PATIENT-IMPORTANT OUTCOMES OF CARDIAC AND NON-CARDIAC SURGERY: DESCRIBING THE LANDSCAPE AND EXPLORING ETIOLOGIES AND INTERVENTIONS

PATIENT-IMPORTANT OUTCOMES OF CARDIAC AND NON-CARDIAC SURGERY: DESCRIBING THE LANDSCAPE AND EXPLORING ETIOLOGIES AND INTERVENTIONS

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ABSTRACT

The patient-important outcomes of cardiac and non-cardiac surgery are well-recognized but poorly understood. The causes of major morbidity and mortality in patients undergoing non-cardiac are not known. This is not the case in cardiac surgery, which is provided to a homogenous patient population that has been well-described through clinical registries. Recent improvements to the care of cardiac surgical patients have led to dramatic decreases in major morbidity and mortality. However, neurocognitive and functional impairments after cardiac surgery remain the most feared by patients and least understood by clinicians. This thesis comprises 6 chapters that inform these knowledge gaps and establish the basis upon which future research will be based.

Chapter 1 is an introduction providing the rationale for conducting each of the included studies.

Chapter 2 reports the VISION Mortality study, which explores the relationship between major complications and death within 30-days of undergoing inpatient, noncardiac surgery.

Chapter 3 reports a study validating the use of the Standardized Assessment of Global activities in the Elderly (SAGE) scale in patients undergoing cardiac surgery.

Chapter 4 presents a pilot observational study that establishes the feasibility of conducting a large, prospective cohort study to determine the relationship between decreases in cerebral saturation during cardiac surgery and postoperative functional decline.

Chapter 5 presents a pilot study conducted to inform the feasibility of a large, randomized cluster crossover trial examining whether an institutional policy of restricted benzodiazepine administration during cardiac surgery (compared to liberal administration) would reduce delirium after cardiac surgery.

Chapter 6 discusses the conclusions, limitations, and implications of the research presented in this PhD thesis.

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CONTRIBUTIONS BY OTHERS

At the end of each chapter is a full description of authors' contributions.

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LIST OF ABBREVIATIONS

3D-CAM: 3D Confusion Assessment Method

ADL: Activities of daily living

AF: Atrial fibrillation

aHR: Adjusted hazard ratio

AKI: Acute kidney injury

APPRAISE: Age and other Predictors of PostopeRative functionAl ImpairmEnt

AUC: Area under the curve

CABG: Coronary artery bypass grafting

CAD: Coronary artery disease

CAM-ICU: Confusion Assessment Method – Intensive Care Unit

CCSC: Canadian Cardiovascular Society Class

CCU: Coronary Care Unit

CHF: Congestive heart failure

CI: Confidence interval

CIHR: Canadian Institutes of Health Research

COPD: Chronic obstructive pulmonary disease

COSMIN: COnsensus-based Standards for the selection of health status Measurement Instruments

DSS: Digit Symbol Substitution

DSST: Digit Symbol Substitution Test

DVT: Deep vein thrombosis

eGFR: Estimated glomerular filtration rate

Euroscore: European System for Cardiac Risk Operative Risk Evaluation

HGH: Hamilton General Hospital

HR: Hazard ratio

hsTnT: High sensitivity troponin T

IADL: Instrumental activities of daily living

ICC: Intracluster correlation coefficient

IPC: Interperiod correlation

IQR: Interquartile range

LTC: Long-term care

mcg: Micrograms

MINS: Myocardial injury after noncardiac surgery

MoCA: Montreal Cognitive Assessment

MR: Magnetic resonance

N: Number

NIRS: Near-infrared spectroscopy

No.: Number

PAC: Preoperative assessment clinics

PAD: Peripheral arterial disease

PE: Pulmonary embolism

PHRI: Population Health Research Institute

POCD: Postoperative cognitive decline

Q1 – Q3: Quartile one to quartile three

RCT: Randomized controlled trial

rScO2: Regional cerebral oxygen saturation

ROC: Receiver Operating Characteristic

SAGE: Standardized Assessment of Global activities in the Elderly scale

TCPS-2: Tri-Council Policy Statement 2

TnT: Troponin T

TUGT: Timed Up and Go Test

Uro/Gyn: Urology/gynecology

USFDA: United States Food and Drug Administration

VISION: Vascular Events in Noncardiac Surgery Patients cohort study

WHO: World Health Organization

WHODAS: World Health Organization Disability Assessment Scale

CHAPTER 1: Introduction

1.1 Background

More than 200 million patients undergo anesthesia for cardiac and non-cardiac surgery globally each year.[1] Due to advances in monitoring that have been incorporated into anesthesia practice, anesthetic-related mortality has decreased 100-fold over the last 100 years.[2] However, clinicians still know very little about the impacts of surgery and anesthesia on major morbidity and mortality. Historically, research in anesthesia has examined the impact of preoperative or intraoperative interventions in laboratory settings or small and selected groups of patients. Often, the outcomes evaluated by these studies have been surrogate markers of patient-important outcomes like major morbidity and mortality. Surrogate markers that have been studied include biomarkers, outcomes in animal models, and changes in physiologic parameters.[3] However, multiple interventions that have been adopted by the perioperative medicine community on the basis of small studies examining surrogate endpoints have later been demonstrated to have no effect or to cause harm when examined in a larger trial evaluating patient-important outcomes.[3]

Leaders in anesthesia and perioperative medicine have recognized this limitation, calling for large studies of patient-important outcomes in anesthesiology and perioperative medicine.[3] These calls have been issued in the setting of a changing scientific milieu of perioperative medicine, with a shift from expertise-based to evidence-based clinical practice,[4] and the need for clinical research to support the use of interventions and approaches to perioperative care. In response, there has been a shift from studies examining the impact of interventions on surrogate outcomes measured during the intraoperative and immediate postoperative period to studies examining the short- and long-term effects of perioperative interventions on major morbidity and mortality. Multiple large observational studies and clinical trials have been conducted examining

patient-important outcomes like major cardiovascular events, neurologic injuries, and death. However, despite improvements, a number of evidence gaps remain, with distinct differences between cardiac and non-cardiac surgery in the questions that need to be addressed.

Non-cardiac surgery is more common than cardiac surgery – particularly in low- and middle-income countries[5] – and offered to a heterogenous population, including patients of all ages who are being treated with surgery for problems stemming from a variety of pathophysiologic states (i.e. infectious, neoplastic, atherosclerotic/vascular, traumatic) affecting a wide range of organ systems (i.e. pulmonary, genitourinary, neurologic, vascular, gastrointestinal, musculoskeletal). Patients undergoing non-cardiac surgery have varying numbers and types of comorbidities and, as a result, have vastly different estimates of perioperative risk. As a result of this heterogeneity, there is limited registry and administrative data describing the non-cardiac surgical population as a whole. The lack of prospective data collected from representative samples of patients undergoing non-cardiac surgery has resulted in uncertainty regarding the incidence of death and the relationship between the major perioperative complications and death in patients undergoing non-cardiac surgery.

Patients undergoing cardiac surgery are different from those undergoing non-cardiac surgery, in that they represent a relatively homogenous population, who are generally older and have more comorbidity. Patients undergoing cardiac surgery are being surgically treated for problems stemming from a small number of pathophysiologic states (the majority being atherosclerotic/vascular) affecting a single system: the heart and thoracic blood vessels. As a result of this homogeneity, several large cardiac surgery clinical registries collect data about this population and the incidence of death – estimated at 2%[6] – and the major perioperative complications in patients undergoing cardiac surgery is readily available.

Despite recent decreases in mortality after cardiac surgery,[6] the patients contemporarily undergoing cardiac surgery are older and have more comorbidity than previous populations of cardiac surgical patients.[6] In 2009, adults aged 65 years in Canada had a life expectancy of 20.2 additional years[7]. Given the increasing age of patients undergoing cardiac surgery, the goals of these procedures need to take into account improvements in quality of life and function, with the decision to proceed with surgery based on anticipated maintenance or improvement in function as well as survival. However, little is known about functional ability after cardiac surgery: no measures have been validated in this population, the impact of cardiac surgery on function is unclear, no predictors of functional decline have been identified, and no studies have investigated interventions to mitigate functional decline after cardiac surgery. This thesis takes step to address these knowledge gaps in order to understand the patient-important outcomes of cardiac and non-cardiac surgery.

1.2 Mortality in patients undergoing noncardiac surgery

More than 100 million adults aged 45 years and older undergo inpatient noncardiac surgery around the world annually.[1] The epidemiology of prognostically important myocardial injury after noncardiac surgery has previously been described,[8,9] and perioperative troponin measurements have been used to define and describe the incidence of myocardial injury after noncardiac surgery (MINS) using both non-high-sensitivity troponin T (TnT)[8] and high-sensitivity troponin T (hsTnT) measurements.[9] However, little is known about the contemporary incidence, timing, and location of death within 30-days of noncardiac surgery in a large, representative population. Furthermore, while the prognostically important troponin elevation after cardiac surgery has been defined, little is known about the epidemiology of MINS in the context of other perioperative complications. These other complications – which are widely

recognized but poorly understood – include pulmonary embolism (PE), deep venous thrombosis (DVT), stroke, bleeding, acute kidney injury (AKI), sepsis and non-sepsis infection, new clinically important atrial fibrillation (AF), and congestive heart failure (CHF). The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study was undertaken to systematically collect observational data pertaining to a representative sample of patients undergoing non-cardiac surgery around the world, including major morbidity and mortality. Chapter 2 presents an analysis of data obtained in VISION, which describes the incidence, timing, and location of death, the incidence of the major perioperative complications, and the relationship of the major perioperative complications with death within 30-days after non-cardiac surgery.

1.3 The assessment of function after cardiac surgery

Few studies have evaluated the functional outcomes of patients undergoing cardiac surgery. The largest prospective study evaluating postoperative function after cardiac surgery administered the Katz activities of daily living (ADL) index 3 months after surgery to a cohort of 475 patients ≥65 years of age, and found that 16% of all patients suffered functional decline.[10] This study was used to validate a predictive measure of postoperative decline, but did not examine any other predictors. In addition, they evaluated only change in postoperative ADL, rather than global functional ability (i.e., ADL, Instrumental Activities of Daily Living (IADL), and cognition). No studies have systematically evaluated short and long-term functional change in a large cohort of consecutive cardiac surgery patients. Moreover, studies have not identified any patient characteristics that predict functional decline after cardiac surgery.

A major barrier to the systematic assessment of function after cardiac surgery is the lack of validated measures of global function that could be feasibly incorporated into large studies

within the cardiac surgery population. Chapter 3 describes the validation of the Standardized Assessment of Global activities in the Elderly (SAGE) scale in a cohort of 150 cardiac surgery patients through comparisons of SAGE scores with corresponding gold standard measures of ADL, IADL, and cognition administered by masters-level occupational therapy students as part of a home functional assessment.

1.4 The relationship between intraoperative cerebral saturations and functional decline after cardiac surgery

More than 1 million patients around the world undergo cardiac surgery annually.[11,12] With longevity comes comorbidity and, in the context of an aging population, the number of people requiring cardiac surgical procedures is rising.[11,12] Improvements in intraoperative management and perioperative care have resulted in substantial decreases in perioperative morbidity and mortality.[13] However, postoperative cognitive impairment remains common and constitutes one of the most devastating and feared sequelae of cardiac surgery, particularly among the elderly population. Although cognitive decline is a patient-important outcome, the way it is currently measured – using psychometric tests – has limited meaning for patients and non-experts. In addition, the relationship between change in cognitive test scores and daily function remains unknown.

Near-infrared spectroscopy (NIRS) is a non-invasive technique that can be used to continuously monitor regional cerebral oxygen saturation (rScO2), which represents the balance between cerebral oxygen delivery and consumption.[14] In adult patients undergoing cardiac surgery, regional cerebral oxygen desaturation measured using NIRS has been shown to be associated with postoperative cognitive decline (POCD),[15] although the prognostically important threshold is uncertain. Furthermore, NIRS has not been studied in relationship to functional

decline. Given that it has been shown that anesthesiologists are able to reverse decreases in intraoperative rScO2[16], algorithm-based care based on intraoperative NIRS during cardiac surgery represents a potential target for intervention to prevent postoperative functional decline. Before a clinical trial assessing this intervention can be conducted, a large observational study to establish the prognostically important threshold needs to be undertaken. Chapter 4 describes a pilot study to determine the feasibility of conducting a large observational study to assess this question.

1.5 The relationship between intraoperative benzodiazepines and delirium after cardiac surgery

Delirium – an acute and temporary state of confusion – is a serious and common problem after cardiac surgery, affecting approximately 15% of patients. After it resolves, patients who have had delirium are more likely to suffer from cognitive decline, functional decline, and to be discharged to an institution after cardiac surgery. Benzodiazepine administration before and after cardiac surgery has been associated with an increased risk of delirium, such that professional practice guidelines from the American Geriatric Society and the Society for Critical Care Medicine recommend that they not be given to patients undergoing cardiac surgery. However, benzodiazepine administration during cardiac surgery remains common,[17] and may be contributing to the incidence of delirium in the cardiac surgery patient population.

The perioperative management of patients undergoing cardiac surgery – who constitute a relatively homogenous population – is normally organized according to standard institutional procedures, like pre- and postoperative care pathways. Given this fact, the most appropriate way to examine whether intraoperative benzodiazepine administration is associated with an increased risk of postoperative delirium is to evaluate this intervention at the level of an institution, by

asking a question about institutional policy change. The study design best suited to answer this type of question – one that relates to the effectiveness of a broadly applied intervention in usual practice – is a large, pragmatic, randomized cluster crossover trial.

Chapter 5 describes the 'Restricted versus liberal benzodiazepine cardiac anaesthesia for reducing delirium (B-Free Pilot) study', a pilot, multi-centre, randomised, cluster crossover trial evaluating the feasibility of conducting this large, pragmatic, randomized cluster crossover trial.

1.6 Conclusion and future directions

Chapter 6 presents conclusions based on this thesis work, describes its limitations, and summarizes future research that will be undertaken based on this thesis work.

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CHAPTER 2

The association between complications and death within 30 days after non-cardiac surgery

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The association between complications and death within 30 days after non-cardiac surgery

The Vascular events In non-cardiac Surgery patIents cOhort evaluatioN

(VISION) Study Investigators

(we report the writing committee, their affiliations, and corresponding author at the end of the paper)

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ABSTRACT

Background: Among adults undergoing contemporary non-cardiac surgery, little is known about the frequency and timing of death and the associations between perioperative complications and mortality. Our objectives included informing the frequency and timing of death, and its association with perioperative complications.

Methods: We conducted a prospective cohort study of patients ≥45 years of age who underwent in-patient non-cardiac surgery at 28 centres in 14 countries. We monitored patients for complications until 30 days after surgery and determined the relationship between these complications and 30-day mortality using a Cox proportional hazards model.

Results: We included 40,004 patients. 715 patients (1.8%) died within 30 days of surgery. Five deaths (0.7%) occurred in the operating room, 500 deaths (69.9%) occurred after surgery during the index hospitalization, and 210 deaths (29.4%) occurred after hospital discharge. Eight complications were independently associated with 30-day mortality. The three complications with the largest attributable fractions (i.e., potential proportion of deaths attributable to these complications) were major bleeding (6238 patients [15.6%]; adjusted hazard ratio [aHR], 2.6; 95% CI, 2.2-3.1; attributable fraction [AF], 17.0%), myocardial injury after non-cardiac surgery (MINS) (5191 patients [13.0%]; aHR, 2.2; 95% CI, 1.9-2.6; AF, 15.9%), sepsis (1783 patients [4.5%]; aHR, 5.6; 95% CI, 4.6-6.8; AF, 12.0%).

Interpretation: 99.3% of the deaths in adults undergoing non-cardiac surgery occur after the procedure and 44.9% of deaths are associated with three complications: major bleeding, MINS, and sepsis. Given this, focusing on the prevention, early identification, and management of these three complications holds promise for reducing perioperative mortality.

INTRODUCTION

Worldwide, 100 million patients ≥45 years of age undergo in-patient non-cardiac surgery each year.[1,12] Although surgery has the potential to improve and prolong quality and duration of life, it is also associated with complications and mortality.

During the last several decades, advances in perioperative care have included less invasive surgery, improved anesthetic techniques, enhanced intraoperative monitoring, and more rapid mobilization after surgery.[12] At the same time, the age and the number of comorbidities of patients undergoing surgery have substantially increased.[13,14] Hence in the current context, the frequency and timing of mortality is uncertain, as is the relation of perioperative complications to mortality.

In a large prospective study (Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation [VISION] Study), we systematically followed patients who underwent non-cardiac surgery and documented perioperative complications and death. Our a priori objectives included informing the frequency and timing of death, and its association with perioperative complications.

METHODS

Study Design and Patients

We have previously reported details of the study design and methods.[3,15] Supplementary Documents list the >70 grants and funding sources, the participating centres, and investigators, Text Box. Appendix 1 reports the study oversight.

VISION was an international, prospective, cohort study. Patients were included if they were ≥45 years of age, underwent non-cardiac surgery, received general or regional anesthesia,

and remained in hospital for at least one night after surgery. We excluded patients previously enrolled in VISION.

Procedures

All centres were academic hospitals. Each academic hospital obtained approval from their research ethics board before commencing patient enrolment. Research personnel identified patients undergoing elective, urgent, or emergent surgery during the day and night, and on weekdays and weekends, through daily screening of patient lists in preoperative assessment clinics, daily surgical lists, surgical lists from the previous day, patient lists on surgical wards and in intensive care units, and patients in the preoperative holding areas. In some centres surgical volume exceeded the capacity of research staff to enroll all eligible patients on consecutive weeks. To facilitate recruitment of a representative sample in these centres, the project office created a recruitment schedule consisting of randomly selected weeks of recruitment or randomly selected surgical services, proportional to the prevalence of the types of surgery at each local centre. Appendix 2 reports the details regarding participant consent.

Research personnel interviewed and examined patients and reviewed charts to obtain baseline variables (e.g., comorbidities), type of surgery (Appendix 3), and type of anesthesia; ensured Troponin T measurement 6 to 12 hours postoperatively and on days 1, 2, and 3 after surgery; and evaluated patients throughout their hospital stay, reviewed hospital charts, and noted outcomes.

All-cause mortality was the primary outcome. The specific complications that we examined were (1) major bleeding, (2) myocardial injury after noncardiac surgery (MINS), (3) sepsis, (4) non-sepsis infection, (5) acute kidney injury (AKI) requiring dialysis, (6) stroke, (7)

congestive heart failure, (8) venous thromboembolism, and (9) new onset atrial fibrillation. Appendix 4 reports the study outcomes and their definitions. Study personnel phoned patients (or, if unavailable, next-of-kin) at 30 days after surgery, and documented patient outcomes. We focused on 30-day outcomes because studies demonstrate that non-cardiac surgery is associated with an increased risk of major complications until 30-days after surgery,[16] and most perioperative studies focus on 30-day outcomes.[17-19] Research personnel submitted case report forms and supporting documentation to the data management system (iDataFax, coordinating center, McMaster University, Hamilton, Canada). Data monitoring consisted of central data consistency checks and on-site monitoring. Outcome adjudicators evaluated the outcomes listed in Appendix 5; their decisions were used for the analyses.

Statistical Analyses

Of the patients who died within 30 days after surgery, we determined the proportion who died in the operating room, after surgery during the index hospitalization, and after hospital discharge. We determined the risk of death by geographical region and type of surgery.
To determine the relationships between perioperative complications and mortality, we undertook a Cox proportional hazards model in which the dependent variable was mortality up to 30 days after surgery. Independent variables included preoperative and surgical variables previously associated with 30-day perioperative mortality[15,20] (Appendix 6) and perioperative complications as time-dependent variables. Centre was included in the model as a random effect. Patients who did not complete the 30-day follow-up were censored on the last day their vital status was known. We established our sample size based on the number of events that we would require to include an adequate number of covariates in our risk prediction models. Our sample size of

40,000 patients provided 37 events per variable included in our multivariable analysis,[21] which ensured a stable model.

Based on the results of the Cox proportional hazards model, we determined the attributable fraction for each complication that was independently associated with 30-day mortality.[22] The attributable fraction is a measure that represents the proportional reduction in mortality within a population that would occur if the incidence of a complication was reduced to zero, provided that a causal relationship existed between that complication and 30-day mortality.

For the Cox proportional hazards models, we report the adjusted hazard ratios (aHR) and 95% confidence intervals (CIs). Discrimination was assessed through evaluation of the optimism-corrected C-index. All tests were 2-sided, and a $p<0.05$ was designated as statistically significant. Analyses were performed using SAS version 9/4 (SAS Institute Inc) and R version 3·5·1 (R Project).

RESULTS

Patients were recruited at 28 centres in 14 countries in North and South America, Asia, Europe, Africa, and Australia from August 2007 to November 2013 (Supplemental Table 1). Of the 40,037 patients enrolled in VISION, 40,004 were included in these mortality analyses; we were unable to determine survival status at hospital discharge or 30 days for 31 patients, and 2 patients were missing predictors used in our model (Supplemental Figure 1). We obtained 30-day follow-up data on 39,651 patients (99.1%).

Table 1 reports patients' preoperative characteristics, surgical categories, and type of anesthesia. Half of the patients were women, and the mean age was 63.9 years (SD ± 11.2 years). The most common comorbidities were hypertension (20,152 patients, 50.5%), active

cancer (9832 patients, 24.6%), and diabetes (8332 patients, 20.9%). The most common surgeries were low-risk surgery (14,383 patients, 36.0%), major general surgery (7950 patients, 19.9%), and major orthopedic surgery (6982 patients, 17.5%). Urgent or emergent surgery was performed on 4189 patients (10.5%). The most common types of anesthesia were general only (20,760 patients, 51.9%) and neuraxial only (9557 patients, 23.9%). The median length of hospital stay was 4 days (inter-quartile range [IQR], 2-8 days).

During the 30-day follow-up, 715 patients (1.8%; 95% CI, 1.7-1.9%) died. Mortality varied across regions (Supplemental Table 2), ranging from 96 deaths among 1489 patients (6.4%; 95% CI, 5.3-7.8%) in Africa to 253 deaths among 22,447 patients (1.1%; 95% CI, 1.0-1.3%) in North America, Europe, and Australia. Geographical regions were independent predictors of mortality when added to our model (Supplemental Table 3). Mortality also varied across surgical categories (Supplemental Table 4), ranging from a mortality of 240 deaths among 7950 patients (3.0%; 95% CI, 2.7-3.4) in major general surgery to 24 deaths among 4827 patients (0.5%; 95% CI, 0.3-0.7) in major urology and gynecology surgeries; the latter was lower than what were deemed a priori as low-risk surgeries, for which there were 177 deaths among 14,383 patients (1.2%; 95% CI, 1.1-1.4).

Among the 715 patients who died, 5 deaths (0.7%; 95% CI, 0.3-1.6%) occurred in the operating room, 500 deaths (69.9%; 95% CI, 66.5-73.2%) occurred after surgery during the index hospitalization, and 210 deaths (29.4%; 95% CI, 26.1-32.8%) occurred after hospital discharge. The median time to death was 11 days (IQR, 6-19), and the number of deaths was approximately evenly distributed over the 30-day follow-up (Supplemental Figure 2).

The timing and location of deaths varied across regions (Supplemental Table 5) from Asia in which 73 deaths (37.1%) occurred after hospital discharge, to Africa in which 18 deaths

(18.8%) occurred after hospital discharge. The timing and location of deaths also varied across surgical categories (Supplemental Table 6); of the deaths that occurred, death in the operating room was most common in major vascular surgery (2.7%), and death after hospital discharge was least common in major urology or gynecology surgery (12.5%).

The most common complications were major bleeding (6238 patients, 15.6%), MINS (5191 patients, 13.0%), infection without sepsis (2171 patients, 5.4%), and sepsis (1783 patients, 4.5%) (Table 2). There was variation across surgical categories for major bleeding and MINS. Among the major surgeries, major bleeding occurred most commonly in major orthopedic surgery (2164 patients, 31.0%) and least commonly in thoracic surgery (119 patients, 10.2%). Among the major surgeries, MINS occurred most commonly in major vascular surgery (633 patients, 24.0%) and least commonly in major urological or gynecological surgery (503 patients, 10.4%). The median time to major bleeding was on the day of surgery (IQR 0-2), MINS occurred a median of 1 day after surgery (IQR 0-1), and sepsis occurred a median of 6 days after surgery (IQR 3-11) (Supplemental Figure 2).

Eight perioperative complications were independently associated with 30-day mortality (Table 3), after adjusting for preoperative patient characteristics and surgical categories (Supplemental Table 7). This model had an optimism-corrected C-index of 0.89. The following complications were independently associated with 30-day mortality: major bleeding (361 deaths; aHR, 2.6; 95% CI, 2.2-3.1), MINS (314 deaths; aHR, 2.2; 95% CI, 1.9-2.6), sepsis (215 deaths; aHR, 5.6; 95% CI, 4.6-6.8), infection without sepsis (55 deaths; aHR, 2.3; 95% CI, 1.7-3.0), AKI with new dialysis (49 deaths; aHR, 4.2; 95% CI, 3.1-5.8), stroke (27 deaths; aHR, 3.7; 95% CI, 2.5-5.7), venous thromboembolism (15 deaths; aHR, 2.2; 95% CI, 1.3-3.7), and congestive heart failure (54 deaths; aHR, 2.4; 95% CI, 1.7-3.2). The highest attributable fractions of mortality

risk were associated with major bleeding (17.0%), MINS (15.9%), and sepsis (12.0%). Of the 715 patients who died, 147 (20.6%; 95% CI, 17.8-23.7%) were reported to not have suffered any of the 8 perioperative complications that were associated with 30-day mortality.

Figure 1 presents the Kaplan-Meier estimates of mortality, MINS, major bleeding, and sepsis. These complications varied across regions (Supplemental Table 8). The Venn diagram presents the outcome of patients who did and did not have major bleeding, MINS, and sepsis and patients who had combinations of these events, Figure 2.

Post-hoc analyses that included preoperative estimated glomerular filtration rate and hemoglobin demonstrated similar relationships between the perioperative complications and mortality (Supplemental Table 9).

INTERPRETATION

Principal Findings

In this international study of 40,004 patients who underwent in-patient non-cardiac surgery, 715 patients died (1.8%) within 30-days after surgery. Death in the operating room was rare (i.e., 5 deaths); in contrast, death after hospital discharge was common, accounting for 29.4% of the deaths. The 3 perioperative complications that were independently associated with mortality and had the highest attributable fractions were major bleeding, MINS, and sepsis. The median time to major bleeding was the day of surgery, MINS 1 day after surgery, and sepsis 6 days after surgery.

Our Study in Relation to other Studies

A recent large prospective cohort study that included patients undergoing non-cardiac surgery from 25 countries in Africa reported a lower risk of perioperative mortality (2.1%) compared to our study (i.e., 6.5% risk of mortality in Africa) that may be explained by the younger population and shorter duration of follow-up in the African study.[23] A prospective cohort study of patients undergoing non-cardiac surgery from 28 European countries reported a higher risk of perioperative mortality (4.0%)[24] compared to our study (1.2% risk of mortality in Europe). This study recruited patients over 7 days in each hospital, and it is possible that recruitment did not reflect a representative sample within the participating centres. Moreover, this study reported that 25% of the patients underwent urgent or emergent surgery, whereas in our study 10% of patients underwent urgent or emergent surgery, and in our study urgent or emergent surgery was independently associated with a higher risk of mortality, Supplemental Table 7.

A recent large study evaluated surgeries with death rates >2.0%[25] and, similar to our study, reported that 23.2% of the 30-day deaths occurred after hospital discharge. Similar to our results, a recent Swiss study of adults undergoing non-cardiac surgery reported, in a model predicting 30-day mortality, aHRs associated with MINS of 2.3 (95% CI, 1.2-4.4) and with sepsis of 4.5 (95% CI, 2.2-9.2).[26] A large non-cardiac surgery trial reported that significant perioperative bleeding was independently associated with 30-day mortality (aHR, 1.7; 95% CI, 1.1-2.4);[17] a result similar to our finding.

Strengths and Limitations

Our study's strengths include the large sample of patients from 28 centres in 14 countries. Study personnel systematically followed all patients, and 99.1% of the patients completed the 30-day follow-up. Our mortality model demonstrated excellent discrimination.

Limitations of our study include the following. We did not adjudicate some of our outcomes (i.e., major bleeding, sepsis, infection without sepsis, congestive heart failure, AKI with dialysis). It is possible that this led to an overestimation of some of these events; however, based on these outcome definitions and our data checks, it is likely that these outcomes were accurately reported. The African data were based on a single centre; whereas all other continental data included ≥4 centres and at least 4 times the number of participants. Clinicians should view our finding of higher risk-adjusted mortality in Africa as hypothesis generating.

Implications of These Findings

In our study of patients ≥45 years of age who underwent non-cardiac surgery, 1.8% of patients died within 30 days of surgery. Assuming that worldwide 100 million adults aged 45 years or older undergo non-cardiac surgery annually,[12] then about 1.8 million adults die within 30 days of non-cardiac surgery each year. This indicates that perioperative mortality is a substantial global health problem.

Death in the operating room was uncommon (i.e., 5 patients) and accounted for 0.7% of the deaths. In contrast, postoperative mortality was substantial (i.e., 710 deaths), accounting for 99.3% of the deaths. Moreover, 29.4% of the deaths occurred after patients were discharged from the hospital. These data suggest the need for improved monitoring and management of patients after surgery and into the home setting.

Anesthetic-related mortality has decreased 100-fold over the last 100 years.[27] Improvements in intraoperative mortality have largely been attributed to increased monitoring during surgery, both through the use of electronic monitors (e.g., frequent blood pressure, continuous pulse oximetry and electrocardiography) and the development of a culture of vigilance in anesthesia, as demonstrated by the development of protocols and standards for intraoperative monitoring and care.[28,29]

In the postoperative setting, most patients receive care from their surgeon who is often busy performing surgery, and after hospital discharge they receive care weeks later in a physician's office. After surgery, when patients are usually receiving analgesic medications that can mask symptoms (e.g., chest pain) of some complications,[15] patients typically have their vital signs checked every 4 to 8 hours on a surgical floor.[30] After hospital discharge, most patients only receive monitoring at their 3 to 4-week follow-up.

Studies that obtained continuous pulse oximetry and blood pressure on surgical floors have demonstrated that many patients have prolonged hypoxia and hypotension that is not identified by healthcare providers.[31,32] Given that many studies have demonstrated that hypoxia and hypotension are precursors to postoperative complications,[33,34] remote automated monitoring technology with an available healthcare provider who can respond to early signs of an impending complication has the potential to improve outcomes after surgery, similar to how anesthesiologists and enhanced monitoring improved intraoperative outcomes. These interventions require evaluation in prospective studies.

We identified 8 perioperative complications that were independently associated with 30-day mortality. Three of these complications (i.e., major bleeding, MINS, and sepsis) potentially explained 44.9% of the deaths. These complications represent promising targets for research on

prevention, early identification, and management, to decrease perioperative mortality. The median time to these events provides insights regarding when monitoring for each complication is likely to have the greatest impact.

Conclusions

Given that 99.3% of the deaths in adults undergoing non-cardiac surgery occur after the procedure, efforts to improve post-surgical care – in-hospital and in the home setting – has the potential to reduce mortality. Focusing on the prevention, early identification, and management of major bleeding, MINS, and sepsis holds promise for decreasing perioperative deaths.

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PJ Devereaux contributed to the concept and design of the work, data acquisition and interpretation, drafting of the paper, revising it critically for important content, gave final

approval of the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table 1. Baseline characteristics

Baseline characteristic	All patients N=40,004 n (%)
Age in years	
45-64	22,141 (55.3)
65-74	10,160 (25.4)
≥75	7703 (19.3)
Women	19,877 (49.7)
History of	
Hypertension	20152/39,917 (50.5)
Diabetes	8332/39,905 (20.9)
Coronary artery disease	5159/39,876 (12.9)
Peripheral arterial disease	3203 (8.0)
Chronic obstructive pulmonary disease	3165 (7.9)
Coronary revascularization	2256/39,828 (5.7)
Stroke	1682 (4.2)
Congestive heart failure	1424/39,870 (3.6)
High risk coronary artery disease	384 (1.0)
Cardiac arrest	235/39,868 (0.6)
Coronary revascularization within 6 months	138/39,827 (0.3)
Active cancer	9832 (24.6)
In atrial fibrillation just before surgery	1123/39,876 (2.8)
Preoperative estimated glomerular filtration rate (mL/min/1.73 m_2)	N=37,290
<30	1515 (4.1)
30-44	1774 (4.8)
45-59	3707 (9.9)
>60	30,294 (81.2)
Surgical category*	
Major general	7950 (19.9)
Major orthopedic	6982 (17.5)
Major urology and gynecology	4827 (12.1)
Major vascular	2642 (6.6)
Major neurosurgery	2341 (5.9)
Major thoracic	1165 (2.9)
Low-risk surgery only	14,383 (36.0)

Urgent or emergent surgery	4189 (10.5)
Type of anesthesia	N=39,969
General only	20,760 (51.9)
Neuraxial (spinal or epidural) only	9557 (23.9)
General with nitrous oxide only	3805 (9.5)
General and thoracic epidural only	1658 (4.1)
General and nerve block only	1252 (3.1)
Other	2937 (7.3)

* 280 patients had 2 major surgery categories, 3 patients had 3 major surgery categories

Table 2. 30-day perioperative complications overall and by type of surgery

Outcome	All surgeries N=40,004 n % (95% CI)	Type of Major Surgery						Low-risk surgery only N=14,383 n % (95% CI)
		General N=7950 n % (95% CI)	Vascular N=2642 n % (95% CI)	Neurosurgery N=2341 n % (95% CI)	Orthopedic N=6982 n % (95% CI)	Thoracic N=1165 n % (95% CI)	Uro/Gyn N=4827 n % (95% CI)	
Major bleeding	6238 15.6 (15.2-16.0)	1454 18.3 (17.5-19.2)	666 25.2 (23.6-26.9)	419 17.9 (16.4-19.5)	2164 31.0 (29.9-32.1)	119 10.2 (8.6-12.1)	658 13.6 (12.7-14.6)	876 6.1 (5.7-6.5)
Myocardial injury after non-cardiac surgery	5191 13.0 (12.7-13.3)	980 12.3 (11.6-13.1)	633 24.0 (22.4-25.6)	301 12.9 (11.6-14.3)	1257 18.0 (17.1-18.9)	231 19.8 (17.6-22.2)	503 10.4 (9.6-11.3)	1335 9.3 (8.8-9.8)
Sepsis	1783 4.5 (4.3-4.7)	783 9.8 (9.2-10.5)	140 5.3 (4.5-6.2)	132 5.6 (4.8-6.6)	258 3.7 (3.3-4.2)	54 4.6 (3.6-6.0)	162 3.4 (2.9-3.9)	293 2.0 (1.8-2.3)
Infection without sepsis	2171 5.4 (5.2-5.7)	632 7.9 (7.4-8.6)	152 5.8 (4.9-6.7)	102 4.4 (3.6-5.3)	508 7.3 (6.7-7.9)	44 3.8 (2.8-5.0)	261 5.4 (4.8-6.0)	493 3.4 (3.1-3.7)
Acute kidney injury with dialysis	118 0.3 (0.2-0.4)	49 0.6 (0.5-0.8)	25 0.9 (0.6-1.4)	4 0.2 (0.1-0.4)	14 0.2 (0.1-0.3)	3 0.3 (0.1-0.8)	7 0.1 (0.1-0.3)	17 0.1 (0.1-0.2)
Stroke	132 0.3 (0.3-0.4)	20 0.3 (0.2-0.4)	25 0.9 (0.6-1.4)	34 1.5 (1.0-2.0)	24 0.3 (0.2-0.5)	5 0.4 (0.2-1.0)	7 0.1 (0.1-0.3)	18 0.1 (0.1-0.2)
Venous thromboembolism	299 0.7 (0.7-0.8)	71 0.9 (0.7-1.1)	15 0.6 (0.3-0.9)	22 0.9 (0.6-1.4)	114 1.6 (1.4-2.0)	5 0.4 (0.2-1.0)	38 0.8 (0.6-1.1)	39 0.3 (0.2-0.4)
Congestive heart failure	372 0.9 (0.8-1.0)	113 1.4 (1.2-1.7)	46 1.7 (1.3-2.3)	5 0.2 (0.1-0.5)	120 1.7 (1.4-2.1)	12 1.0 (0.6-1.8)	30 0.6 (0.4-0.9)	53 0.4 (0.3-0.5)
New clinically important atrial fibrillation	370 0.9 (0.8-1.0)	145 1.8 (1.6-2.1)	47 1.8 (1.3-2.4)	9 0.4 (0.2-0.7)	89 1.3 (1.0-1.6)	35 3.0 (2.2-4.1)	29 0.6 (0.4-0.9)	28 0.2 (0.1-0.3)

Mortality	715 1.8 (1.7-1.9)	240 3.0 (2.7-3.4)	73 2.8 (2.2-3.5)	62 2.6 (2.1-3.4)	124 1.8 (1.5-2.1)	20 1.7 (1.1-2.6)	24 0.5(0.3-0.7)	177 1.2 (1.1-1.4)

Abbreviation: Uro/Gyn, urology/gynecology

Table 3: Relationship between perioperative complications and 30-day mortality*

	No. died/ total No.	% (95% CI)	Adjusted HR (95% CI)	Attributable fraction†
Major bleeding	361/6238	5.8 (5.2-6.4)	2.6 (2.2-3.1)	17.0%
No major bleeding	354/33,766	1.0 (0.9-1.2)		
MINS	314/5191	6.0 (5.4-6.7)	2.2 (1.9-2.6)	15.9%
No MINS	401/34,813	1.2 (1.0-1.3)		
Sepsis	215/1783	12.1 (10.6-13.7)	5.6 (4.6-6.8)	12.0%
Infection without sepsis	55/2171	2.5 (2.0-3.3)	2.3 (1.7-3.0)	2.8%
No sepsis or infection	445/36,050	1.2 (1.1-1.4)	Reference	
Acute kidney injury with dialysis	49/118	41.5 (33.0-50.5)	4.2 (3.1-5.8)	1.1%
No acute kidney injury with dialysis	666/39,886	1.7 (1.5-1.8)		
Stroke	27/132	20.5 (14.5-28.1)	3.7 (2.5-5.7)	0.8%
No stroke	688/39,872	1.7 (1.6-1.9)		
Venous thromboembolism	15/299	5.0 (3.1-8.1)	2.2 (1.3-3.7)	0.3%
No venous thromboembolism	700/39,705	1.8 (1.6-1.9)		
Congestive heart failure	54/372	14.5 (11.3-18.5)	2.4 (1.7-3.2)	0.7%
No congestive heart failure	661/39,632	1.7 (1.5-1.8)		
New clinically important AF	44/370	11.9 (9.0-15.6)	1.4 (1.0-2.0)	Not applicable
No new clinically important AF	671/39,634	1.7 (1.6-1.8)		

Abbreviations: AF, atrial fibrillation; HR, hazard ratio; MINS, myocardial injury after non-cardiac surgery; No., number
*Cox proportional hazard model in which the dependent variable was 30-day mortality and the independent variables included preoperative and surgical variables previously associated with 30-day perioperative mortality and perioperative complications as time-dependent variables.

†The attributable fraction is a measure that represents the proportional reduction in mortality within a population that would occur if the incidence of a complication was reduced to zero, provided that a causal relationship existed between that complication and 30-day mortality. The frequency of a complication and the association between the complication and mortality are used to calculation the attributable fraction.

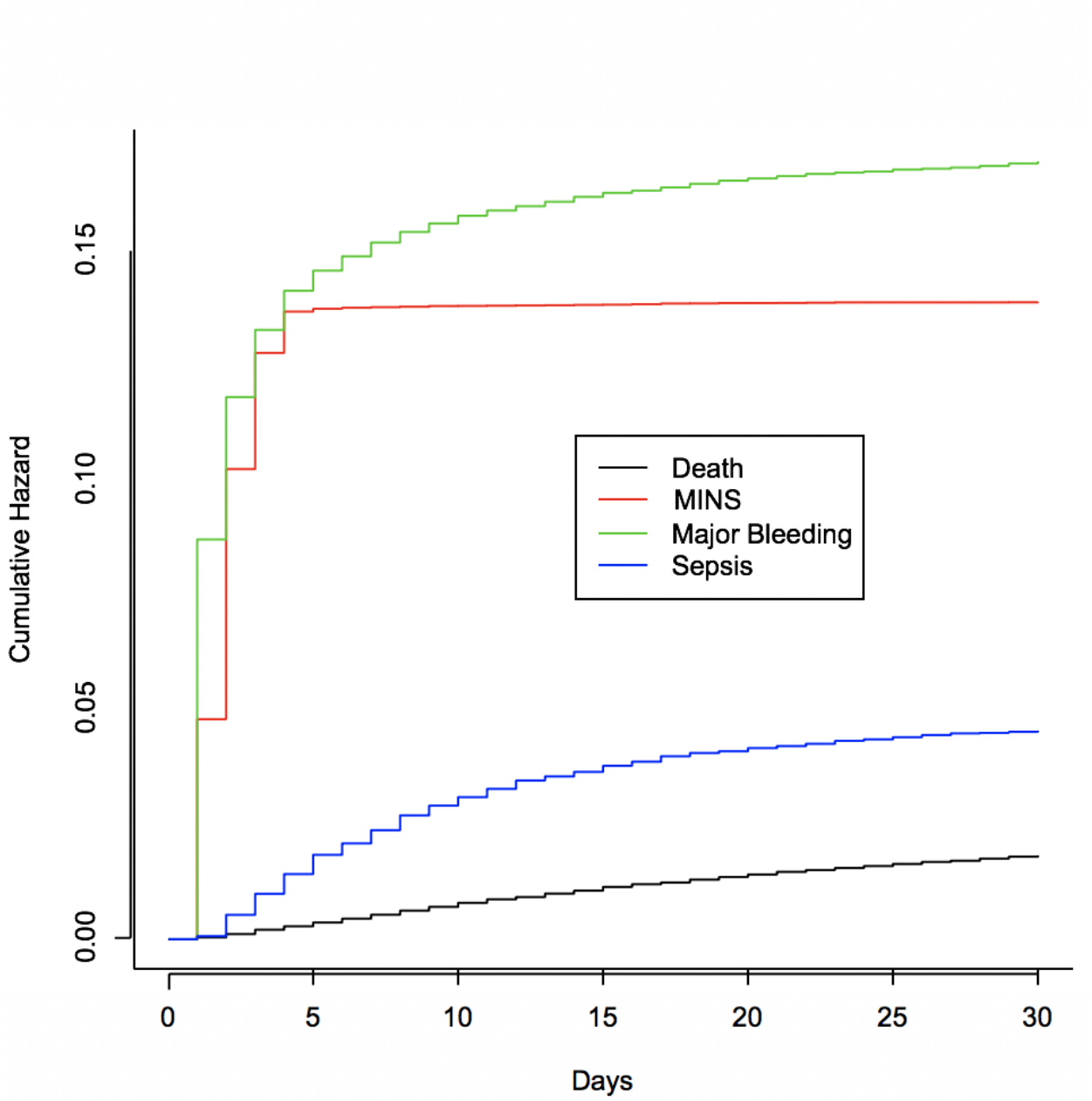

Figure 1. Kaplan-Meier curves for death, MINS, major bleeding, and sepsis. MINS: Myocardial injury after noncardiac surgery.

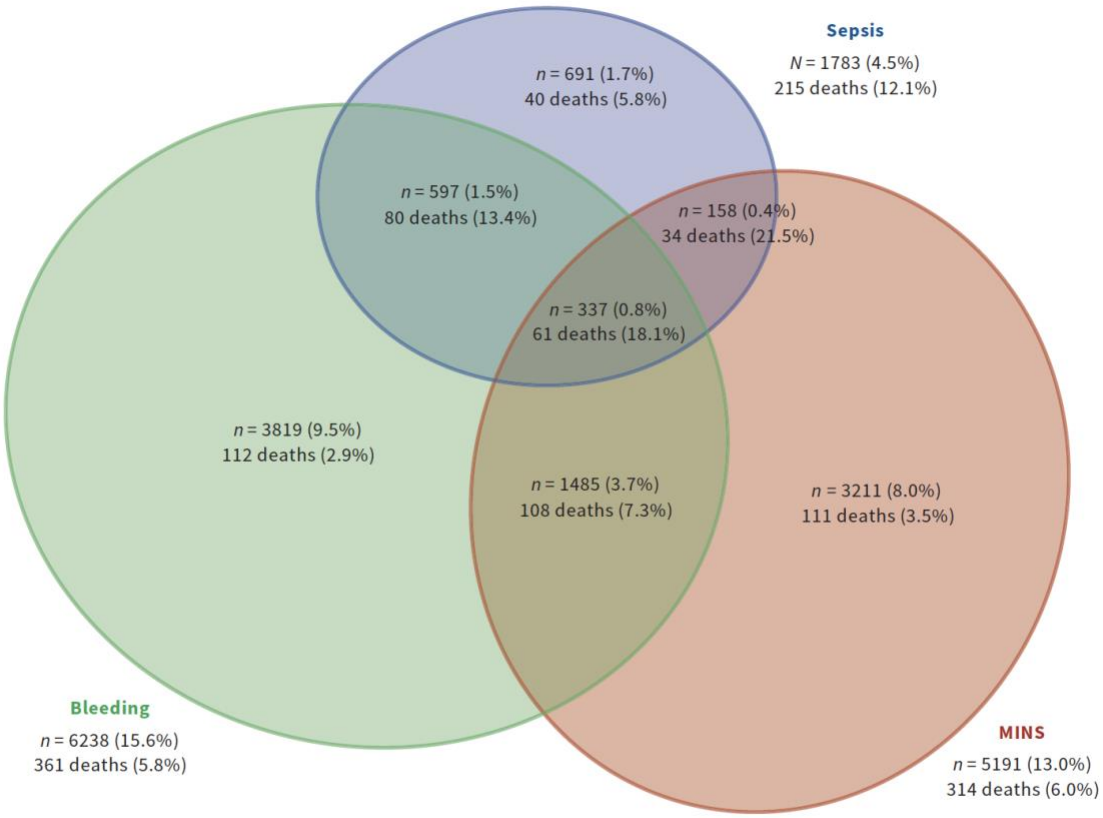

Figure 2: Outcomes among patients who had major bleeding, MINS and sepsis, and patients who had combinations of these events. Notes: MINS = myocardial injury after noncardiac surgery; 29 706 (74.3%) of patients had no bleeding, sepsis or MINS, of whom 169 died (0.6%).

SUPPLEMENTARY DOCUMENTS

1. Supplemental Centres, Investigators, and Funding Sources
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    - VISION funding sources
2. Supplemental Appendices
    - Appendix 1. Study oversight
    - Appendix 2. Participant consent
    - Appendix 3. Surgical categories
    - Appendix 4. Study outcomes and their definitions
    - Appendix 5. Outcome adjudication
    - Appendix 6. Preoperative and surgical variables used in the multivariable analyses to determine the relationships between perioperative complications and 30-day mortality
3. Supplemental Tables
    - Supplemental Table 1. Recruitment by country and centre
    - Supplemental Table 2. 30-day mortality by region
    - Supplemental Table 3. Relationship between region and mortality
    - Supplemental Table 4. 30-day mortality by surgical category
    - Supplemental Table 5. Timing and location of death by region
    - Supplemental Table 6. Timing and location of death by surgical category
    - Supplemental Table 7. Relationship between preoperative patient characteristics and surgical category with 30-day mortality
    - Supplemental Table 8. 30-day complications by region
    - Supplemental Table 9. Main results and post-hoc analyses evaluating relationship between perioperative complications and 30-day mortality
4. Supplemental Figures
    - Supplemental Figure 1. Patient flow chart
    - Supplemental Figure 2. Cumulative proportion of events during 30-day follow-up

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Appendix 1. Study Oversight

This study was coordinated by the Clinical Advances Through Research and Information Translation (CLARITY) project office in the Department of Health Research Methods, Evidence, and Impact (HEI) at McMaster University and the Population Health Research Institute (PHRI), at the Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada.

The Steering Committee designed the study. No VISION funding source had a role in the data collection, analyses, or manuscript write-up. The writing committee prespecified the statistical analysis plan. The last and first author wrote the initial draft of the paper, and the Writing Committee made critical revisions and decided to submit the paper for publication. The last author vouches for the completeness and accuracy of the data.

Appendix 2. Participant consent

Patients provided written informed consent before surgery, and for those from whom we could not obtain preoperative consent (e.g., emergency surgery) research staff obtained consent within 24 hours after surgery. A deferred consent process was used in 9 centres for patients unable to provide consent (e.g., patients who were sedated and mechanically ventilated) and for whom no substitute decision maker was available. This allowed research personnel to collect patient data while awaiting consent from the patient or their substitute decision maker.

Appendix 3. Surgical categories

1. Major orthopedic surgeries – A patient undergoing one or more of the following orthopedic surgeries: major hip or pelvis surgery, internal fixation of femur, knee arthroplasty, above knee amputations, or lower leg amputation (amputation below knee but above foot).
2. Major general surgeries – A patient undergoing one or more of the following general surgeries: complex visceral resection, partial or total colectomy or stomach surgery, other intra-abdominal surgery, or major head and neck resection for non-thyroid tumor.
3. Major urology and gynecology surgeries – A patient undergoing one or more of the following major urology or gynaecology surgeries: nephrectomy, ureterectomy, bladder resection, retroperitoneal tumor resection, exenteration, cytoreduction surgery, hysterectomy, radical prostatectomy, or transurethral prostatectomy.
4. Major neurosurgeries – A patient undergoing one or more of the following neurosurgeries: craniotomy or major spine surgery (i.e., surgery involving multiple levels of the spine).
5. Major vascular surgeries – A patient undergoing one or more of the following vascular surgeries: thoracic aorta reconstructive vascular surgery, aorto-iliac reconstructive vascular surgery, peripheral vascular reconstruction without aortic cross-clamping, extracranial cerebrovascular surgery, or endovascular abdominal aortic aneurysm repair.
6. Major thoracic surgeries – A patient undergoing one or more of the following thoracic surgeries: pneumonectomy, lobectomy, wedge resection of lung, resection of mediastinal tumor, or major chest wall resection.
7. Low-risk surgeries – A patient undergoing one or more of the following surgeries: parathyroid, thyroid, breast, hernia, local anorectal procedure, oopherectomy, salpingectomy, endometrial ablation, peripheral nerve surgery, ophthalmology, ears/nose/throat surgery, vertebral disc surgery, hand surgery, cosmetic surgery, arterio-venous access surgery for dialysis, or any other surgery not mentioned above.

Appendix 4. Study outcomes and their definitions

1. Mortality – All cause mortality.
2. Major bleeding – The diagnosis of major bleeding required bleeding that resulted in a drop in hemoglobin to <70 g/L, transfusion of ≥1 unit of packed red blood cells, or death.
3. Myocardial injury after non-cardiac surgery (MINS) – When we started VISION, patients had a fourth generation, non-high sensitivity Troponin T measured perioperatively. In the 15,313 patients who had a fourth generation Troponin T measurement, the diagnostic criteria for MINS were an elevated postoperative Troponin T (i.e., ≥30 ng/L) judged as resulting from myocardial ischemia (i.e., no evidence of a non-ischemic etiology causing the troponin elevation), without the requirement of an ischemic feature (i.e., ischemic symptom, ischemic electrocardiography finding, new or presumed new wall motion abnormality on echocardiography, or new or presumed new fixed defect on radionuclide imaging). After we had recruited enough patients with data to inform the relationship between the fourth generation Troponin T and mortality, we switched to measuring the fifth generation, high sensitivity Troponin T (hsTnT) assay. For the 22,865 patients who had a hsTnT measurement, the diagnostic criteria for MINS were an elevated postoperative hsTnT (20 to <65 ng/L with an absolute change ≥5 ng/L or an hsTnT ≥65 ng/L) judged as resulting from myocardial ischemia, without the requirement of an ischemic feature.
4. Sepsis – Sepsis was a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Systemic inflammatory response required ≥2 of the following factors: core temperature >38º C or <36º C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute; white blood cell count >12 x 10^9/L or <4 x 10^9/L.
5. Infection without sepsis - 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. Infection without sepsis had to fulfill the definition of infection without fulfilling the definition of sepsis.
6. Stroke – Stroke was defined as a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting >24 hours.
7. Venous thromboembolism was a composite of deep venous thrombosis and pulmonary embolism

Deep venous thrombosis of the leg or arm – The diagnosis of deep venous thrombosis required any one of the following:
i. a persistent intraluminal filling defect on contrast venography;
ii. non-compressibility of one or more venous segments on B mode compression ultrasonography; or
iii. a clearly defined intraluminal filling defect on contrast enhanced CT.

Pulmonary embolus – The diagnosis of pulmonary embolus required any one of the following:
i. a high probability ventilation/perfusion lung scan;
ii. an intraluminal filling defect of a segmental or larger artery on a helical computed tomography (CT) scan;
iii. an intraluminal filling defect on pulmonary angiography; or
iv. a positive diagnostic test for deep venous thrombosis (e.g., positive compression ultrasound) and one of the following: non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan, or a non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan.

8. Congestive heart failure – The definition of congestive heart failure required at least one of the following clinical signs (i.e., an elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and at least one of the following radiographic findings (i.e., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).
9. New clinically important atrial fibrillation – new clinically important atrial fibrillation was defined as new atrial fibrillation that resulted in angina, congestive heart failure, symptomatic hypotension, or that required treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.
10. Acute kidney injury with new dialysis – our definition was an acute kidney injury that resulted in new dialysis defined as the use of a hemodialysis machine or peritoneal dialysis apparatus.

Appendix 5. Outcome adjudication

Expert physician adjudicators evaluated all patients with an elevated Troponin T measurement to determine if myocardial injury after non-cardiac surgery had occurred and all reported cases of stroke, venous thromboembolism, and new clinically important atrial fibrillation.

Appendix 6. Preoperative and surgical variables used in the multivariable analyses to determine the relationships between perioperative complications and 30-day mortality

1. Age – Patient age in years was recorded and categorized as 45-64 years of age, 65-74 years of age, and ≥75 years of age.
2. Recent high-risk coronary artery disease – A physician diagnosis ≤6 months before non-cardiac surgery of: a myocardial infarction, acute coronary syndrome, Canadian Cardiovascular Society Class (CCSC) III angina, or CCSC IV angina
   CCSC III angina - angina occurring with level walking of 1-2 blocks or climbing ≤1 flight of stairs at a normal pace;
   CCSC IV angina - inability to carry on any physical activity without the development of angina.
3. History of stroke – A physician diagnosis of a current or prior stroke, or CT or magnetic resonance (MR) evidence of a stroke.
4. History of peripheral arterial disease – A physician diagnosis of a current or prior history of: intermittent claudication, vascular surgery for atherosclerotic disease, an ankle/arm systolic blood pressure ratio ≤0.90 in either leg at rest, or an angiographic or doppler study demonstrating ≥70% stenosis in a non-cardiac artery.
5. Chronic obstructive pulmonary disease (COPD) – A physician current or prior diagnosis of chronic bronchitis, emphysema, or COPD, or a patient provided a history of daily production of sputum for at least 3 months in 2 consecutive years.
6. Active cancer – A patient was designated as having active cancer if they fulfilled any of the following criteria: i. undergoing surgery for cancer; ii. known metastatic disease; or iii. patient had received active treatment for their cancer (e.g., chemotherapy, radiation, or surgery) within the 6 months before their surgery, but this did not apply to patients with non-melanoma skin cancers or surgery for a biopsy.
7. Urgent/Emergency surgery – Emergency surgery was surgery that occurred <24 hours after a patient developed an acute surgical condition, and urgent surgery was surgery that occurred 24-72 hours after a patient developed an acute surgical condition.
8. Major general surgery – A patient undergoing one or more of the following general surgeries: complex visceral resection, partial or total colectomy or stomach surgery, other intra-abdominal surgery, or major head and neck resection for non-thyroid tumor.
9. Major neurosurgery – A patient undergoing one or more of the following neurosurgeries: craniotomy or major spine surgery (i.e., surgery involving multiple levels of the spine).

Supplemental Table 1. Recruitment by country and centre

Continent, country, city, centre	Participants (n=40,004)
North America	**(11,693)**
Canada	
Hamilton	
Juravinski Hospital and Cancer Centre	3884
Saint Joseph's Healthcare	1003
Hamilton General Hospital	751
McMaster University Medical Centre	642
Winnipeg	
Health Sciences Centre Winnipeg	1697
Edmonton	
Walter C. MacKenzie Health Sciences Centre	1580
London	
Victoria Hospital	747
United States	
Cleveland	
Cleveland Clinic	1248
St. Louis	
Washington University School of Medicine	141
Asia	**(10,005)**
China	
Hong Kong	
Prince of Wales Hospital	4413
India	
Bangalore	
St. John's Medical College Hospital	1996
Ludhiana	
Christian Medical College	1549
Malaysia	
Kuala Lumpur	
University Malaya Medical Centre	2047
Europe	**(9671)**
United Kingdom	
London	
Barts And The London	2007
University College Hospital	880
Leeds	
Leeds Teaching Hospitals	733
Liverpool	
Royal Liverpool University Hospital	722
Spain	

Continent, country, city, centre	Participants (n=40,004)
Barcelona	
Hospital de Sant Pau	1985
Madrid	
Hospital Gregorio Maranon	1764
Poland	
Krakow	
Jagiellonian University Medical College	982
France	
Paris	
Pitie-Salpetriere Hospital	598
South America	**(6063)**
Brazil	
São Paulo	
Hospital do Coracao	1503
Porto Alegre	
Hospital de Clinicas de Porto Alegre	1001
Colombia	
Bucaramanga	
Hospital Universitario de Santander	1392
Bogota	
Foundation CardioInfanil	628
Peru	
Lima	
Hospital Nacional Cayetano Heredia	1539
Africa	**(1489)**
South Africa	
Durban	
Inkosi Albert Luthuli Hospital	1489
Australia	**(1083)**
Australia	
Sydney	
Westmead Hospital	1083

Supplemental Table 2. 30-day mortality by region

Regions	No. of participants	No. of deaths	Percentage dead (95% CI)
North America, Europe, Australia	22,447	253	1.1% (1.0-1.3)
Asia	10,005	197	2.0% (1.7-2.3)
South America	6063	169	2.8% (2.4-3.2)
Africa	1489	96	6.4% (5.3-7.8)
Total	40,004	715	1.8% (1.7-1.9)

Abbreviations: No., number

Supplemental Table 3. Relationship between region and mortality*

Region	Adjusted HR (95% CI)	p value
North America, Europe, Australia	Reference	
Asia	2.2 (1.8-2.6)	<0.001
South America	3.4 (2.7-4.1)	<0.001
Africa	6.9 (5.3-8.9)	<0.001

* model included preoperative variables and perioperative complications as independent variables

Supplemental Table 4. 30-day mortality by surgical category

Surgery	No. of Patients	No. of deaths	Percentage of deaths (95% CI)
Major General Surgery	**7950**	**240**	**3.0 (2.7-3.4)**
Complex visceral resection	1155	35	3.0 (2.2-4.2)
Partial or total colectomy, or stomach surgery	2222	96	4.3 (3.6-5.2)
Other intra-abdominal surgery	4197	114	2.7 (2.3-3.3)
Major head and neck resection for non-thyroid tumour	648	12	1.9 (1.1-3.2)
Major Vascular Surgery	**2642**	**73**	**2.8 (2.2-3.5)**
Thoracic aorta reconstruction	79	5	6.3 (2.7-14.0)
Aorto-iliac reconstruction	646	32	5.0 (3.5-6.9)
Peripheral vascular reconstruction without aortic cross-clamping	1206	28	2.3 (1.6-3.3)
Extracranial cerebrovascular surgery	434	7	1.6 (0.8-3.3)
Endovascular abdominal aortic aneurysm repair	302	3	1.0 (0.3-2.9)
Major Neurosurgery	**2341**	**62**	**2.6 (2.1-3.4)**
Craniotomy	936	54	5.8 (4.4-7.5)
Major spine surgery	1405	8	0.6 (0.3-1.1)
Major Orthopedic Surgery	**6982**	**124**	**1.8 (1.5-2.1)**
Major hip or pelvic surgery	2898	49	1.7 (1.3-2.2)
Internal fixation of femur	750	29	3.9 (2.7-5.5)
Knee arthroplasty	2876	7	0.2 (0.1-0.5)
Above knee amputation	221	30	13.6 (9.7-18.7)
Lower leg amputation	252	9	3.6 (1.9-6.6)
Major Thoracic Surgery	**1165**	**20**	**1.7 (1.1-2.6)**
Pneumonectomy	47	1	2.1 (0.4-11.1)
Lobectomy	469	6	1.3 (0.6-2.8)
Other thoracic surgery	677	13	1.9 (1.1-3.3)

Major Urology and Gynecology	**4827**	**24**	**0.5 (0.3-0.7)**
Visceral resection	1085	10	0.9 (0.5-1.7)
Cytoreductive surgery	293	2	0.7 (0.2-2.5)
Hysterectomy	1388	4	0.3 (0.1-0.7)
Radical hysterectomy	471	4	0.8 (0.3-2.2)
Radical prostatectomy	740	3	0.4 0.1-1.2)
Transurethral prostatectomy	1014	4	0.4 (0.2-1.0)
Low-risk surgery	**15,308**	**192**	**1.3 (1.1-1.4)**
Low-risk surgery with no other surgery	**14,383**	**177**	**1.2 (1.1-1.4)**

Abbreviations: No., number

Supplemental Table 5. Timing and location of death by region

Regions	No. of deaths in operating room % (95% CI)	No. of deaths after surgery during index hospitalization % (95% CI)	No. of deaths after hospital discharge % (95% CI)
North America, Europe, Australia	2 0.8% (0.2-2.8)	177 70.0% (64.0-75.3)	74 29.2% (24.0-35.1)
Asia	2 1.0% (0.3-3.6)	122 61.9% (55.0-68.4)	73 37.1% (30.6-44.0)
South America	0 0.0% (0.0-2.2)	124 73.4% (66.2-79.5)	45 26.6% (20.5-33.8)
Africa	1 1.0% (0.2-5.7)	77 80.2% (71.1-86.9)	18 18.8% (12.2-27.7)
Total	5 0.7% (0.3-1.6)	500 69.9% (66.5-73.2)	210 29.4% (26.1-32.8)

Abbreviations: No., number

Supplemental Table 6. Timing and location of death by surgical category

Surgical category	No. of deaths in operating room % (95% CI)	No. of deaths after surgery during index hospitalization % (95% CI)	No. of deaths after hospital discharge % (95% CI)
Major general	0 0.0% (0.0-1.6)	186 77.5% (71.8-82.3)	54 22.5% (17.7-28.2)
Major vascular	2 2.7% (0.8-9.5)	52 71.2% (60.0-80.3)	19 26.0% (17.3-37.1)
Major neurosurgery	1 1.6% (0.3-8.6)	47 75.8% (63.8-84.8)	14 22.6% (14.0-34.4)
Major orthopedic	1 0.8% (0.1-4.4)	78 62.9% (54.1-70.9)	45 36.3% (28.4-45.0)
Major thoracic	0 0.0% (0.0-16.1)	13 65.0% (43.3-81.9)	7 35.0% (18.1-56.7)
Low risk surgery only	1 0.6% (0.1-3.1)	108 61.0% (53.7-67.9)	68 38.4% (31.6-45.8)
Major urology or gynecology	0 0.0% (0.0-13.8)	21 87.5% (69.0-95.7)	3 12.5% (4.3-31.0)

Abbreviations: No., number

Supplemental Table 7. Relationship between preoperative patient characteristics and surgical category with 30-day mortality*

	No. died/ total No.	% (95% CI)	Adjusted HR (95% CI)
Age in years			
45-64	265/22,141	1.2 (1.1-1.3)	Reference
65-74	179/10,160	1.8 (1.5-2.0)	1.3 (1.1-1.6)
≥75	271/7703	3.5 (3.1-4.0)	2.3 (1.9-2.7)
Recent high risk CAD	31/384	8.1 (5.7-11.2)	2.3 (1.6-3.3)
No recent high risk CAD	684/39,620	1.7 (1.6-1.9)	
History of stroke	82/1682	4.9 (3.9-6.0)	1.6 (1.3-2.1)
No history of stroke	633/38,322	1.7 (1.5-1.8)	
History of PAD	126/3203	3.9 (3.3-4.7)	1.3 (1.0-1.6)
No history of PAD	589/36,801	1.6 (1.5-1.7)	
History of COPD	130/3165	4.1 (3.5-4.9)	1.8 (1.5-2.2)
No history of COPD	585/36,839	1.6 (1.5-1.7)	
Urgent/Emergent surgery	230/4189	5.5 (4.8-6.2)	2.4 (2.0-2.9)
Elective surgery	485/35,815	1.4 (1.2-1.5)	
Active cancer	254/9832	2.6 (2.3-2.9)	1.7 (1.4-2.0)
No active cancer	461/30,172	1.5 (1.4-1.7)	
Major general surgery	240/7950	3.0 (2.7-3.4)	1.6 (1.3-1.9)
Other surgeries	475/32,054	1.5 (1.4-1.6)	
Major neurosurgery	62/2341	2.6 (2.1-3.4)	1.8 (1.4-2.4)
Other surgeries	653/37,663	1.7 (1.6-1.9)	

Abbreviations: CAD, Coronary Artery Disease; CI, Confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; HR, Hazard Ratio; No., Number; PAD, Peripheral Arterial Disease

*Cox proportional hazard model in which the dependent variable was 30-day mortality and the independent variables included preoperative and surgical variables previously associated with 30-day perioperative mortality and perioperative complications as time-dependent variables.

Supplemental Table 8. 30-day complications by region

Regions	No. of participants	No. of major bleeds % (95% CI)	No. of MINS % (95% CI)	No. of sepsis % (95% CI)
North America, Europe, Australia	22,447	3908 17.4% (16.9-17.9)	2886 12.9% (12.4-13.3)	1126 5.0% (4.7-5.3)
Asia	10,005	1579 15.8% (15.1-16.5)	1283 12.8% (12.2-13.5)	336 3.4% (3.0-3.7)
South America	6063	427 7.0% (6.4-7.7)	684 11.3% (10.5-12.1)	232 3.8% (3.4-4.3)
Africa	1489	324 21.8% (19.7-23.9)	338 22.7% (20.6-24.9)	89 6.0% (4.9-7.3)
Total	40,004	6238 15.6% (15.2-16.0)	5191 13.0% (12.7-13.3)	1783 4.5% (4.3-4.7)

Abbreviations: No., number; MINS, myocardial injury after non-cardiac surgery

Supplemental Table 9. Main results and post-hoc analyses evaluating relationship between perioperative complications and 30-day mortality

	Main results reported in Table 2 based on all patients* N=40,004	Post-hoc analysis of patients for whom we had preoperative hemoglobin† N=38,619	Post-hoc analysis of patients for whom we had preoperative eGFR‡ N=37,290
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Major bleeding	2.6 (2.2-3.1)	2.2 (1.9-2.6)	2.5 (2.1-3.0)
MINS	2.2 (1.9-2.6)	2.1 (1.8-2.5)	1.9 (1.6-2.3)
Sepsis	5.6 (4.6-6.8)	5.5 (4.5-6.7)	5.6 (4.5-6.8)
Infection without sepsis	2.3 (1.7-3.0)	2.0 (1.5-2.7)	2.0 (1.5-2.8)
Acute kidney injury with dialysis	4.2 (3.1-5.8)	4.4 (3.2-6.1)	3.6 (2.6-5.1)
Stroke	3.7 (2.5-5.7)	4.2 (2.8-6.5)	3.7 (2.4-5.7)
Venous thromboembolism	2.2 (1.3-3.7)	2.3 (1.4-3.9)	2.2 (1.3-3.7)
Congestive heart failure	2.4 (1.7-3.2)	2.3 (1.7-3.2)	2.5 (1.8-3.4)
New clinically important AF	1.4 (1.0-2.0)	1.5 (1.1-2.1)	1.5 (1.1-2.1)

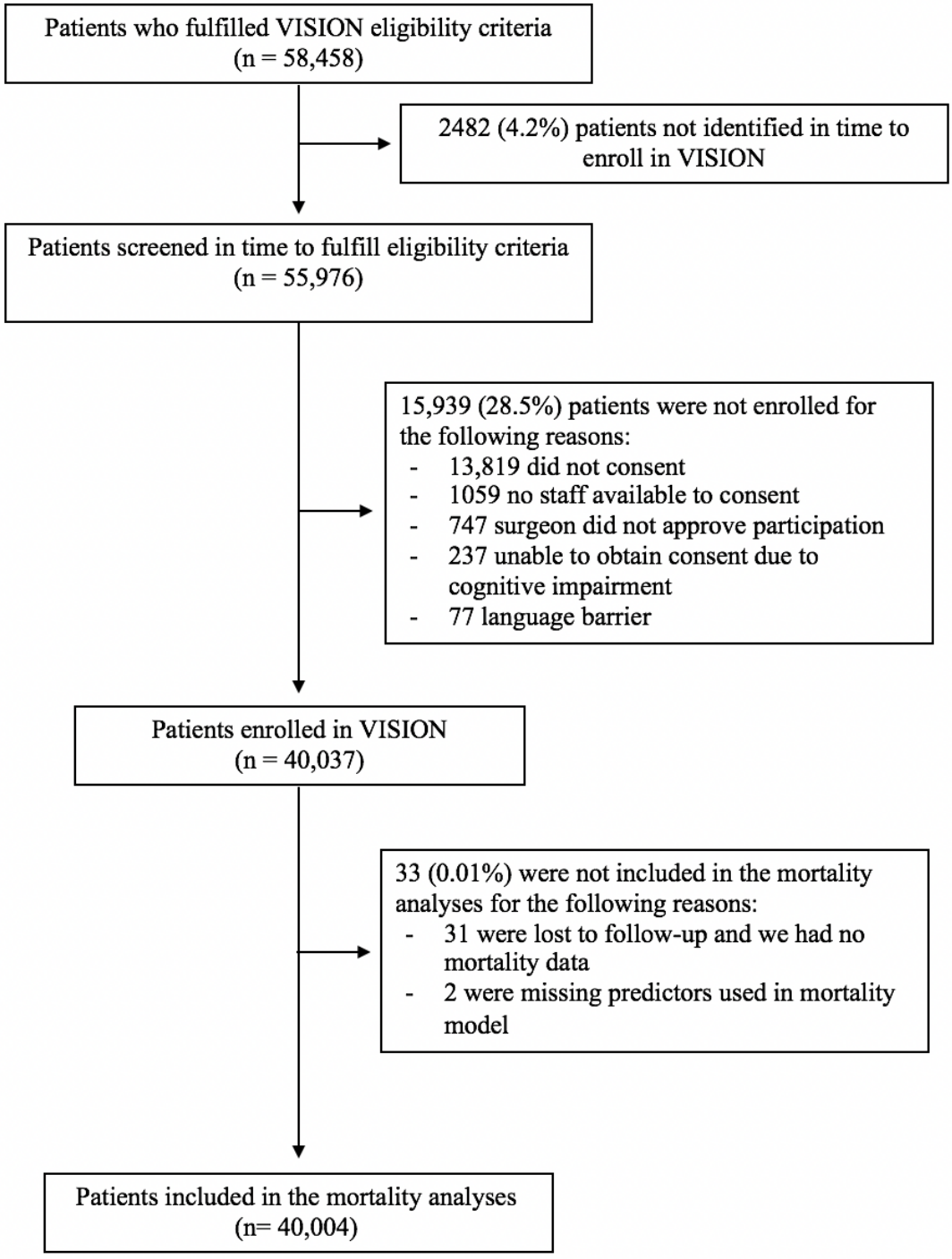
Abbreviations: eGFR, estimated glomerular filtration rate

*Cox proportional hazard model in which the dependent variable was 30-day mortality and the independent variables included preoperative and surgical variables previously associated with 30-day perioperative mortality and perioperative complications as time-dependent variables.

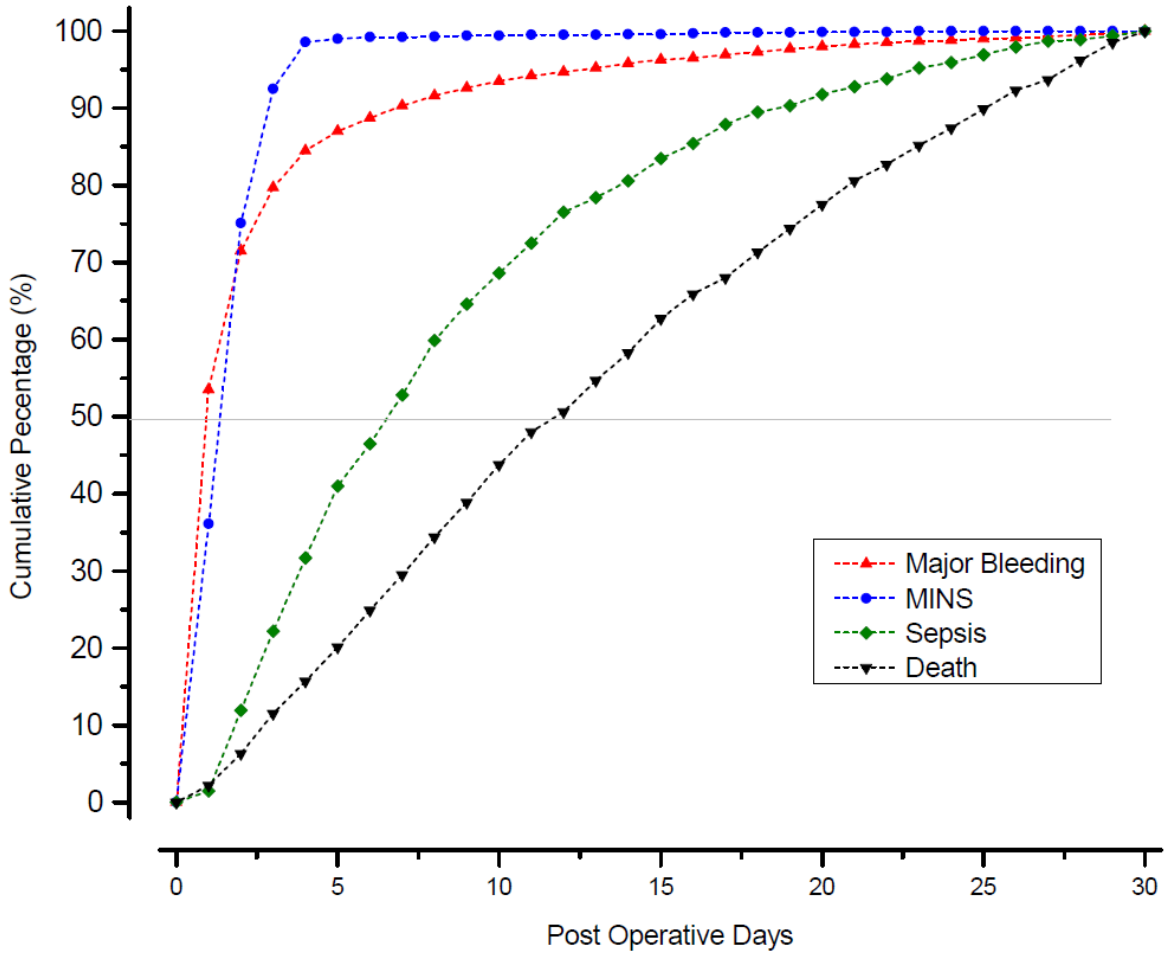
†Cox proportional hazard model in which the dependent variable was 30-day mortality and the independent variables included preoperative hemoglobin (<120 g/L), preoperative and surgical variables previously associated with 30-day perioperative mortality, and perioperative complications as time-dependent variables.

‡Cox proportional hazard model in which the dependent variable was 30-day mortality and the independent variables included preoperative eGFR (<30 ml/minute/1.73m^2 or on dialysis, 30 to 44 ml/minute/1.73m^2, 45 to 59 ml/minute/1.73m^2, and ≥60 ml/minute/1.73m^2), preoperative and surgical variables previously associated with 30-day perioperative mortality, and perioperative complications as time-dependent variables.

Supplemental Figure 1: Patient flow chart



Supplemental Figure 2. Cumulative proportion of events during 30-day follow-up



CHAPTER 3
Validation of the Standardized Assessment of Global activities in the Elderly (SAGE) scale in adult cardiac surgery patients: A substudy of VISION-Cardiac Surgery

Validation of the Standardized Assessment of Global activities in the Elderly (SAGE) scale in adult cardiac surgery patients: A substudy of VISION-Cardiac Surgery

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Abstract

Background: Function describes an individual's ability to perform everyday activities and can be divided into activities of daily living (ADL), instrumental activities of daily living (IADL), and cognition. No measures of function have been validated in cardiac surgery. We assessed the validity of the Standardized Assessment of Global activities in the Elderly (SAGE) scale.

Methods: We undertook an observational sub-study of VISION Cardiac Surgery. Patients who underwent cardiac surgery were assessed after discharge using the SAGE scale and other widely-used measures of ADL, IADL, cognition, moblity and functional status. A second, blinded, assessor re-administered SAGE by phone within 7 days to determine test-retest reliability. The convergent validity of the overall scale and subscales was assessed, with a correlation coefficient of $\geq$0.5 considered adequate. We also sought to identify the SAGE score corresponding to severe functional disability.

Results: 152 patients provided consent. Inter-rater reliability for the in-person and telephone-administered SAGE was excellent (intraclass correlation coefficient 0.99, 95% confidence interval [CI], 0.98 to 0.99). Convergent validity was evident, ranging from adequate for the SAGE score compared to global functioning (0.54, 95% CI 0.42, 0.65) to very good for the SAGE mobility sub-score compared to mobility test (0.80, 95% CI 0.73, 0.85). SAGE was initially poorly correlated with the IADL index (-0.24) but increased to 0.72 after post-hoc adjustment of SAGE scoring. A SAGE score $\geq$7 was associated with severe functional disability and occurred in 42/152 (27.6%).

Conclusion: The results of our study demonstrate the reliability and validity of the SAGE scale as a measure of global function in patients discharged home after cardiac surgery. Scoring revisions may be considered.

Background

Risk stratification for cardiac surgery has typically focused on the outcomes of major morbidity and mortality. However, recent studies report that older adults value preserving functional ability more than preventing major vascular events or death.[1] The central importance of function was recognized in the recent World Health Organization (WHO) report on global aging, which stated that "broad assessments of function are better predictors of positive outcomes in older age than…disease."[2]

Functional status describes an individual's ability to perform everyday activities. 'Everyday activities' are divided into the following: (1) activities of daily living (ADL) (i.e. daily self-care activities, including bathing, dressing, and eating), (2) instrumental activities of daily living (IADL) (i.e., activities not necessary for basic function, but which allow an individual to live independently in the community, including housework, managing finances, and shopping), and (3) cognition (upon which the other two domains are superimposed).

Functional ability is an indicator of overall health. In the context of surgical procedures, it quantifies the consequences of a procedure on one's day-to-day life. Few studies have evaluated the functional outcomes of patients undergoing cardiac surgery and no scales evaluating function or its dimensions have been validated in the setting of cardiac surgery.

The Standardized Assessment of Global activities in the Elderly (SAGE) is a 15-item patient-reported outcome measure developed to measure functional status in patients with vascular disease (see Appendix 1: SAGE scale). SAGE assesses all three functional domains (ADL, IADL, and cognition), is cross-culturally generalizable, available in multiple languages, and can be completed by a patient or surrogate within 15 minutes. We sought to assess the

reliability and validity of the SAGE scale in a sub-study of the Vascular events In Surgery patIents cOhort evaluatioN – Cardiac Surgery (VISION Cardiac Surgery) study.

Methods

Study design: SAGE Validation was a cross-sectional observational sub-study of VISION Cardiac Surgery study designed according to the COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN) checklist.[3]

Study objectives: The objectives of SAGE-Validation were to, in patients who have undergone cardiac surgery, utilize the results of a home functional assessment to for the SAGE scale: 1. inter-rater reliability when administered by telephone as compared to in-person and 2. convergent validity with the a)Barthel Index of Activities of Daily Living, a measure of ADL; b) Lawton Instrumental Activities of Daily Living Scale, a measure of IADL; c) Digit Symbol Substitution Test (DSST), a measure of executive cognitive function; d) Timed Up and Go Test (TUGT), a measure of functional mobility and falls risk; and e) World Health Organization Disability Assessment Scale (WHODAS), a measure of global function. We also aimed to determine the SAGE score corresponding to severe functional disability (as defined by a WHODAS score of 12)[4,5] and to describe the incidence of severe functional disability in our study population.

Study setting and participants: VISION Cardiac Surgery was a prospective observational cohort study of 15,984 adult patients undergoing cardiac surgery at 24 sites in 12 countries.[6] Its primary objective was to determine the relationship between postoperative high-sensitivity troponin measurements and 30-day risk of mortality.[6] Adults undergoing cardiac surgery at a participating site were eligible. Patients previously enrolled in VISION Cardiac Surgery and those who underwent an isolated pericardial window, pericardiectomy, permanent pacemaker or defibrillator implantation were excluded.

At the Hamilton General Hospital (HGH; Ontario, Canada), 3440 patients participated in VISION Cardiac Surgery; those enrolled during the SAGE validation study period (February/2017 to April/2019) and living within 100 km of Hamilton were eligible to participate in the SAGE sub-study.

Recruitment: We obtained research ethics board approval prior to recruitment. Patients who met eligibility criteria were concurrently asked to provide informed consent for SAGE Validation at the time of VISION Cardiac Surgery enrollment. We obtained a convenience sample by contacting all eligible participants by phone and included the first 152 patients who agreed to a home functional assessment. Patients who could not be reached by telephone or who declined a home visit were excluded.

Study procedures: Appendix 2 provides an overview of the procedures for both VISION Cardiac Surgery and SAGE Validation. To assess convergent validity, senior occupational therapy students performed home functional assessment after discharge from hospital following the initial cardiac surgical procedure. To assess inter-rater reliability, an independent and blinded assessor administered SAGE by telephone within 7 days of the home functional assessment.

SAGE development: For details regarding SAGE development, validation, and scoring, see Appendix 3. SAGE was developed at the Population Health Research Institute (PHRI) in Hamilton, Ontario, Canada in recognition of the need for a cross-culturally generalizable functional outcome measure that could be incorporated into international studies. It assesses functional status over the preceding month, with questions examining ADL, IADL, and cognition. For each ADL and IADL item, subjects are asked if they have performed the activity in the preceding month and, if yes, if they have had difficulties. Difficulties in ADL, IADL, and cognition are defined as mild (1 point), moderate (2 points), or severe (3 points). In SAGE,

higher scores correspond to greater functional impairment; the maximum score is 45. If participants have not performed an IADL task in the previous month, they are scored as no difficulty. This is because performance of IADLs is not always usual or necessary for independent living in the current cultural context (e.g. individuals with no functional difficulties may choose to pay someone to prepare their meals). However, ADLs are activities that must be performed for independent living; if participants have not performed an ADL task in the previous month, they are scored as having 'severe' difficulty (3 points).

Sample size calculation: No consensus exists to determine sample size for studies validating scales of patient-reported outcomes.[7] Using the desired convergent validity correlation coefficient of 0.5, 80% power, and two-sided alpha = 0.05 yields a sample size of 29. However, results from a sample of this size may lack credibility. We opted to use the rule of thumb of 10 subjects per scale item,[8] giving a required sample size of 150 participants.

Statistical analysis: We pre-specified analyses in a statistical analysis plan. To assess the reliability and validity of the telephone and in-person administration of the SAGE scale we used the intraclass correlation coefficient (ICC),[9] Bland-Altman plots,[10] and kappa percent agreement.[11] Due to non-normality, Spearman rank correlations (CIs) were used to assess the convergent validity of SAGE total score and ADL, IADL, cognitive, and mobility components with corresponding measures.[12] Confidence intervals were calculated using the Fisher transformation method. In interpreting the strength of all correlations, we considered 0.0 to $<\pm0.3$ negligible, ±0.3 to $<\pm0.5$ low, ±0.5 to $<\pm0.7$ moderate, ±0.7 to $<\pm0.9$ high, and ±0.9 to ±1.0 very high.[13] We sought to demonstrate a correlation ≥0.5 between SAGE, SAGE domains, and each corresponding measure.

To identify the SAGE score associated with severe functional disability we fitted a logistic regression model that had SAGE score (dichotomized at cut-points ranging from 6 to 12 points) as the predictor and WHODAS ≥ 12 as the dependent variable. The optimal SAGE cut-point was determined by assessing predictive performance/C-statistic, sensitivity, specificity, Youden index, and the closest to –(0,1) criterion, which is the minimum distance to point (0,1) on each cut-point's respective receiver operating characteristic (ROC) curve.[14] The cut-point with the highest Youden index, shortest distance to point (0,1), and sensitivity equal to specificity was selected.

We conducted a post-hoc exploratory analysis examining whether correlations changed in objectives 2b and d when items that the subject had not performed within the preceding month were assigned three points (severe difficulty) as opposed to none.

We used SAS version 9.4 (Cary, North Carolina) for statistical analyses and R version 3.6.3 was used for plots. For all analyses, we considered $p<0.05$ to be statistically significant.

Results

Figure 1 describes study flow. From February/2017 until April/2019 876 patients were enrolled in VISION-Cardiac Surgery at HGH; 602 lived within 100 km of Hamilton and were eligible for inclusion. We attempted to contact the first 204 participants; 152 patients completed a home functional assessment. 52 patients were excluded: 5 died, 13 declined to participate, and 34 could not be reached by telephone.

Table 1 reports the baseline demographics of included patients. The mean (standard deviation[SD]) age was 68.8 (9.6) years; 26.3% of patients were female. Patients had undergone isolated coronary artery bypass grafting (CABG) surgery (57.2%), CABG with single valve repair/replacement (20.4%), aorta surgery (9.2%), isolated aortic valve repair/replacement (5.9%), and other surgery (7.2%). The majority (71%) of cardiac surgical procedures were elective; 23.7% were urgent and 5.2% were emergent. The most common comorbidity at VISION Cardiac Surgery enrollment was previous myocardial infarction, occurring in 37.5%. Other comorbidities included stroke (2.6%), peripheral arterial disease (5.9%), chronic obstructive pulmonary disease (12.5%), and diabetes (30.3%). Ninety-two (60.5%) participants had a history of tobacco use.

Table 2 describes the results of the home functional assessment. The median (Quartile 1 – Quartile 3 [Q1-Q3]) number of days after cardiac surgery that patients were assessed was 417 (148-671) days. The majority of participants (80.3%) lived in a house; the remainder lived in an apartment (17.8%) or retirement home (2.0%). No participants resided in a long-term care facility. The median (Q1-Q3) telephone and in-person SAGE scores were 2.5 (0-7.5) and 3 (0-7.5) respectively. There were a median (Q1-Q3) of 2 (1-2) days between telephone and in-person SAGE administration.

The Barthel ADL Index is scored out of 20, with points lost for identified impairments;[15] the mean (SD) score was 19.1 (2.1). The Lawton IADL scale is scored out of 8, with points lost for identified impairments; the mean (SD) score in our sample was 7.0 (1.9).[16] The DSST is an assessment of executive cognitive function where participants copy symbols paired with numbers; the number correct drawn within 90 seconds is the score.[17] The mean (SD) score in our sample was 38.9 (14.6). The TUGT is an assessment of mobility, balance, and falls risk, where the participant is asked to rise from a chair, walk 3 metres, turn around, walk back, and sit down.[18] Time required in seconds is the score; mean (SD) score in our sample was 11.0 (5.7) seconds. The 12-item WHODAS 2.0 scale was developed by the World Health Organization to assess health and disability; higher WHODAS scores correspond to greater disability, with points assigned for identified disabilities to a maximum of 48.[5] The median (Q1-Q3) score in our population was 3.0 (0.0-6.0).

Table 3 reports the correlation between SAGE global and domain scores and the corresponding comparator measure. We present scatter plots illustrating these relationships in Figure 2 and Appendices 5-9. The ICC (95% CI) for in-person and telephone administrations of the SAGE Scale was 0.99 (0.98, 0.99) and the kappa percent agreement (95% CI) was 97.1% (94.5%, 99.6%)(Figure 2 and Appendix 4). Given the very strong convergence, we used the in-person administration of SAGE for all other comparisons. SAGE ADL items had a strong negative correlation with the Barthel index, with a correlation (95% CI) of -0.73 (-0.80, -0.65). SAGE IADL items had a negligible correlation (-0.24; 95% CI -0.38, -0.08) with the Lawton scale. When we scored SAGE such that IADL items that had not been performed were assigned 3 points, the correlation increased to -0.60 (95% CI -0.69, -0.49). SAGE cognitive and mobility items all had moderately strong or high correlations with their respective comparator measures,

with correlations of -0.60, and 0.80 respectively. Overall SAGE score had a moderately strong relationship with the WHODAS; the correlation (95% CI) was 0.54 (0.42, 0.65). The correlation between SAGE and WHODAS did not change when items not performed were assigned three points.

To determine the SAGE score associated with a WHODAS ≥12 (i.e. severe functional disability), we evaluated cut-points ranging from SAGE scores of 6 to 12 (see Appendix 10). Based on an area under the curve (AUC) of 0.82 (95% CI 0.73, 0.91), a Youden index of 0.64 a minimum distance of 0.26, and a sensitivity and specificity of 0.82 and 0.82 respectively, we selected a SAGE score of ≥7. The incidence of severe functional disability in our sample was 42/152 (27.6%)(95% CI, 20.7%, 35.5%).

Discussion

To our knowledge SAGE validation is the first study validating a measure of function in adults who have undergone cardiac surgery. Our results demonstrate that SAGE can be administered by telephone or in person, and that SAGE is a valid measure of ADL, mobility, and cognition in adults after cardiac surgery. We defined the SAGE score associated with severe functional disability, which can be used as a binary and clinically important outcome in perioperative studies. We did not demonstrate that SAGE is a valid measure of IADL as currently scored but believe that the lack of observed convergent validity with the Lawton scale stems from SAGE's greater cross-cultural generalizability and alignment with the norms of contemporary society.

The Lawton IADL scale was developed in 1969 to assess independent living skills in older adults.[19] It measures 8 domains of IADL: using the telephone, managing medications, shopping, communicating via telephone, managing finances, performing housework, driving/using public transportation, and laundering clothing. Historically, women were scored on all 8 domains (with a maximum possible score of 8) and, because of gender roles, men were not scored in the domains of food preparation, housekeeping, and laundry (with a maximum possible score of 5). However, current recommendations are to assess all domains for both genders.[20] Using this approach, SAGE IADL items had a negligible correlation (-0.24; 95% CI -0.38, -0.08) with the Lawton scale. However, when SAGE IADL items that had not been performed were assigned 3 points (equivalent to severe disability), the correlation increased to -0.60 (95% CI -0.69, -0.49). We believe that this difference reflects the fact that SAGE – using its current scoring schema – recognizes that some elements of IADL are not necessary for independent living in the current cultural context, by choice as opposed to inability. For example, individuals

with no functional impairments may employ others to complete certain IADL – like housekeeping, managing finances, and meal preparation – because they choose to, not because they are unable. For this reason, we believe that – despite its negligible correlation with the Lawton scale – SAGE is a valid measure of IADL, a belief that is supported by the strong correlation observed when SAGE scoring was modified to align with the Lawton scale.

Little is known about function after cardiac surgery. In the context of an aging population, where surgical procedures are often offered to improve symptoms and quality of life (rather than quantity of life), understanding the impact of cardiac surgery on patients' ability to function is key. The largest prospective study evaluating function after cardiac surgery administered the Katz ADL index 3 months after surgery to a cohort of 475 patients ≥65 years of age; 16% suffered functional decline.[21] This study validated a predictive measure of functional decline but did not examine other predictors. In addition, only ADL was evaluated.

Two large database studies have evaluated perioperative function in cardiac surgery patients. Lee et al examined the postoperative implications of preoperative frailty – defined as any impairment in ADL, ambulation, or a documented history of dementia – and found that frail patients (157/3826; 4.1%) were at higher risk of in-hospital mortality (OR 1.8, 95% CI 1.1, 3.0) and discharge to institutional care (OR 6.3, 95% CI 4.2, 9.4).[22] Koch et al examined the relationship between functional quality of life after cardiac surgery – assessed using the Duke Activity Status Index (DASI) – and postoperative survival over time in 6305 cardiac surgery patients,[23] with greater functional ability at baseline and follow-up associated with better long-term survival. Neither of these studies was based on an *a priori* question or evaluated function as an outcome. We believe that studying function before and after cardiac surgery is a priority. The

data generated by SAGE validation support the use of the SAGE scale as a measure of functional status after cardiac surgery.

Our study has several strengths, including multi-dimensional assessment of function in the home setting by assessors with formal training. Our study has several limitations. The assessor administering the SAGE scale also administered the comparator measures, which may have introduced confirmation bias. However, there was no difference between SAGE scores obtained in-person and SAGE score administered by an independent and blinded assessor. Finally, SAGE is a patient-reported measure, and relies on an individual's assessment of their own abilities. Patients may have over- or underestimated their own functional ability. However, when compared with objective measures like the DSST and TUGT, SAGE had a moderately strong or high correlation.

A potential barrier to the widespread use of SAGE in cardiac surgery research is that it is unfamiliar to most perioperative clinicians, does not have established population-based norms, and generates a score that may be difficult to interpret. However, SAGE has been incorporated into a large number of multi-centre and international studies.[24-26] As data from these cohorts become available, we will develop normative comparisons derived from more than 50,000 patients. Furthermore, within VISION-Cardiac Surgery, SAGE has been administered to a sample of more than 2500 patients undergoing cardiac surgery around the world at baseline, 30-days, and 1-year after cardiac surgery. Data collected will allow us to describe the trajectory of function after cardiac surgery. The binary outcome (corresponding to severe functional disability) that we have defined in SAGE validation is simple for clinicians to interpret and will allow us to describe the incidence and predictors of severe functional disability after cardiac surgery globally.

Conclusions: Functional ability, which underlies independence, is an outcome of great importance to patients that has been poorly studied in adults undergoing cardiac surgery. This is in part due to the lack of validated measures. We have demonstrated the reliability and validity of the SAGE scale, administered by phone or in-person, in measuring function in the cardiac surgery population.

Contributions:
JS: Responsible for study conception and design, acquisition of data, analysis and interpretation of data, and drafting of final manuscript.
JB: Responsible for study conception and design, acquisition of data, analysis and interpretation of data, and drafting of final manuscript.
EC: Responsible for analysis and interpretation of data and drafting of final manuscript.
SFL: Responsible for analysis and interpretation of data and drafting of final manuscript.
LT: Responsible for analysis and interpretation of data and drafting of final manuscript.
PM: Responsible for acquisition of data and drafting of final manuscript.
EBC: Responsible for analysis and interpretation of data and drafting of final manuscript.
RW: Responsible for acquisition of data, analysis and interpretation of data and drafting of final manuscript.
KB: Responsible for acquisition of data and drafting of final manuscript.
WFM: Responsible for analysis and interpretation of data and drafting of final manuscript.
AL: Responsible for acquisition of data, analysis and interpretation of data and drafting of final manuscript.
PJD: Responsible for study conception and design, analysis and interpretation of data, and drafting of final manuscript.

All authors have reviewed and approved of the final manuscript submitted for publication and agree to be accountable for all aspects of the work.

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Table 1: Patient characteristics at baseline and surgical details

	N=152
Age, years – (Mean [SD])	68.8 (9.6)
Female sex – N (%)	40 (26.3)
Cardiac surgical procedure – N (%)	
Isolated CABG	87 (57.2)
CABG with single valve repair/replacement	31 (20.4)
Aorta surgery	14 (9.2)
Isolated aortic valve repair/replacement	9 (5.9)
Other surgery	11 (7.2)
Surgical urgency rating – N (%)	
Elective	108 (71.1)
Urgent	36 (23.7)
Emergent	8 (5.2)
Comorbidities – N (%)	
Myocardial infarction	57 (37.5)
Stroke	4 (2.6)
Peripheral arterial disease	9 (5.9)
Chronic obstructive pulmonary disease	19 (12.5)
Diabetes	46 (30.3)
History of tobacco use – N (%)	92 (60.5)

Abbreviations: SD: standard deviation; N: number; CABG: Coronary artery bypass grafting

Table 2. Details and results of home functional assessment

	N=152
Time (days) since surgery when home functional assessment completed – median (Q1 – Q3)	417 (148-671)
Time (days) between telephone and in-person SAGE administration – median (Q1 – Q3)	2 (1-2)
Living circumstances at the time of home functional assessment – N (%)	
House	122 (80.3)
Apartment	27 (17.8)
Retirement home	3 (2.0)
Long-term care facility	0 (0.0)
Telephone SAGE* score – median (Q1 – Q3)	2.5 (0-7.5)
In-person SAGE* score – median (Q1 – Q3)	3 (0-7.5)
Barthel Activities of Daily Living Index** – mean (SD)	19.1 (2.1)
Lawton Instrumental Activities of Daily Living Scale+ – mean (SD)	7.0 (1.9)
DSST∞ – mean (SD)	38.9 (14.6)
TUGT$ (seconds) – mean (SD)	11.0 (5.7)
WHODAS score& – median (Q1 – Q3)	3.0 (0.0-6.0)

*Higher SAGE scores correspond to greater functional impairment. Points are assigned for identified impairments, with the maximum possible score = 45.

**Scored out of 20. Points are lost for identified ADL impairments.

+Scored out of 8. Points are lost for identified IADL impairments.

∞Higher scores correspond to higher executive cognitive functioning. Maximum possible score = 133.

$Scored as the time in seconds to rise from a chair, walk three metres, turn around, walk back to the chair, and sit down.

&Higher WHODAS scores correspond to greater disability. Points are assigned for identified physical and psychiatric disabilities, with the maximum possible score = 48.

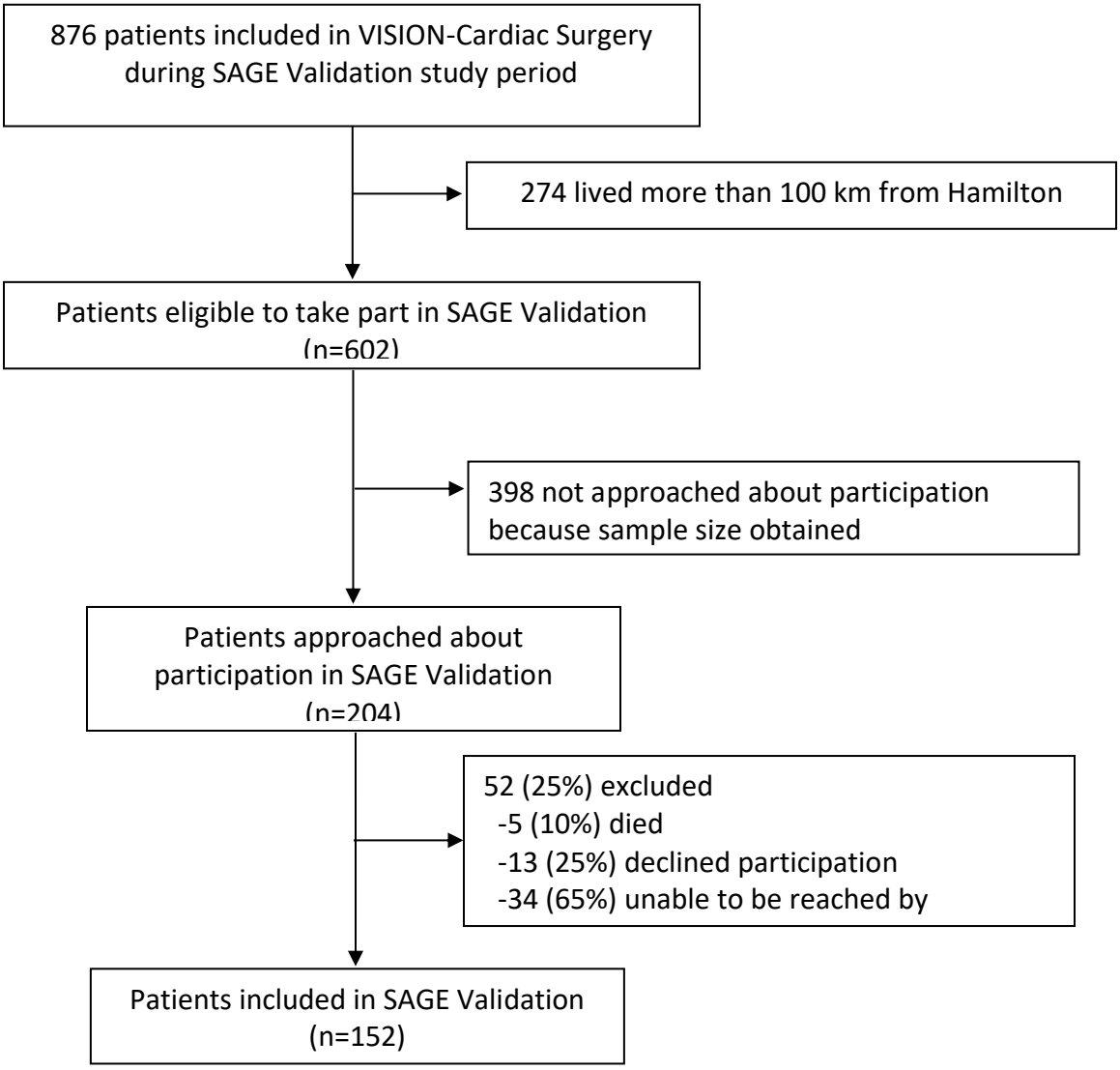
Abbreviations: Q1: Quartile one; Q3: Quartile three; SAGE: Standardized Assessment of Global activities in the Elderly; SD: Standard deviation; DSST: Digit Symbol Substitution Test; TUGT: Timed up and go test; WHODAS: World Health Organization Disability Assessment Scale

Table 3: Correlations between SAGE global and domain scores and the corresponding comparator measure

Comparison	Correlation coefficient (95% CI)
In-person SAGE with telephone-administered SAGE*	0.99 (0.98, 0.99)
SAGE ADL items[1] with Barthel index**	-0.73 (-0.80, -0.65)
SAGE IADL and applied cognition items[2] with Lawton scale	-0.24 (-0.38, -0.08)
SAGE IADL and applied cognition items[2] with Lawton scale with SAGE scoring modification	-0.60 (-0.69, -0.49)
SAGE cognitive and applied cognition items[3] with DSST	-0.60 (-0.70, -0.49)
SAGE mobility with TUGT	0.80 (0.73, 0.85)
SAGE total with WHODAS	0.55 (0.42, 0.65)
SAGE total with WHODAS with SAGE scoring modification	0.54 (0.43, 0.65)

*Assessed using intraclass correlation coefficient (ICC)
**Assessed using Spearman rank correlation
[1]Dressing, transfers, bathing/toileting, and mobility
[2]Community navigation, finances/shopping, medication management, meal preparation, driving/public transportation
[3]Concentration, memory, executive function, community navigation, finances/shopping, medication management, meal preparation, driving/public transportation
Abbreviations: CI: confidence interval; SAGE: Standardized Assessment of Global activities in the Elderly; ADL: activities of daily living; IADL: instrumental activities of daily living; DSST: Digit Symbol Substitution Test; TUGT: Timed Up and Go Test; WHODAS: World Health Organization Disability Assessment Scale

Figure 1: SAGE Validation study flow diagram



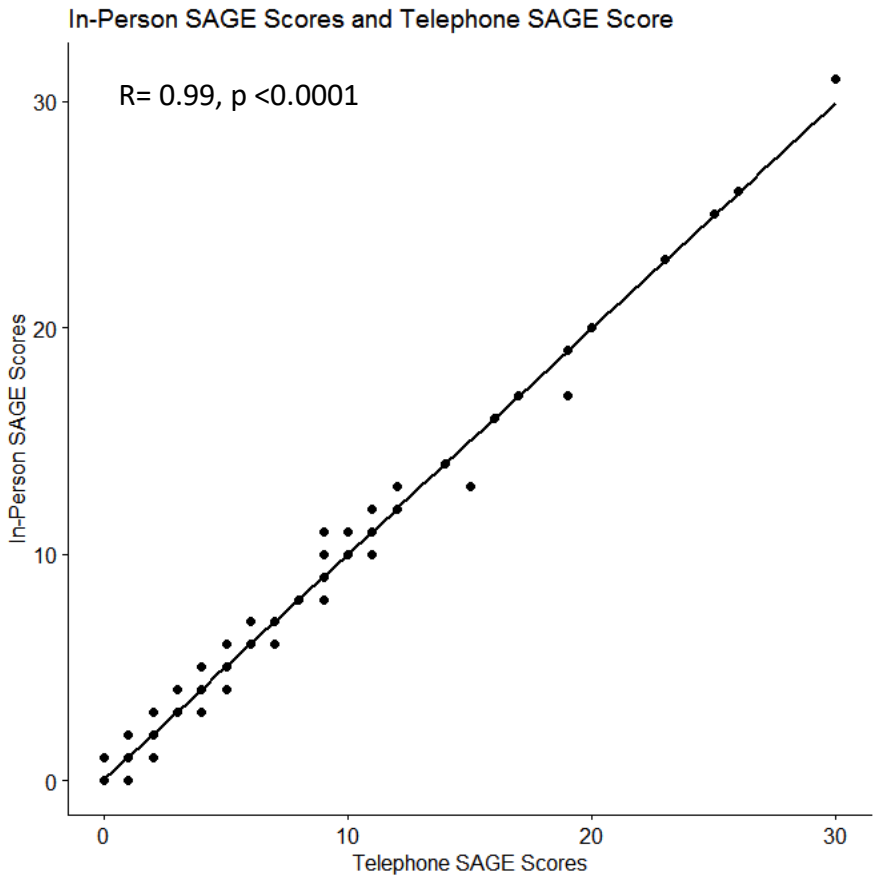


Figure 2: Scatter plot of in-person compared to telephone SAGE scale score. SAGE: Standardized Assessment of Global activities in the Elderly.

Appendix 1: Standardized Assessment of Global activities in the Elderly (SAGE) Scale

Standard Assessment of Global-Activities in the Elderly

SAGE

Version 1.4_20140327

Indicate whether the SAGE is being completed at the Baseline (Screening/Run-In Visit(s) or Randomization), 2 Year Visit, or the Final Visit.

Instructions for Completion of the Standard Assessment of Global-Activities in the Elderly

The SAGE measures what people are doing in their community and their home.

For the questions on the following pages, please indicate the level of difficulty you have had with each, in the past month.

The levels of difficulty are as following:

***Mild*:** minimal/occasional difficulty that does not affect the ability to perform the activity or task.

***Moderate*:** some/regular difficulty that does affect the ability to perform the task, although they may still be able to perform the task.

***Severe*:** extreme/constant difficulty performing the task or the task is not completed and/or is completed by someone else because of its difficulty.

If the participant is unable to complete the form themselves, please ask someone who has knowledge of the participant's ability to perform the tasks, to complete the questionnaire. Indicate that an 'Other person' completed the questionnaire by checking Completed by: 'Other person' box and indicate the relationship to the participant.

Please indicate if this questionnaire was administered via telephone.

Participant ID # ☐☐☐☐ ☐☐☐ **Participant Initials** ☐☐☐
Site # *Participant #* *F M L*

Date completed: ☐☐ / ☐☐ / ☐☐
year / month / day

Completed by: ☐ Participant
☐ Other person
Relationship to participant: _____

Is this being administered via telephone? ☐ No ☐ Yes

Over the past month, did you have any difficulties with the following:

			Mild	Moderate	Severe
1. Keeping your attention or 'train of thought' during a conversation?	☐ None	☐ Some → How much difficulty?	☐	☐	☐
2. Remembering things that happened a few days before? (e.g. conversation, people visiting)	☐ None	☐ Some → How much difficulty?	☐	☐	☐
3. Ability to switch between things that are happening at the same time? (e.g. making tea and talking to someone)	☐ None	☐ Some → How much difficulty?	☐	☐	☐

Over the past month, did you perform any of the following activities:

			None	Mild	Moderate	Severe
4. Playing a game or reading a book that requires concentration? (e.g. of games: crosswords, checkers, chess)	☐ No	☐ Yes → Difficulty?	☐	☐	☐	☐
5. Finding your way around a new building? (e.g. hospital/clinic)	☐ No	☐ Yes → Difficulty?	☐	☐	☐	☐
6. Organizing a trip or social activities? (e.g. vacation or family occasion) (score the activity that the person finds to be the more difficult of the two)	☐ No	☐ Yes → Difficulty?	☐	☐	☐	☐
7. Doing your own finances or shopping? (score the activity that the person finds to be the more difficult of the two)	☐ No	☐ Yes → Difficulty?	☐	☐	☐	☐
8. Organizing and taking your medications?	☐ No	☐ Yes → Difficulty?	☐	☐	☐	☐
9. Preparing a meal and/or doing laundry? (score the activity that the person finds to be the more difficult of the two)	☐ No	☐ Yes → Difficulty?	☐	☐	☐	☐
10. a) Driving? ☐ Do not drive (go to 10b)	☐ No	☐ Yes → Difficulty?	☐	☐	☐	☐
b) Using public transportation? ☐ Do not use (go to 11)	☐ No	☐ Yes → Difficulty?	☐	☐	☐	☐

Participant ID # ☐☐☐☐ ☐☐☐ (*Site #* / *Participant #*) **Participant Initials** ☐☐☐ (*F M L*)

Over the past month, did you perform any of the following activities:

11. Using stairs? (one flight) ☐ No ☐ Yes → Difficulty? None ☐ Mild ☐ Moderate ☐ Severe ☐
Did you require help? ☐ No ☐ Yes → ☐ Walking stick ☐ Elevator/lift ☐ Another person ☐ Other: _____

12. Walking? (approx. 10m or 32ft or 14 steps) ☐ No ☐ Yes → Difficulty? None ☐ Mild ☐ Moderate ☐ Severe ☐
Did you require help? ☐ No ☐ Yes → ☐ Walking stick/rollator ☐ Another person ☐ Other: _____

13. Dressing? ☐ No ☐ Yes → Difficulty? None ☐ Mild ☐ Moderate ☐ Severe ☐
Did you require help? ☐ No ☐ Yes

14. Transfer from bed to chair? ☐ No ☐ Yes → Difficulty? None ☐ Mild ☐ Moderate ☐ Severe ☐
Did you require help? ☐ No ☐ Yes → ☐ Walking stick/rollator ☐ Another person ☐ Other: _____

15. Bathing or toileting? (score the activity that the person finds to be the more difficult of the two) ☐ No ☐ Yes → Difficulty? None ☐ Mild ☐ Moderate ☐ Severe ☐
Did you require help? ☐ No ☐ Yes **Score** ☐

If the participant reports difficulty with any of the items in questions 6-15, please ask:

16. Have any of the following problems limited your ability to perform activities? *(check all that apply)*

☐ Memory problems ☐ Physical injury (e.g. fracture) ☐ Loss of vision ☐ Not sure
☐ Arthritis ☐ Stroke or TIA ☐ Unsteadiness
☐ Shortness of breath ☐ Chronic pain ☐ Other: _____
☐ Chest pain ☐ Heart failure ☐ None of the above

Name of person administering questionnaire: _____ (*Full name*) Date completed: ☐☐☐☐☐☐ (*year / month / day*)

Appendix 2: Detailed summary of SAGE validation and VISION-Cardiac Surgery study procedures

	Screening	Baseline	In-hospital	Postoperative period
Eligibility	X			
Informed Consent	X			
Medical History		X		
Demographics		X		
Operative Details			X	
Events in hospital			X	
Events after hospital discharge*				X
SAGE**				X
Barthel Index of ADL**				X
Lawton IADL Index**				X
DSST**				X
TUGT**				X
Information regarding living circumstances and community supports**				X

*Events after hospital discharge were assessed at 30-days and 1-year after surgery
**Study procedures unique to the SAGE validation study
Abbreviations: SAGE: Standardized Assessment of Global activities in the Elderly; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; DSST: Digit Symbol Substitution Test; TUGT: Timed Up and Go Test

Appendix 3: Development and Validation of the Standardized Assessment of Global activities in the Elderly (SAGE) Scale

Background:

- Recent studies in elderly populations report that preservation of physical and cognitive function is more important to older adults than prevention of major vascular events or death (Depp, Glatt & Jeste 2007).
- Vascular disease of brain, heart, kidney and muscle are all associated with impairments in function.
- Functional impairment has not been a prominent outcome measure in primary prevention hypertension studies (Turnbull et al. 2008).
- We propose that a composite measure of physical and cognitive functioning represents a unifying vascular outcome measure in the elderly. Such an approach reflects the elderly patient's perspective and is anticipated to capture the benefits of risk factor modification at a multi-organ level.
- We developed a scale (SAGE) to measure a person's ability to perform everyday activities, that encompass cognitive, instrumental and basic activities of daily living.
- The SAGE is supplemented with additional measures of cognition, mood, and quality of life.

Description of the development of SAGE:

In general, the natural history of vascular decline is usually the sequential and hierarchical loss of instrumental and basic ADL (IADL and ADL), although discrete losses in basic ADL may occur (Inzitari et al. 2008; Peres et al. 2008; Wadley et al. 2008; Wicklund et al. 2007). In addition, increasing loss of function in each domain represents incremental burden to the individual, the household, and society/healthcare system. In order to monitor these losses in function, we have developed a 15-item scale that represents a measure of ADL across the spectrum of functioning (cognitive, instrumental and basic ADL), that is influenced by both decline in neurocognitive and physical processes and is mediated through a variety of vascular-related mechanism. As instrumental activities are likely to have cultural and socioeconomic variations, we have established a measure that includes generic items in order to allow for such variations.

We observed the following considerations in the development of the SAGE:

1) All items within the scale are considered important and relevant to elderly people
2) Individual items may be considered as 'stand-alone' activities (expert opinion)
3) Selected items are known to be preferentially affected by micro and macrovascular cerebrovascular disease
4) The scale represents the established hierarchical and ordered loss of social, instrumental and basic ADL that are known to occur in community-dwelling persons with hypertension
5) The need to embrace all relevant existing scales in the literature that measures participation and ADL
6) The scale would be feasible and generalizable cross-culturally for men and women, and could be administered or completed by patient or caregiver over the telephone within 15 minutes

7) The population of interest would be community-dwelling elderly patients at risk of vascular disease, without exclusion of person with cognitive, physical or mood disorders, (provided they did not impact on ability to provide informed consent)

Decisions on all these criteria were based on an exhaustive review of the literature. We selected components of the Barthel for ADL (based on validated 5-item subscale) (Hobart & Thompson 2001), and the Lawton & Brody Scale (Graf 2008) for IADL.

Scoring of SAGE:

For the first three SAGE items, which relate to cognition, the person being assessed is asked whether, within the previous month, they have had difficulties (yes or no) with attention, memory, and executive functioning (as described as the ability to do two things at the same time). If difficulties are endorsed, the person is asked to quantify these difficulties as mild (1 point), moderate (2 points), or severe (3 points). For each of the remaining 12 items, the person is asked whether they have performed an activity related to applied cognition, ADL, or IADL. If they have performed the activity, they are asked if they have had difficulty. If they endorse having had difficulty, they are asked to quantify this difficulty as mild, moderate, or severe. Finally, they are also asked if they required help in performing the activity. For each of these 12 items no points are assigned if the person endorses no deficit or denies have performed the activities, with the exception of questions 12-15, which relate to ADL (walking, bathing, transfers, and bathing/toileting). For these items, which assess activities considered integral to daily function and independent living, the person is assigned 3 points if the activity has not been performed. If the person endorses having had difficulties, they are given 1 point for mild difficulties, 2 points for moderate difficulties, and 3 points for severe difficulties. If the person being assessed requires help for stairs, walking, bathing, transfers, or bathing toileting, they are assigned 1 point for each item for which they require help. A maximum of three points can be assigned for any question. The minimum SAGE score – which corresponds to no functional impairments – is 0. The maximum SAGE score – which corresponds to severe global functional impairment – is 45.

Methods for establishing the psychometric properties of SAGE:

Face/content validity: An expert panel assessed the content validity of the measure. In addition, senior scientists from 40 different countries reviewed the measure for cultural sensitivity.

Construct validity: The SAGE was administered to three distinct groups; community living older adults, older adults admitted to hospital with stroke, and older adults living in a long-term care facility, with expectation of a significantly different mean scores between the groups.

Convergent validity: In addition to the SAGE, the Frenchay Activities Index (FAI, a measure of IADL), the Montreal Cognitive Assessment (MoCA, a measure of executive function) and the modified-Rankin scale (general measure of functional outcome) were also administered. Individual scores from each measure were correlated.

Internal consistency: Item scores within the SAGE were correlated with overall mean to ensure the items were measuring a similar construct.

Results of initial psychometric testing:

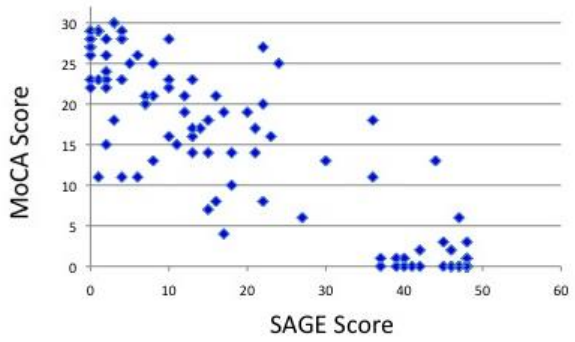
Face validity: The SAGE was revised after receiving comments from the expert panel (3 revisions) and the senior scientists (2 revisions). Further testing was performed on the final version.

A total of 109 participants were recruited; 26 colder adults living in the community (Community), 44 admitted to hospital with stroke (Stroke) and 39 living in a long-term care facility (LTC).

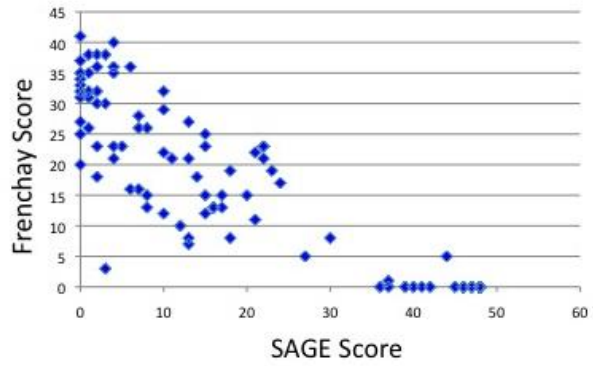
Construct validity: The mean (SD) SAGE score for each group was as follows; Community 2.1 (2.2), Stroke 3.4 (7.2) and LTC 44.9 (1.0), p for difference of <0.0001 (note, higher SAGE scores equate to poorer function).

Convergent Validity: The results for each comparison are shown below:

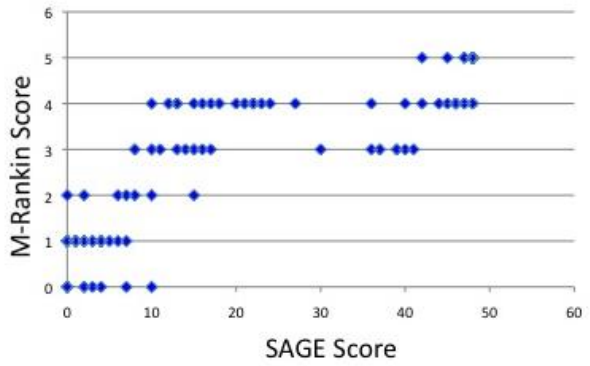
MoCA versus SAGE



Frenchay versus SAGE



Modifed-Rankin versus SAGE



Of the 103 participants who completed the questions, 100 (97%) indicated they found the questionnaire easy to answer, 3 (3%) indicated something was missing, and 4 (4%) indicated that the ordering of items needed to be changed.

Results of internal consistency indicated that the items were well correlated (r=0.85 or greater) except for walking (r=0.66) and transferring bed to chair (r=0.71).

References:

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Graf, C. 2008, "The Lawton instrumental activities of daily living scale", Am J Nurs, vol. 108, no. 4, pp. 52-62.

Hobart, J. C. & Thompson, A. J. 2001, "The five item Barthel index", J Neurol Neurosurg Psychiatry, vol. 71, no. 2, pp. 225-230.

Inzitari, M., Pozzi, C., Ferrucci, L., Chiarantini, D., Rinaldi, L. A., Baccini, M., Pini, R., Masotti, G., Marchionni, N., & Di, B. M. 2008, "Subtle neurological abnormalities as risk factors for cognitive and functional decline, cerebrovascular events, and mortality in older community-dwelling adults", Arch Intern Med, vol. 168, no. 12, pp. 1270-1276.

Peres, K., Helmer, C., Amieva, H., Orgogozo, J. M., Rouch, I., Dartigues, J. F., &Barberger-Gateau, P. 2008, "Natural history of decline in instrumental activities of daily living performance over the 10 years preceding the clinical diagnosis of dementia: a prospective population-based study", J Am Geriatr Soc, vol. 56, no. 1, pp. 37-44.

Turnbull, F., Neal, B., Ninomiya, T., Algert, C., Arima, H., Barzi, F., Bulpitt, C., Chalmers, J., Fagard, R., Gleason, A., Heritier, S., Li, N., Perkovic, V., Woodward, M., & MacMahon, S. 2008, "Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials", BMJ, vol. 336, no. 7653, pp. 1121-1123.

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impairment and everyday function: evidence of reduced speed in performing instrumental activities of daily living", Am J Geriatr Psychiatry, vol. 16, no. 5, pp. 416-424.

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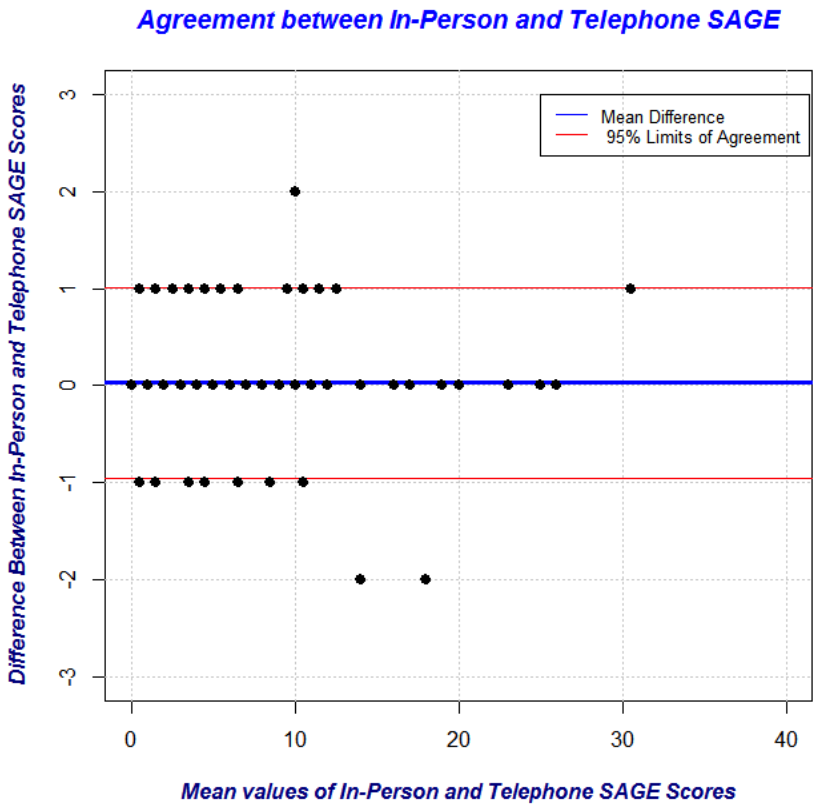
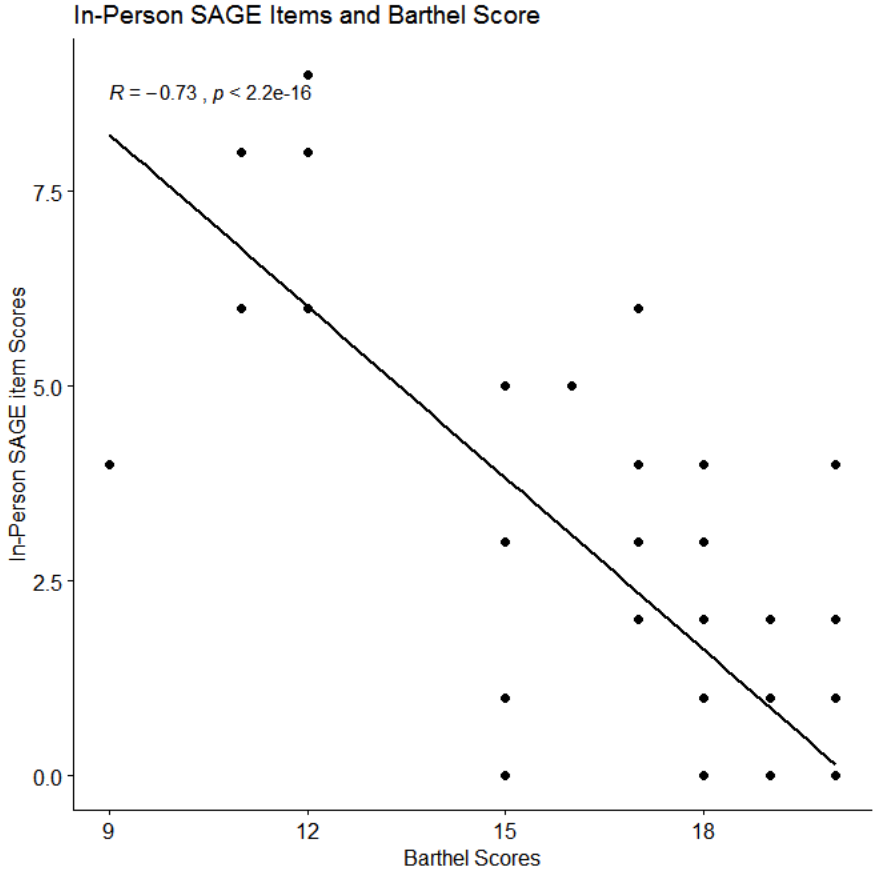
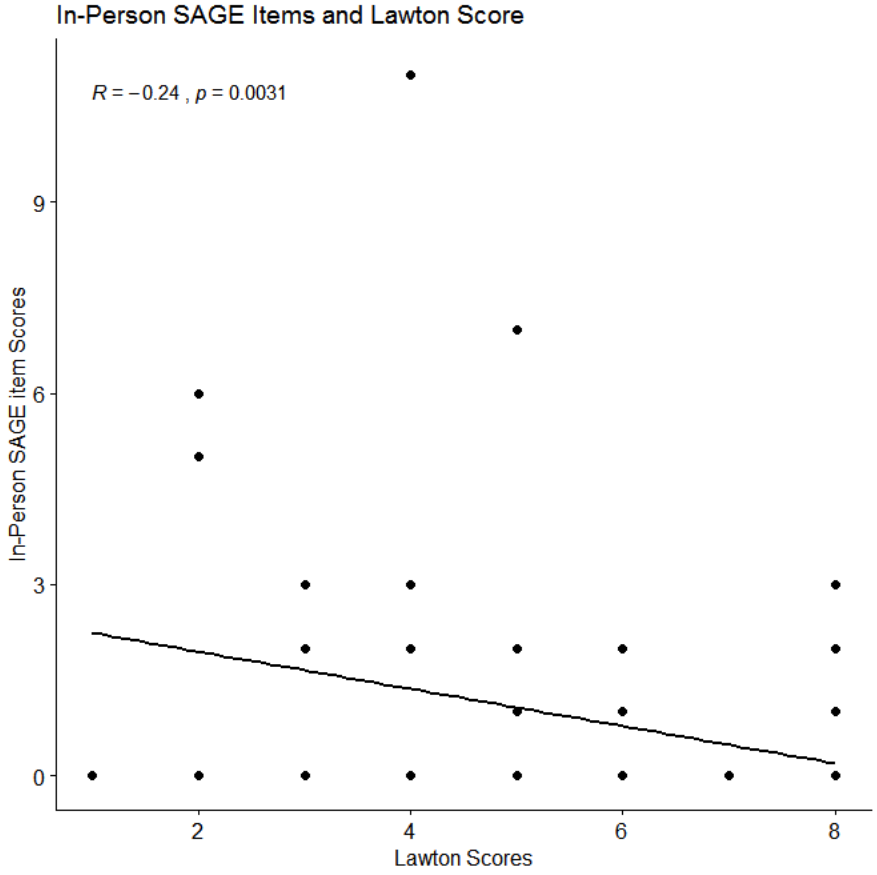
Appendix 4: Bland-Altman plot of in-person versus telephone SAGE scale score. SAGE: Standardized Assessment of Global activities in the Elderly.



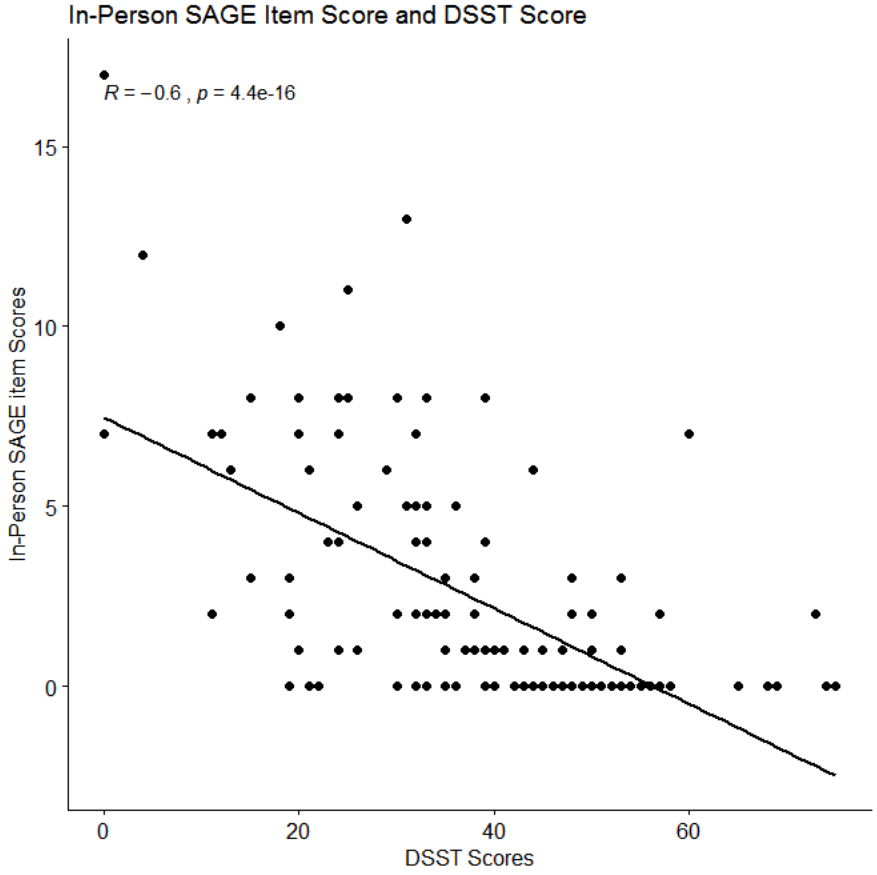
Appendix 5: Scatter plot of SAGE ADL items and Barthel score. SAGE: Standardized Assessment of Global activities in the Elderly. ADL: Activities of daily living.



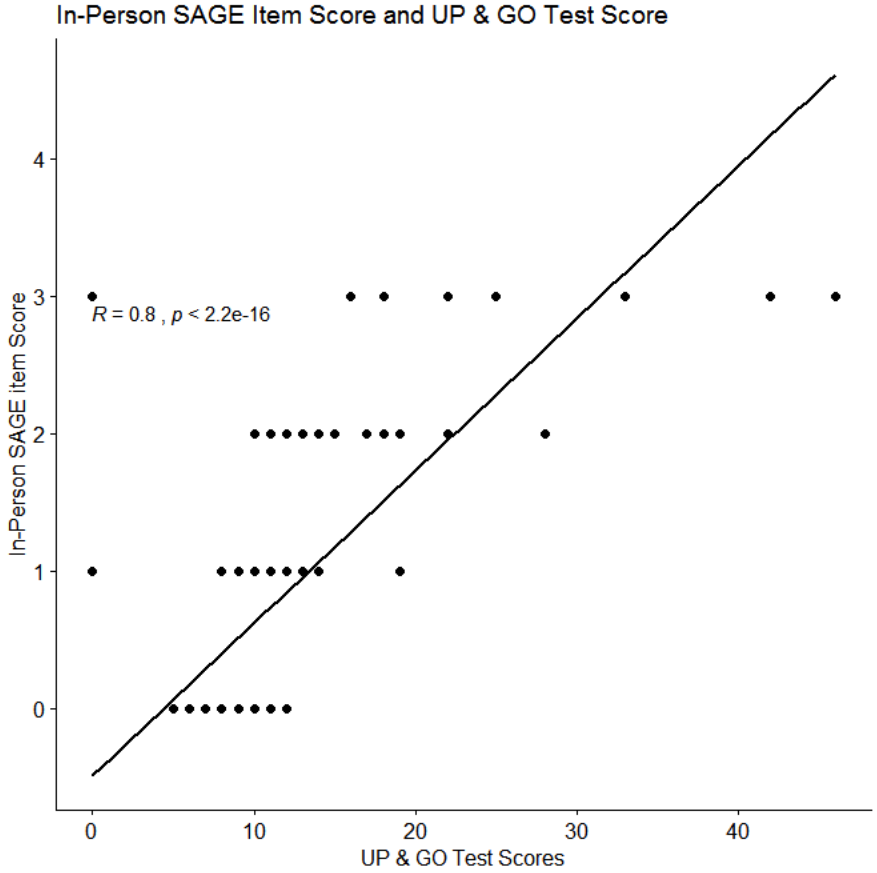
Appendix 6: Scatter plot of SAGE IADL items and Lawton score. SAGE: Standardized Assessment of Global activities in the Elderly. IADL: Instrumental activities of daily living.



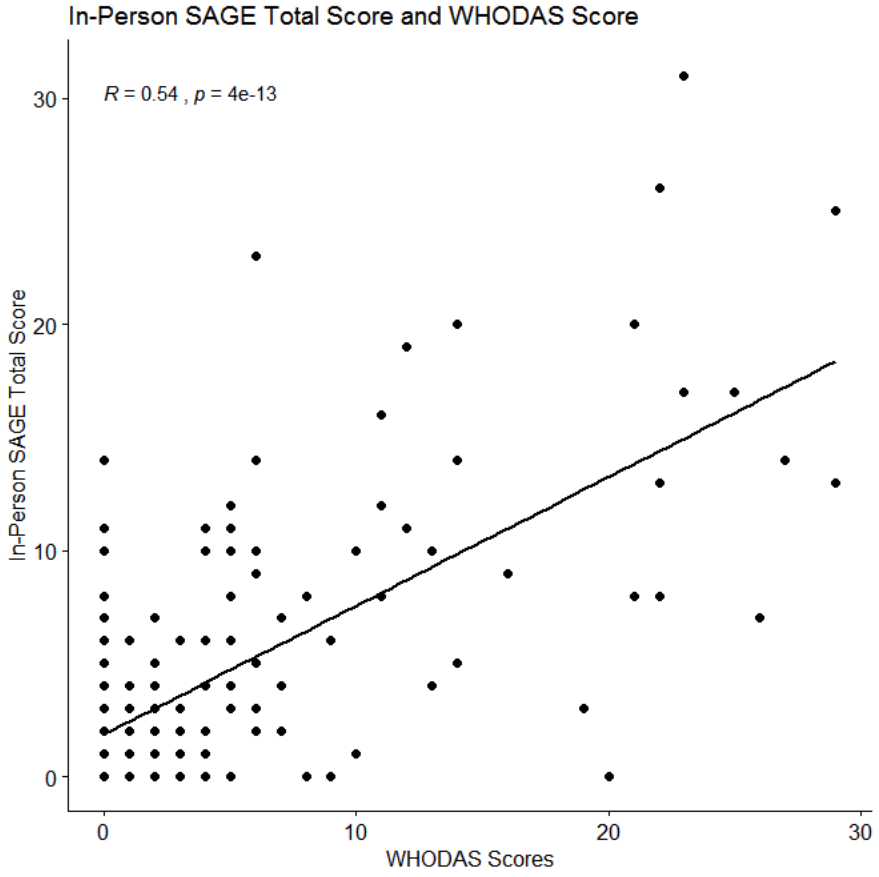
Appendix 7: Scatter plot of SAGE cognitive items and DSST score. SAGE: Standardized Assessment of Global activities in the Elderly. DSST: Digit Symbol Substitution Test.



Appendix 8: Scatter plot of SAGE mobility items with TUGT score. SAGE: Standardized Assessment of Global activities in the Elderly. TUGT: Timed Up and Go Test.



Appendix 9: Scatter plot of total SAGE scale score with WHODAS score. SAGE: Standardized Assessment of Global activities in the Elderly. WHODAS: World Health Organization Disability Assessment Scale.



Appendix 10: Relationship between SAGE cut-points and WHODAS >=12

Cut-point	AUC	95% Confidence intervals		Decision Criteria			
		Lower Limit	Upper Limit	Max Youden Index	D (0,1)	Sensitivity	Specificity
SAGE Score >=6	0.79	0.70	0.88	0.59	0.29	0.82	0.77
SAGE Score >=7	0.82	0.73	0.91	0.63	0.26	0.82	0.82
SAGE Score >=8	0.81	0.71	0.90	0.61	0.28	0.77	0.84
SAGE Score >=9	0.78	0.67	0.88	0.55	0.34	0.68	0.87
SAGE Score >=10	0.76	0.65	0.87	0.52	0.38	0.64	0.88
SAGE Score >=11	0.76	0.65	0.87	0.52	0.41	0.59	0.93
SAGE Score >=12	0.75	0.64	0.86	0.50	0.46	0.55	0.95

Abbreviations: SAGE: Standardized Assessment of Global activities in the Elderly; WHODAS: World Health Organization Disability Assessment Scale; AUC: Area under the curve

CHAPTER 4

Feasibility of studying the association between intraoperative regional cerebral oxygen saturation and postoperative functional decline (ReFUNCTION): A pilot sub-study of NeuroVISION-Cardiac Surgery (Accepted; Canadian Journal of Anesthesia)

Feasibility of studying the association between intraoperative regional cerebral oxygen saturation and postoperative functional decline (ReFUNCTION): A pilot sub-study of NeuroVISION-Cardiac Surgery

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Implication statement: We undertook a pilot study to determine the feasibility of conducting a large observational study examining the relationship between decreases in cerebral saturation during cardiac surgery and postoperative functional decline.

Abstract

Purpose: Function describes an individual's ability to perform everyday activities. In the context of cardiac surgery, functional changes quantify the effect of surgery on one's day-to-day life. Decreases in regional cerebral oxygen saturation (rScO2) measured using near infrared spectroscopy (NIRS) has been shown to be associated with postoperative cognitive decline but its relationship with function has not been studied. We sought to determine the feasibility of conducting a large observational study examining the relationship between decreases in rScO2 during cardiac surgery and postoperative functional decline.

Methods: We undertook a single centre, pilot sub-study of the NeuroVISION-Cardiac Surgery pilot study; all patients enrolled in NeuroVISION-Cardiac Surgery were included. Function was evaluated at baseline, 30-days, and 3-months using the Standardized Assessment of Global activities in the Elderly (SAGE) Scale. Blinded NIRS monitors were affixed for the duration of surgery. Our feasibility outcomes were to: recruit 1 patient per week, obtain complete NIRS data in ≥ 90%, obtain SAGE at all timepoints in ≥90%, and determine the time required for NIRS data collection.

Results: 49/50 patients enrolled in NeuroVISION-Cardiac Surgery were recruited over 48 weeks (1.02 patients/week). Of the 49 included patients, 49 (100%) had complete NIRS data and 44 (90%) had complete SAGE data. The time required for NIRS data collection was a mean (Standard Deviation) of 5.5 (1.8) minutes per patient.

Conclusion: This pilot study demonstrates the feasibility of conducting a large observational study examining the relationship between decreases in cerebral saturation during cardiac surgery and postoperative functional decline.

Background

More than 1 million patients around the world undergo cardiac surgery annually.[1,2] With longevity comes comorbidity and, in the context of an aging population, the number of people requiring cardiac surgical procedures is rising.[1,2] Improvements in intraoperative management and perioperative care have resulted in substantial decreases in perioperative morbidity and mortality.[3] However, postoperative cognitive impairment remains common and constitutes one of the most devastating and feared sequelae of cardiac surgery, particularly among the elderly population. Although cognitive decline is a patient-important outcome, the way it is currently measured – using psychometric tests – has limited meaning for non-experts. In addition, the relationship between change in cognitive test scores and daily function remains unknown.

Function is a multi-dimensional construct that describes an individual's ability to perform everyday activities and can be broken down into the following: (1) activities of daily living (ADL) (i.e. daily self-care activities, including bathing, dressing, and eating), (2) instrumental activities of daily living (IADL) (i.e., activities that are not necessary for basic function, but allow an individual to live independently in the community, including housework, managing finances, and shopping), and (3) applied cognition, upon which the other two functional dimensions are predicated. Functional ability is an indicator of overall health. In the context of surgical procedures, functional changes quantify the implications of having had a procedure on one's day-to-day life. Unfortunately, there is little known about mitigating functional decline after cardiac surgery, and no modifiable risk factors have been identified.

Near-infrared spectroscopy (NIRS) is a non-invasive technique that can be used to continuously monitor regional cerebral oxygen saturation (rScO2), which represents the balance between cerebral oxygen delivery and consumption.[4] In adult patients undergoing cardiac

surgery, regional cerebral oxygen desaturation measured using NIRS has been shown to be associated with postoperative cognitive decline (POCD),[5] although it has not been studied in relationship to functional decline.

It has been shown that anesthesiologists are able to reverse cerebral desaturations.[6] If a relationship between cerebral desaturation and functional decline was established, it would represent a modifiable risk factor that could be targeted for intervention. However, before this trial can be undertaken, a large observational study examining the relationship between decreases in intraoperative rScO2 and postoperative functional decline needs to be conducted. This study would also need to establish the optimal prognostically important rScO2 threshold associated with patient-important outcomes. The thresholds evaluated in the literature vary widely and are limited by small sample sizes.[5] It is unclear whether the optimal rScO2 target should be an absolute rScO2 value, a proportional decrease from baseline rScO2 value, or the duration of time below a given rScO2 value. To assess the feasibility of conducting a large observational study to determine the optimal prognostically important rScO2 threshold associated with postoperative cognitive and functional decline, we performed a pilot sub-study of NeuroVISION-Cardiac Surgery.

Methods

Study design: ReFUNCTION was a prospective, observational pilot sub-study of the NeuroVISION-Cardiac Surgery pilot study, whose objective was to establish the feasibility of conducting a large study to evaluate the incidence of covert stroke in adult patients undergoing coronary artery bypass grafting (CABG) and to evaluate the relationship between covert stroke and postoperative delirium and postoperative cognitive decline.

Patients: All participants in NeuroVISION-Cardiac Surgery were included in the ReFUNCTION pilot study. Patients were included in NeuroVISION-Cardiac Surgery if they were ≥21 years old, scheduled to undergo isolated CABG using a median sternotomy approach at the Hamilton General Hospital (HGH), Hamilton, Ontario, Canada, and had at least one of the following preoperative risk factors: cerebrovascular disease, peripheral vascular disease, renal insufficiency (eGFR <60mL/min/1.73m2), diabetes mellitus (on an oral hypoglycemic agent or insulin), urgent surgery (i.e., inpatient awaiting revascularization for acute coronary syndrome or myocardial infarction), recent (within the past year) smoker, or left ventricular ejection fraction <35%. Patients undergoing emergency or repeat surgery, in whom intraoperative circulatory arrest was planned, previously diagnosed dementia, or who had a contra-indication to MRI were excluded.

Recruitment: Research staff screened potential participants in surgeons' clinics, the preoperative assessment clinics (PAC), cardiac surgery ward, and cardiac care unit (CCU). They used a variety of approaches (e.g. screening the daily surgical list, review of patients in the preoperative holding area, cardiac surgical wards or CCU) to capture patients admitted through the emergency department and who did not attend the PAC. All NeuroVISION- Cardiac Surgery study patients were concurrently asked to provide informed consent for ReFUNCTION.

Outcomes: The ReFUNCTION pilot feasibility outcomes were as follows: 1. to recruit on average 1 patient per week, 2. to obtain in ≥90% of patients complete intraoperative NIRS data (i.e. a recording transcript that was within 15% of the duration of the surgical procedure), 3., to collect complete functional (Standardized Assessment of Global activities in the Elderly [SAGE] scale) outcome data at baseline, 30-days, and 3 months in ≥90% of patients, and 4. to collect data on the time required for the study research assistant to download and transcribe intraoperative data. These four objectives were selected both to ensure feasibility and to inform planning for the main trial. SAGE is a 15-item, composite measure of physical and cognitive functioning that was developed to measure functional decline in patients with vascular disease.[7] It measures all three functional domains (ADL, IADL, and cognition), is cross-culturally generalizable, and can be completed by a patient or their caregiver in person or over the phone, within 15 minutes.[7] Each item within the scale relates to one of the three functional domains, and can be evaluated alone, in combination with other items from the same functional domain, or as a composite measure of global function. Higher SAGE scores denote greater functional impairment. SAGE has previously been validated in the cerebrovascular disease population.[7] Our group is currently validating this measure in the cardiac surgery population within a sub-study of VISION-Cardiac Surgery.[8]

Study procedures: Table 1 provides an overview of the procedures involved in both the NeuroVISION-Cardiac Surgery and the ReFUNCTION pilot studies. The Montreal Cognitive Assessment (MoCA) and Digit Symbol Substitution (DSS) test were administered pre-operatively, at hospital discharge, and at the initial follow-up visit 4-6 weeks after surgery. SAGE was administered pre-operatively, at the initial follow-up visit 4-6 weeks after surgery, and by telephone follow-up at 3 months after surgery. Delirium was assessed daily until

discharge using the Confusion Assessment Method – Intensive Care Unit (CAM-ICU)[9,10] while patients were in the ICU and the 3D-Confusion Assessment Method (3D-CAM)[11] while patients were on the cardiac surgery ward. The research assistants who were responsible for cognitive and functional outcomes assessment were blinded to whether the patient had an intraoperative decrease in rScO2 or postoperative covert stroke detected on MRI.

Bilateral NIRS monitoring straps were affixed to patients' foreheads by a trained research assistant in the operating room before the start of anesthesia. The monitoring straps were connected to an InVOS 5100C (Medtronic, USA) NIRS monitor, whose screen was securely covered for the purposes of blinding. Baseline rScO2 was recorded before the start of anesthesia. Monitors were removed at the end of the cardiac surgical procedure before patients left the operating room.

Participants underwent a single magnetic resonance imaging (MRI) scan of the head with T1, T2 Flair, and diffusion weighted sequences between postoperative days 3-9. Scans were read at a core lab by a trained radiologist blinded to the clinical status of the patient.

Statistical Analysis: No formal sample size was calculated; we sought to study a convenience sample of 50 patients, which was the size of the NeuroVISION-Cardiac Surgery sub-study. Based on our stated objectives, we believed that 50 patients would be adequate to obtain the feasibility information required.

As this was pilot study designed to assess feasibility, we did not undertake hypothesis testing. Binary and categorical variables are reported as counts and proportions and continuous variables are reported as mean (standard deviation [SD]) or median (interquartile range [IQR]) as appropriate. We report results as the difference between estimates with a 95% confidence interval (CI). Baseline demographics and cognitive and functional test scores are presented

according to two thresholds that have been previously identified as clinically important: 1) a ≥20% decrease in intraoperative rScO2 from recorded baseline[6] and 2) any amount of time with an rScO2 below 50, including baseline rScO2.[12] We defined post-operative cognitive decline (POCD) as a postoperative MoCA score that was ≤2 points below the baseline MoCA score. We defined functional decline as the development of new 'mild' impairment in any two SAGE functional parameters or the development of new 'moderate' or 'severe' impairment in a single SAGE functional parameter.[7]

Results

Figure 1 provides an overview of the ReFUNCTION study flow. A total of 66 participants were enrolled from March/2017 – February/2018; of these 50 (76%) ultimately underwent an MRI scan and were included in NeuroVISION-Cardiac Surgery. One patient did not have intraoperative NIRS monitoring completed because the research assistant was not able to be present to apply the blinded NIRS monitor, resulting in 49/50 (98%) included in ReFUNCTION.

Table 2 presents baseline demographics, neurocognitive test scores, and functional test scores according to the presence of ≥20% decline from baseline rScO2 during surgery and the presence of any rScO2 value below 50. The mean (SD) age of all patients was 66.0 (9.4), 14.3% were female, and their mean (SD) Euroscore[13] was 4.8 (2.4). The mean (SD) MoCA and DSS scores at baseline were 24.1 (3.1) and 43.5 (14.0) respectively. The median (IQR) SAGE score at baseline was 2 (0-3). Patients who experienced an intraoperative decrease in rScO2 using either definition were more likely to be female, representing 26.1% of those who had intraoperative cerebral desaturation and 3.8% of those who did not have intraoperative cerebral desaturation. There was no difference in baseline cognitive and functional test scores between patients who had intraoperative cerebral desaturation and patients who did not have intraoperative cerebral desaturation, regardless of which definition was applied.

Table 3 describes the feasibility outcomes of the ReFUNCTION pilot study. 49 patients were recruited over 48 weeks, with an average recruitment rate of 1.02 patients per week. Of the 49 patients who were included in the study, 49 (100%) had a complete intraoperative NIRS transcript (i.e. a recording within 15% of the time in minutes between when the patient entered the operating room before surgery and left the operating room after surgery). Among all patients,

48/49 (98%) had a baseline SAGE scale (insufficient time before surgery to complete), 47/49 (96%) had a 30-day SAGE scale (1 patient where medical condition did not allow for assessment, 1 refusal for follow-up), and 46/49 (94%) had a 3-month SAGE scale (1 death, 2 refusals to follow-up). 44/49 (90%) of patients had a SAGE scale at each of these three timepoints. There was no difference in SAGE completion rates between the patients who had intraoperative rScO2 decline and those who did not have intraoperative decline using either definition. The mean (SD) amount of time in minutes required for the research assistant to transcribe the intraoperative NIRS transcript into the study case report forms (CRFs) was 5.5 (1.8) minutes.

Table 4 describes patients' neurocognitive and functional outcomes according to the two pre-established NIRS desaturation thresholds. There were no differences between groups (using either definition of rScO2 desaturation) in postoperative delirium, new lesions detected on MRI, neurocognitive test scores at discharge and 30-days, SAGE score at 30-days and 3-months, and POCD. Among all patients, the mean (SD) MoCA score at discharge and 30-days was 24.9 (3.6) and 26.2 (3.1) and the mean (SD) DSS at discharge and 30-days was 46.4 (16.3) and 57.3 (15.4). The median (IQR) SAGE score at 30-days was 0 (0-2) and at 3-months was 0 (0-1). Overall, 9 (21%) of patients had POCD at discharge and 3 (7.9%) of patients had POCD at 30-days. The overall incidence of functional decline was 26% at 30-days and 26% at 3 months. There was no difference in the incidence of functional decline between patients who did or did not have a decrease in rScO2 that was greater or equal to 20% of their baseline value. Patients who had any rScO2 value below 50 were more likely to have functional decline at 30-days when compared to those in whom all values were 50 or greater, with an incidence of 39% (9/22) compared to 12% (3/25). This difference was no longer present at 3 months.

Discussion

The ReFUNCTION pilot study demonstrates the feasibility of conducting a large, observational study to establish the relationship between intraoperative decreases in cerebral oxygen saturation and postoperative function. We were able to recruit a minimum of one patient per week, which satisfies our pre-established feasibility threshold. The ReFUNCTION pilot was a sub-study of NeuroVISION-Cardiac Surgery pilot. For this reason, recruitment was limited by local MRI scan capacity, which is restricted to one scan for research purposes per week. If, in planning for the main trial, it becomes apparent that this recruitment rate is not acceptable, we may consider conducting ReFUNCTION as an independent study. However, given the similar objectives of ReFUNCTION and NeuroVISION-Cardiac Surgery, in addition to the improved efficiency and decreased costs from pairing research questions, we believe that addressing these two research questions within the same study represents the optimal approach.

We were able to obtain complete intraoperative NIRS transcripts in 100% of patients, which demonstrates the feasibility of collecting complete data pertaining to our exposure variable of interest. The mean time required to download and enter transcript data into the study CRFs was 5.5 minutes, which demonstrates that there will be minimal research assistant time required to complete this aspect of the study.

Finally, we were able to obtain complete SAGE scale data in 90% of patients, including measurements at baseline, 30-days, and 3 months after cardiac surgery. Complete collection of SAGE scales is of key importance, as SAGE score represents the primary outcome of our main trial. Previous research has found that patients with lower cognitive status are more likely to be lost to follow-up, resulting in potential attrition bias.[14,15] We believe the following features of the SAGE scale will help to minimize potential attrition bias in the full trial: it can be administered

in person or over the phone, does not require specialty training to administer, is available in more than 15 languages, and can be completed by patients or their surrogates in under fifteen minutes. The results of our pilot study support this belief.

Postoperative cognitive impairment – as defined by decreases in cognitive test scores – is a recognized entity, affecting 3-79% of patients after cardiac surgery.[16] However, how these decreases in cognitive test scores affect patient's functional ability (i.e. applied cognition) may be of greater importance to patients. Functional decline may affect 16-36%[17,18] of patients after cardiac surgery, although its true incidence is unclear. Published evidence pertaining to function after cardiac surgery has been limited by small sample sizes, varying definitions of functional decline, and differences in the duration between cardiac surgery and functional assessment. The largest prospective study evaluating postoperative function of cardiac surgery patients administered the Katz ADL Index 3 months after surgery in a cohort of 475 patients ≥65 years of age.[17] They found that 16% of all patients and 20% of those ≥70 years suffered functional decline. This study was used to validate a predictive measure of postoperative decline but did not examine any other predictors. In a study of 190 patients undergoing cardiac surgery, Rudolph et al. found that postoperative delirium was associated with functional decline at 1 but not 12 months postoperatively.[18] No studies have systematically evaluated short and long-term functional change in a large cohort of consecutive cardiac surgery patients, nor have individual patient predictors been identified. Our group is currently determining the true incidence and predictors of functional decline through a large, prospective cohort study of patients undergoing cardiac surgery.[8] Once these are established, interventions to mitigate perioperative functional decline need to be evaluated.

A potential intervention to mitigate postoperative functional decline in patients undergoing cardiac surgery is intraoperative management guided by cerebral oximetry. Limited research has linked the prevention of intraoperative cerebral desaturation – as measured using cerebral oximetry – to benefits in other patient-important perioperative outcomes.[5] A recent meta-analysis of 15 randomized controlled trials (RCTs) that included 2057 patients found that anesthesia guided by intraoperative cerebral oximetry was associated with a reduction in the incidence of POCD (relative risk 0.54; 95% confidence interval [CI], 0.33 to 0.90; P = 0.02; I_2 = 85%) compared to standard care.[5] Additional outcomes including postoperative delirium, perioperative myocardial infarction, and surgical site infection were examined but did not have a statistically significant relationship with management guided by cerebral oximetry. The authors of this meta-analysis expressed a belief that all results were underpowered, and advocated for a large study evaluating the impact of intraoperative management guided by cerebral oximetry on patient-important outcomes.[5] We agree with the authors and believe that one of the primary outcomes of such a large trial should be postoperative functional decline. Before conducting such a trial, a larger observational study is required to (i) firmly establish the relationship between intraoperative decreases in rScO2 and (ii) determine the optimal rScO2 value that has a prognostically important relationship with postoperative patient-important outcomes, including functional decline. In the ReFUNCTION pilot, we have established the feasibility of conducting this large observational study.

Our pilot study has several strengths. To our knowledge, it is the only study that has evaluated the relationship of intraoperative decreases in rScO2 with postoperative functional ability. Even though the work described here is focused on establishing feasibility, by doing so it provides the foundation for future work examining this poorly understood but highly patient-

important outcome. We were able to obtain blinded intraoperative NIRS transcripts in all patients and blinded outcomes data including postoperative MRI, cognitive testing, and functional assessment using SAGE. Our pilot study has several limitations, including a small sample size drawn from a single centre. However, given that this primary objective of this pilot study was to establish the feasibility of the main study protocol, we believe that the information that we have obtained is adequate to meet our objectives.

Conclusions:

Postoperative functional ability is a poorly understood but patient-important outcome. In this pilot study, we established the feasibility of conducting a large observational trial examining the relationship between intraoperative decreases in cerebral oxygen saturation with postoperative functional decline, with the objective to identify a prognostically important threshold for intervention.

Contributions:
JS: Responsible for study conception and design, acquisition of data, analysis and interpretation of data, and drafting of final manuscript.
AL: Responsible for study conception and design, acquisition of data, analysis and interpretation of data, and drafting of final manuscript.
JB: Responsible for study conception and design, analysis and interpretation of data, and drafting of final manuscript.
LT: Responsible for analysis and interpretation of data and drafting of final manuscript.
SG: Responsible for analysis and interpretation of data and drafting of final manuscript.
PP: Responsible for acquisition of data and drafting of final manuscript.
AB: Responsible for analysis and interpretation of data and drafting of final manuscript.
JM: Responsible for analysis and interpretation of data and drafting of final manuscript.
PJD: Responsible for study conception and design, analysis and interpretation of data, and drafting of final manuscript.

All authors have reviewed and approved of the final manuscript submitted for publication and agree to be accountable for all aspects of the work.

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Table 1: Study procedures for NeuroVISION-Cardiac Surgery and ReFUNCTION pilot studies

Time period	Screening	Baseline	Operating Room (OR)	Post-op	Hospital discharge	Clinic visit (4-6 weeks)	Telephone (3 months)
Eligibility	X						
Informed Consent	X						
Medical History		X					
Demographics		X					
Medications		X					
Euroscore		X					
Operative Details			X				
MRI head				X			
CAM-ICU				X (while in ICU)			
3D-CAM				X (while on ward)			
MoCA		X			X	X	
DSS		X			X	X	
SAGE		X				X	X
Events				X	X	X	X
Intraoperative cerebral oxygenation*			X				

Abbreviations: Euroscore: European System for Cardiac Operative Risk Evaluation; MRI: Magnetic Resonance Image; CAM-ICU: Confusion Assessment Method – Intensive Care Unit; ICU: Intensive Care Unit; 3D-CAM: 3D Confusion Assessment Method; MoCA: Montreal Cognitive Assessment; DSS: Digit Symbol Substitution Test; SAGE: Standardized Assessment of Global activities in the Elderly

*Study procedures unique to the ReFUNCTION pilot study

Table 2: Baseline demographics, neurocognitive test scores, and functional test scores
Abbreviations: NIRS: Near-infrared spectroscopy; CI: Confidence Interval; SD: Standard

	Patients with ≥20% decline in NIRS (n=23)	Patients without ≥20% decline in NIRS (n=26)	Difference in estimates (95% CI)	Patients with any NIRS value <50% (n=23)	Patients with no NIRS values <50% (n=26)	Difference in estimates (95% CI)
Age (years) – mean (SD)	64.7 (9.9)	67.1 (9.3)	2.4 (-3.1, 7.9)	65.7 (9.4)	66.2 (9.9)	0.5 (-5.1, 6.1)
Female sex – n (%)	6 (26)	1 (3.8)	22% (3, 42)	6 (26)	1 (3.8)	22% (3, 42)
Euroscore - Mean (SD)	4.4 (2.5)	5.1 (2.2)	0.7 (-0.7, 2.1)	5.2 (2.3)	4.2 (2.4)	-1.0 (-2.4, 0.4)
MoCA baseline – Mean (SD)	24.9 (3.3) (n=22)	23.5 (2.8) (n=24)	-1.4 (-3.2, 0.4)	24.8 (3.9) (n=21)	23.7 (2.2) (n=26)	-1.1 (-7.2, 5.0)
DSS baseline – Mean (SD)	45.6 (14.8) (n=22)	41.3 (12.7) (n=25)	-4.3 (-12.4, 3.8)	42.0 (13.7) (n=21)	44.4 (13.3) (n=26)	2.4 (-5.6, 10.4)
SAGE* baseline – Median (IQR)	1 (0-3) (n=22)	2 (0-3) (n=25)	1 (-1.4, 1.8)	1 (0-3) (n=22)	2 (0-3) (n=25)	1 (-1.4, 1.6)

Deviation; Euroscore: European System for Cardiac Operative Risk Evaluation; MoCA: Montreal Cognitive Assessment; DSS: Digit Symbol Substitution Test; SAGE: Standardized Assessment of Global activities in the Elderly; IQR: Interquartile Range
*Higher SAGE scores correspond to greater functional impairment.

Table 3: Feasibility outcomes of the ReFUNCTION pilot study

	All patients (n=49)	Feasibility criterion
Recruitment rate	1 / week	1 / week
Complete NIRS transcript – n (%)	49 (100)	44 (90)
Baseline SAGE completed – n (%)	48 (98)	-
30-day SAGE completed – n (%)	47 (96)	-
3-month SAGE completed – n (%)	46 (94)	-
Complete collection of baseline, 30-day, and 3 month SAGE scales – n (%)	44 (90)	44 (90)
Time to transcribe data (minutes) – Mean (SD)	5.5 (1.8)	-

Abbreviations: SAGE: Standardized Assessment of Global activities in the Elderly; SD: Standard Deviation

Table 4: Neurocognitive and functional outcomes by intraoperative decline in NIRS

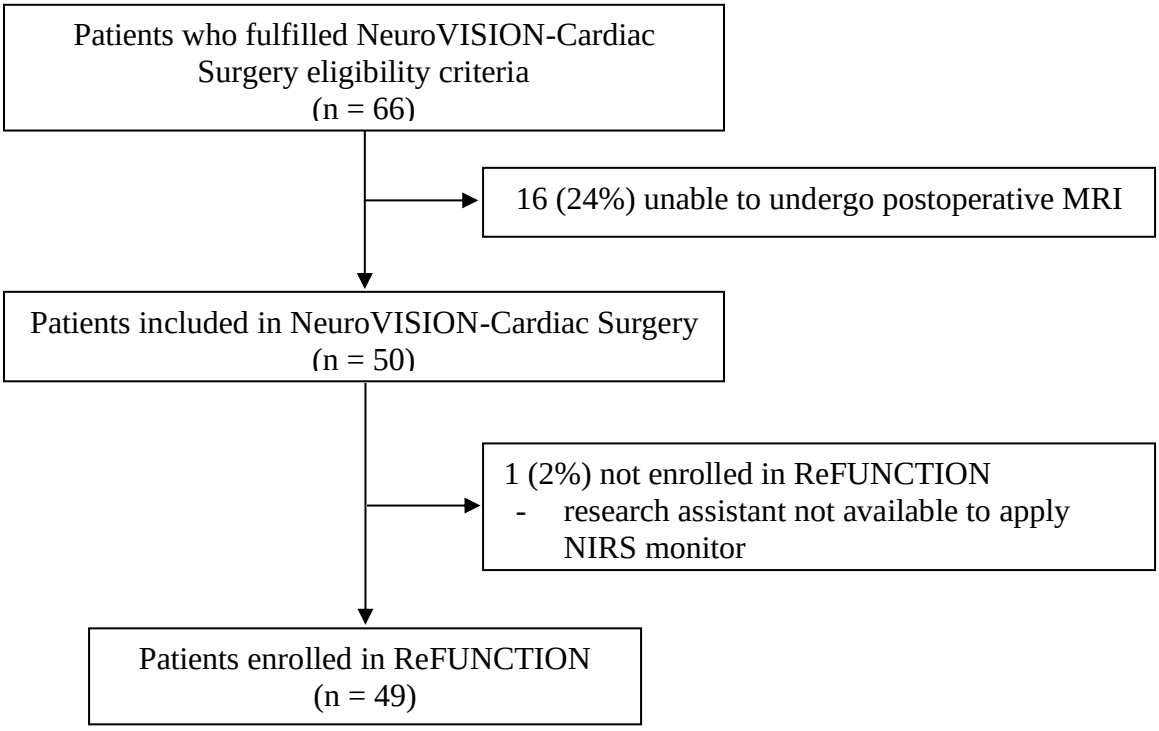
	Patients with ≥20% decline in NIRS (n=23)	Patients without ≥20% decline in NIRS (n=26)	Difference in estimates (95% CI)	Patients with any NIRS value <50% (n=23)	Patients with no NIRS values <50% (n=26)	Difference in estimates (95% CI)
CAM+ delirium	6 (26)	5 (19)	7% (-17, 30)	6 (26)	5 (19)	7% (-17%, 30%)
New lesions on MRI	10 (44)	9 (35)	9% (-19, 36)	10 (44)	9 (35)	9% (-19, 36)
MoCA discharge – mean (SD)	25.7 (3.7) n=20	24.2 (3.5) n=23	1.5 (-0.7, 3.7)	25.2 (4.0) n=19	24.7 (3.4) n=24	0.5 (-1.8, 2.8)
MoCA 30-days – mean (SD)	27.2 (1.9) n=17	25.4 (3.5) n=22	1.8 (0.1, 3.5)	27.2 (1.9) n=17	25.4 (3.5) n=22	1.8 (0.1, 3.5)
>=2-point decline in MoCA at discharge – n (%)	4 (25) n=20	5 (23) n=22	2% (-28, 22)	5 (26) n=19	4 (17) n=23	9% (-16, 34)
>=2-point decline in MoCA at 30 days – n (%)	2 (12) n=17	1 (5) n=21	7% (-11, 25)	2 (12) n=17	1 (5) n=21	7% (-11, 25)
DSS discharge – mean (SD)	50.5 (16.3) n=20	42.9 (14.6) n=23	7.6 (-1.7, 16.9)	45.3 (17.3) n=19	47.3 (14.6) n=24	-2.0 (-11.7, 7.7)
DSS 30 days – mean (SD)	62.8 (15.0) n=17	53.0 (14.6) n=22	9.8 (0.4, 19.2)	58.9 (16.6) n=17	56.0 (14.6) n=22	2.9 (-7.1, 12.9)
SAGE* 30 days – median (IQR)	0 (0-1) n=23	0 (0-2) n=24	0 (-1.4, 2.9)	0 (0-4) n=22	0 (0-1) n=25	0 (-3.3, 1.0)
SAGE* 3 months – median (IQR)	0 (0-1) n=23	0 (0-1) n=23	0 (-1.4, 2.9)	0 (0-2) n=21	0 (0-2) n=25	0 (-2.1, 2.1)
Functional decline at 30 days** – n (%)	6 (26) n=23	6 (25) n=24	1% (-24, 26)	9 (39) n=22	3 (12) n=25	27% (5, 53)
Functional decline at 3 months** – n (%)	7 (30) n=23	5 (22) n=23	8% (-17, 34)	7 (30) n=21	5 (20) n=25	10% (-12, 39)

Abbreviations: NIRS: Near infrared spectroscopy; CI: Confidence interval; CAM+: Confusion Assessment Method positive; MRI: Magnetic resonance imaging; SD: Standard deviation; MoCA: Montreal Cognitive Assessment; DSS: Digit symbol substitution test; SAGE: Standardized Assessment of Global activities in the Elderly

*Greater SAGE scores correspond to greater functional impairment

**Functional decline was defined as 'mild' impairment on any two single SAGE parameters or 'moderate' or 'severe' impairment on any one SAGE parameter that was not present at baseline (prior to surgery).

Figure 1: ReFUNCTION study flow diagram



CHAPTER 5

Restricted versus liberal benzodiazepine cardiac anaesthesia for reducing delirium (B-Free Pilot): A pilot, multi-centre, randomised, cluster crossover trial (Accepted; British Journal of Anaesthesia)

Restricted versus liberal benzodiazepine cardiac anaesthesia for reducing delirium (B-Free Pilot): A pilot, multi-centre, randomised, cluster crossover trial

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Background: Delirium is common after cardiac surgery and associated with adverse outcomes. Perioperative benzodiazepines are associated with delirium. Benzodiazepine use is common during cardiac surgery, which may increase the risk of postoperative delirium. We undertook a pilot study to inform the feasibility of a large, randomised cluster crossover trial examining whether an institutional policy of restricted benzodiazepine administration during cardiac surgery (compared to liberal administration) would reduce delirium.

Methods: We conducted a two-centre, pilot, randomised cluster crossover trial with four, four-week crossover periods. Each centre was randomised to a policy of restricted or liberal use and then alternated between the two policies during the remaining three periods. Our feasibility outcomes were: adherence to each policy (goal ≥80%) and outcome assessment (one delirium assessment per day in the ICU in ≥90% of participants). We also evaluated the incidence of intraoperative awareness in one site using serial Brice questionnaires.

Results: 800 patients underwent cardiac surgery during the trial period; 127/800 (15.9%) had delirium. 355/389 (91.3%) received benzodiazepines during the liberal benzodiazepine periods and 363/411 (88.3%) did not receive benzodiazepines during the restricted benzodiazepine periods. Among the 800 patients, 740 (92.5%) had ≥1 postoperative delirium assessment per day in the ICU. Of 521 patients screened for intraoperative awareness 1 patient (0.2%) - managed during the restricted benzodiazepine period (but received benzodiazepine) - had intraoperative awareness.

Conclusions: This pilot demonstrates the feasibility of a large, multi-centre, randomised, cluster crossover trial examining whether an institutional policy of restricted versus liberal benzodiazepine use during cardiac surgery will reduce postoperative delirium.

Keywords: Benzodiazepines, Delirium, Cardiac Anaesthesia, Pilot Study, Randomised Cluster Crossover, Pragmatic

Introduction

Delirium affects 15-25% of adults after cardiac surgery[1,2] and is associated with prolonged length of stay,[3] hospital readmission,[3] long-term cognitive[4] and functional decline,[3,4] and death.[5] Observational studies have suggested an association between perioperative benzodiazepine administration and delirium in both cardiac[6] and noncardiac surgery populations,[7,8] as well as in mechanically ventilated patients in the intensive care unit (ICU).[9] A recent meta-analysis of randomised controlled trials (RCTs) comparing benzodiazepines to dexmedetomidine for intensive care unit sedation demonstrated a trend towards increased delirium with benzodiazepine sedation, with a relative risk (RR) of 1.23 (95% Confidence Interval [CI] 0.93-1.67). Despite not being statistically significant, this result was judged by the Society for Critical Care Medicine (SCCM) to be underpowered[10] and clinically important enough to influence guideline recommendations.

As a result, guidelines from the SCCM[10] and the American Geriatric Society[11] recommend minimizing the use of benzodiazepines in the critically ill and older adult populations; however, the intraoperative administration of benzodiazepines during cardiac surgery remains common.[12] This use is likely secondary to their favourable hemodynamic profile and amnestic properties that are thought to prevent intraoperative awareness. No RCT evidence is available pertaining to the effects of intraoperative benzodiazepine administration. There are two general approaches to intraoperative benzodiazepine administration in current cardiac anaesthesia practice: one which rarely includes benzodiazepines and one which rarely does not include benzodiazepines.[12] There is a need for a trial to evaluate whether broadly implementing an approach to cardiac anaesthesia that rarely includes intraoperative benzodiazepines reduces the incidence of postoperative delirium in adults after cardiac surgery.

In order to reduce complications and increase efficiency, cardiac surgery is performed in specialized high-volume institutions and is based in large part on the use of institutional standardized procedures, such as preoperative assessment and pre-and postoperative care pathways.[13] Because cardiac care is organized through standard institutional policies, such policies can facilitate evaluating the impact of restricted versus liberal intraoperative use of benzodiazepine. Testing the effects of different institutional policies also facilitates a pragmatic trial design, with randomisation of institutions rather than patients, such that the treatment is tested in the setting where it will be used. Thus, we designed a pragmatic randomised cluster crossover trial to test whether an institutional policy of restricted use of benzodiazepines during surgery (compared to liberal use) reduces post-operative delirium.

To assess the feasibility of this trial we performed a pilot study (i.e., the B-Free Pilot). Our feasibility objectives included assessing the degree of physician adherence to each institutional policy to which the hospital was randomised, and then to the alternate policy to which the hospital crossed over. We also wanted to determine whether measurement of delirium could be achieved using data collected as a part of routine clinical care. Our final goal was to determine the incidence of intraoperative awareness during the restricted benzodiazepine periods.

Methods

Study Design

This pilot study was a cluster crossover trial conducted at two sites with 4 four-week crossover periods (Figure 1). An independent statistician created a computer-generated randomisation sequence. Each site was randomised to either the restricted or liberal intraoperative benzodiazepine policy and then alternated between policies during the remaining three periods. Sites were notified of their initial allocation one week prior to the start of the study.

Study setting and participants

Two Canadian sites participated in the B-Free Pilot. These sites were the Hamilton General Hospital (HGH) in Hamilton, Ontario, Canada, which provides cardiac surgical care to approximately 1700 patients annually and the St. Boniface General Hospital (SBGH) in Winnipeg, Manitoba, Canada, which provides cardiac surgical care to approximately 800 patients annually. Before starting the pilot, it was ensured that all practitioners within each group had clinical equipoise and believed that they could provide cardiac anaesthesia using either policy (*i.e.*, restricted or liberal intraoperative benzodiazepine). In doing so, we held meetings with each group of cardiac anaesthesiologists, where the rationale for the study and details of the protocol were discussed. Individual anaesthesiologists had the opportunity to ask questions of investigators and to discuss concerns regarding study implementation. Thereafter, in a separate meeting not attended by study investigators, each cardiac anaesthesiology group reviewed the trial protocol and made a group decision to participate.

Prior to the start of the trial at each site, we provided information in the form of rounds presentations and emails summarizing the trial protocol to cardiac surgeons and intensivists

practicing in the cardiac surgical ICU. While there was no formal consensus process, investigators at each site spoke personally with members of these stakeholder groups to confirm their support of the trial.

With the exception of intraoperative benzodiazepine administration – which was standardized according to crossover period – all perioperative care of patients undergoing cardiac surgery during the pilot study took place according to standard operating procedures at each site, with no prompts from the study team.

The B-Free Pilot, (clinicaltrials.gov NCT03053869), was undertaken between April 3 to July 21, 2017 at the HGH and from September 18, 2017 to January 7, 2018 at SBGH. All adult patients who underwent cardiac surgery at each site when the study was being conducted were included in the analysis for the period to which the hospital was assigned (*i.e.*, restricted or liberal intraoperative benzodiazepine), regardless of their actual treatment. Patients who underwent more than one procedure during the trial were evaluated for their first procedure only.

Patients were provided with a letter before surgery stating that administrative data were being collected as part of an institutional practice evaluation and would be stored anonymously in a database. The letter also contained contact information for research staff, whom they could contact if they wished to withdraw their individual data from the trial. Before starting the trial, we obtained institutional ethics board approval at both sites.

Policies being evaluated: We compared two hospital policies for intraoperative benzodiazepine administration during cardiac anaesthesia. The *restricted benzodiazepine use policy* consisted of no administration of intraoperative benzodiazepines. The *liberal benzodiazepine use policy* consisted of routine administration of intraoperative benzodiazepine. The protocol explicitly allowed exceptions to both policies if there was a strong clinical indication for doing so.

Recognized reasons for an exception to the *restricted benzodiazepine use policy* included alcohol withdrawal or benzodiazepine dependence. Recognized reasons for an exception to the *liberal benzodiazepine use policy* included previous adverse reactions to these medications. We anticipated that exceptions to either policy would not occur in more than 20% of patients. We did not specify pre- and post-operative benzodiazepine use but collected these data.

The pilot feasibility objectives were as follows: 1. we aimed to demonstrate that ≥80% of patient care would comply with the assigned benzodiazepine administration policy (which was the threshold determined by both cardiac anaesthesia groups to be the minimum proportion of patients who could be managed using either policy, taking into account estimates of the proportion of patients who would require benzodiazepines and for whom benzodiazepines would be clearly contraindicated); 2. we sought to show that at least 95% of patients would have at least one delirium assessment completed in the ICU and that at least 90% of patients would have daily delirium assessments while admitted to the ICU during the study period; and 3. we sought to demonstrate an incidence of intraoperative awareness of no more than 2% (which represents the upper 95% confidence interval of the pooled incidence of awareness in cardiac surgery patients reported in the literature) during the restricted benzodiazepine period.[14-16] We selected our feasibility threshold for the frequency of delirium assessment because many cardiac surgery patients may have delirium assessed only once per day (despite institutional guidelines mandating assessment every 12 hours). This stems from a required level of consciousness ≥ - 3 on the Richmond Agitation and Sedation Scale (RASS) to administer the CAM-ICU and the fact that many patients remain in the cardiac surgical ICU for less than 24 hours postoperatively. We also evaluated the primary and secondary outcomes of the full trial: the incidence of delirium in the cardiac surgical ICU, ICU length-of-stay (LOS), hospital LOS, and in-hospital mortality.

Delirium assessment: Delirium was assessed in both sites using the Confusion Assessment Method – Intensive Care Unit (CAM-ICU)[17] as part of routine practice by nurses in the cardiac surgical ICU. Assessments were conducted at least once every twelve hours (i.e. per nursing shift) and with any changes in acuity or mental status.

Blinding: Given the pragmatic nature of our study, which was incorporated into routine clinical care, we elected not to blind cardiac anaesthesiologists to crossover period. Similarly, we did not blind the cardiac surgical ICU nurses who were assessing delirium, as they needed to be able to access all relevant clinical documentation (including anesthetic records) for patient care. However, we neither informed them that we were conducting a study of intraoperative benzodiazepine administration nor did we communicate the crossover period allocation.

Study data collection: Study personnel extracted intraoperative drug administration from patient charts. All other data were obtained from patients' electronic medical records in Hamilton and from a clinical registry in Winnipeg. We assessed for intraoperative awareness at one site (HGH) by individual patient interview using serial administration of the Brice questionnaire,[18] (see eSupplement 1: Procedure for Assessment of Intraoperative Awareness).

Sample size**:** We sought to demonstrate our ability to successfully implement and crossover between the two benzodiazepine policies, as well as demonstrate an acceptable difference in benzodiazepine use between study arms. As such, we decided to implement the trial for four, 4-week crossover periods, which would require practitioners to crossover three times between four treatment periods (such that each institutional policy would be used twice at each site).

Statistical analyses: For crude comparisons of the demographic characteristics of the pilot population at each site and across policies, we compared proportions using Pearson's Chi-square test or Fisher's exact test and continuous variables using 2-sample t-test or Wilcoxon rank-sum

test as appropriate. We evaluated the feasibility outcomes of this pilot study using descriptive statistics.

Results

During the study periods, 800 patients (540 at HGH, 260 at SBGH) underwent cardiac surgery in the 2 centres, 411 during the restricted benzodiazepine periods and 389 during the liberal benzodiazepine periods. No patient requested to withdraw their data from the study; we included all patients in our analyses. Table 1 describes the patient demographics, surgical characteristics, and perioperative benzodiazepine and intraoperative opioid administration by intervention arm. There were no differences between arms in terms of patient age, sex, urgency of procedure, or type of procedure. Among all participants the mean age was 67.0 years and 77.4% were male. The majority of patients (61.5%) underwent elective cardiac surgical procedures; 30.0% underwent urgent cardiac surgical procedures (*i.e.* those that were performed while the patient was admitted to hospital as an inpatient), and 8.5% underwent emergent cardiac surgical procedures (*i.e.* those that were required within ≤8 hours). The most common procedure performed was isolated CABG (57.4%), followed by cardiac surgery that included two procedures (*e.g.* CABG and single valve replacement; 21.5%), single, non-CABG procedures (*e.g.* single valve replacement; 16.6%), and three procedures (*e.g.* double valve replacement and CABG; 4.3%). Only 2 patients (0.3%) underwent cardiac surgery that involved more than 3 procedures.

There were no differences between arms with respect to pre- and postoperative benzodiazepine administration, with 12.6% of patients receiving benzodiazepines before cardiac surgery and 11.6% of patients receiving benzodiazepines after cardiac surgery. Consistent with each policy, 11.7% of patients received intraoperative benzodiazepines during the restricted benzodiazepine periods and 91.3% of patients received intraoperative benzodiazepines during the liberal benzodiazepine periods. We did not document reasons that each policy was not

applied but did informally discuss this with clinical anaesthesia staff. These anecdotal discussions suggested that predictors of patients receiving benzodiazepines during restricted periods included patient history of alcohol/drug use and hemodynamic instability/emergency case status and that predictors of patients not receiving benzodiazepines during liberal periods included extreme old age/frailty and history of adverse reaction to benzodiazepines.

When intraoperative benzodiazepines were given, midazolam was used in the majority of cases. The mean (standard deviation [SD]), dose of midazolam was 5.1 (3.4) mg when midazolam was administered, although 117/389 (30.1) of patients who received midazolam in the liberal periods received a dose that equal to or less than 2 mg. There was no difference between the restricted and liberal benzodiazepine periods with respect to the total dose of opioid in fentanyl equivalents, with a median (IQR) dose of 1300 (870.0 - 2000) mcg given during the restricted benzodiazepine periods and a mean (SD) dose of 1250 (760.0 - 2000) mcg given during the liberal benzodiazepine periods, p=0.848. eSupplement 2 presents the patient demographics, surgical characteristics, and delirium scale completion organized by site.

Figure 1 provides an overview of the pilot study flow and protocol adherence. Table 2 describes the primary feasibility and main trial outcomes by intervention arm. There was a statistically significant higher rate of adherence during the liberal benzodiazepine periods (p = 0.04), with 365 of 411 patients (88.8%) who underwent surgery during the restricted benzodiazepine periods managed according to the assigned policy, and 362 of 389 patients (93.1%) who underwent surgery during liberal benzodiazepine periods managed according the assigned policy (Figure 1 and Table 2). There was no difference in delirium scale completion between intervention arms. Overall, a minimum of one nurse-administered delirium scale was collected for 770 of the participants (96.3%) during their ICU admission and 740 participants

(92.5%) had at least one nurse-administered delirium scale measurement per 24h in the ICU. The frequency of delirium scale completion did not differ significantly between sites (see eSupplement 1).

At one site (HGH), we evaluated 521 of 540 enrolled patients (96.5%) for intraoperative awareness, 263 of 274 participants (96.0%) during the restricted benzodiazepine periods and 258 of 266 participants (97.0%) during the liberal benzodiazepine periods. The remaining patients were not screened because of intraoperative death, transfer to another hospital or death before extubation, or communication barrier. Four possible cases of awareness were flagged and forwarded for adjudication, two during the restricted benzodiazepine periods and two during the liberal benzodiazepine periods. Of these four cases, one of 521 participants (0.2%), who was managed during a restricted benzodiazepine period, was adjudicated as having intraoperative awareness. Despite being managed during a 'restricted benzodiazepine' period this patient received an intraoperative benzodiazepine.

There were no differences between intervention arms with respect to the clinical outcomes, including delirium in the cardiovascular ICU, ICU LOS, hospital LOS, and in-hospital mortality. The overall incidence of delirium of 15.9%, with 17.5% of patients experiencing delirium during the restricted benzodiazepine periods and 14.1% of patients experiencing delirium during the liberal benzodiazepine periods ($p = 0.19$; relative risk increase [95% CI] 24.1% [-21.1%, 27.1%]). The median (IQR) ICU LOS was 24 (24-72) hours and the median (IQR) hospital LOS was 7 (5-11) days. The overall incidence of in-hospital mortality was 1.1%.

Discussion

The B-Free pilot trial demonstrates the feasibility of a large cluster crossover trial evaluating restricted versus liberal intraoperative benzodiazepine strategies in patients undergoing cardiac surgery. Our results demonstrate these two approaches to care can be implemented using a cluster crossover design, with both policies applied by anaesthesiologists to more than 85% of patients during each treatment period. The high adherence rate to both policies by individual practitioners demonstrates the clinical acceptability of both approaches by credentialed physicians, further supporting the equipoise in practice and the feasibility of a large trial.

Delirium can be assessed in adequate numbers using delirium scales that are administered and documented by nurses caring for patients after cardiac surgery. By ensuring that we are able to collect the outcomes of our main trial in a high proportion of patients using nurse-administered delirium scales, the pilot trial minimizes concerns about incomplete outcome ascertainment based on the use of administrative data in the main trial. Obtaining the trial outcomes using administrative data in the main trial will improve trial efficiency. The pragmatic approach to the implementation of the two benzodiazepine policies and data collection will enhance the external validity of the main trial, as the 2 policies will be evaluated in everyday clinical practice.

Finally, we showed that intraoperative awareness is rare. In doing so, we used a conventionally recognized approach to assessing awareness, including serial administration of the Brice questionnaire and blinded adjudication. Even though we were not powered to definitively establish the absence of a relationship between benzodiazepine administration and prevention of intraoperative awareness, the fact that only one patient (randomised to the

restricted benzodiazepine period who actually received a benzodiazepine) experienced intraoperative awareness is reassuring. We believe this finding, in association with the lack of published evidence supporting benzodiazepines as a means of intraoperative awareness prevention, justifies not formally assessing for awareness as part of the full trial.

The perioperative care of cardiac surgery patients is highly protocolized based on evidence supporting best practice. This includes pre- and postoperative care pathways, intraoperative management strategies, and standardized quality metrics, including the incidence of postoperative delirium. These types of standardized operating procedures (SOPs) are common within perioperative and anaesthesia practice.[13,19] This is because patient care driven by SOPs have previously demonstrated improvement in individual patient and system outcomes,[20-22] as reflected in the recently published cardiac Enhanced Recovery After Surgery (ERAS) guidelines.[13] The cardiac surgery ERAS guidelines for best practice provide 22 recommendations for approaches to care before, during, and after cardiac surgery. Of note, the ERAS guidelines do not provide a recommendation either for or against the use of benzodiazepines, which reflects the lack of supporting evidence. Both restricted and liberal approaches to benzodiazepine administration are routinely used in clinical practice,[12] though the approach selected probably has more to do with practitioner preference than patient characteristics. As perioperative cardiac surgical care is typically standardized using centre-level SOPs, we have chosen to evaluate the impact of standardizing intraoperative benzodiazepine administration using two alternate institutional policies.

Our pilot trial has several limitations and generates a number of learning points that have informed the design of the main trial. Though we included a large number of patients from two centres, studying two centres does not mean that we will not encounter issues with adherence and

outcome data collection in other sites, as part of the main trial. Thus, we have decided that we will only include sites in the trial that have had a formal meeting of their cardiac anaesthesia providers where the trial and policies are fully explained and discussed amongst the group. After the meeting, cardiac anaesthesia groups will discuss amongst themselves, and will only be included in the trial if 95% of providers commit to following both policies. We are confident that this, in combination with the communication strategies refined during our pilot trial, will ensure high adherence during the main trial.

In keeping with our pragmatic approach, we did not control for pre- or postoperative benzodiazepine administration, nor did we stipulate a minimum benzodiazepine dose for the liberal benzodiazepine policy. However, 13.9% of patients received benzodiazepines before surgery, 11.6% of patients received benzodiazepines after surgery, and 30.1% of patients managed under the liberal benzodiazepine policy received a dose of 2 mg of Midazolam or less. In order to minimize confounding in the main trial, we require that in the absence of patient-driven reasons (e.g. benzodiazepine dependence, alcohol withdrawal, seizure), pre- and postoperative benzodiazepines are not administered throughout the duration of the trial, in keeping with current practice guidelines. In order to ensure an adequate difference in benzodiazepine administration between intervention arms, in the main trial we have stipulated a minimum dose in the liberal benzodiazepine arm of 0.03mg/kg ideal body weight Midazolam equivalent.

A key challenge in studying delirium using a pragmatic approach is the variability between institutions and individuals in the rigour and accuracy with which delirium is assessed. During the pilot study we did not conduct any formal quality assurance, though the incidence that we identified in each site was aligned with locally reported delirium rates. Recognizing the

variability in the fidelity with which delirium is assessed, we have taken a number of steps to address this in the main trial. Foremost of these are the appointment of Dr. Michael Avidan to the trial Steering Committee as the Scientific advisor for the assessment of delirium. We will utilize a strategy to optimize the assessment of delirium developed by Dr. Michael Avidan. In order to participate in the main trial, each site must – as part of their standard practice – provide nurses working in the cardiac surgical ICU with formal delirium assessment training and mandate that cardiac surgery patients be assessed for delirium at least once every 12 hours using either the Confusion Assessment Method – Intensive Care Unit (CAM-ICU)[17] or the Intensive Care Delirium Screening Checklist (ICDSC)[23] while they are admitted to the cardiac surgical ICU. To supplement the training that site nurses already receive, as well as ensure standardization across centres, Dr. Avidan has created educational videos about the importance and appropriate use of both the CAM-ICU and ICDSC in assessing delirium. As part of site initiation activities, all cardiac surgical nurses in each participating centre review an educational package that includes these videos. Finally, while we have taken significant efforts to ensure that all participating centres assess delirium with similar rigour, we recognize that there may be variability across centres and individuals with respect to how accurately delirium is assessed. These differences – reflected in part as variability across centres in the incidence of delirium – are accounted for statistically by the intra-cluster correlation (ICC), which was used in the calculation of our sample size requirement.

Our pilot study was not powered to adequately assess the main trial's primary outcome of delirium. However, the fact that the observed direction of effect was opposite from that anticipated led us to recognize the importance of collecting data about the intraoperative anesthetic medications administered in the absence of benzodiazepines. We did not identify a

difference in opioid administration between arms in the pilot study. However, we did not collect and thus could not explore the impact of alternate agents, including propofol, ketamine, and etomidate. Thus, we will collect data regarding all intraoperative medications within in the main trial.

Based on the success of the pilot study, we have established the feasibility of the definitive trial, which will begin in early 2020. There are several unique considerations in determining the sample size requirement for a cluster-randomised trial, including the intracluster correlation coefficient (ICC) – which accounts for the relatedness of clustered data – and the interperiod correlation coefficient (IPC) – which accounts for the temporal nature of patient-important health outcomes at the level of a cluster. The full trial will include 16 hospitals, with an overall average annual case volume of 1000 cardiac surgeries per hospital. Hospitals will be randomised to complete twelve, 4-week crossover periods. This design will give us 80% power to detect a relative risk reduction of 15% in the incidence delirium during the restricted benzodiazepine policy periods, based on an assumed incidence of delirium of 15% in the liberal benzodiazepine periods, a conservative ICC of 0.02 based on values determined by Gulliford et al using several large administrative data sets,[24] and an IPC = 0.5*ICC. Sites will be randomised to twelve, 4-week crossover periods, blocking in periods of 2 to minimize period effects.

Finally, there are ethical considerations that are unique to cluster randomised trials, particularly those examining questions related to clinical effectiveness. Individual patient efficacy trials are useful to establish the clinical efficacy of an intervention amongst a carefully selected population under optimal following detailed protocols. However, such trials do not address questions of clinical effectiveness, which conditions are questions about how well an intervention or policy actually works in clinical practice. The question that we are asking within

the B-Free trial is a question about the clinical effectiveness of a general approach to care applied at the level of an institution. Thus, in this cluster crossover trial, we are randomising hospitals (i.e. clusters), rather than individual patients. It is not possible to answer a question about the impact of an intervention at the level of a hospital (i.e. cluster) without alterations to individual patient consent.

The Tri-Council Policy Statement (TCPS 2) and United States Food and Drug Administration (US FDA),[25,26] has established requirements to justify a waiver of or modification to individual patient consent: (i) altered consent is required to answer the research question, (ii) the research involves minimal risk, (iii) lack of *a priori* consent will not adversely affect participant welfare, (iv) information about the research being conducted is provided to participants when possible, and (v) benefits of undertaking the research outweigh the risks of not obtaining *a priori* consent.

The research question evaluated within the context of the B-Free trial both requires cluster randomisation and satisfies the criteria for waiver of individual consent. We are asking what happens to hospital delirium incidence when an institutional policy of one therapeutic strategy is compared to another. This question can only be answered by randomising at the institutional level, as in the cluster cross-over trial that we are conducting. Many factors may impact effectiveness, beyond the efficacy of the policy itself. Specifically, issues around practitioner adherence to the policy (reflecting knowledge translation) or policy application at the level of the individual patient (reflecting population selection) are not accounted for in individual participant randomized trials but are captured by cluster trials utilizing alterations to individual patient consent. B-Free evaluates two different cardiac anaesthesia policies related to the use of benzodiazepines (restricted versus liberal intraoperative administration), both of which are used

by credentialed anaesthesiologists in routine practice.[12] Whether a patient undergoing cardiac surgery receives or does not receive benzodiazepines is largely determined by practitioner preference, rather than patient considerations. To satisfy the criteria for minimal risk, patients exposed to both intervention and control arms must experience no more risk than they would in routine practice. Given that both approaches to benzodiazepine administration are currently used in routine practice, this satisfies the criteria for minimal risk.

Given that patients do not routinely consent to their cardiac anaesthetic (as consent to anaesthesia is implied with consent to surgery) we do not believe that the lack of a priori consent will adversely affect patient welfare, as both benzodiazepine approaches are routinely used, exceptions are allowed when clinically indicated, and only anonymised data is being collected. Within the trial, we notify patients (through provision of a letter of information), that the hospital in which they are undergoing cardiac surgery is currently studying alternate institutional policies with respect to the medications that comprise their cardiac anaesthetic. Within the letter patients are informed of the two policies and notified that if their anaesthesiologist believes that there is a clinical reason that would make policy application unsafe in their individual case, the policy will not be applied. Patients are also notified that anonymised data is being collected as part of the study (although they will not be contacted by research staff) and that, if they object to this, they may request to have their personal information withdrawn from the trial database. Finally, establishing the optimal approach to intraoperative benzodiazepine use is important to guide cardiac anaesthesia practice. The information obtained has the potential to benefit both patients and society by reducing delirium and its associated morbidity in patients undergoing cardiac surgery, thus satisfying the final requirement for alterations to individual patient consent.

Conclusions: Delirium continues to occur in 15-20% of patients in the ICU after cardiac surgery. It is associated with significant morbidity and mortality and may be due to ongoing use of benzodiazepines during surgery. Alternatives to benzodiazepines exist, and there is now uncertainty as to whether or not benzodiazepines should be used during surgery, as demonstrated by the large variation in clinical practice in Canada. The heterogeneity in practice reflects the lack of evidence.

There is a need for a trial to determine the optimal approach to benzodiazepine (i.e., restricted versus liberal) administration during cardiac surgery. In the B-Free pilot trial we have demonstrated the feasibility of a multi-centre cluster crossover trial addressing this important question. We have demonstrated that we can achieve widespread adherence to both intervention arm policies, collect the primary outcomes of the main trial using only delirium assessments collected as part of routine clinical care, and that a restricted intraoperative benzodiazepine approach is not associated with an increased risk of intraoperative awareness.

Details of authors' contributions:

JS: Responsible for study conception and design, acquisition of data, analysis and interpretation of data, and drafting of final manuscript.
EBC: Responsible for study conception and design, acquisition of data, analysis and interpretation of data, and drafting of final manuscript.
EJ: Responsible for study conception and design, analysis and interpretation of data, and drafting of final manuscript.
SFL: Responsible for study conception and design, analysis and interpretation of data, and drafting of final manuscript.
RW: Responsible for study conception and design, analysis and interpretation of data, and drafting of final manuscript.
SB: Responsible for study conception and design, analysis and interpretation of data, and drafting of final manuscript.
SS: Responsible for study conception and design, acquisition of data, and drafting of final manuscript.
AS: Responsible for acquisition of data.
SM: Responsible for acquisition of data.
AL: Responsible for acquisition of data.
SL: Responsible for acquisition of data.
KU: Responsible for acquisition of data.
WM: Responsible for acquisition of data and drafting of final manuscript.
MK: Responsible for acquisition of data.
IF: Responsible for acquisition of data.
RA: Responsible for study conception and design and acquisition of data.
AL: Responsible for study conception and design and drafting of final manuscript.
SC: Responsible for study conception and design, analysis and interpretation of data, and drafting of final manuscript.
PJD: Responsible for study conception and design, analysis and interpretation of data, and drafting of final manuscript.

All authors have reviewed and approved of the final manuscript submitted for publication and agree to be accountable for all aspects of the work.

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Declaration of interests: Philip J. Devereaux is a member of a research group with a policy of not accepting honorariums or other payments from industry for their own personal financial gain. They do accept honorariums or payments from industry to support research endeavours and costs to participate in meetings. Based on study questions Dr. Devereaux has originated and grants he has written, he has received grants from Abbott Diagnostics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Coviden, Octapharma, Philips Healthcare, Roche Diagnostics, Siemens and Stryker. Dr Devereaux has participated in advisory board meetings for GlaxoSmithKline and Boehringer Ingelheim. He also attended an expert panel meeting with AstraZeneca and Boehringer Ingelheim. No other competing interests are declared.

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Table 1: Baseline demographics, surgical characteristics, perioperative benzodiazepine and intraoperative opioid administration by treatment arm

	Restricted benzodiazepines N = 411	Liberal benzodiazepines N = 389	p-value
Patient demographics and surgical characteristics			
Age – Mean (SD)	66.7 (11.3)	67.2 (10.0)	0.484
Male – N (%)	317 (77.1)	302 (77.6)	0.864
Urgency of procedure			0.117
Elective – N (%)	255 (62.0)	237 (60.9)	-
Urgent – N (%)	129 (31.4)	111 (28.5)	-
Emergent – N (%)	27 (6.6)	41 (10.5)	-
Type of Procedure – N (%)			0.531
Isolated CABG*	228 (55.5)	231 (59.4)	-
Single, non-CABG procedure	72 (17.5)	61 (15.7)	-
2 procedures	89 (21.7)	83 (21.3)	-
3 procedures	20 (4.9)	14 (3.6)	-
>3 procedures	2 (0.5)	0 (0.0)	-
Perioperative benzodiazepine administration			
Preoperative benzodiazepines – N (%)	61 (14.8)	40 (10.3)	0.056
Postoperative benzodiazepines – N (%)	53 (12.9)	40 (10.3)	0.249
Intraoperative benzodiazepine administration – N (%)	48 (11.7)	355 (91.3)	<0.0001
Midazolam – N (%)	47 (97.9)	348 (98.0)	1.00**
Dose given (mg) – Mean (SD)	4.6 (2.7)	5.2 (3.5)	0.233
Diazepam – N (%)	1 (2.1	8 (2.3)	1.00**
Dose given (mg) – Mean (SD)	10.0 (-)	12.5 (4.6)	-
Intraoperative opioid administration			
Intraoperative opioid administration – N (%)	411 (100)	388 (99.7)	0.304
Sufentanil – N (%)	350 (85.2)	334 (85.9)	0.778
Dose given (mcg) – Mean (SD)	148.1 (80.8)	145.8 (142.4)	0.800
Fentanyl – N (%)	65 (15.8)	56 (14.4)	0.576
Dose given (mcg) – Mean (SD)	1108 (637.4)	1245 (588.4)	0.221
Remifentanil – N (%)	29 (7.1)	46 (11.8)	0.021
Dose given (mcg) – Mean (SD)	163.2 (93.8)	175.2 (139.6)	0.660

Hydromorphone – N (%)	82 (20.0)	78 (20.1)	0.972
Dose given (mg) – Mean (SD)	1.6 (0.7)	1.8 (2.3)	0.419
Morphine – N (%)	2 (0.5)	2 (0.5)	1.00**
Dose given (mg) – Mean (SD)	7.5 (3.5)	5.0 (0.0)	1.00***
Total dose given in Fentanyl equivalents (mcg) – Median (IQR)	1300 (870.0 - 2000)	1250 (750.0 - 2000)	0.432***

*Single non-CABG procedure includes any single cardiac surgical procedure that did not involve coronary artery bypass grafting. Examples of this include single valve repair/replacement, isolated aortic repair, pericardiectomy.
**Fisher exact test was used.
***Wilcoxon rank-sum test was us

Table 2: Feasibility outcomes and clinical outcomes of main B-Free trial by intervention arm

	Restricted benzodiazepines N = 411	**Liberal benzodiazepines N = 389**	**p-value**
Feasibility outcomes			
Proportion of patients managed according to policy – N (%)	363 (88.3)	355 (91.3)	0.171
Proportion of patients with at least one delirium scale assessment in the cardiovascular intensive care unit – N (%)	398 (96.8)	372 (95.6)	0.369
Proportion of patients with at least one delirium scale assessment per day in the cardiovascular intensive care unit – N (%)	382 (92.9)	358 (92.0)	0.624
Incidence of intraoperative awareness – N (%)	1 (0.4%)* (n=263)	0 (0) (n=258)	1.00**
Outcomes of main trial			
Delirium – N (%)	72 (17.5)	55 (14.1)	0.191
ICU LOS (hours) – Median (IQR)	24 (24-48)	24 (24-72)	0.148***
Hospital LOS (days) – Median (IQR)	7 (5-11)	7 (5-11)	0.393***
In-hospital mortality – N (%)	5 (1.2)	4 (1.0)	0.801

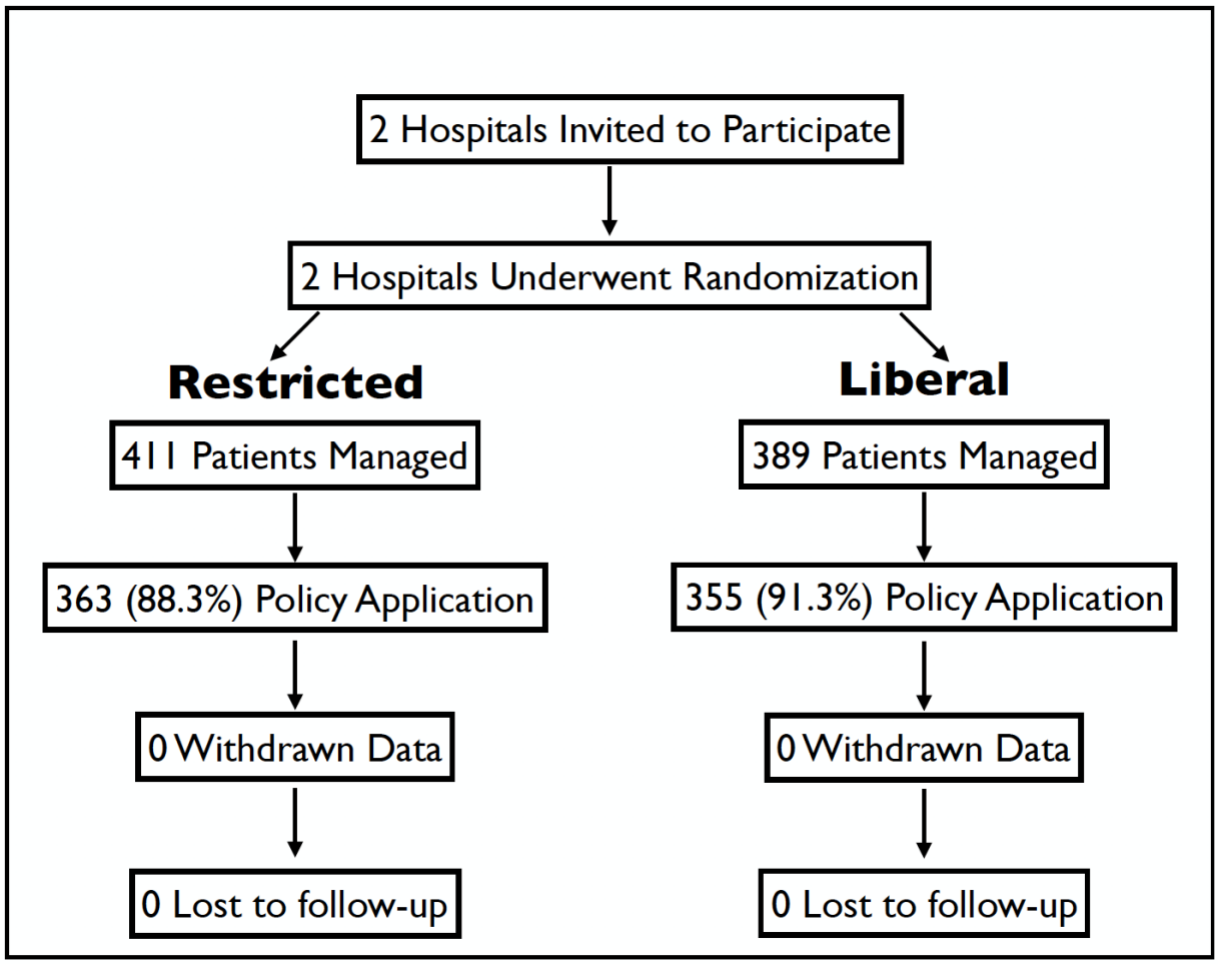
Abbreviations: CVICU: Cardiovascular Intensive Care Unit; LOS: Length-of-stay; IQR: Interquartile Ratio

*Managed during limited benzodiazepine period but received benzodiazepine

**Fisher's exact test was used.

***Wilcoxon rank-sum test was used.

Figure 1: B-Free pilot study flow



eSupplement 1: Procedure for Assessment of Intraoperative Awareness

All patients at Hamilton General Hospital who undergo cardiac surgery were assessed for intraoperative awareness with a standardized questionnaire using a procedure that has been established.[1] This procedure was used in the BAG-RECALL Trial, the largest (6041 patients) randomized controlled trial that has evaluated the outcome of intraoperative awareness.[2]

Interviews were conducted by trained research assistants within the first 12-24 hours after extubation and before hospital discharge. The interviews consisted of the following five standardized questions:

1. What was the last thing you remembered before you went to sleep?
2. What is the first thing you remembered after your operation?
3. Can you remember anything in between?
4. Can you remember if you had any dreams during your operation?
5. What was the worst thing about your operation?

All patients who indicated dreams or possible recall of intraoperative events during the postoperative interview were interviewed a second time (using the same set of questions) by one of the study investigators to have their answers confirmed. Each case where patients indicated dreams or possible recall of intraoperative events was reviewed by an independent endpoint adjudication committee of three experienced anesthesiologists, blinded to the randomization period during which the patient was managed. Each member of the committee evaluated each possible case as either 'awareness,' 'possible awareness,' or 'no awareness.' We defined cases of awareness as a unanimous coding of 'awareness' by all three adjudicators, or two members coding as 'awareness' and the third as 'possible awareness.'

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eSupplement 2: Baseline characteristics and delirium scale completion by site

	Winnipeg N=260	**Hamilton N=540**	**p-value**	**All patients N=800**
Baseline characteristics				
Age in years - Mean (SD)	65.8 (11.3)	67.6 (10.3)	0.031	67.0 (10.7)
Women – N (%)	71 (27.3%)	108 (20.1%)	0.020	179 (22.4%)
Surgical characteristics				
Urgency of Procedure – N (%) Elective Urgent Emergent	 226 (86.9%) 14 (5.4%) 20 (7.7%)	 262 (48.5%) 229 (42.4%) 49 (9.1%)	 <0.001 <0.001 0.514	 488 (61.0%) 243 (30.4%) 69 (8.6%)
Type of Procedure – N (%) Isolated CABG Single, non-CABG procedure 2 procedures 3 procedures >3 procedures	 135 (51.9%) 66 (25.3%) 48 (18.5%) 9 (3.5%) 2 (0.8%)	 322 (59.6%) 66 (12.2%) 127 (23.5%) 25 (4.6%) 0	 0.039 <0.001 0.105 0.443 0.105	 457 (57.1%) 132 (16.5%) 175 (21.8%) 34 (4.3%) 2 (0.3%)
Delirium scale completion				
Completion of at least one delirium scale – N (%)	252/260 (96.9%)	518/540 (95.9%)	0.487	770/800 (96.3%)
Completion of at least one delirium scale per day in ICU – N (%)	234/260 (90.0%)	505/540 (93.5%)	0.079	740/800 (92.5%)

*Single non-CABG procedure includes any single cardiac surgical procedure that did not involve coronary artery bypass grafting. Examples of this include single valve repair/replacement, isolated aortic repair, and pericardiectomy.
Abbreviations: SD: Standard deviation; CABG: Coronary artery bypass grafting; ICU: Intensive care unit

CHAPTER 6
CONCLUSION

CHAPTER 6: Conclusions and future directions

6.1 Summary of findings

This doctoral thesis explored knowledge gaps about the patient-important outcomes of adults undergoing cardiac and non-cardiac surgery. The presented studies describe the epidemiology of morbidity and mortality in patients after non-cardiac surgery, and foundational and feasibility data necessary to study the functional outcomes of patients undergoing cardiac surgery.

6.2 The incidence, timing, and location of death after non-cardiac surgery, and potential future targets for intervention to prevent death after non-cardiac surgery

Chapter 2 describes the VISION mortality analysis, which reported the incidence, timing, location, and relationship of the major complications with death within 30-days of non-cardiac surgery in a cohort of more than 40,000 patients from 28 centres in 14 countries in North and South America, Asia, Europe, Africa, and Australia. We found that 715 patients died (1.8%) within 30-days of surgery but that death in the operating room was rare (i.e., 5 deaths). However, death after hospital discharge was common, accounting for 29.4% of deaths. The 3 perioperative complications independently associated with mortality and with the greatest population impact (described using the attributable fraction) were major bleeding, MINS, and sepsis. The median time to major bleeding was the day of surgery, MINS 1 day after surgery, and sepsis 6 days after surgery.

Based on the assumption that 100 million adults aged 45 years or older undergo non-cardiac surgery around the world each year,[1] roughly 1.8 million adults die within 30 days of non-cardiac surgery annually. This indicates that perioperative mortality is a substantial global

health problem. The findings of this study provide preliminary information regarding what outcomes to focus on and when to prevent deaths.

Death in the operating room was uncommon but, in contrast, postoperative mortality was substantial (i.e. 99.3% of deaths), one third (29.3%) of which occurred after the patient had been discharged from hospital. These data suggest the need for studies examining alternate approaches to postoperative monitoring, including increased in-hospital monitoring and longer hospital stays for at-risk patients, more intensive outpatient follow-up models, and new technologies that enable monitoring in the community setting.

We identified 8 perioperative complications that were independently associated with 30-day mortality. Three of these complications (i.e. major bleeding, MINS, and sepsis) potentially explained 44.9% of the deaths. These three complications represent promising targets to prevent death after non-cardiac surgery. Research evaluating strategies to prevent, anticipate, identify, and manage major bleeding, MINS, and sepsis will inform strategies to decrease perioperative mortality. The median time to major bleeding, MINS, and sepsis suggests when monitoring for each complication is likely to have the greatest impact.

6.3 Laying the foundations for the study of function after cardiac surgery

Functional ability – which underlies independence – is an outcome of great importance to patients that has been poorly studied in adults undergoing cardiac surgery. This is in part due to the lack validated measures. In Chapter 3 we demonstrated the validity of the SAGE scale – administered by phone or in-person – in measuring function after cardiac surgery. We also defined a patient-important binary outcome based on SAGE score. Going forward, SAGE will be used to describe the epidemiology of function in adults undergoing cardiac surgery, identify at-

risk populations and targets for intervention, and evaluate responses to treatments applied within the context of large clinical trials.

Within the Age and other Predictors of PostopeRative functionAl ImpairmEnt (APPRAISE) sub-study of VISION-Cardiac Surgery, more than 2500 patients around the world have had function assessed using SAGE at baseline, 30-days, and 1-year after cardiac surgery. Data collected will allow us to describe the trajectory of function after cardiac surgery. The binary outcome (corresponding to severe functional disability) defined in SAGE validation is simple for clinicians to interpret and will allow us to describe the incidence and predictors of severe functional disability after cardiac surgery globally. Identification of the predictors of clinically important functional decline after cardiac surgery is a crucial step towards developing and studying interventions to mitigate this outcome of great importance to patients.

6.4 The feasibility of studying the relationship between intraoperative decreases in cerebral oxygen saturation and functional decline after cardiac surgery

The relationship between intraoperative regional cerebral oxygen saturation measured near-infrared spectroscopy (NIRS) and function after cardiac surgery is unknown. In order to evaluate whether there is a relationship between cerebral desaturation and functional decline, a large observational study examining the relationship between decreases in intraoperative rScO2 and postoperative functional decline is required. This study would also need to establish the optimal prognostically important rScO2 threshold associated with patient-important outcomes, including cognitive and functional decline.

The pilot study described in Chapter 4 demonstrates the feasibility of conducting such a cohort study. We were able to recruit a minimum of one patient per week, to obtain complete intraoperative NIRS transcripts in 100% of patients, and to obtain complete SAGE scale data in

90% of patients, including measurements at baseline, 30-days, and 3 months after cardiac surgery. We also obtained data describing the mean time required to download and enter NIRS transcript data study CRFs was 5.5 minutes, which reassured us that there will be minimal research assistant time required to complete this aspect of the study. This information will be helpful to inform the design and resource requirements of a large observational trial.

Assuming a conservative incidence of functional decline of 10%,[5] the desire to include as many as 40 covariates in our multivariable model, and an anticipated loss to follow-up (based on our pilot study) of 10%, we will require a sample size of 4400. A sample of this size would allow us to explore the relationship between various cerebral oxygen saturation thresholds and functional decline, including an absolute cerebral oxygen saturation value, a proportional decrease from baseline cerebral oxygen saturation, and varying amounts of time below different cerebral oxygen saturation values.

6.5 The feasibility of a multicenter randomized cluster crossover trial assessing an institutional policy of restricted intraoperative benzodiazepine administration on the incidence of delirium after cardiac surgery

In the B-Free pilot study, we demonstrated the feasibility of conducting a multi-centre randomized cluster crossover trial examining whether an institutional policy of restricted intraoperative benzodiazepine use (as compared to liberal use) decreases the incidence of delirium in the ICU after cardiac surgery. We showed that we could obtain acceptable rates of adherence to each policy in all cardiac surgery patients, that we could collect the primary outcome of our main trial in an acceptable proportion of patients using only data collected as a part of routine clinical care, and we showed that avoiding benzodiazepines during cardiac surgery most likely does not increase the risk of intraoperative awareness.

Based on the success of the pilot study, we have established the feasibility of the definitive trial. There are several unique considerations in determining the sample size requirement for a cluster-randomized trial, including the intracluster correlation coefficient (ICC) – which accounts for the relatedness of clustered data – and the interperiod correlation coefficient (IPC) – which accounts for the temporal nature of patient-important health outcomes at the level of a cluster. The full trial will include a minimum of 16 hospitals, with an overall average annual case volume of 1000 cardiac surgeries per hospital. Hospitals will be randomised to complete twelve, 4-week crossover periods. This design will give us 80% power to detect a relative risk reduction of 15% in the incidence delirium during the restricted benzodiazepine policy periods, based on an assumed incidence of delirium of 15% in the liberal benzodiazepine periods, a conservative ICC of 0.02 based on values determined by Gulliford et al using several large administrative data sets,[24] and an IPC = 0.5*ICC. Sites will be randomised to twelve, 4-week crossover periods, blocking in periods of 2 to minimize period effects. The full B-Free trial obtained Canadian Institute of Health Research (CIHR) funding. From November/2019 – March/2020, 16 sites had been enrolled, with an additional 5 clusters planned to begin in April/2020.

6.6 Future directions

By conducting the studies included in this thesis, I have acquired the methodological knowledge and experience required to answer clinically important research questions using a multi-design programmatic approach. I will apply this knowledge throughout my career to answer questions whose answers will improve patient-important perioperative outcomes and inform clinical practice.

In addition, in the process of answering the research questions in this thesis, I have recognized other unanswered key clinical questions requiring further investigation. For example, after considering the results of the B-Free pilot, which demonstrated a trend opposite to that expected, where a smaller proportion of patients who received benzodiazepine during cardiac surgery (as compared to patients who did not receive benzodiazepine during cardiac surgery) developed delirium in the intensive care unit after surgery. Given that benzodiazepine administration is associated with a smaller decrease in blood pressure when compared to alternative agents (e.g. propofol), I wondered whether the observed direction of effect could be attributed to differences in blood pressure between the two groups. I will be further exploring the impact of intraoperative blood pressure during cardiac surgery on patient-important outcomes by conducting a systematic review of the literature and an observational sub-study of the B-Free full trial. The information generated may be used to justify and inform the design and planning of a large randomized trial examining an intraoperative blood pressure target as an intervention.

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