

COVERT CEREBRAL ISCHEMIA AFTER NONCARDIAC SURGERY

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the
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ABSTRACT

Background

200 million patients undergo noncardiac surgery every year. Overt stroke after noncardiac surgery is not common, but has a substantial impact on duration and quality of life. Covert stroke in the nonsurgical setting is much more common than overt stroke, and associated with an increased risk of cognitive decline and dementia. Little is known about covert stroke after noncardiac, noncarotid artery surgery.

Methods

We undertook a prospective cohort pilot study to inform the incidence of covert stroke after noncardiac, noncarotid artery surgery, and to determine the feasibility of a full prospective cohort study to characterize the epidemiology of perioperative covert stroke. Patients underwent a brain MRI study between postoperative days 3-10, and were followed up at 30 days after surgery.

Results of the pilot study

We enrolled a total of 100 patients from 6 centres in 4 countries, demonstrating excellent recruitment and no loss to follow-up at 30 days after surgery. The incidence of perioperative covert stroke was 10.0% (10/100 patients, 95% confidence interval 5.5% to 17.4%).

Full study protocol

We describe a proposal for a prospective cohort study of 1,500 patients. An MRI study of the brain will be performed between postoperative days 2 and 9. The primary outcome is cognitive function, measured 1 year after surgery using the Montreal Cognitive Assessment tool. We will perform multivariable logistic regression analysis where the dependent variable is the change in cognitive function 1 year after surgery, and the independent variables are incidence of perioperative covert stroke and other risk factors for cognitive decline.

Conclusions

This international multicentre pilot study suggests that 1 in 10 patients ≥ 65 years of age experiences a perioperative covert stroke. The proposed protocol describes a larger study which will determine the impact of perioperative covert stroke on patient-important outcomes.

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List of Abbreviations

ADAS: Alzheimer Disease Assessment Scale

ADC: apparent diffusion co-efficient

CAM: Confusion Assessment Method

DSST: Digit-Symbol Substitution Test

DWI: Diffusion-weighted imaging

GDS-5: Geriatric Depression Scale

iADL: instrumental Activities of Daily Living

LADIS: Leukoaraiosis And Disability Study

MoCA: Montreal Cognitive Assessment

MR: Magnetic Resonance

MRI: Magnetic Resonance Imaging

NINDS: Neurological Disorders and Stroke

NIRS: Near-Infrared Reflectance Spectroscopy

POCD: Postoperative cognitive dysfunction

POISE: PeriOperative Ischemic Evaluation – 2 Trial

rSO₂: regional cortical oxygen saturation

TMT: Trail Making Test

VCI: Vascular Cognitive Impairment

VIF: Variance Inflation Factor

VISION: CerebroVascular Events In Noncardiac Surgery PatIents: A Cohort
EvaluationN

INTRODUCTION

This thesis outlines a program of research that is directed towards understanding a newly identified phenomenon of covert stroke after noncardiac surgery.

Chapter 1 of this thesis is a review of the literature that demonstrates that, albeit uncommon, overt perioperative stroke is far more devastating than stroke that occurs in the nonsurgical settings. Covert stroke is common after cardiac surgery and after carotid artery surgery, but there is no study evaluating covert stroke after non-carotid noncardiac surgery. Although covert stroke in the nonsurgical setting is associated with an increased risk of dementia, overt stroke and death, no studies have characterized the impact of covert stroke after surgery.

Chapter 2 of the thesis reports the findings of a pilot study of covert stroke after noncardiac surgery. In this pilot study we demonstrated that covert stroke may be common after noncardiac surgery, and we confirmed the feasibility of a full study to determine the impact of perioperative covert stroke.

Chapter 3 of the thesis describes the protocol of a full study that is designed to characterize the impact of covert stroke after noncardiac surgery.

Chapter 4 of the thesis discusses the strengths and the limitations of the overall research, as well as possible future directions.

CHAPTER 1: CEREBRAL ISCHEMIA AFTER NONCARDIAC SURGERY:

BACKGROUND

200 million patients worldwide undergo noncardiac surgery every year. Overt stroke is a serious complication of noncardiac surgery with significant impact on quality and duration of life. Covert stroke is 10 times more common than overt stroke after cardiac surgery and carotid artery procedures. Covert stroke in the non-surgical setting is associated with an increased risk of dementia, overt stroke and death.

The epidemiology of covert stroke after noncardiac surgery is not well characterized, risk factors have not been identified and its clinical consequences are unknown in this population.

1.1 Epidemiology of overt stroke

The true incidence of overt stroke after noncardiac surgery is not known, and the estimate of the risk of stroke in the current literature varies widely (Table 1). Although population characteristics and type of surgery are likely to be associated with perioperative overt stroke, other differences between studies may also contribute to the variability (e.g., year undertaken, size of study, quality of study). Larsen et al. reported a low risk of stroke (0.2%) in an unselected population undergoing noncardiac, noncarotid artery surgery.[1] However, a study of patients with a history of cerebrovascular disease undergoing noncardiac, noncarotid artery surgery demonstrated a greater than 10-fold higher risk of perioperative stroke (2.9%).[2] Studies of patients undergoing orthopedic or vascular surgery have demonstrated a high incidence of perioperative stroke (i.e., 3.9% and 4.3% respectively).[3, 4]

The POISE Trial enrolled 8351 patients undergoing noncardiac surgery in 190 hospitals from 23 countries.[5] In this trial, 60 patients (0.7%) suffered an overt stroke (defined as a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours) within the first 30 days. We are currently conducting the Vascular events In noncardiac Surgery patients cohort evaluation (VISION) Study, a 40,000 patient international prospective cohort study of a representative sample of patients ≥ 45 years of age undergoing in-hospital noncardiac surgery. The first interim analysis of 7,857 patients showed that the

incidence of overt stroke was 0.6%. In VISION patients ≥ 65 years of age had an incidence of overt stroke of 0.9% (Table 1).

Table 1: Incidence of overt stroke after noncardiac surgery in large population cohort studies

First Author	Year	Study Design	n/N	Risk of Stroke	Population
Devereaux VISION*	2009	Prospective Cohort	46/7857	0.6%	Patients undergoing non cardiac surgery requiring overnight hospitalization, 45 years and older.
Devereaux VISION* (≥65 years)	2009	Prospective Cohort	33/3721	0.9%	Patients undergoing non cardiac surgery requiring overnight hospitalization, 65 years and older.
Popa[5]	2009	Retrospective Cohort	76/1886	3.9%	Patients undergoing orthopedic surgery, 65 years and older
Devereaux POISE[2]	2008	RCT	60/8351	0.7%	Patients undergoing noncardiac surgery with, or at risk of atherosclerotic disease
Landescaper [4]	1990	Retrospective Cohort	5/173	2.9%	Patients with a history of cerebrovascular disease undergoing surgery under general anesthesia. Cardiac surgery, carotid artery surgery and neurosurgery were excluded.
Larsen[3]	1988	Prospective Cohort	6/2463	0.2%	Patients undergoing noncardiac, noncarotid artery surgery older than 40 years of age.
Turnipseed[6]	1980	Prospective Cohort	7/160	4.3%	Patients undergoing peripheral vascular surgery

* Interim analysis

Although rates under 1% may appear small, in a global context this suggests 1 to 2 million perioperative overt strokes annually. Moreover, the strokes that were identified in the VISION Study and in the POISE Trial had a high degree of morbidity and mortality. In POISE, 32 % of patients with a stroke died within 30 days. Of the

survivors, 58% were left with major disability. In the VISION Study, the interim analysis demonstrated that overt stroke was associated with a 30% mortality rate at 30 days, and 35% of survivors were left with major disability. In comparison, an analysis of individual patient-level data from six major RCTs of thrombolysis for acute stroke in the non-operative setting demonstrated significantly lower morbidity and mortality in the placebo groups, despite the fact that these studies excluded patients with minor strokes, (i.e. those with rapidly improving clinical symptoms or those without significant neurological deficits were excluded).[6] In the placebo groups of the six trials, 181 (13%) of total 1384 patients died within 3 months, and among the survivors 390 patients (28%) were left with a major disability.

Considering the outcome discrepancy between nonoperative and perioperative strokes, and that patients after surgery are commonly immobile and are administered narcotics, there is a possibility that physicians miss a significant number of perioperative strokes with mild or moderate severity. Furthermore, these events that may carry an important prognostic relevance. As we show below, evidence suggests this may be the case.

1.2 Epidemiology of covert stroke

Covert stroke is an acute cerebral ischemic event that has no apparent clinical manifestations, but may contribute to subacute and chronic disability. Modern neuroimaging techniques (magnetic resonance imaging sequences) can detect acute covert stroke with a high degree of accuracy.[7] While a number of large studies have determined the prevalence of covert stroke in the general population of older adults, only a few small studies have evaluated the frequency of covert stroke in the perioperative setting, and these studies were confined to cardiac and carotid artery surgery populations.

1.2.1 Incidence and prevalence of covert stroke in the non-operative setting

Epidemiologic studies in non-operative populations confirm a high ratio of covert to overt stroke on magnetic resonance imaging (MRI) studies. In a substudy of 2081 patients in the Framingham Heart Study without a past history of stroke, 12.3% (95% CI, 10.9-13.8%) of all adults 34 to 97 years old had evidence of covert stroke on MRI.[8] The Rotterdam Scan Study of unselected adults 60 to 90 years of age found that 3.3% had a history of symptomatic stroke (95% CI, 2.1-5.0%), and a further 18.4% of patients had MRI evidence of covert stroke (95% CI, 15.6-21.6%). On 5-year follow-up, 1.8% (12/668; 95% CI, 1.0-3.2%) of patients had an overt stroke, and 12.1% (81/668; 95% CI, 9.8-14.9%) suffered a new covert stroke. The incidence of covert stroke on 5-year follow-up differed between patients with MRI

findings of covert stroke at baseline (30%, 37/123) and those that did not have evidence of covert stroke at baseline (9%, 49/523) (RR 3.2, 95% CI, 2.1 to 4.8, $p < 0.001$).[9] Age, blood pressure, diabetes mellitus, cholesterol, homocysteine levels, intima-media thickness, carotid plaques, and smoking were associated with new covert strokes in this non-operative population.

One major limitation of the studies of non-operative covert stroke is that they did not characterize covert stroke in the acute phase, as this would require MRI studies on a very frequent basis. Instead, they were able to detect the incidence of covert stroke during a period between several years.

A study of perioperative covert stroke would have the advantage of detecting covert stroke in the acute phase, and when the patient is in a monitored setting where detailed and extensive data can be collected to inform potential mechanisms.

1.2.2 Diagnosis of acute covert stroke

An MRI study using the DWI sequence has the ability to detect acute cerebral ischemia that has occurred during the time window of minutes before the study up to approximately 10 days prior.[10] Thus, it is not necessary to obtain a preoperative MRI scan in order to measure the incidence of perioperative covert stroke. DWI MRI is very sensitive for the diagnosis of symptomatic cerebral ischemia, with sensitivity approaching 100%, when compared to final clinical diagnosis. [7, 10-12] The apparent diffusion coefficient (ADC) maps aid in

determining whether a DWI lesion is new or old. A component of the DWI signal comes from T2 prolongation and discriminating new from old lesions is routinely done by assessing the ADC map for evidence of restricted diffusion. The ability of this particular sequence to detect only acute lesions obviates the need for a preoperative MRI study. Prior studies of perioperative covert stroke have used the same or similar protocols.[13-15]

1.2.3 Incidence and prevalence of covert stroke after carotid artery and cardiac surgery

A recent systematic review of carotid artery surgery trials[16] demonstrated that the incidence of overt stroke was 3.4% (46/1363; 95% CI, 2.5-4.5%) after carotid artery stenting and 2.1% (16/754; 95% CI, 1.3-3.5%) after carotid endarterectomy, while the incidence of covert stroke was 37.0% (504/1363; 95% CI, 34.4-39.6%) and 10.3% (78/754; 95% CI, 8.3-12.8%), respectively (Table 2).

Table 2: Summary of systematic review[11] examining the incidence of covert stroke after carotid artery procedures

Procedure	Number of studies	Total number of patients	Incidence of overt stroke (%)	Incidence of covert stroke (%)
Carotid artery stenting	23	1363	3.5%	37.0%
Carotid endarterectomy	15	754	2.1%	10.3%

We performed a literature review of the non-carotid artery surgical studies characterizing the incidence of perioperative covert stroke. We identified 8 prospective cohort studies, all in the cardiac surgery population, (Table 3). No studies were identified in patients undergoing non-carotid artery, noncardiac surgery. In cardiac surgery studies, the incidence of overt stroke was 3.0% (10/331; 95% CI, 1.5-5.6%), whereas 31.7% (105/331; 95% CI, 26.8-37.1%) of the patients suffered a covert stroke.

Thus covert stroke is 10.5 (95% CI, 2.6-19.7) times more common than overt stroke after cardiac surgery, 10.5 (95%CI, 7.9-14.0) times more common after carotid artery stenting, and 4.9 (95% CI, 2.9-8.3) times more common after carotid artery surgery.

Table 3: Summary of studies examining the incidence of covert stroke after cardiac procedures

First Author	Year	Study Design	Surgery Type	N	Risk of overt stroke	Risk of covert stroke
Djaiani[99]	2006	Prospective Cohort	CABG	26	3.8%	31.0%
Knipp[100]	2005	Prospective Cohort	CABG	30	0%	45.0%
Djaiani[101]	2004	Prospective Cohort	CABG	50	2.0%	16.0%
Bendszus[70]	2002	Prospective Cohort	CABG	35	0%	26.0%
Barber[41]	2008	Prospective Cohort	Cardiac surgery	40	5.0%	43.0%
Cook[71]	2007	Prospective Cohort	Cardiac surgery	50	2.0%	32.0%
Floyd[102]	2006	Prospective Cohort	Cardiac surgery	34	5.9%	18.0%
Knipp[103]	2004	Prospective Cohort	Cardiac surgery	29	0%	45.0%

* Covert stroke is defined as a new ischemic lesion on DWI MRI sequence

1.2.4 Pathophysiology of perioperative covert stroke

The pathophysiology of perioperative stroke is not clear. Unlike cardiac surgery and carotid artery procedures, noncardiac surgery does not directly manipulate the arterial blood supply of the brain, but all three may have a similar incidence of covert stroke. The POISE trial demonstrated an association of perioperative hypotension with perioperative stroke, but the neuroimaging findings in perioperative stroke are most typical of cardioembolic, rather than a watershed

infarct etiology.[17] Although atrial fibrillation is a risk factor for perioperative stroke, one finding that challenges the cardioembolic theory is that perioperative metoprolol in POISE increased the risk of stroke while decreasing the risk of atrial fibrillation.

A recent narrative review[13] included seven studies [5, 12, 14-18] that characterized risk factors for overt perioperative stroke in patients undergoing noncardiac, non-carotid artery surgery. The risk factors that were identified were similar to the risk factors for non-operative stroke, and included age, past history of stroke, atrial fibrillation, hypertension, peripheral vascular disease, diabetes, cardiac disease, and renal impairment. Intraoperative hypotension has been associated with perioperative stroke in a recent case-control study[19], in the POISE trial,[2] and a systematic review[20]. No study has attempted to characterize risk factors for covert stroke in the perioperative setting.

The divergent trends of stroke and atrial fibrillation in the POISE trial raise questions regarding the assumed embolic etiology of perioperative covert stroke.

1.3 Impact of covert stroke

1.3.1 Impact of covert stroke in the non-operative setting

Epidemiological studies of covert stroke in the non-surgical population have shown covert stroke to have a substantial impact on cognitive function and ability to conduct activities of daily living. The Cardiovascular Health Study in 3,660 patients 65 years or older demonstrated a high prevalence of covert stroke (1131/3660 patients, 30.9%), and showed that covert strokes were independently associated with decreased ability to perform instrumental activities of daily living (partial correlation coefficient 0.058, $p < 0.05$ when adjusted for age and sex where a score of 0 indicates no problems with iADL and 1 indicates problems with iADLs).[18] The Rotterdam Scan Study of 1077 participants 60 to 90 years of age demonstrated a 1.8% incidence (12/668 patients with a follow-up MRI) of overt stroke and a 12% incidence (81/668 patients) of covert stroke over a 5-year follow-up. In this study, covert stroke was associated with impaired performance on neuropsychological testing, a steeper decline in global cognitive function, and a doubling of the risk of dementia (hazard ratio 2.26; 95 percent confidence interval, 1.09 to 4.70). Of the 123 patients with a silent brain infarct at baseline, 30 patients (24%) suffered a new silent brain infarct, and 7 patients (5.7%) suffered a new symptomatic stroke. [19]

The Leukoaraiosis and Disability (LADIS) Study was conducted in 633 participants 65 to 84 years of age, with evidence of small vessel ischemic disease on MRI. It found that the severity of ischemic burden on MRI was independently

associated with poorer performance on the Mini Mental State Examination (MMSE) and Alzheimer Disease Assessment Scale (ADAS).[20]

1.3.2 Impact of covert stroke in the postoperative setting

1.3.2.1 Potential association of perioperative covert stroke with cognitive dysfunction

Postoperative cognitive dysfunction (POCD) is a persistent change in cognitive performance as assessed by neuropsychological tests.[21, 22] Several risk factors have been identified for POCD. Specific interventions, such as cardiac surgery and orthopedic surgery have a high prevalence of POCD,[23-25] and surgeries requiring overnight hospitalization carry higher risk than outpatient procedures.[26] Age, low education level, history of benzodiazepine use, impairment in physical function and history of stroke are all risk factors for POCD. [27]

The etiology of POCD remains poorly understood. Theories regarding the causative mechanism of POCD have been proposed, and have been subsequently disproved. [28, 29] For example, it was originally believed that the high incidence of POCD in cardiac surgery was due to cardiopulmonary bypass. However, off-pump bypass does not reduce the incidence of POCD. [28] In noncardiac surgery, it was postulated that general anesthesia increased the risk of POCD due to its effects on the central nervous system. However, a meta-analysis of 19 RCTs and 4

observational studies concluded that neuraxial anesthesia compared with general anesthesia does not reduce the risk of POCD.[29]

A small single-centre study demonstrated that the risk of POCD after cardiac surgery increases in proportion to the number and size of postoperative ischemic lesions as detected by MRI. A total of 37 patients were enrolled, and 16 patients had at least one acute ischemic lesion on the postoperative MRI. Cognitive decline was seen in all patients with ischemic lesions, and 35% of those without ischemic lesions ($p < 0.001$), and there was an association between the number of abnormal cognitive tests and ischemic burden ($p < 0.001$).[13]

A recent systematic review of POCD in the noncardiac surgery setting included 48 studies. POCD was common after noncardiac surgery, with a prevalence of 6% to 56% in the postoperative period 22 days to 6 months after surgery. There was significant heterogeneity due to differences in the definition of POCD, length of follow-up, variation in the instruments used to assess POCD, differences in surgical procedures, as well as the baseline characteristics of the study populations. Many of these comparative studies had small sample sizes and were underpowered to detect a significant difference in the incidence of POCD between the comparator groups. Six studies only used a generic screening instrument that lacks the sensitivity to detect subtle cognitive changes, and four studies only tested a single cognitive domain.[30]

The largest study was ISPOCD-1, an international prospective cohort study of 1218 patients. It demonstrated an incidence of POCD of 10% three months after

surgery, compared to a 2.8% incidence of cognitive dysfunction in matched controls who did not undergo surgery during the same time period. Older patients are particularly susceptible to neurological dysfunction and persistent cognitive deficits in the postoperative period.[24, 25, 31] In addition to an increased risk of adverse clinical events, patients with POCD require prolonged hospitalization,[32] and have increased utilization of health resources.[25]

Although the epidemiology of POCD after noncardiac surgery has been characterized, none of the past studies examined the association between POCD and covert stroke, as the necessary technology (DWI MRI) was not available. Modern MRI sequences required to detect acute ischemia are now widely available as part of routine clinical practice, and are affordable for implementation in large epidemiological studies.[7] Furthermore, the DWI sequence allows the accurate detection of acute cerebral ischemic events up to 10 days after the actual event (see section 2.2.2 for details regarding the specific MRI protocol). Thus, it is not necessary to obtain a preoperative MRI scan in order to measure the incidence of acute perioperative covert stroke.

An increased ischemic burden is associated with an increased risk of cognitive impairment, postoperative cognitive dysfunction, and poorer physical health in the non-operative setting. These associations provide evidence for a possible causal relationship between these events. However, an accurate estimate of the incidence of covert stroke in patients undergoing noncardiac surgery is not

available, and the association between perioperative covert stroke and cognitive function has not been studied. In the past, calls have been made for all large studies to perform routine neuroimaging,[33] as these will be best suited for determining the true incidence of cerebral ischemic events in the perioperative period and its association with neurological dysfunction after surgery.

1.3.2.2 Potential association of perioperative covert stroke with delirium

In the immediate postoperative period, delirium is a common type of neurocognitive dysfunction. Delirium is defined as an acute-onset of a fluctuating disturbance in consciousness and a change in cognition due to a physiological insult.[34] A systematic review of delirium after noncardiac surgery that included 25 studies found an incidence of delirium between 5 to 52% in patients undergoing noncardiac surgery,[35] and an associated increased risk of functional decline, longer postoperative hospitalization, increased utilization of health care resources and increased risk of short-term and long-term mortality.[36-40] Most delirium develops in the immediate postoperative period, within 72 hours of surgery.[36, 41-43] Although generally viewed as a reversible condition, some patients have persistent delirium.[44, 45] A recent study of ICU patients found that delirium was associated with acute changes in the white matter as measured by an MRI study at hospital discharge.[46] As in other settings, the etiology of delirium and persistent

cognitive impairment is unclear in this population, and may be related to covert stroke in the perioperative period.

1.3.2.3 Potential association of perioperative covert stroke with physical function and quality of life

The majority of elective surgery is performed with the specific goal of improving physical function and quality of life, rather than correcting an immediate life-threatening illness. As outlined above, covert stroke in the non-operative setting has been associated with decreased physical function and quality of life. However, this association has been poorly characterized in patients undergoing noncardiac surgery.

CHAPTER 2: PILOT STUDY OF CEREBRAL ISCHEMIA AFTER NONCARDIAC SURGERY

We performed a pilot study (NeuroVISION Pilot Study) to establish the feasibility of a full study to characterize the impact of covert stroke after noncardiac surgery.

2.1 Rationale for the NeuroVISION pilot study

Perioperative covert stroke may be common after noncardiac surgery, and may have an impact on postoperative cognition, function and quality of life, as well as the risk of future stroke and death. A large, well designed study (Neurological impact of Vascular events In noncardiac Surgery patients cOhort evaluation: NeuroVISION Study) is required to characterize the epidemiology of the phenomenon of perioperative covert cerebral ischemia.

The full study will require substantial resources, and we performed a pilot study (NeuroVISION Pilot Study) to establish the feasibility of a full study.

2.2 Overview of the NeuroVISION Pilot Study

The NeuroVISION Pilot Study was a multicentre prospective cohort pilot study of patients undergoing noncardiac surgery. Patients were recruited from centres in Canada, China, India, and the United States.

2.3 Objectives for the NeuroVISION Pilot Study

2.3.1 Primary objectives of the NeuroVISION Pilot Study

The primary objectives were:

- 1) To develop a preliminary estimate of the incidence of perioperative covert stroke.

This is the first study of covert stroke after noncardiac surgery, and there are no previous studies to provide a preliminary estimate. We felt that a full study would not be feasible if the incidence of acute cerebral ischemia was less than 5 percent for the following reasons: 1. the required sample size of the full study would be very large (more than 2,000 patients to capture fewer than 100 events); 2. low incidence of covert stroke in the pilot study would indicate a low burden of disease in the population. This would lower the potential clinical impact of the full study.

- 2) To determine the feasibility performing an MRI study of the brain in the immediate postoperative period after noncardiac surgery, in multiple centres around the world.

MRI studies are not performed routinely in the immediate postoperative period after noncardiac surgery. Although MRI is not contraindicated in the postoperative setting, perioperative changes (eg. surgical staples are compatible with MRI technology), we needed to demonstrate this process can be completed safely and efficiently.

2.3.2 Secondary objectives of the NeuroVISION Pilot Study

Our secondary clinical objectives were to develop a preliminary estimate of cognitive and physical function preoperatively, to determine a preliminary incidence of postoperative delirium.

2.4 Methods of the NeuroVISION Pilot Study

2.3.1 Inclusion criteria

Patients ≥ 65 years of age undergoing noncardiac surgery requiring an anticipated hospital admission for at least three days were eligible for the NeuroVISION Pilot Study.

2.3.2 Exclusion criteria

We excluded patients who:

- 1) Were scheduled to undergo carotid artery surgery, as there have been several studies of covert stroke in this population
- 2) Had a contraindication to a magnetic resonance imaging (MRI) study (e.g., implanted devices not safe for MRI studies, or severe claustrophobia)
- 3) Were unable to complete a telephone interview, as this was the method of data collection at the 30-day follow-up.

4) Had a previously documented history of dementia, or resided in a nursing home. The potential impact of covert stroke on quality of life or on cognitive function in this patient population would be minimal.

5) Did not receive neuraxial or general anesthesia.

2.3.3 Patient recruitment

We developed a recruitment schedule that ensured proportionate representation of patients in the NeuroVISION Pilot Study that reflected the worldwide surgical population, as documented in the VISION Study, a 40,000-patient international prospective cohort study of unselected adult patients undergoing noncardiac surgery requiring hospital admission.[47]

Patients were considered enrolled in the NeuroVISION Pilot Study once the MRI study was completed in the postoperative period.

2.3.4 Data collection

Research staff obtained patient consent and collected baseline assessments prior to the day of surgery. Baseline clinical variables included the type of surgery (see Appendix 1), vascular risk factors and comorbidities, a cognitive screen using the Montreal Cognitive Assessment (MoCA) instrument,[48] functional assessments using the modified Rankin score [49] and Lawton iADL questionnaire, [50] and

quality of life as measured by the EQ-5D questionnaire.[51] During the hospital stay, the research staff assessed patients twice daily to collect data on clinical outcomes and the presence of delirium using the Confusion Assessment Method.[52] Research staff contacted patients by telephone 30 days after the surgery to collect data regarding clinical outcomes, physical function, and quality of life.

2.3.5 MRI Study Protocol

Standardized MRI of the brain was performed between postoperative days 3 and 10, as soon as the patient was able to tolerate this procedure. The MRI study sequences included axial fluid attenuated inversion recovery, gradient echo, T2, and diffusion-weighted imaging (DWI). MRI sequences were performed according to the local standard of care with a minimum 1.5 Tesla MRI machine, and a slice thickness of 3 to 5 mm, with no gap.

In the POISE Trial and the VISION Study, we found that the majority of overt strokes occurred within the first 48 hours after surgery, and we expect that covert stroke has a similar temporal distribution. The timing of the MRI study enabled us to detect these events, and prior studies of perioperative covert stroke have used the same or similar protocols.[13-15]

The MRI imaging results were not blinded to the patients, attending physicians, radiologists, or the study team.

Patient identifiers were removed, and MRIs were electronically transferred via a secure encrypted connection to the central imaging interpretation centre. A neurologist and neuroradiologist who were blinded to the baseline characteristics and clinical outcomes independently assessed the MRI studies in duplicate, and provided their individual interpretations regarding the presence of imaging lesions that represented acute perioperative cerebral ischemia and chronic ischemic findings, defined according to recent consensus criteria.[53] All disagreements were resolved by consensus. Chance-corrected agreement between assessors was quantified using Cohen's kappa.

2.3.6 Statistical Analysis

For the first primary objective, we report the incidence of acute covert stroke in the study population and the 95% confidence intervals (CI). We also report the incidence of acute overt stroke, diagnosed prior to the MRI scan, overt stroke diagnosed within 24 hours after the MRI scan and overt stroke diagnosed >24 hours after the MRI scan.

For the second primary objective, we report the rate of enrollment of patients in the study, and separately in each participating centre.

We determined the clinical characteristics at baseline in the entire study population, and separately for patients who did and did not suffer a covert stroke. We determined the change from baseline to 30 days after surgery for the functional

assessments in the entire study population, and separately for patients who did and did not suffer a covert stroke. We used the t-test to calculate a p-value for the difference in change of the mean scores between patients with covert stroke and those without a covert stroke. All analyses were performed using SAS version 9.2 (Cary, North Carolina).

2.4 Results of the NeuroVISION Pilot Study

From September 2011 until December 2012, the NeuroVISION Pilot Study enrolled 100 patients from 6 centres in 4 countries (see Table 4); all patients completed the 30-day follow-up.

Table 4: Patient Recruitment in the NeuroVISION Pilot Study.

Site	Number of Patients enrolled in NeuroVISION	Date first patient enrolled	Date last patient enrolled	Total number of weeks of enrollment	Number of patients/week
Hamilton	25	Oct 31/11	April 3/12	22.1	1.1
Edmonton	5	Jul 13/12	Jul 30/12	2.4	2.1
London	25	Nov 9/11	April 16/12	22.7	1.1
Hong Kong	20	Sept 14/11	March 8/12	25.1	0.8
India	20	Jun 20/12	Dec 10/12	24.7	0.8
Cleveland	5	Jul 16/12	Aug 1/12	2.3	2.2

Table 5 reports the preoperative characteristics. Forty-three percent of enrolled patients were ≥ 75 years of age and 47% of patients were women. The most

common cardiovascular risk factors were hypertension (71 patients), diabetes (21 patients), and a history of coronary artery disease (18 patients). Five patients had a history of stroke, 4 patients had a history of a transient ischemic attack, and 4 patients were in atrial fibrillation prior to surgery. The most common surgeries were major orthopedic (41 patients), major general (27 patients), and urological/gynecological (22 patients).

All patients had an MRI study of the brain between postoperative days 3 and 10 (median postoperative day 4, interquartile range 3-5.25 days after surgery). There was a high prevalence of chronic ischemic lesions (reported in 33% of the overall population) and ischemic leukoaraiosis (reported in 64% of the overall population).

Table 5: Preoperative participant characteristics and type of surgery

Patient characteristics and type of surgery	All patients (N=100)	No Covert Stroke (n=90)	Covert Stroke (n=10)
Age (n, %)			
65-74 years	57 (57.0)	53 (58.9)	4 (40.0)
≥75 years	43 (43.0)	37 (41.1)	6 (60.0)
Females (n, %)	47 (47.0)	42 (46.7)	5 (50.0)
Risk factors (n, %)			
History of coronary artery disease	18 (18.0)	16 (17.8)	2 (20.0)
History of stroke	5 (5.0)	4 (4.4)	1 (10.0)
History of a transient ischemic attack	4 (4.0)	3 (3.3)	1 (10.0)
Diabetes	21 (21.0)	20 (22.2)	1 (10.0)
Hypertension	71 (71.0)	66 (73.3)	5 (50.0)
Current atrial fibrillation	4 (4.0)	4 (4.4)	0 (0.0)
Obstructive sleep apnea	8 (8.0)	8 (8.9)	0 (0.0)
Chronic obstructive pulmonary disease	11 (11.0)	11 (12.2)	0 (0.0)
Type of surgery (n, %)			
Major vascular	1 (1.0)	1 (1.1)	0 (0.0)
Major general	27 (27.0)	24 (26.7)	3 (30.0)
Major thoracic	1 (1.0)	1 (1.1)	0 (0.0)
Major urology or gynecology	22 (22.0)	19 (21.1)	3 (30.0)
Major orthopedic	41 (41.0)	38 (42.2)	3 (30.0)
Major neurosurgery	1 (1.0)	1 (1.1)	0 (0.0)
Low-risk	12 (12.0)	11 (12.2)	1 (10.0)
Chronic neuroimaging findings			
Old ischemic lesions	33 (33.0%)	29 (32.2%)	4 (4.0%)
Leukoaraiosis	64 (64.0%)	58 (64.4%)	6 (6.0%)

The incidence of covert stroke was 10.0% (10/100 patients; 95% CI, 5.5-17.4%). Five of 6 centres reported at least one covert stroke (Table 6). Covert stroke occurred 3 of 41 patients (7.3%) who underwent major orthopedic, 3 of 27 patients (11%) who underwent major general, 3 of 22 patients (14%) who underwent major urological/gynecological surgery, and 1 of 12 patients (8%) who underwent low-risk surgery. The chance-corrected agreement between MRI interpreters for the presence of acute ischemic lesions was very good (kappa = 0.94). A single disagreement was resolved by consensus. Table 7 reports the clinical outcomes.

Table 6: Covert stroke result at each centre

Acute covert stroke	Total (N=100)
All centres	10 (10.0%); 95% CI, 5.5-17.4
Hamilton, Canada	3/25 (12.0%)
Edmonton, Canada	0/5 (0.0%)
London, Canada	2/25 (8.0%)
Hong Kong, China	2/20 (10.0%)
Bangalore, India	2/20 (10.0%)
Cleveland, United States	1/5 (20.0%)

Table 7: Clinical outcomes

Clinical outcome	All Patients (N=100)	No Covert Stroke (N=90)	Covert stroke (N=10)
Delirium within first 3 days after surgery n (%; 95% CI)†	8 (8.1, 3.8-15.8)	7 (7.9, 3.5-16.1)	1 (10.0, 0.0-4.6)
Death during first 30 days after surgery n (%; 95% CI)	0 (0.0, 0.0-0.0)	0 (0.0, 0.0-0.1)	0 (0.0, 0.0-0.3)
Elevated troponin marker during first 30 days after surgery n (%; 95% CI)	17 (17.0, 10.5-26.1)	15 (16.7, 9.9-26.3)	2 (20.0, 0.0-55.8)

† N=99 (N=89 for no covert stroke, N=10 for covert stroke) as delirium assessments were not performed on a single patient..

A single overt stroke was clinically diagnosed only after the research MRI study of the brain demonstrated findings of an acute ischemia on postoperative day 6. In this patient who underwent a liver resection, the routine daily clinical assessments did not document the presence of a neurological deficit, and we documented this as a covert stroke as per the research protocol. However, a neurology consult was requested due to the findings on the research MRI study. The detailed neurological clinical assessment documented a substantial right-sided ataxia that was in keeping with the imaging findings.

Eight patients in the overall study population (1/10 patients with covert stroke) developed delirium during the first 3 days after surgery. No patients died in the 30-day postoperative follow-up. Routine cardiac troponin concentrations were measured as a part of the standard of care, and 17 patients out of 100 (2/10 patients with covert stroke) had an elevated troponin measurement after surgery.

Table 8 reports the changes in the measures of quality of life and physical function from preoperative baseline until 30 days after surgery. There was no statistically significant difference between patients with and without a covert stroke.

Table 8: Change in cognition and physical function between preoperative and 30 day assessments

Instrument	No Covert Stroke		Covert Stroke		p-value
	N	Mean change (SD)	N	Mean change (SD)	
EQ-5D index score	86*	0.03 (0.21)	10	0.001 (0.24)	0.73
Lawton iADL score	85*	-1.14 (1.83)	10	-1.90 (1.85)	0.22
Modified Rankin Score	85*	0.19 (0.82)	10	0.70 (1.16)	0.08

* Incomplete follow-up for the quality of life and physical function questionnaires occurred due to an administrative error in a single centre, resulting in the loss of completed questionnaires

2.5 Discussion of the NeuroVISION Pilot Study

The NeuroVISION Pilot Study demonstrated a 10% incidence of covert stroke after noncardiac surgery. Covert stroke was documented in patients across a broad group of noncardiac surgeries (i.e., orthopedic, general, urological/gynecological, and low risk surgeries).

One patient experienced an overt stroke which was diagnosed as a result of the research MRI study; based on the MRI result a neurology consult was undertaken and the patient was found to have previously unappreciated neurological deficits. This incident demonstrates how neurologic symptoms due to

stroke may be missed in the postoperative period due to the effects of postoperative pain, medication, and limited mobility, raising the possibility that some perioperative strokes go unrecognized clinically. The study protocol did not mandate a neurological examination in all patients with acute perioperative covert strokes, and we cannot exclude the possibility that other patients with covert infarcts had clinical manifestations that were not detected in the process of routine post-operative care.

We found a high prevalence of chronic ischemic findings on MRI imaging, and patients had a high prevalence of vascular disease and risk factors for vascular disease. The high burden of medical comorbidity in the study population is in keeping with the findings of the VISION Study, a recently published large prospective cohort study of a representative sample of adults undergoing noncardiac surgery.[47]

2.5.1 Strengths of the NeuroVISION Pilot Study

The NeuroVISION Pilot Study is the first study of covert stroke after noncardiac, noncarotid artery, surgery and one of the largest studies of perioperative covert stroke. We demonstrated a similar incidence of perioperative covert stroke as has been documented in studies of patients undergoing carotid endarterectomy (pooled estimate 10%) and this is also in the range of what has been documented after cardiac surgery (range 16% to 45%).[13-15, 54-58] Patients

in the NeuroVISION Pilot were recruited from a broad range of surgical disciplines, and the surgical distribution was similar to that of worldwide patients undergoing noncardiac, noncarotid artery surgery.[47] We also demonstrated the feasibility of the study protocol with an excellent recruitment rate and good protocol adherence. No patients were lost to follow-up. However, the rate of follow-up for quality of life and physical function was decreased (94%) due to these data being unavailable from a single centre.

2.5.2 Limitations of the NeuroVISION Pilot Study

The major limitation of the NeuroVISION Pilot Study is that it was not powered to inform the clinical and the cognitive impact of covert stroke. Covert cerebral ischemia in the nonsurgical setting is associated with an increased risk of cognitive impairment, overt stroke and death,[59] but the impact of perioperative covert stroke has not been studied. Patients with perioperative covert stroke may suffer a decline in physical function, quality of life, and cognitive function. Given the large volume of surgery worldwide, covert stroke after noncardiac surgery may represent a substantial population risk factor for the development of cognitive impairment.[60] We have successfully demonstrated the feasibility of a large study to characterize the impact of covert stroke.

CHAPTER 3: PROTOCOL FOR A FULL STUDY OF THE IMPACT OF COVERT STROKE AFTER NONCARDIAC SURGERY

The NeuroVISION Pilot Study suggests that the annual incidence of covert stroke is high during the perioperative period after noncardiac surgery (i.e., potentially 5-10 million adults globally). However, the importance of this finding is unclear, as no study has examined the long-term impact of perioperative covert stroke on cognitive function or other clinical outcomes. The main goal of the NeuroVISION study is to determine the impact of covert stroke by determining the association of covert stroke to patient-relevant cognitive and clinical outcomes.

This will be the largest and the most comprehensive study of perioperative covert stroke undertaken.

3.1 Study outline

The NeuroVISION Pilot Study suggests that covert stroke may be common after noncardiac surgery, but no study has characterized the impact of acute perioperative covert stroke on patient-important outcomes.

NeuroVISION is a multicentre prospective cohort study to characterize the impact of covert stroke after noncardiac surgery.

3.2 Primary objectives for the NeuroVISION Study

Our primary objective is to characterize the impact of perioperative covert stroke on neurocognitive function 1 year after elective noncardiac surgery.

3.3 Secondary objectives for the NeuroVISION Study

Our secondary objectives are to characterize the:

1. overall incidence of perioperative covert stroke;
2. association of perioperative covert stroke with cognitive dysfunction;
3. clinical risk factors for perioperative covert stroke;
4. relationship between covert stroke and delirium;
5. association of covert stroke with major adverse cardiovascular events;
- and
6. association of covert stroke with physical function and quality of life.

3.4 Hypothesis of the NeuroVISION Study

We hypothesize that perioperative covert stroke is associated with cognitive dysfunction at 1 year after surgery.

3.5 Eligibility criteria for the NeuroVISION Study

3.5.1 Inclusion criteria

Patients must fulfill the following criteria:

1. age \geq 65 years;
2. anticipated length of hospital stay of at least 2 days after elective noncardiac surgery that occurs under general or neuraxial anesthesia; and
3. written informed consent for potential participation prior to noncardiac surgery.

3.5.1 Exclusion criteria

Patients fulfilling any of the following criteria will be excluded:

1. contraindication to MRI (e.g. implanted devices not safe for MRI studies, claustrophobia);
2. unable or unwilling to attend the follow-up appointments;
3. documented history of dementia;
4. residing in a nursing home;
5. undergoing carotid artery surgery or intracranial surgery;

6. unable to complete neurocognitive testing due to language, vision or hearing impairment; and
7. unable to communicate with the research staff due to language barriers.

3.6 Outcomes of the NeuroVISION Study

3.6.1 Primary outcome for the NeuroVISION Study

Our primary outcome is postoperative cognitive dysfunction, as measured by a decrease of two or more points on the Montreal Cognitive Assessment (MoCA) scale from the preoperative baseline test to the 1-year follow-up.

The National Institute of Neurological Disorders and Stroke (NINDS) has coined the term “vascular cognitive impairment” (VCI) for neurological dysfunction that is caused by, or associated with vascular factors.[61] They have recommended the Montreal Cognitive Assessment (MoCA) instrument as a tool for neurocognitive testing of patients with suspected VCI,[61] and MoCA has shown good correlation when compared with the full 60-minute NINDS VCI Battery neuropsychological assessment.[62]

The MoCA is used extensively in the assessment of cognitive function after stroke and cerebrovascular disease.[62-66] It has proved superior to the Mini-Mental State Exam (MMSE), in assessments of language skills, visuo-spatial and executive function, and in the diagnosis of cognitive dysfunction after stroke.[63, 65]

The neurocognitive impact of covert stroke after surgery has not been studied in the past, and it is not known whether it affects the same cognitive domains as ambulatory covert stroke. The MoCA instrument assesses multiple cognitive domains, and this will provide a thorough assessment of the impact of acute perioperative covert stroke. A change of two points on the MoCA score has been deemed relevant to patient care, and has been used as a cut-off for significant cognitive decline in published literature.[65] There are no studies of MoCA score changes that patients. However, a small study of 38 alcoholic patients undergoing an alcohol detoxification program demonstrated an improvement in the MoCA score from a baseline of 22.0 to 24.7 (increase of 2.7, $p < 0.01$) at the 12-week follow-up.[67]

Cognitive function spans a number of domains and reliance on a single test may be insensitive to change.[61] In addition to the MoCA, we will also test neurocognitive function using the Digit-Symbol Substitution Test (DSST) [66] and the Trail-Making Test (TMT).[67] The use of several standardized measures of cognition will allow testing of multiple cognitive domains, and to assess if the cognitive changes are associated with patient-important outcomes of physical function and quality of life. Furthermore, these additional tests are endorsed for the assessment of cognitive function after stroke[59] and in the perioperative period.[68] Studies of covert stroke in the nonoperative setting have used these

tests,[69] and thus we will be able to compare the impact of perioperative covert stroke with the neurocognitive impact of covert stroke in the non-operative setting.

3.6.2 Secondary outcomes for the NeuroVISION Study

3.6.2.1 Measuring the incidence of acute perioperative covert stroke

We will detect perioperative covert strokes using a MRI study of the brain that will be performed between postoperative days 2 and 9, and as soon as the patient is able to tolerate this procedure.

The MRI in the pilot study was performed between postoperative days 3 and 9. We made the decision to perform the MRI studies starting on postoperative day 2 for several reasons:

1. This protocol would still capture the majority of the overt perioperative strokes that occur within the first 48 hours after surgery
2. There is an ongoing worldwide trend of decreasing hospital length of stay. As an example, the average length of stay after hip arthroplasty in the USA decreased from 9.1 days in 1991-1992 to 3.7 days in 2007-2008 (P=0.002), despite an increase in age and patient comorbidities.[68] .

3.6.2.2 Measuring postoperative delirium

The diagnosis of delirium is based on the criteria outlined in the DSM-IV. The Cognitive Assessment Method (CAM) is a bedside rating scale that has been

developed to allow clinical staff without specialized training to diagnose delirium with high specificity and sensitivity.[73] Nurses and trained lay research staff perform as well as psychiatrists in scoring the CAM.[51] The sensitivity and specificity of the CAM for the diagnosis of delirium against the gold standard of a psychiatrist diagnosis are high (95% or greater).[73] A recent meta-analysis concluded that the CAM has the best supportive data as a bedside instrument for the diagnosis of delirium.[74] At least nine studies have used CAM to determine the incidence of postoperative delirium in elderly patients undergoing elective and emergent orthopedic surgery, general surgery, and major elective surgery (see Table 9). We will use the CAM in this study to diagnose delirium.

Table 9: Summary of studies using CAM to diagnose delirium in elderly patients undergoing non-cardiac surgery from systematic review by Dasgupta et al.[47]

First Author	Surgery Type	Sample Size	Incidence of delirium
Freter	Elective arthroplasty	132	13.6%
Kudoh	Elective orthopedic	328	26.0%
Fisher	Elective orthopedic	80	17.5%
Morrison	Emergent hip fracture	541	16.0%
Zakriya	Emergent hip fracture	168	28.0%
Galankis	Emergent or elective hip	105	23.8%
Sasajima	Elective peripheral vascular bypass	110	29.1%
Marcantonio	Major elective	876	9.0%
Yoshimura	Elective liver resection	100	17.0%

Research personnel will follow patients throughout their time in hospital. The patients will be screened for delirium twice daily during the first 72 hours after surgery. This measurement strategy is based on preliminary data from the Cleveland Clinic (Dr. D. Sessler) showing that once-daily measurements are insufficient, and that 95% of postoperative delirium is detected within three days.

Assessment for delirium will be based on the Confusion Assessment Method (CAM). It will include a short patient interview, an interview of the family when available, staff (nursing staff or attending physician) interview, and a chart review. The research assistants will attend a CAM training session at the start of the study, and the site PI will review the patient case record forms and research study charts prior to submission to the central coordination centre, to ensure that the incidence of delirium and other meaningful outcomes are correctly recorded.

Patients will be diagnosed with delirium if they meet the following CAM criteria for delirium: 1) acute onset of fluctuating cognitive impairment, 2) deficits of attention, and 3) either altered level of consciousness or disorganized thought processes. Criterion 1 will be met if there is documentation of an acute change or fluctuation in mental status noted either in the medical record or when interviewing the patient, staff, or caregiver. Criteria 2 and 3 will be judged based upon the patient's response to the interview questions. If delirium is identified, no further CAM assessments will be performed during the hospital stay.

3.6.2.3 Measuring physical function after surgery

Physical function will be measured using two instruments. The Modified Rankin Scale is a functional disability scale weighted to neurological function; it has been validated as an important measure of stroke outcome, and used in most major trials in patients with stroke for this purpose.[69-74] It is not sensitive to minor changes in physical function, but using it will allow us to compare the NeuroVISION Study patients with other populations of patients with stroke.

The Lawton Instrumental Activities of Daily Living (iADL) Scale is used for the assessment of functional status, and measures the patients' ability to perform tasks necessary to live independently in the community. Performance of iADLs requires mental as well as physical capacity, and the iADL scale measures the functional impact of emotional, cognitive, and physical impairments. The decision to include this instrument was made because the ability to live independently will be of high importance to patients.

3.6.2.4 Measuring quality of life after surgery

Postoperative overt stroke has a significant impact on the patients' quality of life, and the majority of the affected patients suffer significant functional impairment.[5] The impact of covert stroke on the health-related quality of life in the postoperative period is unknown. We will use the EQ-5D questionnaire to assess the patients' health-related quality of life. This is a short, self-reported questionnaire

that is designed as a generic measure of health status, and can be collected during a face-to-face or telephone interview.

The EQ-5D questionnaire consists of two parts. The first part contains the EQ-5D descriptive system, comprising of 5 questions regarding mobility, self-care, usual activities, pain, and depression. The second part is a vertical, visual analogue scale with the end-points of “best imaginable health state” and “worst imaginable health state”. EQ-5D has been used as a measure of health-related quality of life in patients who have suffered a stroke,[75, 76] have been diagnosed with dementia,[77] and in those undergoing surgery.[78, 79] The EQ-5D questionnaire performs well for evaluating the health-related quality of life in a population with cognitive impairment,[80] and has also been adapted for administration by proxy. A systematic review identified 10 studies assessing the properties of EQ-5D in the elderly, and found that this questionnaire has good reliability, validity, and responsiveness in this population.[81]

3.6.2.5 Measuring depressive symptoms after surgery

Depression is an important consequence of overt stroke. A recent systematic review included 51 studies, and calculated a pooled estimate of the incidence of depression among survivors of stroke to be 33% (95% CI, 29% to 36%).[88] We will use the 5-question version of the Geriatric Depression Scale (GDS-5) to assess depressive symptoms in the NeuroVISION Study. This tool has been used in older

stroke survivors,[88] and it is the most validated instrument in the assessment of depressive symptoms in hospitalized older adults.[89] GDS-5 was evaluated by Rinaldi et al in 60 hospitalized elderly people with a good performance employing a threshold of ≥ 2 points for the diagnosis of depression (sensitivity of 0.94; 95% CI, 0.91–0.98 and specificity of 0.81; 95% CI, 0.75–0.87).[90]

3.6.2.6 Measuring clinical outcomes

We will measure the following clinical outcomes:

1. Acute cerebral ischemia
2. Covert Stroke
3. Overt Stroke
4. Transient Ischemic Attack
5. Delirium
6. Death
7. Myocardial Infarction (MI)
8. Myocardial Injury after Noncardiac Surgery (MINS)
9. Nonfatal cardiac arrest
10. Major adverse cardiovascular events (composite)
11. Cardiac revascularization procedures
12. Bleeding
13. New atrial fibrillation

14. Clinically important hypotension
15. Congestive heart failure
16. New acute renal failure
17. Infection
18. Dementia and mild cognitive impairment

Appendix 2 provides the definitions for all clinical outcomes

3.7 Enrollment of patients into the NeuroVISION Study

We will recruit 1500 patients into the NeuroVISION Study over a 2-year period. Centres in Hamilton, London, Edmonton, Hong Kong, Bangalore (India), Cleveland Clinic (USA) have already participated in the NeuroVISION pilot, and the cognitive tests have been validated in the local languages.

The study personnel are well versed in the study protocol, and numerous studies involving MRI have been successfully completed in these centres. We will approach other potential centres with a history of successful MRI studies.

Research personnel will screen the patient list in the preoperative assessment clinic to identify patients who fulfill the eligibility criteria. Research personnel will approach all patients who fulfill the eligibility criteria to obtain informed consent.

3.8 Sampling strategy in the NeuroVISION Study

In the NeuroVISION Pilot Study, there were approximately 15 to 30 eligible patients per centre each week, but due to limitations on the availability of the MRI scanners, each centre was able to recruit up to two patients per week. Because of the disparity between the number of eligible patients and the MRI capacity, we will employ a sampling strategy that we used in the pilot study to ensure proportionate representation of patients that reflects the overall surgical population.

In the VISION Study,[47] approximately 31% of patients are undergoing general surgery, 30% undergoing major orthopedic surgery, 24% are undergoing urological or gynecological surgery, and 14% are undergoing vascular, thoracic, or neurosurgery (see Appendix 1 for surgery definitions, and Table 10 for distribution of surgical patients). In order to ensure proportionate representation of patients in the NeuroVISION Study that reflects the overall surgical population, we will randomly assign centres the surgical group they are to recruit each week and the day of the week they are to start recruitment. Study personnel will then start recruiting the assigned surgical group for the week starting on the designated start day of the week. They will approach consecutive eligible patients until they have filled the maximum number of MRI slots they have available for the week. We successfully employed this strategy in the NeuroVISION Pilot Study.

Table 10: Distribution of surgical patients in VISION and recruitment allocation for NeuroVISION

Type of Surgery	Percent of total surgeries in VISION (excluding minor surgery)	Percent of total recruitment in NeuroVISION
Vascular	4.4	
Thoracic	2.4	
Neurosurgery	7.3	
Vascular, Thoracic and Neurosurgery combined	14.1	15
General Surgery	31.2	30
Urological or gynecological	24.2	25
Major Orthopedic	30.8	30

3.9 Data collection

Table 11 provides a summary of the data collection protocol.

Table 11: Summary of data collection

Time period	Data collection required
Preoperative (before day of surgery)	<ol style="list-style-type: none"> 1. Neurocognitive, Physical Function and Quality of Life assessments 2. Clinical variables
Day of Surgery	<ol style="list-style-type: none"> 1. Clinical and haemodynamic variables
Postoperative (during hospitalization)	<ol style="list-style-type: none"> 1. CAM delirium screening, twice daily for the first 72 hours after surgery 2. MRI exam between postoperative day 3 and day 9 inclusive with the following sequences: <ol style="list-style-type: none"> a. Axial FLAIR b. GRE c. T2 d. DWI 3. Clinical variables
Postoperative (30 day follow up)	<ol style="list-style-type: none"> 1. Physical function and Quality of Life assessments 2. Clinical Variables
Postoperative (1 year follow up)	<ol style="list-style-type: none"> 1. Neurocognitive, Physical Function and Quality of Life assessments 2. Clinical Variables

3.9.1 Data collection in the preoperative period

After obtaining written informed consent from eligible patients or their legal decision makers, research personnel will administer the Montreal Cognitive Assessment questionnaire, the DSST and TMT instruments to assess baseline cognitive function. They will also administer the Lawton iADL Scale, modified

Rankin Scale, GDS-5 and the EQ-5D to assess physical function, mood and health-related quality of life at baseline. The administration of the questionnaires will require approximately 30 minutes. The research personnel will interview patients and review their charts to obtain information on patient characteristics (Appendix 2 and 3 for definitions). Preoperative and postoperative laboratory assessments will be completed for clinical reasons and data collected as available.

3.9.2 Data collection during the hospital stay

Research personnel will evaluate patients and review their medical records to collect data on perioperative outcomes that may be associated with perioperative covert stroke (see Appendix 3 for definitions).

3.9.3 Data collection after hospital discharge

Research personnel will contact patients by phone 30 days after surgery. They will administer the Lawton iADL Scale, Modified Rankin Scale, GDS, and EQ-5D questionnaires over the telephone. The telephone interview is expected to last approximately 30 minutes. The research staff will also collect data regarding overt stroke and other clinical study outcomes (Appendix 2). If the patient indicates they have experienced a stroke, the research personnel will contact their physicians to obtain the appropriate documentation.

Research personnel will assess the patients in person at 1 year after surgery. They will collect data regarding clinical outcomes, and administer the MoCA, DSST, TMT, Lawton iADL Scale, Modified Rankin Scale, GDS, and EQ-5D questionnaires.

3.10 MRI Study Protocol

Study personnel will arrange a MRI study of the brain that will be performed between postoperative days 2 and 9, and as soon as the patient is able to tolerate this procedure. The entire MRI study is expected to last approximately 20 minutes.

MRI study sequences will consist of axial FLAIR, GRE, T2 and Diffusion-weighted imaging (DWI) with ADC map. The specific MRI sequences will be performed according to the local standard of care with a minimum 1.5 Tesla MRI machine, and a slice thickness of 3 to 5 mm, with no gap.

3.10.1 MRI Study Interpretation

The MRI sequences in the NeuroVISION Study are performed routinely for the diagnosis of stroke, thus all centres will have significant experience with the imaging protocols. The MRI studies will have patient identifiers removed, and will then be electronically transferred via a secure connection to a central study repository at PHRI within 1 week of image sequence acquisition. MRI studies will be independently interpreted by 2 neuroimaging experts at the imaging interpretation centre within 3 weeks of the original image upload.

Neuroimaging experts will be blinded to the baseline characteristics and clinical outcomes. Disagreements will be resolved by consensus and if consensus is not possible after discussing the reasons for their differing decision, a third neuroimaging expert will adjudicate the case and their decision will be final. If we identify any issues regarding imaging quality, we will immediately address them with the centre.

3.11 Ensuring protocol adherence

Several procedures to ensure overall data quality will be followed including:

- 1) all research personnel will undergo a training session prior to study commencement to ensure consistency in study procedures including data collection and reporting, particularly regarding the assessment of delirium and cognitive function;
- 2) all centres will have a detailed study operations manual that will outline each step of the protocol;
- 3) investigators can use a toll free phone number to a help line at the project office to resolve any problems or questions that arise;
- 4) the project office personnel will evaluate all data as soon as it is received and quality control checks will identify any errors or omissions and the project office personnel will notify the sender of any such issues via secure internet, fax, telephone, or visit if necessary;
- 5) the project office personnel will review detailed monthly reports on screening, enrollment, patient follow-up, data transmission, consistency and

thoroughness of data collection, and event rates, and they will immediately address any identified issues with the appropriate sites.

3.12 Statistical methods

3.12.1 Sample size

Our sample size calculation is based upon our primary objective, the proportion of patients with a decrease of two or more points on the MoCA scale from preoperative baseline test to the 1-year follow-up. We will undertake a multivariable analysis to determine if perioperative covert stroke is associated with the incidence of postoperative cognitive dysfunction as measured by the MoCA, at 1 year after surgery (i.e., the dependent variable). Based on the ISPOCD-1 study, we expect a 10% event rate for postoperative cognitive dysfunction (95%CI, 8.2-12.1%). From non-operative literature, we expect that covert stroke will be associated with a 2-fold increase in the risk of cognitive dysfunction.[19, 59]

We will include a sample size of 1500 patients, as this will allow us to detect a minimum odds ratio of 1.98 for the risk of cognitive dysfunction after a covert perioperative stroke, at a power of 80% and two-sided alpha of 0.05, assuming a 10% incidence of postoperative cognitive dysfunction and a 10% incidence of perioperative covert stroke (Table 12).

Table 12: Sample size calculation: Minimum detectable odds ratios at a power of 80% and alpha of 0.05 for a sample size of 1500, according to incidence of cognitive dysfunction and covert stroke

Incidence of postoperative covert stroke	Incidence of postoperative cognitive dysfunction		
	8%	10%	12%
8%	2.30	2.16	2.07
10%	2.09	1.98	1.93
12%	2.05	1.94	1.86

Furthermore, we will evaluate 11 potential predictors in our multivariable analysis (see section 11.2.1 below). Simulation studies demonstrate that logistic models require 10 to 15 events per predictor to produce stable estimates.[82, 83] A sample size of 1500 patients will ensure a stable model – if the event rate is 10%, we will have more than 12 events per variable, but even if the event rate is 8% (i.e. the lower limit of 95% confidence interval for estimate), we will still have 10 events per variable.

3.12.2 Analysis plan for primary objective

Our primary objective is to characterize the impact of perioperative covert stroke on neurocognitive function 1 year after elective noncardiac surgery. We will undertake a multivariable logistic regression analysis to develop a generic model in which the dependent variable is the change in cognitive function 1 year after surgery, and the independent variables are incidence of perioperative covert stroke

(present or absent), , age, sex, ethnicity, family history of dementia in a first-degree relative, education level, baseline physical impairment as measured by the Lawton scale, depression score as measured by GDS, baseline neurocognitive function as measured by MoCA, and chronic use of psychotropic medications. The predictors were selected based on clinical relevance. For all regression models, we will report the odds ratios [OR], corresponding standard error, 95% confidence intervals and associated p-values. For all tests, we will use two-sided alpha = 0.05 level of significance. Examination of residuals will provide an assessment of model assumptions for regression analyses. Goodness-of-fit for the models will be performed using appropriate Hosmer-Lemeshov tests. For multivariable regression analysis, we anticipate multicollinearity (correlations among predictor variables).[84] We will assess collinearity using the variance inflation factor (VIF), which measures the extent to which the variance of the model coefficients will be inflated (because of the correlation of the variable with other predictor variables) if that variable is included in the model. We will consider variables with $VIF > 10$ collinear, and if this occurs we will exclude one of the collinear variables from the analysis.

3.12.3 Analysis plan for secondary objectives

We will report the incidence of perioperative covert stroke as total numbers of events and relative percentage with a 95% confidence interval. We will undertake

multivariate logistic regression analyses in order to address the secondary objectives of determining clinical risk factors for perioperative covert stroke, characterize the association of covert stroke with cognitive dysfunction and delirium, and characterize the association of covert stroke with major adverse cardiovascular events. The details of dependent and independent variables for the analyses of these secondary outcomes are outlined in Table 13. For all tests, we will use $\alpha = 0.05$ level of significance. Examination of residuals will provide an assessment of model assumptions for regression analyses. Goodness-of-fit for the models will be performed using appropriate Hosmer-Lemeshov tests. For multivariable regression analysis, we anticipate multicollinearity (correlations among predictor variables).[84] We will assess collinearity using the variance inflation factor (VIF). We will consider variables with $VIF > 10$ collinear and we will exclude one of them from the analysis. We will undertake a multivariable ANCOVA analysis in order to address the secondary objective of characterizing the association of covert stroke with a change in physical function and quality of life 1 year after surgery. The details of dependent and independent variables for this analysis are outlined in Table 14.

Table 13: Statistical Analysis of secondary outcomes: dependent and independent variables for multivariate logistic regression

Secondary Objective	Dependent Variable	Expected incidence of dependent variable*	Independent Variable
Characterize clinical risk factors for perioperative covert stroke	Perioperative covert stroke	10%	1. Age 3. History of: - Cerebrovascular disease - Hypertension - Diabetes 4. Incidence of hypotension 5. Presence of atrial fibrillation in the postoperative period
Characterize the association of covert stroke with delirium	Delirium	10%	1. Perioperative covert stroke 3. Age 4. Surgical procedure 5. Baseline physical impairment as measured by iADL 6. Use of sedating or psychotropic medications 7. Baseline neurocognitive function as measured by MoCA
Characterize the association of covert stroke with major adverse cardiovascular events	Major adverse cardiovascular events	15%	1. Perioperative covert stroke 2. Age 3. Surgical procedure 4. History of - recent CAD - peripheral vascular disease - stroke - COPD - Active cancer - Congestive heart failure

* Based on literature, as well as the results of the VISION Study and NeuroVISION Pilot Study

Table 14: Statistical analysis of secondary outcomes: dependent and independent variables for multivariable ANOVA analysis

Secondary Objective	Dependent variable	Independent variables
Characterize the impact of covert stroke on physical function	Change in Lawton iADL score at 1 year	<ol style="list-style-type: none"> 1. Incidence of perioperative covert stroke 2. Age 3. Surgical procedure 4. Incidence of delirium 5. Baseline physical impairment as measured by the Lawton iADL scale 4. Baseline depression score on GDS-5 7. Baseline neurocognitive function as measured by MoCA
Characterize the impact of covert stroke on quality of life	Change in EQ-5D score at 1 year	<ol style="list-style-type: none"> 1. Incidence of perioperative covert stroke 2. Age 3. Surgical procedure 4. Incidence of delirium 5. Baseline physical impairment as measured by the Lawton iADL scale 6. Baseline depression score on GDS-5 7. Baseline neurocognitive function as measured by MoCA

3.12.4 Statistical analysis with missing data

All attempts will be made to obtain complete assessments in hospital, at 30 days and 1 year after surgery. We were able to follow up with 100% of the patients enrolled in the NeuroVISION Pilot Study at 30 days. The rates of loss to follow-up have been low (<1%) in our past perioperative studies.[5, 47] In the POISE Trial, 20/8531 patients were lost to follow-up, and in the VISION study 40/15,133

patients were lost to follow-up. The quality of data was also very high, as only 29 patients in the VISION study had any missing data on the 24 preoperative variables that were collected.

Furthermore, Dr. Dasgupta (co-investigator) has recently completed a prospective cohort study of 355 hospitalized patients with delirium, and achieved a 3-month follow-up rate of 97% in this population. Dr. Chan (co-investigator) recently completed a randomized controlled trial of bispectral index monitoring in 921 older adult patients undergoing major noncardiac surgery, and also achieved a 3-month follow-up rate of 97%[98]. These past successes of the study investigators indicate that the rate of loss to follow-up in the NeuroVISION study should be low.

Despite encouraging data to suggest that the rate of loss to follow-up will be minimal (see Section 13.2), even small proportions of missing data can bias the study results. Furthermore, cognitive decline may increase the risk of loss to follow-up and the risk of incomplete cognitive assessment. This may introduce systematic bias in the study analysis. It is possible to counteract this bias if the reason for missing data is known.[85, 86] We will collect the reasons for missing data, and will use a method of evidence-informed data imputation to minimize systematic bias from incomplete cognitive assessments (Table 15).

Table 15: Evidence-informed Data Imputation of missing data for cognitive assessments

Probability of Cognitive Decline	Reported Reason for Missing	Data Imputation	Missing Data Clarification
Confirmed	New diagnosis of dementia	Multiple imputations centered at the average MoCA score change for patients with new diagnosis of dementia, mild cognitive impairment, or those started on medication to treat cognitive impairment	Informative Missing
	New diagnosis of mild cognitive impairment		
	Started medication to treat cognitive impairment (acetylcholinesterase inhibitor, NMDA receptor antagonist)		
Probable	New diagnosis of stroke	Multiple imputations centered at the average MoCA score change for those with MRI findings of old stroke or old cerebral small vessel disease	
	Cardiovascular death		
	Impairment on other related scale: decreased iADL (Lawton), depression (GDS-5)		
	Admission to long term care facility or similar institution		
	Significant cognitive impairment reported by family or care-giver		
Unlikely	Refusal or missed, but reported well	Multiple imputations centered at zero change in MoCA value	
Unknown	Lost to Follow up (likely <1%)	Imputed directly through mixed model	Missing at Random

3.13 Ethical considerations

3.13.1 Blinding of the MRI study results

The results of the MRI scans will be blinded until the 1-year follow-up

appointment. If relevant incidental clinical findings are present (e.g., tumor, vascular malformations), the neuroimaging experts will make the decision whether unblinding needs to occur. If it is thought the incidental findings require unblinding, these findings will be reported to the local principal investigator and to the patient's physicians as soon as the scans are interpreted.

We have decided to blind health care providers and patients to the MRI results until the 1 year follow-up for several reasons:

- (1) blinding of the study results will eliminate potential bias in the ascertainment of the study outcomes;
- (2) this study is not a part of the standard of care in the postoperative period;
- (3) the implications of acute covert stroke in the perioperative period are not clear and any management decisions on the basis of the MRI study results would not be based on evidence which could impact outcomes;
- (4) any incidental findings, such as a tumor, will be unblinded and the results will be communicated to the attending physicians, and this is beneficial to the patient;
- (5) the research MRI study will be available for future comparisons if required for clinical care after the completion of the study, and may be beneficial to the patient.

3.14 Discussion of the NeuroVISION Full Study Protocol

The NeuroVISION Study will characterize the epidemiology of covert stroke and its clinical consequences. This multicentre prospective cohort study will determine the impact of perioperative covert stroke on neurocognitive function 1 year after surgery. The secondary objectives are to estimate the overall incidence of perioperative covert stroke; characterize clinical risk factors for perioperative covert stroke; characterize the association of covert stroke with delirium and major adverse cardiovascular events; and to determine the impact of covert stroke on physical function and quality of life.

1500 patients will participate in the NeuroVISION Study. Eligibility criteria include: age ≥ 65 years, hospital admission for at least three days after noncardiac surgery. Patients with a contraindication to MRI, who reside in a nursing home or those who have documented cognitive impairment will be excluded from the study. A magnetic resonance imaging (MRI) study of the brain will be performed between postoperative days 2 and 9, and as soon as the patient is able to tolerate this procedure. The DWI sequence will enable the detection of acute covert stroke (i.e. that has occurred within 10 days of the study), without the need for a preoperative MRI study. In the POISE-1 Trial and the VISION Study we found that the majority of overt strokes occurred within the first 48 hours, and we expect that incidence of covert stroke will have a similar temporal distribution. The timing of the MRI study will enable us to detect these events.

Study personnel will collect data regarding clinical outcomes, and will perform a daily cognitive assessment of study participants throughout their hospitalization. We will assess cognitive function, physical function and health-related quality of life 1 year after surgery, and will collect data regarding clinical outcomes at 30-days and 1 year after surgery.

3.14.1 Strengths of the NeuroVISION Study

The NeuroVISION Study will be the first study to characterize the epidemiology and the impact of covert stroke after surgery. This will be the largest ever study of perioperative stroke. This is a prospective study that uses validated, sensitive, comprehensive and patient-relevant measures of the impact of perioperative covert stroke.

3.14.2 Limitations of the NeuroVISION Study

3.14.2.1 Lack of insight into the pathophysiology of covert stroke

The mechanism of perioperative covert stroke may be different than the traditionally accepted pathophysiology of stroke in the nonsurgical setting. The NeuroVISION study is not designed to characterize physiological mechanisms of covert stroke, as it is far more important to determine the impact on patient-relevant outcomes. If covert stroke has no impact on patient health and function, it

may not be fruitful to dedicate significant resources in further investigations of a benign incidental process.

3.14.2.2 The overall impact of the NeuroVISION Study on patient care

The only means of diagnosis of covert stroke is with routine MRI screening, and the implementation of the NeuroVISION protocol into clinical practice is limited by the availability and the cost of MRI studies.

However, even if routine postoperative MRI screening is not a part of clinical practice, the findings of the NeuroVISION Study will have an immediate impact on patient care, as well as a significant contribution to further research on stroke in the perioperative and the ambulatory settings. The greatest concern of patients undergoing elective surgery is brain damage and memory loss.[87] Given the worldwide surgical volumes (200 million patients undergo major noncardiac surgery every year) [88], up to 10 million patients may be suffering a perioperative covert stroke every year. The NeuroVISION Study will impact patient care immediately, as it will identify patients at high risk of perioperative covert stroke prior to surgery. This will change the discussion regarding the risks of elective surgery (eg. patient considering elective knee replacement, looking to improve quality of life may not wish to risk a covert stroke that impacts cognitive function)

3.14.2.3 The timing of cognitive assessments in the NeuroVISION Study

The primary outcome of the NeuroVISION Study is neurocognitive function 1 year after surgery. More frequent measurements of cognitive function would provide more data regarding cognitive trajectories of patients with and without covert stroke after noncardiac surgery. However, multiple cognitive assessments may create learning bias in the patient population. Furthermore, even if covert stroke does impact cognition in the short term, the long term cognitive function (measured at 1 year) would be much more important to patients.

3.14.2.4 Covert stroke may be a surrogate marker for patients at risk for postoperative cognitive decline

It is possible that perioperative covert stroke does not directly cause a decline in cognitive function, but instead is a surrogate marker of patients who are at risk of cognitive decline (eg. due to further covert strokes in the nonsurgical setting). Our statistical analysis will adjust for known factors associated with cognitive decline. Even if covert stroke is a surrogate measure of an unknown risk factor for cognitive decline, as long as an association with cognitive decline is present this will improve patient care regardless of the pathophysiology by stimulating further research in the area.

CHAPTER 4: CONCLUSION

This chapter summarizes the overall thesis, and discusses further possible venues of research in the field.

4.1 Summary of thesis

The idea for the thesis originated from an observation regarding the unexpectedly high severity of perioperative stroke during a randomized controlled trial. We performed a literature search to inform the background for the development of a research program that will characterize the epidemiology of perioperative stroke, and its clinical impact. The literature review indicated that covert stroke is more common than overt stroke in the nonsurgical setting, as well as after cardiac and carotid artery surgery, but did not identify any research regarding covert stroke after noncardiac surgery. Furthermore, evidence shows that covert stroke in the nonsurgical setting is associated with an increased risk of dementia, overt stroke and death. No studies of the impact of perioperative stroke were identified.

The pilot study of perioperative covert stroke after noncardiac surgery demonstrated the feasibility of a full study, along with a relatively high incidence of covert stroke (10%, 95% CI, 5.5-17.4).

The protocol for the full study will demonstrate the impact of covert stroke after noncardiac surgery, and will serve as a platform for further research on this topic.

4.2 Further research directions

Studies of covert stroke in the ambulatory setting are limited by the lack of ability to study the acute phenomenon of covert stroke (only “old” silent infarcts are captured with population-based MRI screening). Patients in the NeuroVISION study will be monitored in the hospital setting at the time of their acute covert stroke. This will yield an unprecedented amount of high-quality information regarding the pathophysiology of acute covert stroke.

If the NeuroVISION study demonstrates an association between covert stroke and cognitive dysfunction, a validation study in a different perioperative setting should be performed to demonstrate external validity.

The ability to study acute covert stroke has the potential to yield novel risk factors, physiological insights and therapeutic targets that may not be identified by the population-based studies of chronic covert stroke.

The NeuroVISION Study will serve as the foundation for a new research program to prevent and treat acute covert stroke in the perioperative and ambulatory settings.

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APPENDIX

6.1 Appendix 1: Study Definitions for specific surgeries and groups of comparable surgeries

MAJOR VASCULAR SURGERY includes:

- Thoracic aorta reconstructive vascular surgeries – thoracic aortic aneurysm repair, repair of supra-aortic trunks not requiring total cardiopulmonary bypass, thoracoabdominal aortic aneurism repair with or without aorto-femoral bypass.
- Aorto-iliac reconstructive vascular surgery – open abdominal aortic aneurysm repair, aorto-femoral bypass, iliac-femoral bypass, renal artery revascularization, celiac artery revascularization, superior mesenteric artery revascularization.
- Peripheral vascular reconstruction without aortic cross-clamping – axillo-femoral bypass, femoral-femoral bypass, femoro-infragenicular bypass, profundoplasty, or other angioplasties of the infrainguinal arteries.

OTHER VASCULAR SURGERY includes endovascular abdominal aortic aneurysm repair (EVAR).

MAJOR THORACIC SURGERY includes:

- Pneumonectomy
- Lobectomy

OTHER THORACIC SURGERY includes:

- Wedge resection of lung
- Resection of mediastinal tumor
- Major chest wall resection.

MAJOR ORTHOPEDIC SURGERY includes:

- Major hip or pelvic surgery – hemi or total hip arthroplasty, internal fixation of hip, pelvic arthroplasty, hemipelvectomy
- Internal fixation of femur
- Knee arthroplasty
- Above-knee amputation
- Lower leg amputation – amputation below knee but above foot.

OTHER ORTHOPEDIC SURGERY includes:

- Shoulder or elbow arthroplasty
- Rotator cuff repair
- Internal fixation of humerus or tibia

- Knee or hip osteotomy
- Ankle fusion

MAJOR UROLOGY OR GYNECOLOGY SURGERY includes:

- Visceral resection – nephrectomy, renal transplant, ureterectomy, bladder resection, retroperitoneal tumor resection, exenteration [i.e. radical procedure for cancer to remove pelvic organs].
- Cytoreductive surgery – “debulking” done when cancer has spread in the pelvic/abdominal area, to remove as much of the tumor as possible.
- Radical hysterectomy – to remove the uterus, cervix and part of the vagina.
- Radical prostatectomy – to remove entire prostate gland and surrounding tissue.

OTHER UROLOGICAL OR GYNECOLOGICAL SURGERY includes:

- Hysterectomy (to remove the uterus and usually the cervix)
- Transurethral prostatectomy (to remove overgrowth of prostate tissue)

MAJOR GENERAL SURGERY includes:

- Complex visceral resection - surgery involving the liver, esophagus, pancreas, or multiple organs.
- Partial or total colectomy, or stomach surgery, small bowel resection
- Major head and neck resection for non-thyroid tumor

OTHER GENERAL SURGERY includes other intra-abdominal surgery such as gallbladder, appendix, adrenals, spleen, regional lymph node dissection.

MAJOR SPINAL SURGERY includes surgery involving multiple levels of the spine.

LOW RISK SURGERIES includes any other surgery not listed above, or any of the following surgeries: parathyroid, thyroid, breast, hernia, local anorectal procedure, oophorectomy, salpingectomy, endometrial ablation, peripheral nerve surgery, ophthalmology, vertebral disc surgery, hand surgery, metatarsal resection, cosmetic surgery, arterio-venous access surgery for dialysis.

6.2 Appendix 2: Clinical Outcome Definitions

Acute cerebral ischemia

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

Covert Stroke

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

Overt Stroke

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

Transient Ischemic Attack

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

Delirium

Patients will be diagnosed with delirium if they meet the Confusion Assessment Method (CAM) criteria:

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

Sub Classification of Death

Judicial outcome assessors will classify all deaths as either vascular or non-vascular.

Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy).

Major Adverse Cardiovascular Events

This is a composite outcome of nonfatal myocardial infarction, nonfatal overt stroke, vascular death, and nonfatal cardiac arrest.

Myocardial Infarction

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

1. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism). This criterion also requires that 1 of the following must also exist:

- a. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema)
- b. development of pathologic Q waves present in any two contiguous leads that are > 30 milliseconds
- c. ECG changes indicative of ischemia (i.e., ST segment elevation [> 2 mm in leads V1, V2, or V3 OR > 1 mm in the other leads], ST segment depression [> 1 mm], or symmetric inversion of T waves > 1 mm) in at least two contiguous leads
- d. coronary artery intervention (i.e., PCI or CABG surgery)
- e. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging

2. Pathologic findings of an acute or healing myocardial infarction

3. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event

MINS

The diagnosis of MINS requires one of the following:

1. A diagnosis of myocardial infarction (definition as above) that occurs during or within 30 days after noncardiac surgery, OR
2. An new elevation in the serum troponin level within 30 days after surgery, that is:
 - i. NOT due to a documented non-ischemic etiology (e.g., pulmonary embolism, sepsis, cardioversion), AND
 - ii. NOT due to a known chronically elevated troponin measurement.

Nonfatal Cardiac Arrest

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

Bleeding

We will collect the outcomes of Life-threatening bleeding, Major bleeding and Minor bleeding

Life-Threatening Bleeding

Life threatening bleeding is bleeding that

- is fatal
- leads to significant hypotension requiring inotrope therapy
- leads to urgent (within 24 hours) intervention (other than superficial vascular or wound repair)
- intracranial hemorrhage

Major Bleeding

Major Bleeding is bleeding that is not specified under “Life-Threatening Bleeding” above, and that

- results in a postoperative hemoglobin ≤ 70 g/L and that requires a transfusion of ≥ 2 units of red blood cells
- results in a hemoglobin drop of ≥ 50 g/L and that requires a transfusion of ≥ 2 units of red blood cells
- requires a transfusion of ≥ 4 units of red blood cells within a 24 hour period.
- leads to any other intervention (eg. embolization, superficial vascular repair, nasal packing)
- is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging)

Minor Bleeding

Minor bleeding is

- is any other administration of pRBC or whole blood not meeting above definitions

New Atrial Fibrillation/Flutter

New atrial fibrillation/flutter is defined as atrial fibrillation or flutter that is documented on an ECG or a rhythm strip.

Pulmonary Embolism

The diagnosis of Pulmonary Embolism (PE) requires any ONE of the following:

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

Deep venous thrombosis

The diagnosis of Deep Vein Thrombosis (DVT) requires any ONE of the following findings present in a deep vein of the arm or leg:

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

Clinically Important Hypotension

Clinically important hypotension is defined as a systolic blood pressure < 90 mm Hg requiring fluid resuscitation, intra-aortic balloon pump, or administration of an inotropic or vasopressor agent.

New Congestive Heart Failure

The definition of new congestive heart failure requires at least one of the following clinical signs (i.e., any of the following signs: elevated jugular venous pressure, respiratory râles/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).

Cardiac Revascularization Procedures (coronary interventions)

Cardiac revascularization procedures include PCI and CABG surgery.

Infection

Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms. The outcome of infection will be documented if there is a positive culture in a normally sterile fluid or body cavity, or if there is a physician diagnosis of infection in the absence of a positive culture that is treated with one of:

- a. Tissue debridement or irrigation
- b. Antibiotic therapy

Sepsis

Sepsis is a clinical syndrome defined by the presence of both infection and a systemic inflammatory response.

Systemic inflammatory response requires 2 or more of the following factors:

- a. Core temperature > 38°C or < 36°C
- b. Heart rate > 90 bpm
- c. Respiratory rate > 20 breaths/min
- d. White blood cell count > 12 x 10⁹/L or < 4 x 10⁹/L

New Acute Renal Failure

New acute renal failure defined as new requirement for dialysis (i.e., use of dialysis machine or peritoneal dialysis apparatus in patients without dialysis prior to elective noncardiac surgery.

New Dementia and Mild Cognitive Impairment

The outcome of dementia will be documented if the study participant has been diagnosed with dementia by a physician. The outcome of mild cognitive impairment (MCI) will be documented if the patient was diagnosed with MCI or with cognitive impairment, but did not meet the criteria for dementia.

New Clinical Depression or Anxiety Disorder

New Clinical Depression or Anxiety Disorder will be documented if a patient has been diagnosed by a physician with depression disorder (e.g., depression, dysthymia, bipolar disorder) or an anxiety or panic disorder (e.g., phobia, obsessive-compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, panic disorder), AND fulfils ONE of the following:

- 1) Has been prescribed an antidepressant, antipsychotic or mood-stabilizing medication
- 2) Has been hospitalized for the treatment of anxiety or depression

- 3) Has received electroconvulsive therapy for the treatment of depression or anxiety
- 4) Has received psychotherapy (eg. cognitive behavioural therapy, interpersonal psychotherapy, psychodynamic psychotherapy or motivational interviewing) for the treatment of depression or anxiety

6.3 Appendix 3: Preoperative Patient Characteristic Definitions

Nursing home

A nursing home is defined as a place that gives care to people who have physical or mental disabilities and need help with activities of daily living (such as taking a bath, getting dressed, and going to the bathroom) but do not need to be in the hospital

Clinical Depression or Anxiety Disorder

Clinical Depression or Anxiety Disorder will be documented if a patient has been diagnosed by a physician with depression disorder (e.g., depression, dysthymia, bipolar disorder) or an anxiety or panic disorder (e.g., phobia, obsessive-compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, panic disorder), AND fulfils ONE of the following:

- 1) Has been prescribed an antidepressant, antipsychotic or mood-stabilizing medication
- 2) Has been hospitalized for the treatment of anxiety or depression
- 3) Has received electroconvulsive therapy for the treatment of depression or anxiety
- 4) Has received psychotherapy (eg. cognitive behavioural therapy, interpersonal psychotherapy, psychodynamic psychotherapy or motivational interviewing) for the treatment of depression or anxiety

History of delirium

Past history of delirium as diagnosed by a physician

Coronary artery disease

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

Recent high-risk coronary artery disease

A physician diagnosis < 6 months prior to noncardiac surgery of: a myocardial infarction, acute coronary syndrome, 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

Recent coronary artery revascularization

PCI or CABG surgery < 2 months prior to noncardiac surgery

Atrial fibrillation

A patient with a current history of atrial fibrillation

Cerebrovascular disease

A physician diagnosis of stroke, CT or MRI evidence of a prior stroke, or physician diagnosis of a prior transient ischemic attack (TIA)

Peripheral vascular disease

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

Congestive heart failure

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

Critical aortic valvular stenosis

An aortic valve area $< 0.75 \text{ cm}^2$

Diabetes

Patient states they have been diagnosed with diabetes or a physician has previously recorded that the patient has diabetes. Includes current gestational diabetes, does not include past gestational diabetes that has resolved.

Hypertension

A physician diagnosis of hypertension

Cirrhosis

A physician diagnosis of cirrhosis, or a past liver biopsy documenting cirrhosis.

Hypercholesterolemia treated with drug therapy

A patient taking drug therapy (e.g., statin, fibrate) for hypercholesterolemia in the week prior to surgery

Smoking history

A patient with a current history of smoking

History of cardiac arrest

A patient with a prior history of a cardiac arrest

Renal insufficiency

A patient on chronic hemodialysis or peritoneal dialysis.

COPD

Chart or physician indication that a patient has chronic bronchitis, emphysema or chronic obstructive pulmonary disorder (COPD) will be accepted as a patient having COPD. If there is no mention of this but the patient tells you they have had daily production of sputum for at least 3 months in 2 consecutive years then they should be marked as having COPD.

Obstructive sleep apnea

A physician or sleep study diagnosis of obstructive sleep apnea

Family History of dementia

A patient with diagnosed dementia in a first degree relative

Prior Deep Vein Thrombosis (DVT)

Patient states they have been diagnosed with a DVT in the past by a physician, or there is record in the chart of physician diagnosis of DVT, or there is a record of any ONE of the following findings present in a deep vein of the arm or leg:

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

Prior Pulmonary Embolus (PE)

Patient states they have been diagnosed with a PE in the past by a physician, or there is record in the chart of physician diagnosis of PE, or there is a record of any ONE of the following findings:

1. A high probability ventilation/perfusion lung scan
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan
3. An intraluminal filling defect on pulmonary angiography
4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) AND one of the following:
 - a. non-diagnostic (i.e., low or intermediate probability)
ventilation/perfusion lung scan

- b. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan

Active Cancer

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

Metastatic Cancer

Physician diagnosis of metastatic cancer, defined as solid neoplasm that has spread beyond the primary tumor location.