980 (12.3, 11.6-13.1)	203 (17.6, 15.4-19.9)	297 (13.4, 12.0-14.9)	439 (10.5, 9.5-11.4)	77 (11.9, 9.5-14.6)
Sepsis	783 (9.8, 9.2-10.5)	197 (17.1, 14.9-19.4)	312 (14.0, 12.6-15.6)	291 (6.9, 6.2-7.7)	36 (5.6, 3.9-7.6)
Infection without sepsis	634 (8.0, 7.4-8.6)	99 (8.6, 7.0-10.3)	245 (11.0, 9.8-12.4)	262 (6.2, 5.5-7.0)	65 (10.0, 7.8-12.6)
Acute Kidney injury with dialysis	49 (0.6, 0.5-0.8)	15 (1.3, 0.7-2.1)	16 (0.7, 0.4-1.2)	18 (0.4, 0.3-0.7)	3 (0.5, 0.1-1.3)
Stroke	20 (0.3, 0.2-0.4)	1 (0.1, 0.0-0.5)	8 (0.4, 0.2-0.7)	7 (0.2, 0.1-0.3)	4 (0.6, 0.2-1.6)
Any Venous thromboembolism	71 (0.9, 0.7-1.1)	12 (1.0, 0.5-1.8)	25 (1.1, 0.7-1.7)	36 (0.9, 0.6-1.2)	6 (0.9, 0.3-2.0)
Congestive heart failure	113 (1.4, 1.2-1.7)	200 (17.3, 15.2-19.6)	53 (2.4, 1.8-3.1)	42 (1.0, 0.7-1.4)	5 (0.8, 0.3-1.8)
New, clinically important atrial fibrillation	145 (1.8, 1.5-2.1)	41 (1.2, 0.7-2.0)	57 (2.6, 1.9-3.3)	48 (1.1, 0.8-1.5)	10 (1.5, 0.7-2.8)
Death	240 (3.0, 2.7-3.4)	35 (3.0, 2.1-4.2)	96 (4.3, 3.5-5.3)	114 (2.7, 2.2-3.3)	12 (1.9, 1.0-3.2)

No.=Number; MINS=myocardial injury after noncardiac surgery

Table 3a: Relation between perioperative complications and 30-day mortality in general surgery

Outcome	No. of patients who died/total no. of patients with the outcome	Percentage (95% CI) of patients who died	Adjusted HR* (95% CI)	Attributable Fraction (AF) %
Major bleeding	123/1454	8.46 [7.07-10.01]	2.49 [1.87-3.33]	21.2
No major bleeding	117/6496	1.80 [1.49-2.15]	Ref.	
Sepsis	90/783	11.49 [9.34-13.94]	6.52 [4.72-9.01]	15.6
Infection without sepsis	19/634	2.99 [1.81-4.64]	2.12 [1.26-3.58]	0.05
No sepsis or infection	131/6532	2.00 [1.68-2.38]	Ref.	
MINS	86/980	8.78 [7.08-10.72]	2.00 [1.50-2.67]	14.4
No MINS	154/6970	2.21 [1.88-2.58]	Ref.	
Acute kidney injury with dialysis	18/49	36.7 [23.42-51.71]	3.55 [2.06-6.14]	3.2
No acute kidney injury with dialysis	222/7900	2.8 [2.46-3.20]	Ref.	
Stroke	5/20	25 [8.66-49.10]	12.78 [6.83-23.90]	1.1
No stroke	235/7930	2.96 [2.60-3.36]	Ref.	
Venous thromboembolism	4/71	5.63 [1.56-13.80]	1.06 [0.38-2.92]	NA
No venous thromboembolism	236/7879	2.99 [2.63-3.40]	Ref.	
Congestive heart failure	14/113	12.39 [6.94-19.9]	1.29 [0.71-2.33]	NA
No congestive heart failure	226/7836	2.88 [2.52-3.28]	Ref.	
New, clinically important atrial fibrillation	19/145	13.10 [8.08-19.70]	1.29 [0.75-2.22]	NA
No new, clinically important atrial fibrillation	221/7805	2.83 [2.47-3.22]	Ref.	

No.=Number; CI=confidence interval; HR=Hazard Ratio; MINS=myocardial injury after noncardiac surgery; Ref.=Reference; NA=Not applicable
*Adjusted variables were as follows: age category, recent history of high risk coronary artery disease, history of stroke, history of peripheral vascular disease, history of chronic obstructive pulmonary disease, surgery urgency (elective, urgent, emergent), cancer status at time of surgery

Table 4b: Results of variables adjusted for in cox regression model

Variable	Adjusted HR* (95% CI)
Age 45-65 years	Ref.
Age 65-75 years	1.28 (0.92-1.79)
Age ≥75 years	2.05 (1.51-2.79)
Recent history of high risk CAD	0.53 (0.24-1.14)
History of stroke	1.80 (1.11-2.90)
History of PVD	0.69 (0.42-1.12)
History of COPD	0.85 (0.57-1.27)
History of cancer	174 (1.29-2.33)
Surgery urgency – elective	Ref.
Surgery urgency – urgent	4.90 (3.57-6.73)
Surgery urgency – emergent	3.08 (1.89-5.01)

CI=confidence interval; HR=Hazard Ratio; Ref.=Reference; CAD=coronary artery disease; PVD=peripheral vascular disease; COPD=chronic obstructive pulmonary disease

Figure 1: Patient flow diagram for inclusion in VISION general surgery substudy

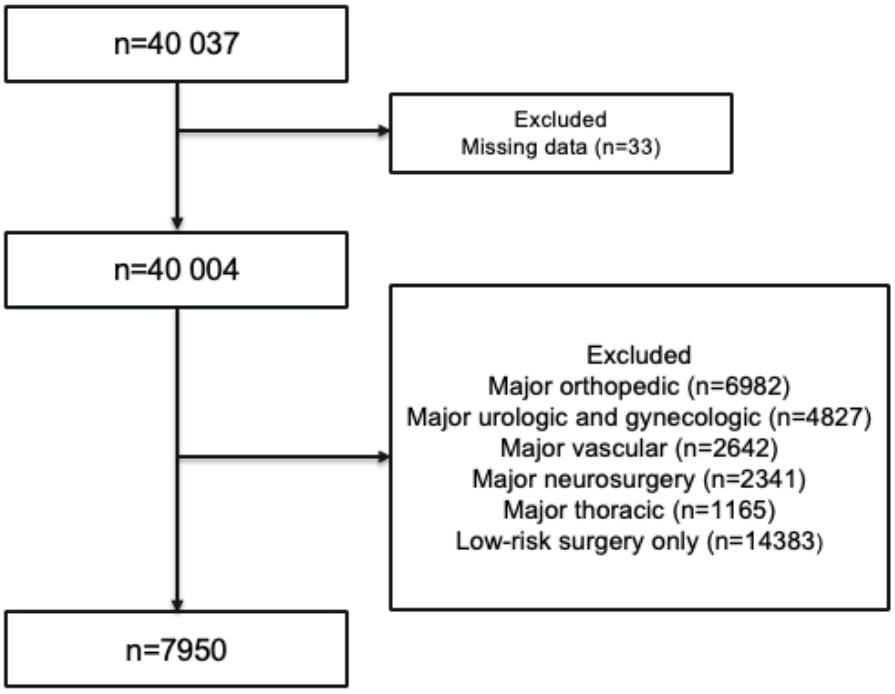
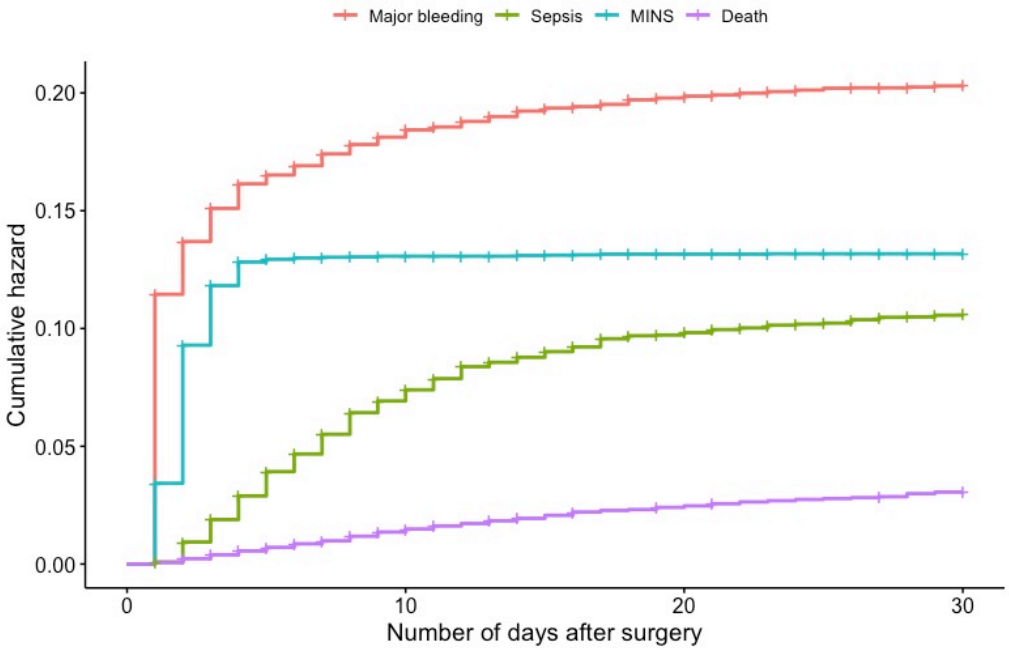


Figure 2: Cumulative hazard curve for death, major bleeding, MINS, and sepsis



MINS=myocardial injury after noncardiac surgery

CHAPTER 3: ASSOCIATION BETWEEN COMPLICATIONS AND DEATH WITHIN 30 DAYS AFTER ORTHOPEDIC SURGERY: A VASCULAR EVENTS IN NONCARDIAC SURGERY PATIENTS COHORT EVALUATION (VISION) SUBSTUDY

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3.1 Abstract

Introduction: The contemporary causes of postoperative mortality in orthopedic surgery are not well characterized. The objective was to describe the epidemiology of postoperative complications among adult orthopedic surgery patients and inform their relationships with 30-day mortality.

Methods: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) was a prospective cohort study involving 40,004 adult patients who underwent noncardiac surgery across 28 centres in 14 countries. For the subset of orthopedic surgery patients, a Cox proportional hazards model was used to determine time-dependent associations between various surgical complications and 30-day postoperative mortality. Analyses were adjusted for preoperative and surgical variables.

Results: Among 8385 patients who underwent an orthopedic surgery in VISION, 132 (1.6%) patients died within 30 days of surgery. Of these deaths, 84 (63.6%) occurred in hospital during the index hospitalization, while 48 (36.4%) deaths occurred after discharge. The incidence of death across the subcategories of orthopedic surgery was: above knee amputation (30/221, 13.6%), internal fixation of femur (29/750, 3.9%), lower leg amputation (9/252, 3.6%), major hip or pelvic surgery (49/2898, 1.7%), major spine surgery (8/1405, 0.6%), and knee arthroplasty (7/2876, 0.2%). Six postoperative complications (myocardial injury after noncardiac surgery [MINS], major bleeding, infection without sepsis, sepsis, stroke, atrial fibrillation) were associated with death. The greatest attributable fraction of postoperative mortality (i.e., proportion of deaths in the cohort that can be attributed to each complication, if causality were established) were

from MINS (N=1454, 17.3%, hazard ratio [HR] 2.08, 95% confidence interval [CI] 1.38-3.14, p<0.001, attributable fraction 20.7%), major bleeding (N=2422, 28.9%, HR 1.95, 95%CI 1.34-2.85, p<0.001, attributable fraction 16.5%), and sepsis (N=318, 3.8%, HR 6.24, 95%CI 3.85-10.12, p<0.001, attributable fraction 9.7%).

Conclusion: The complications most attributable to 30-day mortality following orthopedic surgery were MINS, major bleeding, and sepsis. These findings highlight areas for further study to mitigate perioperative mortality in orthopedic surgery. MINS demonstrated the highest attributable fraction for mortality (20.7%), emphasizing the importance of appropriate MINS diagnosis and management.

3.2 Introduction

Globally, there was an estimated 22.3 million orthopedic surgeries performed in 2017, with this number forecasted to increase by 4.9% annually and approaching 31.4 million procedures by 2024.[66] Among these patients, the mortality rate is broadly estimated to be between 0.6 to 8.7%. Even at the lower end of this estimated range, mortality after orthopedic surgery represents a substantial health issue. [67–70] Much of the existing mortality data are derived from hip fracture and orthopedic trauma patients, which represents only a small fraction of the entire orthopedic surgery population. [67–70] This highlights the need to better elucidate mortality rates in a broad sample of general contemporary orthopedic surgery patients.

The largest study to date in this area utilized the National Hospital Discharge survey to identify risk factors for mortality in orthopedic surgery across a nationwide sample of hospitals in the United States.[70] However, this study is limited by the retrospective nature of the study, reliance on administrative data, and older data. Furthermore, although the National Hospital Discharge survey is considered to be accurate for mortality, it is thought to be less reliable in reflecting morbidity and complications.[70–75] Considering this, an updated and accurate understanding of modifiable risk factors for death in a diverse, representative, orthopedic surgery population is needed.

The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) was a large prospective cohort study that included a representative sample of adults who underwent noncardiac surgery and were systematically followed to document postoperative complications, including mortality.[76] We previously reported the incidence

of perioperative complications and associated mortality for the entire VISION study population. Patients undergoing orthopedic surgery represent a unique population that is increasingly comprised of geriatric patients with rising prevalence of cardiovascular disease.[77–79] This necessitates specialty-specific epidemiologic data.

The objective of this prospective cohort substudy was to describe the epidemiology of postoperative complications and death, evaluate the associations between these postoperative complications and death, report the attributable fractions of each complication for death, and determine the risk of death and major cardiovascular complications at 30-days after orthopedic surgery according to preoperative troponin levels.

3.3 Methods

Study design

The design and methods of the VISION study have been previously described.[76] In summary, VISION was an international prospective cohort study of a representative sample of adults who underwent in-patient noncardiac surgery (i.e., patients who underwent elective, urgent, or emergency surgery during the day or night and on a weekday or weekend). VISION enrolled 40,004 noncardiac surgery patients across 28 centres in 14 countries from August 2007 to November 2013. Patients aged 45 years or older, who underwent noncardiac surgery, receiving general or regional anesthesia, and requiring at least 1 overnight hospital stay after surgery were eligible for inclusion. Each participating hospital obtained approval from their research ethics board, prior to the start

of patient enrollment. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was followed.

Analysis population

Patients who were enrolled in the VISION study and underwent an orthopedic procedure (including spine surgery) were included in this sub study. According to the VISION definitions, this would include surgeries categorized as: major hip or pelvic surgery, internal fixation of femur, knee arthroplasty, above knee amputation, lower leg amputation, and major spine surgery.

Follow up

Patients were followed for 30 days following their surgery and were censored at the time of their last assessment if the 30-day follow-up was not complete.

Variable definitions

Definitions for all variables included in the analyses are provided in Appendix 2-2. The primary outcome was time to all-cause mortality. The following postoperative complications during the first 30 days after surgery were investigated: myocardial injury after noncardiac surgery (MINS), venous thromboembolism (VTE), stroke, bleeding, acute kidney injury (AKI) resulting in dialysis, sepsis, non-sepsis infection, new clinically important atrial fibrillation, and congestive heart failure (CHF). These variables were selected for clinical relevance while being parsimonious to preserve model stability. Post-operative complications collected in the VISION study, which involved an intervention (percutaneous coronary intervention, coronary artery bypass graft surgery, amputations

etc.,) were excluded. Sepsis and infection without sepsis were two separate binary variables (i.e., not ordinal).

MINS was defined as any myocardial infarction or any postoperative troponin elevation within 30 days after surgery, that was judged to be secondary to myocardial ischemia. All troponin measurements included in this analysis utilized the Roche fourth or fifth generation Elecsys assays (Basel, Switzerland). Based on prior analyses establishing prognostic relevance, postoperative troponin elevation was defined as follows: a non-high-sensitivity troponin T ≥30 ng/L or a high-sensitivity troponin T (hs-TnT) of 20 to <65 ng/L with an absolute change ≥5 ng/L or a hs-TnT ≥65 ng/L.[46] Baseline troponin elevation was any value above the threshold for MINS as established in prior VISION publications. Since all preoperative assays in this cohort utilized hs-TnT, a value greater than or equal to 20ng/L was considered to be elevated. In separate sensitivity analyses, we utilized a second definition of baseline troponin elevation as any value above the 99th percentile of the upper reference limit that was proposed by the troponin assay manufacturer (i.e., hsTnT ≥14 ng/L). Of note, systematic collection of post-operative troponin occurred as per the study protocol while there was no protocol for pre-operative troponin collection. VTE was a composite outcome that included pulmonary emboli (PE) or deep vein thrombosis (DVT). Sepsis required the evidence of an infection as well as a systemic inflammatory response. Major bleeding was defined as a bleeding episode associated with 1) transfusion of at least one unit of packed red blood cell (pRBC), 2) a hemoglobin drop to <70g/L, 3) re-operation, or 4) death. Major cardiovascular complications was a composite of MINS, CHF, stroke, and death.

Statistical analysis

An a priori statistical analysis plan was written before undertaking analyses for this study, which was finalized in June 2023**.** Descriptive statistics were used to report patient characteristics. We determined the incidence of death and each of the postoperative complications during the first 30 days after surgery and the corresponding 95% confidence intervals (CI). Since the incidence of AKI resulting in dialysis was less than 0.2%, this variable was omitted from the model to preserve model stability.

To determine the relationship between complications and 30-day mortality, we used a time-dependent Cox proportional hazards model and adjusted for baseline characteristics that were known to be independently associated with 30-day mortality, according to previous VISION analyses.[76] This base model was adjusted for age category (65-75 years vs 45-65, and age ≥75 vs 45-65), cancer at the time of surgery, history of chronic obstructive pulmonary disease (COPD), surgery urgency (emergent: <24 hours from admission for an acute surgical condition, urgent: 24-72 hours from admission for an acute surgical condition, elective: all other surgeries), and history of peripheral arterial disease (PAD). All variables included in the model were selected a priori. We reported the adjusted hazard ratios (HR) and corresponding 95% CI for each postoperative complication evaluated. Model performance was assessed using the c-statistic corrected for optimism using 1000 bootstrapped samples.[51] We calculated the attributable risk of death for each of the postoperative complications that were found to be independently associated with 30-day mortality, using an established method.[53] The attributable fraction represents the proportion of deaths that potentially would not have occurred in the

VISION orthopedic cohort if the complication had not occurred, if we assumed a causal relationship between the complication and death. There were 10 events per variable included in the model, which supports model stability. [80]

To determine the relationship between preoperative troponin levels and death, we conducted a secondary analysis including preoperative troponin elevation (i.e., hsTnT ≥20 ng/L) as a binary independent variable into the base model with the dependent variable of all-cause mortality. Another model was created for the composite outcome for cardiovascular complications, which included death, MINS, stroke, and CHF at 30 days after orthopedic surgery. An a priori planned sensitivity analysis was conducted, which considered a lower preoperative troponin elevation threshold (i.e., hsTnT ≥14 ng/L). All analyses were adjusted for the aforementioned baseline and surgical variables.

For all tests, we used alpha <0.05 as the level of significance. Analyses were performed using R statistical Software (version 4.2.2; R Core Team 2022) using the "survival", "epiR", "ggplot2" packages.

3.4 Results

Patient characteristics

Within the 40,004 patients enrolled in the overall VISION study, 8385 (21.0%) patients underwent an orthopedic surgery and were included in these analyses. Figure 3 demonstrates the flow of patient inclusion. Table 4 demonstrates the baseline characteristics of included participants and corresponding 30-day mortality. Over half the patients were over the age of 64 and 57.3% were female. Among participants, 59% had a

history of hypertension, 21.8% diabetes, 15% coronary artery disease, 7.6% COPD, 6.2% PAD, and 3.8% had active cancer at the time of their surgery.

Among 8385 patients, 2898 (34.6%) underwent a major hip or pelvic surgery, 2876 (34.3%) underwent knee arthroplasty, 1405 (16.8%) underwent a major spine surgery, 750 (8.9%) underwent internal fixation of femur, 252 (3.0%) underwent lower leg amputation, and 221 (2.6%) underwent above knee amputation. The majority of patients (87.9%) underwent elective surgery.

Incidence of death within 30 days after surgery

There were 132 (1.6%) deaths in the orthopedic surgery cohort within 30 days after surgery (Table 5). Of these deaths, 84 (63.6%) occurred in hospital during the index hospitalization, while the remaining 48 (36.4%) deaths occurred after discharge. Two (1.5%) patients died in the operating room. The median time to death was 13.5 days (IQR 6-21). Incidence of death occurred as follows across the subcategories of orthopedic surgery: above knee amputation (30/221, 13.6%), internal fixation of femur (29/750, 3.9%), lower leg amputation (9/252, 3.6%), major hip or pelvic surgery (49/2898, 1.7%), major spine surgery (8/1405, 0.6%), and knee arthroplasty (7/2876, 0.2%). Death rates by elective, urgent, and emergent surgeries were 81/7288 (1.1%), 46/812 (5.7%), and 5/153 (3.3%), respectively. Risk of 30-day mortality was increased in non-elective (i.e., emergent and urgent surgeries) compared to elective surgeries in adjusted analyses (HR 2.30, 95% CI 1.61-3.42, $p<0.001$).

Postoperative complications and relationship with 30-day mortality

Table 5 demonstrates the incidence of postoperative complications and death within 30 days among those with complications. The most common complication was bleeding (2422 patients; 28.0%), followed by MINS (1454 patients; 17.3%), infection without sepsis (562 patients; 6.7%), sepsis (318 patients, 3.8%), then VTE (123 patients, 1.5%), CHF (124 patients, 1.5%), new atrial fibrillation (93 patients, 1.1%), stroke (27 patients, 0.3%), and AKI resulting in dialysis (17 patients, 0.2%). The median time from surgery to bleeding was 2 days (interquartile range [IQR] 1-3), MINS 2 days (IQR 1-3), infection without sepsis 10 days (IQR 5-17), and sepsis 8 days (IQR 4-13).

Postoperative complications associated with 30-day mortality (Table 6) included major bleeding (adjusted HR [aHR] 1.95, 95%CI 1.34-2.85), MINS (aHR 2.08, 95% CI 1.38-3.14), sepsis (aHR 6.24, 95% CI 3.85-10.12), infection without sepsis (aHR 2.74, 95% CI 1.54-4.85), stroke (aHR 6.01, 95% CI 2.19-16.56), and new clinically important atrial fibrillation (aHR 2.65, 95% CI 1.25-5.65). The c-statistic for model performance before and after correction for optimism was 0.87 and 0.85, respectively. See Table 6 for details.

Among the postoperative complications significantly associated with mortality, the greatest attributable fraction was for MINS (20.6%), followed by major bleeding (16.5%), then sepsis (9.7%), infection without sepsis (3.8%), new atrial fibrillation (2.2%), and stroke (1.5%).

Relationship between preoperative troponin levels and death

Preoperative troponin levels were available for 2174 (25.9%) of orthopedic surgery patients and are summarized in Table 7. The overall median preoperative hsTnT

levels was 7.2 ng/L (IQR 4.1-13.0). Median preoperative hsTnT levels for elective and non-elective patients were 7.0 (IQR 4.0-13.0) and 11.0 (IQR 6.0-24.4), respectively. Troponin was elevated in 289/2095 (13.8%) elective patients, and in 24/79 (30.4%) non-elective patients.

Preoperative troponin elevation (i.e., hsTnT ≥20 ng/L) was not significantly associated with all-cause 30-day mortality (aHR 1.23, 95% CI 0.30-5.07, p=0.78), but was significantly associated with major postoperative cardiovascular complications (aHR 4.53, 95% CI 3.65-5.63, p<0.001). Sensitivity analysis with preoperative troponin elevation as any value greater than 14 ng/L for the fifth generation assay demonstrated similar results. There was no significant association with all-cause 30-day mortality (HR 3.03, 95% CI 0.64-14.3, p=0.16). The significant association with major cardiovascular complications persisted (HR 5.90, 95% CI 4.75-7.34).

3.5 Discussion

This large international prospective cohort study involving 8385 orthopedic surgery patients demonstrated a 1.6% mortality rate and identified most common complications to be major bleeding, MINS, infection without sepsis and sepsis. These complications, in addition to stroke and new clinically important atrial fibrillation, were significantly associated with 30-day mortality following adjustment for baseline characteristics. Among these, the greatest attributable fraction for death in our cohort was from MINS (21%), major bleeding (17%), sepsis (10%), infection without sepsis (4%), stroke (2%), and new atrial fibrillation (2%). Preoperative troponin elevation

demonstrated significant association with major cardiovascular complications and a non-significant trend toward greater risk for 30-day mortality.

Although prior older studies with methodological limitations have reported 30-day mortality rates ranging from 0.6 to 8.7%,[67–69] VISION demonstrated a 1.6% mortality rate. Our study also demonstrated substantial variation across subcategories of orthopedic surgery and urgency of surgery. Traditional pre-operative risk scoring systems do not consider the nuances between surgical procedures that contribute to notable variations in mortality risk.[81] We found substantial mortality differences across surgical procedures within orthopedic surgery, which urgers greater consideration of procedure type for pre-operative risk stratification and consideration of higher level post-operative monitoring (e.g., admission to intensive cardiac care unit, telemetry).

Among the few studies that investigate complications associated with mortality in orthopedic surgery, pneumonia, acute renal failure, stroke, myocardial infarction, and MINS have been reported.[70,82] Our results are unique in identifying major bleeding to be a risk factor for death in the orthopedic surgery cohort. Previous studies did not select postoperative bleeding as a potential variable to explore, despite 80% of 739 orthopedic surgeons and 50 anesthesiologists in an international survey responding that they were either concerned or very concerned for bleeding in orthopedic surgery populations.[83] Our results demonstrate that major bleeding in orthopedic surgery is common and is associated with mortality, necessitating further investigations in this area to improve patient outcomes.

Although a major bleeding event was the most common complication in our cohort, MINS demonstrated the greatest attributable fraction for death. In other words, although an overall smaller number of patients experienced MINS, a greater number of patients with MINS died within 30 days of surgery compared to the number of patients who experienced major bleeding. This is unique to the orthopedic surgery cohort compared to the overall VISION mortality analyses and general surgery mortality substudy, where bleeding was the most common complication and had the highest attributable fraction for death.[76] Certainly, the varying risk profiles, propensity for bleeding, and cardiovascular stress by surgical subspecialties contribute to the differences in these results. This emphasizes the need for specialty-specific data to inform surgery specific practice.

Another potential explanation is the unique practice of bleeding prophylaxis that is commonplace in orthopedic surgery.[84–87] Orthopedic surgery-specific research demonstrates a reduction in perioperative bleeding with the use of prophylactic tranexamic acid (TXA), an antifibrinolytic agent, particularly in orthopedic trauma, joint surgery, and spine surgery contexts. [84–89] With consistent signals favouring the use of TXA, it has been routine practice in orthopedic surgery for many years, whereas this is not commonplace in other noncardiac surgical specialties, despite recent evidence to support its safety and efficacy in these contexts.[7,13,62,84–86] Future studies exploring uptake of TXA use across different surgical subspecialties are needed to elucidate this further. However, the longstanding practice of routine prophylaxis for perioperative bleeding in orthopedic surgery may have contributed to reduced bleeding severity and lower

attributable fraction for death in this cohort compared to the overall and general surgery cohorts. If this were to be true, it is also worth noting that the rate of VTE in this orthopedic cohort was only around 1%, which is similar to the incidence found in the noncardiac and general surgery cohorts.[76]

Preoperative troponin measurements were only available for 25.9% of our cohort. Although underpowered to demonstrate association with death our analyses demonstrated associations with increased cardiovascular complications. This supports the findings of a previous retrospective cohort study that found preoperative troponin elevation to be associated with major adverse cardiac events (adjusted HR 3.75, 95% CI 2.09-6.17, $p<0.01$).[90] We demonstrated MINS had the highest attributable fraction for death in our cohort. Previous VISION analyses utilizing non-high-sensitivity troponin T demonstrated prevalence of MINS to be 1 in 8 patients undergoing orthopedic surgery.[77] With the inclusion of spine surgeries and the use of high-sensitivity troponin T in the analysis herein, the incidence of MINS was greater at 1 in 6. Furthermore, the previous VISION study by Thomas *et al.* reported that 81.3% (95% CI 76.3-85.4%) of patients with MINS were asymptomatic.[77] Altogether, this highlights the importance of routine postoperative monitoring for MINS in orthopedic surgery patients and supports the need for further investigations to understand the role of preoperative troponin in perioperative risk stratification.

One-third of the deaths that occurred happened after hospital discharge. Since this study was undertaken, patients are now discharged home sooner.[91] This highlights the need for surgical transition programs that follow and monitor at-risk patients discharged

home after orthopedic surgery. Without such programs, it is likely that more patients will have delays in recognizing complications and therefore may have worse outcomes.[91]

Limitations

There are a few limitations to consider. The granularity of the data is limited to the subcategories of orthopedic surgery that were predefined before the start of the study. For instance, major hip and pelvic surgery could include hemi or total hip arthroplasty or internal fixation of the hip, but the specific breakdown of these procedures was not collected. Furthermore, internal fixation of femur could have included internal fixation of the hip if, at the discretion of the centre, proximal femur fractures, which are also anatomically considered the hip, were categorized as such. [92–94] The stability of a Cox regression model is dependent on the events per variable. Most studies advocate for 10-30 events per variable for model stability.[80,95] The base model meets the lower cut off at 10 events per variable, and so there is limited power and potential risk for overfitting. However, the negligible change in the c-statistic after correcting for optimism, suggests overfitting may not be a significant issue.[51] Finally, preoperative troponin levels were not systematically collected. Therefore, patients for which preoperative troponin were available likely represent a sicker cohort, increasing the risk of confounding in our analyses.

To our knowledge, this is the first large prospective study exploring the association of various postoperative complications and death in a global prospective orthopedic surgery study. The inclusion of diverse participants across 14 countries, increases the generalizability of our results. Furthermore, with no loss to follow-up and

the collection of time dependent data, we were able to increase precision and reduce bias in fulfilling our objectives by creating a realistic model that accounts for the changes in risk factors for survival that occurs over time.

3.6 Conclusion

This large international prospective cohort study of patients undergoing orthopedic surgery (88% elective) demonstrated a 30-day mortality rate of 1.6%. Adjusted analyses demonstrated major bleeding, MINS, sepsis, infection without sepsis, stroke and atrial fibrillation to be associated with mortality. The highest attributable fraction of death in our cohort was contributed by MINS, major bleeding, sepsis, and infection without sepsis, which highlights areas for further study to reduce mortality among orthopedic surgery patients. Elevated preoperative troponin levels were associated with postoperative cardiovascular outcomes. Further studies are needed to understand the value of baseline troponin measurement for risk stratification in orthopedic surgery.

Table 5: Patient baseline characteristics for orthopedic surgery cohort

Characteristic	Participants with Characteristic, No. (%)	Number of deaths within 30 days (%)
Age, years		
45–64	3411 (40.7)	31 (0.9)
65–74	2418 (28.8)	20 (0.8)
≥ 75	2556 (30.5)	81 (3.2)
Sex, female	4802 (57.3)	76 (1.6)
History of		
Hypertension	4948 (59.0)	89 (1.8)
Diabetes	1823 (21.8)	44 (2.4)
Coronary artery disease	1253 (15.0)	41 (3.3)
Peripheral arterial disease	519 (6.2)	39 (7.5)
Chronic obstructive pulmonary disease	640 (7.6)	33 (5.2)
Coronary revascularization	470 (5.6)	6 (1.3)
Stroke	398 (4.7)	20 (5.0)
Congestive heart failure	401 (4.8)	20 (5.0)
Active cancer	320 (3.8)	13 (4.1)
Atrial fibrillation	323 (3.9)	11 (3.4)
Preoperative estimated glomerular filtration rate (mL/min/1.73 m^2)		
< 30	294 (3.7)	26 (8.8)
30–44	503 (6.2)	22 (4.4)
45–59	988 (12.3)	12 (1.2)
≥ 60	6264 (77.8)	67 (1.1)
Types of Orthopedic Surgery		
Major hip or pelvic surgery	2898 (34.6)	49 (1.7)
Internal fixation of femur	750 (8.9)	29 (3.9)

Knee arthroplasty	2876 (34.3)	7 (0.2)
Above knee amputation	221 (2.6)	30 (13.6)
Lower leg amputation	252 (3.0)	9 (3.6)
Major spine surgery	1405 (16.8)	8 (0.6)
Subcategory of surgery		
Elective	7369 (87.9)	81 (1.1)
Urgent/Emergent	1016 (12.1)	51 (5.0)
Type of anesthesia		
General only	2436 (29.1)	36 (1.5)
Neuraxial (spinal or epidural) only	4182 (49.9)	72 (1.7)
General with nitrous oxide only	424 (5.1)	10 (2.4)
General and thoracic epidural only	10 (0.1)	0
General and nerve block only	424 (5.1)	2 (0.5)
Other	903 (10.8)	12 (1.3)

No.=number; mL=millilitre; min=minute; m=metre

Table 6: Thirty–day perioperative complications overall and by subtypes of orthopedic surgery

Outcome	No. (%, 95% CI) of patients						
	All orthopedic surgery *n* = 8385	Subtypes of orthopedic surgery					
		Major hip or pelvic surgery *n* = 2898	Internal fixation of femur *n* = 750	Knee arthroplasty *n* = 2876	Above knee amputation *n* = 221	Lower leg amputation *n* = 252	Major spine surgery *n* = 1405
Major bleeding	2422 (28.9)	965 (33.3)	287 (38.3)	725 (25.2)	103 (46.6)	96 (38.1)	258 (18.4)
MINS	1454 (17.3)	563 (19.4)	165 (22.0)	347 (12.1)	95 (43.0)	95 (37.7)	197 (14.0)
Sepsis	318 (3.8)	124 (4.3)	33 (4.4)	53 (1.8)	30 (13.6)	20 (7.9)	60 (4.3)
Infection without sepsis	562 (6.7)	251 (8.7)	63 (8.4)	153 (5.3)	14 (6.3)	29 (11.5)	54 (3.8)
Acute Kidney injury with dialysis	17 (0.2)	4 (0.1)	3 (0.4)	2 (0.1)	2 (0.9)	3 (1.2)	3 (0.2)
Stroke	27 (0.3)	9 (0.3)	6 (0.8)	6 (0.2)	1 (0.5)	2 (0.8)	3 (0.2)
Venous thromboembolism	123 (1.5)	29 (1.0)	16 (2.1)	69 (2.4)	1 (0.5)	0 (0.0)	8 (0.6)
Congestive heart failure	124 (1.5)	50 (1.7)	29 (3.9)	23 (0.8)	13 (5.9)	6 (2.4)	4 (0.3)
New, clinically important atrial fibrillation	93 (1.1)	46 (1.6)	13 (1.7)	28 (1.0)	2 (0.9)	1 (0.4)	4 (0.3)
Death	132 (1.6)	49 (1.7)	29 (3.9)	7 (0.2)	30 (13.6)	9 (3.6)	8 (0.6)

No.=Number; MINS=myocardial injury after noncardiac surgery

Table 7: Relation between perioperative complications and 30-day mortality in orthopedic surgery

Outcome	No. of patients who died/total no. of patients with the outcome	Percentage (95% CI) of patients who died	Adjusted HR* (95% CI)	Attributable Fraction (AF) %
Major bleeding	75/2422	3.1 (2.44-3.87)	1.95 (1.34–2.85)	16.5
No major bleeding	57/5960	0.96 (0.73-1.24)	Ref.	
MINS	63/1454	4.33 (3.35-5.51)	2.08 (1.38–3.14)	20.6
No MINS	69/6931	0.99 (0.78-1.26)	Ref.	
Sepsis	30/318	9.4 (6.46-13.19)	6.24 (3.85–10.12)	9.7
Infection without sepsis	17/562	3.02 (1.77-4.80)	2.74 (1.54–4.85)	3.8
No sepsis or infection	85/7503	1.13 (0.91-1.40)	Ref.	
Acute kidney injury with dialysis	7/17	41.18 (18.44-67.07)	NA	
No acute kidney injury with dialysis	125/8366	1.49 (1.25-1.78)	NA	
Stroke	4/27	14.81 (4.19-33.73)	6.01 (2.19–16.56)	1.5
No stroke	128/8356	1.53 (1.28-1.82)	Ref.	
Venous thromboembolism	3/123	2.44 (0.51-6.96)	2.24 (0.70–7.13)	
No venous thromboembolism	129/8261	1.56 (1.31-1.85)	Ref.	
Congestive heart failure	19/124	15.32 (9.48-22.89)	1.54 (0.81–2.94)	
No congestive heart failure	113/8259	1.37 (1.13-1.64)	Ref.	
New, clinically important atrial fibrillation	10/93	10.75 (5.28-18.89)	2.65 (1.25–5.65)	2.2
No new, clinically important atrial fibrillation	122/8290	1.47 (1.22-1.75)	Ref.	

No.=Number; CI=confidence interval; HR=Hazard Ratio; MINS=myocardial injury after noncardiac surgery; Ref.=Reference; NA=Not applicable

*Adjusted variables were as follows: age, history of peripheral vascular disease, history of chronic obstructive pulmonary disease, surgery urgency, active cancer

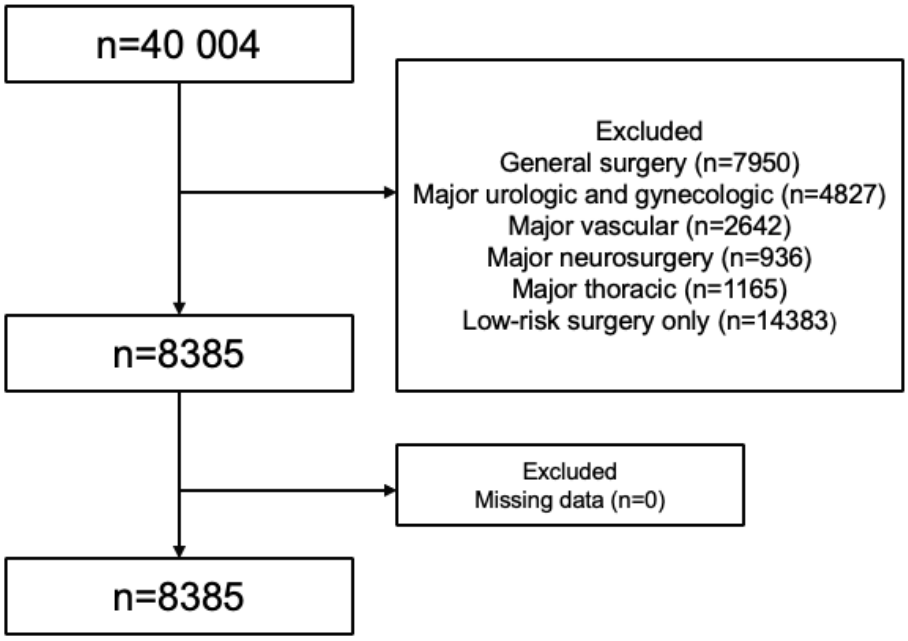
Table 8: Baseline troponin values by surgical urgency in orthopedic surgery

Surgery urgency	**Median value [IQR], ng/L, n=2174**
Urgent/emergent	11.0 [6.0-24.4]
Elective	7.0 [4.0-13.0]
Overall	7.2 [4.1-13.0]

*all troponin tests were high-sensitivity troponin T

ng=nanograms; L=litres; IQR=interquartile range

Figure 3: Flow of patient inclusion in the VISION orthopedic surgery substudy



CHAPTER 4: SAFETY AND EFFICACY OF TRANEXAMIC ACID USE IN GENERAL SURGERY PATIENTS: A SUBSTUDY OF THE PERIOPERATIVE ISCHEMIC EVALUATION-3 (POISE-3) RANDOMIZED CONTROLLED TRIAL

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4.1 Abstract

Importance: Clinically important perioperative bleeding is common in general surgery (GS). The POISE-3 (PeriOperative ISchemic Evaluation-3) trial demonstrated the efficacy of prophylactic tranexamic acid (TXA) compared to placebo in preventing major bleeding without increasing vascular outcomes in noncardiac surgery.

Objective: To determine the safety and efficacy of prophylactic TXA use specifically in GS.

Design: We conducted sub-group analyses comparing randomized treatment of TXA or placebo according to whether patients underwent GS or non-GS in the POISE-3 blinded randomized controlled trial (RCT). Cox proportional hazards models were conducted, incorporating tests of interaction.

Setting: International multi-centre perioperative RCT.

Participants: Participants were ≥45 years of age, undergoing noncardiac surgery, with increased cardiovascular risk, and expected to require at least an overnight hospital admission after surgery. Among 26,581 eligible patients identified, 17,046 were excluded.

Intervention: Prophylactic 1g bolus of intravenous TXA before and after surgery.

Main Outcome(s) and Measure(s): The primary efficacy outcome was a composite of life-threatening bleeding, major bleeding, or bleeding into a critical organ. The primary safety outcome was a composite of myocardial injury after noncardiac surgery, non-hemorrhagic stroke, peripheral arterial thrombosis, or symptomatic proximal venous thromboembolism at 30 days.

Results: Among 9535 POISE-3 participants, 3,260 underwent a GS procedure. Mean age was 68.6 years (standard deviation [SD] 9.6) and 53.4% were male. Among GS patients, 8.0% in the TXA group and 10.5% in the placebo group had the primary efficacy outcome (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.59-0.93), p=0.01) with no difference in the primary safety outcome (11.9% vs. 12.5%, HR 0.95, 95%CI 0.78-1.16, p=0.63). There was no significant interaction by type of surgery (GS versus non-GS), on the primary efficacy (interaction p=0.81) and safety (interaction p=0.37) outcomes. Across subtypes of GS, TXA decreased the composite bleeding outcome in hepatopancreaticobiliary (HR 0.55, 95% CI 0.34-0.91, n=332) and colorectal surgery (HR 0.67, 95% CI 0.45-0.98, n=940), and there was no significant interaction across subtypes of GS (interaction p=0.68).

Conclusions and Relevance: TXA significantly reduced the risk of perioperative bleeding without increasing cardiovascular risk in patients undergoing GS procedures.

Trial Registration: ClinicalTrials.gov number, NCT03505723.

4.2 Introduction

Globally, there are over 70.5 million general surgery procedures performed annually. [42] General surgery encompasses a wide range of surgical procedures that span from minimally invasive to complex open procedures, all with varying propensities for bleeding. A large prospective cohort study involving over 40,004 patients having noncardiac surgery demonstrated that major bleeding was significantly associated with 30-day postoperative mortality. Furthermore, bleeding was the postoperative complication with the largest attributable fraction for mortality (i.e., 16% of deaths were likely attributable to bleeding).[6] A general surgery substudy demonstrated the same, with major bleeding again demonstrating statistically significant association with 30-day mortality with the highest attributable fraction (i.e., 21.1%). [96] Major perioperative bleeding can also lead to significant morbidity requiring re-interventions, re-operations, myocardial infarction, stroke, kidney injury, longer length of hospital stay, and increased transfusion need.[17] There is a need to identify ways to reduce perioperative bleeding.

Tranexamic acid (TXA) is an antifibrinolytic medication, that was shown to reduce bleeding risk in patients undergoing noncardiac surgery.[97] This drug is a lysine analogue that can support physiologic hemostasis by inhibiting plasmin activity, and by extension, fibrin degradation.[98] Given its mechanism, there is theoretical risk for venous thromboembolism (VTE) with TXA use. Thus, the efficacy and safety profile of intravenous TXA was evaluated in the The PeriOperative ISchemic Evaluation-3 (POISE-3) trial, an international, randomized controlled trial (RCT) that included 9,535 patients having noncardiac surgery who were at risk for bleeding and cardiovascular events.[7] In

this trial, TXA proved to be superior to placebo for the primary efficacy outcome (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.67 to 0.87; absolute difference, −2.6%; 95% CI, −3.8 to −1.4), but did not meet noninferiority for the composite cardiovascular safety outcome (HR 1.02; 95% CI, 0.92 to 1.14; noninferiority margin 1.125; absolute difference, 0.3%; 95% CI, −1.1 to 1.7).[97] An updated meta-analysis including 191 RCTs (40,621 patients) has since reported that the POISE-3 non-inferiority margin has been met for perioperative cardiovascular thromboembolic events (risk ratio 1.02; 95% CI, 0.94-1.11).[62]

Although the evidence to support the use of TXA in noncardiac surgery is strong, data specific to general surgery is lacking. In a systematic review investigating TXA efficacy in extrahepatic abdominal surgery, only 3/19 studies or 154/2205 (7%) patients had undergone a general surgery procedure.[99] In a survey among oncologic surgeons in a Canadian tertiary centre, 63% of respondents had stated that they felt a trial was needed in their own surgical field to determine the efficacy and safety of TXA.[100] This highlights the importance of specific TXA evidence in patients undergoing general surgery.

In the POISE-3 trial, 3542 participants underwent a general surgery procedure.[97] This represents the largest population of general surgery patients to date in which the effect of TXA has been evaluated. In this POISE-3 substudy, the objective was to determine whether perioperative TXA affected the risk of a composite bleeding or major cardiovascular outcome at 30 days among patients who underwent general surgery. We hypothesized that TXA would have a similar effect in patients undergoing general surgery compared to patients undergoing non-general surgery. Specifically, we anticipated that

TXA would reduce the risk of a composite bleeding outcome without differences in the risk of major cardiovascular outcomes.

4.3 Methods

Study Design

Details of the POISE-3 trial has been previously reported.[101] In summary, the POISE-3 trial was an international multicentre RCT that compared the efficacy and safety of prophylactic TXA versus placebo among adult patients undergoing noncardiac surgery. Participants, healthcare providers, data collectors, and adjudicators were blinded to treatment allocation. A partial factorial design was also utilized, of a perioperative hypotension-avoidance versus hypertension-avoidance strategy. Local ethics board approval was provided by all participating centres before patient recruitment.

Participants and setting

Patients were enrolled if they were ≥45 years of age, planned to undergo noncardiac surgery, were expected to require at least an overnight hospital admission after surgery, and were deemed to be at risk of perioperative bleeding and cardiovascular complications. Patients undergoing cardiac surgery or intracranial neurosurgery were excluded. Full details of the trial including the eligibility criteria for POISE-3 are reported elsewhere and provided in Appendix 2-3.

Intervention and Placebo

Once informed consent was obtained, participants were randomized by means of a central computerized system in a 1:1 ratio to receive a 1-g intravenous bolus of tranexamic acid or placebo at the start and end of surgery.

Study Outcomes

Appendix 2-4 reports all outcome definitions. The primary efficacy outcome was a composite of life-threatening bleeding, major bleeding, and critical organ bleeding at 30 days after randomization. The primary safety outcome was a composite of myocardial injury after non cardiac surgery (MINS), non-hemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism at 30 days after randomization.

Secondary outcomes included the following: individual components of the safety and efficacy composite outcomes, bleeding independently associated with mortality after noncardiac surgery (BIMS)[102]; transfusions (i.e., proportion of patients who received ≥1 unit of packed red blood cells [pRBC] transfusion); transfusion of ≥2 units of pRBC; and transfusion of 2-4 units of pRBC.

Tertiary outcomes included the following: a net risk-benefit outcome as a composite of vascular death, non-fatal life-threatening, major, or critical organ bleeding, MINS, stroke, peripheral arterial thrombosis, and symptomatic proximal VTE; all-cause mortality; vascular mortality; International Society on Thrombosis and Haemostasis (ISTH) major bleeding; and infection/sepsis.

Analysis population and General Surgery definitions

The overall POISE-3 trial categorized participants into 9 surgery categories (i.e., general, orthopedic, vascular, urologic, spinal, gynecologic, thoracic, plastic, and low risk). The focus of this paper are patients undergoing general surgery, as defined by the original study protocol (Appendix 1-5). The POISE-3 trial included 3542 participants

undergoing general surgery (1769 TXA, 1773 placebo) and 73 participants (TXA 39, placebo 24) who underwent a low-risk general surgery procedure.

Study personnel recorded the category of surgery the participant underwent but not the specific procedure each patient underwent. To conduct subgroup analyses by subcategories of general surgery, all centres that enrolled participants undergoing either general surgery or low-risk surgeries were contacted to obtain the specific name of the procedure that each participant underwent.

Subcategories of General Surgery

Subcategories of general surgery were defined a priori with broad subcategories including: hepatopancreaticobiliary, colorectal, upper gastrointestinal, head and neck procedures, other major general, and other minor general (Appendix 1-6). These subcategories were developed in consultation with practising general surgeons from various subspecialties. Each procedure was sub-categorized independently and in duplicate by two, senior general surgery residents. Disagreements were resolved through consultation of independent practising general surgeons.

Statistical Analyses

A statistical analysis plan was finalized on November 16, 2023 before undertaking the analyses. For all analyses, the TXA group was compared to the placebo group. For the primary efficacy outcome, we followed the modified intention to treat principle and analyzed all recruited participants in the treatment groups to which they were randomized, regardless of treatments received or duration of trial participation. For the primary safety outcome, we included participants who received both doses of the study

drug, thereby following the per-protocol principle. Any participants lost to follow-up were right-censored.

Cox proportional hazards models incorporating tests of interaction, were used to compare TXA to placebo in the primary efficacy and safety outcomes. These models were adjusted for the blood pressure strategy allocation, considering the partial factorial design. Tests for interaction were conducted between TXA allocation and general surgery status (yes versus no), as well as cancer status (yes versus no), and prespecified subcategories of general surgery. We did not anticipate that the relative effectiveness or safety of the intervention would be different based on general surgery versus non general surgery procedure, active cancer versus no active cancer status, and by subcategories of general surgery. An interaction p-value <0.05 was considered to provide statistical evidence of a subgroup effect. Estimated HRs and associated two-sided 95% CIs were reported.

The separate associations of TXA versus placebo within each subgroup were performed, regardless of whether there was a statistically significant interaction. The between-group differences as proportions who had the event were reported, along with the calculated absolute risk differences with the associated 95% CI. All analyses were conducted using Stata version 17.

4.4 Results

We contacted all 87 participating sites that enrolled general surgery patients, for information on the specific procedure that each of the participants underwent (3542

general surgery and 73 low risk surgery). Responses were provided by 70 centres. At the end of data collection, there were 326 general surgery procedures, which remained unknown but were assumed to be correctly categorized to general surgery. There were 282 participants that were originally categorized as general surgery were re-categorized to a non-general surgery procedure and 23 low risk surgery procedures were identified to be low risk general surgery procedures.

Among 9535 participants included in the POISE-3 trial, 3260 underwent general surgery procedures (1635 TXA, 1625 placebo), 6208 underwent non-general surgery procedures (3093 TXA, 3115 placebo), and 67 underwent an unknown category of noncardiac surgery. Figure 4 demonstrates the flow of patient inclusion.

Patient Characteristics

Table 8 describes the participant characteristics. Among the 3260 general surgery participants the mean age was 68.6 years (standard deviation [SD] 9.6), 53.4% were male, and 40.8% had active cancer. There were a range of comorbidities among the general surgery participants, 90.1% had with a history of hypertension, 13.7% coronary revascularization, 10.4% myocardial infarction, and 9.3% atrial fibrillation. There were 940 (28.8%) colorectal surgery procedures, 793 (24.3%) other low risk general surgery, 433 (13.3%) head and neck procedures, 332 (10.2%) hepatopancreaticobiliary procedures, 275 (8.4%) upper gastrointestinal (GI) procedures, and 161 (4.9%) other major general surgery procedures (Appendix 1-6).

Primary efficacy outcome

Table 9 and Figure 5 summarizes the primary efficacy and safety outcome analyses. Among general surgery participants, there was a lower risk of experiencing the composite bleeding outcome in the intervention group compared to the placebo group (8.0% vs. 10.5%, HR 0.74, 95% CI 0.59-0.93, p-value=0.01). Among the individual component endpoints of the composite outcome, there was reduced risk for major bleeding among those in the TXA group compared to the placebo group (6.7% vs. 9.4%, HR 0.71, 95% CI 0.55-0.90, p-value=0.005). The p-values for interaction were not significant between participants in the general surgery and non-general surgery cohorts across the composite efficacy outcome (p=0.81) nor the individual component endpoints.

Primary safety outcome

There were no differences in the primary safety outcome between the TXA and placebo groups in the general surgery cohort (11.9% vs. 12.5%, HR 0.95, 95% CI 0.78-1.16). There were also no differences across the components of the composite outcome. The p-values for interaction between general surgery and non-general surgery participants were not statistically significant across the composite safety outcome (p=0.37) and the individual component endpoints.

Subgroup analyses by subcategories of general surgery

Among the subcategories of general surgery, a statistically significant lower risk of the composite bleeding outcome with TXA use was seen among those undergoing hepatopancreaticobiliary surgery (25.0% vs. 15.0%, HR 0.55, 95% CI 0.34-0.91, p-value=0.02) and colorectal surgery (13.6% vs. 9.3%, HR 0.67, 95% CI 0.45-0.98, p-value=0.04). Regarding the composite safety outcome, those who underwent head and

neck procedures in the TXA group had a lower risk of experiencing an event (4.2% vs. 10.4%, HR 0.39, 95% CI 0.18-0.84, p=0.02). The p-values for interaction were not significant across the subcategories of general surgery for both the efficacy and safety outcomes. Appendix 1-7 provides further details.

Subgroup analyses by cancer status

There were no interactions by cancer status within the general surgery cohort as the p-values for interaction for the primary efficacy and safety outcomes were not significant at 0.21 and 0.77, respectively. Of note, the VTE rates were not statistically significant among those with and without active cancer. Further details are provided in Appendix 1-8.

Secondary Outcomes

Participants who received TXA in the general surgery subgroup demonstrated reduced risk of BIMS (7.7% vs 9.8%, HR 0.77, 95% CI 0.61-0.97, p=0.03) and receipt of ≥1 unit of RBC transfusion (8.6% vs. 10.8%, OR 0.77, 95% CI 0.61-0.97, p=0.03). The p-values for interaction were 0.84 and 0.86, respectively. There were no differences between the TXA and placebo groups regarding the need for transfusion of 2 or more RBC units, or 2-4 RBC units, within the general surgery subgroup. The p-value for interaction was significant for needing 2-4 units of RBC transfusion (p=0.03). Details are provided in Appendix 1-9.

Tertiary Outcomes

Across the tertiary outcomes, general surgery participants in the TXA group experienced less bleeding according to the ISTH definition for major bleeding (6.9% vs.

9.0%, HR 0.76, 95% CI 0.59-0.97, p=0.03). There were no statistically significant differences among the general surgery cohort regarding other tertiary outcomes including all-cause mortality, vascular mortality, infection, and sepsis. The net risk-benefit composite outcome was not statistically significant within the general nor non-general subgroups and the p-value for interaction was 0.24. However, within the general surgery subgroup, there was a trend toward favouring TXA (18.1% vs. 20.5%, HR 0.87, 95% CI 0.74-1.01, p=0.07). None of the p-value for interactions were statistically significant. Appendix 1-10 provides further details.

4.5 Discussion

This POISE-3 substudy demonstrated TXA resulted in a significant reduction in major bleeding without an impact on the primary safety outcome within the general surgery subgroup. There were no significant interaction p-values between the general surgery and non-general surgery subgroups for efficacy (p=0.81) or safety (p=0.37), suggesting that there is no subgroup effect. Within the subcategories of general surgery, TXA demonstrated an efficacy in bleeding reduction in the hepatopancreaticobiliary (HR 0.55, 95% CI 0.34-0.91) and colorectal (HR 0.67, 95% CI 0.45-0.98) groups without differences in the safety outcome. Subgroup analyses by cancer status also demonstrated no statistically significant p-values for interaction suggesting that TXA is equally effective among participants undergoing general surgery versus non-general surgery and in participants with or without cancer at the time of surgery.

The use of TXA have been supported by literature in specific perioperative and acute care settings, namely in post-partum hemorrhage following caesarean sections,

cardiac surgery, major orthopedic and spine surgeries, and trauma.[103–108] Existing studies on TXA use outside of these contexts are commonly limited by small sample sizes.[109,110] The POISE-3 trial addressed the knowledge gap for TXA use in noncardiac surgery.[97]

This publication provides results for patients who underwent general surgery or surgery for cancer. These results highlighting TXA benefits, without any increase in documented risks among general surgery patients, will hopefully facilitate improved care among patients undergoing general surgery, where routine prophylactic TXA is rarely used.

The POISE-3 trial enrolled the largest general surgery population to date in the evaluation of prophylactic TXA use. The specific subcategory of general surgery that each participant underwent was collected from participating sites, and these subcategories of general surgery were determined a priori and driven by biological rationale. The added granularity of data re-demonstrating TXA efficacy and safety without subgroup effect by general surgery, bolsters external validity to encourage clinical practice uptake in general surgery contexts.

TXA is a synthetic lysine analogue that inhibit the interaction of plasminogen with plasmin and fibrin, thereby exerting its antifibrinolytic effect and supporting physiologic hemostasis.[111,112] In essence, TXA helps slow the breakdown of physiologic fibrinolysis.[111,112] Considering this mechanism of action of TXA, there are limitations in its hemostatic abilities. Specifically, it is unlikely that TXA is sufficient in the management of profuse, brisk bleeding, as there would not be formed clots for stabilization by TXA. For instance, in the CRASH-2 trial (n=20,211), TXA demonstrated reduced mortality

when administered within 3 hours of injury in a trauma population with low injury severity and low rates of penetrating trauma (14.5% vs 16.0%; RR 0.91, 95% CI 0.85-0.97, p = 0.0035).[108] However, in the HALT-IT trial, which randomized 12,009 patients with significant upper and lower gastrointestinal bleeding, there were no differences in death from bleeding within 5 days of randomization (4% in both groups, RR 0.99, 95% CI 0·82–1·18).[113] Instead of interpreting these results to be contradictory, these trials suggest the limitations of TXA efficacy in certain contexts. These contextual nuances may introduce variability that obscures TXA effectiveness, underscoring the importance of large-scale studies to elucidate its true therapeutic potential while acknowledging its limitations. Although TXA likely cannot address all forms of bleeding, our work demonstrates it is able to reduce the risk of clinically important bleeding in general surgery contexts considering the use of TXA was associated with a reduction in composite bleeding events and at least 1 unit of RBC transfusion outcome.

The mechanism of action of TXA also raises the theoretical concern for increased thromboembolic events. In the overall POISE-3 trial, it was concluded that there was a low probability of a small increase in the incidence of composite cardiovascular outcome events with an absolute difference of 0.3% (95% CI -1.1 to 1.7).[97] A large meta-analysis including 191 RCTs and 40,621 patients in total has since demonstrated that the non-inferiority margin was met (RR 1.02, 95% CI 0.94-1.11, p=0.65, i^2=0, n=37, 512) but demonstrated through trial sequential analysis that the diversity adjusted required information size was 58,036 patients.[62] Although this suggests more trials are needed to definitively determine the effect of TXA on composite cardiovascular thromboembolic

outcomes, it also highlights the rare occurrence of these events compared to bleeding events. In a recent prospective cohort study including 7950 contemporary general surgery patients, major bleeding was found to be the most common post-operative complication (18.3%) with greatest attributable fraction of death in the cohort. However, any venous thromboembolism was comparatively uncommon (0.9%) and did not show association with 30-day mortality. Altogether, this demonstrates the urgent need to reduce perioperative bleeding prompting clinicians and patients to carefully consider the clear beneficial reduction in the incidence of composite bleeding against the unlikely low probability of a small increase in the incidence of cardiovascular outcome events. [7]

Limitations

There are a few limitations to consider. Firstly, this was a subgroup analysis of the POISE-3 trial, and as such, the study was not powered for the subgroups and subcategories explored. However, there was biological rationale underpinning the subgroups and subcategories, which were determined a priori. We also utilized p-values for interactions to investigate for subgroup effects. This is the largest general surgery population to date in which the safety and efficacy of TXA has been investigated.

4.6 Conclusion

The POISE-3 trial provides the best estimate of effect for TXA in noncardiac surgery, including general surgery. In POISE-3, TXA reduced the risk of a composite bleeding outcome without increasing the risk of a composite cardiovascular risk outcome. There were no significant interactions between participants undergoing general surgery and non-general surgery and across subcategories of general surgery or cancer status. The

absence of subgroup effects suggests that TXA reduces bleeding without increasing cardiovascular risk for both general surgery and non-general surgery patients.

Table 9: Baseline characteristics of general surgery versus non-general surgery patients in the POISE-3 Trial

	General Surgery (n=3260)				Non-General Surgery (n=6208)			
	TXA (n=1635)		Placebo (n=1625)		TXA (n=3093)		Placebo (n=3115)	
Characteristics and pre-operative lab assessments	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	68.8	9.6	68.4	9.5	69.9	9.3	69.7	9.3
Weight (kg)	78.3	20.1	78.4	20.6	80.8	19.5	80.9	19.6
Height (cm)	165.6	9.9	165.7	9.9	167.1	9.9	167.0	10.0
Body-mass index (kg/m^2)	28.4	6.3	28.4	6.6	28.9	6.0	28.9	6.4
Heart rate (bpm)	76.3	13.1	76.1	13.5	74.8	13.2	75.4	12.9
Serum creatinine (µmol/L)	84.7	27.0	85.6	32.5	87.5	28.9	88.2	30.1
Hemoglobin (g/L)	128.3	19.0	128.9	19.3	133.0	18.8	132.5	18.7
Baseline History	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Male	867	53.0	873	53.7	1788	57.8	1789	57.4
Female	768	47.0	752	46.3	1305	42.2	1326	42.6
Hx of Hypertension	1473	90.1	1464	90.1	2794	90.3	2823	90.6
Hx of Myocardial infarction	151	9.2	188	11.6	421	13.6	453	14.5
Hx of Stroke	123	7.5	124	7.6	275	8.9	260	8.3
Hx of Atrial fibrillation	163	10.0	139	8.6	312	10.1	300	9.6
Hx of Dementia	7	0.4	4	0.2	58	1.9	38	1.2
Hx of Cancer	666	40.7	664	40.9	639	20.7	686	22.0
Hx of Receiving ongoing dialysis	1	<0.1	0	0	0	0	1	<0.1
Hx of Angiography only	119	7.3	123	7.6	298	9.6	297	9.5
Hx of coronary revascularization	227	13.9	220	13.5	518	16.7	529	17.0
PCI(BMS stent)	70	4.3	62	3.8	162	5.2	148	4.8
PCI(DES stent)	98	6.0	112	6.9	217	7.0	232	7.4
CABG	84	5.1	69	4.2	202	6.5	203	6.5
Previous tobacco use	603	36.9	634	39.0	1503	48.6	1448	46.5

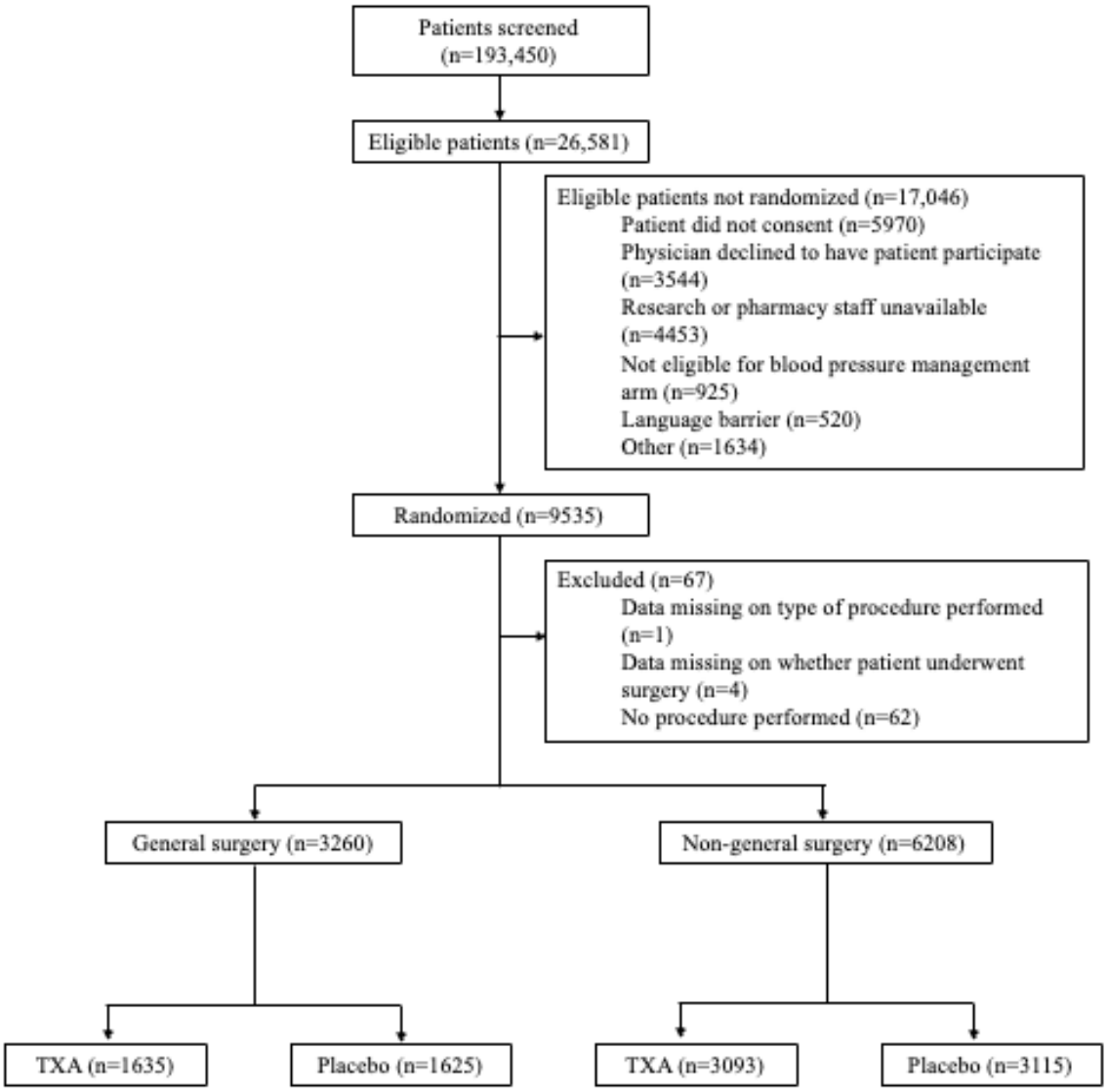
*TXA=tranexamic acid; SD= standard deviation; kg=kilograms; cm=centimetres; m=metres; bpm=beats per minute; µmol=micromole; L=litre; g=gram; PCI=percutaneous coronary intervention; BMS=bare metal stent; DES=drug eluting stent; CABG=coronary artery bypass graft surgery; Hx=history

Table 10: Primary safety and efficacy outcomes at 30 days comparing general surgery versus non general surgery subgroups

	TXA (n=4728)	Placebo (n=4740)	TXA vs. Placebo		
	n(%)	n(%)	HR (95% CI)	P Value	P value for interaction
Co-Primary Efficacy Outcomes					
Composite					0.81
General Surgery	130 / 1635 (8.0)	171 / 1625 (10.5)	0.74 (0.59-0.93)	0.01	
Non-General Surgery	304 / 3093 (9.8)	393 / 3115 (12.6)	0.77 (0.66-0.89)	0.0006	
Life threatening Bleeding					0.91
General Surgery	25 / 1635 (1.5)	25 / 1625 (1.5)	0.99 (0.57-1.73)	0.98	
Non General Surgery	53 / 3093 (1.7)	56 / 3115 (1.8)	0.95 (0.66-1.39)	0.81	
Major Bleed					0.85
General Surgery	110 / 1635 (6.7)	152 / 1625 (9.4)	0.71 (0.55-0.90)	0.005	
Non General Surgery	254 / 3093 (8.2)	347 / 3115 (11.1)	0.73 (0.62-0.85)	0.0001	
Critical Organ Bleed					0.11
General Surgery	4 / 1635 (0.2)	2 / 1625 (0.1)	1.98 (0.36-10.8)	0.43	
Non General Surgery	8 / 3093 (0.3)	19 / 3115 (0.6)	0.42 (0.19-0.97)	0.04	
Co-Primary safety Outcomes					
Surgery Type					0.37
General Surgery	195 / 1635 (11.9)	203 / 1625 (12.5)	0.95 (0.78-1.16)	0.63	
Non General Surgery	476 / 3093 (15.4)	454 / 3115 (14.6)	1.06 (0.93-1.21)	0.36	
MINS					0.67
General Surgery	184 / 1635 (11.3)	186 / 1625 (11.4)	0.98 (0.80-1.20)	0.85	
Non General Surgery	424 / 3093 (13.7)	415 / 3115 (13.3)	1.04 (0.90-1.19)	0.62	
Non-hemoraghic stroke					0.28
General Surgery	4 / 1635 (0.2)	5 / 1625 (0.3)	0.80 (0.22-2.98)	0.74	
Non General Surgery	20 / 3093 (0.6)	11 / 3115 (0.4)	1.83 (0.88-3.82)	0.11	
PAT					0.54
General Surgery	2 / 1635 (0.1)	1 / 1625 (<0.1)	1.97 (0.18-21.8)	0.58	
Non General Surgery	20 / 3093 (0.6)	22 / 3115 (0.7)	0.91 (0.50-1.68)	0.77	
VTE					0.23
General Surgery	9 / 1635 (0.6)	12 / 1625 (0.7)	0.75 (0.32-1.78)	0.51	
Non General Surgery	23 / 3093 (0.7)	16 / 3115 (0.5)	1.45 (0.76-2.74)	0.26	
Amputation					>0.99
General Surgery	0 / 1635 (0)	0 / 1625 (0)	-	-	
Non General Surgery	14 / 3093 (0.5)	22 / 3115 (0.7)	0.64 (0.33-1.25)	0.19	
Seizure					0.15
General Surgery	2 / 1635 (0.1)	2 / 1625 (0.1)	0.99 (0.14-7.00)	0.99	
Non General Surgery	8 / 3093 (0.3)	1 / 3115 (<0.1)	8.11 (1.01-64.8)	0.05	

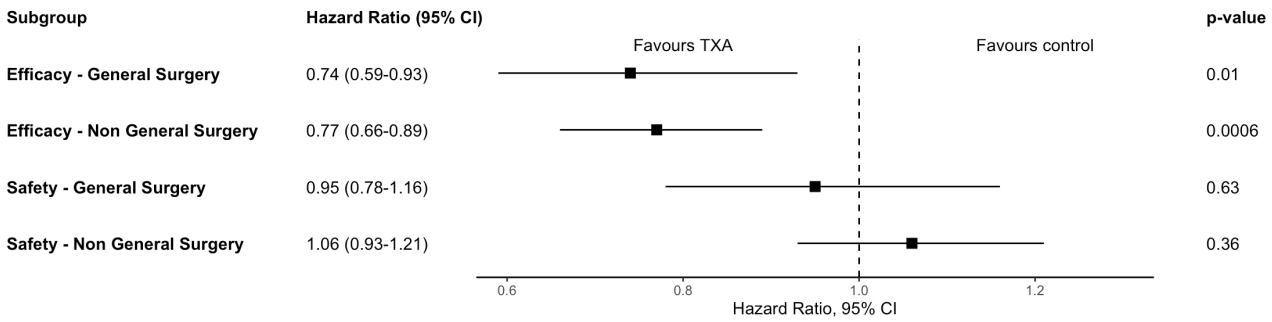
*TXA=tranexamic acid; MINS=myocardial injury after noncardiac surgery; PAT=peripheral arterial thrombosis; VTE=venous thromboembolism; HR=Hazard Ratio; CI=Confidence Interval

Figure 4: Patient flowchart for POISE-3 general surgery substudy



*TXA=tranexamic acid

Figure 5: Forest plot of primary efficacy and safety outcomes



*TXA=tranexamic acid; CI=confidence interval

CHAPTER 5: CONCLUSION

5.1 Main Findings

There are three main findings from the results of the studies included as part of this thesis. Firstly, we demonstrated in a large contemporary general surgery cohort that major bleeding remains a common post-operative complication that is associated with 30-day mortality. Importantly, through established statistical methods, we also demonstrated that major bleeding had the highest attributable fraction of death, meaning it was attributable to the largest percentage of deaths in the 7950 patient cohort, if causality were to be assumed. This highlights the urgency of major bleeding as an area requiring further study for interventions to address this issue if we are to improve patient outcomes in general surgery.

A similar study investigating post-operative complications and associations with mortality in the orthopedic surgery cohort identified similar post-operative complications to be associated with 30-day mortality as compared to the general surgery cohort. However, in the orthopedic surgery group, a larger proportion of deaths were attributable to MINS as opposed to major bleeding. This highlights the differences across surgical specialties in terms of not only the rate of complications but how they are associated with patient-important outcomes like mortality.

Identification of major bleeding as the largest contributor of mortality in the general surgery cohort developed the foundation for the POISE-3 general surgery substudy, with the goal to understand the efficacy and safety of prophylactic TXA use. This study demonstrated that two 1-g boluses of TXA during surgery was associated with reduced composite efficacy outcome of major bleeding without differences in the composite safety outcome of cardiovascular events, compared to placebo, in the general surgery cohort. Importantly, with no statistically significant p-value for interaction across the general surgery versus non-general surgery groups, this

suggested that TXA works similarly independent of whether a patient is undergoing general surgery or not. As the largest trial to date investigating TXA use in general surgery, this is an important addition to existing literature with promise to reduce perioperative bleeding in general surgery. Of note, the effectiveness of TXA was remonstrated across different endpoints for bleeding including ISTH definitions, need for transfusion, and BIMS.

5.2 Future Directions

To continue providing specialty-specific evidence on the efficacy and safety of TXA, future works will focus on meta-analyses amalgamating the subcategories of general surgery (e.g., colorectal surgery, surgical oncology, bariatric surgery). As subspecialties within general surgery become further specialized, this will help provide evidence specific to their fields in the hopes of facilitating clinical uptake.

Other future work will focus on knowledge translation of the findings of this thesis, particularly in the uptake of TXA use. Once an intervention, like TXA, demonstrates clinical benefit through well-substantiated research, there are often delays in adoption to routine clinical practice.[114,115] Clinicians and society should view these delays as patient safety issues, as they identify patients who are not receiving optimal care, when based on high-quality evidence. Knowledge translation (KT) research aims to understand and address these gaps in care with the goal to increase the transfer of knowledge to clinicians, improve clinical decision-making, and ultimately improve the quality of patient care.[114–116] The findings of the projects in this thesis demonstrate major bleeding to be a common complication associated with poor outcomes with TXA demonstrating a clear benefit in reducing perioperative bleeding as well as safety of this intervention. Despite these findings, uptake of prophylactic TXA in clinical practice has been suboptimal. Informal surveys conducted across noncardiac non-orthopedic surgeons in Hamilton

demonstrated that surgeons administer prophylactic TXA to 1% of eligible patients, on average. These low rates of TXA use are also consistent with practice beyond Hamilton.[13]

The delay in the uptake of prophylactic TXA is likely multifactorial. In order to elucidate this further, our future work will focus on surveys conducted across noncardiac surgeons, including general surgeons. Furthermore, based on our informal interviews with local surgeons, it is probable that an important contributor to this delay is the human memory being prone to errors and oversights, especially as it relates to adjusting routine practice to new evidence.[115] For example, despite the abundant evidence for and awareness of the benefits of the Surgical Safety Checklist, implementation remains suboptimal in many centres.[117] Recently, a novel technology-based intervention was studied whereby the Surgical Safety Checklist required completion on a mobile device before the connected cautery machine could be turned on.[118] This increased the completion of the surgical safety checklist from 27% to 100%.[118]

In a similar fashion, we will plan to evaluate the impact of an electronic medical record-facilitated order (EMR-FO) on the uptake of TXA use in surgical practice. This intervention would be integrated into the surgeon's electronic-based pre-operative order set where they must accept or decline default administration of prophylactic TXA before they are able to proceed with operating room booking. We believe that this will serve as a repeated memory aid to trigger consideration of TXA use and function as a nidus for conversation among surgeons within surgical divisions, that may influence attitudes surrounding prophylactic TXA to effectively encourage practice change.[115,117,119] We will plan for a multi-site stepped wedge cluster RCT, where EMR-FO will be sequentially introduced across pre-determined clusters over one-month periods. By the end of the study period, all clusters will have been allocated to the intervention, and therefore be prompted to consider administration of prophylactic TXA. The primary

outcome would be to assess the proportion of patients that are ordered to receive TXA at the start and end of surgery among those who should receive it. As per existing evidence, this would include patients aged 45 years or older undergoing major noncardiac surgery, deemed at risk of a major bleeding event.

Altogether, these future studies will focus on the identifying the barriers to uptake of research evidence surrounding TXA and supporting application of the present thesis findings to clinical practice with the hopes of improving patient outcomes.

5.3 Conclusion

Through a large prospective cohort study, we were able to determine that major bleeding remains an important and common post-operative complication in general surgery that was the greatest contributor of 30-day mortality in this cohort. A study using the same methodology in a different surgical specialty demonstrated that MINS was the greatest contributor of 30-day mortality in the orthopedic surgery cohort. Altogether, the overall complications associated with 30-day mortality were similar between the two specialties, which support the plausibility of continued amalgamation of noncardiac surgeries for improved power in answering perioperative research questions. At the same time, the differences in the ranking of contributors for mortality demonstrates the nuances between the surgical specialties that should be recognized by distillation of large noncardiac data to provide specialty-specific data. Finally, the POISE-3 general surgery substudy demonstrates TXA as an effective intervention to reduce perioperative bleeding and therefore mortality in general surgery patients. Altogether, these studies lay the foundation for future work that will aim to apply these important research findings into clinical practice to improve outcomes for surgical patients.

APPENDIX
Appendix 1: Supplemental Tables

Appendix 1-1: Recruitment by geography: n=7950

Continent, country, city, centre	**Participants, No.**	**Percentage**
North America	n= 2244	n=546
Canada		
Hamilton		
Juravinski Hospital and Cancer Centre	532	164
St. Joseph's Hamilton Healthcare	134	17
McMaster University Medical Centre	240	58
Hamilton General Hospital	99	30
London		
Victoria Hospital	180	36
Edmonton		
Walter C. MacKenzie Health Sciences Centre	301	68
Winnipeg		
Health Sciences Centre Winnipeg	324	81
United States		
Cleveland		
Cleveland Clinic	405	89
St. Louis		
Washington University School of Medicine	29	3
Europe	n=1928	n=367
United Kingdom		
London		
Barts and The London	477	97
University College Hospital	167	17
Leeds		
Leeds Teaching Hospitals	348	18
Liverpool		
Royal Liverpool University Hospital	76	14
Spain		
Barelona		
Hospital de Sant Pau	464	117
Madrid		
Hospital Gregorio Maranon	360	100
Poland		
Krakow		
Jagiellonian University Medical College	11	2
France		
Paris		
Pitie-Salpetriere Hospital	25	2

Asia	n=1689	n=332
China		
Hong Kong		
Prince of Wales Hospital	1051	179
India		
Bangalore		
St. John's Medical College Hospital	182	42
Ludhiana		
Christian Medical College	225	31
Malaysia		
Kuala Lumpur		
University Malaya Medical Centre	231	70
South America	n=1683	n=121
Brazil		
Sao Paulo		
Hospital do Coracao	87	4
Porto Alegre		
Hospital de Clinicas de Porto Alegre	372	21
Colombia		
Bucaramanga		
Hospital Universitario de Santander	501	80
Bogota		
Foundation CardioInfanil	188	15
Peru		
Lima		
Hospital Nacional Cayetano Heredia	535	1
Africa	n=93	n=40
South Africa		
Durban		
Inkosi Albert Luthuli Hospital	93	40
Australia	n=313	n=58
Australia		
Sydney		
Westmead Hospital	313	58

Appendix 1-2: Mortality rates by continent: n=7950

Continent	No. of Participants, No. (%)	No. of Deaths	Percentage Dead (95% Confidence Interval)
North America	2244 (28.2)	44	1.96 (1.43-2.62)
Europe	1928 (24.3)	35	1.82 (1.27-2.52)
Asia	1689 (21.2)	49	2.9 (2.15-3.82)
South America	1683 (21.2)	91	5.41 (4.38-6.60)
Africa	93 (1.2)	12	12.9 (6.85-21.45)
Australia	313 (3.9)	9	2.88 (1.32-5.39)
Total	7950	240	3.02 (2.65-3.42)

Appendix 1-3: Relation between perioperative complications and 30-day mortality in elective surgeries only

Outcome	No. of patients who died/total no. of patients with the outcome (%)	Adjusted HR* (95% CI)	Attributable Fraction (AF) %
Major bleeding	77/1262 (6.1)	2.21 [1.54-3.16]	20.2
Sepsis	57/669 (8.5)	5.25 [3.51-7.86]	15.2
MINS	57/832 (6.9)	2.43 [1.70-3.46]	16.2
Acute kidney injury resulting in dialysis	12/38 (2.7)	4.16 [2.09-8.26]	3.3
Stroke	5/14 (35.7)	16.9 [6.72-42.50]	2.1
Infection without sepsis	10/552 (1.8)	2.02 [0.13-4.00]	NA
Venous thromboembolism	1/61 (1.6)	0.34 [0.05-2.46]	NA
Congestive heart failure	12/91 (13.2)	1.35 [0.68-2.68]	NA
New, clinically important atrial fibrillation	12/120 (10)	1.48 [0.76-2.89]	NA

No.=Number; CI=confidence interval; HR=Hazard Ratio; MINS=myocardial injury after noncardiac surgery; Ref.=Reference; NA=Not applicable
*Adjusted variables were as follows: age category, recent history of high risk coronary artery disease, history of stroke, history of peripheral vascular disease, history of chronic obstructive pulmonary disease, surgery urgency (elective, urgent, emergent), cancer status at time of surgery

Appendix 1-4: Relation between perioperative complications and 30-day mortality in non-elective surgeries only

Outcome	No. of patients who died/total no. of patients with the outcome (%)	Adjusted HR* (95% CI)	Attributable Fraction (AF) %
Major bleeding	46/192 (24.0)	2.73 [1.67-4.49]	30.1
Sepsis	33/114 (28.9)	7.30 [4.23-12.58]	17.7
Venous thromboembolism	3/10 (30.0)	5.20 [1.50-18.00]	0.7
Infection without sepsis	9/82 (11.0)	2.15 [0.92-4.95]	NA
MINS	29/148 (19.6)	1.33 [0.80-2.21]	NA
Acute kidney injury with dialysis	6/12 (50.0)	2.36 [0.85-6.57]	NA
Stroke	0/6 (0)	NA	NA
Congestive heart failure	2/23 (8.7)	0.77 [0.18-3.30]	NA
New, clinically important atrial fibrillation	7/25 (28.0)	1.23 [0.48-3.16]	NA

No.=Number; CI=confidence interval; HR=Hazard Ratio; MINS=myocardial injury after noncardiac surgery; Ref.=Reference; NA=Not applicable
*Adjusted variables were as follows: age category, recent history of high risk coronary artery disease, history of stroke, history of peripheral vascular disease, history of chronic obstructive pulmonary disease, surgery urgency (elective, urgent, emergent), cancer status at time of surgery

Appendix 1-5: Definitions of original surgical categorizations in the POISE-3 trial

Major General Surgery	Complex visceral resection (i.e., surgery involving the liver, esophagus, pancreas, or multiple organs), or
	Partial or total colectomy, stomach surgery, small bowel resection, or
	Major head and neck resection for non-thyroid tumor.
Other General Surgery	Other intra-abdominal surgery such as gallbladder, appendix, adrenals, spleen, and regional lymph node dissection.
Low Risk Surgery	Surgery involving any one of the following: parathyroid, thyroid, breast, hernia, local anorectal procedure, oophorectomy, salpingectomy, endometrial ablation, peripheral nerve surgery, ophthalmologic surgery, vertebral disc surgery, hand surgery, metatarsal resection, cosmetic surgery, arterio-venous access surgery for dialysis, laparoscopy, pleuroscopy

Appendix 1-6: Breakdown of subcategories of general surgery

Subcategory of General Surgery	Surgical procedures	n	Total
Hepatopancreaticobiliary	Whipple	135	332
	Liver Resection	99	
	Other HPB	98	
Colorectal	Colon/rectal bowel resection	841	940
	Colorectal surgery not involving bowel resection (i.e., ileostomy reversal, colostomy reversal)	99	
Upper GI	Esophageal	42	275
	Duodenal	4	
	Gastric (non-bariatric)	153	
	Bariatric (all weight loss surgery)	76	
Low risk general surgery	Cholecystectomy	340	793
	Appendectomy	15	
	Hernia (simple, no bowel resection)	233	
	Breast	66	
	Lymph node dissection	10	
	Lysis of Adhesion, I&D, exploratory laparoscopy only	86	
	Minor transrectal, anal, or perianal procedures	43	
Other major general surgery	Hernia repair (complex, with flaps or requiring bowel resection)	56	161
	Spleen	7	
	Adrenalectomy	19	
	Retroperitoneal tumour resection	17	
	Pelvic exenteration	9	
	Other multiorgan surgery	53	
Head and neck	All head and neck procedures	433	
Uncategorized general surgery	Unknown	326	326

*HPB=hepatopancreaticobiliary; GI=gastrointestinal; I&D=incision and drainage

Appendix 1-7: Primary safety and efficacy outcomes at 30 days across subcategories of general surgery

	TXA (N=4728)	Placebo (N=4740)	TXA vs. Placebo		
	N(%)	N(%)	HR (95% CI)	P Value	P value for interaction
Co-Primary Efficacy Outcomes					
Primary efficacy outcome					0.68
HPB	24 / 160 (15.0)	43 / 172 (25.0)	0.55 (0.34-0.91)	0.02	
Colorectal	45 / 485 (9.3)	62 / 455 (13.6)	0.67 (0.45-0.98)	0.04	
Upper GI	15 / 142 (10.6)	15 / 133 (11.3)	0.90 (0.44-1.85)	0.77	
Acute Care surgery	13 / 402 (3.2)	17 / 391 (4.3)	0.73 (0.36-1.51)	0.40	
Other Major General	19 / 75 (25.3)	20 / 86 (23.3)	1.28 (0.68-2.43)	0.45	
Head and Neck	3 / 212 (1.4)	4 / 221 (1.8)	0.73 (0.16-3.26)	0.68	
Non-general Surgery	304 / 3093 (9.8)	393 / 3115 (12.6)	0.77 (0.66-0.89)	0.0006	
Unknown	11 / 159 (6.9)	10 / 167 (6.0)	1.15 (0.49-2.70)	0.76	
Life threatening Bleeding					0.52
HPB	7 / 160 (4.4)	9 / 172 (5.2)	0.82 (0.30-2.20)	0.69	
Colorectal	4 / 485 (0.8)	9 / 455 (2.0)	0.42 (0.13-1.35)	0.15	
Upper GI	0 / 142 (0)	1 / 133 (0.8)	-	-	
Acute Care surgery	2 / 402 (0.5)	0 / 391 (0)	-	-	
Other Major General	9 / 75 (12.0)	4 / 86 (4.7)	3.40 (1.01-11.4)	0.05	
Head and Neck	0 / 212 (0)	1 / 221 (0.5)	-	-	
Non-general Surgery	53 / 3093 (1.7)	56 / 3115 (1.8)	0.95 (0.66-1.39)	0.81	
Unknown	3 / 159 (1.9)	1 / 167 (0.6)	3.12 (0.32-30.0)	0.32	
Major Bleed					0.84
HPB	19 / 160 (11.9)	38 / 172 (22.1)	0.50 (0.29-0.86)	0.01	
Colorectal	41 / 485 (8.5)	54 / 455 (11.9)	0.70 (0.46-1.05)	0.08	
Upper GI	15 / 142 (10.6)	14 / 133 (10.5)	0.97 (0.47-2.02)	0.94	
Acute Care surgery	11 / 402 (2.7)	17 / 391 (4.3)	0.61 (0.29-1.31)	0.21	
Other Major General	13 / 75 (17.3)	17 / 86 (19.8)	0.94 (0.45-1.95)	0.86	
Head and Neck	3 / 212 (1.4)	3 / 221 (1.4)	0.97 (0.19-4.80)	0.97	
Non-general Surgery	254 / 3093 (8.2)	347 / 3115 (11.1)	0.73 (0.62-0.85)	0.0001	
Unknown	8 / 159 (5.0)	9 / 167 (5.4)	0.92 (0.36-2.39)	0.87	
Critical Organ Bleed					>0.99

	TXA (N=4728)	Placebo (N=4740)	TXA vs. Placebo		
	N(%)	N(%)	HR (95% CI)	P Value	P value for interaction
HPB	2 / 160 (1.3)	0 / 172 (0)	-	-	
Colorectal	0 / 485 (0)	1 / 455 (0.2)	-	-	
Upper GI	0 / 142 (0)	0 / 133 (0)	-	-	
Acute Care surgery	0 / 402 (0)	1 / 391 (0.3)	-	-	
Other Major General	2 / 75 (2.7)	0 / 86 (0)	-	-	
Head and Neck	0 / 212 (0)	0 / 221 (0)	-	-	
Non-general Surgery	8 / 3093 (0.3)	19 / 3115 (0.6)	0.42 (0.19-0.97)	0.04	
Unknown	0 / 159 (0)	0 / 167 (0)	-	-	
Co-Primary safety Outcomes					
Surgery Type					0.04
HPB	33 / 160 (20.6)	27 / 172 (15.7)	1.32 (0.79-2.20)	0.28	
Colorectal	65 / 485 (13.4)	76 / 455 (16.7)	0.79 (0.57-1.10)	0.17	
Upper GI	20 / 142 (14.1)	18 / 133 (13.5)	1.03 (0.54-1.96)	0.92	
Acute Care surgery	30 / 402 (7.5)	25 / 391 (6.4)	1.19 (0.70-2.03)	0.51	
Other Major General	11 / 75 (14.7)	18 / 86 (20.9)	0.73 (0.34-1.57)	0.42	
Head and Neck	9 / 212 (4.2)	23 / 221 (10.4)	0.39 (0.18-0.84)	0.02	
Non-general Surgery	476 / 3093 (15.4)	454 / 3115 (14.6)	1.06 (0.93-1.21)	0.36	
Unknown	27 / 159 (17.0)	16 / 167 (9.6)	1.84 (0.99-3.41)	0.05	
MINS					0.09
HPB	29 / 160 (18.1)	24 / 172 (14.0)	1.29 (0.75-2.21)	0.36	
Colorectal	63 / 485 (13.0)	70 / 455 (15.4)	0.84 (0.60-1.18)	0.31	
Upper GI	20 / 142 (14.1)	18 / 133 (13.5)	1.03 (0.54-1.96)	0.92	
Acute Care surgery	25 / 402 (6.2)	22 / 391 (5.6)	1.12 (0.63-1.99)	0.70	
Other Major General	11 / 75 (14.7)	14 / 86 (16.3)	0.93 (0.42-2.08)	0.86	
Head and Neck	9 / 212 (4.2)	23 / 221 (10.4)	0.39 (0.18-0.84)	0.02	
Non-general Surgery	424 / 3093 (13.7)	415 / 3115 (13.3)	1.04 (0.90-1.19)	0.62	
Unknown	27 / 159 (17.0)	15 / 167 (9.0)	1.95 (1.04-3.67)	0.04	
Non-hemorrhagic stroke					>0.99
HPB	2 / 160 (1.3)	1 / 172 (0.6)	2.25 (0.20-24.9)	0.51	
Colorectal	0 / 485 (0)	3 / 455 (0.7)	-	-	

	TXA (N=4728)	Placebo (N=4740)	TXA vs. Placebo		
	N(%)	N(%)	HR (95% CI)	P Value	P value for interaction
Upper GI	0 / 142 (0)	0 / 133 (0)	-	-	
Acute Care surgery	2 / 402 (0.5)	1 / 391 (0.3)	2.04 (0.18-22.5)	0.56	
Other Major General	0 / 75 (0)	0 / 86 (0)	-	-	
Head and Neck	0 / 212 (0)	0 / 221 (0)	-	-	
Non-general Surgery	20 / 3093 (0.6)	11 / 3115 (0.4)	1.83 (0.88-3.82)	0.11	
Unknown	0 / 159 (0)	0 / 167 (0)	-	-	
PAT					>0.99
HPB	1 / 160 (0.6)	1 / 172 (0.6)	0.96 (0.06-15.4)	0.98	
Colorectal	0 / 485 (0)	0 / 455 (0)	-	-	
Upper GI	0 / 142 (0)	0 / 133 (0)	-	-	
Acute Care surgery	1 / 402 (0.2)	0 / 391 (0)	-	-	
Other Major General	0 / 75 (0)	0 / 86 (0)	-	-	
Head and Neck	0 / 212 (0)	0 / 221 (0)	-	-	
Non-general Surgery	20 / 3093 (0.6)	22 / 3115 (0.7)	0.91 (0.50-1.68)	0.77	
Unknown	0 / 159 (0)	0 / 167 (0)	-	-	
VTE					>0.99
HPB	2 / 160 (1.3)	2 / 172 (1.2)	1.08 (0.15-7.70)	0.94	
Colorectal	4 / 485 (0.8)	3 / 455 (0.7)	1.26 (0.28-5.64)	0.76	
Upper GI	0 / 142 (0)	0 / 133 (0)	-	-	
Acute Care surgery	3 / 402 (0.7)	2 / 391 (0.5)	1.52 (0.25-9.11)	0.65	
Other Major General	0 / 75 (0)	4 / 86 (4.7)	-	-	
Head and Neck	0 / 212 (0)	0 / 221 (0)	-	-	
Non-general Surgery	23 / 3093 (0.7)	16 / 3115 (0.5)	1.45 (0.76-2.74)	0.26	
Unknown	0 / 159 (0)	1 / 167 (0.6)	-	-	
Amputation					>0.99
HPB	0 / 160 (0)	0 / 172 (0)	-	-	
Colorectal	0 / 485 (0)	0 / 455 (0)	-	-	
Upper GI	0 / 142 (0)	0 / 133 (0)	-	-	
Acute Care surgery	0 / 402 (0)	0 / 391 (0)	-	-	
Other Major General	0 / 75 (0)	0 / 86 (0)	-	-	
Head and Neck	0 / 212 (0)	0 / 221 (0)	-	-	

	TXA (N=4728)	Placebo (N=4740)	TXA vs. Placebo		
	N(%)	N(%)	HR (95% CI)	P Value	P value for interaction
Non-general Surgery	14 / 3093 (0.5)	22 / 3115 (0.7)	0.64 (0.33-1.25)	0.19	
Unknown	0 / 159 (0)	0 / 167 (0)	-	-	
Seizure					>0.99
HPB	0 / 160 (0)	1 / 172 (0.6)	-	-	
Colorectal	1 / 485 (0.2)	0 / 455 (0)	-	-	
Upper GI	0 / 142 (0)	0 / 133 (0)	-	-	
Acute Care surgery	0 / 402 (0)	0 / 391 (0)	-	-	
Other Major General	0 / 75 (0)	1 / 86 (1.2)	-	-	
Head and Neck	0 / 212 (0)	0 / 221 (0)	-	-	
Non-general Surgery	8 / 3093 (0.3)	1 / 3115 (<0.1)	8.11 (1.01-64.8)	0.05	
Unknown	1 / 159 (0.6)	0 / 167 (0)	-	-	

*HPB=hepatopancreaticobiliary; GI=gastrointestinal; MINS=myocardial injury after noncardiac surgery; PAT=peripheral arterial thrombosis; VTE=venous thromboembolism; HR=Hazard Ratio; CI=Confidence Interval

Appendix 1-8: Primary safety and efficacy outcomes at 30 days by cancer status among general surgery patients

	TXA (n=1635)	Placebo (n=1625)	TXA vs. Placebo		
	n(%)	n(%)	HR (95% CI)	P Value	P value for interaction
Co-Primary Efficacy Outcomes					
Primary Efficacy					0.21
History of Cancer - Yes	94 / 666 (14.1)	112 / 664 (16.9)	0.82 (0.62-1.08)	0.16	
History of Cancer - No	36 / 969 (3.7)	59 / 961 (6.1)	0.60 (0.39-0.90)	0.01	
Life threatening Bleeding					0.77
History of Cancer - Yes	16 / 666 (2.4)	17 / 664 (2.6)	0.94 (0.47-1.86)	0.86	
History of Cancer - No	9 / 969 (0.9)	8 / 961 (0.8)	1.12 (0.43-2.90)	0.82	
Major Bleed					0.16
History of Cancer - Yes	82 / 666 (12.3)	101 / 664 (15.2)	0.79 (0.59-1.06)	0.11	
History of Cancer - No	28 / 969 (2.9)	51 / 961 (5.3)	0.54 (0.34-0.85)	0.008	
Critical Organ Bleed					>0.99
History of Cancer - Yes	4 / 666 (0.6)	1 / 664 (0.2)	3.84 (0.43-34.4)	0.23	
History of Cancer - No	0 / 969 (0)	1 / 961 (0.1)	-	-	
Co-Primary safety Outcomes					
Primary Safety					0.48
History of Cancer - Yes	101 / 666 (15.2)	112 / 664 (16.9)	0.89 (0.68-1.17)	0.40	
History of Cancer - No	94 / 969 (9.7)	91 / 961 (9.5)	1.02 (0.77-1.37)	0.87	
MINS					0.53
History of Cancer - Yes	97 / 666 (14.6)	104 / 664 (15.7)	0.92 (0.70-1.22)	0.57	
History of Cancer - No	87 / 969 (9.0)	82 / 961 (8.5)	1.05 (0.78-1.42)	0.75	
Non-hemoraghic stroke					0.31
History of Cancer - Yes	1 / 666 (0.2)	3 / 664 (0.5)	0.34 (0.04-3.26)	0.35	
History of Cancer - No	3 / 969 (0.3)	2 / 961 (0.2)	1.50 (0.25-8.96)	0.66	
PAT					>0.99
History of Cancer - Yes	2 / 666 (0.3)	1 / 664 (0.2)	2.04 (0.18-22.5)	0.56	
History of Cancer - No	0 / 969 (0)	0 / 961 (0)	-	-	
VTE					0.88
History of Cancer - Yes	4 / 666 (0.6)	5 / 664 (0.8)	0.81 (0.22-3.00)	0.75	
History of Cancer - No	5 / 969 (0.5)	7 / 961 (0.7)	0.71 (0.23-2.24)	0.56	

	TXA (n=1635)	Placebo (n=1625)	TXA vs. Placebo		
	n(%)	n(%)	HR (95% CI)	P Value	P value for interaction
Amputation					-
History of Cancer - Yes	0 / 666 (0)	0 / 664 (0)	-	-	
History of Cancer - No	0 / 969 (0)	0 / 961 (0)	-	-	
Seizure					>0.99
History of Cancer - Yes	1 / 666 (0.2)	2 / 664 (0.3)	0.47 (0.04-5.23)	0.54	
History of Cancer - No	1 / 969 (0.1)	0 / 961 (0)	-	-	

TXA=tranexamic acid; MINS=myocardial injury after noncardiac surgery; PAT=peripheral arterial thrombosis; VTE=venous thromboembolism; HR=Hazard Ratio; CI=Confidence Interval

Appendix 1-9: Secondary outcomes at 30 days by general surgery versus non-general surgery

	TXA (n=4728)	Placebo (n=4740)	TXA vs. Placebo		
	n(%)	n(%)	HR (95% CI)	P Value	P value for interaction
BIMS					0.84
General Surgery	126 / 1635 (7.7)	160 / 1625 (9.8)	0.77 (0.61-0.97)	0.03	
Non General Surgery	290 / 3093 (9.4)	384 / 3115 (12.3)	0.75 (0.64-0.87)	0.0002	
RBCs Transfusion			**ODDS ratio**	**P value**	**P value for interaction**
General Surgery	141 / 1635 (8.6)	177 / 1625 (10.8)	0.77 (0.61-0.97)	0.0294	0.8584
Non General Surgery	308 / 3093 (9.9)	399 / 3115 (12.8)	0.75 (0.64 -0.88)	0.0004	
RBCs Transfusion 2 or more unit					
General Surgery	102 / 1635 (6.2)	114 / 1625 (7.0)	0.88 (0.67-1.16)	0.3728	0.1091
Non General Surgery	195 / 3093 (7.0)	284 / 3115 (9.1)	0.67 (0.55 -0.81)	<0.0001	
RBCs Transfusion 2-4 unit					
General Surgery	76 / 1635 (4.6)	82 / 1625 (5.0)	0.96 (0.71-1.29)	0.7842	0.0295
Non General Surgery	147 / 3093 (4.7)	231 / 3115 (7.4)	0.63 (0.52-0.78)	<0.0001	

TXA=tranexamic acid; BIMS=bleeding independently associated with mortality after noncardiac surgery; HR=hazard ratio; CI=confidence interval; RBC=red blood cell

Appendix 1-10: Tertiary outcomes at 30 days by general surgery versus non-general surgery

	TXA (n=4728)	Placebo (n=4740)	TXA vs. placebo		
	n(%)	n(%)	HR (95% CI)	P Value	P value for interaction
ISTH major bleeding					0.91
General Surgery	113 / 1635 (6.9)	146 / 1625 (9.0)	0.76 (0.59-0.97)	0.03	
Non General Surgery	202 / 3093 (6.5)	270 / 3115 (8.7)	0.74 (0.62-0.89)	0.002	
All-cause mortality					0.44
General Surgery	23 / 1635 (1.4)	21 / 1625 (1.3)	1.09 (0.60-1.98)	0.77	
Non General Surgery	28 / 3093 (0.9)	35 / 3115 (1.1)	0.80 (0.49-1.32)	0.39	
Vascular death					0.22
General Surgery	10 / 1635 (0.6)	7 / 1625 (0.4)	1.42 (0.54-3.72)	0.48	
Non General Surgery	15 / 3093 (0.5)	22 / 3115 (0.7)	0.68 (0.36-1.32)	0.26	
Infection					
General Surgery	218 / 1635 (13.3)	185 / 1625 (11.4)	1.18 (0.97-1.44)	0.09	
Non General Surgery	281 / 3093 (9.1)	304 / 3115 (9.8)	0.93 (0.79-1.09)	0.35	
Sepsis					0.36
General Surgery	38 / 1635 (2.3)	29 / 1625 (1.8)	1.30 (0.80-2.11)	0.29	
Non General Surgery	31 / 3093 (1.0)	33 / 3115 (1.1)	0.94 (0.58-1.54)	0.82	
A net risk-benefit composite outcome					0.24
General Surgery	296 / 1635 (18.1)	333 / 1625 (20.5)	0.87 (0.74-1.01)	0.07	
Non General Surgery	685 / 3093 (22.1)	710 / 3115 (22.8)	0.97 (0.87-1.08)	0.56	

TXA=tranexamic acid; HR=hazard ratio; CI=confidence interval; ISTH=International society on Thrombosis and Haemostasis

Appendix 2: Methodologic supplementary

Appendix 2-1: Definition of General surgery

Type of general surgery performed included the following:

1. Complex visceral resection (surgery involving the liver, esophagus, pancreas, or multiple organs)
2. Partial or total colectomy or stomach surgery
3. Other intra-abdominal surgery (gallbladder, appendix, adrenals, spleen, regional lymph node dissection)
4. Major head and neck resection for non-thyroid tumor

Appendix 2-2: VISION Post-operative complications and baseline variable definitions

MINS was defined as any myocardial infarction (as defined below), and any elevated troponin (higher than the local lab threshold) judged to be due to myocardial ischemia (i.e. without evidence of a non-ischemic etiology [e.g. chronic elevation, pulmonary embolism, sepsis, cardioversion]) that occurred within the first 30 days after the initiation of surgery. The only exceptions to the definition of an elevated troponin will be to use a higher threshold for troponin T (TnT) of ≥30 ng/L, and for high-sensitivity troponin T (hsTnT) of 20 to <65 ng/L with an absolute change of at least 5 ng/L or an hsTnT level ≥65 ng/L. These threshold for TnT and hsTnT are based upon data from a large international prospective perioperative cohort study that established troponin thresholds that were independently associated with 30-day mortality after noncardiac surgery.

Myocardial Infarction was diagnosed if any one of the following criteria were met:

1. Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
    A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);
    B. development of pathologic Q waves present in any two contiguous leads that are ≥ 30 milliseconds;
    C. new or presumed ECG changes indicative of ischemia (i.e., ST segment elevation [≥ 2 mm in leads V1, V2, or V3 OR ≥ 1 mm in the other leads], ST segment depression [≥ 1 mm], or symmetric inversion of T waves ≥ 1 mm) in at least two contiguous leads;
    D. new left bundle branch block (LBBB); or
    E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging
    F. identification of intracoronary thrombus on angiography or autopsy

2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

3. Percutaneous coronary intervention (PCI) related myocardial infarction is defined by elevation of a troponin value (>5 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL) or a rise of a troponin measurement >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

4. Stent thrombosis associated with myocardial infarction when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one of value above the 99th percentile URL.

5. Coronary artery bypass grafting (CABG) related myocardial infarction is defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic

documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

6. For patients who are believed to have suffered a myocardial infarction within 28 days of a MINS event or within 28 days of a prior myocardial infarction, the following criterion for myocardial infarction is required:

   Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) and 20% higher than the last troponin measurement related to the preceding event together with evidence of myocardial ischemia with at least one of the following:
   A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);
   B. development of pathologic Q waves present in any two contiguous leads that are > 30 milliseconds;
   C. new or presumed new ECG changes indicative of ischemia (i.e., ST segment elevation [> 2 mm in leads V1, V2, or V3 OR > 1 mm in the other leads], ST segment depression [> 1 mm], or symmetric inversion of T waves > 1 mm) in at least two contiguous leads;
   D. new LBBB; or
   E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging
   F. identification of intracoronary thrombus on angiography or autopsy

Venous thromboemboli (VTE) was diagnosed if the patient had either a pulmonary embolism or deep vein thrombosis as defined below:

Pulmonary embolism (PE) was diagnosed if any of the following were true:

1. A high probability ventilation/perfusion lung scan
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan
3. An intraluminal filling defect on pulmonary angiography
4. A positive diagnostic test for DVT(i.e., positive compression ultrasound) and a non-diagnostic (i.e.,low or intermediate probability) ventilation/perfusion lung scan
5. A positive diagnostic test for DVT(i.e., positive compression ultrasound) and a non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan

Deep vein thrombosis (DVT) was diagnosed if any of the following were true:

1. A persistent intraluminal filling defect on contrast venography
2. Non-compressibility of one or more venous segments on B mode compression ultrasonography
3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography

Stroke was diagnosed in patients who developed a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours.

Acute kidney injury (AKI) resulting in dialysis was diagnosed if there were any new acute renal failure requiring the use of dialysis within 30-days of major general surgery. Dialysis was defined as the use of a hemodialysis machine or peritoneal dialysis apparatus.

Infection was defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms.

Sepsis was defined as the presence of infection and a systemic inflammatory response. Systemic inflammatory response requires 2 or more of the following factors: core temperature > 38 ºC or < 36 ºC; heart rate > 90 bpm; respiratory rate > 20 breaths/min; white blood cell count > 12 x 10^9/ L or < 4 x 10^9/ L.

Atrial fibrillation was diagnosed when a patient experienced a new AF episode within 30-days of general surgery that resulted in angina, congestive heart failure, symptomatic hypotension, or that required treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.

Congestive heart failure (CHF) was diagnosed if a patient developed at least one of the following clinical signs: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3 AND at least one of the following radiographic findings: vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema.

Bleeding was defined as bleeding which results in postoperative hemoglobin <70g/L, or leads to a transfusion, reoperation, or is thought to be the cause of death.

Recent high risk coronary artery disease – 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 – inability to perform any physical activity without the development of angina

COPD – Noted if the chart or a physician had ever indicated that a patient has had chronic bronchitis. If there is no mention of this but the patient states they have had daily production of sputum for at least 3 months in 2 consecutive years then they were marked as having COPD. If a physician has ever indicated that a patient has emphysema or if a patient's Pulmonary Function Tests (PFT) stated fixed or irreversible airflow limitation and/or emphysema then they were marked as having COPD.

Peripheral vascular disease – A current or prior history of: physician diagnosed 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.

Active Cancer – Defined as a patient with a diagnosis of cancer who is or has received active treatment for their cancer (e.g., chemo, radiation, or surgery) within the previous 6 months; however, it does not apply to patients with non-melanoma skin cancers. Examples of surgery to treat active cancer include resection of primary or metastatic tumour, palliative surgery such as intestinal bypass to relieve symptoms, or reconstructive surgery. It does not apply to surgery for a biopsy.

Appendix 2-3: Eligibility criteria for the POISE-3 Trial

Inclusion criteria – patients had to fulfill the following inclusion criteria:

1. ≥45 years of age;
2. undergoing noncardiac surgery;
3. expected to require at least one overnight hospital admission after surgery;
4. fulfilled ≥1 of the following 6 criteria (A-F):
    A. N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥200 ng/L;
    B. history of coronary artery disease as defined by any one of the following 7 criteria:
        I. history of angina,
        II. history of myocardial infarction or acute coronary syndrome,
        III. history of a regional cardiac wall motion abnormality on echocardiography or a segmental fixed defect on radionuclide imaging,
        IV. history of a radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test demonstrating cardiac ischemia,
        V. history of a coronary angiographic or computer tomography coronary angiographic evidence of atherosclerotic stenosis ≥50% of the diameter of any coronary artery,
        VI. electrocardiogram with pathological Q waves in two contiguous leads, or
        VII. previous coronary artery revascularization (i.e. percutaneous coronary intervention or coronary artery bypass graft surgery);
    C. history of peripheral arterial disease as defined by a physician diagnosis of a current, or prior, history of any one of the following 4 criteria:
        I. intermittent claudication,

II. vascular surgery for atherosclerotic disease,
III. an ankle/arm systolic blood pressure ratio <0.90 in either leg at rest, or
IV. angiographic or doppler study demonstrating >70% stenosis in a noncardiac artery;

D. history of stroke as defined by any one of the following 2 criteria
I. a physician diagnosis of stroke, or
II. computed tomography or magnetic resonance imaging evidence of a prior stroke;

E. undergoing major vascular surgery defined as all vascular surgery except arteriovenous shunt, vein stripping procedures, carotid endarterectomies, and endovascular abdominal aortic aneurysm repair; or

F. any 3 of the following 9 risk criteria:
I. undergoing major surgery defined as intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery (i.e., hip arthroplasty, internal fixation of hip or femur, pelvic arthroplasty, knee arthroplasty, above-knee amputation, or amputation below the knee but above the foot),
II. history of congestive heart failure defined as 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,
III. history of a transient ischemic attack,
IV. diabetes and currently taking an oral hypoglycemic agent or insulin,
V. age >70 years,
VI. history of hypertension,
VII. serum creatinine >175 μmol/L (>2.0 mg/dL) based on most recent measurement before randomization,
VIII. history of smoking within 2 years of surgery, or
IX. undergoing emergent/urgent surgery defined as surgery that a surgeon schedules to go to the operating room within 48 hours of an acute presentation to the hospital; and

5. provided written informed consent to participate in the POISE-3 Trial.

Exclusion criteria – patients fulfilling any of the following criteria were excluded:

1. undergoing cardiac surgery or intracranial neurosurgery;
2. planned use of systemic tranexamic acid during surgery;
3. low-risk surgical procedure, based on individual physician's judgment;
4. hypersensitivity or known allergy to tranexamic acid;
5. creatinine clearance <30 mL/min (Cockcroft-Gault equation) or on chronic dialysis;
6. history of seizure disorder;
7. recent (<3 months) stroke, myocardial infarction, acute arterial thrombosis, or venous thromboembolism;
8. fibrinolytic condition following consumption coagulopathy;
9. subarachnoid hemorrhage within the past 30 days;
10. women of childbearing potential who are not taking effective contraception, pregnant or breast-feeding; or
11. previously enrolled in the POISE-3 trial.

Appendix 2-4: Outcome Definitions for the POISE-3 Trial

Life-threatening bleeding: Bleeding that was fatal, or led to: significant hypotension that requires inotrope therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.

Major bleeding: Bleeding that was not specified under "life- threatening bleeding" as above, and required one of the following criteria: resulted in a postoperative hemoglobin ≤70 g/L; a transfusion of ≥1 unit of red blood cells; or led to an intervention (i.e., embolization, superficial vascular repair, or nasal packing).

Critical organ bleeding: A bleeding event was bleeding that was intracranial, intraocular, intraspinal, pericardial, retroperitoneal, or intramuscular with compartment syndrome.

Bleeding independently associated with mortality after noncardiac surgery (BIMS):
BIMS was bleeding meeting any of the following 3 criteria:

1. associated with a postoperative hemoglobin <70 g/L;
2. resulting in transfusion of one or more units of red blood cells; or
3. judged to be the immediate cause of death.

International Society on Thrombosis and Haemostasis (ISTH) major bleeding:
ISTH major bleeding was bleeding that met any of the following criteria:

1. fatal bleeding;
2. bleeding that was symptomatic and occurred in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon;
3. extra-surgical site bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or
4. more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 hours to the bleeding;
5. surgical site bleeding that required a second intervention - open, arthroscopic, endovascular – or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or
6. delayed wound healing, resulting in prolonged hospitalization or a deep wound infection; or
7. surgical site bleeding that was unexpected and prolonged or sufficiently large to cause
8. hemodynamic instability, as assessed by the surgeon. There should be an associated fall in
9. hemoglobin level of 20 g/L (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least
10. two units of whole blood or red cells, with temporal association within 24 hours to the bleeding.

Myocardial injury after noncardiac surgery (MINS): MINS was defined as any myocardial infarction (as defined below), and any elevated troponin (i.e., a value higher than the local laboratory threshold) judged to be due to myocardial ischemia (i.e., without evidence of a nonischemic etiology [e.g., chronic elevation, pulmonary embolism, sepsis, cardioversion]) that occurred within the first 30 days after the initiation of surgery. The only exceptions to the definition of an elevated troponin was to use a higher threshold for troponin T (TnT) of ≥30 ng/L, and for high-sensitivity troponin T (hsTnT) of 20 to <65 ng/L with an absolute change of at least 5 ng/L or an hsTnT level ≥65 ng/L. These threshold for TnT and hsTnT are based upon data from a large international prospective perioperative cohort study that established troponin thresholds that were independently associated with 30-day mortality after noncardiac surgery.1,2

Myocardial infarction: If the diagnostic criteria for myocardial infarction includes an elevated troponin, then the definition of MINS must be met to fulfill the diagnostic criteria for myocardial infarction (universal definition). The diagnosis of myocardial infarction requires any one of the following criteria.

1. Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
   G. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);
   H. development of pathologic Q waves present in any two contiguous leads that are ≥ 30 milliseconds;

I. new or presumed ECG changes indicative of ischemia (i.e., ST segment elevation [≥ 2 mm in leads V1, V2, or V3 OR ≥ 1 mm in the other leads], ST segment depression [≥ 1 mm], or symmetric inversion of T waves ≥ 1 mm) in at least two contiguous leads;
J. new LBBB; or
K. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging
L. identification of intracoronary thrombus on angiography or autopsy

2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

3. Percutaneous coronary intervention (PCI) related myocardial infarction is defined by elevation of a troponin value (>5 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL) or a rise of a troponin measurement >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

4. Stent thrombosis associated with myocardial infarction when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one of value above the 99th percentile URL.

5. Coronary artery bypass grafting (CABG) related myocardial infarction is defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

6. For patients who are believed to have suffered a myocardial infarction within 28 days of a MINS event or within 28 days of a prior myocardial infarction, the following criterion for myocardial infarction is required: Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) and 20% higher than the last troponin measurement related to the preceding event together with evidence of myocardial ischemia with at least one of the following:
G. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);
H. development of pathologic Q waves present in any two contiguous leads that are > 30 milliseconds;
I. new or presumed new ECG changes indicative of ischemia (i.e., ST segment elevation [> 2 mm in leads V1, V2, or V3 OR > 1 mm in the other leads], ST segment depression [> 1 mm], or symmetric inversion of T waves > 1 mm) in at least two contiguous leads;
J. new LBBB; or
K. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging
L. identification of intracoronary thrombus on angiography or autopsy

MINS not fulfilling the universal definition of myocardial infarction: Any elevated troponin (higher than the local lab threshold) judged to be due to myocardial ischemia (i.e., without evidence of a non-ischemic etiology [e.g., chronic elevation, pulmonary embolism, sepsis, cardioversion]) that occurred with the first 30 days after surgery, and not fulfilling the definition of MI (as defined above).

Stroke: Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death. Stroke will be sub-classified into hemorrhagic and non-hemorrhagic stroke. Non-hemorrhagic stroke will sub-classified into ischemic, ischemic with secondary transformation, or stroke of uncertain classification. Hemorrhagic stroke will be sub-classified into primary intracerebral hemorrhage and primary subarachnoid hemorrhage.

1. ***Ischemic stroke:*** focal brain infarction caused by an arterial (or rarely venous) obstruction and as documented by CT/MRI that is normal or shows an infarct in the clinically expected area.

2. ***Secondary hemorrhagic transformation of ischemic stroke***: hemorrhagic transformation of ischemic stroke may be symptomatic or asymptomatic.
   A. Symptomatic transformation of ischemic stroke is defined as a hematoma occupying 30% or more of the infarcted tissue associated with a significant neurologic deterioration (consistent with a decrease of 4 points in the NIHSS) compared to immediately before the worsening and an absence of an alternative explanation for deterioration.
   B. Asymptomatic transformation of ischemic stroke is defined as a hemorrhagic transformation not meeting the criteria for symptomatic transformation.

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

4. ***Hemorrhagic stroke***: hemorrhagic stroke requires neuroimaging or autopsy confirmation and includes two subcategories: primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage. Intracranial bleeding caused by head trauma, bleeding associated with tumors, hemorrhagic transformation of ischemic stroke and subdural/epidural hematomas are not considered as hemorrhagic strokes (but these will be counted separately as major hemorrhages). Microbleeds are not considered intracranial hemorrhage.
   A. Primary intracerebral hemorrhage: These are symptomatic hemorrhagic strokes with CT/MRI or autopsy evidence of bleeding into the substance of the brain or ventricular spaces. Large or superficial intracerebral hemorrhages often are associated with minor amounts of subarachnoid hemorrhage, but these should be classified as intracerebral hemorrhages. Does not include secondary hemorrhage into cerebral infarct (i.e. hemorrhagic transformation which is defined separately), or intracerebral bleeding (i.e. contusions) due to trauma, or microbleeds detected by MRI.
   B. Primary subarachnoid hemorrhage: Typical clinical syndrome of sudden onset headache, with or without focal signs (subarachnoid hemorrhage may not have focal deficits), and CT or cerebrospinal fluid evidence of bleeding primarily into the subarachnoid space. Subarachnoid bleeding due to ruptured intracranial aneurysms and vascular malformation are counted as hemorrhagic strokes, but traumatic subarachnoid hemorrhage is not.

Peripheral Arterial Thrombosis: We consider a peripheral arterial thrombosis to have occurred where there is clear evidence of abrupt occlusion of a peripheral artery (i.e., not a stroke related to an intracranial artery or myocardial infarction) consistent with either an acute local thrombotic event or a peripheral arterial embolism. To fulfill this definition we require at least one of the following objective findings of peripheral arterial thrombosis:
1. Surgical report indicating evidence of arterial thrombosis/ peripheral arterial embolism,
2. Pathological specimen demonstrating arterial thrombosis/ peripheral arterial embolism,
3. Imaging evidence consistent with arterial thrombosis/ peripheral arterial embolism, or
4. Autopsy reports documenting arterial thrombosis/ peripheral arterial embolism

Symptomatic Proximal Venous Thromboembolism: Venous thromboembolism that includes symptomatic pulmonary embolism or symptomatic proximal deep vein thrombosis

Symptomatic Pulmonary Embolism (PE): The diagnosis of symptomatic PE requires symptoms (e.g., dyspnea, pleuritic chest pain) or signs (e.g., hypoxia, increased work of breathing) and any one of the following:
1. A high probability ventilation/perfusion lung scan,
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan,
3. An intraluminal filling defect on pulmonary angiography, or
4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following:
   A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan, or
   B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan

Symptomatic Proximal Deep Venous Thrombosis (DVT):

The diagnosis of symptomatic proximal deep venous thrombosis requires:
1. symptoms or signs that suggest DVT (e.g., leg pain or swelling),
2. thrombosis involving the popliteal vein or more proximal veins for leg DVT OR axillary or more proximal veins for arm DVTs

Any of the following defines evidence of vein thrombosis:
   A. a persistent intraluminal filling defect on contrast venography (including on computed tomography),
   B. noncompressibility of one or more venous segments on B mode compression ultrasonography, or
   C. A clearly defined intraluminal filling defect on doppler imaging in a vein that cannot have compressibility assessed (e.g., iliac, inferior vena cava, subclavian).

Nonfatal cardiac arrest: Nonfatal cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.

Amputation: Amputation is defined as an amputation procedure, or auto amputation after the initial surgery.

Seizure: Seizure was defined as the abrupt onset of focal or generalized experiential, motor, sensory or cognitive phenomena, in absence of another etiology for the event (e.g., movement or psychiatric disorder).

Infection: Infection was defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms.

Sepsis: The Third International Consensus Definitions Task Force defined sepsis as a "life-threatening organ dysfunction due to a dysregulated host response to infection." Based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria, sepsis required a quick Sequential Organ Failure Assessment (qSOFA) Score ≥2 points due to infection.

The qSOFA included the following items and scoring system:
1. Glasgow Coma Scale (GCS) score of 13 or less (1 point)
2. systolic blood pressure of 100 mm Hg or less (1 point), and
3. respiratory rate of 22 breaths/min or more (1 point).

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