A COMPARISON OF OUTCOMES FOR ACUTE STROKE PATIENTS HOSPITALIZED IN MICHIGAN, USA AND ONTARIO, CANADA USING HOSPITAL DISCHARGE DATA (2010-2012)

By

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ABSTRACT

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Previous studies have compared cardiovascular disease outcomes between Canada and the United States; however, there are limited data for stroke. This thesis compares hospital discharge data to compare mortality and readmission rates after stroke between Michigan and Ontario. Eligible acute stroke patients (both ischemic and hemorrhagic) were hospitalized between January 1, 2010 and December 31, 2012. A total of 47,364 and 35,648 patients were included in Michigan and Ontario, respectively. To ensure comparability of patient risk profiles between Michigan and Ontario, we applied a Michigan risk-adjustment model to Ontario patients to generate directly standardized outcome rates for Ontario. Results indicate that Ontario stroke patient population was older (mean age: 72.4 vs. 69.5 years), had longer hospital length of stay (mean length of stay: 12.5 vs. 5.4 days), and experienced higher frequencies of acute ischemic heart disease and cancer, whereas the Michigan stroke patient population exhibited higher frequencies of chronic ischemic heart disease, diabetes, heart failure, and renal failure. Ontario had a higher risk-standardized in-hospital mortality rate (13.3%) compared to Michigan (7.6%); however, risk-standardized 30-day readmission rates were similar (5.3% vs. 4.5%). Other performance metrics, such as 30-day mortality, are required to make valid comparisons regarding mortality, but was not possible with the datasets used in this study.

To my family and friends for their love and support.

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CHAPTER 1: BACKGROUND

Significance

Every country seeks to provide efficient, effective, and equitable health care, yet health care systems vary across countries to reflect the uniqueness of its population, economic status, and disease burden. The substantial variation in health systems between countries provides the opportunity to compare health outcomes across systems that differ in terms of organization, quality of care, and economics. Specifically, in stroke research, comparing two contrasting health systems can aid in understanding how differences in organization and delivery of stroke care may be reflected in differences in stroke outcomes. Disparities in stroke outcomes across different health systems may also aid in the identification of strengths and weaknesses of specific systems that influence quality of care and outcomes. Canada and the United States are bordering developed nations with significant cultural, infrastructural, and economic similarities, but their fundamentally different health care systems offer an intriguing opportunity to conduct cross boarder comparisons of health outcomes.

American and Canadian Health Care Systems

There are notable differences between the American and Canadian health care systems, particularly related to health care organization, specialty medical care allocation, and payer source. The American health care system consists of public and private stakeholders that market privatized health insurance to governmental and corporate entities, as well as directly to individuals, with minimal governmental oversight.[1] In 1965, the US government legislated the creation of the Medicare and Medicaid programs, both being government-provided (public) health care coverage for the elderly and citizens on social assistance, respectively.[2] Since their

implementation in the mid-1960s, both Medicare and Medicaid have undergone changes to become more inclusive programs. Medicare was initially for the elderly population (at least 65 years of age), but as of 1973, additionally included persons with certain disabilities. Likewise for Medicaid, its initial purpose was to provide coverage for persons on welfare assistance, but now also includes adults with qualifying disabilities, pregnant women and children of families in poverty. Since state governments regulate their own Medicaid programs, there is statewide variation in Medicaid eligibility. In 2012, Medicaid covered 35% of all children, 41% of pregnant women, 40% of parents below the federal poverty line (FPL), and 45% of adults younger than 65 years below the FPL.[3] Collectively in 2013, the Medicare and Medicaid programs accounted for 35% of all US national health expenditures (NHE); $585.7 billion USD (20% of NHE) and $449.4 billion USD (15% of NHE), respecitvely.[4]

The largest health care reform since the establishment of Medicare and Medicaid was the Patient Protection and Affordable Care Act (ACA), which was implemented in the United States in 2011.[1] The ACA requires all US residents to have some form of health coverage. Before the ACA was legislated, a major difference between the American and Canadian health systems was the proportion of uninsured or under-insured residents, because Canada possesses a universal health care system that guarantees health care to all its citizens[5]. In the US prior to the implementation of key components of the ACA, 18% of US residents under the age of 65 lacked any form of health insurance.[1] More recent data from the US Department of Health & Human Services show that the ACA now includes 11.4 million enrollees as of early 2015[6], and the proportion of uninsured US residents younger than 65 year of age has fallen to 15.3%[7]. Specifically for Medicaid, 2015 enrollment in the US has seen a 20% increase since before the implementation of the ACA.[8]

In contrast, health care in Canada is governmentally mandated to provide universal access to essential hospital and physician services for all eligible Canadian residents.[5] If a service is deemed medically necessary, it is considered an insured service under the Canada Health Act.[9] Seventy percent of the Canadian health system is funded by tax revenue from the federal, provincial, and territorial governments.[5] As federally mandated in the Canada Health Act, the individual provincial governments are responsible for passing legislation that ensures universal health coverage for necessary medical services. Furthermore, coverage must be public, inclusive of the broad scope of all essential medical services, and be universally accessible to all eligible residents. In addition to the mandate set forth for the provinces to follow, the federal government oversees health surveillance, public health initiatives, and safety, while also administering federal revenue to provinces for use on health care-related expenses. The provincial governments also set physician remuneration rates.

Prior research has shown that the substantial organizational differences between Canada and the United States, result in substantial differences in services utilization between these two systems.[10] Authors of a 2013 study of nationally representative surveys in the US and Canada showed that Canadians are more likely to visit a specialist, have a medical doctor, and stay overnight in hospital. Specifically among the poor and less educated, Canadians have demonstrated the higher likelihood to utilize health care services, such as specialist and general physician visits, than Americans of the same class.[10] Among the elderly in both countries, Canadians received more evaluative visits, such as visits to hospital or doctor's offices, but less procedures than Americans (i.e. major orthopedic procedures); the authors attributed the more liberal approach to evaluation to the lower fee for service in Canada, but the budgetary restraints of a universal health system cause lower procedure utilization in comparison to the multi-payer

system of the United States.[11] Diagnostic testing use was 32% higher in the United States compared to Canada, particularly in the use of CT and MRI imaging.[12] Contrary to the above health care utilization differences; emergency department use was found to be very similar between Canada and the US.[13]

The US spends more on health care than any other developed nation.[1] In 2011, the US spent $2.7 trillion USD on health care that accounts for 17.9% of US gross domestic product (GDP)[14]. By 2019, this figure is projected to reach $4.5 trillion USD representing 19.3% of the US GDP.[15] In 2012, Canada allocated $205.4 billion CDN or 11.3% of their GDP to health care spending.[16] On a per capita basis, Canada spends substantially less, $4,445 USD compared to $8,233 USD the US spends.[1] Specifically related to stroke, annual direct and indirect costs totaled $33.6 billion in the US[17], and $3.6 billion in Canada[18].

Stroke Burden and Delivery of Care

Even though the organization of health care is different between the two countries, the burden of stroke is very similar. Stroke is the 3rd leading cause of death in Canada, accounting for 5.5% of all Canadian deaths in 2011.[19] Similarly in the United States, stroke is the 4th leading cause of death accounting for 5.1% of all deaths in 2011.[20] In 2011, the age-adjusted stroke mortality rates for Canada and the United States were 24.8 and 37.9, respectively per 100,000 population.[17,21] Stroke is the leading cause of disability in both Canada[22] and the United States[23]. Stroke burden was discovered to be different in terms of stroke hospitalizations; the rate in the US was 31.8 per 10,000 population in 2009[24], compared to only 12 per 10,000 population in Canada in 2005[25]. To counter the burden of stroke in Canada and the US, both countries have implemented their own organized stroke health systems to improve the delivery of stroke care.[26]

Stroke care in the United States and Canada has undergone substantial changes in recent decades as new systems of stroke care have been developed in response to the availability of new acute treatments for stroke. In the US since 2000, the Brain Attack Coalition of the American Stroke Association (ASA) has laid the groundwork for necessary improvements to stroke care that are required to lessen the stroke burden on mortality and morbidity.[27,28] Since these recommendations were released, the ASA has implemented stroke quality improvement initiatives[29,30], and promoting the delivery of specialized stroke care services[31]. Regional stroke systems of care in the United States have been shown to increase access to stroke-specific care and services.[26,27] In conjunction with The Joint Commission, the ASA created a disease-specific primary stroke center (PSC) certification program[28], to recognize centers that have more intensive stroke-specific procedural capabilities, dedicated stroke units, and actively participate in stroke research[32]. The Brain Attack Coalition made recommendations on a two-tier system of stroke care in the United States: primary stroke centers (PSC) and comprehensive strokes centers (CSC).[28,33] Primary stroke centers are designed to provide acute treatments, such as tissue plasminogen activator (tPA), and stroke unit care to all acute stroke patients as necessary[28], whereas a CSC is designed to provide care to the most severe and complex patients, who may require highly specialized endovascular procedures[33]. Unlike trauma centers in the United States, there is no central organization for the placement of comprehensive and primary stroke centers, which has resulted in geographic disparities in access to primary stroke centers in the US.[34] Michigan, USA currently has 30 PSC and 3 CSC.[35] In addition to the comprehensive and primary stroke center certifications, the Joint Commission is implementing a third level of certification in July 2015 called Acute Stroke-Ready hospitals; these centers will have the capability of administering thrombolysis and have stroke specialists on standby via telephone.[36]

Substantial changes in the organization of acute stroke care have also occurred in Canada in recent years. In 1998, the Ontario Ministry of Health and Long-Term Care answered the demand of the Canadian Stroke Systems Coalition, which was to implement a systems-based approach to stroke care in Canada.[37] As in the United States, Canada implemented a similar stroke care delivery system led by the Heart and Stroke Foundation.[38] This new system focused on province-wide organized systems of care and was intended to decrease the burden of stroke nationwide by focusing on all facets in the continuum of stroke care. Hospitals in Ontario were designated into 3 categories: regional stroke centers (RSC), district stroke centers (DSC), and non-designated community hospitals. Regional stroke centers provide care to all stroke patients, regardless of severity and requirement for surgery; district stroke centers can admit stroke patients and administer thrombolytic therapy, but do not have the infrastructure for advanced surgical procedures. Regarding the hierarchy of stroke care delivery in Canada and the United States, regional and district stroke centers in Ontario can broadly be regarded as the equivalence of CSC and PSC in the US, respectively. Non-designated community hospitals in Ontario accept stroke patients who are not in requirement of advanced surgical procedures or thrombolytic therapy, but also receive patients that are transferred from more advanced centers following initial intervention (i.e. thrombolytic therapy).

In contrast to the US stroke care system, the Canadian system is more centrally organized, and thus the placement of stroke centers depends upon the distance to other stroke centers, as well as the population size and hospital resources in the region it is serving.[38] Ontario currently possesses 11 regional stroke centers, and 18 district stroke centers.[39] Improved patient outcomes have been shown to be associated with the implementation of an organized system of stroke care delivery in Ontario.[40] In addition to specialized inpatient stroke care, the Ontario

government established 45 stroke prevention clinics[39], which includes post-stroke outpatient care, focusing on secondary prevention, for those who were either admitted to hospital or sought emergency department care for a transient ischemic attack or minor stroke.[41] Referral to an outpatient stroke prevention clinic reduced 1-year all-cause mortality among ischemic stroke patients.

Comparative analyses of stroke outcomes between Canada and the US could determine which system produces better patient outcomes, and lead to further studies that help identify the drivers of outcome differences. Michigan, USA and Ontario, Canada would be appropriate regions to compare since they are similar in population size and distribution[42,43], number of hospitals[44,45], and a regional stroke care delivery system[39,46]. Even though stroke hospitalization rates have been steadily decreasing in both regions, Ontario still has substantially lower rates than Michigan.[47,48] Table 1 shows a breakdown of demographic, geographic, and hospital characteristics between Michigan and Ontario.[39,42-55]

Canada/US Comparison: Cardiovascular-Related Mortality and Risk Factors

In 2011, Canada and the United States shared the same top 5 leading causes of death, but in different order.[20,21] Canada's top 5 causes of death in descending order were: cancer, heart disease, stroke, chronic lower respiratory disorders, and accidental death.[20] Similarly in the US in descending order were: heart disease, cancer, chronic lower respiratory disorders, stroke, and accidental death.[21] Reported common causes of death due to vascular-related disease or complications were Alzheimer's disease, diabetes, kidney disease, and heart disease. Diabetes contributed to slightly more Canadian deaths (3.0% vs. 2.9%) in 2011, whereas the opposite was true for Alzheimer's disease (3.4% vs. 2.6%), kidney disease (1.8% vs. 1.4%), and heart disease (23.7% vs. 19.7%).[20,21]

Aside from mortality data, Canada and the United States both possess nationally representative surveys that provide useful information on cardiovascular risk factors in the respective countries: the US National Health and Nutrition Examination Survey (NHANES) and Canadian Health Measures Survey (CHMS).[56,57] Hypertension is one of the most important risk factors for stroke[58]; recent data shows that hypertension is more prevalent in the United States compared to Canada (31% vs. 23%).[59,60] The national databases (NHANES and CHMS) were used to compare hypertension prevalence and control between Canada and the US, and assess the impact of other cardiovascular risk factors on hypertension.[61] McAlister and colleagues found that the US NHANES sample had higher prevalence rates of hypertension (40.2% vs. 27.1%) compared to the CHMS sample. Additionally, uncontrolled hypertension (i.e. average blood pressure greater than 140/90 mm Hg) was more prevalent among the NHANES sample (57.6% vs. 41.4%), and thus saw higher prevalent rates of controlled or treated hypertension among the Canadian sample (58.6% vs. 42.4%) as a result thereof. Furthermore, several other studies that have compared Canada and US cardiovascular outcomes have found higher prevalence rates of hypertension in the US.[62-67] This may be indicative of a poorer cardiovascular health state in the US.

Other comparisons of cardiovascular risk factors between Canada and the United States include cholesterol and smoking.[68-72] National data shows that high levels of low-density lipoproteins (LDL) are more prevalent in the US (37.8% vs. 23%), but high total cholesterol is more prevalent in Canada (39% vs. 30%).[68-70] However, the age range at which this cholesterol data is based complicates the interpretation of these differences; the American data comes from only adults[69,70], whereas the Canadian data consists of an age range 6-79 years old[68]. Apart from cholesterol, recent 2013 data for smoking shows that the prevalence of current regular smokers is

slightly higher in Canada (19.3%) compared to the US (17.8%).[71,72] The Canadian data is more inclusive of age, as it includes regular smokers aged 12 and older, whereas the US data includes regular smoking adults only; these inclusion criteria may be the reason for the national differences in smoking prevalence.

Canada/US Comparison: Cardiovascular Outcomes and Processes of Care

Several previous studies have compared outcomes, quality of care, and service utilization between Canada and the United States for cardiovascular diseases, including acute myocardial infarction, heart disease, and stroke.[62-66]. Studies that compared heart failure (HF) outcomes identified more favorable short-term outcomes in the United States, compared to Canada, including lower unadjusted in-hospital mortality[62] (3.4% vs. 11.1%) and 30-day mortality[63] (8.9% vs. 10.7%), however, the mean length of stay among the American samples of both studies was significantly lower than the Canadian samples which makes the direct comparison of in-hospital mortality rates invalid [62,63]. However, the differences in short-term outcomes between Canada and the US was not reflected in longer-term outcomes of HF patients, such as 1-year mortality (32.2% vs. 32.3%).[63] Ko and colleagues[63] discussed that the differences between short-term and long-term outcomes may be because of differences in the allocation of services and resources between the two countries, with more intensive in-hospital care provided in the US, but better post-discharge care in Canada.

More intensive in-hospital care in the US was also common among studies comparing acute myocardial infarction (AMI) patients.[64-66] The authors found that US patients had undergone a more intensive hospital stay, which included higher rates of cardiac procedures. Tu et al. found that a differences in services utilization (i.e. coronary angiography, coronary artery bypass surgery, etc.) were reflected in slightly more favorable short-term mortality in the US

elderly (at least 65 years of age) compared to the Canadian elderly (30-day mortality: 21.4% vs. 22.3%), but did not result in better long-term outcomes (1-year mortality: 34.3% vs. 34.4%).[66] In summary, from previous comparative analyses of patients with cardiac-related diseases, US cohorts generally have better short-term outcomes, while longer-term outcomes are comparable between Canada and the US.[62-64,66]

Two trials (one each for HF and AMI, respectively) compared outcomes between Canada and the US patients[62,65] and found contradictory results compared to prior comparative analyses[63,64,66]. A 2004 study of the GUSTO-I trial (which compared the effectiveness of four thrombolytic treatments in patients with AMI[73]) comparing long-term mortality in Canada and US AMI patients showed better long-term outcomes in the US (5-year mortality: 19.6% vs. 21.4%).[65] The authors speculated that the more intensive regimen in the US, which entailed 3-fold higher rates of revascularization procedures, yielded better mortality in the US. Related to heart failure, a 2013 comparison of American and Canadian patients enrolled in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial showed that despite a similarity in unadjusted 30-day mortality rates between the American and Canadian samples (3.7% vs. 2.2%, p-value = 0.09), Canadians had lower odds (OR= 0.46) of 30-day mortality after adjustment for baseline factors.[62] Additionally, Canadians had a more improved functional status 30-days post-discharge as measured by a trial-related index score on quality of life, even after adjustment for age, sex, and baseline quality of life index score.

Specifically related to stroke, a 1999 comparison of aneurysmal subarachnoid hemorrhage patients between Canada and the United States in a trial testing the benefit of tirilazad mesylate (a medication designed to improve cerebral blood flow[74]), did not find any significant differences in survival 90 days after hospitalization.[66] A previous comparative

analyses of stroke care delivery conducted on North Carolina, USA and Ontario, Canada found that patients in North Carolina had a more intensive hospital stay (i.e. higher rates of tPA); however, outcomes were not compared (mortality or readmission) between the two regions.[75] To the best of our knowledge, previous studies have not compared stroke outcomes between Canada and the United States using population-based data sources, especially in regions that have implemented regional systems of stroke care delivery.

Study Aims

To compare acute stroke outcomes between Michigan and Ontario, this study has two primary aims:

- Aim 1: To assess the impact of applying an established administrative data-based risk adjustment model for in-hospital stroke mortality and 30-day readmission by comparing the distributions of crude (unadjusted) rates and risk-adjusted rates in both Michigan and Ontario hospitals.
- Aim 2: In order to produce comparable outcome rates in Michigan and Ontario, we generated directly standardized outcome rates for Ontario by applying the Michigan administrative data-based risk-adjustment model to the Ontario sample. This allowed us to determine whether the outcome (mortality and readmission) was different between Michigan and Ontario, having accounted for the differences in risk profile between the two health care systems.

CHAPTER 2: METHODS

Hospital Discharge Databases

Hospital discharge databases were used to identify acute stroke patients in both Michigan and Ontario. These databases include information on patient demographics, including age, sex, primary and secondary diagnoses, comorbid conditions, length of stay, and discharge destination.[76,77] Hospital-level information, including stroke center designation, is publically available and was linked to all hospitals in the two databases.[37,41]

Discharge data for the Michigan hospitals was accessed from the Michigan Department of Community Health (MDCH). Michigan hospitals submit all discharge abstracts to the Michigan Health & Hospital Association (MHA), who facilitates the compilation of all discharge data in the Michigan Inpatient Database (MIDB).[78] The data is then released to other organizations, such as the MDCH and the Healthcare Cost and Utilization Project (HCUP) which is organized by the Agency for Healthcare Research and Quality (AHRQ). In the US, HCUP maintains all state-level inpatient databases, like the MIDB in Michigan.[76] The State Inpatient Databases (SID) includes 47 of the US states, and 97% of all public hospitals across the US. The SID collects discharge abstract databases from participating health institutions, and formats patient-level data to be accessible for researchers. Regardless of payer source, the SID includes information on patient demographics, diagnoses, procedures, length of stay, admission and discharge characteristics, and medical costs. The Michigan version of the SID, MIDB, contains data on 150 Michigan hospitals, with 146 of these hospitals reporting information on all hospital stays of Michigan residents.[79] Currently to our knowledge, there are no previous reports regarding data quality of the MIDB.

The Canadian Institute for Health Information – Discharge Abstract Database (CIHI-DAD) represents the entire Ontario hospital patient population since all hospital discharges are included in this database.[80] By law, each acute inpatient facility is required to submit discharge information to the CIHI-DAD.[81] Because the data contains every stroke admission from every hospital in the province it can be regarded as population-based. Similar to their counterpart in Michigan, the CIHI-DAD includes information on patient demographics, admission and discharge information, diagnoses, past medical history, length of stay, and medical costs.[80] We accessed the CIHI-DAD from the Institute for Clinical Evaluative Sciences in Toronto, Ontario. By re-abstracting admissions records of 18 Ontario hospitals, a 2006 validation study of the CIHI-DAD found an agreement over 97% for non-medical information (demographics, admission/discharge information), and kappa scores of 0.81, 0.74, and 0.79 for primary diagnoses of cerebral infarction, non-specified stroke, and intracerebral hemorrhage, respectively.[82]

One notable difference between these databases in Michigan and Ontario that warranted special consideration before case ascertainment is the presence of unique patient identifiers. In the MIDB, a unique patient can only be identified within each institution using the medical record number (MRN), thus a single patient will have a different MRN for each hospital that she/he was admitted to. On the contrary, a unique patient in Ontario can be traced across all institutions using the ICES key number (IKN), which is a unique patient identifier centrally assigned by the Institute for Clinical Evaluative Sciences (ICES), not the hospitals themselves.

Case Ascertainment

The study sample consisted of hospitalized patients in Michigan or Ontario, during the 3-year period between January 1, 2010 and December 31, 2012 (inclusive), with a principal

diagnosis of acute stroke (ischemic or hemorrhagic) at time of discharge. If an eligible subject was admitted more than once in the 3-year period with a principal diagnosis of stroke, we excluded subsequent stroke-related hospitalizations and only utilized their first admission for analysis in this study. The CIHI-DAD uses a more recent revision of the International Classification of Disease (ICD) compared to the MIDB. In the MIDB, acute stroke discharges were identified using ICD-9 (International Classification of Disease, 9th Revision) codes 430, 431, 432, 433, 434, and 436, whereas in Ontario, the study sample was identified using ICD-10 (International Classification of Disease, 10th Revision) codes I60 (excluding I60.8), I61, I62, I63 (excluding I63.8), and I64. Descriptions of the codes used to identify strokes are listed in Table S1. The Centers for Disease Control and Prevention (CDC) publishes comparability ratios to show the impact on the number of events after implementation of a new ICD revision.[83] For any specific cause of death, a comparability ratio is defined as the number of deaths reported by the ICD-9 code divided by the number of deaths reported by the ICD-10 code. The comparability ratio published by the CDC for cerebrovascular diseases was 1.06, which indicates a 6% increase in the attribution of cerebrovascular disease as the underlying cause of death after ICD-10 implementation. Statistics Canada also reported 1.06 as the comparability ratio for cerebrovascular diseases.[84] Patients under the age of 18, or admitted to hospital for a transient ischemic attack were not included in this study. To ensure completeness of patient comorbidity information in both Michigan and Ontario databases, patient discharge records were retrospectively reviewed for three years prior to their index stroke admission date to search for comorbidity diagnosis codes. Since the unique patient identifier in Michigan can only be tracked within the same hospital, comorbidity data for Michigan stroke patients was only searched within

the same admitting hospital up to 3 years from the index stroke admission. ICD codes used to identify past medical history (patient comorbidity data) are seen in Table S2.

Study Exclusions

Prior to applying the study exclusions, we started with 70,259 Michigan and 40,976 Ontario stroke patients (Figure 1). Exclusions for this study are presented in Figure 1, along with the number of patients excluded following each criterion. The values in Figure 1 are mutually exclusive, since each exclusion criteria was applied in a stepwise manner, and not simultaneously. Only non-elective admissions are included in the analysis, which is standard practice of the Canadian Hospital Reporting Project, when reporting risk-adjusted 30-day in-hospital stroke mortality rates and 28-day stroke readmission rates for stroke[85]. In both the Michigan and Ontario datasets, elective admissions were identified by an "admission type" variable that identified an admission as being "elective". The total number of elective admissions that were subsequently excluded totaled 12,370 (17.6% of starting sample) Michigan patients and 622 (1.5%) Ontario patients. The substantial discrepancy in elective admissions between Michigan and Ontario is not easily explainable, but obviously is more liberally utilized in the MIDB. This discrepancy in elective admissions is further discussed in Chapter 4.

This study also excluded in-hospital strokes (i.e. stroke events that occur after being admitted for another reason) (Figure 1). Both datasets (MIDB and CIHI-DAD) have specific variables that identify all diagnoses as either pre-admit or post-admit, and was thus used to identify strokes occurring post-admission (i.e. in-hospital strokes); this excluded 3,804 (5.4% of starting sample) Michigan and 743 (1.8%) Ontario patients. As this study aims to rank and compare hospitals based on stroke outcome measures, excluding these patients would reduce the variation due to non-stroke diagnoses that occur before an in-hospital stroke event.[85] Since

hospice care focuses on end-of-life care, we excluded 2,957 (4.2%) Michigan and 275 (0.7%) Ontario patients discharged to palliative care since we were unable to track deaths once a patient was discharged from hospital.[87] CMS excludes patients enrolled in the Medicare Hospice program from their stroke mortality measures.[88] To ascertain an inception stroke cohort (patients with first strokes only), we employed a washout method previously undertaken in prior stroke research.[89] All patients who met the study inclusion criteria, but were admitted to hospital for stroke in the 3 year period prior to the start of the cohort, i.e. between January 1, 2007 and December 31, 2009 (inclusive), were excluded from the study. Therefore, a single patient could only be counted once in the denominator population for both primary outcomes - in-hospital mortality and 30-day readmission. Since previous strokes affect subsequent stroke outcomes, this methodology creates a study sample with a more similar cerebrovascular health state and baseline risk. The washout period applied to 150 (0.2%) Michigan patients and 1,491 (3.6%) Ontario patients; this difference in patients identified in Michigan and Ontario using the washout procedure[89] is likely due to the fact that the IKN in Ontario was able to track a unique patient over time and across multiple hospitals, whereas the MRN in Michigan was not.

Since readmission measures are used to gauge quality of care, planned readmissions (usually indicative of elective procedures) were not included (Figure 1). A specific variable exists in the CIHI-DAD that identifies all elective readmissions, and thus allowed us to perform the exclusion to 142 (0.3% of starting sample) Ontario patients using this variable; we sought alternatives to identify planned/elective readmissions in Michigan since a variable of this nature does not exist in the MIDB. As in a previous publication using the Michigan Stroke Registry[90], we used the following procedure codes (ICD-9) to help identify 2,357 (3.4%) Michigan patients

with elective readmissions: 0061, 0063, 380.2, 381.2, 382.2, 383, 384.1, and 384.2. Descriptions of these procedure codes are included in Table S3.

Twelve (0.01%) Michigan patients with missing hospital-level information (ex. stroke center certification, teaching status, or acute bed size) were excluded from this study. We also excluded hospitals with a stroke case load less than 75 patients over the three year period of case ascertainment (2010-2012), and as such eliminated 1,275 (1.8%) Michigan and 2,043 (5.0%) Ontario patients. As a measure of data quality, 12 (0.03%) Ontario patients were excluded for having an index admission listed chronologically after death; this procedure was conducted at the Institute for Clinical Evaluative Sciences before the data was given to investigators.

Outcome Definitions

There were two primary outcomes used in this study: in-hospital mortality and 30-day readmission following discharge. In-hospital mortality was defined as death due to any cause during the hospital stay after being admitted for stroke; 30-day readmission was a non-elective readmission to hospital, for any reason (not just stroke), within 30 days of discharge. The denominator population for the in-hospital mortality measure includes all stroke patients (satisfying study eligibility criteria listed in Figure 1) admitted to hospital from 2010 to 2012, whereas the denominator population for 30-day readmission includes stroke patients who were discharged alive, excluding those patients discharged to hospice/palliative care. Since unique patient tracking post-discharge is not possible in Michigan, we were unable to use 30-day mortality as an outcome in this study, and so instead relied on in-hospital mortality. Readmission in Michigan cannot be tracked across multiple health institutions, so only readmissions to the same facility as the index admission were included in Michigan. Although readmissions across different facilities can be tracked in Ontario, we also restricted Ontario readmissions to those at

the same facility as the index event to promote comparability between the two data sources. A 2014 population-based cohort study by Staples and colleagues found that approximately 82% of patients are readmitted to the original hospital.[91] Although this study was not disease-specific, it can be assumed that our capture of Ontario stroke readmissions was underestimated by approximately 18%.

Statistical Analyses: Descriptive

Due to privacy restrictions in Michigan and Ontario, the respective datasets remained in their own regions, and the datasets analyzed separately. Summary estimates of patient and hospital characteristics were compared between the two regions using a t-test for continuous variables, and chi-square tests for categorical variables.

Rationale for Risk Adjustment

When comparing health outcomes, like mortality and readmission, across health institutions or jurisdictions (i.e. hospitals or provinces), it is crucial to account for the differences in patient risk (i.e. presence of risk factors that pre-dispose patient to a particular health outcome).[92-94] Risk adjustment models are used to account for differences in patient characteristics that result in one patient having a higher likelihood of experiencing an outcome compared to another. If risk adjustment models account for all differences in patient risk, then any outcome variation after risk-adjustment can be assumed to be due to differences in hospital performance (i.e. quality) and not patient case mix[92]. In terms of aggregate-level data when comparing stroke outcomes across hospitals, comparability is essential since some hospitals, particularly referral centers, may treat patients that are more severe, or of higher risk profile, and would therefore have more adverse outcomes as a result.[95] It would have been unfair to compare

a hospital that does not treat the same patient risk profile as another hospital; risk-adjustment allows for a fair comparison across hospitals.

Statistical Analyses: Risk-Adjustment Models

CIHI implemented the Canadian Hospital Reporting Project (CHRP) to create outcome measures that are generalizable to all regions across Canada, and so that health officials can use these measures to compare their hospital, health jurisdiction, or province against others; these measures include both mortality and readmission.[85] Outcome measures reported by CIHI are risk-adjusted for age and sex, as well as comorbidities related to the specific disease; these outcome measures include various diseases (or conditions) in addition to stroke (i.e. AMI, obstetrics, surgery). In this study, we employed an established administrative data-based risk-adjustment model developed by CIHI for 30-day in-hospital stroke mortality and 28-day readmission after stroke.[96] Although these CIHI models are stroke-specific, it is important to note its similarities to the CIHI acute myocardial infarction (AMI) models with the same outcomes (30-day in-hospital mortality and 28-day readmission). Likenesses among the 30-day in-hospital mortality models for AMI and stroke include: age, gender, shock, renal failure, heart failure, cancer, and pulmonary edema. Similarities for the 28-day readmission models include: age, gender, diabetes, and renal failure. This model was selected because it was developed using the CIHI-DAD[85], which is our data source for Ontario stroke patients. Furthermore, the model can be applied to the MIDB (Michigan data source), since the variables required for the model can also be searched for in the MIDB. Currently to our knowledge, this model has not been validated outside of Canada. Variables included in the in-hospital mortality model are shown in Table 3 and include age, gender, stroke type, and past medical history of cancer, shock, heart failure, pulmonary edema, ischemic heart disease (acute and chronic), renal failure, liver disease, and

hospital stroke certification. Variables included in the 30-day readmission model included (Table 4) include age, gender, stroke type, diabetes, acute ischemic heart disease, renal failure, and hospital stroke certification. For this study, a stroke-certified center in Michigan included all comprehensive and primary stroke centers, and likewise in Ontario included all regional and district stroke centers. The ICD-10 codes used to identify past medical history in the Ontario data are listed in Table S2. These same risk-adjustment models were applied to the MIDB; however, past medical history/comorbidity data was identified using ICD-9 codes which are again shown in Table S2. Since the mortality and readmission outcomes in this study were binary (i.e. both outcomes are dichotomous), we used multivariable logistic regression models, which describe the relationship of the binary outcome with this set of covariates.[97]

Aim 1: Hospital-Level Risk Profiling Comparison

Hierarchical logistic regression models (HLM) were used to risk-adjust for differences in patient case mix and hospital characteristics in order to report hospital-level outcome rates in each region. Hierarchical, or multilevel modeling, accounts for patient clustering within hospitals.[98] Other advantages of multilevel modeling include the ability to profile individual hospitals based on the random effect intercepts and the fact that estimates from smaller hospitals are more reliable.[95,99] The hierarchical models (HLM) for mortality and readmission in aim 1 were generated using the PROC GLIMMIX procedure in SAS, and model fit was assessed using the Akaike information criterion (AIC).

Hospitals were ranked based on their performance with regard to stroke outcomes (in-hospital mortality and 30-day readmission) by generating hospital-specific predicted over expected (P/E) ratios[95] generated by applying the hierarchical CIHI administrative data-based logistic regression model to the Michigan and Ontario data separately. Patient-level predicted

and expected probabilities were aggregated and summed at each hospital to create the P/E ratios. This method of multilevel modeling (i.e. random effects model) uses hospital-specific random intercepts to account for hospital-specific effects on the outcome while accounting for patient case mix and clustering within each hospital.[95,100] The predicted probability is based on the estimated random intercept from each hospital after accounting for patient case mix.[95] The expected probability uses the average of all hospital intercepts within a specific region (e.g. all Michigan hospitals), and as such represents an estimation of the baseline risk at the hypothetical average hospital after accounting for case mix differences between hospitals. The P/E ratio quantifies each hospital's performance in relation to the average performing hospital with the same case mix profile; a P/E ratio less than one means that the hospital's performance exceeds that of the average hospital within that region (i.e. outcome at this hospital is more favorable than the average hospital). On the contrary, a P/E ratio greater than one means that the hospital's performance is inferior to that of the average hospital within that region (i.e. outcome at this hospital is less favorable than the average hospital). After hospitals were ranked according to their predicted over expected ratios for the mortality and readmission model, good and poor performing outlier hospitals in Michigan and Ontario were identified by the top 10% and bottom 10% respectively in each region (Tables 6 and 7), as previously defined by the American Stroke Association[95].

To calculate risk-adjusted outcome rates for each Michigan and Ontario hospital, the hospital-specific P/E ratios were multiplied by the observed outcome rate of all Michigan and Ontario patients, respectively. In order to assess the impact of applying the administrative data-based risk adjustment models on in-hospital mortality and 30-day readmission, we examined the

correlation between hospital-specific crude and risk-adjusted outcome rates, in both Michigan and Ontario separately, using the Spearman rank correlation.

Aim 2: Patient-Level Risk Standardization

Upon applying the risk-adjustment model to the Michigan and Ontario patient population separately as in aim 1, there were differences in risk profile between the Michigan and Ontario patient populations. The differences in risk profile occurred due to two different phenomena: firstly, the prevalence rates of the risk factors/comorbidities included in the models were very different (see Table 2), and secondly, the risk factors in the models had different magnitudes of effect (i.e. different adjusted odds ratios) on the outcomes in the two samples (see Tables 7 and 8). To be able to report comparable outcomes rates between Michigan and Ontario patients, we needed to account for the difference in risk profiles between the Michigan and Ontario patient populations. To do this, we applied the model parameter coefficients from the Michigan model to the Ontario cohort, to ensure that the effect magnitude (i.e. adjusted OR) of each model parameter was the same in both regions. In the process of applying the Michigan risk-adjustment model coefficients to the Ontario patients, clearly it makes no sense to apply specific hospital-specific intercepts from Michigan hospitals to those in Ontario. To alleviate this methodological problem, we used the generalized estimating equations (GEE) procedure to predict patient-specific probabilities, while account for patient clustering within hospitals without the necessity of generating hospital-specific random intercepts[95].

The GEE procedure was applied (CIHI model as used in aim 1) to the Michigan patient sample to generate patient-level predicted probabilities of experiencing the outcomes of interest. We then applied the model parameter coefficients from the Michigan GEE model (Tables 8 and 9) to the Ontario cohort, ensuring that the predicted probability of each Ontario patient was based

on Michigan parameter estimates (i.e. same parameter magnitudes of effect in Michigan and Ontario). Once the procedure was applied, differences in the patient-specific predicted probabilities between Michigan and Ontario would be due to differences in risk factor prevalence (i.e. risk profile of patients) between Michigan and Ontario. The GEE models for mortality and readmission in aim 2 were generated using the PROC GENMOD procedure in SAS, and fit was assessed using the quasi-likelihood information criterion (QIC); fit statistics are shown in Table 5. Since we applied the Michigan model coefficients to the Ontario population, we only listed the Michigan model QIC and c-statistic values.

After applying the Michigan-based model to the Ontario data, Michigan and Ontario patients were stratified into risk deciles, based on their predicted probabilities. The patient risk deciles were determined by the risk distribution of Michigan patients. To further adjust for differences in risk distribution between the Michigan and Ontario study populations, we then directly standardized the Ontario patient population to the risk distribution of the Michigan sample.[63] Standardization allows for the controlling of a confounding variable (differences in patient risk distribution in this situation) that prevents the outcomes from being comparable between two distinct populations.[101] Directly standardized outcome rates for the Ontario patient population were calculated by multiplying the proportion of Michigan patients within each risk stratum, by the crude Ontario outcome rate (mortality or readmission) in the corresponding risk stratum.[63] The stratum-specific standardized Ontario rates were summed to produce the standardized summary rates used for direct comparison to the crude Michigan outcome rate. This procedure allows the calculation of standardized Ontario outcome rates that would have been observed if the Ontario patients had the same risk distribution as the Michigan patients. We calculated 95% confidence intervals for the standardized summary outcome rates in both regions

and then determined if a statistically significant difference existed between Michigan and Ontario. A step-by-step outline describing the direct risk standardization procedure used in this analysis is shown in Figure 2. Ultimately, this direct risk standardization used in aim 2 was only able to standardize the magnitude of effect for each model covariate between the two patient samples, but other sources of variation still included the substantial differences in the risk factor frequencies (Table 2), and the fact that Ontario patients are on average staying seven days longer in hospital compared to Michigan patients (also shown in Table 2).

Ethics Approval

This study received institutional review board approval from Michigan State University, as well as the governing bodies of the databases used - Michigan Department of Community Health (Lansing, Michigan) and Institute for Clinical Evaluative Sciences (Toronto, Ontario).

CHAPTER 3: RESULTS

Descriptive Characteristics

Once the study exclusions were applied (Figure 1), our final cohort included 47,364 stroke patients from Michigan, USA and 35,648 stroke patients from Ontario, Canada. Patient- and hospital-level characteristics for the Michigan and Ontario cohorts are described in Table 2. Compared to Michigan, the Ontario cohort contained more male patients (50.8% vs. 49.1%), was older (mean age: 72.4y vs. 69.5y), and stayed longer in hospital (mean length of stay: 12.5d vs. 5.4d). Differences also existed in stroke diagnosis coding, as the Michigan sample had a significantly higher frequency of ischemic strokes (80.8% vs. 63.4%), and a significantly lower frequency of unidentifiable strokes (13.2% vs. 0.1%). Additionally, the Michigan sample had slightly lower frequencies of subarachnoid hemorrhages (4.6% vs. 5.5%), intracranial hemorrhages (9.4 vs. 11.5), and other hemorrhages (5.2% vs. 6.4%). There were large differences in the frequencies of comorbidities between the two datasets (Table 2). Ontario stroke patients had higher prevalence rates for acute ischemic heart disease (7.6% vs. 4.0%) and cancer (8.2% vs. 3.4%). In contrast, the Michigan cohort had substantially higher prevalence rates for chronic ischemic heart disease (30.7% vs. 13.8%), diabetes (34.0% vs. 27.0%), heart failure (16.0% vs. 8.7%), and renal failure (21.5% vs. 9.2%).

In terms of hospital-level characteristics (as presented in Table 2), the Michigan cohort was more frequently admitted to a stroke-certified center (65.9% vs. 60.0%) and teaching hospital (36.1% vs. 34.5%). The mean acute bed size of Michigan hospitals was also higher than Ontario hospitals (465.8 vs. 289.8).

The stroke-specific admissions rate in our patient samples (using the population figures from Table 1, and final sample figures from Figure 1) was 47.8 per 10,000 population and 26.1 per 10,000 population, respectively for Michigan and Ontario. Michigan had substantially lower unadjusted outcomes rates of in-hospital mortality (7.6% vs. 14.0%) as well as lower 30-day readmission rates (4.5% vs. 5.1%) (Table 2).

Length of Stay

The length of stay distributions for the Michigan and Ontario patient samples are shown in Figure 3. The median length of stay (LOS) was shorter in our Michigan sample (4.0 days vs. 7.0 days). Figure 3 shows an upward shift in the Ontario patient LOS distribution. In Michigan, 50% of patients were discharged (dead or alive) between 2-6 days after admission, whereas 50% of Ontario patients were discharged (dead or alive) between 4-13 days after admission. Discharge patterns for Michigan and Ontario stroke patients were vastly different especially in the first week after admission (Figure 4). The proportion of Michigan patients discharged alive after two days in hospital was more than double that of Ontario (24.2% vs. 11.6%). By the seventh day, 75% of Michigan patients had been discharged alive, compared to only 45% in Ontario. Thus, the 7-day in-hospital mortality rate was lower in Michigan compared to Ontario (6.2% vs. 8.7%).

Aim 1: Hospital-Level Risk Profiling Comparison

- To assess the impact of applying an established administrative data-based risk adjustment model for in-hospital stroke mortality and 30-day readmission by comparing the distributions of crude (unadjusted) rates and risk-adjusted rates in both Michigan and Ontario hospitals.

The fit statistics for both hierarchical models applied separately to the Michigan and Ontario samples are shown in Table 5. The Akaike Information Criterion (AIC) for the Michigan models was 21485.3 for the in-hospital mortality model, and 16030.3 for the 30-day readmission model. AIC values in Ontario were 26401.6 for in-hospital mortality and 14153.1 for 30-day readmission.

The results of the hierarchical logistic regression risk-adjustment model for in-hospital mortality for the two datasets are shown in Table 3. Age was shown to increase risk of in-hospital mortality for Michigan and Ontario stroke patients. In other words, for every one-year increase in age, a Michigan stroke patient's risk of in-hospital mortality increases by 2% (adjusted odds ratio = 1.02). Similarly in Ontario, each year increase in age constitutes a 4% increase in risk of in-hospital mortality (aOR = 1.04). Among the Michigan sample (Table 3), subarachnoid, intracranial, and other hemorrhages significantly increased the risk of in-hospital mortality compared to ischemic strokes (adjusted odds ratios were 7.63, 8.85, and 4.88, respectively). A similar phenomenon was discovered in the Ontario cohort, but the effect magnitudes were not as large for subarachnoid, intracranial, or other hemorrhages (adjusted odds ratios were 3.96, 3.81, 2.18, respectively) relative to ischemic strokes. Michigan stroke patients, who were diagnosed with unidentifiable (UTD) strokes, had similar risk of in-hospital mortality as ischemic stroke patients (aOR = 0.69, p-value = 0.72). This is also true for our Ontario sample (aOR = 1.00, p-value = 0.9671), but the increased frequency of Ontario UTD stroke patients compared to Michigan (13.2% vs. 0.1%) leads to the assumption that these patients are true ischemic stroke patients, but instead were classified as "unable to determine".

Acute ischemic heart disease (aOR = 2.25), cancer (aOR = 1.41), heart failure (aOR = 1.38), liver disease (aOR = 1.32), pulmonary edema (aOR = 2.40), renal failure (aOR = 1.30), and shock (aOR = 9.01) were associated with an increased risk of in-hospital mortality in Michigan (Table 3). For Ontario patients, AIHD (aOR = 1.24), cancer (aOR = 1.72), heart failure (aOR = 1.78), liver disease (aOR = 1.63), renal failure (aOR = 1.41), and shock (aOR = 2.37) increased risk of in-hospital mortality. Common between Michigan and Ontario, chronic ischemic heart disease was not associated with increased risk. Michigan had meaningfully larger adjusted odds ratios for AIHD (2.25 vs. 1.24), pulmonary edema (2.4 vs. 1.26), and shock (9.01 vs. 2.37). In terms of hospital-level characteristics, patients admitted to a stroke-certified center in Michigan or Ontario was not associated with risk of in-hospital mortality.

The results of the two hierarchical logistic regression risk-adjusted models for 30-day readmission are shown in Table 4. Age was not associated with risk of 30-day readmission in Michigan and Ontario. Michigan females had an approximately 16% reduced odds of being readmitted to hospital within 30 days of discharge (aOR = 0.84), relative to Michigan males. Gender was not associated with risk of 30-day readmission among Ontario patients. Relative to ischemic strokes in Michigan, subarachnoid (aOR = 0.54) and intracranial (aOR = 0.55) hemorrhages reduced risk of 30-day readmission by almost one half. Likewise was true in Ontario for intracranial hemorrhages (aOR = 0.75), although the risk reduction was not as significant as in Michigan. Diagnoses of other hemorrhage in Michigan (aOR = 1.47) and Ontario (aOR = 1.55) increased risk of 30-day readmission relative to ischemic strokes. Similarly in both regions, unidentifiable strokes presented similar risk of 30-day readmission as ischemic strokes.

Past medical history of acute ischemic heart disease, diabetes, and renal failure were all associated with increased risk of 30-day readmission in Michigan and Ontario (Table 4). Although not substantially different across regions, the adjusted odds ratios were higher in Ontario, compared to Michigan, for past medical history of diabetes (1.27 vs. 1.22) and renal failure (1.62 vs. 1.56), but lower for AIHD (1.33 vs. 1.51). Being admitted to a stroke-certified center in Michigan increased the risk of 30-day readmission (aOR = 1.60), but association of risk among Ontario patients admitted to stroke-certified centers presented a null finding (aOR = 0.98, p-value = 0.7449).

There was a total of 78 Michigan and 83 Ontario hospitals included in the hospital-level analysis. Each hospital's performance was quantified using a predicted over expected (P/E) ratio, which if less than 1, means that the hospital is performing better than the hypothetical average hospital with a similar case mix. Hospital-specific P/E ratios are shown in ascending sequence in Tables 6 and 7 for mortality and readmission, respectively. Stroke-certified centers are indicated by the bold text, while the shaded boxes enclose hospitals in the top and bottom 10%. We compared the distributions of the hospital-specific P/E ratios, as shown in Figures 5 and 6. For in-hospital mortality, the range of P/E ratios among Ontario hospitals was narrower than Michigan hospitals (Figure 5). In Michigan, there were a total of 8 positive outliers (top 10%), and 8 negative outliers (bottom 10%). The two worst performing hospitals (i.e. those with the highest mortality after adjusting for case mix) in Michigan and Ontario had P/E ratios of 1.8321 and 1.4323, respectively; while the two best performing hospitals (i.e. those with the lowest mortality after adjusting for case mix) had a P/E ratio of 0.5316 and 0.6354, respectively in Michigan and Ontario. The range of P/E ratios for the Ontario hospitals were substantially narrower than Michigan hospitals when using 30-day readmission as a performance measure

(Figure 6). We discuss possible causes of this phenomenon in Chapter 4. P/E ratios for 30-day readmission are listed in Table 7. After removing 3 outliers in Michigan, P/E ratios of the worst performing hospitals were 2.0684 and 1.15346, and best performing hospitals were 0.49828 and 0.86939, respectively for Michigan and Ontario. Figure 7 and 8 alluded to similar findings in Figures 5 and 6. Figure 7 (in-hospital mortality) shows the similar effect of risk-adjustment on Michigan and Ontario hospitals using the hierarchical logistic regression model; Michigan and Ontario hospitals have similar regression line slopes when plotting observed vs. risk-adjusted outcome rates. Only difference noted is the shift upward of Ontario hospital-specific rates, which is driven by the higher patient length of stay in Ontario. As displayed in Figure 8, risk adjustment had different effects on Michigan hospitals compared to Ontario hospitals when using 30-day readmission as the outcome. Regression line slopes are very different, which is consequence of the substantial narrowing of the hospital-specific P/E distribution among Ontario hospitals (Figure 6). This difference is elaborated on in Chapter 4.

For both primary outcomes, the hospital rank correlation between observed (crude) and risk-adjusted rates was higher in Ontario (Figure 7 and 8). The rank correlation between hospital-specific observed and risk-adjusted outcomes rates was quantified using the Spearman rank correlation. A Spearman rank correlation of 1 means that the hospital ranking of observed rates is identical to that of risk-adjusted rates. A lower hospital rank correlation in Michigan means that after risk-adjustment, there is a greater shift in hospital rankings among Michigan hospitals, compared to Ontario. Relative to Michigan, the Ontario hospital Spearman coefficient was higher for in-hospital mortality (0.95 vs. 0.84) and 30-day readmission (0.93 vs. 0.86).

Aim 2: Patient-Level Risk Standardization

- In order to produce comparable outcome rates in Michigan and Ontario, we generated directly standardized outcome rates for Ontario by applying the Michigan administrative data-based risk-adjustment model to the Ontario sample. This allowed us to determine whether the outcome (mortality and readmission) was different between Michigan and Ontario, having accounted for the differences in risk profile between the two health care systems.

Justification for using the GEE (generalized estimating equations) procedure to predict Michigan patient-specific probabilities is shown in Tables 8 (in-hospital mortality) and 9 (30-day readmission). By comparing the HLM (hierarchical logistic model) and GEE procedures, it is apparent that the adjusted odds ratios produced from these methods are very similar. The adjusted odds ratios generated from the GEE procedure were then applied to the Ontario patient population to produce Ontario patient-specific predicted probabilities to utilize for the direct standardization in Aim 2.

Upon using the Michigan patient risk distribution as the cut points of the risk deciles (Tables 10 and 11), we noticed little change in the patient proportions across all but two risk deciles between Michigan and Ontario for in-hospital mortality; the largest difference was approximately 2.5% more Ontario patients in the highest two risk deciles (Table 10). Therefore applying the Michigan model coefficients to the Ontario population only impacted in the highest two risk deciles. The unadjusted in-hospital mortality rate was higher in Ontario (14.0%), compared to Michigan (7.6%), but by directly standardizing the Ontario patients to the risk distribution of Michigan patients, the risk-standardized in-hospital mortality rate for the Ontario patient sample was 13.3%, exhibiting little change from the crude rate of 14.0%. This direct

standardization procedure had little effect on the overall risk-standardized in-hospital mortality rate in Ontario. There was substantial variation in stratum-specific observed in-hospital mortality rates among our Michigan sample, ranging from 1.7% in the lowest risk decile, to 29.2% in the highest risk decile. This was similarly the case in Ontario, as the observed rates of the lowest and highest risk deciles ranged from 3.4% to 31.0%.

The crude Ontario 30-day readmission rate increased from 5.1% to a risk-standardized rate of 5.3% after standardizing the Ontario patient population to the risk distribution of our Michigan sample (Table 11). The 5.3% Ontario figure was higher than the crude 30-day readmission rate of 4.5% in Michigan. There were clear distinctions between the risk distributions of Michigan and Ontario patients for readmission, opposed to the similarities of we found for in-hospital mortality. The proportion of Ontario patients nested within the risk deciles (cut points set by risk distribution of Michigan patients) ranged from 4.9% to 15.5%. Additionally, there was little variation in the stratum-specific observed readmission rates for Michigan and Ontario, in comparison to in-hospital mortality. There was a 7.5% difference in the observed readmission rate among the highest and lowest risk decile in Michigan; 4.5% was likewise the case in Ontario.

CHAPTER 4: DISCUSSION

This comparison of outcomes in hospitalized acute stroke patients between Michigan, USA and Ontario, Canada, provides both hospital-level and patient-level comparison, which highlight differences between the two health systems that complicate our interpretation of the outcomes under study. Our study shows how differences in health care structure between Canada and the United States can create fundamental differences in outcomes that hinder our ability to compare across the two systems (length of stay and in-hospital mortality, for example). Because the interpretations of the outcomes in this study are complicated, we cannot definitively determine which system produces more favorable outcomes. Aside from the previous Ontario and North Carolina comparison of processes of care[75], to the best of our knowledge, this is the first study that utilizes population-based data sources to compare stroke outcomes between Canada and the United States.

To compare outcomes between hospitals in each region (Michigan and Ontario), we calculated hospital-specific predicted over expected (P/E) ratios. The P/E ratio for each hospital quantifies its performance in relation to the hypothetical average performing hospital in their region with similar case mix. Risk-adjustment models were applied separately in each region, to examine the impact of risk adjustment (using the CIHI administrative model) on the hospital ranking of Michigan and Ontario hospitals. We found a greater variance in P/E ratios – both in-hospital mortality and 30-day readmission in Michigan hospitals compared to Ontario hospitals (Figures 5 and 6). More specifically, the distribution was drastically narrower among Ontario hospitals for the 30-day readmission outcome measure (Figure 6). Although the distribution of Ontario hospitals is shifted upward for in-hospital mortality (Figure 7), it is noticeable that risk-adjustment had a similar effect on Michigan and Ontario crude mortality rates (i.e. plots are

distributed in somewhat similar fashion although the Ontario hospitals are more closely plotted along the regression line). This is not the case for 30-day readmission (Figure 8). For Ontario hospitals, the distribution of P/E ratios is too small, and there is less than two percentage points between the lowest and highest risk-adjusted readmission rate among Ontario hospitals, as shown in Figure 6. Furthermore as displayed in Figures 6 and 7, Ontario hospitals had a higher Spearman rank correlation than Michigan hospitals for both mortality and readmission, respectively. This finding suggests that Ontario hospitals more closely resemble their average hospital, relative to Michigan hospitals and their own average.

As shown in Figures 5 and 6, it is quite apparent that the Ontario P/E ratios for the mortality and readmission models are so vastly different, suggesting that the significantly narrower range of Ontario hospital-specific P/E ratios for readmission (Figure 6) could be an artifact of the hierarchical logistic regression model, or suggest an error in the Ontario data used for the readmission model. Comparatively, the P/E ratio distributions for mortality between Michigan and Ontario hospitals are similar (Figure 5), but very different for readmission (Figure 6). The significant narrowing of Ontario hospital-specific P/E ratios from the readmission model may also have been the result of systematic differences between the Michigan and Ontario stroke patient populations (i.e. risk profile), whereby the hierarchical model employed would behave differently in Michigan compared to Ontario. Risk profile differences can be seen in Tables 8 and 9, listing noteworthy differences in adjusted odds ratios between Michigan and Ontario. The risk profile difference shown between Michigan and Ontario may be a true picture, but this difference could have been influenced by systematic differences in Michigan and Ontario administrative datasets, specifically related to the ascertainment of cases and past medical history (i.e. risk factor prevalence).

The multilevel logistic regression models we used for the hospital-level analysis quantifies the association of a binary outcome (i.e. mortality or readmission) with a set of known variables[97], in this case patient- and hospital-level characteristics. The prevalence of risk factors included in the model would have a direct impact on the model, and its output of P/E ratios for each hospital. As shown in Table 2, there is substantial variation in the prevalence of risk factors included in our mortality and readmission models. This variation is not necessarily the true snapshot of the cardiovascular health state among Michigan and Ontario patients, as there were systematic differences in how past medical information was acquired in the two datasets. As previously noted, the patient identifiers in Michigan (MRN) and Ontario (IKN) had unique characteristics; because the MRN in Michigan was only traceable within the admitting hospital, we were only able to search for past medical history within a single hospital. This was due to the fact that the Michigan hospitals themselves assign the MRN to patients, thereby not being traceable across multiple institutions; on the contrary the Ontario IKN is traceable across all institutions since the Institute of Clinical Evaluative Sciences centrally assigns it. Aside from patient identifiers, there are other potential drivers of differences in the prevalence of stroke-related risk factors. The Michigan dataset utilized ICD-9 diagnosis codes, whereas ICD-10 was used in Ontario. Published comparability ratios for risk factors included in our model are as follows: ischemic (chronic and acute) heart disease (0.99), diabetes (1.01), cancer (1.01), renal failure (1.30), liver disease (1.04), shock (1.19), heart failure (1.04), and pulmonary circulatory diseases (1.12).[83] Since some of these ratios are meaningfully different than 1, this could be another source of variation in risk factor reporting in Michigan and Ontario. Lastly, the different health care structures could contribute to this difference as well. In a multi-payer system as in the United States[1], there may be incentive for hospitals to more completely record medical history

on discharge abstracts, before submitting the information to insurance companies for remuneration; this would not apply in a universal health care system as in Canada[5].

Throughout the course of our analyses, we discovered differences for many variables in how patients included in the hospital discharge databases were being coded (i.e. principal diagnoses, admission type, past medical history, etc.). We also found huge differences among some of our exclusion criteria. Firstly, there were 11,748 more patients excluded in the MIDB (Michigan) compared to the CIHI-DAD (Ontario) for elective admissions; this accounted for about 17.6% and 1.5% of the starting samples, respectively. There are no clear explanations for this difference, but a similar code existed within the Michigan and Ontario datasets that identified the admission type as "elective". In a separate descriptive analysis, we identified over 80% of these elective admissions as having elective procedure codes (same procedure used to identify elective readmission as listed in Table S3), so the majority of these exclusions are truly elective admissions. In Michigan, admission type is acquired from the claims form that the hospital completes at time of discharge for each patient before sending the claim to the insurance company for remuneration.[103] The technical definition in the MIDB is "patient's condition permits adequate time to schedule services". In Ontario, admission type is acquired from data abstractors examining admission information retrospectively; abstractors base their determination of admission type solely from patient's status at admission.[104] The definition in Ontario is "patient on elective booking list" or "who have scheduled admission for treatment and/or assessment". The difference in variable definition (and its interpretation) could be a source of the discrepancy in elective admissions. Furthermore, it could also be the source of information to which is being used to determine admission type. Ontario abstractors solely use patient status at admission only to acquire admission type. Since more information is available in

Michigan (i.e. patient information from entire duration of hospital stay) when the claims form is being completed, it may lead to a more liberal use of the "elective" admission type. The exclusion for elective admissions was the largest discrepancy in our study, but there were other important differences. For example the number of in-hospital strokes that were identified and excluded varied considerably (3,804 (5.4%) and 743 (1.8%) in-hospital strokes, respectively for Michigan and Ontario). This also could be a difference in coding use between the two regions, because the variable we used to identify an in-hospital stroke was similar in the sense that it identified a stroke diagnosis as being present at admission or not. If the primary diagnosis was stroke, but was listed as not present at admission, we excluded these patients as having in-hospital strokes. Again, we can find no clear explanation for these differences, but this variable seems to be utilized more in Michigan, even though an in-hospital stroke was identified using a single variable with similar language in both the CIHI-DAD and MIDB. Potential sources of the coding usage differences are not obvious (for both elective admission and in-hospital strokes), but could be a result of how the variables are being interpreted by hospital officials who input the data. The number of patients being discharged to hospice was also different between the two regions, identifying 2,927 (4.2%) Michigan patients and 275 (0.7%) Ontario patients. Reasons for this discrepancy may not be result of administrative coding differences, but instead differences in the respective health care systems. Palliative care is covered in the United States for Medicare patients deemed as terminally ill by their physician, whereas this type of hospice coverage does not exist in Ontario.[102] In Ontario, palliative care is usually provided by specialized end-of-life care units within a hospital. Lastly, (as shown in Table S2), there was a difference in the number of patients excluded by the washout period we employed in this study to identify patients in our cohort that were admitted to hospital for a stroke between 2007 and

2009. This procedure excluded 150 (0.2%) patients in Michigan and 1,491 (3.6%) patients in Ontario. This difference can be attributed to the inability of the Michigan patient identifier to track past stroke admissions across other hospitals, and because of this, the number of Michigan patients being excluded is an underestimation of the true proportion of patients that have previously suffered from a stroke from 2007 to 2009. The accumulation of systematic differences between the Michigan and Ontario patient populations hinders our ability to make direct comparisons of the hospital-level analyses (aim 1), as well as the fact that the models were applied separately in each region. In the event that the datasets could be combined, region (i.e. Michigan or Ontario) could be included as a model covariate, and thus be able to directly compare patient-specific risk (predicted probability of experiencing outcome) between Michigan and Ontario patients, because any variation in the outcome caused by receiving care in different regions would be statistically accounted for in this instance.

In order to draw a direct outcome comparison across both patient populations (aim 2), we needed to account for the difference in risk profile between Michigan and Ontario (Tables 7 and 8). We applied the Michigan risk-adjustment model coefficient estimates from the GEE procedure (described previously in Chapter 2) to the Ontario patient population, so that the magnitude of effect of each risk factor was equal in both populations. To further promote comparability, we also used a patient-level direct standardization process[60] that enabled the calculation of a standardized outcome rate, had the Ontario patients possessed the same risk distribution as the Michigan patients. However, standardizing the Ontario patients to the risk distribution of the Michigan patients had little effect on the Ontario outcome, because we were unable to control for the fundamental difference in outcomes caused by the variation in patient length of stay (Figure 3), as well as the resounded differences in risk factor frequencies (Table

2). Despite the Michigan sample having a more favorable risk-standardized in-hospital mortality rate, this measure is not effective in portraying a fair comparison until we can effectively account for LOS. However, risk-standardized 30-day readmission rates were similar between Michigan and Ontario. The longer Ontario LOS is a result of the Canadian health care structure[5]; the longer stay in hospital is of no financial burden to the patient, or financial incentive to the hospital, so the physician is not obligated to discharge a patient earlier than necessary. More intensive short-term care may also be a result of the shorter hospital stay in Michigan, which was also noted for other cardiovascular diseases[60-63]. In this study, to alleviate the methodological pitfall of different lengths of stay between Michigan and Ontario, we explored the possibility of replacing in-hospital mortality with a time-specific outcome measure (ex. 3-day or 7-day in-hospital mortality), but was not possible since the same LOS disparity was found in the first seven days of hospital stay after stroke (Figure 4), as Michigan and Ontario hospitals exemplified unique discharge behaviors. Furthermore, because we are unable to track deaths in the MIDB once a patient was discharged from hospital, the 7-day in-hospital mortality rate may not be a reliable measure for 7-day post-stroke case fatality since this data does not capture deaths that occur after discharge. Thus 7-day in-hospital mortality is likely an underestimation of the true 7-day case fatality although we believe the difference is likely to be small. Additionally, the underestimation of the true 7-day post-stroke case fatality will be different because of the different proportions of patients being discharged to hospice (4.2% vs. 0.7%) between Michigan and Ontario. In contrast to in-hospital mortality, 30-day readmission is not directly confounded by patient length of stay, and may be a more suitable outcome to compare between Michigan and Ontario. Interpretation of the similarity in 30-day readmission rates may also prove challenging however. Because of the difference in LOS, a Michigan patient will be discharged earlier in the course of disease

compared to an Ontario patient, and therefore experience less days under hospitalized care before being discharged, and thus beginning the 30-day time interval to which a possible readmission is tracked. Canadians experiencing a longer hospital stay would be discharged later, and therefore the starting point of readmission tracking begins later in the natural history of the disease. As a result, we would expect 30-day readmission rates to be lower in Ontario. To create a fairer comparison, this could be countered by starting the "readmission clock" at either stroke onset or arrival date at the hospital.

Aside from the fundamental outcome differences between Michigan and Ontario, there are other limitations that are worth noting. Firstly, the use of administrative data has well known limitations when used to assess differences in stroke outcomes. The utilization of a stroke registry to ascertain clinical data would allow the inclusion of stroke severity (i.e. National Institutes of Health Stroke Scale) in our model, which has been shown to improve a model's predictive ability.[105] Clinical data may also include vital information such as arrival to hospital by ambulance, door-to-needle (DTN) times, more accurate past medical history, and more detailed information on the processes of care once they arrive at the hospital. Secondly, the Michigan and Ontario stroke outcomes reported may not reflect the remainder of their respective countries. By comparing acute myocardial infarction outcomes and services utilization in Canada and the United States, Ko et al. demonstrated regional-level disparities among different geographic areas of the United States.[64] A comparison of stroke-related mortality and readmission outcomes between other American and Canadian regions has not been conducted, so our outcomes may only be applicable to Michigan and Ontario, and not be representative of their nation as a whole. For example, according to national HCUP data from the United States, the 30-

day all-cause readmission rate for US stroke patients in 2011 was 13.7%.[106] Even though this includes elective readmissions, it is still far off from our 4.5% Michigan figure in Table 2.

In conclusion, we were able to demonstrate a cross-systems comparison of stroke outcomes, but lack of comparability hinders our interpretation of hospital- and patient-level risk-standardized outcomes. Comparing the Michigan and Ontario health systems using in-hospital mortality was complicated by the difference in LOS after stroke; 30-day mortality rates would be a better comparative measure. Despite the substantial variation in risk profile (i.e. risk factor frequencies and magnitudes of effect) between Michigan and Ontario stroke patients (as shown in Tables 2-3), we found risk-standardized readmission rates to be similar. The fundamental outcome differences between Michigan, USA and Ontario, Canada will hinder our ability to determine which system produced better outcomes until we can successfully account for the existing sources of variation (i.e. length of stay and risk factor frequencies).

APPENDICES

APPENDIX A

Tables

Table 1: Comparison of demographic, geographic, and health care characteristics between Michigan, USA and Ontario, Canada (2000-2013)

Characteristics	Michigan, USA	Ontario, Canada
Demographic		
Population, Total	9,909,877	13,678,700
65 and Older, %	15.0	15.6
GRP, $	432,573,000 USD	695,705,000 CDN
Rural Population, %	25.3	14.9
Geographic		
Land Area, km sq.	146,435	917,741
Health Care		
Hospitals		
Total, N	120	238
CSC & RSC, N	3	11
PSC & DSC, N	30	18
Stroke Hospitalizations		
Total, N	27,719	15,623
Unadjusted Stroke Admission Rate*	28	14.4
Adjusted Stroke Admission Rate*	25.5***	12.8****
Stroke Mortality		
Total, N	4,451	4,930
Proportion of All Deaths, %	5	5.5
Adjusted Stroke Mortality Rate**	38.7***	24***

Abbreviations: GRP - gross regional product, CSC - comprehensive stroke center (Mich.), PSC - primary stroke center (Mich.), RSC - regional stroke center (Ont.), DSC - district stroke center (Ont.)

*Per 10,000 population

**Per 100,000 population

***Age-adjusted

****Age- and sex-adjusted

Table 2: Regional comparison of patient- and hospital-level characteristics in the final Michigan and Ontario study samples.

Characteristics	Michigan (N = 47364)	Ontario (N = 35648)	P-Value
Patient-Level			
Gender, N (%)			<0.001
Male	23253 (49.1)	18092 (50.8)	
Female	24111 (50.9)	17556 (49.2)	
Age, Mean (Median)	69.5 (71.0)	72.4 (75.0)	<0.001
Age Category, N (%)			<0.001
18-24	180 (0.4)	107 (0.3)	
25-44	2338 (4.9)	1276 (3.6)	
45-64	14869 (31.4)	8518 (23.9)	
65-84	21719 (45.9)	18035 (50.6)	
≥85	8258 (17.4)	7712 (21.6)	
LOS, Mean (Median), Days	5.4 (4.0)	12.5 (7.0)	<0.001
Stroke Type, N (%)			<0.001
Ischemic	38246 (80.8)	22611 (63.4)	
Subarachnoid Hemorrhage	2178 (4.6)	1966 (5.5)	
Intracranial Hemorrhage	4450 (9.4)	4092 (11.5)	
Other Hemorrhage	2459 (5.2)	2288 (6.4)	
Unable To Determine	31 (0.1)	4691 (13.2)	
Past Medical History, N (%)			
AIHD	1879 (4.0)	2713 (7.6)	<0.001
Cancer	1599 (3.4)	2923 (8.2)	<0.001
CIHD	14537 (30.7)	4915 (13.8)	<0.001
Diabetes	16097 (34.0)	9610 (27.0)	<0.001
Heart Failure	7589 (16.0)	3094 (8.7)	<0.001
Liver Disease	812 (1.7)	418 (1.2)	<0.001
Pulmonary Edema	200 (0.4)	124 (0.4)	0.089
Renal Failure	10169 (21.5)	3285 (9.2)	<0.001
Shock	353 (0.8)	170 (0.5)	<0.001
Hospital-Level			
Stroke-Certified Center, N (%)	31202 (65.9)	21384 (60.0)	<0.001
Teaching Hospital, N (%)	17119 (36.1)	12299 (34.5)	<0.001
Hospital Bed Size, Mean (SD)	465.8 (280.1)	289.8 (165.9)	<0.001
Outcomes			
Crude Rate, N (%)			
In-Hospital Mortality	3617 (7.6)	4987 (14.0)	<0.001
30-Day Readmission	2117 (4.5)	1805 (5.1)	<0.001

Abbreviations: LOS - length of stay, AIHD - acute ischemic heart disease, CIHD - chronic ischemic heart disease, SD - standard deviation

NOTE: Stroke-certified centers in Michigan include comprehensive and primary stroke centers, and regional and district stroke centers in Ontario

Table 3: Regional comparison of adjusted odds ratios from the hierarchical logistic regression model used to profile hospital performance for in-hospital mortality.

Characteristics	Michigan (95% CI)	P-Value	Ontario (95% CI)	P-Value
Patient-Level				
Age (Years)	1.02 (1.02-1.03)	<0.0001	1.04 (1.03-1.04)	<0.0001
Gender				
Male	REF		REF	
Female	1.00 (0.93-1.08)	0.9881	1.05 (0.98-1.12)	0.1516
Stroke Type				
Ischemic	REF		REF	
Subarachnoid Hemorrhage	7.63 (6.70-8.70)	<0.0001	3.96 (3.47-4.52)	<0.0001
Intracranial Hemorrhage	8.85 (8.09-9.69)	<0.0001	3.81 (3.50-4.15)	<0.0001
Other Hemorrhage	4.88 (4.32-5.52)	<0.0001	2.18 (1.94-2.45)	<0.0001
Unable To Determine	0.69 (0.09-5.22)	0.7182	1.00 (0.90-1.11)	0.9671
Past Medical History				
AIHD				
No	REF		REF	
Yes	2.25 (1.94-2.62)	<0.0001	1.24 (1.10-1.40)	0.0006
Cancer				
No	REF		REF	
Yes	1.41 (1.18-1.69)	0.0002	1.72 (1.56-1.90)	<0.0001
CIHD				
No	REF		REF	
Yes	0.92 (0.85-1.01)	0.0772	1.00 (0.90-1.10)	0.9483
Heart Failure				
No	REF		REF	
Yes	1.38 (1.24-1.52)	<0.0001	1.78 (1.61-1.97)	<0.0001
Liver Disease				
No	REF		REF	
Yes	1.32 (1.05-1.67)	0.0199	1.63 (1.26-2.11)	0.0003
Pulmonary Edema				
No	REF		REF	
Yes	2.40 (1.67-3.45)	<0.0001	1.26 (0.81-1.97)	0.2916
Renal Failure				
No	REF		REF	
Yes	1.30 (1.19-1.42)	<0.0001	1.41 (1.28-1.56)	<0.0001
Shock				
No	REF		REF	
Yes	9.01 (7.05-11.52)	<0.0001	2.37 (1.67-3.38)	<0.0001
Hospital-Level				
Stroke-Certified Center				
No	REF		REF	
Yes	1.02 (0.83-1.27)	0.83	1.03 (0.89-1.20)	0.661

Abbreviations: AIHD - acute ischemic heart disease, CI – confidence interval, CIHD - chronic ischemic heart disease, REF - reference

Table 4: Regional comparison of adjusted odds ratios from the hierarchical logistic regression model used to profile hospital performance for 30-day readmission.

Characteristics	**Michigan (95% CI)**	**P-Value**	**Ontario (95% CI)**	**P-Value**
Patient-Level				
Age (Years)	1.00 (0.99-1.00)	0.1787	1.00 (1.00-1.01)	0.0512
Gender				
Male	REF		REF	
Female	0.84 (0.76-0.92)	0.0003	1.00 (0.91-1.11)	0.9314
Stroke Type				
Ischemic	REF		REF	
Subarachnoid Hemorrhage	0.54 (0.40-0.72)	<0.0001	0.87 (0.68-1.12)	0.2814
Intracranial Hemorrhage	0.55 (0.46-0.67)	<0.0001	0.75 (0.63-0.89)	0.0011
Other Hemorrhage	1.47 (1.24-1.76)	<0.0001	1.55 (1.31-1.84)	<0.0001
Unable To Determine	0.87 (0.12-6.54)	0.8946	1.10 (0.95-1.27)	0.1867
Past Medical History				
AIHD				
No	REF		REF	
Yes	1.51 (1.27-1.81)	<0.0001	1.33 (1.13-1.55)	0.0007
Diabetes				
No	REF		REF	
Yes	1.22 (1.11-1.34)	<0.0001	1.27 (1.14-1.41)	<0.0001
Renal Failure				
No	REF		REF	
Yes	1.56 (1.40-1.72)	<0.0001	1.62 (1.41-1.86)	<0.0001
Hospital-Level				
Stroke-Certified Center				
No	REF		REF	
Yes	1.60 (1.17-2.19)	0.0036	0.98 (0.87-1.10)	0.7449

Abbreviation: AIHD - acute ischemic heart disease, CI – confidence interval, REF - reference

Table 5: Fit statistics for all models performed in aims 1 and 2.				
Region	Outcome	AIC (Aim 1)	QIC (Aim 2)	C-Statistic
Michigan	In-Hospital Mortality	21485.33	21848.63	0.784
	30-Day Readmission	16030.26	17040.4	0.626
Ontario	In-Hospital Mortality	26401.56	N/A	N/A
	30-Day Readmission	14153.11	N/A	N/A

Table 6: List of predicted over expected ratios (in ascending sequence) used to quantify hospital performance for in-hospital mortality.

Michigan, USA (N = 78)			Ontario, Canada (N = 83)		
0.53697	0.91581	**1.21586**	**0.63543**	**0.9334**	**1.1069**
0.54937	0.91606	1.22258	**0.69513**	0.93484	1.12166
0.60038	0.92451	1.2463	**0.69953**	0.94597	1.13595
0.60455	**0.95912**	1.25339	**0.70475**	0.95035	**1.163**
0.609	0.97572	1.33597	0.73836	0.95552	**1.1754**
0.64701	0.98092	1.39002	0.73981	0.9635	1.17742
0.6577	**0.99091**	1.41329	**0.77114**	0.97232	**1.18183**
0.66042	1.0105	1.45983	0.78168	0.98436	1.19054
0.66651	**1.01156**	1.46377	0.78825	0.99545	1.22257
0.67282	**1.01272**	**1.47857**	0.78888	0.99573	**1.22985**
0.6972	1.01752	1.51295	**0.80435**	0.99933	1.23697
0.73448	**1.03166**	**1.51307**	0.81535	1.00683	1.23943
0.782	1.04245	**1.52404**	0.82295	1.00782	1.30554
0.79568	1.04796	**1.56347**	0.83997	**1.01278**	**1.31526**
0.80423	**1.05319**	**1.72592**	**0.84019**	1.01598	1.32057
0.80797	**1.05916**	1.74282	0.8475	1.01858	**1.32884**
0.8104	**1.07923**	**1.75209**	**0.84929**	1.02634	1.33087
0.82466	**1.08201**	1.85382	0.85765	**1.02854**	**1.35825**
0.82727	1.10248		0.87147	1.02875	1.36426
0.83001	1.11916		0.88436	1.04129	1.36922
0.83042	**1.12547**		0.88477	1.04557	**1.40873**
0.83212	**1.13116**		**0.88945**	1.04655	1.42028
0.83469	**1.14224**		0.88977	**1.04842**	**1.43232**
0.84804	1.14953		0.89349	**1.06274**	
0.86832	1.16775		0.89667	**1.07702**	
0.88566	1.16841		0.89914	1.08553	
0.88849	1.17547		**0.90281**	1.09514	
0.89916	1.17742		**0.90713**	1.09782	
0.90476	1.19011		0.91458	**1.10176**	
0.90847	1.20849		**0.91666**	**1.10513**	

NOTE: Shaded values indicate positive and negative outliers (top and bottom 10%, respectively), and bolded values indicate stroke-certified centers.

Table 7: List of predicted over expected ratios (in ascending sequence) used to quantify hospital performance for 30-day readmission.

Michigan, USA (N = 78)			Ontario, Canada (N = 83)		
0.49828	**0.84523**	1.25527	**0.86939**	0.98568	1.01747
0.53558	**0.85274**	1.27221	**0.88865**	0.98632	**1.01779**
0.54475	**0.89919**	**1.33097**	0.92937	**0.98704**	1.02049
0.56081	**0.8995**	1.35442	0.92955	0.98774	1.02268
0.566	**0.90552**	1.38007	**0.93498**	0.98791	1.02369
0.57724	**0.91193**	1.38157	0.94808	0.98879	1.02649
0.59477	0.91845	1.46017	0.94912	0.99068	1.02936
0.59613	**0.93472**	**1.4769**	0.95177	0.99284	**1.0354**
0.63054	**0.94012**	1.51552	0.95318	0.99338	**1.03867**
0.63348	0.95814	1.57243	0.95792	0.99412	**1.04085**
0.67537	**0.96268**	**1.60505**	0.96455	0.99447	1.04551
0.68285	0.97037	1.66689	**0.96535**	**0.99558**	1.04687
0.69258	0.9885	1.72271	**0.96711**	0.99714	**1.05115**
0.69872	**0.99024**	**1.93778**	0.96824	0.99837	1.05197
0.72755	**0.9978**	**2.0684**	0.972	0.99868	**1.06573**
0.73323	1.00835	**5.22967**	**0.9729**	**1.00017**	**1.06794**
0.73886	1.01012	5.42608	0.97321	1.00029	**1.07331**
0.7577	**1.04519**	7.71385	0.9733	**1.00153**	**1.0757**
0.75848	1.04765		**0.97491**	1.00364	**1.09861**
0.76927	1.05554		**0.97757**	**1.0049**	1.09943
0.77113	1.05654		0.978	1.00496	1.09961
0.77638	1.09923		0.97815	**1.00534**	1.1061
0.78923	**1.10792**		**0.97893**	1.00671	1.15346
0.79105	1.15418		0.98215	1.00717	
0.79668	**1.16849**		0.98236	**1.00975**	
0.80146	1.16995		0.98244	1.01142	
0.81546	**1.17389**		0.98294	**1.01356**	
0.82417	1.17693		**0.98335**	1.0136	
0.83493	1.23083		**0.98381**	1.01362	
0.84342	1.23254		**0.98478**	1.01653	

NOTE: Shaded values indicate positive and negative outliers (top and bottom 10%, respectively), and bolded values indicate stroke-certified centers.

Table 8: Comparison of adjusted odds ratios for the Michigan sample, generated from the hierarchical logistic regression (HLM) and generalized estimating equations (GEE) methods for in-hospital mortality.

Characteristics	HLM Method (95% CI)	P-Value	GEE Method (95% CI)	P-Value
Patient-Level				
Age (Years)	1.02 (1.02-1.03)	<0.0001	1.02 (1.02-1.03)	<0.0001
Gender				
Male	REF		REF	
Female	1.00 (0.93-1.08)	0.9881	1.00 (0.93-1.07)	0.9804
Stroke Type				
Ischemic	REF		REF	
Subarachnoid Hemorrhage	7.63 (6.70-8.70)	<0.0001	7.27 (5.52-9.58)	<0.0001
Intracranial Hemorrhage	8.85 (8.09-9.69)	<0.0001	8.36 (7.46-9.35)	<0.0001
Other Hemorrhage	4.88 (4.32-5.52)	<0.0001	4.63 (3.81-5.63)	<0.0001
Unable To Determine	0.69 (0.09-5.22)	0.7182	0.64 (0.04-9.79)	0.7484
Past Medical History				
AIHD				
No	REF		REF	
Yes	2.25 (1.94-2.62)	<0.0001	2.17 (1.87-2.51)	<0.0001
Cancer				
No	REF		REF	
Yes	1.41 (1.18-1.69)	0.0002	1.37 (1.17-1.62)	0.0001
CIHD				
No	REF		REF	
Yes	0.92 (0.85-1.01)	0.0772	0.93 (0.85-1.01)	0.085
Heart Failure				
No	REF		REF	
Yes	1.38 (1.24-1.52)	<0.0001	1.35 (1.22-1.50)	<0.0001
Liver Disease				
No	REF		REF	
Yes	1.32 (1.05-1.67)	0.0199	1.31 (1.06-1.63)	0.0125
Pulmonary Edema				
No	REF		REF	
Yes	2.40 (1.67-3.45)	<0.0001	2.33 (1.66-3.27)	<0.0001
Renal Failure				
No	REF		REF	
Yes	1.30 (1.19-1.42)	<0.0001	1.29 (1.16-1.43)	<0.0001
Shock				
No	REF		REF	
Yes	9.01 (7.05-11.52)	<0.0001	8.51 (6.18-11.71)	<0.0001
Hospital-Level				
Stroke-Certified Center				
No	REF		REF	
Yes	1.02 (0.83-1.27)	0.83	0.97 (0.78-1.21)	0.7769

Abbreviations: AIHD - acute ischemic heart disease, CIHD - chronic ischemic heart disease, REF - reference

Table 9: Comparison of adjusted odds ratios for the Michigan sample, generated from the hierarchical logistic regression (HLM) and generalized estimating equations (GEE) modeling methods for 30-day readmission.

Characteristics	HLM Method (95% CI)	P-Value	GEE Method (95% CI)	P-Value
Patient-Level				
Age	1.00 (0.99-1.00)	0.1787	1.00 (0.99-1.00)	0.2299
Gender				
Male	REF		REF	
Female	0.84 (0.76-0.92)	0.0003	0.85 (0.77-0.92)	0.0002
Stroke Type				
Ischemic	REF		REF	
Subarachnoid Hemorrhage	0.54 (0.40-0.72)	<0.0001	0.56 (0.43-0.73)	<0.0001
Intracranial Hemorrhage	0.55 (0.46-0.67)	<0.0001	0.57 (0.48-0.68)	<0.0001
Other Hemorrhage	1.47 (1.24-1.76)	<0.0001	1.44 (1.13-1.83)	0.0035
Unable To Determine	0.87 (0.12-6.54)	0.8946	0.88 (0.17-4.69)	0.8853
Past Medical History				
AIHD				
No	REF		REF	
Yes	1.51 (1.27-1.81)	<0.0001	1.54 (1.32-1.80)	<0.0001
Diabetes				
No	REF		REF	
Yes	1.22 (1.11-1.34)	<0.0001	1.21 (1.11-1.32)	<0.0001
Renal Failure				
No	REF		REF	
Yes	1.56 (1.40-1.72)	<0.0001	1.55 (1.33-1.81)	<0.0001
Hospital-Level				
Stroke-Certified Center				
No	REF		REF	
Yes	1.60 (1.17-2.19)	0.0036	1.82 (1.15-2.88)	0.0106

Abbreviation: AIHD - acute ischemic heart disease, REF - reference

Table 10: Direct standardization procedure to produce comparable in-hospital mortality rates between Michigan, USA and Ontario, Canada

Risk Decile Range*	Michigan, USA Study Sample, n (%)	Mortality, n (%)	Ontario, Canada* Study Sample, n (%)	Mortality, n (%)	Direct Standardization**	Standardized Ontario Rate, %
X <= 0.024594	4787 (10.1)	79 (1.7)	3476 (9.8)	119 (3.4)	0.101 x 3.4	0.35
0.024594 < X <= 0.029453	4687 (9.9)	81 (1.7)	3137 (8.8)	181 (5.8)	0.099 x 5.8	0.57
0.029453 < X <= 0.034083	4779 (10.1)	103 (2.2)	3270 (9.2)	216 (6.6)	0.101 x 6.6	0.67
0.034083 < X <= 0.039126	4680 (9.9)	140 (3.0)	3154 (8.9)	276 (8.8)	0.099 x 8.8	0.87
0.039126 < X <= 0.044446	4680 (9.9)	160 (3.4)	3491 (9.8)	328 (9.4)	0.099 x 9.4	0.93
0.044446 < X <= 0.050790	4818 (10.2)	204 (4.2)	3871 (10.9)	507 (13.1)	0.102 x 13.1	1.34
0.050790 < X <= 0.061373	4718 (10.0)	264 (5.6)	3151 (8.8)	532 (16.9)	0.100 x 16.9	1.69
0.061373 < X <= 0.10586	4743 (10.0)	383 (8.1)	3242 (9.1)	647 (20.0)	0.100 x 20.0	2
0.10586 < X <= 0.20310	4735 (10.0)	822 (17.4)	4412 (12.4)	802 (18.2)	0.100 x 18.2	1.82
X > 0.20310	4737 (10.0)	1381 (29.2)	4444 (12.5)	1379 (31.0)	0.100 x 31.0	3.1
Total	47364 (100)	3617 (7.6)	35648 (100)	4987 (14.0)		13.32
Standardized Mortality Rate, % (95% CI****)		**7.6 (7.4-7.9)**				**13.3 (13.0-13.7)*** **

*Patient risk was ascertained from the patient-level predicted probability of experiencing the outcome. The Michigan risk distribution was used to calculate the deciles cut points; after using Michigan coefficients to produce Ontario patient probabilities, Ontario patients were also nested in the risk deciles.

**Calculated by multiplying the proportion of Michigan patients in a specific stratum with the Ontario observed mortality rate in the same strata.

***Standardized to the Michigan patient risk distribution.

****95% confidence interval = $P \pm 1.96\sqrt{[(P(1-P))/N]}$, P = proportion, N = total sample size

Table 11: Direct standardization procedure to produce comparable 30-day all readmission rates between Michigan, USA and Ontario, Canada						
Risk Decile Range*	Michigan, USA Study Sample, n (%)	Readmission, n (%)	Ontario, Canada* Study Sample, n (%)	Readmission, n (%)	Direct Standardization**	Standardized Ontario Rate, %
X <= 0.023337	4697 (9.9)	122 (2.6)	5535 (15.5)	244 (4.4)	0.099 x 4.4	0.44
0.023337 < X <= 0.027146	4791 (10.1)	139 (2.9)	4825 (13.5)	225 (4.7)	0.101 x 4.7	0.47
0.027146 < X <= 0.030975	4721 (10.0)	157 (3.3)	3693 (10.4)	138 (3.7)	0.100 x 3.7	0.37
0.030975 < X <= 0.039575	4865 (10.3)	151 (3.1)	4433 (12.4)	238 (5.4)	0.103 x 5.4	0.55
0.039575 < X <= 0.041792	4634 (9.8)	171 (3.7)	3225 (9.1)	153 (4.7)	0.098 x 4.7	0.46
0.041792 < X <= 0.047662	4641 (9.8)	197 (4.2)	3766 (10.6)	185 (4.9)	0.098 x 4.9	0.48
0.047662 < X <= 0.049714	4877 (10.3)	207 (4.2)	2829 (7.9)	113 (4.0)	0.103 x 4.0	0.41
0.049714 < X <= 0.058168	4639 (9.8)	223 (4.8)	2874 (8.1)	161 (5.6)	0.098 x 5.6	0.55
0.058168 < X <= 0.071354	4780 (10.1)	274 (5.7)	2715 (7.6)	192 (7.1)	0.101 x 7.1	0.71
X > 0.071354	4719 (10.0)	476 (10.1)	1753 (4.9)	156 (8.9)	0.100 x 8.9	0.89
Total	47364 (100)	2117 (4.5)	35648 (100)	1805 (5.1)		5.34
Standardized Readmission Rate, % (95% CI****)		**4.5 (4.3-4.7)**				**5.3 (5.1-5.6)*** **

* Patient risk was ascertained from the patient-level predicted probability of experiencing the outcome. The Michigan risk distribution was used to calculate the deciles cut points; after using Michigan coefficients to produce Ontario patient probabilities, Ontario patients were also nested in the risk deciles.

**Calculated by multiplying the proportion of Michigan patients in a specific stratum with the Ontario observed mortality rate in the same stratum.

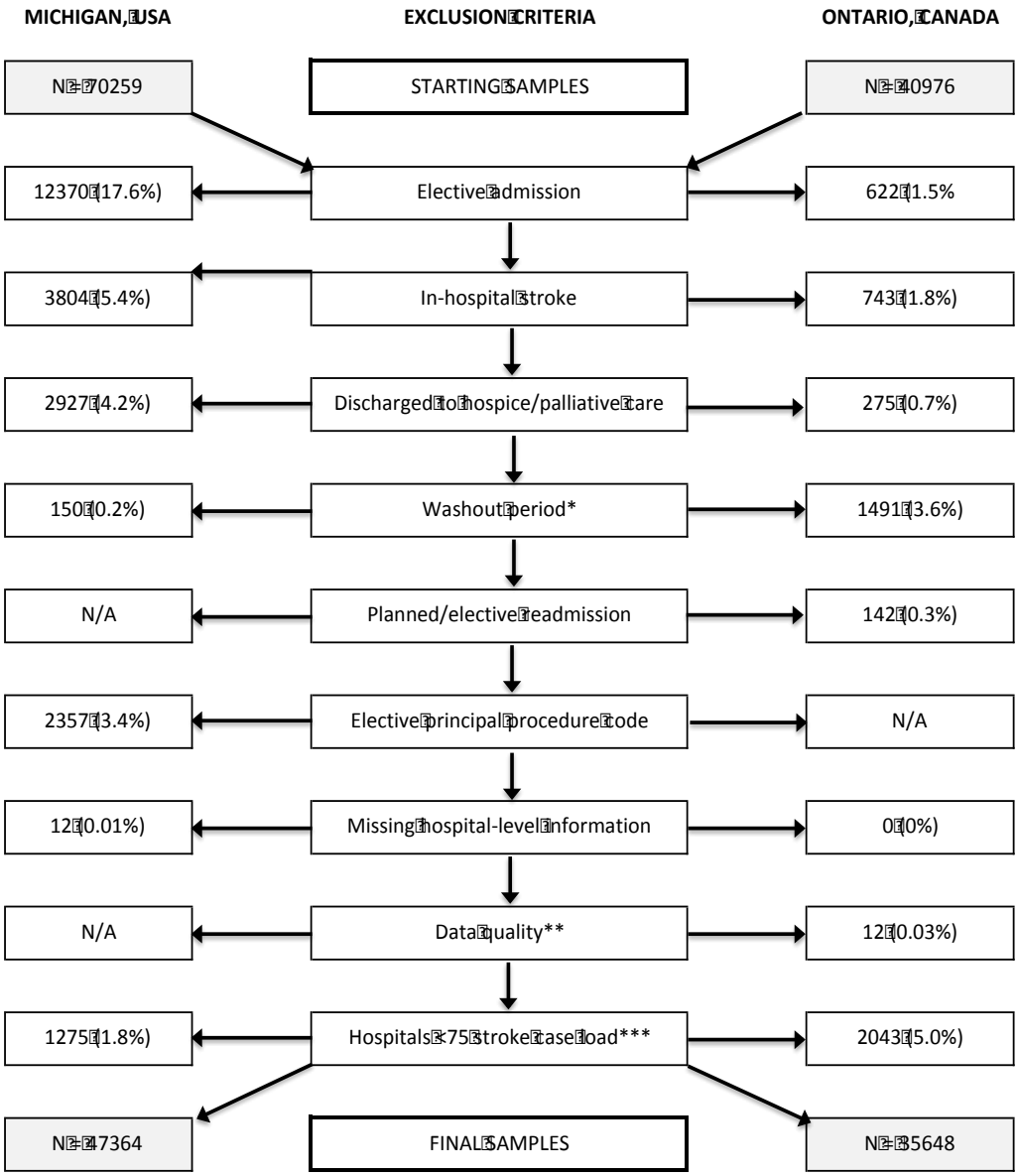
***Standardized to the Michigan patient risk distribution.

****95% confidence interval = $P \pm 1.96\sqrt{[(P(1-P))/N]}$, P = proportion, N = total sample size

APPENDIX B

Figures

Figure 1: Exclusions applied to the Michigan and Ontario study samples (in the order shown)



*Washout period applies to all patients admitted for acute stroke between January 1, 2007 and December 31, 2009 (inclusive).

**Index admission after death.

***Less than 75 stroke cases over 3-year period (2010-2012).

N/A: Exclusion criteria not available, or already performed by governing institution before data provided to investigators.

NOTE: Values in parentheses are percentages of starting sample being excluded by the exclusion criterion.

Figure 2: Outline of the procedure used to account for differences in risk profile and distribution between the Michigan and Ontario patient samples.

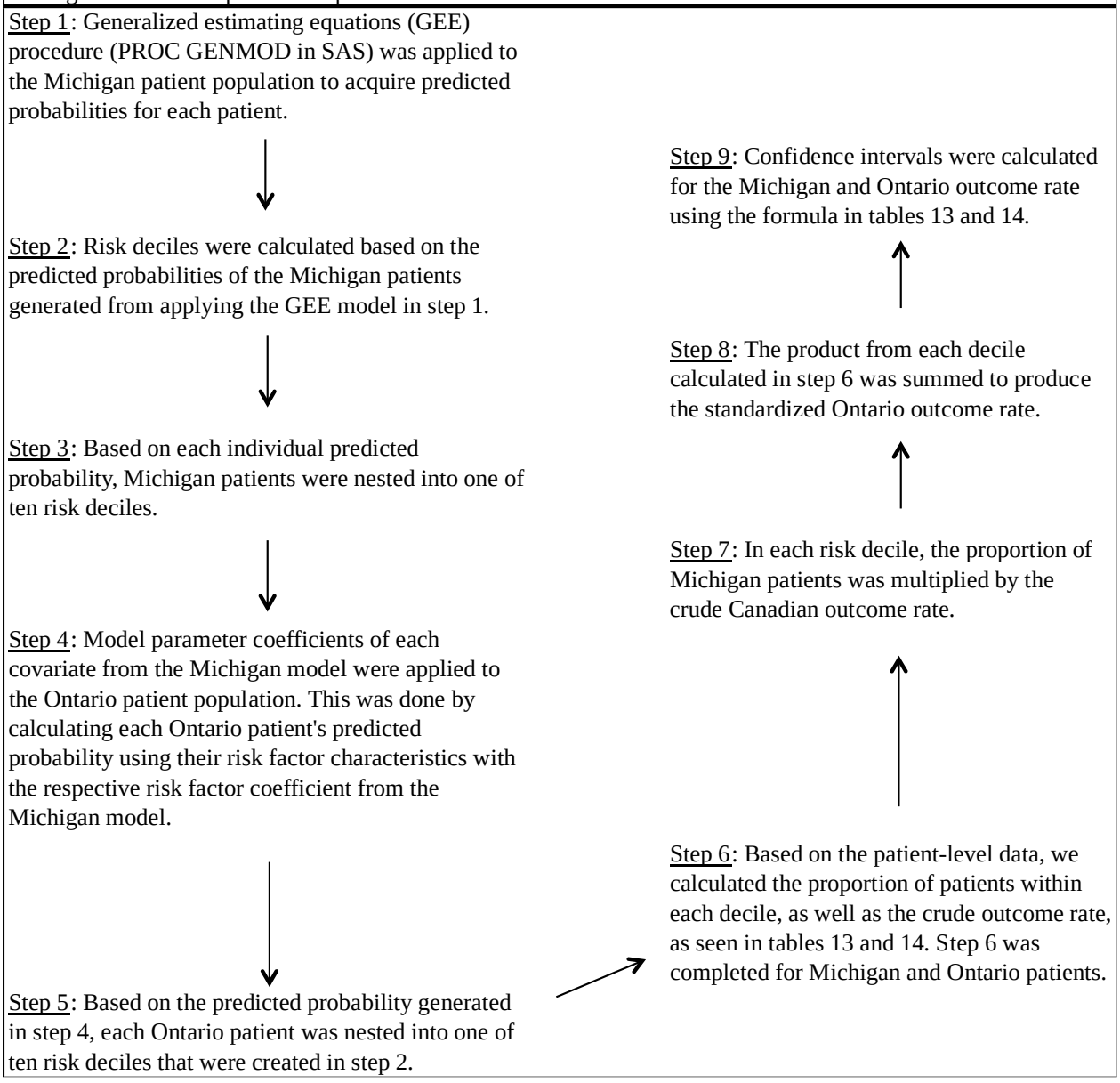
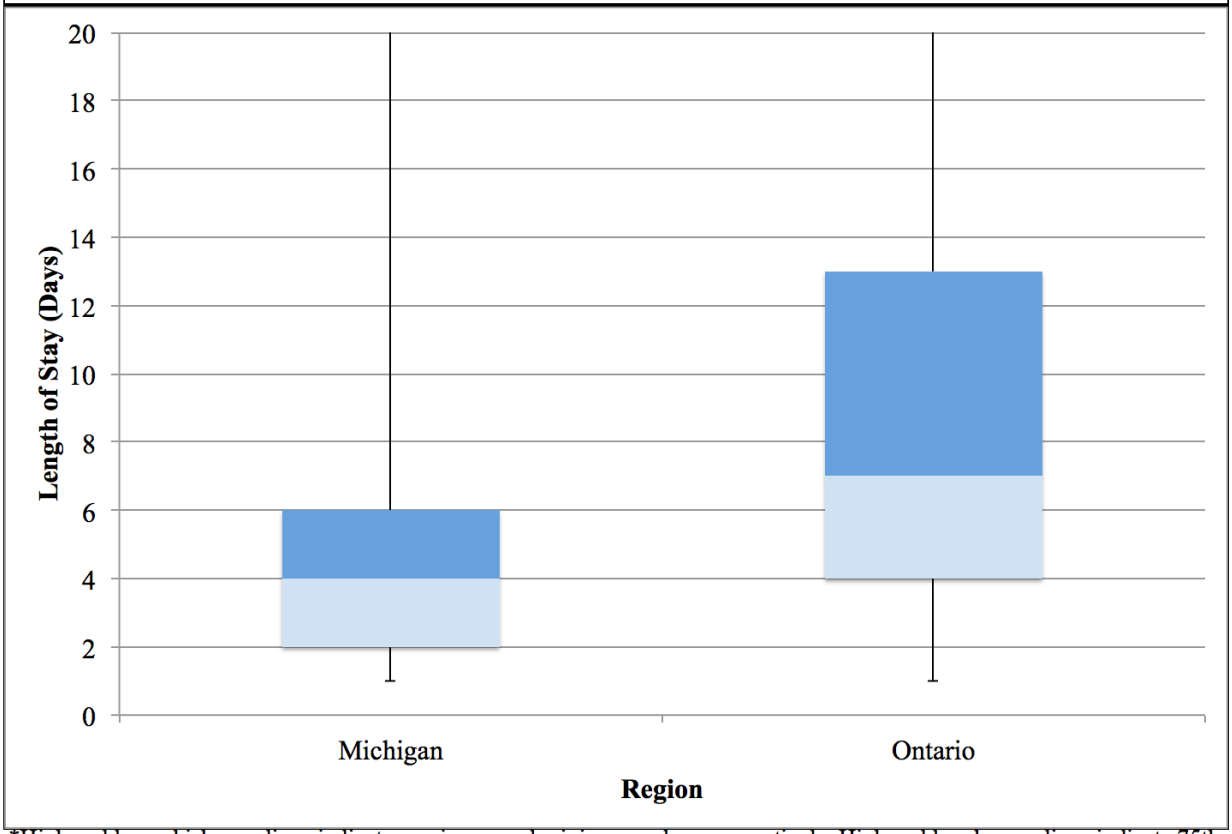


Figure 3: Length of stay distributions for the Michigan and Ontario patient samples.*



*High and low whisker endings indicate maximum and minimum values, respectively. High and low box endings indicate 75th and 25th percentiles, respectively. Median is indicated by center box line.
NOTE: Maximum length of stay for Michigan and Ontario was 149 and 675 days, respectively.

Figure 4: Discharge patterns for hospitalized stroke patients during the first 7 days following hospital admission in Michigan, USA and Ontario, Canada.

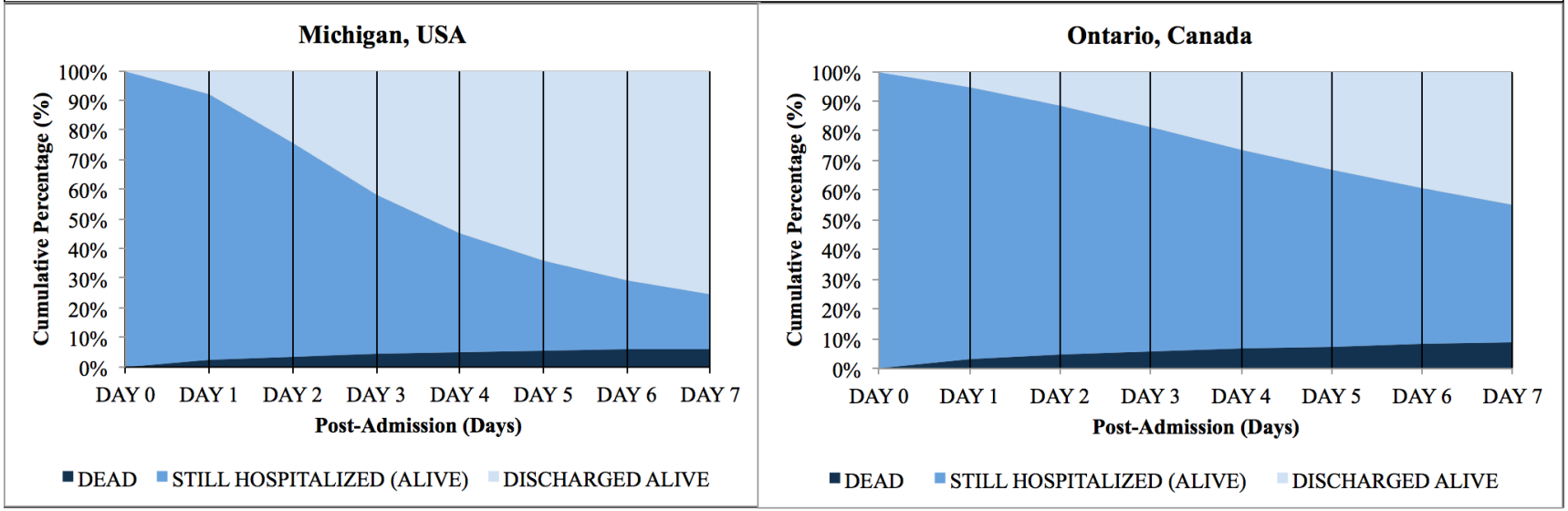
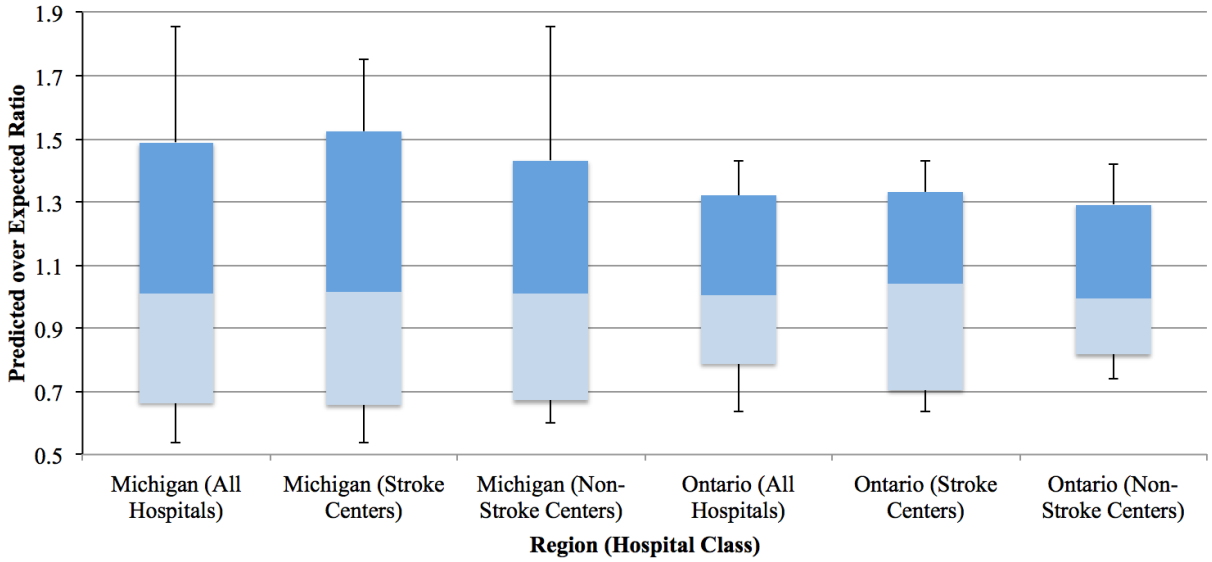
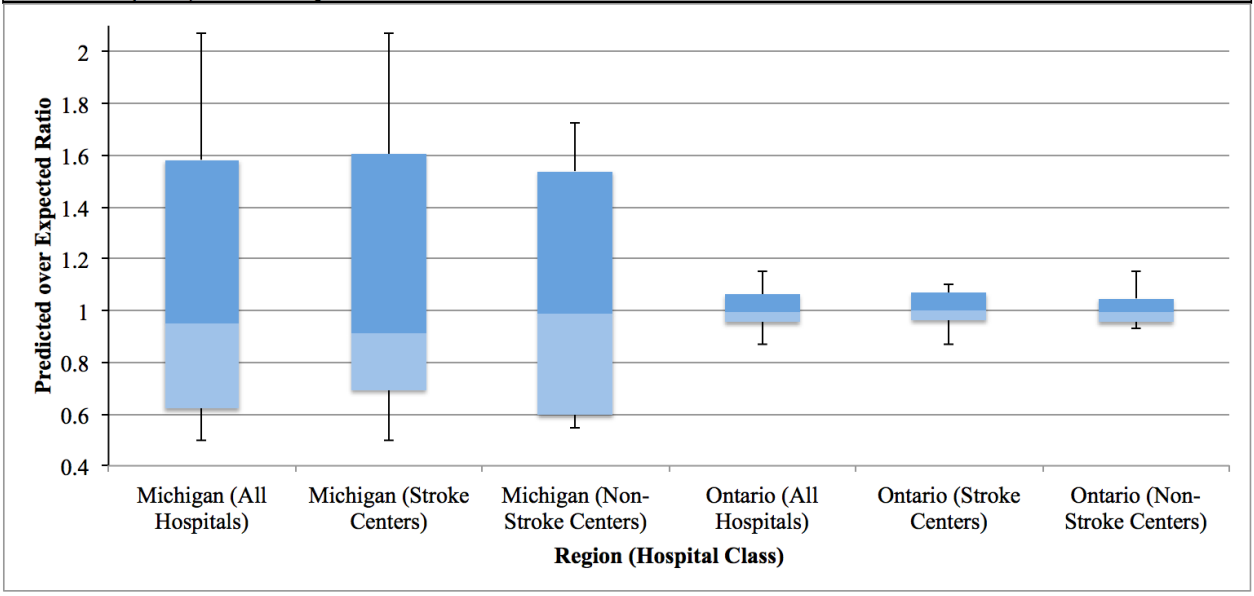


Figure 5: Distribution of predicted over expected ratios of in-hospital mortality performance for Michigan and Ontario hospitals, stratified by stroke center certification.*



*High and low whisker endings indicate maximum and minimum values, respectively. High and low box endings indicate 90th and 10th percentiles, respectively. Median is indicated by center box line.
NOTE: Only includes hospitals with a stroke care load ≥75 over 3-year period (2010-2012). Based on 78 Michigan hospitals and 83 Ontario hospitals. Stroke centers in Michigan include comprehensive and primary stroke centers. Stroke centers in Ontario include

Figure 6: Distribution of predicted over expected ratios of 30-day readmission performance for Michigan and Ontario hospitals, stratified by stroke center certification.*



*High and low whisker endings indicate maximum and minimum values, respectively. High and low box endings indicate 90th and 10th percentiles, respectively. Median is indicated by center box line.
NOTE: Only includes hospitals with a stroke care load ≥75 over 3-year period (2010-2012). Based on 78 Michigan hospitals and 83 Ontario hospitals. Stroke centers in Michigan include comprehensive and primary stroke centers. Stroke centers in Ontario include

Figure 7: Rank correlation between observed and risk-adjusted in-hospital mortality rates for Michigan and Ontario hospitals (2010-2012).

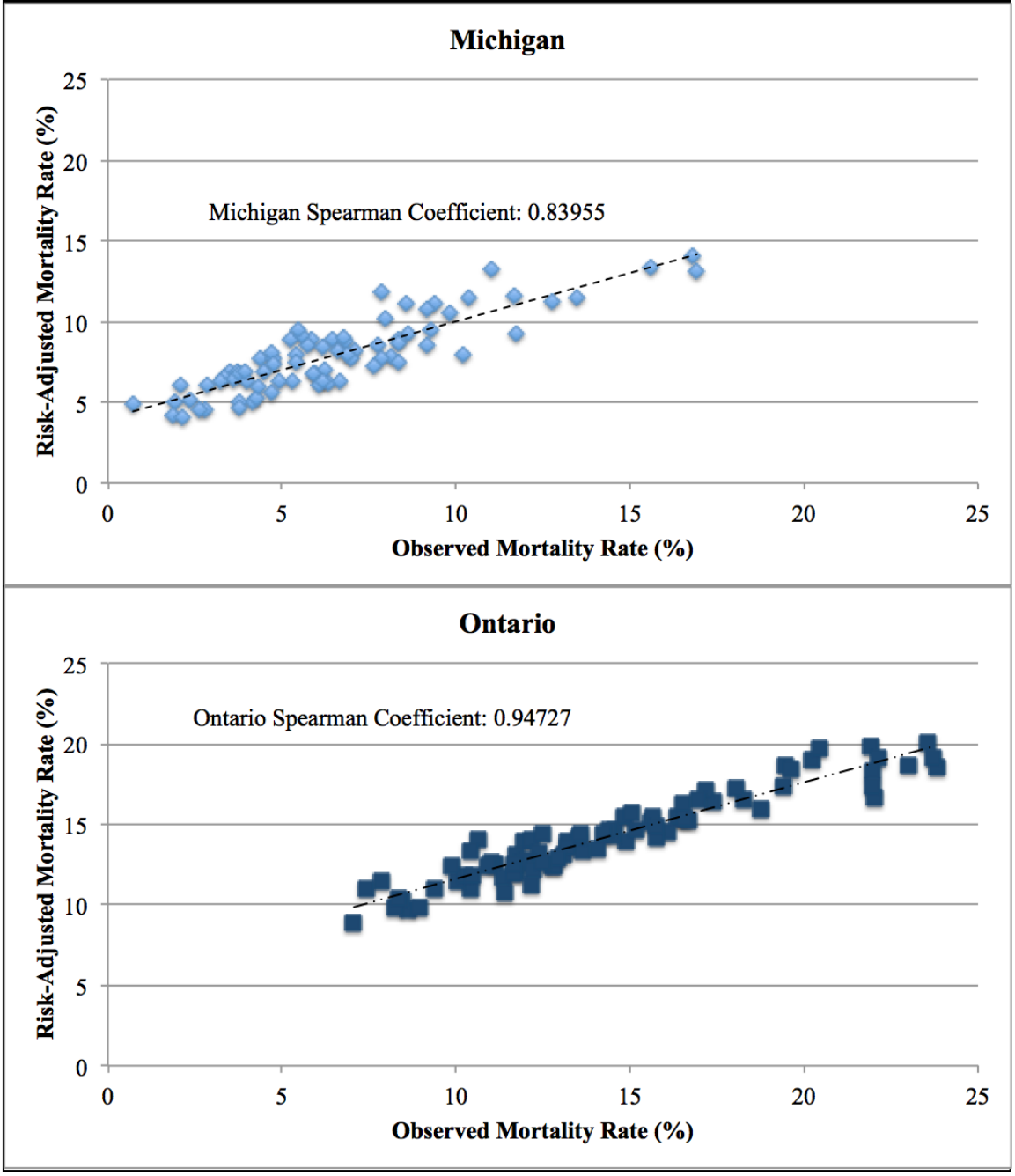
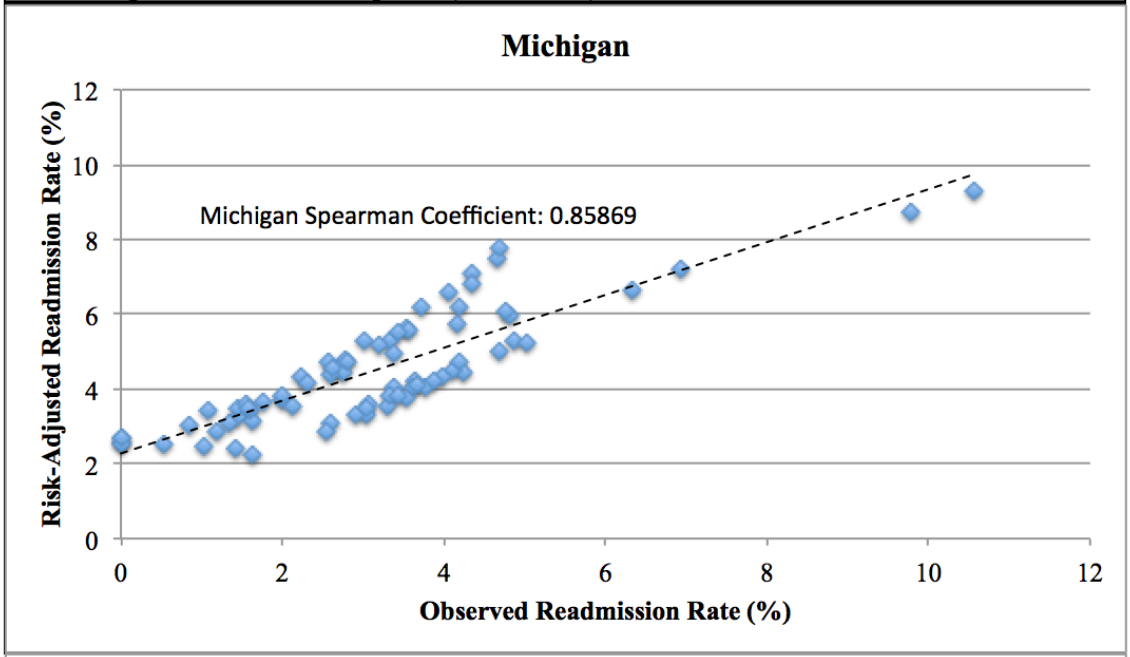
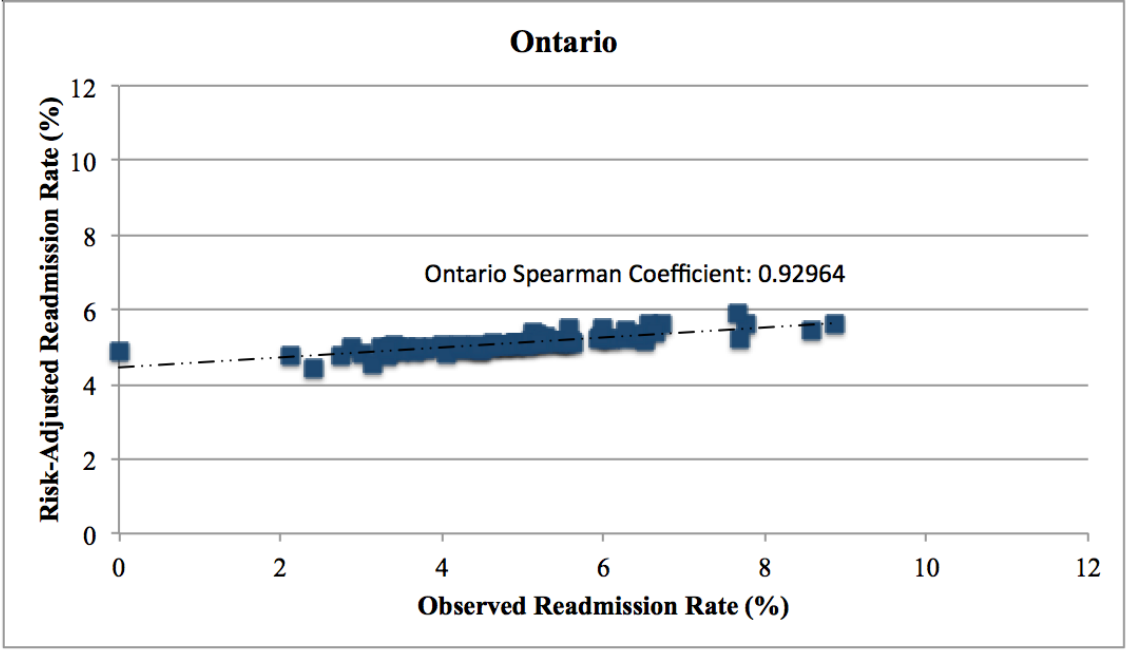


Figure 8: Rank correlation between observed and risk-adjusted 30-day readmission rates for Michigan and Ontario hospitals (2010-2012).





APPENDIX C

Supplemental Tables

Table S1: Description of codes used in Michigan (ICD-9) and Ontario (ICD-10) to identify strokes.

Michigan (ICD-9)	Ontario (ICD-10)	Description
430	I60	Subarachnoid hemorrhage
431	I61	Intracerebral hemorrhage
432	I62	Other hemorrhage
433, 434	I63	Ischemic stroke
436	I64	Unable to determine

NOTE: ICD-9 and ICD-10 code descriptions were referenced from the Centers for Medicare and Medicaid Services (CMS) and Institute for Clinical Evaluative Sciences (ICES), respectively.

Table S2: List of diagnosis codes used to identify past medical history in the respective discharge databases in Michigan and Ontario.

Past Medical History	Michigan, USA (ICD-9)	Ontario, Canada (ICD-10)	Comparability Ratios
AIHD	410-411.99, 413-413.99	I20, I21, I22, I24	0.99 (all ischemic heart disease)
Cancer	140-202.99, V580, V581	C00-C26, C30-C44, C45-C97, Z51.0, Z51.1	1.01
CIHD	414.0-414.19, 414.8-414.99, 412-412.99, 429.2-429.29	I25	0.99 (all ischemic heart disease)
Diabetes	250-250.99	E10.0-E10.7, E11.0-E11.7, E13.0-E13.7, E14.0-E14.7	1.01
Heart Failure	428-428.99	I50	1.04
Liver Disease	456.0-456.19, 571-571.99, 572.8-572.89, 573-574.99, V427	B16.1, B16.9, B17, B18, I85, K70.0, K70.2, K70.3, K70.4, K70.9, K72.1, K72.9, K73, K74, K76.0, K76.6, Z94.4	1.04
Pulmonary Edema	514-514.99, 518.4-518.49	J81	1.12
Renal Failure	584.5-584.99, 585-586.99	N17, N18, N19	1.30
Shock	785.5-785.59	R57	1.19

Abbreviation: AIHD - acute ischemic heart disease, CIHD - chronic ischemic heart disease
NOTE: Comparability ratios from reference 83.

Table S3: Description of ICD-9 procedure codes used to identify elective readmissions in the MIDB.	
ICD-9 Code	**Code Description**
0061	Percutaneous angioplasty of extracranial vessel(s)
0063	Percutaneous insertion of carotid artery stent(s)
380.2	Incision of vessel, other vessels of head and neck
381.2	Endarterectomy, other vessels of head and neck
383	Resection of vessel with anastomosis, any site
384.1	Resection of vessel with replacement, intracranial vessels
384.2	Resection of vessel with replacement, other vessels of head and neck

NOTE: ICD-9 code descriptions were referenced from the Centers for Medicare and Medicaid Services (CMS); http://www.cms.gov/Medicare/Coding/ICD9ProviderDiagnosticCodes/codes.html

APPENDIX D

IRB Approval Letter

MICHIGAN STATE
UNIVERSITY

Initial IRB Application Determination *Exempt*

December 19, 2014

To: Mathew Reeves
B614 W Fee Hall
East Lansing, MI 48824

Re: **IRB# x14-1311e** Category: Exempt 4
Approval Date: December 19, 2014

Title: Comparison of acute stroke outcomes between Michigan and Ontario hospitals

The Institutional Review Board has completed their review of your project. I am pleased to advise you that **your project has been deemed as exempt** in accordance with federal regulations.

The IRB has found that your research project meets the criteria for exempt status and the criteria for the protection of human subjects in exempt research. **Under our exempt policy the Principal Investigator assumes the responsibilities for the protection of human subjects** in this project as outlined in the assurance letter and exempt educational material. The IRB office has received your signed assurance for exempt research. A copy of this signed agreement is appended for your information and records.

Renewals: Exempt protocols do not need to be renewed. If the project is completed, please submit an ***Application for Permanent Closure***.

Revisions: Exempt protocols do not require revisions. However, if changes are made to a protocol that may no longer meet the exempt criteria, a new initial application will be required.

Problems: If issues should arise during the conduct of the research, such as unanticipated problems, adverse events, or any problem that may increase the risk to the human subjects and change the category of review, notify the IRB office promptly. Any complaints from participants regarding the risk and benefits of the project must be reported to the IRB.

Follow-up: If your exempt project is not completed and closed after three years, the IRB office will contact you regarding the status of the project and to verify that no changes have occurred that may affect exempt status.

Please use the IRB number listed above on any forms submitted which relate to this project, or on any correspondence with the IRB office.

Good luck in your research. If we can be of further assistance, please contact us at 517-355-2180 or via email at IRB@msu.edu. Thank you for your cooperation.

Sincerely,

H. McGee

Harry McGee, MPH
Vice Chair, BIRB

c: Joshua Cerasuolo

Office of Regulatory Affairs
Human Research Protection Programs

Biomedical & Health Institutional Review Board (BIRB)

Community Research Institutional Review Board (CRIRB)

Social Science Behavioral/Education Institutional Review Board (SIRB)

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