EVALUATION OF THE EFFECTS OF HYPERGLYCEMIA ON STROKE OUTCOMES

by

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Abstract

This thesis evaluated the association between blood glucose and stroke outcomes in patients in the Registry of the Canadian Stroke Network. In ischemic stroke patients, after adjusting for stroke severity and other risk factors, blood glucose was an independent predictor of death after stroke (adjusted hazard ratio [HR] 1.050 per mmol/l unit glucose increase, $p<0.001$). Receiver operating characteristic (ROC) curve analysis identified a glucose cut-off >7.5 mmol/l to be associated with death after ischemic stroke; this cut-off had an adjusted HR 1.349 for death ($p<0.001$). In patients with intracerebral hemorrhage (ICH), glucose was also an independent predictor of death (adjusted HR 1.025 per mmol/l unit glucose increase, $p=0.04$). ROC curve analysis identified a glucose cut-off >8.5 mmol/l to be associated with death after ICH; the adjusted HR for death was 1.574 ($p<0.001$). These results support the association between glucose and poor stroke outcomes in patients with ischemic and hemorrhagic stroke.

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I dedicate this thesis to my parents; to my mother, Valerie Casaubon, and my father, Roger Casaubon (1942–2003), for the unending love and support they provided me throughout all of my years of education. I also dedicate this thesis to my husband, Luc S. D'Aoust, with many thanks for his patience and loving support.

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List of Abbreviations

AGE	Advanced Glycation End-products
APACHE II	Acute Physiology and Chronic Health Evaluation II
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
CABG	Coronary Artery Bypass Graft
CASES	Canadian Alteplase for Stroke Effectiveness Study
CCRS	Continuing Care Reporting System
CI	Confidence Interval
CIHI	Canadian Institute of Health Information
CNS	Canadian Neurological Scale
CREATE-ECLA	Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation - Estudios Cardiologicos LatinoAmerica
CT	Computed Tomography
DAD	Discharge Abstract Database
DBP	Diastolic Blood Pressure
DIGAMI	Diabetes Insulin-Glucose in Acute Myocardial Infarction
DM	Diabetes Mellitus
DVT	Deep Venous Thrombosis
GCS	Glasgow Coma Scale
GI	Gastrointestinal
GIST	Glucose In Stroke Trial
HbA1c	Hemoglobin A1c
HR	Hazard Ratio
ICES	Institute for Clinical Evaluative Sciences
ICH	Intracerebral Hemorrhage
ICU	Intensive Care Unit
IKN	ICES Key Number
INR	International Normalized Ratio
IS	Ischemic Stroke
IV	Intravenous
LAC	Lacunar
LOC	Level Of Consciousness
LTC	Long-Term Care
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
mRS	modified Rankin Scale

NACRS	National Ambulatory Care Reporting System
NH	Nursing Home
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
OCSP	Oxfordshire Community Stroke Project
ODB	Ontario Drug Benefit
ODD	Ontario Diabetes Database
OHIP	Ontario Health Insurance Plan
OR	Odds Ratio
PAC	Partial Anterior Circulation
PHIPA	Personal Health Information Protection Act
POC	Posterior Circulation
PROACT	Prolyse (pro-urokinase) in Acute Cerebral Thromboembolism
Q1-Q5	Income Quintiles (Q1 = lowest; Q5 = highest)
RCSN	Registry of the Canadian Stroke Network
RIND	Reversible Ischemic Neurologic Deficit
ROC	Receiver Operating Characteristic
RPDB	Registered Persons Database
RR	Relative Risk
rt-PA	recombinant tissue-Plasminogen Activator
SBP	Systolic Blood Pressure
SC	Subcutaneous
SES	Socioeconomic Status
SPSS	Statistical Package for the Social Sciences
SSS	Scandinavian Stroke Scale
TAC	Total Anterior Circulation
TIA	Transient Ischemic Attack
UTD	Unable to determine
UTI	Urinary Tract Infection
WHO	World Health Organization

CHAPTER 1

1. Introduction

1.1 Rationale

Hyperglycemia is commonly noted in the early post-stroke period. Though hyperglycemia appears to be associated with poor outcomes in stroke patients, debate still exists as to the importance of this factor and whether a causal relationship exists between hyperglycemia and poor stroke outcomes. Currently, only one randomized, controlled treatment trial of elevated glucose in stroke patients has been completed but did not show a benefit of aggressive glucose lowering; little is known about the optimal management of hyperglycemia in stroke. This thesis will examine the effects of blood glucose on stroke outcomes in a large cohort using the clinical database from the Registry of the Canadian Stroke Network.

1.2 Research Questions

The thesis will address the following primary research question:

1) Is elevated blood glucose, noted on presentation to hospital in patients with ischemic stroke, associated with death after stroke?

The thesis will also examine the following secondary research questions:

1) Is there a specific cut-off level of random-sample blood glucose that is associated with increased 30-day case fatality after stroke?
2) Is hyperglycemia associated with worse functional outcome upon hospital discharge following ischemic stroke?
3) In patients with intracerebral hemorrhage, is hyperglycemia associated with death following stroke?

4) Is hyperglycemia associated with worse functional outcome upon hospital discharge in patients with intracerebral hemorrhage?

1.3 Hypothesis

This thesis will assess the main hypothesis that elevated blood glucose documented upon hospital presentation in patients with ischemic stroke is associated with an increased risk of death (based on time-to-death) after stroke.

The secondary hypotheses are that elevated blood glucose is associated with poor functional outcome at hospital discharge in ischemic stroke patients, based on increased severity of residual neurologic deficits or discharge to a chronic care facility. Also, in patients with intracerebral hemorrhage, the thesis will assess the hypotheses that elevated blood glucose is associated with increased risk of death after stroke and with poor functional outcome.

CHAPTER 2

2. Background

This chapter will provide a review of the existing literature on hyperglycemia in patients with stroke. First, background information regarding stroke will be provided. This will be followed by a review of the evidence from human studies regarding the association between glucose and stroke outcomes. The pathophysiologic basis for the effects of glucose in stroke will be examined through studies of animal models of stroke. Finally, the effects of hyperglycemia and its management in other medical conditions will be reviewed.

2.1 Stroke Epidemiology

2.1.1 Stroke Incidence and Outcomes

Stroke outcomes including premature death and functional disability have a major impact on society. Strokes occur in 40,000 to 50,000 Canadians annually and the costs of stroke, both social and economical, are considerable.[1-4] In 1997, the total annual cost for stroke care including direct and indirect costs in Canada was $3.2 billion dollars.[5] Up to 300,000 people in Canada are living survivors of stroke and over 50% will have a moderate to severe disability.[1] Case fatality from all stroke types combined is up to 20% at one month and 30% at one year following the index event.[6, 7] For ischemic stroke alone, case fatality at one month is around 10%.[6] Case-fatality rates at one month are higher for patients with intracerebral hemorrhage, reported to be around 60%, and for subarachnoid hemorrhage, nearly 50%.[6, 8]

2.1.2 Risk Factors for Stroke

Modifiable vascular risk factors that significantly increase the risk of stroke include hypertension, diabetes, hyperlipidemia, smoking, atrial fibrillation, and carotid artery atherosclerosis.[9, 10] Non-modifiable stroke risk factors include age, male sex, race, and positive family history.[10, 11] Hypertension is the most robust of the modifiable vascular risk factors with a relative risk of stroke of 2.0 - 4.0 in adults between the ages of 50 and 70 years and prevalence in the adult population of 30% to 40%. Diabetes mellitus has an estimated relative risk of 1.5 - 3.0 with a prevalence of 4% to 8% in the population. Hyperlipidemia has a relative risk of 1.0 - 2.0 and is much more prevalent from 6% to 50%. Smoking is another important risk factor, with an estimated prevalence of 20% to 40% in the population and a relative risk of 1.5 - 2.9. Finally, though atrial fibrillation is less prevalent, estimated at 1% in the population, it has the highest relative risk of stroke at 5.6 - 17.6.[9]

Other stroke risk factors for which there is compelling evidence include obesity, sedentary lifestyle, and excess alcohol consumption,[12] street drugs (such as cocaine and crack cocaine, amphetamines, heroin, and hallucinogens),[13] and medications (for example, oral contraceptives and hormone replacement therapy).[14] Factors also shown to be associated with stroke but that are not clearly risk factors include elevated C-reactive protein[15] and homocysteine.[9, 16]

2.2 Stroke and Diabetes

2.2.1 Definition of Diabetes

Diabetes is a metabolic condition consisting of impairment in the body's use of glucose as an energy source with consequent episodes of hyperglycemia, resulting from either insulin

hyposecretion (Type 1) or insulin resistance (Type 2) or both (Type 2).[17] The diagnosis is made based on clinical symptoms including excessive thirst, polyuria, weight loss, and less often, altered sensorium proceeding to coma. The World Health Organization (WHO) recommendations for the diagnosis of diabetes based on laboratory criteria are: fasting plasma glucose ≥ 7.0 mmol/l (≥ 126 mg/dl) or 2-hour post-glucose challenge plasma glucose ≥ 11.0 mmol/l (≥ 200 mg/dl).[18] The WHO classifies patients with impaired glucose tolerance if the fasting plasma glucose is ≥ 6.1 mmol/l (≥ 110 mg/dl) and < 7.0 mmol/l (< 126 mg/dl) or 2-hour post-glucose challenge plasma glucose is ≥ 7.8 mmol/l (≥ 140 mg/dl) and < 11.1 mmol/l (< 200 mg/dl).

2.2.2 Diabetes and Vascular Disease

People with diabetes have a higher risk of vascular disease, including cardiac disease, stroke, and peripheral vascular disease, than people with no diabetes history. In Ontario, hospitalizations reported in 1999 for acute myocardial infarction were 3-fold higher in patients with diabetes compared to patients with no diabetes, adjusting for age and sex differences between the groups.[19] Hospitalizations for stroke in Ontario (1999 data) were also nearly 3-fold higher in patients with diabetes than patients with no diabetes history.[20] In a population-based study in Sweden, one-year mortality in stroke patients with diabetes was 4- to 5-fold higher than in patients with no diabetes, and the population attributable risk for stroke related to diabetes was 18% in men and 22% in women.[21] In the population-based greater Cincinnati/Northern Kentucky Stroke Study, the risk of stroke attributable to diabetes alone was 5.2% in Caucasians but for diabetes and hypertension together was 20.6%.[22] Finally, in patients with diabetes, the risk of developing peripheral arterial disease is reported to be 2- to 4-fold higher than in patients with no diabetes history and often leads to chronic

disability.[23, 24] In addition to the increased risk of vascular disease in patients with diabetes, growing evidence shows that people with impaired glucose tolerance are also likely at increased risk of developing vascular disease, though this association is still being studied.[25]

In patients presenting with a stroke, a major risk factor for poor outcome is a history of diabetes. Diabetes increases mortality in stroke patients and reduces functional recovery after a stroke.[26-29] Unrecognized diabetes also poses a risk to these patients; an estimated 16% to 24% of patients admitted to hospital with a stroke have previously unrecognized diabetes based on elevated fasting blood glucose and hemoglobin A1c levels.[30]

2.3 Hyperglycemia and Stroke Outcomes

2.3.1 Natural History of Transient Hyperglycemia in Stroke Patients

The prevalence of acute transient hyperglycemia in admitted stroke patients ranges from 20% to 61% in studies that have included both patients with no history of diabetes and those with diabetes.[29, 31-35] The reported prevalence is variable, based on the definition used for hyperglycemia in any particular study. Hyperglycemia noted upon admission in stroke patients with and without diabetes has been shown to resolve spontaneously within the first 48 hours following stroke onset in about 30% of patients,[28] and mean serum glucose levels continue to decrease over 3 months.[31, 32, 36]

Studies evaluating the effects of blood glucose in patients with stroke have mainly been observational, retrospective studies. Historically, two hypotheses have emerged regarding the meaning of elevated blood glucose in this patient population. The first is that elevated blood glucose measurements noted in the acute to subacute time frame following stroke onset

are the consequence of a physiologic stress response related to the severity of cerebral damage, resulting from an increased production of stress hormones including cortisol, epinephrine, and norepinephrine.[31, 36-38] Some studies, though, have found no association between hyperglycemia and initial stroke severity, countering the 'stress' hypothesis.[34, 35] Others have shown an association between elevated glucose levels and stroke outcomes independent of the initial stroke severity.[7, 28, 31, 32, 39-46] An alternate hypothesis would be that elevated glucose levels in stroke patients may occur as an initial stress response to the acute brain injury, but may also be a predictor of worse stroke outcomes independent of initial stroke severity. As such, serum glucose might be a modifiable factor and potential target for treatment to improve outcome in stroke patients. However, overall there is still no consensus as to the importance of elevated blood glucose on outcomes in this patient population or regarding its optimal management.

2.3.2 Hyperglycemia and Stroke Severity

'Stress' hyperglycemia is described as a transient elevation in plasma glucose levels noted in patients with stroke (or other acute medical conditions) that occurs as a consequence of physiologic derangements in stress hormones related to the acute medical condition. Studies supporting this notion propose that hyperglycemia in stroke patients is merely reactive, due to the degree of cerebral damage caused either by the ischemic or hemorrhagic insult, and has no direct effect on stroke outcome. Murros *et al.* showed a strong correlation between the degree of hyperglycemia and initial stroke severity; initial mean glucose values were higher in non-diabetic stroke patients who died at 3 months (7.3 mmol/l) compared to those still living (5.8 mmol/l) ($p < 0.05$).[38] In the same study, poor glucose control preceding the stroke as identified by elevated hemoglobin A1c levels (HbA1c) was not significantly correlated

with stroke outcome. Thus, the elevated glucose levels on admission were deemed a stress response consequent to the stroke event and not a prognostic factor. Candelise *et al.* showed in a prospective cohort of 72 patients that in non-diabetic stroke patients presenting with elevated glucose levels (defined as fasting glucose > 110 mg/dl [> 6.1 mmol/l]) there was a positive correlation between elevated initial glucose measures and worse clinical stroke severity, presence of coma, and infarct size (volume) on CT imaging studies.[31] This correlation was not found in patients with diabetes. Thirty-day mortality was highest in non-diabetic stroke patients with hyperglycemia (78%), compared to patients with diabetes (45%) and non-diabetic, euglycemic patients (29%) ($p < 0.001$). Further evidence to support a 'stress' hypothesis for post-stroke hyperglycemia comes from evaluation of serial measures of blood glucose. In one study, glucose levels were found to increase over the first 12 hours following acute stroke.[47] The increase in glucose levels was correlated with stroke severity, with the largest increases occurring in those with the most severe strokes. However, one pathologic study examining 77 autopsy cases of patients who died in hospital following a hemispheric ischemic stroke found no correlation between infarct volume and hyperglycemia (defined as glucose ≥ 6.4 mmol/l).[35]

Cerebral imaging studies have evaluated the relationship between the size (volume) of stroke lesions and glucose levels using computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS) brain imaging to evaluate the hypothesis of 'stress' hyperglycemia related to initial stroke severity and size. Several studies have shown no difference in either stroke location or volume between patients with and without hyperglycemia at stroke onset, suggesting that increasing initial stroke size is not associated with higher glucose levels.[37, 44] Other studies have also shown no correlation

between hyperglycemia and initial stroke volume, but show a greater extension of stroke volume on subsequent imaging in patients with hyperglycemia on presentation. Baird *et al.* used continuous subcutaneous glucose monitoring over the first 72 hours following stroke onset in 20 patients and showed that above a mean glucose of 7.0 mmol/l, there was a significant increase in infarct volume on brain MRI from the initial infarct size to day 3 or day 6.[43] In that study, glucose > 7.0 mmol/l also predicted increased 3-month infarct volume on MRI and worse functional outcome (using the modified Rankin Scale score) that was independent of initial stroke severity, time to initial MRI, and pre-stroke glycemic control. Another study using MRI and MRS showed that in patients with an initial perfusion-diffusion mismatch (signifying the existence of an ischemic penumbra of at-risk brain tissue) there was reduced spontaneous rescue of the penumbra in patients with hyperglycemia.[48] Consequently, with repeat imaging, larger final infarct volumes were seen in the hyperglycemic patient group. Increased lactate-to-choline ratios on MRS over the acute-to-subacute timeframe of 0 to 3 days post-stroke correlated with progression of the perfusion-diffusion mismatch to infarction, suggesting that hyperglycemia may work by causing a lactic acidosis that leads to increased ischemic injury in cerebral tissue at risk.

2.3.3 Hyperglycemia and Stroke Functional Outcome and Survival

The premise that hyperglycemia results in poorer functional outcome after stroke suggests that the effects of elevated blood glucose are more complex than glucose being merely a marker of a 'stress' response related to the severity of underlying stroke damage.[51] To examine this association in humans, clinical studies have looked at the following outcomes: case-fatality rates in hospital and at 30-days, 3-months, and 6-months following the index stroke, and functional outcome at hospital discharge, 30 days, 3 months, and 6 months after

stroke using validated neurological scales (modified Rankin Scale score, mRS, Canadian Neurological Scale score, CNS, and Scandinavian Stroke Scale score, SSS).

Studies that oppose a simple 'stress' hypothesis of hyperglycemia in stroke have either shown glucose levels not to be correlated with initial stroke severity or have found that hyperglycemia documented at stroke onset was a predictor of mortality or worse functional outcome, independent of stroke severity. Jorgensen *et al.* reported on the largest cohort study to date that included 1,135 patients, showing that hyperglycemia in non-diabetic stroke patients resulted in worse functional outcome and increased mortality and that this was independent of initial stroke severity.[26, 41] Similar findings corroborating the independent association between hyperglycemia and poor stroke outcomes have been reported in several other smaller studies.[7, 28, 32-34, 37, 39, 40, 43-46, 49, 50] Of note, hyperglycemia was not consistently found to be an independent predictor of outcome in patients with diabetes in these cohorts, though in general, patients with diabetes had worse outcomes than those with no history of diabetes when these groups were compared.[29, 39, 45, 50,

The association between hyperglycemia and poor stroke outcomes has not been consistently reported across all stroke subtypes and certain patient subgroups, including patients with or without a known history of diabetes. Several studies report an association between elevated blood glucose levels on presentation and increased mortality specifically in patients with no known history of diabetes.[26, 37, 39, 45] Jorgensen *et al.* reported glucose was an independent predictor of mortality in patients with no known diabetes (adjusted odds ratio [OR] 1.2 per mmol/l unit glucose increase, $p = 0.04$); in patients with diabetes, this association was not found.[26] Stollberger *et al.* evaluated glucose quartiles in 992 patients and found a 4-fold

increased crude case-fatality rate comparing the upper glucose quartile (> 9.2 mmol/l) to the bottom quartile (< 5.7 mmol/l) in patients without diabetes ($p < 0.0001$).[45] Other studies have shown an association between elevated blood glucose levels and poor outcome both in patients with and without a pre-existing diabetes diagnosis.[7, 32, 34]

Patients presenting with different clinical stroke subtypes may or may not show an association between early hyperglycemia and poor stroke outcomes. In one imaging based study of 82 patients, hyperglycemic patients presenting with intracranial arterial occlusions and good collateral blood supply had smaller than predicted infarct sizes (smaller in 82%), compared to published standardized stroke volumes for the particular arterial occlusion. Only 64% percent of patients with no early hyperglycemia had infarcts smaller than predicted, and no patients with diabetes had smaller than predicted strokes ($p < 0.05$).[52] In patients with poor or absent collateral blood supply, no difference was shown between the three patient groups. These results suggest that hyperglycemia in non-diabetic patients with good collateral blood supply may be beneficial in reducing final stroke size. However, data from 1,259 patients enrolled in the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) were analysed for the effects of hyperglycemia on stroke outcomes, and in patients with non-lacunar stroke, elevated glucose at hospital presentation was associated with worse functional outcome at 3 months (for favourable outcome, OR 0.74 for each 100 mg/dl [5.6 mmol/l] blood glucose increase, $p = 0.02$).[53] There was no association between elevated blood glucose and outcome in patients with lacunar stroke in the TOAST cohort. Other studies have mainly included all ischemic stroke subtypes and thus do not provide further evidence regarding the potential differential effects of hyperglycemia in small end-arteriolar strokes versus strokes related to medium-to-large arterial occlusion.

Overall, there is evidence to support an association between hyperglycemia documented at stroke onset and increased risk of death and increased neurologic disability. However, elevated glucose is not consistently shown to be associated with worse stroke outcomes and this may or may not be related to patient characteristics, such as diabetes history. In addition, the proportion of patients presenting with elevated blood glucose levels that have underlying glucose intolerance (random glucose > 7.8 mmol/l) or previously undiagnosed diabetes that may influence stroke outcomes is not known in most studies. Evidence is also lacking regarding the effects of hyperglycemia in different stroke subtypes and requires further investigation.

2.3.4 Thrombolysis for Ischemic Stroke and Effects of Hyperglycemia

Thrombolysis with intravenous recombinant tissue Plasminogen Activator (rt-PA) is the only approved therapy for acute ischemic stroke and is the standard of care for eligible patients presenting within 3 hours of the onset of stroke symptoms.[54] In the NINDS rt-PA stroke trial, patients treated with rt-PA had an 11% absolute increase in the chance of an excellent functional recovery at 3 months after the stroke, as defined by a modified Rankin Scale score of 0 or 1.[54, 55] However, risks of symptomatic hemorrhage in the trial were 6.4%. In the Canadian Alteplase for Stroke Effectiveness Study (CASES), a prospective observational study of patients treated with rt-PA following its approval in Canada in 1999, the hemorrhage rate was 4.6%.[56] In Canada, the rate of thrombolysis for patients with acute ischemic stroke presenting to acute care hospitals with dedicated stroke expertise is 8.9%.[57]

Hyperglycemia in acute stroke patients treated with thrombolysis may be associated with undesired effects including reduced efficacy of the rt-PA or increased risk of intracerebral

hemorrhage. Two large thrombolysis trials, the NINDS rt-PA Stroke Trial, and an intra-arterial trial of urokinase, PROACT II, have evaluated the effects of hyperglycemia on stroke outcomes and risk of hemorrhage.[58, 59] In the NINDS trial, for patients with an admission glucose level > 300 mg/dl (> 16.7 mmol/l) hyperglycemia was not a significant independent predictor for symptomatic hemorrhage.[60] However, a subsequent analysis using NINDS data showed patients with elevated glucose on presentation had worse clinical outcomes at 3 months and an increased risk of symptomatic hemorrhage.[58] In PROACT II, patients presenting with glucose > 200 mg/dl (> 11.1 mmol/l) and treated with intra-arterial urokinase thrombolysis had a 4-fold increased risk of symptomatic intracranial hemorrhage (36% symptomatic ICH in hyperglycemic patients, versus 9% in normoglycemic patients).[59] Other studies have evaluated cut-off levels of glucose between 8.0 mmol/l and 8.8 mmol/l and found that initial glucose levels above that range were associated with increased risk of intracranial hemorrhage, reduced rates of arterial recanalization, and clinical worsening with thrombolytic therapy even if recanalization occurred.[61-64] Hill *et al.* similarly found hyperglycemia to be an independent predictor of symptomatic intracranial hemorrhage with an adjusted odds ratio of 1.6 (95% confidence interval [CI] 1.2 - 2.3) for each 5 mmol/l increase in initial blood glucose.[56] Saposnik *et al.* also found that baseline glucose < 8.0 mmol/l was an independent predictor of major neurologic improvement within 24 hours of receiving thrombolytic therapy.[61]

2.3.5 Intracerebral Hemorrhage

The importance of hyperglycemia in patients presenting with intracerebral hemorrhage is less well understood. Fewer studies have evaluated the effects of elevated serum glucose in this patient population alone; studies have often included both ischemic stroke and intracerebral

hemorrhage patients in the same cohort.[31, 34, 37, 40, 47, 49, 65, 66] Given that there are important differences in the pathophysiology of intracerebral hemorrhage compared with ischemic stroke and in outcomes for each stroke type, different mechanisms for the effects of hyperglycemia in each stroke subtype are plausible. For this reason, understanding the effects of hyperglycemia in intracerebral hemorrhage patients alone is important.

In cohorts of patients with primary intracerebral hemorrhage (not related to trauma, tumors, or vascular lesions), hyperglycemia has been shown to be associated with initial hematoma size and clinical features of stroke severity, including decreased level of consciousness, and midline shift of cerebral structures.[67, 68] Such associations are consistent with a 'stress' hypothesis for hyperglycemia as postulated by several studies in the ischemic stroke population. However, particularly in patients without a history of diabetes, hyperglycemia may also be an important independent predictor of death at one month in this stroke subtype.[68, 69] In patients with intracerebral hemorrhage, level of consciousness is one of the strongest predictors of outcome; presenting to hospital in a comatose state is associated with poor functional outcome and a high risk of death. In one study that excluded comatose patients, a glucose level > 130 mg/dl (> 7.2 mmol/l) was an independent predictor of 30-day and 3-month mortality in non-diabetic patients with intracerebral hemorrhage.[69] Hyperglycemic non-diabetic patients and diabetic patients were also found to have more in-hospital complications than euglycemic non-diabetic patients in that series. However, comparing these findings to other studies of hyperglycemia in intracerebral hemorrhage is difficult because of differences in patient characteristics in the various series. Other studies have included a more heterogeneous population with comatose and alert patients, and patients with and without diabetes. Also, patients with intracerebral hemorrhage are often

evaluated within a cohort of ischemic stroke patients. At present, there is no solid evidence to support an independent deleterious effect of glucose on outcome after intracerebral hemorrhage but further evidence is required to better understand the effects of this factor in this stroke type.

2.3.6 Limitations of Studies Evaluating Hyperglycemia and Stroke Outcomes

Several factors have possibly contributed to conflicting information regarding the importance of hyperglycemia in stroke outcomes. Important limitations of previous research in this area include:

Variability in the definition of 'hyperglycemia'. Studies have used varying glucose cut-off values that are based on either the upper limits of normal for laboratory testing of glucose,[31, 52] or general diabetes guidelines,[29, 37, 41, 43, 66] and in some studies the reasoning is not clearly reported or appears arbitrary.[7, 32-35, 39, 40, 44, 49, 70, 71] A few studies have used statistical techniques to identify a glucose cut-off above which to define hyperglycemia.[28, 38, 45-48, 65] Glucose cut-off levels used in studies evaluating the effects of hyperglycemia in stroke patients range from > 6.0 mmol/l to > 10.0 mmol/l (see Table 1).

Heterogeneity of patient populations. Most studies include heterogeneous groups of patients in evaluating the effects of hyperglycemia and stroke outcomes. Studies have mainly evaluated both ischemic stroke and intracerebral hemorrhage patients together.[29, 31, 34, 37, 40, 41, 45, 47, 49, 65, 66] Patients with a history of diabetes and patients without known diabetes are also usually included. In ischemic stroke cohorts, stroke subtypes are typically evaluated

together or the stroke subtypes in the patient sample are not reported; also some patients in the ischemic stroke cohorts may have received thrombolysis.

There is growing evidence in both human and animal studies that hyperglycemia may affect certain groups of stroke patients and stroke subtypes differently and as such may contribute to the conflicting results of these studies. Most studies consist of small heterogeneous cohorts that may limit their power to determine if hyperglycemia has an important effect in individual patient subgroups. Also, pre-stroke glucose control (based on HbA1c level upon presentation) is unavailable in most studies so that patients with unrecognized diabetes may be included in the cohort of patients deemed not to have diabetes. Patients with elevated HbA1c may have an inherently worse prognosis after a stroke than patients with normal glucose control prior to stroke, though this has not been confirmed. Findings of some studies interpreted as showing deleterious effects of post-stroke hyperglycemia may simply be demonstrating the negative effects of diabetes in patients who were previously undiagnosed.

2.4 Pathophysiologic Basis for the Effects of Hyperglycemia in Stroke

2.4.1 Animal Models of Stroke

The effects of hyperglycemia in global and focal cerebral ischemia and intracerebral hemorrhage have been evaluated in animal models of stroke. Several postulated mechanisms for the effects of hyperglycemia have been examined.

Animal models have been used to study diffuse cerebral injury following circulatory failure from various causes as occurs in humans. In studies evaluating the effects of hyperglycemia in global ischemia, animals are pre-treated with dextrose solutions to produce a

hyperglycemic state prior to the onset of ischemia. Studies in rats have demonstrated widespread changes in the blood-brain barrier with increased extravasation of fluid in the interstitial spaces in animals with induced hyperglycemia compared to those with euglycemia.[72, 73] Pathological analysis has demonstrated diffuse neuronal injury throughout the neocortex associated with edema.[73] One study in dogs following cardiac arrest and resuscitation showed that at 2 hours post-resuscitation, hyperglycemic animals had significantly more neurologic deficits and by 9 hours a majority developed seizure activity with subsequent death.[74] Of the animals that survived, those with hyperglycemia had worse neurologic impairment compared to control animals, all of which had no deficits at 24 hours. A similar cardiac arrest model in cats showed that hyperglycemic animals were less likely to be alert on day 2 and on day 7 were more likely to have neurologic deficits of behavior and gait.[75] This study, however, did not demonstrate a significant difference in the neuropathological findings between groups to correlate with the clinical findings, aside from extra neuronal loss in the cerebellar region in hyperglycemic animals. Disparities in these studies' findings may relate to differences in protocols of induced global ischemia.

Induced focal ischemia in animals is a model for human ischemic stroke. Hyperglycemic animals often demonstrate worse pathological cerebral injury and neurologic outcomes in these models.[76-82] In cats with middle cerebral artery occlusion, elevated glucose levels are associated with increased edema in the peri-infarct region.[77] Particularly when vessel occlusion is temporary, cerebral edema surrounding the infarct is worsened upon reperfusion. Death due to edema formation is significantly higher in animals with hyperglycemia, especially with recanalization of the involved cerebral vessel.[77] In a rat model of

intracerebral hemorrhage, a similar finding of increased total brain water content was seen in hyperglycemic animals, with increased peri-hematoma cell death.[83]

A postulated mechanism of neuronal damage from hyperglycemia following stroke is increased lactic acidosis. Chew *et al.* performed a MRI and magnetic resonance spectroscopy study in cats with middle cerebral artery occlusion and concurrent treatment with a calcium channel blocker, nicardipine, for neuroprotection.[79] Control animals with normal glucose levels had only mild metabolic changes in the peri-infarct region and smaller infarcts. Animals with induced hyperglycemia had significantly altered energy metabolism noted by elevated lactate levels around the infarct. The hyperglycemic animals had larger infarcts, with no neuroprotective benefit gained after treatment with nicardipine. Detrimental effects of lactic acid on ischemic neurons are the presumed cause of worsened stroke in this animal model. Other studies counter the lactic acidosis hypothesis of increased neuronal damage. Schurr *et al.* studied levels of lactic acid and corticosterone, the rodent equivalent of human cortisol, in animals pre-treated with glucose prior to global cerebral ischemia.[84, 85] With glucose loading prior to ischemic insult, increased neuronal damage in hippocampal slices occurred when corticosterone level peaks corresponded to the onset of ischemia. Peaks of corticosterone occurred within 15 to 30 minutes following glucose infusion; in animals pre-treated with glucose at 120 minutes prior to ischemic injury, corticosterone levels had returned to baseline prior to the ischemic insult and no increase in neuronal damage was noted. Measurement of lactate levels showed similarly elevated lactate in animals pre-treated with glucose both at 15 minutes and at 120 minutes prior to ischemic injury, thus refuting the hypothesis that elevated lactate levels lead to neuronal injury in ischemia. Treatment with a corticosterone synthesis blocker, however, was not shown to reduce the deleterious effects of

hyperglycemia in a model of reversible focal cerebral ischemia, suggesting either a more complex relationship between hyperglycemia and cerebral injury or different mechanisms between models of focal and global cerebral ischemia.

Animal models of focal ischemia have also implicated other mechanisms for the deleterious effects of glucose. Accumulation of extracellular glutamate in the cortex and hippocampus was demonstrated in a rat model of forebrain ischemia; in hyperglycemic animals there were significantly higher levels of glutamate in the cortex, and corresponding neuronal injury, than in euglycemic controls.[86] However, other studies have found reduced levels of extracellular glutamate with either topical or systemic administration of glucose.[87] Another postulated mechanism is the accumulation of advanced glycation end-products (AGE), proteins that develop with age and abnormal glucose status over time that may mediate capillary leakage, cytokine production, and production of reactive oxygen species. In a rat model of focal ischemia, animals with systemically administered AGE sustained larger ischemic lesions and an increase in regional cerebral blood flow.[81]

Some studies using animal models have not shown a deleterious effect of hyperglycemia in focal ischemia. Ginsberg *et al.* used directed photochemical thrombosis in cerebral cortical vessels to induce small, localized infarcts in rats.[88] In the euglycemic rats the mean infarct volume was 12.5 mm^3 and in those with hyperglycemia the mean infarct size was only 9.3 mm^3 ($p < 0.05$). One possible reason for this finding relates to glucose metabolism in the ischemic region. In focal cerebral ischemia models, using a 2-deoxyglucose tracer has shown increased glucose metabolism in the peri-infarct zone in euglycemic animals with consequent increased neuronal damage; in hyperglycemic animals glucose metabolism was

normal and infarcts were smaller.[89, 90] A similar purported protective effect of hyperglycemia was demonstrated in a rat model of severe focal cerebral ischemia after permanent middle cerebral artery occlusion, with smaller infarcts in hyperglycemic animals compared with control animals.[91] In addition, another model of permanent middle cerebral artery occlusion showed larger cortical infarcts correlated with higher glucose levels, but that the volume of deep end-arteriolar ischemic lesions in the same animals were not affected by glucose status.[78] In these models, it is possible that hyperglycemic animals had smaller infarcts because they involved end-arteriolar vessels or vascular territories with poor collaterals. Elevated glucose levels may have improved the metabolic state of the ischemic penumbra and reduced the extent of infarction. Based on these studies, further investigation into specific stroke subgroups that may not be negatively affected by elevated glucose is warranted.

2.4.2 Human Studies on the Pathophysiology of Hyperglycemia in Stroke

Several hypotheses regarding the pathophysiologic basis of hyperglycemia in stroke have been postulated. The main hypothesis is that lactic acidosis results in worsening cerebral damage.[92] In non-ischemic brain tissue, glucose metabolism produces the required amount of energy, as adenosine triphosphate (ATP), for normal cellular processes. In cellular hypoxia, anaerobic metabolism occurs and results in increasing lactate and hydrogen ion production creating an intracellular acidosis. Lactic acidosis is detrimental to several cellular processes and can lead to cellular energy failure and neuronal cell death. With hyperglycemia, increased extra- and intracellular glucose are believed to exacerbate the production of lactic acid to worsen ischemic tissue damage.

The physiologic basis for the 'stress' hypothesis of hyperglycemia in stroke has been examined in human studies. One study of 23 stroke patients with no diabetes history found levels of the stress hormones cortisol, insulin, and glucagon to be significantly associated with initial glucose levels.[36] Regression analysis including the three stress hormones and glucose showed only cortisol to be an independent predictor of poor functional outcome. Neither glucose nor any of the stress hormones was a significant independent predictor of death after stroke, suggesting that glucose was a reflection of the intensity of the physiologic stress response related to the stroke. Catecholamine levels have also been found to be increased in ischemic stroke patients.[93] However, in one study, though norepinephrine levels were shown to be associated with initial stroke severity ($p = 0.005$), norepinephrine was not associated with glucose level, HbA1c level, or stroke type.[34] In this study, euglycemia was associated with better stroke outcome (73% minor deficit, compared with 53% in patients with hyperglycemia, $p = 0.047$), suggesting that elevated glucose in stroke patients is not a simple 'stress' response. Overall, the association between hyperglycemia and stroke outcomes in the context of the physiologic stress of cerebral ischemia appears to be complex and requires further investigation.

In patients with ischemic stroke treated with thrombolysis, the mechanism for the deleterious effects of glucose is not well understood. One hypothesis for lower recanalization rates with hyperglycemia is that glucose induces prothrombotic factors and vasoactive substances that impair the effectiveness of thrombolysis and also may lead to recurrent thrombosis of cerebral vessels following thrombolysis.[94] Further work is required to better elucidate the mechanisms for poor outcome in this patient group.

2.5 Effects of Hyperglycemia on Outcomes in Other Medical Conditions

The association between elevated blood glucose and outcome has been evaluated in patients with acute medical conditions other than stroke including critically ill patients with trauma, infections, or after major surgery and patients with acute myocardial infarction. These studies provide information regarding the effects of hyperglycemia in the setting of acute illness, which may assist in better understanding the association between glucose and outcomes in stroke patients.

2.5.1 Hyperglycemia in Intensive Care Patients

Patients with critical illness are often found to have elevated glucose levels after admission to the intensive care unit (ICU). In a large retrospective analysis of 1,826 patients in a general ICU, glucose was independently associated with mortality after adjusting for the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.[95] Mortality rates in these ICU patients were as high as 42.5% with glucose levels > 16.7 mmol/l (> 300 mg/dl), and as low as 9.6% with initial glucose levels in the range of 4.4 - 5.5 mmol/l (80 - 99 mg/dl). Another study evaluated glucose levels over the first seven days of ICU stay in patients with severe trauma and found that certain patterns of glucose were associated with poor outcomes. Particularly, persistently elevated, worsening, and highly variable glucose levels over the study time frame were associated with increased ICU and hospital length of stay, increased days on a ventilator, increased rates of infection, and increased mortality after adjusting for other predictor variables.[96] The specific use of glucose-based intravenous infusions that are commonly used as maintenance solutions has also been shown to be associated with increased mortality in the ICU setting.[97]

2.5.2 Hyperglycemia in Acute Myocardial Infarction

Patients with acute myocardial ischemia also appear to be at risk for adverse outcomes related to hyperglycemia. A meta-analysis of 15 cohort studies of patients with acute myocardial infarction showed that in patients with hyperglycemia upon hospital admission, but no history of diabetes, the unadjusted relative risk of in-hospital mortality was 3.9 (95% CI 2.9 - 5.4).[98] The effect was not as robust in patients with diabetes, though still the unadjusted relative risk of in-hospital mortality in that group was 1.7 (95% CI 1.2 - 2.4). The prevalence of hyperglycemia in these studies ranged from 5% - 47%.

The postulated mechanisms for the deleterious effects of glucose in acute myocardial infarction patients include a relative insulin resistance that hampers the uptake of glucose in the ischemic myocardial cells, as well as toxic effects of free fatty acids that accumulate within the ischemic tissue.[99] The strategy of treating patients with acute myocardial infarction with an infusion of glucose, insulin, and potassium was derived from this purported pathophysiology; providing insulin to restrict the release of free fatty acids from adipose tissue and to enhance the uptake of glucose by the ischemic myocardium.

2.6 Effects of Glucose Management on Outcomes in Acute Medical Conditions

Studies evaluating the management of glucose in patients in the ICU and patients with acute myocardial infarction provide some support for the hypothesis that hyperglycemia has deleterious effects and that aggressive lowering of glucose may improve patient outcomes. These findings have been extrapolated by some to guide management in the stroke patient population, though the patient populations in the ICU studies have not included important numbers of stroke patients to support this. However, the postulated mechanisms for the

deleterious effects of hyperglycemia and the potential beneficial effects of therapy may be applicable to stroke patients, and results of these other studies could be used to guide further research in the stroke population.

2.6.1 Glucose Management and Intensive Care Patient Outcomes

In ICU patients, aggressive management of glucose has been evaluated in several studies. The largest randomized trial of intensive insulin treatment in 1,548 patients ventilated in a surgical ICU showed a 42% relative risk reduction in ICU mortality (8.0% in the conventional treatment group versus 4.6% in the treatment group, $p < 0.04$).[100] The goal treatment glucose level was ≤ 6.1 mmol/l (≤ 110 mg/dl). This study also found significant differences in secondary outcomes, including lower in-hospital mortality overall, fewer cases of sepsis, less acute renal failure requiring dialysis, and fewer patients developing critical-illness polyneuropathy in the group receiving intensive insulin therapy. A meta-analysis of 35 treatment trials included patients admitted to ICU with either acute myocardial infarction (20 studies), following coronary artery bypass graft surgery (11 studies) or cardiac valve replacement (2 studies), patients requiring mechanical ventilation (1 study), and stroke (1 study).[101] The combined data showed an overall decrease in mortality of 15% (95% CI 0.75 - 0.97). However, in the subgroup of studies evaluating only patients with acute myocardial infarction there was a non-significant decrease in mortality favoring glucose treatment (relative risk [RR] 0.84, 95% CI 0.70 - 1.00).

A net benefit was seen over all of the trials of glucose treatment in patients with acute medical conditions and critical illness. This is reflected in practice recommendations from the American Diabetes Association that encourage treatment of hyperglycemia in patients

with acute medical conditions.[25] The use of insulin infusion protocols in ICUs and coronary care units has become more widely used, with the premise of improving outcomes in patients with acute myocardial infarction and with other critical conditions.[102] However, evidence from randomized treatment trials is still lacking for the aggressive treatment of glucose in many patient populations, including non-surgical ICU patients and general medical patients.

2.6.2 Glucose Management in Acute Myocardial Infarction

In the cardiac literature, the first use of a glucose-potassium-insulin infusion in myocardial ischemia was in 1962.[103] One of the larger studies to support its use was the DIGAMI study. This study evaluated the effects of treating hyperglycemia in 620 patients with diabetes who presented with acute myocardial infarction. At one year, there was a 29% relative risk reduction in mortality in the group treated with insulin infusion (18.6% deaths in the treatment group and 26.1% deaths in the control group, $p = 0.027$).[104] In 2005, DIGAMI 2 again evaluated patients with diabetes who presented with acute myocardial infarction. The protocol differed slightly from the initial DIGAMI study in that there were three study arms: 1) 24-hour glucose-insulin infusion followed by long-term insulin treatment, 2) 24-hour glucose-insulin infusion followed by regular glucose management, and 3) a control group with glucose management at the discretion of the treating physician, though without the use of insulin infusion.[105] For the primary endpoint of mortality at one year, there was no significant difference between groups 1 and 2 (23.4% deaths in group 1 and 22.6% deaths in group 2, hazard ratio [HR] 1.03, 95% CI 0.79 - 1.34). There was also no difference in mortality comparing groups 2 and 3. Possible reasons why the second trial did not demonstrate a difference between aggressive glycemic control and routine management included contamination of the management protocol in the control group, where 14% of

control patients received insulin infusion, lower baseline glucose levels in all patients at study entry and better than expected glucose control in the groups receiving less aggressive therapy (groups 2 and 3), and a smaller reduction in the mean glucose in group 1 (a –3.4 mmol/l change in DIGAMI 2 versus –5.8 mmol/l in DIGAMI).

Another study, CREATE-ECLA, included both patients with and without a prior history of diabetes and found no significant difference in mortality at 30 days and no difference in other adverse outcomes comparing patients treated with a glucose-potassium-insulin infusion versus controls.[106] There was a small but significant reduction in the risk of recurrent ischemia at 24 hours (1.5% treatment group versus 1.9% controls, HR 0.80, p = 0.047) and at day 7 (5.6% treatment group versus 6.5% controls, HR 0.85, p = 0.004), but the main outcomes at day 7 and day 30 were negative. However, at 24 hours, there was a notable increase in mean glucose levels in the treatment group that may suggest inadequate glucose control with the insulin infusion protocol used.

Both the DIGAMI 2 and the CREATE-ECLA trials had important limitations that may have contributed to the negative study results. In contrast with the DIGAMI 2 and CREATE-ECLA studies, a meta-analysis of another 9 randomized studies (1,932 patients) from 1966 to 1996 evaluated the effect of aggressive glucose treatment in acute myocardial infarction and demonstrated an overall 28% relative risk reduction for in-hospital mortality (16.1% deaths in the treatment groups versus 21% deaths in controls, odds ratio [OR] 0.72, 95% CI 0.57 - 0.90, p = 0.004).[107]

2.6.3 Studies Evaluating Glucose Management in Stroke Patients

The one randomized, controlled trial of early glucose treatment completed in the stroke patient population is the Glucose in Stroke Trial (GIST). In 1999, the GIST pilot study tested the safety of a 24-hour intravenous infusion of glucose, potassium, and insulin compared to normal saline infusion in 53 stroke patients presenting within 24 hours of stroke onset.[108] The insulin infusion protocol was deemed safe, with only one patient experiencing symptomatic hypoglycemia. Glucose levels achieved in the treatment group were slightly lower, but not significantly different from controls. In the main GIST study, over 900 patients were enrolled in total. For the first 452 patients randomized in the trial, Gray *et al.* reported no significant difference in the primary outcome measure, mortality at 30 days, between patients treated with insulin infusion compared to controls.[109] There was also no difference in 30-day functional outcomes. Final results for the entire 933 patients showed a non-significant reduction in 90-day mortality compared to normal saline controls (odds ratio [OR] 1.14, 95% CI 0.86 - 1.51, $p = 0.37$).[110] For the secondary combined outcome of severe disability or death at 90 days, no significant difference was found with the glucose-potassium-insulin infusion (OR 0.96, 95% CI 0.70 - 1.32). Mean plasma glucose in the treatment group was significantly lower, with a mean difference 0.57 mmol/l (95% CI 0.27 - 0.86, $p < 0.0001$).

Though the GIST results were negative, several factors may have affected the results. First, the trial was stopped early due to poor recruitment and may have been underpowered to demonstrate a treatment effect. Second, over 50% of patients presented with initial blood glucose levels within the treatment target range of plasma glucose < 8.0 mmol/l. Moreover, glucose levels decreased spontaneously in control patients; within eight hours of study

enrolment, mean glucose levels for both treatment and control groups fell within the therapeutic target range. In both groups, blood pressure also dropped spontaneously, though more in the treatment group, and is of unclear importance to the study results. Overall, though the study showed no benefit with aggressive treatment of glucose in stroke patients, further research is needed to clarify these results.

Only a few other smaller non-randomized studies have evaluated the benefits of treating glucose in stroke patients. Concerns over the potentially deleterious effects of overly aggressive glucose lowering in stroke patients may be a limiting factor for investigating optimal strategies for managing glucose in the acute post-stroke period.[111] One study used an insulin infusion to decrease glucose levels in 24 stroke patients with diabetes and determined that the protocol was safe in the setting of acute cerebral ischemia; this study did not evaluate stroke outcomes.[112] Two studies have examined the management of glucose and potential long-term benefits for stroke prevention. The use of pioglitazone, a thiazolidinedione, in non-diabetic stroke patients deemed to have impaired insulin sensitivity following a stroke was evaluated in one study.[113] Insulin sensitivity improved by 62% among patients treated with this agent compared to a 1% decline with placebo ($p = 0.0006$); specific stroke outcomes were not assessed and thus it is not clear whether improving the insulin sensitivity would reduce the risk of recurrent stroke. A large, multi-center, randomized controlled trial is currently in progress comparing pioglitazone to placebo to evaluate the efficacy of this agent in the prevention of recurrent stroke or myocardial infarction in patients with an index stroke.[114] Even if this trial shows promise in reducing recurrent stroke risk with improved insulin sensitivity, the question regarding the acute management of hyperglycemia in stroke patients with or without a history of diabetes requires ongoing investigation.

2.7 Summary

An association between glucose and poor outcomes in stroke patients has been shown in a number of studies. However, the real importance of this factor remains to be resolved. Some studies show that elevated glucose is an independent predictor of mortality and worsened functional outcome after stroke, but other studies have demonstrated that elevated glucose is merely a reflection of the severity of stroke damage in these patients. Defining what constitutes 'hyperglycemia' has been inconsistent in studies evaluating the effects of glucose on stroke outcomes and must be clarified. Moreover, studies often include heterogeneous groups of stroke patients in whom the effects of glucose may be variable; this may contribute to inconsistencies in study results. In other patient groups, including patients with critical illness, there appears to be a benefit to lowering glucose in the acute setting and further research is required to determine if the same benefit may be afforded to patients with stroke.

CHAPTER 3

3. Methodology

3.1 Data Sources

3.1.1 Clinical Database

The sample for this study was derived from patient data collected in the database of the Registry of the Canadian Stroke Network (RCSN), housed at the Institute for Clinical Evaluative Sciences (ICES) in Toronto, Ontario.[115, 116] The RCSN was initiated in 2001, and is now in Phase 3. Phase 1 and 2 included hospital sites from across Canada, and required written informed consent from patients or a surrogate decision maker for a patient to be included in the database. Phase 3, which began collecting data July 1, 2003, currently includes 11 acute care hospitals in Ontario and one additional site in Halifax. In 2004, the RCSN became a prescribed entity under the Personal Health Information Protection Act (PHIPA) and informed consent was no longer a requirement to collect patient health information.[117, 118] All consecutive patients seen in the Emergency Department or admitted to designated RCSN centres with an ischemic stroke, transient ischemic attack (TIA), intracerebral hemorrhage (ICH) or subarachnoid hemorrhage are entered into the RCSN clinical database. Each patient record in the RCSN is anonymized with a unique identifying number (an ICES key number) and all data are encrypted.

Patients from the 11 hospital sites in Ontario included in the RCSN Phase 3 during the period from July 1, 2003 and June 30, 2005 comprised the patient sample for this thesis. Approval for this project was obtained from the Research Ethics Board of Sunnybrook Health Sciences Centre.

Variables in the RCSN

The RCSN collects data including sociodemographic information (age, sex, and ethnicity), pre-hospital and emergency medical services data, stroke symptoms and time of onset, as well as time of hospital arrival. For all patients, relevant comorbid illnesses and pre-hospital medications are also documented.

Clinical details regarding stroke symptoms are used to determine the clinical stroke classification based on the Oxfordshire Community Stroke Project (OCSP). The OCSP classification was originally derived from a community-based study of 675 patients with first ever ischemic stroke and includes four main stroke types: TAC, total anterior circulation infarcts involving both cortical and subcortical brain structures; PAC, partial anterior circulation infarcts with predominantly smaller cortical areas of involvement; POC, posterior circulation infarcts involving the brainstem and/or cerebellum; and LAC, lacunar infarcts that are small infarcts isolated to deep structures supplied by small perforating arteries. These clinically defined stroke types have prognostic significance, with TAC strokes having the highest case-fatality rates (death at 30 days in 39%, and at one year, 60%) and rates of functional disability (at 30 days, 56% dependent, and at one year, 36% dependent).[119] The OCSP classification has not been well validated in patients with intracerebral hemorrhage; only one study was found that used the OCSP classification in this stroke type.[120] As such, in the current study, the OCSP classification was used only for patients presenting with ischemic stroke.

In addition to the OCSP stroke classification, the neurological examination documented on hospital presentation is used in the RCSN database to determine stroke severity based on the

Canadian Neurological Scale (CNS) score. The CNS score is an 11.5 point scale, with a score of 11.5 indicating no neurological deficits, and is a well validated measure of stroke severity.[121, 122] Predictive validity has been demonstrated for three clinical endpoints; the CNS score was an independent predictor of death at six months, any vascular event at six months, and functional independence at five months. The CNS score was also shown to correlate more closely with the neurological examination ($r = 0.769$, 95% CI 0.675 - 0.863) than the Glasgow Coma Scale score ($r = 0.563$, 95% CI 0.418 - 0.708).[122] The CNS score provides useful prognostic information; based on the validation cohort, a score ≤ 8 indicated a severe stroke with 13.2% case fatality within six months compared to 2.1 % case fatality with a score ≥ 11 (for increasing CNS score, OR 0.73, 95% CI 0.60 - 0.88).

In the RCSN database, other measures of stroke severity are captured. Initial level of consciousness (LOC) and Glasgow Coma Scale (GCS) score are documented. For patients who receive thrombolysis for acute ischemic stroke, the National Institutes of Health Stroke Scale (NIHSS) score is also used as a measure of stroke severity.[123]

Processes of care are documented in detail in the RCSN. From the Emergency Department, aspects of medical care including investigations completed and treatments provided, as well as a final Emergency Department disposition are noted in the database. For patients admitted to hospital, aspects of in-hospital care are detailed in the database, including investigations (brain CT/MRI, carotid Doppler, and echocardiography), interventions (cerebral angiography with endovascular stroke management, craniotomy, aneurysm coiling, carotid endarterectomy, and nasogastric or gastrostomy tube feeding), medications, and in-hospital complications. Also, consultations to specialty services are noted.

Finally, information regarding hospital disposition is documented, including hospital discharge status (alive or dead), discharge destination (home, active rehabilitation, other acute care facility, long-term care), and discharge medications. A functional outcome measure used at hospital discharge is the modified Rankin Scale (mRS) score. The mRS is a seven-point score, where a score 0 represents no neurological symptoms, 1, mild symptoms, 2, symptoms with mild disability, 3, moderate disability, requiring assistance for activities but remains ambulatory, 4, moderate to severe disability and unable to ambulate without assistance, 5, severe disability, requiring full care, and 6, death. The mRS scale has excellent test-retest reliability (kappa value 0.94 - 0.99).[124] The scale also has moderate to excellent inter-rater reliability with weighted kappa values of 0.71 - 0.91 and up to 0.91 - 0.93 when a structured clinical interview is used to determine the score. Several studies have demonstrated a mRS > 2 or > 3 after stroke is associated with poor outcomes at 6 months and a favourable outcome measure of mRS ≤ 2 is widely used in clinical stroke trials.[124]

Validity of the RCSN

Data are abstracted from patient charts by trained neurology research nurse coordinators at each designated RCSN site. The RCSN software automatically verifies completeness of data entry and internal consistency of the data. In addition, re-abstraction studies of a 10% sample of RCSN charts have shown excellent agreement with kappa values > 0.8 for key variables, including age, sex, stroke type, and use of thrombolytic therapy.[116]

Strengths and Limitations of the Clinical Database

The RCSN database has been used in several studies on the epidemiology and care processes of stroke in Ontario and in Canada.[115] The main strengths of this database lie in the

validation of stroke diagnoses and the depth of clinical details recorded for each consecutive patient hospital encounter across the timeframe from pre-hospital care, through the Emergency Department stay, and if admitted to hospital, through hospital discharge. This clinical detail provides important advantages over administrative databases for the interrogation of clinical stroke research questions. The RCSN is a well-managed database and is maintained with the high standards for health services research set through ICES. The RCSN Phase 3 includes a large sample of consecutive patients presenting to hospital with cerebrovascular disease. One limitation is that it represents the care and outcomes of stroke patients presenting to either tertiary care Regional Stroke Centres or District Stroke Centres where organized stroke care programs exist. The RCSN data may not reflect precisely the patient characteristics, care processes and outcomes for patients in other hospitals in the province, though stroke patients presenting to RCSN hospitals account for 20% to 30% of all strokes in the province (unpublished data). In addition to the main RCSN database, a biennial audit with random sampling of stroke patients presenting to all hospitals within Ontario is also conducted to evaluate stroke care and outcomes across the province.[125]

3.1.2 Administrative Data Sources

Data for patients in the RCSN database were linked to administrative databases held at ICES using unique identification numbers based on patients' encrypted Ontario health insurance plan (OHIP) numbers. Linkage of patient records to administrative databases permitted the evaluation of out-of-hospital outcomes in our patient sample.[126]

The Ontario Registered Persons Database (RPDB) is a database managed by the Ministry of Health and Long-Term Care and provides demographic information on all people in Ontario

possessing a provincial health insurance number.[127] At ICES, this database is linked to other administrative databases including those maintained by the Canadian Institute for Health Information (CIHI) (the Discharge Abstract Database [DAD], the National Ambulatory Care Reporting System [NACRS], and the Continuing Care Reporting System [CCRS]) to establish reliable dates of death. For the current analysis, the date of death was determined for any patient in our sample who died from July 1, 2003 to Oct. 31, 2006. The RPDB was used to determine all-cause mortality after stroke, whether death occurred in or out of hospital.

The Canada Census (last iteration on May 16, 2006) contains data on social and economic characteristics of the population.[128] For this study, the 2001 Canada Census was used to determine socioeconomic status (SES). In the RCSN, SES is based on aggregate level measures of income determined by calculating the median income for the neighbourhood surrounding each person's principal residence (based on the smallest geographic units used for reporting Census data, including 400 to 700 individuals).[129] The SES is reported in income quintiles, with quintile 1 being the lowest and quintile 5, the highest.

The Ontario Diabetes Database (ODD) is held at ICES and is derived from linkage to other administrative data sources including DAD, RPDB, and OHIP physician service claims.[128] The ODD tracks the incidence and prevalence of diabetes in Ontario. The diagnosis of diabetes is made based on either two OHIP physician service claims for diabetes within a 2-year period or one hospital discharge abstract with a diagnosis of diabetes listed. The database has been validated by primary care patient chart audit and through ODB claims for diabetes medication prescriptions. The sensitivity for the diagnosis of diabetes is 0.86 and

the positive predictive value is 0.80.[130] We used the ODD to validate the prevalence of diabetes mellitus in the RCSN cohort, using the timeframe from the start of ODD data collection (fiscal year 1992) to a six-month period after June 30, 2005, the final date of eligibility for inclusion in our study.

3.2 Patient Sample

In our cohort, we included patients over 18 years of age who presented to the Emergency Department or were admitted to hospital between July 1, 2003 and June 30, 2005 with either ischemic stroke or primary intracerebral hemorrhage (that is, not due to aneurysms, vascular malformations, tumours, or trauma). Patients with transient neurologic symptoms lasting < 24 hours were included only if there was imaging evidence of a cerebral infarction or hemorrhage either by computed tomography (CT) or magnetic resonance imaging (MRI). Patients presenting more than 24 hours from stroke onset (from the time last known to not have a neurologic deficit) were excluded from the analysis. Those with initial serum glucose < 4.0 mmol/l were also excluded. Only the first stroke event was included for patients with multiple presentations to hospital for cerebrovascular events captured in the RCSN during the study time frame. Any patients without a valid ICES key number were excluded, as those RCSN patient records could not be linked to the administrative databases for out-of-hospital outcomes.

3.3 Key Variables and Definitions

Baseline characteristics included variables with previously demonstrated predictive value for outcomes (mortality or functional disability) after stroke and variables deemed clinically relevant in the context of the research question for this project. Variables included were: age,

sex, history of diabetes,[26] hypertension,[131] hyperlipidemia, history of cerebrovascular disease (previous documented transient ischemic attack, ischemic stroke, or intracerebral hemorrhage), cardiovascular disease (past myocardial infarction, angina, or previous coronary angioplasty or coronary arterial bypass),[131] and smoking (current or past), pre-hospital use of insulin or oral hypoglycemic agents, pre-morbid functional status (independent defined as mRS ≤ 2), income quintile,[129, 132] presenting stroke type (ischemic or intracerebral hemorrhage), measures of stroke severity including the Canadian Neurological Scale (CNS) score,[121, 122] level of consciousness on arrival,[7, 133] and the Oxfordshire Community Stroke Project (OCSP) classification (for patients with ischemic stroke),[6] and initial values of systolic blood pressure, diastolic blood pressure, International Normalized Ratio (INR), and random serum glucose. The Charlson Comorbidity Index, a validated score that reflects the burden of comorbid illness based on a patient's medical history derived through medical chart abstraction, was also included.[134-136]

We captured variables relating to the hospital encounter, including the proportion of patients that received: (i) any insulin (either intravenous or subcutaneous) in hospital, (ii) oral hypoglycemic agents in hospital, and (iii) insulin or oral hypoglycemic agents at hospital discharge. The frequency of in-hospital complications was also examined, including cardiac arrest, decubitus ulcer, depression, deep venous thrombosis, embolism (pulmonary), falls (causing injury), gastrointestinal hemorrhage, myocardial infarction, pneumonia, seizure, urinary tract infection, and neurological worsening.

3.4 Outcomes

The primary outcome measure was time-to-death. Secondary outcomes were: (i) modified Rankin Scale (mRS) score at hospital discharge, dichotomized to > 2 versus ≤ 2 to evaluate moderate to severe disability (mRS 3-5) or death (mRS 6) versus excellent functional outcome (mRS ≤ 2), (ii) a combined endpoint of death at hospital discharge or discharge to a long-term care (LTC) facility or nursing home, and (iii) hospital length of stay.

3.5 Statistical Analyses

3.5.1 Categorization of Patients Based on Initial Blood Glucose Level

A receiver operating characteristic (ROC) curve was constructed for the cohort of patients with ischemic stroke, and separately for the cohort with intracerebral hemorrhage, to categorize patients with and without hyperglycemia. Since the 1950's, ROC curve analysis has been used as a methodology for evaluating the diagnostic accuracy of a test in detecting a "signal", or an outcome of interest.[137] In the medical field, ROC curve analysis is commonly used to determine the accuracy of a test in discriminating between two health states. Studies have also used ROC curve methodology to compare the diagnostic accuracy of two tests, or to evaluate a particular test's ability to predict prognosis.[138, 139] The sensitivity and specificity for all points throughout the range of results for a diagnostic test are derived to create the ROC curve; for any particular test the ROC curve demonstrates graphically the trade-off between true-positive and false-positive values for the possible test results.[137, 140, 141] The area under the curve (AUC) is the summary measure of the accuracy of a test.

Using ROC curve analysis, an optimal cut-off point to best predict the "signal" (for example, a diagnosis or an outcome) can be identified for a test. One methodology that has been used

to select a cut-off value is the "closest-to-(0,1) criterion" for the point closest to the upper left-hand corner coordinates of the ROC curve; this point theoretically maximizes the sensitivity of the test and minimizes false-positive classification of patients.[141-143] Balancing false-positive and false-negative results of a test is necessary when identifying a threshold, or cut-off, on which clinical decision-making will be based.[137, 140] Depending on the clinical situation, the cost of falsely classifying patients must be considered and several cut-off values on the ROC curve may be investigated, balancing false-positive and false-negative patient classification and incorporating clinical judgement to assist in identifying an optimal cut-off.

The ROC curve analysis was used in the current study to determine what cut-off level of random blood glucose was associated with death within 30 days from initial stroke onset. The sensitivity and specificity corresponding to all values of blood glucose in our cohort ≥ 4.0 mmol/l were evaluated and a cut-off level was identified. Initial cut-off value selection was carried out using the "closest-to-(0,1) criterion" for the point closest to the upper left-hand corner coordinates of the ROC curve to maximize sensitivity and minimize false-positive classification of patients.[141-143] The sensitivity and the false-positive fraction (1 - specificity) for the cut-off point were evaluated. Other cut-off points were also considered if deemed appropriate based on the ROC curve and clinical judgement was used to balance the false-positive and false-negative classification of patients. For this study, clinical judgement was used to minimize false-positive categorization of patients as being hyperglycemic for several reasons: the potential risks of treatment with insulin in this stroke patient group, particularly the risk of developing hypoglycemia, the use of extra resources required to manage glucose with aggressive insulin therapy and close monitoring, likely in an ICU or other monitored setting, and the costs of such care. In addition, we balanced the

decision to minimize false-positive patient classification with the sensitivity of the test for any candidate cut-off level. Lower sensitivity of the test would result in more false-negative patient classification that could result in patients at risk missing out on possibly beneficial therapies, if the cut-off were to be used in future treatment decision-making. In our cohort, optimal cut-off levels were determined separately for patients with ischemic stroke and for patients with intracerebral hemorrhage.

For the purposes of this study, we defined 'hyperglycemia' based on the blood glucose cut-off level determined using ROC curve analysis. The cohort was divided into patients presenting with 'hyperglycemia' (defined as blood glucose above the ROC curve cut-off value) and those without 'hyperglycemia' (blood glucose below the cut-off) for evaluation of the primary and secondary outcomes.

3.5.2 Analyses in the Ischemic Stroke Patient Cohort

Baseline continuous variables were expressed as a mean and median. For categorical variables, the proportion of patients with each characteristic was noted. Baseline characteristics were compared between patients with and without hyperglycemia, using Chi-square analysis for categorical variables and independent-samples t-test for continuous variables. Median values were compared using the Mann-Whitney U test. All statistical tests were two-sided. The level of significance was < 0.05 for all analyses.

Survival of patients with and without hyperglycemia was explored using Kaplan-Meier survival analysis; adjusted survival curves were derived from Cox proportional hazards modeling for the outcome, time-to-death. The survival time variable was calculated based on

the stroke onset date and the date of death including RPDB information updated to Oct. 31, 2006. In addition to overall survival, all-cause 30-day and 6-month case fatality was evaluated comparing patients with and without hyperglycemia.

Cox proportional hazards were used to evaluate demographic and clinical variables as predictors of the primary outcome. Univariable models evaluated age, sex, stroke severity (increasing ordinal CNS score), OCSP classification (each stroke subtype compared to TIA), history of TIA, ischemic stroke, intracerebral hemorrhage, diabetes, hypertension, hyperlipidemia, cardiovascular disease, smoking (current), pre-morbid functional status (dependent), socioeconomic status (each quintile compared to the highest, quintile 5), initial systolic blood pressure, diastolic blood pressure, and INR. Continuous variables with missing values had values imputed based on the median for the variable in the cohort. For non-continuous variables with values missing or 'unable to be determined' (UTD) through chart abstraction, those patients were deemed not to possess the characteristic. In the univariable Cox model, glucose was used as a continuous variable to evaluate the relationship with the primary outcome based on unit increments of glucose. Glucose was also used as a categorical variable, dichotomized at the cut-off level determined by the ROC curve analysis.

Multivariable Cox proportional hazards models were constructed using backward stepwise procedures to evaluate variables as independent predictors of the outcome, time-to-death. All variables examined in the univariable analyses were included in the multivariable models. The main model was constructed for the primary outcome, time-to-death. In this model, glucose was initially included as a continuous variable. Individual comorbid conditions were

included in the main model as binary categorical variables. The CNS score was used as an ordinal variable, with comatose patients given a score of zero. For any patient with a missing CNS score, a score with imputed based on the median CNS score of the cohort. In a second multivariable Cox model for the primary outcome, glucose was included as a dichotomous variable. The multivariable model was used specifically to evaluate glucose status (either having hyperglycemia or not) as an independent predictor of death after stroke while adjusting for stroke severity and other relevant variables.

Multivariable logistic regression models were constructed for the functional secondary outcome measures including modified Rankin Scale score > 2 at hospital discharge, and death at discharge or discharge to a long-term care facility or nursing home. A generalized linear model was used to evaluate predictors of hospital length of stay. In each of these models, glucose was used as a continuous variable. All other variables were maintained in their initial form (binary categorical, ordinal, or continuous, based on the individual variable).

3.5.3 Analyses in the Intracerebral Hemorrhage Cohort

Secondary analyses were carried out in patients with intracerebral hemorrhage. A glucose cut-off level was determined by ROC curve analysis in patients with intracerebral hemorrhage, as described for the ischemic stroke group analysis, to compare outcomes in patients with and without hyperglycemia. Baseline characteristics, in-hospital course, and outcomes were evaluated comparing patients with and without hyperglycemia.

A Kaplan-Meier survival analysis was completed for patients with intracerebral hemorrhage; adjusted survival curves were also derived from multivariable Cox modeling. Univariable and multivariable Cox proportional hazards models, multivariable logistic, and generalized linear models were constructed for the intracerebral hemorrhage cohort as described for the analysis of patients with ischemic stroke. The multivariable models were used to evaluate glucose as an independent predictor of outcome while adjusting for stroke severity and other variables.

Statistical analyses were completed using the Statistical Package for the Social Sciences (SPSS), version 14.0. Verification of the ROC curve analysis was done using SAS statistical software; generalized linear modeling was also carried out by a statistical programmer at ICES using SAS software.

CHAPTER 4

4. Results

4.1 RCSN Patient Cohort

A total of 14,069 patient records were available in the RCSN database at the time of cohort creation. Of these records, for the study timeframe from July 1, 2003 to June 30, 2005, there were 3,930 patients who met inclusion criteria for this study. A flow diagram of patient records excluded from the analysis is shown in Figure 1. Chart audits were carried out for 11 patients to verify data outliers and 2 patient records were excluded for date data inaccuracies. The final cohort comprised 3,928 patients; 3,193 (81.3%) with ischemic stroke and 735 (18.7%) with intracerebral hemorrhage.

4.1.1 Characteristics of Patients in the RCSN Cohort

Demographic and clinical characteristics of the entire cohort are summarized in Table 2. The mean age of patients in the cohort was 72.2 years. There were 2,058 (52.4%) men and 1,874 (47.6%) women. For stroke severity on presentation, 2,034 (54.0%) patients presented with a CNS score ≤ 8; the median CNS score was 7.5. Of all patients, 273 (7.0%) presented in a coma and were given a CNS score of zero. Five percent of patients presented clinically with a TIA, though on imaging either an infarct or hemorrhage was confirmed in all patients.

Comorbid medical conditions in the entire cohort included hypertension in 65.9%, hyperlipidemia in 31.6%, a history of myocardial infarction in 15.2%, past coronary angioplasty or bypass surgery in 8.8%, a history of stroke in 22.0%, TIA in 15.7%, and ICH in 2.1%, and a history of smoking (past or current) in 35.4% of patients (16.6% current). The

mean Charlson Comorbidity Index score was 1.4 and 1,267 (32.3%) patients had a Charlson Index ≥ 2. Eighty percent of patients were independent prior to hospital presentation.

4.1.2 Diabetes and Glucose Status in the RCSN Cohort

A history of diabetes mellitus was documented in 866 (22.0%) patients in the entire cohort based on RCSN data. In addition, the ODD revealed another 242 patients with a history of diabetes that had not been captured in the RCSN, giving overall 1,108 (28.2%) patients with diabetes. The RCSN and ODD had very good agreement with a kappa value 0.76 for the diagnosis of diabetes ($p < 0.001$). Any history of diabetes documented in either database was considered a past medical history of diabetes for patients in these analyses. Prior to hospitalization, 506 (12.9%) patients were on oral hypoglycemic agents and another 168 (4.3%) patients were on insulin therapy. On presentation to hospital, in the entire cohort the mean random serum glucose level was 7.8 mmol/l; the mean was 7.7 mmol/l in patients with ischemic stroke and 8.4 mmol/l in those with intracerebral hemorrhage. The distribution of initial blood glucose values in the entire patient cohort and based on diabetes history is shown in Figure 2a and 2b.

4.2 Categorization of Patients with and without Hyperglycemia

4.2.1 Ischemic Stroke Cohort

Using ROC curve analysis, the ROC curve for the ischemic stroke cohort had an area under the curve of 0.592 (95% CI, 0.564 - 0.619) (see Figure 3a). A cut-off level of blood glucose 7.5 mmol/l was identified using the "closest-to-(0,1)" criterion as a candidate threshold to best predict death at 30 days for patients following an ischemic stroke (see Appendix A). The sensitivity for the cut-off glucose value 7.5 mmol/l was 0.48 - 0.49 and the false-positive

fraction (1-specificity) was 0.33 - 0.34. The ROC curve for the ischemic stroke group also demonstrated a second possible glucose cut-off level at 6.5 mmol/l based on the "closest-to-(0,1)" criterion, with a sensitivity between 0.65 - 0.69 and a false-positive fraction between 0.52 - 0.54. For all other glucose values above 7.5 mmol/l, the sensitivity (true-negative fraction) for any potential cut-off declined well below 50% and thus these values were not considered clinically appropriate cut-off points (see Appendix A). Based on clinical judgement, the cut-off glucose level 7.5 mmol/l was considered preferable to 6.5 mmol/l since a cut-off 6.5 mmol/l was associated with a false-positive classification rate of > 50%, potentially resulting in the unnecessary treatment of a large number of patients, exposing the patients to the associated risks of insulin therapy, and adding extra costs for the medical system. Therefore, a random blood glucose > 7.5 mmol/l was identified as the optimal cut-off for the ischemic stroke cohort in this study and was used to define 'hyperglycemia' for the remainder of the analyses in this group.

Using the 7.5 mmol/l cut-off value from the ROC curve analysis, a multivariable Cox proportional hazards model for the primary outcome, time-to-death, was constructed to evaluate the dichotomous glucose variable as a prognostic factor (see below, section 4.3.4). As a sensitivity analysis, the cut-off glucose level 6.5 mmol/l was also examined in a multivariable Cox model to determine its performance as a predictor of death.

4.2.2 Intracerebral Hemorrhage Cohort

For patients with intracerebral hemorrhage, the ROC curve had an area under the curve of 0.668 (95% confidence interval, 0.629 - 0.704) (see Figure 3b). A glucose cut-off level 8.5 mmol/l was identified using the "closest-to-(0,1)" criterion as a candidate threshold to

best predict death at 30 days for patients following intracerebral hemorrhage (see Appendix B). This cut-off glucose value had a sensitivity of 0.56 and a false-positive fraction (1 - specificity) between 0.25 - 0.26. No other cut-off values were identified that were clinically relevant or that had an acceptable balance of sensitivity and false-positive rate (see Appendix B). Therefore, random blood glucose > 8.5 mmol/l was identified as the optimal cut-off for the intracerebral hemorrhage cohort in this study, based on the low false-positive classification of patients.

Glucose as a dichotomous variable, based on the candidate cut-off level 8.5 mmol/l, was evaluated as a prognostic factor in a multivariable Cox proportional hazards model for the primary outcome, time-to-death (see below, section 4.4.4). As a sensitivity analysis, separate Cox models for the outcome of death were constructed using glucose cut-offs of 7.5 mmol/l and 6.5 mmol/l, which were the values derived from the ischemic stroke cohort. The rationale for this sensitivity analysis was that identifying a single glucose cut-off value for both ischemic and hemorrhagic stroke might have clinical utility, as it would allow for a single treatment strategy for patients with both types of stroke and would potentially permit glucose to be appropriately treated prior to neuroimaging being obtained in these patients.

The cut-off levels determined by the ROC curve analysis were used to define 'hyperglycemia' in our study. Based on the selected cut-off levels, 1,395 (35.5%) patients in the entire cohort had hyperglycemia on presentation. Hyperglycemia was seen in 1,115 (34.9%) patients with ischemic stroke and 280 (38.1%) patients with intracerebral hemorrhage.

4.3 Evaluation of Patients with Ischemic Stroke

4.3.1 Baseline Characteristics

Demographic and clinical characteristics of the ischemic stroke cohort are summarized in Table 3. There were 1,660 (52.0%) men and 1,533 (48.0%) women. The mean age was 73 years. Patients arrived to hospital within 5.9 hours of stroke onset on average, with a median time to arrival of 3.0 hours. The majority of patients (85.4%) were awake and alert on arrival. The median CNS score was 8.0; 1,557 (50.6%) patients had a CNS score ≤ 8. Using the OCSP stroke classification, approximately 40% of patients presented with a partial anterior circulation (PAC) stroke, almost 15% with a total anterior circulation (TAC) stroke, 22% with a posterior circulation (POC) stroke, and 18% had a lacunar (LAC) stroke. Almost 5% of patients presented as a TIA but had an infarct confirmed on neuroimaging. The mean Charlson Comorbidity Index score was 1.5; 1,093 (34.2%) patients had a Charlson Index score ≥ 2. Twenty-three percent of patients had a prior history of stroke, 17.5% prior TIA, and 1.3% prior ICH. A history of diabetes was documented in 22.9% of patients based on RCSN data; including data from the ODD, another 201 patients were shown to have a prior history of diabetes thus making the total prevalence of diabetes 29.2%.

4.3.2 Comparison of Baseline Characteristics based on Glucose Status

In the ischemic stroke cohort 2,078 (65.1%) patients presented with an initial random serum glucose level ≤ 7.5 mmol/l; 1,115 (34.9%) patients had glucose > 7.5 mmol/l (see Table 3). Patients with hyperglycemia were older (mean age 73.8 years versus 72.5 for years, $p = 0.006$) and fewer were men (49.2% versus 53.5%, $p = 0.023$). Patients with hyperglycemia were more likely to present in a drowsy or comatose state ($p < 0.001$) and had more severe strokes (median CNS score 7.5 versus 8.5, $p < 0.001$). Fifty-five percent of

hyperglycemic patients had a CNS score ≤ 8 compared with 48% of those with glucose ≤ 7.5 mmol/l ($p < 0.001$). Patients with hyperglycemia had more comorbid illness, including a history of diabetes, hypertension, hyperlipidemia, myocardial infarction, and smoking history. The mean Charlson Index score was 1.8, compared to 1.3 in patients without hyperglycemia ($p < 0.001$). In addition, a higher proportion of patients with hyperglycemia were from the lowest socioeconomic quintile (27.3% versus 20.1%, $p < 0.001$).

4.3.3 In-Hospital Stroke Care and Hospital Course

In acute stroke patients who received rt-PA, no differences were seen in the proportion of patients with and without hyperglycemia (see Table 4). More patients with elevated glucose received oral hypoglycemic agents or insulin, both in hospital and at hospital discharge, though this does not take into account the proportion with a diabetes history. In hospital, 32.6% of hyperglycemic patients received either intravenous or subcutaneous insulin, whereas 15.7% of patients were discharged on insulin. Oral hypoglycemic agents were used in 34.9% of hyperglycemic patients in hospital and 28.8% were discharged home on these agents. Less than 6% of patients with initial glucose ≤ 7.5 mmol/l received glucose management therapies.

In-hospital complications following stroke were more common in patients with hyperglycemia. First, these patients were more likely to have neurological worsening following initial presentation (23.5% versus 15.4%, $p < 0.001$). Neurological worsening was attributed to a reported new stroke in 5.0% of hyperglycemic patients, versus 3.1% of patients without hyperglycemia ($p = 0.011$). Higher proportions of hyperglycemic patients also had in-hospital cardiac arrest, seizure, gastrointestinal bleeding, pneumonia, and urinary

tract infection. Overall, patients with hyperglycemia were significantly more likely to have at least one complication in hospital (35.5% versus 27.5%, $p < 0.001$).

4.3.4 Outcomes in Patients with Ischemic Stroke

Survival Analysis and Out-of-Hospital Outcomes

Patients with hyperglycemia had a significantly higher risk of dying over the course of the study compared to patients without hyperglycemia demonstrated by Kaplan-Meier survival analysis ($p < 0.001$ for the comparison between survival curves) (see Figure 4a). Survival curves based on Cox proportional hazards analysis that was adjusted for stroke severity, as well as age, sex, comorbid medical conditions, pre-morbid functional status and socioeconomic status, also showed a significantly higher risk of death in patients with hyperglycemia (see Figure 4b). Death within 30 days of initial stroke onset occurred in 19.6% of hyperglycemic patients but in only 11.5% of patients with glucose ≤ 7.5 mmol/l ($p < 0.001$) (see Table 5). The majority of these deaths occurred in hospital. Deaths at 30 days based on quintiles and deciles of glucose show a relatively linear relationship between glucose and death (see Figure 5a and 5b). At six months, a larger proportion of patients with initial hyperglycemia had died (27.8% versus 18.1%, $p < 0.001$).

In the univariable Cox proportional hazards model, examining predictors of death following stroke, increasing glucose conferred a 3.7% increased relative risk of death per mmol/l elevation in glucose level at hospital presentation ($p < 0.001$) (see Table 6). Using glucose as a dichotomous variable, above the cut-off 7.5 mmol/l, there was a 46% unadjusted relative increase in the risk of death ($p < 0.001$). Other variables deemed significant in the unadjusted univariable analysis are shown in Table 6.

Adjusting for stroke severity and other predictor variables, the multivariable Cox model revealed glucose (as a continuous measure) to be a significant independent predictor of death with a hazard ratio of 1.050 (95% CI 1.031-1.069, $p < 0.001$) (see Table 7). Other independent predictors of death included lower CNS score, increasing age, male sex, higher initial INR, history of hyperlipidemia, past myocardial infarction, past stroke, current smoking, and poor pre-morbid functional status. In repeating the Cox model to evaluate glucose using the cut-off > 7.5 mmol/l while adjusting for other predictor variables, the model demonstrated a significantly increased risk of death for hyperglycemic patients; the hazard ratio was 1.394 (95% CI 1.231 - 1.578, $p < 0.001$) (see Table 8). A separate multivariable Cox model was constructed to evaluate the effect of choosing a glucose cut-off > 6.5 mmol/l, identified by ROC curve analysis, as a predictor of death compared to the cut-off > 7.5 mmol/l. Glucose > 6.5 mmol/l had an adjusted hazard ratio for risk of death of 1.172 (95% CI 1.028 - 1.336, $p = 0.017$).

Other In-hospital Outcomes

In hospital, the case-fatality rate for all ischemic stroke patients was 13.3%. More patients with hyperglycemia died (18.8% versus 10.3%, $p < 0.001$) (see Table 5). In addition, patients with hyperglycemia had worse functional outcome at hospital discharge. Only 30% of patients with glucose > 7.5 mmol/l had a mRS score ≤ 2 compared to patients without hyperglycemia, where 41% had excellent functional outcome ($p < 0.001$). Glucose was a significant independent predictor of the combined outcome of moderate to severe disability (mRS 3-5) or death (mRS 6), with an odds ratio of 1.052 (95% CI 1.024 - 1.081, $p < 0.001$), adjusting for stroke severity and other covariates (see Table 9). Lower CNS score, increasing age, OCSP classification of any stroke subtype (versus TIA presentation), increasing initial

systolic blood pressure, history of TIA, poor pre-morbid functional status, and low socioeconomic status were also independent predictors of disability or death at hospital discharge following stroke.

Comparing patients with and without hyperglycemia, a small but statistically significant difference was seen in median length of stay (10 days versus 9 days, $p = 0.047$) (see Table 5). Patients with hyperglycemia were less likely to be discharged home (40.7% versus 48.5%, $p = 0.003$), though a higher proportion was discharged to a rehabilitation facility (36.6% versus 32.8%). Fourteen percent of patients with hyperglycemia required admission to a long-term care facility following hospital discharge. Multivariable regression analysis for the combined outcome of death at hospital discharge or discharge to a long-term care facility or nursing home revealed glucose to be an independent predictor of outcome, after adjusting for age, sex, stroke severity, and comorbid conditions, with an odds ratio of 1.069 (95% CI 1.037 - 1.102, $p < 0.001$). Other independent predictor variables for death or institutionalization are outlined in Table 10. Glucose was also a significant independent predictor of increased hospital length of stay after adjusting for other prognostic variables (unstandardized B coefficient 0.006, 95% CI 0.002 - 0.009, $p = 0.0006$) (see Table 11). Increasing age, lower CNS score, OCSP classification (any stroke subtype versus TIA), higher initial systolic blood pressure, and lower SES were also independent predictors of increased length of stay.

4.4 Evaluation of Patients with Intracerebral Hemorrhage

4.4.1 Baseline Characteristics

Baseline characteristics of the intracerebral hemorrhage cohort are outlined in Table 12. The mean age of patients was 68.8 years, slightly lower than the ischemic stroke cohort. The

cohort comprised 398 (54.1%) men and 337 (45.9%) women. Mean time to hospital arrival was 6.0 hours from stroke onset and the median time to arrival was 3.7 hours. Unlike patients presenting with ischemic stroke, one-quarter of patients with intracerebral hemorrhage were unconscious on arrival, and only 49.5% were awake and alert. The mean CNS score was 5.2 (median 5.0), reflecting the more severe strokes in this stroke type. Seventy percent of patients had a CNS score ≤ 8.

Comorbid medical conditions in patients with intracerebral hemorrhage included a history of diabetes in 23.8% (including both RCSN and ODD data), hypertension in 60.1%, hyperlipidemia in 21.6%, history of myocardial infarction in 7.9% and coronary intervention in nearly 5%, current smoking history in 13.5%, a past history of stroke in 15.9%, past TIA in 7.9%, and prior ICH in 5.4%. The mean Charlson comorbidity index was 1.1; 23.7% of patients had a Charlson index ≥ 2. Prior to hospital presentation, 81.4% of patients with intracerebral hemorrhage were functioning independently.

4.4.2 Comparison of Baseline Characteristics based on Glucose Status

Hyperglycemia defined by glucose > 8.5 mmol/l occurred in 280 (38.1%) patients with intracerebral hemorrhage (see Table 12). Baseline age was similar in patients with and without hyperglycemia and no difference was seen in the proportion of women in each group. Patients with hyperglycemia were much more likely to present in a comatose state (41.4% versus 13.4%, $p < 0.001$). Not surprisingly, the median CNS score was 2.5; without including comatose patients the median CNS score was 6.5 in patients with hyperglycemia. More patients with hyperglycemia had a history of diabetes (38.2% versus 14.9%, $p < 0.001$). Hyperglycemic patients were also slightly less likely to be previously independent.

However, a higher proportion of patients with glucose ≤ 8.5 mmol/l had other comorbid medical conditions including past myocardial infarction, any smoking history, past TIA, and prior intracerebral hemorrhage. There was no difference in socioeconomic status between the groups.

4.4.3 In-Hospital Stroke Care and Hospital Course

Patients with hyperglycemia were more likely to be treated with either insulin or oral hypoglycemic agents both in hospital and upon hospital discharge (see Table 13). Thirty-five percent of patients with initial glucose > 8.5 mmol/l were treated with insulin in hospital but only 8.9% of those patients were discharged from hospital on insulin. Oral hypoglycemic agents were given to 18.2% of hyperglycemic patients in hospital and 10.4% of those patients were discharged from hospital on these medications. In the group with glucose ≤ 8.5 mmol/l, 11.6% of patients were treated with insulin at some point in hospital and 3.1% were discharged from hospital on insulin.

4.4.4 Outcomes in Patients with Intracerebral Hemorrhage

Survival Analysis and Out-of-Hospital Outcomes

Over the course of the study follow-up time, Kaplan-Meier survival analysis revealed a significantly increased risk of death in patients with hyperglycemia ($p < 0.001$ for the comparison between survival curves) (see Figure 6a). Survival curves adjusted for stroke severity and other variables also showed a significantly higher risk of death in patients with hyperglycemia on presentation (see Figure 6b). Death within 30 days of stroke onset occurred in 315 patients (42.9%) with intracerebral hemorrhage (see Table 14). These deaths occurred in 62.5% of patients with hyperglycemia at hospital presentation, whereas only

30.8% of patients with glucose ≤ 8.5 mmol/l died ($p < 0.001$). Nearly all of the deaths in both groups occurred in hospital. Deaths at 30 days based on quintiles and deciles of glucose showed a possibly non-linear relationship between glucose and death in the intracerebral hemorrhage cohort (see Figure 7a and 7b).

Evaluating predictors of death with univariable Cox proportional hazards analysis revealed glucose to be a predictor when examined as a continuous variable, with an unadjusted hazard ratio of 1.035 ($p < 0.001$) for each mmol/l increase in glucose at baseline (see Table 15). Using glucose as a dichotomous variable, a 2-fold increased risk of death was conferred in the group with glucose > 8.5 mmol/l (unadjusted HR 2.078, 95% CI 1.711 - 2.524, $p < 0.001$). Other variables that were predictors of death included increasing age, female sex, lower CNS score, higher initial systolic blood pressure, higher initial INR, history of diabetes, history of smoking (current), past history of stroke and TIA, poor pre-morbid functional status, and low socioeconomic status. For the CNS score, a score ≤ 8 had an unadjusted hazard ratio 3.749 for risk of death ($p < 0.001$).

A multivariable Cox proportional hazards model showed that glucose, as a continuous variable, was an independent predictor of death after adjusting for stroke severity, age, sex, and comorbid conditions. Glucose had an adjusted hazard ratio for the risk of death of 1.025 per mmol/l glucose unit increase at hospital presentation (95% CI 1.001 - 1.049, $p = 0.040$) (see Table 16). Variables that were also independent predictors of death in this model included lower CNS score, increasing age, higher initial systolic blood pressure, higher initial INR, history of hypertension, history of past stroke, and lower SES (quintiles 1 and 4, compared to the highest, quintile 5).

A multivariable Cox model was constructed using glucose as a dichotomous variable and in this model, glucose > 8.5 mmol/l was an independent predictor of death with a hazard ratio of 1.574 (95% CI 1.280 - 1.935, $p < 0.001$) (see Table 17). Other variables deemed independent predictors of death were similar to the initial multivariable Cox model. Further Cox models were constructed using the two other cut-off values for glucose derived from ROC curve analysis; with a glucose cut-off > 7.5 mmol/l, the adjusted hazard ratio for risk of death was 1.419 (95% CI 1.149 - 1.752, $p = 0.001$) and for a glucose cut-off > 6.5 mmol/l, the adjusted hazard ratio was not significant (HR 1.114, 95% CI 0.867 - 1.432, $p = 0.399$).

Other In-hospital Outcomes

In hospital, case fatality for all intracerebral hemorrhage patients was 41.9% (see Table 14). For patients presenting with hyperglycemia though, in-hospital case fatality was 61.1%, which was double that of patients presenting without hyperglycemia ($p < 0.001$). Patients with hyperglycemia had worse functional outcome at hospital discharge, with a median mRS score 6, than those patients without hyperglycemia, with a median mRS score 4 ($p < 0.001$). In patients surviving through hospital discharge, the median mRS score was 4 in hyperglycemic patients; in patients without hyperglycemia the median mRS score was 3. Only 8.2% of patients with initial hyperglycemia had an excellent functional outcome, based on a mRS score ≤ 2, compared with 22.2% of patients with glucose ≤ 8.5 ($p < 0.001$). In the multivariable regression analysis for the combined outcome of moderate to severe disability or death at hospital discharge, glucose (as a continuous variable) was not an independent predictor (adjusted OR 1.018, 95% CI 0.929 - 1.115, $p = 0.703$) (see Table 18a and 18b). Variables that were independent predictors in the model included increasing age, lower CNS score, and history of past stroke.

Mean length of stay was not significantly different between the group of patients with and without hyperglycemia; though the median length of stay was longer in patients with glucose ≤ 8.5 mmol/l ($p < 0.001$) (see Table 14). For patients surviving through hospital discharge, there was no significant difference in discharge destination between patients with and without hyperglycemia. Nearly one-quarter of patients with hyperglycemia were discharged home, compared with 31.4% of patients without hyperglycemia. Discharge from hospital to a rehabilitation facility occurred in 36.4% of patients with hyperglycemia; 29.2% of patients presenting without hyperglycemia went to rehabilitation from hospital. More patients in the group with glucose ≤ 8.5 mmol/l went to long-term care or nursing home from hospital compared with patients in the hyperglycemic group (15.1% versus 10.9%). For the combined outcome of discharge disposition to long-term care or death at hospital discharge, glucose (as a continuous variable) was not an independent predictor, with an odds ratio 1.044 (95% CI 0.988 - 1.103, $p = 0.122$) (see Table 19a). Variables that were independent predictors of the combined outcome included increasing age, lower CNS score, higher initial systolic blood pressure, higher initial INR, and poor pre-morbid functional status (see Table 19b). Glucose (as a continuous variable) was a significant independent predictor of longer length of stay (unstandardized B coefficient 0.024, 95% CI 0.020 - 0.029, $p < 0.001$) (see Table 20).

CHAPTER 5

5. Discussion

5.1. Outcomes in Patients with Ischemic Stroke

5.1.1 Association between Glucose and Death after Stroke

In this study, we evaluated the association between glucose and stroke outcomes with a patient sample from a large clinical stroke registry. For the primary analysis evaluating the association between glucose level and death following stroke we examined blood glucose based on one random sample taken at presentation to hospital. In our ischemic stroke cohort of 3,193 patients, we found blood glucose to be a significant independent predictor of death after stroke, with a modest increase in the hazard ratio for the risk of death of 1.050 per mmol/l unit increase in initial glucose level, after adjusting for initial stroke severity and other important factors including age, sex, stroke type, and comorbid conditions. This finding is consistent with the conclusions of past studies that have demonstrated an association between elevated glucose and increased mortality after stroke.

The magnitude of the increased risk of death associated with higher glucose levels in our cohort is somewhat less than previously reported, though consistent with other studies of cohorts having similar baseline characteristics. Reported unadjusted relative risks of death with hyperglycemia range from 0.56 to 12.86 (pooled RR 1.30) in patients with diabetes and from 2.47 to 11.88 (pooled RR 3.07) in patients with no diabetes history.[144] In our study, we evaluated both patients with and without a history of diabetes together and this may have affected the magnitude of the hazard ratio for glucose and death after stroke, if in fact there is a differential effect of hyperglycemia in these groups of stroke patients. Interestingly, in our ischemic stroke cohort a history of diabetes had an unadjusted hazard ratio 1.136 for risk of

death but this did not reach statistical significance ($p = 0.055$). In the multivariable analysis, a history of diabetes was removed by the model and would not have had an effect on the glucose variable included in the model. Examining glucose as a dichotomous variable, two studies have reported higher hazard ratios than in our study. Weir *et al.* reported a hazard ratio 1.87 for risk of death (95% CI 1.43 - 2.45, $p < 0.0001$) in patients with random glucose > 8.0 mmol/l.[40] Vermeer *et al.* also reported an increased hazard of death in patients with impaired glucose tolerance, defined as glucose > 7.8 mmol/l to 11.0 mmol/l (HR 1.8, 95% CI 1.1 - 3.0).[46] However, the results from both studies pertain to patients with no diabetes history; this may explain the discrepancy with our results that showed an increased hazard of 1.4 for risk of death in all patients with glucose > 7.5 mmol/l.

Other important predictors of the primary outcome were identified. Increasing initial stroke severity is a known predictor of poor stroke outcome. In our study, stroke severity was defined based on initial CNS score and the OCSP stroke classification; an unadjusted hazard ratio 3.251 ($p < 0.001$) was demonstrated for CNS score ≤ 8 and for a total anterior circulation (TAC) clinical stroke presentation, an unadjusted hazard ratio 4.907 ($p < 0.001$, compared with the reference category, TIA with an infarct on imaging) for death. Other independent predictors of death included a pre-morbid dependent functional status that resulted in a 53% relative increase in risk of death, history of cardiovascular disease or previous cerebrovascular disease each with an approximate 20% increased relative risk of death, as well as the presence of hyperlipidemia and current smoking. Females had a 23% lower relative risk of death following ischemic stroke in our cohort, after adjusting for other prognostic factors. Increasing age was also a significant predictor of death after stroke.

5.1.2 Functional Outcome and Length of Stay

For the secondary outcome measure, glucose was shown to be an independent predictor of the combined outcome of moderate to severe disability (mRS 3-5) or death (mRS 6) at hospital discharge in patients with ischemic stroke. Given concerns regarding reliability inherent to a mRS score assigned at the time of hospital discharge,[145] poor functional outcome was also evaluated using the combined outcome of discharge to a long-term care facility or nursing home or death at hospital discharge. With this combined measure, glucose was shown to be an independent predictor of outcome. In addition, glucose was an independent predictor of increased hospital length of stay.

5.1.3 Identifying a Glucose Cut-off Associated with Outcome

In our ischemic stroke cohort, we identified an optimal cut-off level of glucose to predict death within 30 days following stroke using the statistical method of receiver operating characteristic curve analysis. The area under the ROC curve is the overall measure for the accuracy of the test; the ROC curve for glucose in our patient sample had an area of 0.592. A diagnostic test is typically considered moderate to good at discriminating between two alternative health states with an area between 0.70 and 0.80, and excellent above an area of 0.90.[146, 147] In this regard, the robustness of random blood glucose as an individual prognostic measure for death after stroke would be deemed fair to moderate.

In our ischemic stroke cohort, a random-sample blood glucose level > 7.5 mmol/l was identified as the cut-off to maximize the sensitivity of the test in predicting the outcome, while minimizing the false-positive classification of patients. This cut-off had a sensitivity of about 50%, with a false-positive rate of just over 30%. A second point on the ROC curve,

6.5 mmol/l, was also deemed a potential cut-off based on the ROC curve. This second cut-off gave a sensitivity of just over 65%, but this lower glucose level was associated with over a 50% false-positive rate of patient classification, which was not deemed clinically acceptable. Taking into account the purpose of the test, which was to define a glucose threshold associated with poor outcome, and the costs related to falsely classifying patients including the potential risks of treatment-related adverse effects if patients determined to have hyperglycemia may have glucose levels aggressively treated, the glucose cut-off level > 7.5 mmol/l was deemed the optimal cut-off.

5.1.4 Outcomes in Patients with Hyperglycemia

Blood glucose > 7.5 mmol/l was used to define 'hyperglycemia' in our cohort of ischemic stroke patients based on the potential increased risk of poor outcomes above that glucose level. With this threshold, 35% of our entire ischemic stroke cohort was deemed to have hyperglycemia and as such were at risk for worse outcomes merely on the basis of their initial blood glucose level. Patients with hyperglycemia in our cohort were more likely to develop complications in hospital; nearly 50% had at least one complication and/or neurological worsening following initial presentation to hospital compared to only 33% of patients without hyperglycemia. Also, more recurrent strokes were reported in hospital in patients with hyperglycemia. We found no studies demonstrating an association between hyperglycemia on stroke presentation and early recurrent stroke. At least one ongoing randomized controlled trial of pioglitazone treatment in patients with recent stroke and possible insulin resistance, looking at a combined outcome of total fatal and non-fatal strokes and myocardial infarctions, may provide some insight.[148]

Case fatality in patients with hyperglycemia was clearly higher than in those patients without hyperglycemia in our cohort. Nearly twice as many hyperglycemic patients died in hospital compared to patients without hyperglycemia and this difference was maintained to six months following the incident stroke. In addition, though our 30-day case fatality in our ischemic stroke patient cohort was similar to, or lower than, previously reported case-fatality rates, patients with hyperglycemia in our cohort were at the higher end of the range.[131, 149]

5.2 Outcomes in Patients with Intracerebral Hemorrhage

5.2.1 Association between Glucose and Stroke Outcomes

In our cohort of 735 patients with intracerebral hemorrhage, glucose was a significant independent predictor of death after adjusting for initial stroke severity and other important factors including age, sex, and comorbid conditions. The unadjusted univariable Cox proportional hazards model showed a 3.5% relative increase in the risk of death for each mmol/l unit increase in glucose. In the adjusted model, there was a 2.5% relative increase in the risk of death per mmol/l increase at hospital presentation. Other independent predictors of death after stroke identified in this cohort included increasing age, higher initial systolic blood pressure, higher initial INR, past history of stroke, history of hypertension, and increasing stroke severity (based on lower CNS score). Worse stroke severity, particularly with coma on presentation, is well recognized as a strong predictor of poor outcomes in patients with intracerebral hemorrhage.[70, 133] In our cohort, one quarter of patients were unconscious upon hospital arrival; 40% of patients in with initial glucose > 8.5 mmol/l presented in coma. It is possible that the strong association between increasing stroke severity and death may have modified the estimated effect of glucose as a predictor of death after stroke in our intracerebral hemorrhage cohort.

Glucose was not found to be an independent predictor for the secondary functional outcome measures, but was associated with increased hospital length of stay. For each of the functional outcome measures, important independent predictors included increasing age and a lower CNS score. For the combined outcome of moderate to severe disability or death at hospital discharge, a history of past stroke was also important. Finally, for the combined outcome of discharge disposition to long-term care or death at hospital discharge, other important independent predictors were pre-admission dependent functional status, increasing initial systolic blood pressure and increasing initial INR.

5.2.2 Identifying a Glucose Cut-off Associated with Outcome

For patients with intracerebral hemorrhage in our study, we identified an optimal cut-off level of glucose, > 8.5 mmol/l, which was associated with death at 30 days following stroke using ROC curve analysis. Nearly 40% of patients with intracerebral hemorrhage had initial blood glucose measurements above the cut-off level and of this hyperglycemic group nearly two-thirds of patients died in hospital. For the ROC curve analysis, the area under the curve for glucose in patients with intracerebral hemorrhage was 0.668, showing glucose to be a moderate prognostic measure for death after stroke in this stroke type.

Evaluating glucose as a dichotomous variable, it was a significant independent predictor of death after stroke, with a 54% relative increased risk of death with glucose > 8.5 mmol/l. Based on our data, it appears that the relationship between glucose and death may not be linear and as such, glucose used as a binary variable may be more appropriate than as a continuous variable when evaluating it as a prognostic factor. However, as the glucose cut-off 8.5 mmol/l was derived from this patient cohort, using the dichotomous variable in the

Cox models in the same cohort may be a concern because a bias may have been introduced that resulted in a stronger effect size for this prognostic factor. Therefore, these results must be interpreted with some caution. The identified glucose cut-off 8.5 mmol/l must be validated in a separate patient sample.

5.3 Limitations of the Analysis

This study was a large retrospective cohort analysis using patient data from the Registry of the Canadian Stroke Network. Retrospective analyses have inherent limitations related to making conclusions regarding cause or effect; only associations can be described between variables and outcomes. Therefore, in our study, we report an association was found between elevated glucose and increased case fatality and worse functional outcome in ischemic stroke patients but cannot further conclude whether early hyperglycemia was causally related to poor outcome.

Database analyses have particular limitations. Though the RCSN clinical database is rigorously maintained, with internal and external validation and very good data quality, complete data accuracy cannot be guaranteed. Chart abstraction of patient charts to clarify data outliers for this analysis revealed some errors in dates and initial glucose values and one record had a presumed error in the RPDB data for date of death (date of death documented in RPDB was years before date of stroke onset in RCSN data). Overall, known data errors were uncommon and missing values for any one variable were typically < 5% of data. One variable that had a higher proportion of missing data was the CNS score, missing in 7% of patients with intracerebral hemorrhage. Missing CNS values were replaced by median values for each patient group (ischemic stroke and intracerebral hemorrhage); it is possible

that this may have underestimated patients with more severe strokes (presenting in coma) or less likely, underestimated milder strokes in our analyses.

Certain variables were not available in the RCSN database relevant to the study question regarding the effects of glucose on stroke outcomes. Hemoglobin A1c was not collected in the RCSN Phase 3 during the study time frame (though it has been included as a variable since September 2006) and as such, the pre-stroke glucose status in our cohort of patients was not known. It is postulated that a proportion of stroke patients who present acutely with hyperglycemia but no known history of diabetes are actually either in a pre-diabetes state (with glucose intolerance, for example) or have previously undiagnosed diabetes that may explain why they have worse stroke outcomes.[30] In addition to HbA1c, a second glucose measurement done later during hospital admission would better delineate which stroke patients had persisting hyperglycemia, which may be more strongly associated with poor outcomes after stroke.[43] A second glucose reading was not available in the RCSN Phase 3 data during the study time frame.

Limitations using data from administrative databases are commonly related to inaccurate coding for medical diagnoses, procedures or care processes. Through linkages with various administrative data sources at ICES, the reliability of capturing deaths both in and out of hospital is very good. Because the RCSN does not collect follow-up information on patients after hospital discharge, we planned to link our dataset to administrative databases to evaluate out-of-hospital functional outcome. We attempted to link our data set with the Ontario Continuing Care Reporting System[150] database to identify patients residing in chronic care facilities, but up to 40% of patients in our RCSN cohort could not be linked with

this database making it unreliable to evaluate this surrogate marker of long-term functional outcome following stroke. For this reason, we only evaluated functional outcome based on the modified Rankin Scale score at hospital discharge, which may have somewhat less reliability than an out-of-hospital functional measure, and the surrogate measure of hospital discharge to a chronic care facility.

Theoretical limitations are inherent in the use of regression modeling to evaluate variables as independent predictors of outcome.[151] Although we included known key prognostic indicators for survival after stroke in our models, it is possible that the models did not adequately adjust for all potentially important variables. With numerous variables included in the models, it is possible that over fitting may have occurred. In our cohort, for the primary outcome there were 1,043 deaths over the study follow-up time in the ischemic stroke group and 412 deaths in the intracerebral hemorrhage group. Given this number of outcome events, over fitting was less likely a concern. In the models, confounding between covariates may exist. An association between stroke severity and initial blood glucose levels has been shown in other studies;[31, 38] thus, collinearity between these variables may exist in our models. Collinearity was not tested and interaction terms were not examined in the models for this analysis. Also, the models were not validated and thus their stability and predictive ability is not known.

An important limitation in the interpretation of the study results relates to the analysis of glucose as a dichotomized measure and the relationship with poor stroke outcomes. First, there are limitations in identifying a threshold level using ROC curve analysis and a certain amount of expert clinical judgement was used to determine the optimal cut-off in this patient

cohort. The ROC curve is not dependent on the prevalence of the disease or the sample size; but in a different cohort another cut-off might be selected based on characteristics of patients in that cohort and clinical judgement used to balance false-positive and false-negative classification of patients. Second, as the glucose cut-off level 7.5 mmol/l was derived from this patient cohort, a bias was possibly introduced when the binary form of this variable was used in the Cox proportional hazards model for the primary outcome. It is possible we obtained a larger hazard for the risk of death for glucose > 7.5 mmol/l because of this bias. Given this concern, analyses for all secondary outcome measures used glucose as a continuous variable only. However, the models using the dichotomous glucose variable were carried out specifically to examine whether blood glucose above the derived cut-off level was a predictor of outcome after adjusting for all other important covariates including initial stroke severity, age, and other comorbid conditions. This cut-off level of glucose must be validated in a separate cohort of ischemic stroke patients. Similarly, in our cohort of intracerebral hemorrhage patients, the glucose cut-off > 8.5 mmol/l must be validated in a separate cohort.

5.4 Clinical Implications of this Study

This study is the largest cohort analysis to date that has examined the relationship between glucose and stroke outcomes. We found that elevated random-sample blood glucose at the time of hospital presentation is an independent predictor of death after both ischemic stroke and intracerebral hemorrhage. Blood glucose was also found to be an independent predictor of severe neurologic disability, institutionalization and death at hospital discharge in patients with ischemic stroke. Our results support the hypothesis that elevated blood glucose at stroke onset is associated with death and poor functional outcome after stroke, having a

deleterious effect on patients with stroke and not only reflecting a stress response related to initial stroke severity. The magnitude of the increased risk of death and poor functional outcome is not as large in our cohort as reported in previous studies, possibly reflecting our cohort characteristics with the inclusion of patients with and without a history of diabetes. However, the large size of our cohort makes our results more robust than smaller past studies. We also found that more patients with hyperglycemia had neurological worsening and developed post-stroke complications in hospital, which may provide some insight into why these patients have a higher risk of death and poor functional outcome after stroke. However, in this study, these findings were not adjusted for stroke severity and as patients with hyperglycemia also had more severe strokes, that may in part account for the increased complications. Further evaluation is warranted to better understand why stroke patients with hyperglycemia have worse outcomes.

In our cohort, we identified a cut-off level of random blood glucose of > 7.5 mmol/l in ischemic stroke patients that was associated with 30-day case fatality after stroke. A cut-off value of > 8.5 mmol/l was associated with 30-day case fatality after stroke in patients with intracerebral hemorrhage. The majority of past studies evaluating the importance of glucose in stroke have relied on cut-off levels that are either arbitrarily chosen or that are derived from definitions of hyperglycemia used in the diagnosis of diabetes that may not be relevant to stroke patient outcomes. Using a valid statistical methodology and expert clinical judgement, we defined an optimal cut-off level of glucose that is associated with an important stroke outcome, death at 30 days. The results of this study may allow for better classification of stroke patients based on their risk profile; providing further guidance for practice recommendations regarding glucose monitoring following stroke. Identifying this

cut-off level is also important as it can be used as a treatment target in planning future randomized clinical trials to evaluate glucose management strategies in patients with stroke. Certainly, further rigorously designed and executed randomized clinical trials will be imperative to evaluate the effects of early, aggressive management of blood glucose on outcomes in stroke patients.

Another important contribution from this study is that we evaluated patients with intracerebral hemorrhage separately from patients with ischemic stroke, whereas a large proportion of studies in the literature have evaluated outcomes for this stroke type within larger cohorts of ischemic stroke patients. Based on known differences in the pathophysiology of these two stroke types and weaker evidence for an association between elevated glucose and outcomes in animal models of intracerebral hemorrhage, it was important to evaluate the association between glucose and outcomes in this stroke subtype alone. Our results showed that elevated blood glucose was associated with increased case fatality after stroke, though it was not an independent predictor of poor functional outcome after stroke.

5.5 Future Research

The next step in this research is to validate the 7.5 mmol/l glucose cut-off level in a separate cohort of ischemic stroke patients and the 8.5 mmol/l glucose cut-off in another cohort of patients with intracerebral hemorrhage. Using data from the Ontario Stroke Audit, this work will be carried out in a sample of stroke patients from hospitals across Ontario to further evaluate the association between glucose and stroke outcomes. Stratifying these analyses by

stroke severity may provide a better understanding of the relationship between glucose and case fatality after ischemic stroke and intracerebral hemorrhage.

Further research to evaluate differences in the effects of glucose on stroke outcomes in other subgroups of stroke patients will be important, as this may better define which stroke patients may benefit from aggressive glucose management after stroke. Comparing patients with and without a pre-morbid history of diabetes is planned as a further analysis to the current study and will be an important step to clarify results of previous studies suggesting that patients with no prior history of diabetes may have worse outcomes related to modestly elevated glucose levels. Using the history of diabetes in the RCSN and ODD databases, this analysis could be carried out on the current data set. Alternatively, the stroke audit data would be used, which would have the advantage of examining measures including HbA1c and a second glucose reading during hospital admission, both available in the audit data, to better determine patients' diabetes status prior to stroke and which patients have truly persistent post-stroke hyperglycemia that may be deleterious.

Another subgroup of stroke patients that may experience worse outcomes related to post-stroke hyperglycemia is the group of patients treated with thrombolysis for acute ischemic stroke. Further to the current analysis, this subgroup of the RCSN ischemic stroke cohort will be evaluated for outcomes including functional disability and secondary hemorrhagic transformation of the stroke following thrombolysis. Finally, evaluating ischemic stroke patients based on OSCP stroke classification, comparing patients with large-artery or cardio-embolic stroke versus lacunar stroke may be important to determine whether hyperglycemia may be particularly deleterious in one ischemic stroke subtype over the other.

5.6 Final Conclusions

Elevated blood glucose, noted in stroke patients within 24 hours of stroke onset, was an independent predictor of death after stroke, severe disability or death at hospital discharge, and institutionalization following ischemic stroke in our large patient cohort. The risk of poor outcome increased with higher initial glucose levels; a glucose cut-off > 7.5 mmol/l appeared to optimally classify patients as having hyperglycemia, but this prognostic threshold must be validated.

In patients presenting with intracerebral hemorrhage, elevated blood glucose was associated death after stroke but was not an independent predictor of severe disability or death at hospital discharge, or institutionalization following stroke. A glucose cut-off level > 8.5 mmol/l was identified as the optimal cut-off level associated with an increased risk of death after stroke, but this must be confirmed in further studies.

This study has provided important prognostic information regarding the increased risks of death and poor functional outcome related to elevated blood glucose levels in patients with ischemic stroke and in patients with intracerebral hemorrhage. Further randomized clinical trials are needed to evaluate whether early glucose lowering in stroke patients will result in better stroke outcomes.

CHAPTER 6

6. Illustrations

6.1 Tables

Table 1. Range of plasma glucose levels used to define 'hyperglycemia' in past studies.

Author	Year	Stroke Type	Subjects	Glucose Cut-off to Define Hyperglycemia (in mmol/l)	Method of Choosing Glucose Cut-off
Pulsinelli [39]	1983	IS *	107	> **6.6**	- not specified
Candelise [31]	1985	IS/ICH	72	> **6.1** (fasting)	- upper normal value
Woo [65]	1988	IS/ICH *	252	-	- mean glucose
Gray [49]	1989	IS	136	≥ **8.0**	- 'arbitrary' cut-off
Woo [66]	1990	IS/ICH *	239	> **7.8** (fasting)	- based on WHO criteria
Cambon [35]	1991	IS *	77 autopsies	≥ **6.4**	- not specified
Tuhrim [70]	1991	ICH	187	> **10.0**	- not specified
Kiers [37]	1992	IS/ICH *	176	> **7.8** (fasting)	- based on WHO criteria
Matchar [71]	1992	IS *	146	≥ **6.7** (random)	- not specified
Murros [38]	1992	IS *	99	-	- compared mean glucose
Van Kooten [34]	1993	IS/ICH *	91	≥ **8.0** (random) ≥ **6.7** (fasting)	- not specified
Sacco [7]	1994	IS *	323	> **7.8** (random)	- not specified
Jorgensen [26]	1994	IS *	1,135	> **6.0** (random) - for non-DM	- regression analysis
Toni [52]	1994	IS *	82	> **6.6** (fasting)	- upper normal value
Weir [40]	1997	IS/ICH (DM also)	750 non-DM 61 DM	> **8.0** (random) > **6.5** (fasting)	- not specified
Jorgensen [41]	2001	IS/ICH	396	≥ **6.5**	- DM guidelines
Szczudlik [32]	2001	IS *	262	≥ **7.8** (random) ≥ **6.4** (fasting)	- not specified
Christensen [47]	2002	IS/ICH	445	-	- repeated glucose x 24h
Parsons [48]	2002	IS	63	≥ **8.0** (random)	- animal study cut-off
Williams [33]	2002	IS	656	≥ **7.2**	- not specified
Baird [43]	2003	IS	25	≥ **8.0** (random)	- other studies
Dora [44]	2004	IS *	46	≥ **7.8**	- not specified
Stollberger [45]	2005	IS/ICH *	992	> **7.0**	- logistic regression
Gentile [28]	2006	IS	940	≥ **7.27**	- ROC curve analysis
Matz [29]	2006	IS/ICH	238	-	- based on WHO criteria
Vermeer [46]	2006	IS *	272	> **7.7** (random)	- glucose quintiles

IS = ischemic stroke; **ICH** = intracerebral hemorrhage; **DM** = diabetes mellitus; **WHO** criteria = World Health Organization criteria for the definition and diagnosis of diabetes; **ROC** = receiver operating characteristic.

* indicates studies specifically stating that patients with diabetes and without diabetes were included together in analyses.

Table 2. Baseline demographic characteristics for the entire patient cohort and by diagnosis of ischemic stroke or intracerebral hemorrhage.

	All Patients n = 3,928		**Patients with Ischemic Stroke** n = 3,193		**Patients with Intracerebral Hemorrhage** n = 735	
Age, years						
Mean	72.2		73.0		68.8	
Median	75		76		71	
Range	20 - 104		21 - 104		20 - 101	
Sex – male, n (%)	2058	(52.4)	1660	(52.0)	398	(54.1)
Time to hospital arrival, hours						
Mean	5.9		5.9		6.0	
Median	3.1		3.0		3.7	
Level of consciousness, n (%)						
Awake	3091	(78.7)	2727	(85.4)	364	(49.5)
Drowsy	557	(14.2)	365	(11.4)	192	(26.1)
Unconscious	273	(7.0)	96	(3.0)	177	(24.1)
CNS score						
Mean	7.1		7.5		5.2	
Median (all patients)	7.5		8.0		5.0	
Median (excluding coma)	8.0		8.5		7.0	
CNS $\leq$ 8, n (%)	2034	(54.0)	1557	(50.6)	477	(69.6)
missing, n (%)	163	(4.1)	113	(3.5)	50	(6.8)
OCSP Classification, n (%)						
PAC	-	-	1225	(39.3)	-	-
TAC	-	-	439	(14.1)	-	-
LAC	-	-	570	(18.3)	-	-
POC	-	-	700	(22.4)	-	-
Other	-	-	39	(1.3)	-	-
TIA presentation	-	-	147	(4.7)	-	-
Blood glucose - mean (median)	7.8	(6.8)	7.7	(6.7)	8.4	(7.6)
Initial SBP - mean (median)	164.3	(160)	161.5	(159)	176.9	(172)
Initial DBP - mean (median)	85.5	(84)	83.9	(83)	93.0	(89)
INR - mean (median)	1.2	(1.0)	1.1	(1.0)	1.3	(1.0)
Pre-admission medications						
Oral hypoglycemics, n (%)	506	(12.9)	443	(13.9)	63	(8.6)
Insulin, n (%)	168	(4.3)	148	(4.6)	20	(2.7)

	All Patients n = 3,928		Patients with Ischemic Stroke n = 3,193		Patients with Intracerebral Hemorrhage n = 735	
Comorbidities, n (%)						
Diabetes (RCSN data)	866	(22.0)	732	(22.9)	134	(18.2)
including ODD data	1108	(28.2)	933	(29.2)	175	(23.8)
Hypertension	2588	(65.9)	2146	(67.2)	442	(60.1)
Hyperlipidemia	1241	(31.6)	1082	(33.9)	159	(21.6)
UTD	286	(7.3)	220	(6.9)	66	(9.0)
Myocardial infarction	595	(15.2)	537	(16.8)	58	(7.9)
CABG/angioplasty	346	(8.8)	311	(9.7)	35	(4.8)
Smoking (ever)	1378	(35.4)	1185	(37.5)	193	(26.4)
UTD	1011	(26.0)	731	(23.1)	280	(38.3)
Smoking (current)	652	(16.6)	553	(17.3)	99	(13.5)
Past stroke	863	(22.0)	746	(23.4)	117	(15.9)
Past TIA	618	(15.7)	560	(17.5)	58	(7.9)
Past ICH	82	(2.1)	42	(1.3)	40	(5.4)
Preadmission status - Independent	3142	(80.0)	2544	(79.7)	598	(81.4)
UTD	153	(3.9)	107	(3.4)	46	(6.3)
Charlson Index						
Mean	1.4		1.5		1.1	
Median	1.0		1.0		1.0	
Charlson Index ≥ 2	1267	(32.3)	1093	(34.2)	174	(23.7)
Socioeconomic status, n (%)						
Q1	854	(22.6)	694	(22.6)	160	(22.6)
Q2	839	(22.2)	691	(22.5)	148	(20.9)
Q3	692	(18.3)	553	(18.0)	139	(19.7)
Q4	655	(17.3)	529	(17.2)	126	(17.8)
Q5	738	(19.5)	604	(19.7)	134	(19.0)

CNS = Canadian Neurological Scale; **OCSP** = Oxfordshire Community Stroke Project classification; **PAC** = partial anterior circulation; **TAC** = total anterior circulation; **LAC** = lacunar; **POC** = posterior circulation; **TIA** = transient ischemic attack; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **INR** = International Normalized Ratio; **RCSN** = Registry of the Canadian Stroke Network; **ODD** = Ontario Diabetes Database; **CABG** = coronary artery bypass graft; **ICH** = intracerebral hemorrhage; **Q1-Q5** = income quintiles; **UTD** = unable to determine by chart abstraction.

Note: Variables with > 5% data deemed 'UTD' or 'missing' in the RCSN database have 'UTD' or 'missing' values noted in the table.

Table 3. Comparison of baseline demographics in patients with ischemic stroke with or without admission hyperglycemia (cut-off blood glucose from ROC curve analysis).

	All Ischemic Stroke Patients		Glucose ≤ 7.5 mmol/l		Glucose > 7.5 mmol/l		P-value
	n = 3,193		n = 2,078		n = 1,115		
Age, years							
Mean	73.0		72.5		73.8		0.006
Median	76		75		76		
Sex – male, n (%)	1660	(52.0)	1111	(53.5)	549	(49.2)	0.023
Time to hospital arrival, hours							
Mean	5.9		6.0		5.6		0.098
Median	3.0		3.1		2.9		
Level of consciousness, n (%)							< 0.001
Awake	2727	(85.4)	1813	(87.2)	914	(82.0)	
Drowsy	365	(11.4)	218	(10.5)	147	(13.2)	
Unconscious	96	(3.0)	46	(2.2)	50	(4.5)	
CNS score							
Mean (all patients)	7.5		7.6		7.2		< 0.001
Median (all patients)	8.0		8.5		7.5		
Median (excluding coma)	8.5		8.5		8.0		0.001
CNS ≤ 8, n (%)	1557	(50.6)	971	(48.0)	586	(55.3)	< 0.001
OCSP Classification, n (%)							0.003
PAC	1225	(39.3)	809	(39.7)	416	(38.5)	
TAC	439	(14.1)	277	(13.6)	162	(15.0)	
LAC	570	(18.3)	385	(18.9)	185	(17.1)	
POC	700	(22.4)	427	(20.9)	273	(25.3)	
Other	39	(1.3)	27	(1.3)	12	(1.1)	
TIA presentation	147	(4.7)	114	(5.6)	33	(3.1)	
Blood glucose - mean (median)	7.7	(6.7)	6.0	(6.0)	10.8	(9.6)	< 0.001
Initial SBP - mean (median)	161.5	(159)	160.5	(158)	163.4	(160)	0.011
Initial DBP - mean (median)	83.9	(83)	83.6	(83)	84.3	(83)	0.280
INR - mean (median)	1.1	(1.0)	1.1	(1.0)	1.2	(1.0)	0.136
Pre-admission medications							
Oral hypoglycemics, n (%)	443	(13.9)	108	(5.2)	335	(30.0)	< 0.001
Insulin, n (%)	148	(4.6)	41	(2.0)	107	(9.6)	< 0.001

	All Ischemic Stroke Patients		Glucose ≤ 7.5 mmol/l		Glucose > 7.5 mmol/l		P-value
	n = 3,193		n = 2,078		n = 1,115		
Comorbidities, n (%)							
Diabetes (RCSN data)	732	(22.9)	215	(10.4)	517	(46.8)	< 0.001
including ODD data	933	(29.2)	339	(16.3)	594	(53.3)	
Hypertension	2146	(67.2)	1315	(63.3)	831	(74.5)	< 0.001
Hyperlipidemia	1082	(33.9)	660	(31.8)	422	(37.8)	0.001
UTD	220	(6.9)	137	(6.6)	83	(7.4)	
Myocardial infarction	537	(16.8)	319	(15.4)	218	(19.6)	< 0.001
CABG/angioplasty	311	(9.7)	194	(9.3)	117	(10.5)	0.294
Smoking (ever)	1185	(37.5)	832	(40.4)	353	(32.1)	< 0.001
UTD	731	(23.1)	452	(21.9)	279	(25.4)	
Smoking (current)	553	(17.3)	383	(18.4)	170	(15.2)	0.372
Past stroke	746	(23.4)	472	(22.7)	274	(24.6)	0.477
Past TIA	560	(17.5)	377	(18.1)	183	(16.4)	0.446
Past ICH	42	(1.3)	34	(1.6)	8	(0.7)	0.085
Preadmission status - Independent	2544	(79.7)	1674	(80.6)	870	(78.0)	0.081
Charlson Index							
Mean	1.5		1.3		1.8		< 0.001
Median	1.0		1.0		1.0		
Charlson Index ≥ 2	1093	(34.2)	598	(28.8)	495	(44.4)	< 0.001
Socioeconomic status, n (%)							< 0.001
Q1	694	(22.6)	401	(20.1)	293	(27.3)	
Q2	691	(22.5)	447	(22.4)	244	(22.7)	
Q3	553	(18.0)	349	(17.5)	204	(19.0)	
Q4	529	(17.2)	361	(18.1)	168	(15.6)	
Q5	604	(19.7)	438	(21.9)	166	(15.4)	

CNS = Canadian Neurological Scale; **OCSP** = Oxfordshire Community Stroke Project classification; **PAC** = partial anterior circulation; **TAC** = total anterior circulation; **LAC** = lacunar; **POC** = posterior circulation; **TIA** = transient ischemic attack; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **INR** = international normalized ratio; **RCSN** = Registry of the Canadian Stroke Network; **ODD** = Ontario Diabetes Database; **CABG** = coronary artery bypass graft; **ICH** = intracerebral hemorrhage; **Q1-Q5** = income quintiles; **UTD** = unable to determine by chart abstraction.

Fisher's exact test used for p-value for dichotomous variables; Pearson Chi-Square test used for p-value for categorical variables with > 2 categories; Mann-Whitney U test used to compare median values.

Note: Variables with > 5% data deemed 'UTD' or 'missing' in the RCSN database have 'UTD' or 'missing' values noted in the table.

Table 4. In-hospital course for patients with ischemic stroke.

	All Patients with Ischemic Stroke n = 3,193	Glucose ≤ 7.5 mmol/l n = 2,078	Glucose > 7.5 mmol/l n = 1,115	P-value
Treatments provided, n (%)				
rt-PA	598 (18.7)	396 (19.1)	202 (18.1)	0.536
Insulin (IV or SC)				
In hospital	488 (15.3)	125 (6.0)	363 (32.6)	< 0.001
At hospital discharge	224 (7.0)	49 (2.4)	175 (15.7)	< 0.001
Oral hypoglycemics				
In hospital	511 (16.0)	122 (5.9)	389 (34.9)	< 0.001
At hospital discharge	428 (13.4)	107 (5.1)	321 (28.8)	< 0.001
Complications, n (%)				
Neurologic worsening	580 (18.2)	319 (15.4)	261 (23.5)	< 0.001
New stroke	120 (3.8)	65 (3.1)	55 (5.0)	0.011
Ischemic	83 (2.6)	48 (73.8)	35 (63.6)	0.241
ICH	37 (1.2)	17 (26.2)	20 (36.4)	
New TIA	36 (1.1)	25 (1.2)	11 (1.0)	0.725
Seizure	79 (2.5)	37 (1.8)	42 (3.8)	0.001
Depression	187 (5.9)	125 (6.0)	62 (5.6)	0.636
Cardiac arrest	125 (3.9)	67 (3.2)	58 (5.2)	0.007
Decubitus ulcer	40 (1.3)	25 (1.2)	15 (1.3)	0.740
DVT	30 (0.9)	19 (0.9)	11 (1.0)	0.849
Fall (with injury)	9 (0.3)	7 (0.3)	* *	0.509
GI bleed	50 (2.0)	29 (1.7)	21 (2.4)	0.028
Transfusion required	20 (38.5)	12 (38.7)	8 (38.1)	0.469†
missing	664 (20.8)	418 (20.1)	246 (22.1)	
Myocardial infarction	83 (2.6)	45 (2.2)	38 (3.4)	0.047
Pneumonia	228 (7.1)	124 (6.0)	104 (9.4)	0.001
Pulmonary embolus	24 (0.8)	16 (0.8)	8 (0.7)	0.874†
UTI	409 (12.8)	240 (11.6)	169 (15.2)	0.004
At least 1 complication	968 (30.3)	572 (27.5)	396 (35.5)	< 0.001
At least 1 complication and/or neurologic worsening	1192 (37.3)	689 (33.2)	503 (45.1)	< 0.001

rt-PA = recombinant tissue Plasminogen Activator; **IV** = intravenous; **SC** = subcutaneous; **ICH** = intracerebral hemorrhage; **TIA** = transient ischemic attack; **DVT** = deep venous thrombosis; **GI** = gastrointestinal; **UTI** = urinary tract infection.

Fisher's exact test used for P-value, unless noted by † (Pearson Chi-Square test for P-value).

* *Note*: results suppressed in cells with ≤ 5 counts based on ICES privacy policies.

Table 5. In-hospital, 30-day, and 6-month outcomes for patients with ischemic stroke.

Outcome	All Patients with Ischemic Stroke n = 3,193		Glucose ≤ 7.5 mmol/l n = 2,078		Glucose > 7.5 mmol/l n = 1,115		P-value
Length of stay, days							
Mean	16.1		15.6		17.1		0.091
Median	9		9		10		0.047**
In-hospital death, n (%)	424	(13.3)	214	(10.3)	210	(18.8)	< 0.001*
Discharge mRS score							
Median (all patients)	3		3		4		< 0.001**
Median (survivors)	3		3		3		< 0.001†
mRS ≤ 2, n (%)	1201	(37.6)	861	(41.4)	340	(30.5)	< 0.001*
Discharge location, n (%)							0.003†
Home	1271	(45.9)	903	(48.5)	368	(40.7)	
Active rehab	942	(34.0)	611	(32.8)	331	(36.6)	
Acute care hospital	163	(5.9)	100	(5.4)	63	(7.0)	
Long-term care / NH	353	(12.8)	223	(12.0)	130	(14.4)	
Other	39	(1.4)	26	(1.4)	13	(1.4)	
Death at 30 days, n (%)	457	(14.3)	239	(11.5)	218	(19.6)	< 0.001*
Death at 6 months, n (%)	687	(21.5)	377	(18.1)	310	(27.8)	< 0.001*

mRS = modified Rankin Scale; **NH** = nursing home.

* Fisher's exact test used for P-value; † Pearson Chi-Square test used for P-value; ** Mann-Whitney U test used to compare median values.

Table 6. Univariable Cox proportional hazards analysis for the outcome death in patients with ischemic stroke.

Variables	B	Hazard Ratio	95% Confidence Interval	P-Value
Age	0.051	1.053	1.046 - 1.059	< 0.001
Sex (female vs. male)	0.131	1.140	1.009 - 1.287	0.035
CNS score				
Ordinal scale (unit increase)	- 0.230	0.794	0.779 - 0.810	< 0.001
Dichotomous (≤ 8 vs. > 8)	1.179	3.251	2.833 - 3.732	< 0.001
OCSP classification				
PAC	0.805	2.237	1.493 - 3.351	< 0.001
TAC	1.591	4.907	3.251 - 7.406	< 0.001
LAC	0.428	1.535	1.002 - 2.351	0.049
POC	0.679	1.972	1.301 - 2.989	0.001
Other	0.917	2.503	1.518 - 4.126	< 0.001
TIA (reference)	-	-	-	-
Blood glucose				
Continuous (per mmol/l)	0.036	1.037	1.020 - 1.054	< 0.001
Dichotomous (> 7.5 mmol/l)	0.380	1.463	1.293 - 1.654	< 0.001
Initial SBP (per unit increase)	0.000	1.000	0.998 - 1.002	0.886
Initial DBP (per unit increase)	- 0.004	0.996	0.992 - 1.000	0.032
Initial INR (per unit increase)	0.145	1.156	0.071 - 1.249	< 0.001
Comorbidities				
Diabetes	0.128	1.136	0.997 - 1.295	0.055
Hypertension	0.121	1.128	0.989 - 1.287	0.073
Hyperlipidemia	- 0.271	0.762	0.667 - 0.871	< 0.001
Myocardial infarction	0.264	1.302	1.120 - 1.514	0.001
CABG/angioplasty	0.013	1.013	0.827 - 1.242	0.901
Smoking (current)	- 0.262	0.769	0.647 - 0.914	0.003
Past stroke	0.379	1.461	1.279 - 1.668	< 0.001
Past TIA	- 0.037	0.964	0.821 - 1.132	0.655
Past ICH	- 0.446	0.640	0.343 - 1.193	0.160
Preadmission status - (dependent vs. independent)	0.933	2.543	2.226 - 2.905	< 0.001
Charlson Index (ordinal)	0.158	1.171	1.144 - 1.199	< 0.001
Socioeconomic status				
Q1	0.026	1.027	0.853 - 1.235	0.780
Q2	- 0.079	0.924	0.765 - 1.116	0.412
Q3	- 0.159	0.853	0.695 - 1.046	0.126
Q4	- 0.134	0.875	0.712 - 1.074	0.201
Q5 (reference)	-	-	-	-

B = unstandardized coefficient (slope estimate) for each predictor variable ("-" sign signifies a negative correlation between the predictor variable and the outcome); **CNS** = Canadian Neurological Scale; **OCSP** = Oxfordshire Community Stroke Project classification; **PAC** = partial anterior circulation; **TAC** = total anterior circulation; **LAC** = lacunar; **POC** = posterior circulation; **TIA** = transient ischemic attack; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **INR** = International Normalized Ratio; **CABG** = coronary artery bypass graft; **ICH** = intracerebral hemorrhage; **Q1-Q5** = income quintiles.

Table 7. Multivariable Cox proportional hazards model for the outcome death in patients with ischemic stroke.

Variables	B	Hazard Ratio	95% Confidence Interval	P-value
Glucose (continuous)	0.048	1.050	1.031 - 1.069	< 0.001
Age	0.048	1.049	1.042 - 1.057	< 0.001
Sex (female vs. male)	- 0.263	0.768	0.676 - 0.873	< 0.001
CNS score (ordinal)	- 0.192	0.825	0.807 - 0.844	< 0.001
OCSP classification				
LAC	- 0.095	0.909	0.591 - 1.399	0.666
Other	0.384	1.469	0.885 - 2.438	0.137
PAC	0.053	1.054	0.698 - 1.591	0.803
POC	0.162	1.176	0.772 - 1.793	0.450
TAC	0.410	1.507	0.982 - 2.313	0.061
TIA (reference)	-	-	-	-
Initial INR	0.117	1.124	1.020 - 1.239	0.018
Hyperlipidemia	- 0.177	0.838	0.730 - 0.962	0.012
Past myocardial infarction	0.212	1.236	1.059 - 1.442	0.007
Smoking (current)	0.406	1.500	1.245 - 1.807	< 0.001
Past stroke	0.167	1.182	1.027 - 1.359	0.020
Past ICH	- 0.556	0.574	0.306 - 1.075	0.083
Preadmission status (dependent)	0.427	1.532	1.323 - 1.775	< 0.001

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **OCSP** = Oxfordshire Community Stroke Project classification; **LAC** = lacunar; **PAC** = partial anterior circulation; **POC** = posterior circulation; **TAC** = total anterior circulation; **TIA** = transient ischemic attack; **INR** = International Normalized Ratio; **ICH** = intracerebral hemorrhage.

Table 8. Multivariable Cox proportional hazards model for the outcome death with glucose as a dichotomous variable based on the ROC curve analysis cut-off in patients with ischemic stroke.

Variables	B	Hazard Ratio	95% Confidence Interval	P-value
Glucose (> 7.5 mmol/l)	0.332	1.394	1.231 - 1.578	< 0.001
Age	0.047	1.048	1.041 - 1.055	< 0.001
Sex (female vs. male)	- 0.270	0.763	0.672 - 0.867	< 0.001
CNS score (ordinal)	- 0.192	0.825	0.807 - 0.843	< 0.001
OCSP classification				
LAC	- 0.100	0.905	0.588 - 1.391	0.648
Other	0.368	1.445	0.870 - 2.398	0.155
PAC	0.038	1.038	0.688 - 1.568	0.858
POC	0.147	1.158	0.759 - 1.766	0.496
TAC	0.386	1.471	0.958 - 2.259	0.078
TIA (reference)				-
Initial INR	0.112	1.119	1.017 - 1.231	0.021
Hyperlipidemia	- 0.181	0.835	0.727 - 0.958	0.010
Past myocardial infarction	0.219	1.245	1.068 - 1.452	0.005
Smoking (current)	0.391	1.478	1.227 - 1.779	< 0.001
Past stroke	0.180	1.198	1.041 - 1.378	0.012
Past ICH	- 0.567	0.567	0.303 - 1.063	0.077
Preadmission status (dependent)	0.429	1.536	1.326 - 1.780	< 0.001

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **OCSP** = Oxfordshire Community Stroke Project classification; **LAC** = lacunar; **PAC** = partial anterior circulation; **POC** = posterior circulation; **TAC** = total anterior circulation; **TIA** = transient ischemic attack; **INR** = International Normalized Ratio; **ICH** = intracerebral hemorrhage.

Table 9. Multiple logistic regression for moderate to severe disability (mRS 3-5) or death (mRS 6) at hospital discharge in patients with ischemic stroke.

Variables	B	Odds Ratio	95% Confidence Interval	P-value
Glucose (continuous)	0.051	1.052	1.024 - 1.081	< 0.001
Age	0.025	1.025	1.018 - 1.032	< 0.001
CNS score (ordinal)	- 0.351	0.704	0.677 - 0.733	< 0.001
OCSP classification				
LAC	2.907	18.295	8.158 - 41.027	< 0.001
Other	2.085	8.046	3.245 - 19.948	< 0.001
PAC	2.875	17.725	7.982 - 39.363	< 0.001
POC	3.056	21.245	9.495 - 47.535	< 0.001
TAC	3.768	43.309	18.311 - 102.433	< 0.001
TIA (reference)	-	-	-	-
Initial SBP	0.004	1.004	1.001 - 1.006	0.013
Past TIA	0.272	1.312	1.046 - 1.647	0.019
Preadmission status (dependent)	1.031	2.805	2.122 - 3.706	< 0.001
Socioeconomic status				
Q1	0.431	1.538	1.175 - 2.014	0.002
Q2	0.192	1.212	0.928 - 1.583	0.159
Q3	0.011	1.011	0.763 - 1.341	0.938
Q4	0.171	1.186	0.892 - 1.577	0.239
Q5 (reference)	-	-	-	-

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **OCSP** = Oxfordshire Community Stroke Project classification; **LAC** = lacunar; **PAC** = partial anterior circulation; **POC** = posterior circulation; **TAC** = total anterior circulation; **TIA** = transient ischemic attack; **SBP** = systolic blood pressure; **Q1-Q5** = income quintiles.

Table 10. Multiple logistic regression for the combined outcome of discharge to a long-term care facility or death at hospital discharge in patients with ischemic stroke.

Variables	B	Odds Ratio	95% Confidence Interval	P-value
Glucose (continuous)	0.067	1.069	1.037 - 1.102	< 0.001
Age	0.062	1.064	1.053 - 1.075	< 0.001
CNS score (ordinal)	- 0.299	0.742	0.715 - 0.769	< 0.001
OCSP classification				
LAC	- 0.289	0.749	0.367 - 1.526	0.426
Other	0.842	2.320	1.018 - 5.287	0.045
PAC	0.268	1.308	0.664 - 2.577	0.438
POC	0.458	1.581	0.791 - 3.161	0.195
TAC	0.608	1.838	0.905 - 3.732	0.092
TIA (reference)	-	-	-	-
Hyperlipidemia	- 0.218	0.804	0.651- 0.993	0.043
Smoking (current)	0.321	1.379	1.023 - 1.858	0.035
Preadmission status (dependent)	1.378	3.966	3.144 - 5.003	< 0.001

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **OCSP** = Oxfordshire Community Stroke Project classification; **LAC** = lacunar; **PAC** = partial anterior circulation; **POC** = posterior circulation; **TAC** = total anterior circulation; **TIA** = transient ischemic attack.

Table 11. Generalized linear model for length of stay in patients with ischemic stroke.

Variables	B	Standard Error	95% Confidence Interval (for B)	P-Value
Glucose (continuous)	0.006	0.002	0.002 - 0.009	0.0006
Age	0.009	0.0004	0.009 - 0.010	< 0.001
Sex (female vs. male)	0.014	0.009	- 0.005 - 0.032	0.140
CNS score (ordinal)	- 0.049	0.001	- 0.052 - -0.045	< 0.001
OCSP classification				
LAC	0.799	0.034	0.732 - 0.867	< 0.001
OTHER	0.539	0.042	0.457 - 0.622	< 0.001
PAC	0.724	0.034	0.658 - 0.790	< 0.001
POC	0.726	0.034	0.659 - 0.793	< 0.001
TAC	0.919	0.035	0.850 - 0.988	< 0.001
TIA (reference)	-	-	-	-
Initial SBP	0.001	0.0002	0.001 - 0.001	< 0.001
Initial DBP	- 0.005	0.0003	- 0.005 - -0.004	< 0.001
Initial INR	0.014	0.009	- 0.004 - 0.033	0.121
Comorbidities				
Diabetes	- 0.001	0.012	- 0.025 - 0.023	0.942
Hypertension	0.013	0.010	- 0.006 - 0.033	0.188
Hyperlipidemia	0.032	0.010	0.012 - 0.051	0.001
Myocardial infarction	- 0.074	0.012	- 0.098 - -0.049	< 0.001
CABG/angioplasty	0.054	0.016	0.023 - 0.085	0.0006
Smoking (current)	0.066	0.010	0.046 - 0.085	< 0.001
Past stroke	- 0.005	0.011	- 0.026 - 0.016	0.635
Past TIA	0.058	0.012	0.036 - 0.081	< 0.001
Past ICH	0.130	0.037	0.057 - 0.202	0.0004
Preadmission status - (independent)	- 0.134	0.011	- 0.156 - -0.112	< 0.001
Socioeconomic status				
Q1	0.183	0.014	0.155 - 0.211	< 0.001
Q2	0.152	0.014	0.123 - 0.180	< 0.001
Q3	0.177	0.015	0.148 - 0.207	< 0.001
Q4	0.145	0.015	0.115 - 0.175	< 0.001
Q5 (reference)	-	-	-	-

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **OCSP** = Oxfordshire Community Stroke Project classification; **LAC** = lacunar; **PAC** = partial anterior circulation; **POC** = posterior circulation; **TAC** = total anterior circulation; **TIA** = transient ischemic attack; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **INR** = International Normalized Ratio; **CABG** = coronary artery bypass graft; **ICH** = intracerebral hemorrhage; **Q1-Q5** = income quintiles.

Table 12. Comparison of baseline demographics in patients with intracerebral hemorrhage with or without admission hyperglycemia (cut-off blood glucose from ROC curve analysis).

	All Patients with Intracerebral Hemorrhage		Glucose ≤ 8.5 mmol/l		Glucose > 8.5 mmol/l		P-value
	n = 735		n = 455		n = 280		
Age, years							
Mean	68.8		68.8		68.8		0.960
Median	71		72		71		
Sex – male, n (%)	398	(54.1)	259	(56.9)	139	(49.6)	0.057
Time to hospital arrival, hours							
Mean	6.0		6.0		5.8		0.644
Median	3.7		3.5		3.7		
Level of consciousness, n (%)							< 0.001
Awake	364	(49.5)	279	(61.3)	85	(30.4)	
Drowsy	192	(26.1)	114	(25.1)	78	(27.9)	
Unconscious	177	(24.1)	61	(13.4)	116	(41.4)	
CNS score							
Mean (all patients)	5.2		6.2		3.6		< 0.001
Median (all patients)	5.0		6.5		2.5		
Median (excluding coma)	7.0		7.0		6.5		0.026
CNS ≤ 8, n (%)	477	(69.6)	265	(62.5)	212	(81.2)	< 0.001
missing, n (%)	50	(6.8)	31	(6.8)	19	(6.8)	
Blood glucose - mean (median)	8.4	(7.6)	6.6	(6.6)	11.4	(10.3)	< 0.001
Initial SBP - mean (median)	176.8	(172)	173.3	(170)	182.5	(177)	0.001
Initial DBP - mean (median)	93.0	(89)	92.0	(89)	94.6	(90)	0.131
INR - mean (median)	1.3	(1.0)	1.3	(1.0)	1.3	(1.0)	0.396
Pre-admission medications							
Oral hypoglycemics, n (%)	63	(8.6)	19	(4.2)	44	(15.7)	< 0.001
Insulin, n (%)	20	(2.7)	6	(1.3)	14	(5.0)	0.004
Comorbidities, n (%)							
Diabetes (RCSN data)	134	(18.2)	47	(10.5)	87	(32.7)	< 0.001
including ODD data	175	(23.8)	68	(14.9)	107	(38.2)	
Hypertension	442	(60.1)	265	(58.2)	177	(63.2)	0.233
Hyperlipidemia	159	(21.6)	99	(21.8)	60	(21.4)	0.432
UTD	66	(9.0)	36	(7.9)	30	(10.7)	
Myocardial infarction	58	(7.9)	38	(8.4)	20	(7.1)	0.002
UTD	27	(3.7)	8	(1.8)	19	(6.8)	
CABG/angioplasty	35	(4.8)	21	(4.6)	14	(5.0)	0.021
Smoking (ever)	193	(26.4)	136	(30.0)	57	(20.4)	< 0.001
UTD	280	(38.3)	146	(32.2)	134	(48.0)	
Smoking (current)	995	(13.5)	73	(16.0)	26	(9.3)	0.101

	All Patients with Intracerebral Hemorrhage	Glucose ≤ 8.5 mmol/l	Glucose > 8.5 mmol/l	P-value
	n = 735	n = 455	n = 280	
Comorbidities, n (%)				
Past stroke	117 (15.9)	70 (15.4)	47 (16.8)	0.139
Past TIA	58 (7.9)	39 (8.6)	19 (6.8)	0.011
UTD	28 (3.8)	10 (2.2)	18 (6.4)	
Past ICH	40 (5.4)	32 (7.0)	8 (2.9)	0.018
Preadmission status - Independent	598 (81.4)	378 (83.1)	220 (78.6)	< 0.001
UTD	46 (6.3)	16 (3.5)	30 (10.7)	
Charlson Index				
Mean	1.2	1.1	1.2	0.382
Median	1.0	0.0	1.0	
Charlson Index ≥ 2	174 (23.7)	101 (22.2)	73 (26.1)	0.246
Socioeconomic status, n (%)				0.456
Q1	160 (22.6)	103 (23.4)	57 (21.4)	
Q2	148 (20.9)	95 (21.5)	53 (19.9)	
Q3	139 (19.7)	88 (20.0)	51 (19.2)	
Q4	126 (17.8)	81 (18.4)	45 (16.9)	
Q5	134 (19.0)	74 (16.8)	60 (22.6)	

ICH = intracerebral hemorrhage; **CNS** = Canadian Neurological Scale; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **INR** = International Normalized Ratio; **RCSN** = Registry of the Canadian Stroke Network; **ODD** = Ontario Diabetes Database; **CABG** = coronary artery bypass graft; **TIA** = transient ischemic attack; **Q1-Q5** = income quintiles; **UTD** = unable to determine by chart abstraction.

Fisher's exact test used for P-value for dichotomous variables; Pearson Chi-Square test used for P-value for categorical variables with > 2 categories; Mann-Whitney U test used to compare median values.

Note: Variables with > 5% data deemed 'UTD' or 'missing' in the RCSN database have 'UTD' or 'missing' values noted in the table.

Table 13. In-hospital course for patients with intracerebral hemorrhage.

	All Patients with ICH n = 735		Glucose ≤ 8.5 mmol/l n = 455		Glucose > 8.5 mmol/l n = 280		P-value
Treatments provided, n (%)							
Insulin (IV or SC)							
In hospital	152	(20.7)	53	(11.6)	99	(35.4)	< 0.001
At hospital discharge	39	(5.3)	14	(3.1)	25	(8.9)	0.001
Oral hypoglycemics							
In hospital	69	(9.4)	18	(4.0)	51	(18.2)	< 0.001
At hospital discharge	42	(5.7)	13	(2.9)	29	(10.4)	< 0.001
Complications, n (%)							
Neurologic worsening	293	(39.9)	165	(36.3)	128	(45.9)	0.010
New stroke	41	(5.6)	21	(4.6)	20	(7.2)	0.184
Ischemic	13	(31.7)	7	(33.3)	6	(30.0)	1.000
ICH	28	(68.3)	14	(66.7)	14	(70.0)	
New TIA	*	*	*	*	*	*	1.000
Seizure	47	(6.4)	31	(6.8)	16	(5.7)	0.642
Depression	25	(3.4)	14	(3.1)	11	(3.9)	0.536
Cardiac arrest	91	(12.4)	40	(8.8)	51	(18.3)	< 0.001
Decubitus ulcer	15	(2.0)	11	(2.4)	*	*	0.431
DVT	25	(3.4)	13	(2.9)	12	(4.3)	0.302
Fall (with injury)	*	*	*	*	*	*	0.637
GI bleed	12	(2.1)	6	(1.7)	6	(2.8)	0.380
Transfusion required	*	*	*	*	*	*	0.549†
missing	173	(23.5)	104	(22.9)	69	(24.6)	
Myocardial infarction	13	(1.8)	8	(1.8)	*	*	1.000
Pneumonia	81	(11.0)	44	(9.7)	37	(13.3)	0.146
Pulmonary embolus	9	(1.2)	6	(1.3)	*	*	1.000
UTI	103	(14.0)	67	(14.7)	36	(12.9)	0.513
At least 1 complication	287	(39.0)	160	(35.2)	127	(45.4)	0.006
At least 1 complication and/or neurologic worsening	421	(57.3)	234	(51.4)	187	(66.8)	< 0.001

ICH = intracerebral hemorrhage; **IV** = intravenous; **SC** = subcutaneous; **TIA** = transient ischemic attack; **DVT** = deep venous thrombosis; **GI** = gastrointestinal; **UTI** = urinary tract infection.

Fisher's exact test used for P-value, unless noted by † (Pearson Chi-Square test for P-value).

* *Note:* results suppressed in cells with ≤ 5 counts based on ICES privacy policies.

Table 14. In-hospital, 30-day, and 6-month outcomes for patients with intracerebral hemorrhage.

Outcome	All Patients with Intracerebral Hemorrhage n = 735		Glucose ≤ 8.5 mmol/l n = 455		Glucose > 8.5 mmol/l n = 280		P-value
Length of stay, days							
Mean	16.9		18.0		15.9		0.363
Median	8		9		6		< 0.001**
In-hospital death, n (%)	308	(41.9)	137	(30.1)	171	(61.1)	< 0.001*
Discharge mRS score							
Median (all patients)	5		4		6		< 0.001**
Median (survivors)	4		3		4		0.031†
mRS ≤ 2, n (%)	124	(16.9)	101	(22.2)	23	(8.2)	< 0.001*
Discharge location, n (%)							0.447†
Home	127	(29.7)	100	(31.4)	27	(24.8)	
Active rehab	133	(31.1)	93	(29.2)	40	(36.4)	
Acute care hospital	95	(22.2)	68	(21.4)	27	(24.5)	
Long-term care / NH	60	(14.0)	48	(15.1)	12	(10.9)	
Other	12	(2.8)	9	(2.8)	††	††	
Death at 30 days, n (%)	315	(42.9)	140	(30.8)	175	(62.5)	< 0.001*
Death at 6 months, n (%)	359	(48.8)	176	(38.7)	183	(65.4)	< 0.001*

mRS = modified Rankin Scale; **NH** = nursing home.

* Fisher's exact test used for P-value; † Pearson Chi-Square test used for P-value; ** Mann-Whitney U test used to compare median values.

†† *Note:* results suppressed in cells with ≤ 5 counts based on ICES privacy policies.

Table 15. Univariable Cox proportional hazards analysis for the outcome death in patients with intracerebral hemorrhage.

Variables	B	Hazard Ratio	95% Confidence Interval	P-Value
Age	0.028	1.028	1.021 - 1.036	< 0.001
Sex (female vs. male)	0.256	1.291	1.064 - 1.566	0.010
CNS score				
Ordinal scale (unit increase)	- 0.195	0.823	0.801 - 0.846	< 0.001
Dichotomous (≤ 8 vs. > 8)	1.322	3.749	2.837 - 4.956	< 0.001
Blood glucose				
Continuous (per mmol/l)	0.034	1.035	1.019 - 1.051	< 0.001
Dichotomous (> 8.5 mmol/l)	0.731	2.078	1.711 - 2.524	< 0.001
Initial SBP (per unit increase)	0.005	1.005	1.002 - 1.007	0.001
Initial DBP (per unit increase)	0.001	1.001	0.996 - 1.005	0.799
Initial INR (per unit increase)	0.218	1.243	1.144 - 1.351	< 0.001
Comorbidities				
Diabetes	0.222	1.248	1.003 - 1.553	0.047
Hypertension	0.030	1.031	0.846 - 1.256	0.763
Hyperlipidemia	- 0.030	0.970	0.765 - 1.231	0.804
Myocardial infarction	0.079	1.083	0.766 - 1.531	0.653
CABG/angioplasty	0.093	1.098	0.708 - 1.703	0.678
Smoking (current)	- 0.391	0.676	0.498 - 0.919	0.013
Past stroke	0.437	1.548	1.217 - 1.968	< 0.001
Past TIA	0.406	1.501	1.091 - 2.066	0.013
Past ICH	0.012	1.012	0.670 - 1.529	0.955
Preadmission status - (dependent vs. independent)	0.418	1.519	1.167 - 1.977	0.002
Charlson Index (ordinal)	0.125	1.133	1.082 - 1.185	< 0.001
Socioeconomic status				
Q1	0.355	1.427	1.042 - 1.954	0.027
Q2	0.237	1.268	0.915 - 1.757	0.155
Q3	0.223	1.250	0.896 - 1.742	0.189
Q4	0.406	1.501	1.075 - 2.095	0.017
Q5 (reference)	-	-	-	-

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **INR** = International Normalized Ratio; **CABG** = coronary artery bypass graft; **TIA** = transient ischemic attack; **ICH** = intracerebral hemorrhage; **Q1-Q5** = income quintiles.

Table 16. Multivariable Cox proportional hazards model for the outcome death in patients with intracerebral hemorrhage.

Variables	B	Hazard Ratio	95% Confidence Interval	P-value
Glucose (continuous)	0.025	1.025	1.001 - 1.049	0.040
Age	0.034	1.035	1.027 - 1.043	< 0.001
CNS score (ordinal)	- 0.211	0.810	0.786 - 0.835	< 0.001
Initial SBP	0.004	1.004	1.002 - 1.007	0.002
Initial INR	0.215	1.240	1.145 - 1.342	< 0.001
Past hypertension	- 0.219	0.803	0.648 - 0.995	0.045
Past stroke	0.308	1.361	1.059 - 1.749	0.016
Socioeconomic status				
Q1	0.383	1.446	1.067 - 2.016	0.018
Q2	0.249	1.283	0.922 - 1.783	0.139
Q3	0.272	1.312	0.938 - 1.835	0.112
Q4	0.449	1.567	1.116 - 2.201	0.010
Q5 (reference)	-	-	-	-

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **SBP** = systolic blood pressure; **INR** = International Normalized Ratio; **Q1-Q5** = income quintiles.

Table 17. Multivariable Cox proportional hazards model for the outcome death with glucose as a dichotomous variable based on ROC curve analysis cut-off in patients with intracerebral hemorrhage.

Variables	B	Hazard Ratio	95% Confidence Interval	P-value
Glucose (> 8.5 mmol/l)	0.454	1.574	1.280 - 1.935	< 0.001
Age	0.034	1.035	1.027 - 1.042	< 0.001
CNS score (ordinal)	- 0.201	0.818	0.794 - 0.843	< 0.001
Initial SBP	0.004	1.004	1.001 - 1.007	0.006
Initial INR	0.219	1.244	1.147 - 1.349	< 0.001
Past hypertension	- 0.222	0.801	0.647 - 0.992	0.042
Past stroke	0.306	1.358	1.057 - 1.746	0.017
Socioeconomic status				
Q1	0.417	1.517	1.104 - 2.086	0.010
Q2	0.265	1.303	0.938 - 1.810	0.115
Q3	0.298	1.348	0.963 - 1.885	0.081
Q4	0.523	1.687	1.200 - 2.372	0.003
Q5 (reference)	-	-	-	-

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **SBP** = systolic blood pressure; **INR** = International Normalized Ratio; **Q1-Q5** = income quintiles.

Table 18a. Multiple logistic regression (first step) for moderate to severe disability (mRS 3-5) or death (mRS 6) at hospital discharge in patients with intracerebral hemorrhage.

Variables	B	Odds Ratio	95% Confidence Interval	P-value
Glucose (continuous)	0.018	1.018	0.929 - 1.115	0.703
Age	0.035	1.035	1.016 - 1.055	< 0.001
Sex (female vs. male)	0.346	1.413	0.866 - 2.307	0.166
CNS score (ordinal)	- 0.403	0.668	0.613 - 0.728	< 0.001
Initial SBP	- 0.001	0.999	0.990 - 1.009	0.839
Initial DBP	0.009	1.009	0.993 - 1.025	0.266
Initial INR	0.142	1.153	0.811 - 1.640	0.428
Diabetes	- 0.305	0.737	0.395 - 1.377	0.339
Past hypertension	0.124	1.132	0.678 - 1.890	0.636
Hyperlipidemia	- 0.300	0.741	0.407 - 1.350	0.328
Past myocardial infarction	0.121	1.129	0.439 - 2.904	0.802
Past CABG/angioplasty	0.947	2.579	0.652 - 10.205	0.177
Smoking (current)	- 0.259	0.772	0.400 - 1.488	0.439
Past stroke	0.913	2.491	1.101 - 5.634	0.028
Past TIA	1.088	2.969	0.650 - 13.563	0.160
Past ICH	0.125	1.133	0.395 - 3.250	0.817
Preadmission status (dependent)	0.014	1.014	0.388 - 2.651	0.977
Socioeconomic status				
Q1	0.176	1.192	0.576 - 2.465	0.635
Q2	0.537	1.711	0.788 - 3.715	0.174
Q3	0.407	1.502	0.691 - 3.265	0.305
Q4	- 0.291	0.747	0.357 - 1.563	0.439
Q5 (reference)	-	-	-	-

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **INR** = International Normalized Ratio; **CABG** = coronary artery bypass graft; **TIA** = transient ischemic attack; **ICH** = intracerebral hemorrhage; **Q1-Q5** = income quintiles.

Table 18b. Multiple logistic regression (final step) for moderate to severe disability (mRS 3-5) or death (mRS 6) at hospital discharge in patients with intracerebral hemorrhage (glucose removed by the model).

Variables	B	Odds Ratio	95% Confidence Interval	P-value
Age	0.036	1.036	1.020 - 1.053	< 0.001
CNS score (ordinal)	- 0.405	0.667	0.615 - 0.724	< 0.001
Past stroke	0.877	2.403	1.129 - 5.113	0.023
Past TIA	1.117	3.055	0.692 - 13.493	0.141

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **TIA** = transient ischemic attack.

Table 19a. Multiple logistic regression (first step) for the combined outcome of discharge disposition to long-term care or death at hospital discharge in patients with intracerebral hemorrhage.

Variables	B	Odds Ratio	95% Confidence Interval	P-value
Glucose (continuous)	0.043	1.044	0.988 - 1.103	0.122
Age	0.065	1.068	1.050 - 1.085	< 0.001
Sex (female vs. male)	0.185	1.203	0.821 - 1.762	0.343
CNS score (ordinal)	- 0.326	0.722	0.682 - 0.764	< 0.001
Initial SBP	0.006	1.006	0.999 - 1.013	0.113
Initial DBP	0.003	1.003	0.992 - 1.015	0.593
Initial INR	0.342	1.408	1.092 - 1.815	0.008
Diabetes	- 0.051	0.950	0.591 - 1.528	0.833
Past hypertension	- 0.255	0.775	0.514 - 1.168	0.223
Hyperlipidemia	- 0.093	0.911	0.563 - 1.476	0.706
Past myocardial infarction	0.363	1.437	0.689 - 2.997	0.333
Past CABG/angioplasty	0.326	1.385	0.567 - 3.382	0.474
Smoking (current)	0.050	1.051	0.601 - 1.839	0.862
Past stroke	0.466	1.593	0.922 - 2.752	0.095
Past TIA	0.085	1.089	0.545 - 2.177	0.810
Past ICH	- 0.355	0.701	0.286 - 1.716	0.437
Preadmission status (dependent)	0.633	1.883	0.996 - 3.560	0.051
Socioeconomic status				
Q1	0.619	1.857	1.026 - 3.361	0.041
Q2	0.250	1.284	0.711 - 2.316	0.407
Q3	0.148	1.159	0.633 - 2.123	0.633
Q4	0.424	1.528	0.817 - 2.859	0.185
Q5 (reference)	-	-	-	-

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **INR** = International Normalized Ratio; **CABG** = coronary artery bypass graft; **TIA** = transient ischemic attack; **ICH** = intracerebral hemorrhage; **Q1-Q5** = income quintiles.

Table 19b. Multiple logistic regression (final step) for the combined outcome of discharge disposition to long-term care or death at hospital discharge in patients with intracerebral hemorrhage (glucose removed by the model).

Variables	B	Odds Ratio	95% Confidence Interval	P-value
Age	0.064	1.066	1.051 - 1.082	< 0.001
CNS score (ordinal)	- 0.332	0.718	0.679 - 0.758	< 0.001
Initial SBP	0.006	1.006	1.001 - 1.011	0.021
Initial INR	0.371	1.449	1.127 - 1.865	0.004
Preadmission status - (dependent)	0.609	1.838	1.008 - 3.353	0.047

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **SBP** = systolic blood pressure; **INR** = International Normalized Ratio.

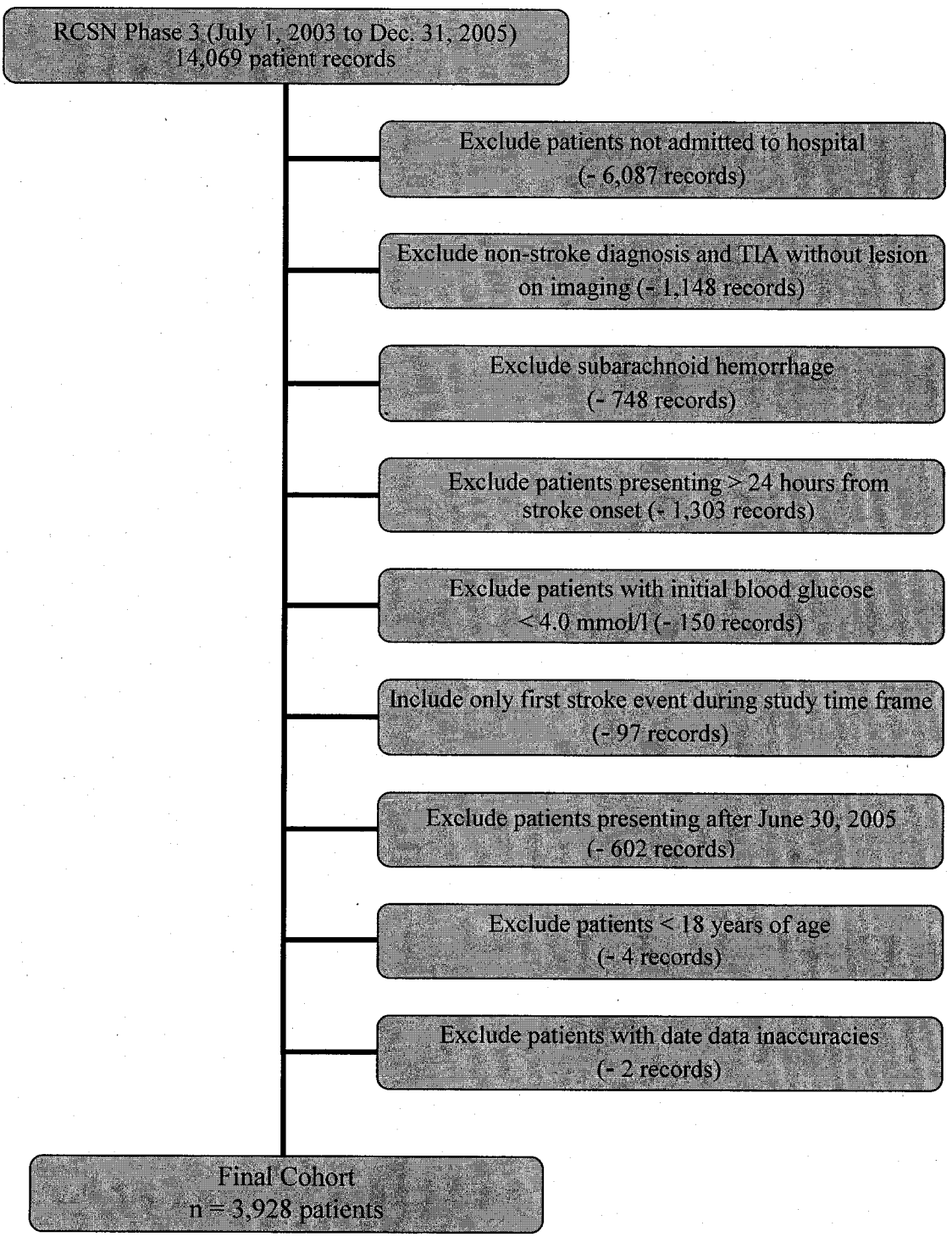
Table 20. Generalized linear model for length of stay in patients with intracerebral hemorrhage.

Variables	B	Standard Error	95% Confidence Interval (for B)	P-Value
Glucose (continuous)	0.024	0.002	0.020 - 0.029	< 0.001
Age	- 0.007	0.0007	- 0.008 - -0.005	< 0.001
Sex (female vs. male)	0.134	0.019	0.097 - 0.170	< 0.001
CNS score (ordinal)	0.044	0.002	0.039 - 0.049	< 0.001
Initial SBP	- 0.0006	0.0003	- 0.001 - 0.0001	0.101
Initial DBP	0.003	0.0006	0.002 - 0.005	< 0.001
Initial INR	- 0.025	0.011	- 0.047 - -0.003	0.027
Comorbidities				
Diabetes	- 0.020	0.026	- 0.071 - 0.031	0.450
Hypertension	0.189	0.020	0.149 - 0.229	< 0.001
Hyperlipidemia	- 0.203	0.025	- 0.251 - -0.154	< 0.001
Myocardial infarction	- 0.027	0.038	- 0.100 - 0.047	0.478
CABG/angioplasty	0.262	0.044	0.175 - 0.348	< 0.001
Smoking (current)	0.098	0.021	0.057 - 0.140	< 0.001
Past stroke	- 0.183	0.028	- 0.238 - -0.128	< 0.001
Past TIA	0.176	0.034	0.110 - 0.242	< 0.001
Past ICH	- 0.087	0.044	- 0.172 - -0.001	0.046
Preadmission status - (independent)	- 0.198	0.025	- 0.247 - -0.148	< 0.001
Socioeconomic status				
Q1	- 0.207	0.027	- 0.261 - -0.154	< 0.001
Q2	- 0.186	0.028	- 0.240 - -0.132	< 0.001
Q3	- 0.481	0.030	- 0.540 - -0.422	< 0.001
Q4	- 0.289	0.029	- 0.347 - -0.232	< 0.001
Q5 (reference)	-	-	-	-

B = unstandardized coefficient (slope estimate) for each predictor variable; **CNS** = Canadian Neurological Scale; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **INR** = International Normalized Ratio; **CABG** = coronary artery bypass graft; **TIA** = transient ischemic attack; **ICH** = intracerebral hemorrhage; **Q1-Q5** = income quintiles.

6.2 Figures

Figure 1. Flow diagram of RCSN patients excluded from study cohort.



RCSN = Registry of the Canadian Stroke Network; **TIA** = transient ischemic attack.

Figure 2a. Distribution of glucose values in the RCSN cohort (n = 3,928).

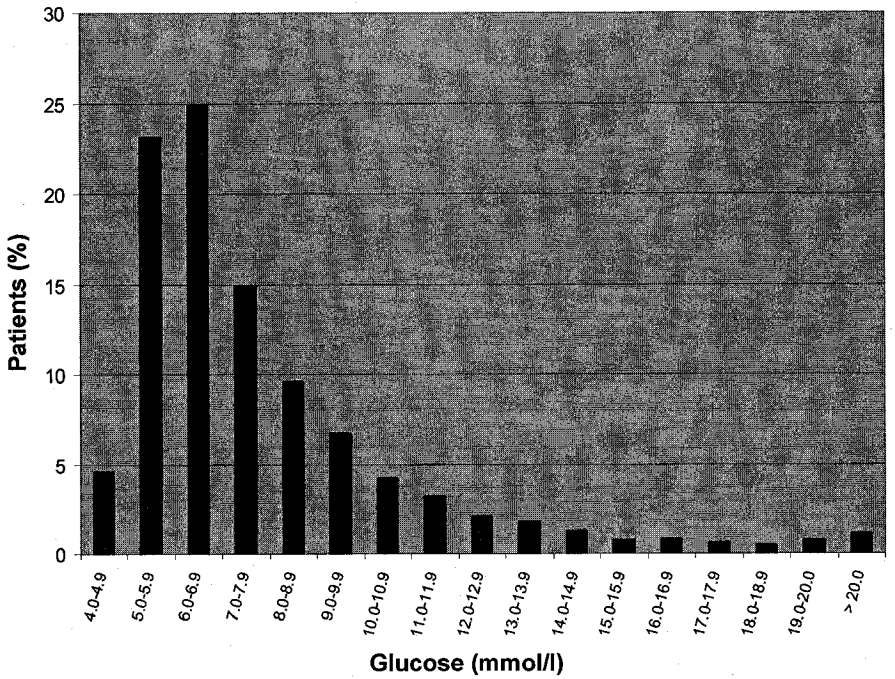


Figure 2b. Distribution of glucose values in the RCSN cohort (n = 3,928) based on diabetes history.

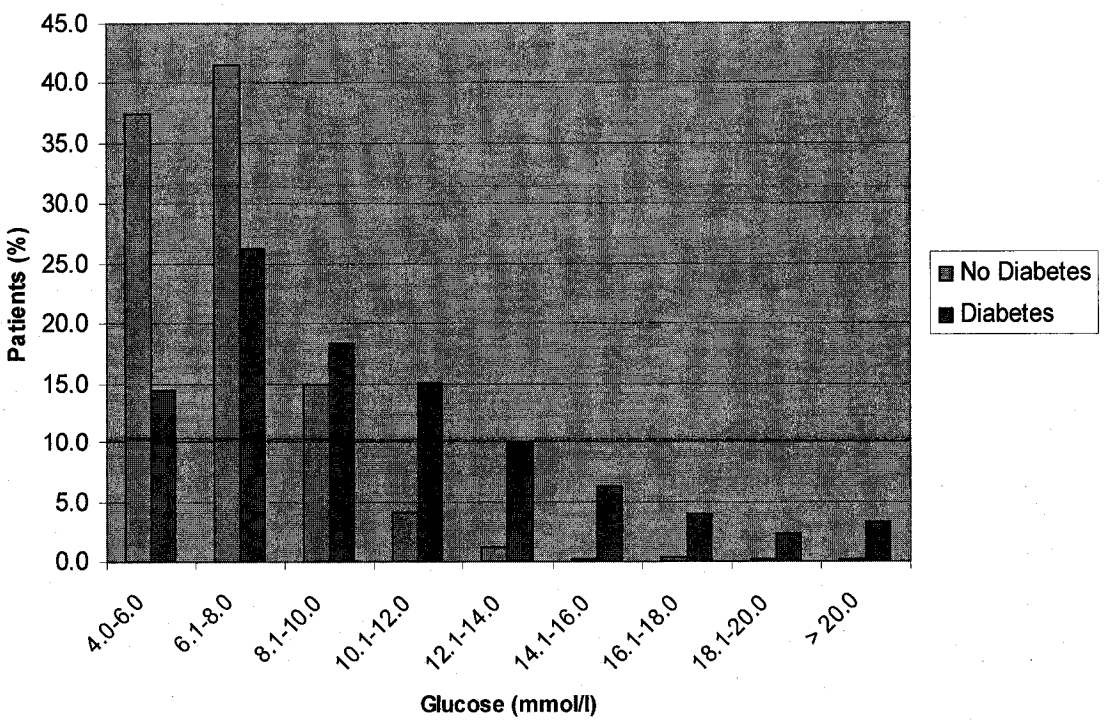
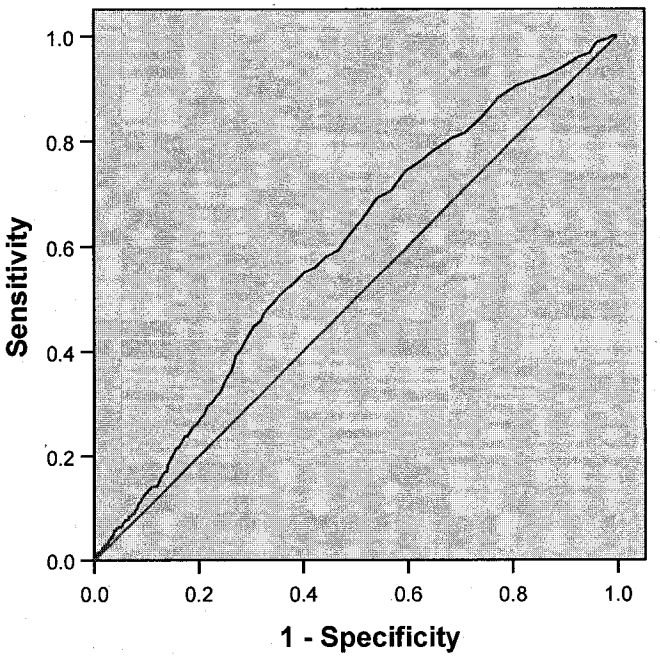
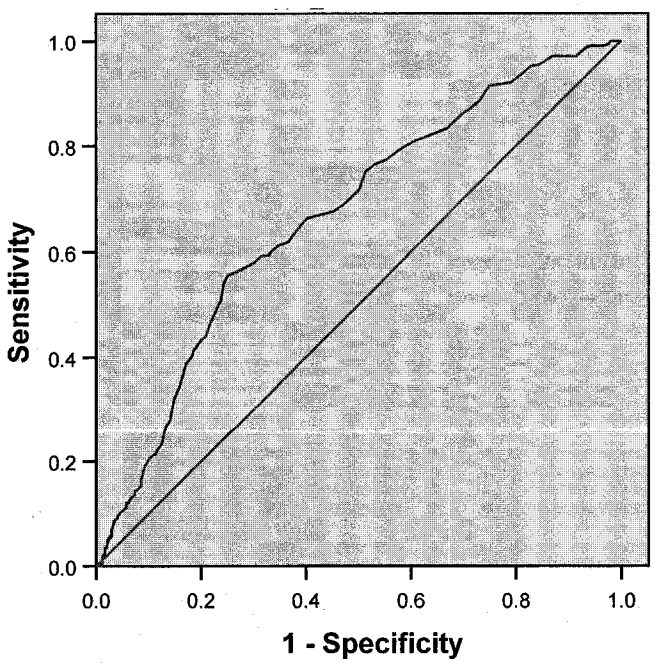


Figure 3a. ROC curve for glucose (independent variable) and 30-day death for patients with ischemic stroke (n = 3,193).



AUC = 0.592
p < 0.001

Figure 3b. ROC curve for glucose (independent variable) and 30-day death for patients with intracerebral hemorrhage (n = 735).



AUC = 0.668
p < 0.001

AUC = area under the ROC curve.

Figure 4a. Kaplan-Meier survival analysis for the ischemic stroke cohort.

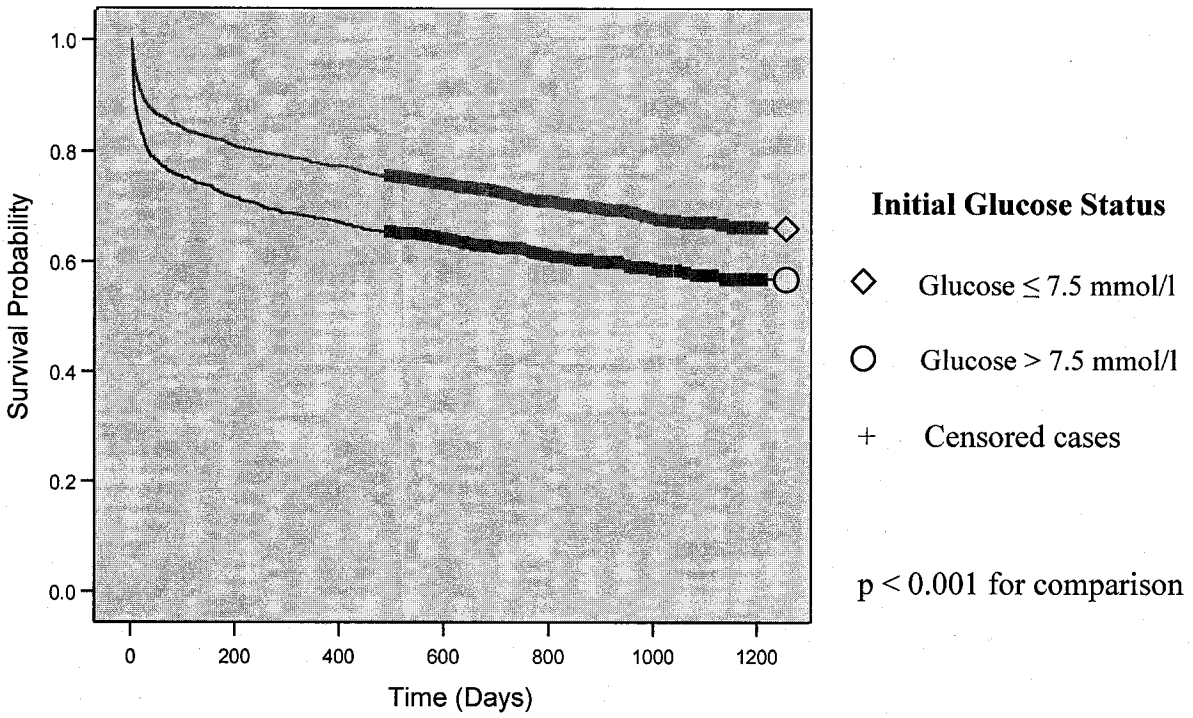


Figure 4b. Adjusted survival analysis for the ischemic stroke cohort.

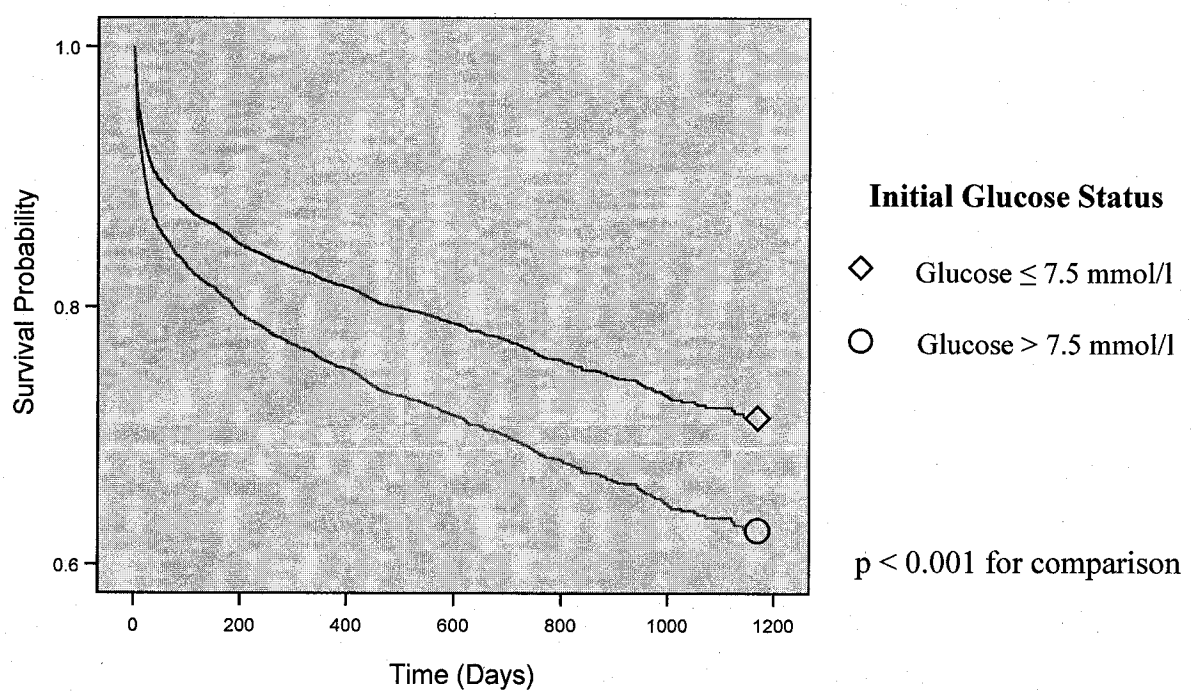


Figure 5a. Thirty-day deaths by glucose quintiles in the ischemic stroke cohort.

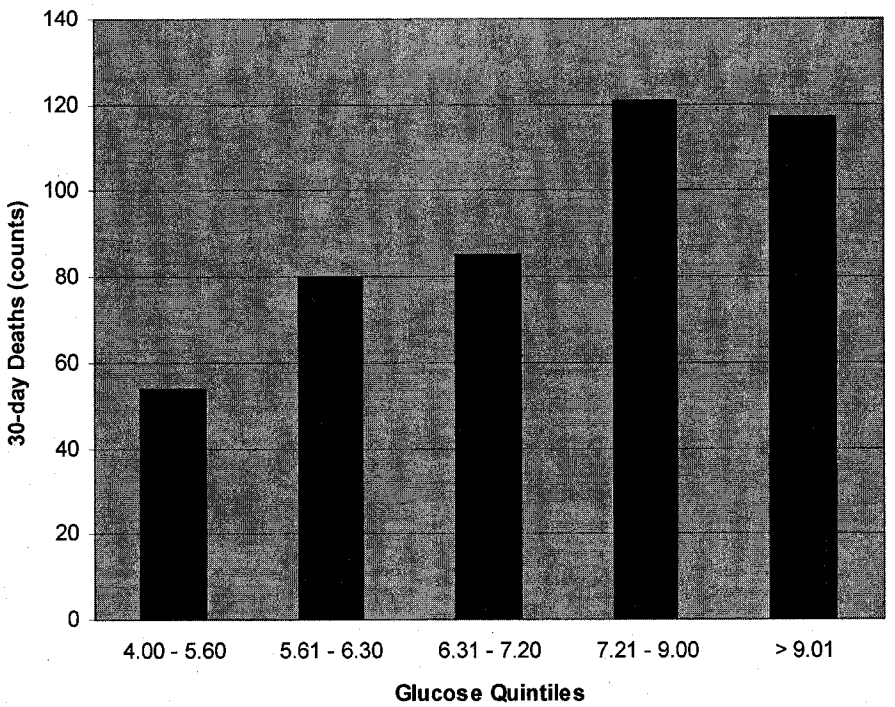


Figure 5b. Thirty-day deaths by glucose deciles in the ischemic stroke cohort.

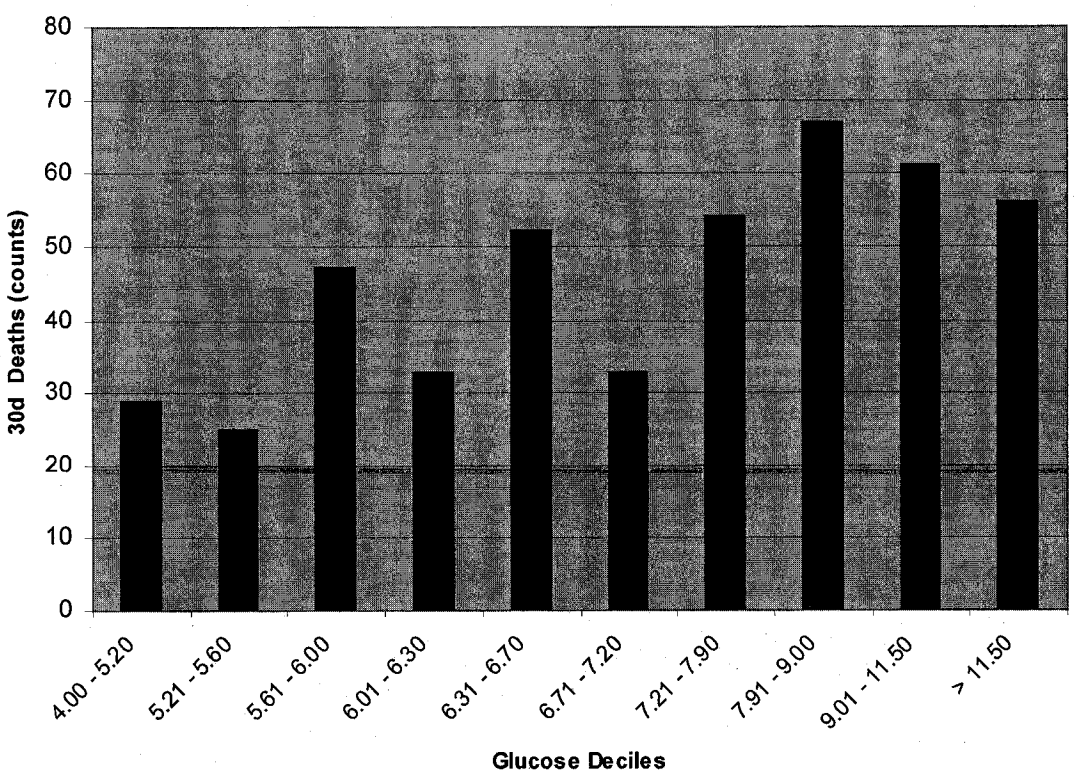


Figure 6a. Kaplan-Meier survival analysis for the intracerebral hemorrhage cohort.

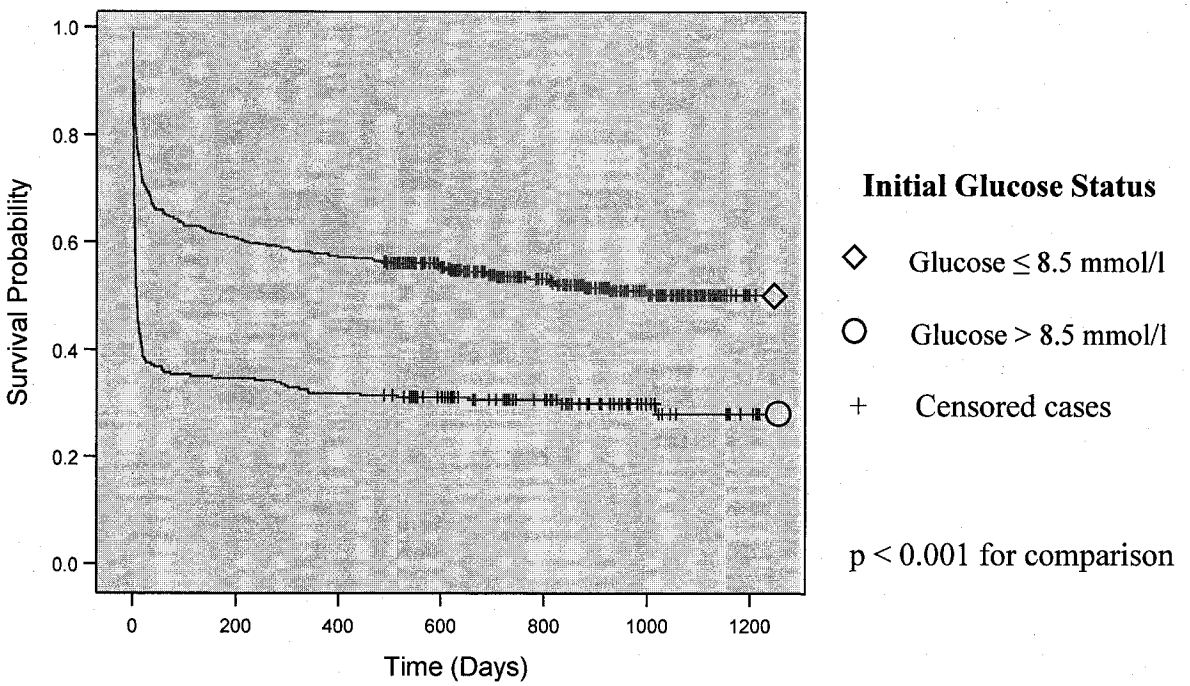


Figure 6b. Adjusted survival analysis for the intracerebral hemorrhage cohort.

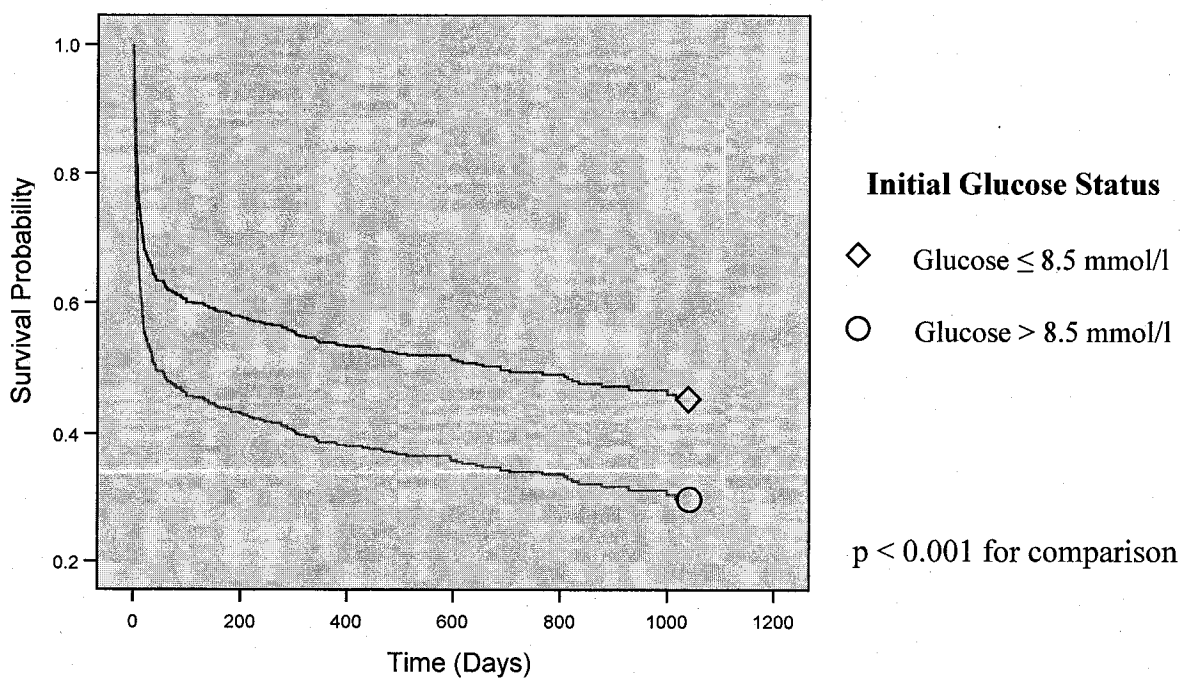


Figure 7a. Thirty-day deaths by glucose quintiles in the intracerebral hemorrhage cohort.

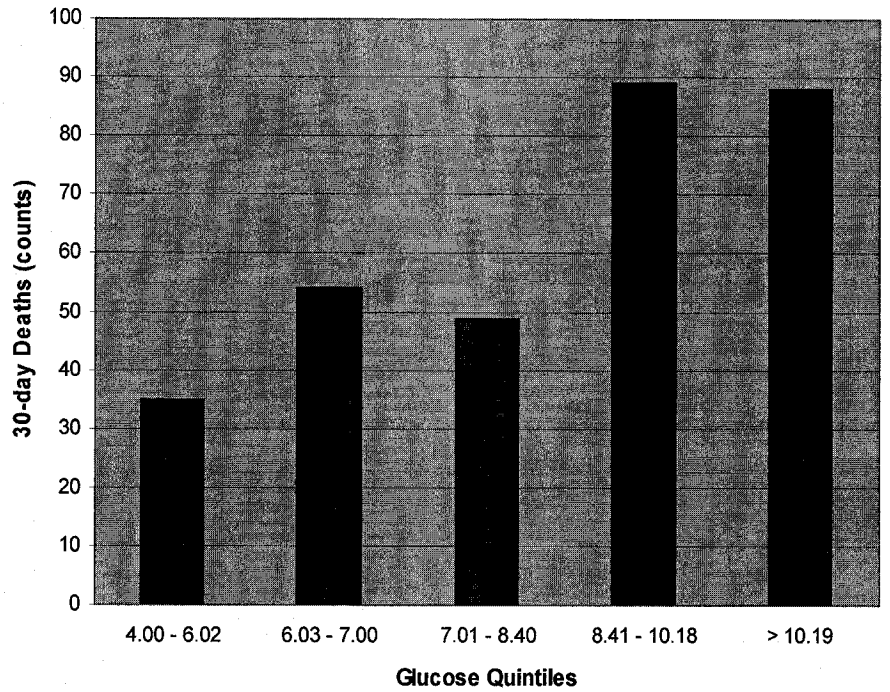
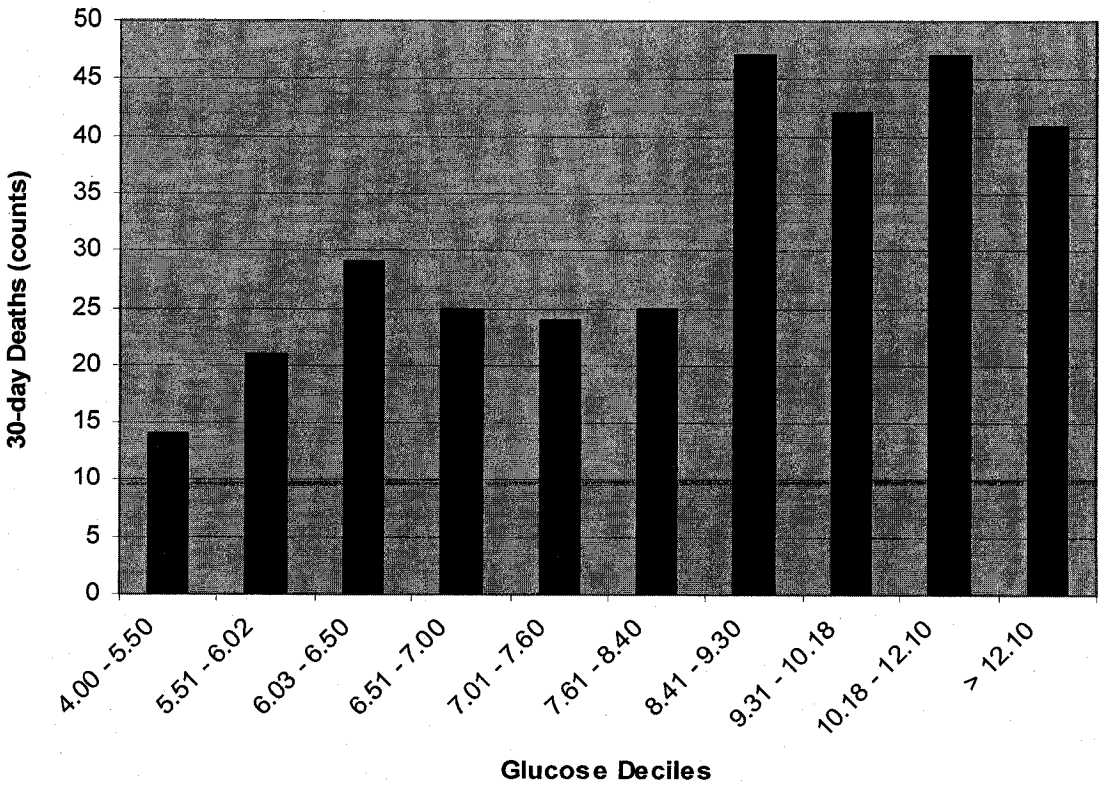


Figure 7b. Thirty-day deaths by glucose deciles in the intracerebral hemorrhage cohort.



CHAPTER 7

7. References

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CHAPTER 8

8. Appendices

8.1 Appendix A - ROC curve analysis coordinates for glucose values in ischemic stroke.

Blood Glucose Thresholds (mmol/l)*	Sensitivity	1 - Specificity
3.0000	1.000	1.000
4.0500	1.000	1.000
4.1500	1.000	0.999
4.2500	1.000	0.997
4.3500	1.000	0.993
4.4500	1.000	0.991
4.5500	0.998	0.988
4.6500	0.993	0.980
4.7500	0.991	0.970
4.8500	0.987	0.961
4.9500	0.967	0.948
5.0500	0.961	0.928
5.1500	0.947	0.908
5.2500	0.937	0.889
5.3500	0.923	0.865
5.4500	0.917	0.841
5.5500	0.906	0.809
5.6500	0.882	0.774
5.7050	0.849	0.746
5.7550	0.849	0.746
5.8500	0.816	0.712
5.9500	0.805	0.685
6.0500	0.779	0.645
6.1500	0.757	0.620
6.2500	0.742	0.596
6.3500	0.707	0.569
6.4500	0.691	0.542
6.5500	0.654	0.516
6.6500	0.624	0.490
6.7400	0.593	0.467
6.7900	0.593	0.467
6.8500	0.580	0.444
6.9500	0.560	0.423
7.0500	0.551	0.403
7.1500	0.536	0.389
7.2500	0.521	0.371
7.3500	0.508	0.356
7.4500	0.492	0.343
7.5500	0.477	0.328
7.6500	0.460	0.319
7.7500	0.449	0.306
7.8500	0.422	0.291
7.9500	0.403	0.280

Blood Glucose Thresholds (mmol/l)*	Sensitivity	1 - Specificity
8.0500	0.394	0.271
8.1500	0.365	0.264
8.2500	0.348	0.252
8.3500	0.324	0.242
8.4500	0.317	0.234
8.5500	0.304	0.226
8.6500	0.295	0.216
8.7500	0.280	0.210
8.8500	0.274	0.204
8.9500	0.260	0.195
9.0500	0.256	0.189
9.1500	0.247	0.183
9.2100	0.241	0.179
9.2600	0.239	0.179
9.3500	0.239	0.173
9.4500	0.232	0.170
9.5500	0.225	0.166
9.6500	0.219	0.163
9.7500	0.214	0.156
9.8500	0.204	0.151
9.9500	0.193	0.145
10.0500	0.184	0.141
10.1500	0.171	0.139
10.2500	0.171	0.136
10.3500	0.168	0.133
10.4500	0.162	0.129
10.5500	0.153	0.124
10.6500	0.144	0.121
10.7500	0.142	0.118
10.8500	0.142	0.115
10.9500	0.142	0.109
11.0500	0.138	0.107
11.1500	0.138	0.106
11.2500	0.136	0.103
11.3500	0.131	0.101
11.4500	0.129	0.098
11.5500	0.123	0.093
11.6500	0.118	0.091
11.7500	0.112	0.088
11.8500	0.109	0.084
11.9500	0.105	0.083
12.0500	0.101	0.081
12.1500	0.096	0.078
12.2500	0.092	0.077
12.3500	0.090	0.076
12.4500	0.090	0.073
12.5500	0.088	0.072
12.6500	0.085	0.071
12.7500	0.085	0.069

Blood Glucose Thresholds (mmol/l)*	Sensitivity	1 - Specificity
12.8500	0.085	0.066
12.9500	0.081	0.065
13.0500	0.079	0.065
13.1500	0.079	0.064
13.2500	0.079	0.063
13.3500	0.077	0.061
13.4500	0.077	0.059
13.5500	0.074	0.058
13.6500	0.072	0.056
13.7500	0.070	0.055
13.8500	0.068	0.054
13.9500	0.063	0.051
14.0500	0.063	0.049
14.1500	0.063	0.048
14.2500	0.063	0.044
14.3500	0.061	0.042
14.4500	0.061	0.042
14.5500	0.059	0.041
14.6500	0.057	0.041
14.7500	0.057	0.040
14.8500	0.057	0.038
14.9500	0.057	0.037
15.0500	0.053	0.037
15.1500	0.048	0.036
15.2500	0.048	0.035
15.3500	0.046	0.034
15.4500	0.046	0.034
15.5500	0.044	0.034
15.6500	0.044	0.033
15.7500	0.044	0.032
15.9000	0.044	0.031
16.0500	0.044	0.031
16.1500	0.042	0.030
16.2500	0.039	0.030
16.3500	0.039	0.028
16.4500	0.039	0.027
16.5500	0.037	0.027
16.6500	0.037	0.027
16.7500	0.035	0.026
16.8500	0.033	0.026
17.0000	0.031	0.024
17.1500	0.031	0.024
17.2500	0.031	0.023
17.3500	0.031	0.022
17.4500	0.028	0.021
17.5500	0.028	0.020
17.6500	0.026	0.019
17.8000	0.024	0.019
17.9500	0.024	0.018

Blood Glucose Thresholds (mmol/l)*	Sensitivity	1 - Specificity
18.0500	0.024	0.017
18.1500	0.024	0.017
18.2500	0.024	0.016
18.4000	0.024	0.015
18.6500	0.024	0.015
18.9500	0.020	0.015
19.2000	0.020	0.014
19.3500	0.018	0.014
19.4500	0.018	0.013
19.5500	0.015	0.013
19.6500	0.015	0.013
19.7500	0.015	0.012
19.8500	0.015	0.011
19.9500	0.015	0.011
20.0500	0.015	0.011
20.1500	0.015	0.010
20.2500	0.013	0.010
20.4000	0.013	0.009
20.6000	0.013	0.008
20.7500	0.013	0.008
20.8500	0.013	0.008
20.9500	0.013	0.007
21.1000	0.013	0.007
21.2500	0.013	0.006
21.4000	0.013	0.005
21.5500	0.013	0.005
21.6500	0.011	0.005
21.7500	0.011	0.005
21.8500	0.011	0.004
22.0500	0.009	0.004
22.2500	0.007	0.004
22.4000	0.004	0.004
22.7000	0.002	0.004
23.3500	0.002	0.004
24.4500	0.002	0.003
25.2500	0.002	0.003
26.3500	0.002	0.003
27.3500	0.002	0.002
27.7500	0.002	0.001
28.1500	0.002	0.001
28.8500	0.002	0.001
30.6000	0.002	0.000
33.0500	0.002	0.000
35.4000	0.000	0.000

* The smallest cut-off value is the minimum observed test value minus 1 and the largest cut-off value is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values.

8.2 Appendix B - ROC curve analysis coordinates for glucose values in intracerebral hemorrhage.

Blood Glucose Thresholds (mmol/l)*	Sensitivity	1 - Specificity
3.2000	1.000	1.000
4.2500	1.000	0.995
4.3500	1.000	0.993
4.4500	1.000	0.990
4.5500	1.000	0.986
4.6500	1.000	0.981
4.7500	0.994	0.976
4.8500	0.990	0.967
4.9500	0.990	0.960
5.0500	0.990	0.943
5.1500	0.987	0.933
5.2500	0.971	0.914
5.3500	0.971	0.890
5.4500	0.971	0.869
5.5500	0.956	0.845
5.6500	0.952	0.829
5.7500	0.943	0.817
5.8500	0.921	0.790
5.9500	0.914	0.750
6.0500	0.889	0.733
6.1500	0.873	0.717
6.2500	0.860	0.698
6.3500	0.835	0.671
6.4500	0.819	0.633
6.5500	0.810	0.607
6.6500	0.794	0.579
6.7500	0.775	0.555
6.8500	0.765	0.531
6.9500	0.752	0.514
7.0500	0.717	0.502
7.1500	0.702	0.486
7.2500	0.689	0.471
7.3500	0.676	0.452
7.4500	0.670	0.429
7.5500	0.663	0.402
7.6500	0.641	0.383
7.7500	0.619	0.367
7.8500	0.613	0.348
7.9500	0.600	0.333
8.0500	0.594	0.329
8.1500	0.594	0.317
8.2500	0.578	0.298
8.3500	0.568	0.279
8.4500	0.562	0.264
8.5500	0.556	0.250
8.6500	0.540	0.243

Blood Glucose Thresholds (mmol/l)*	Sensitivity	1 - Specificity
8.7500	0.508	0.238
8.8500	0.502	0.233
8.9500	0.489	0.229
9.0500	0.463	0.217
9.1500	0.441	0.210
9.2500	0.435	0.202
9.3500	0.413	0.186
9.4500	0.403	0.183
9.5500	0.387	0.171
9.6500	0.362	0.164
9.7500	0.340	0.157
9.8500	0.324	0.150
9.9500	0.302	0.145
10.0500	0.292	0.143
10.1500	0.279	0.140
10.2500	0.270	0.133
10.3500	0.251	0.129
10.4500	0.238	0.126
10.5500	0.232	0.124
10.6500	0.229	0.121
10.7500	0.222	0.117
10.8500	0.213	0.112
10.9500	0.213	0.110
11.0500	0.206	0.102
11.1500	0.203	0.100
11.2500	0.190	0.093
11.3500	0.184	0.090
11.4500	0.165	0.086
11.5500	0.159	0.086
11.7000	0.152	0.086
11.8500	0.146	0.079
11.9500	0.143	0.074
12.0500	0.137	0.074
12.1500	0.130	0.067
12.2500	0.127	0.064
12.3500	0.121	0.062
12.5500	0.121	0.057
12.7500	0.111	0.057
12.8500	0.108	0.052
12.9500	0.105	0.050
13.0500	0.102	0.045
13.1500	0.095	0.040
13.3000	0.092	0.040
13.4500	0.089	0.036
13.6000	0.086	0.036
13.7500	0.086	0.033
13.8500	0.083	0.033
13.9500	0.073	0.031
14.1000	0.070	0.029

Blood Glucose Thresholds (mmol/l)*	Sensitivity	1 - Specificity
14.2500	0.063	0.029
14.4000	0.060	0.029
14.6500	0.057	0.029
15.0000	0.057	0.026
15.2500	0.054	0.026
15.4000	0.054	0.024
15.6000	0.051	0.024
15.7500	0.051	0.021
15.8500	0.048	0.021
15.9500	0.044	0.021
16.0500	0.035	0.019
16.2000	0.035	0.017
16.5000	0.032	0.017
16.9500	0.029	0.017
17.2500	0.025	0.017
17.6000	0.022	0.017
18.0000	0.022	0.014
18.2000	0.019	0.014
18.6000	0.019	0.012
19.2500	0.016	0.012
19.6500	0.013	0.012
19.8500	0.010	0.012
20.0500	0.006	0.012
20.8000	0.003	0.012
21.5500	0.003	0.010
22.3000	0.000	0.010
23.1500	0.000	0.007
24.0500	0.000	0.005
42.4000	0.000	0.002
61.0000	0.000	0.000

* The smallest cut-off value is the minimum observed test value minus 1, and the largest cut-off value is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values.