HOSPITAL POST-CARDIAC ARREST PATIENT VOLUME AND KEY FEATURES OF POST-CARDIAC ARREST CARE

by

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Abstract

Background: Hospitals vary in the number of out-of-hospital cardiac arrest (OHCA) patients they treat on an annual basis. Institutional experience with this type of complex patient may be associated with the quality of post-arrest care delivered by a hospital, specifically targeted temperature management (TTM).

Objectives: 1) To quantify the variability in post-cardiac arrest patient characteristics, treatments, and outcomes across a network of 37 hospitals in Southern Ontario, 2) To evaluate the association between average annual hospital volume of patients with post-cardiac arrest syndrome after out-of-hospital cardiac arrest and several care process and clinical outcomes.

Methods: This was a retrospective, population-based cohort study of consecutive non-traumatic OHCA cases presenting to the 37 hospitals in the Strategies for Post-Arrest Care Network of Southern Ontario from 2007-2013. The study included adult patients who achieved return of spontaneous circulation, survived at least 6 hours post-hospital arrival and were comatose. The study excluded patients with a pre-existing Do-Not-Resuscitate order, who had life sustaining therapy withdrawn within 6 hours of hospital arrival, and who had intracranial or severe bleeding within 6 hours of hospital arrival. The patient population was described and the proportion of patients who achieved specific care-process and clinical outcomes were reported by hospital volume. Several multi-level logistic regression models were constructed with patients (level 1) nested within hospitals (level 2).

Results: The cohort included 2,723 eligible patients at 37 hospitals. Overall, 33% had successful TTM. Successful TTM varied significantly between 3 hospital volume groups (26% (184/721) for <15 patients/year, 33% (342/1024) for 15-25 patients/year, and 38% (369/978) for >25 patients/year; $p<0.05$). The volume groups were comparable on patient factors. The intraclass correlation coefficient demonstrated 11% of the variability in successful TTM was attributable to hospital-level factors. Multilevel analysis revealed for each 10 unit increase in annual volume of patients eligible for TTM, the adjusted odds for successful TTM were almost 30% higher (OR 1.29, CI_{95} 1.03-1.62).

Conclusions: Successful TTM varied markedly between hospitals on the basis of experience with post-OHCA patients. Patients who received successful TTM were more likely to have arrived at hospitals with more experience in post-OHCA patients.

Co-Authorship

This thesis was written by Heather Worthington. Feedback about the content and wording were provided by Heather's primary supervisor, Dr. Steven Brooks. Feedback about content was also obtained from Heather's secondary advisor, Dr. William Pickett.

The study was designed by Heather Worthington with guidance from Dr. Steven Brooks. Some guidance was also provided by Dr. William Pickett. Heather Worthington cleaned and prepared the data for analysis. The analysis and interpretation were completed by Heather Worthington. Guidance was provided primarily by Dr. Steven Brooks, with assistance from Dr. William Pickett as well as the co-investigators of the Strategies for Post-Arrest Resuscitation Care (SPARC) Network: Ms. Cathy Zhan, Dr. Katie Dainty, Dr. Paul Dorian, Dr. Niall Ferguson, Dr. Steve Lin, Dr. Laurie J Morrison, and Dr. Damon Scales.

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List of Abbreviations

AIC ..... Akaike Information Criterion
AED ..... Automated External Defibrillator
CPC ..... Cerebral Performance Category
CPR ..... Cardiopulmonary Resuscitation
DNR ..... Do-Not-Resuscitate
ECG ..... Electrocardiogram
EMS ..... Emergency Medical Services
ICC ..... Intraclass Correlation
ICD ..... Implantable Cardioverter Defibrillator
ICU ..... Intensive Care Unit
MOR ..... Median Odds Ratio
OHCA ..... Out-of-Hospital Cardiac Arrest
PCI ..... Percutaneous Coronary Intervention
PEA ..... Pulseless Electrical Activity
ROC ..... Resuscitation Outcomes Consortium
ROSC ..... Return of Spontaneous Circulation
SPARC ..... Strategies for Post-Arrest Resuscitation Care
STEMI ..... ST-segment Elevation Myocardial Infarction
TTM ..... Targeted Temperature Management
VF ..... Ventricular Fibrillation
VT ..... Ventricular Tachycardia

Chapter 1

Introduction

1.1 Background

Out-of-hospital cardiac arrest (OHCA) is an important clinical and public health concern, with an incidence rate of 126.4 per 100,000 and a mortality rate of approximately 90% in North America.[1] In recent years improvements have been made to pre-hospital resuscitation and care,[2] however it has been difficult to discern any significant increase in the proportion of admitted patients who survive to hospital discharge.[3] The high in-hospital mortality rate of resuscitated patients, close to 70%, is due in great part to the processes of post-cardiac arrest syndrome.[4]

Post-cardiac arrest syndrome is a sepsis-like condition that is associated with multi-organ dysfunction secondary to the initial anoxic insult of the cardiac arrest and subsequent reperfusion injury.[4] There are several features of post-cardiac arrest care that have been emphasized in the guidelines to treat post-cardiac arrest syndrome, the most important being targeted temperature management (TTM).[5] However, best practices are not always implemented for eligible patients resulting in few of them receiving state-of-the-art care.[6] Additionally, extreme variability in survival between hospitals has been reported by studies from around the world.[7–10] Regionalized systems of post-cardiac arrest care have been suggested as a potential solution to improve post-cardiac arrest patient care and outcomes.[11]

A regionalized system of post-cardiac arrest care would have emergency medical service (EMS) systems bring OHCA patients to specialized, high volume, cardiac arrest care centres.[11] This system of care is being developed and has already been implemented in some US states and

other countries around the world,[12–17] but there is no consensus in the literature as to whether this would be effective in improving treatment and outcomes for post-cardiac arrest patients.

1.2 Rationale

It is necessary to determine what phenomena are driving the regional variation in mortality rates for post-cardiac arrest patients in order to address this health inequity. Establishing how specific care processes differ between receiving hospitals may help to explain this variation. Differences in care processes between receiving hospitals are important and warrant addressing by the health system.

As previously discussed, it has been proposed that regional systems of post-cardiac care would improve patient outcomes, yet several studies have investigated the concept of regionalized cardiac arrest care from various countries and there has yet to be a consensus on whether this strategy is actually beneficial to the patient. No study has been sufficiently designed and powered to investigate the nature of post-cardiac arrest treatments received at hospitals and to measure variability across different hospitals based on the number of their experiences with out-of-hospital cardiac arrest.

1.3 Objectives and Hypotheses

The objectives of this study are:

1) To quantify the variability in post-cardiac arrest syndrome patient characteristics, processes, and outcomes by average annual hospital volume of OHCA patients eligible for TTM received across a network of 37 hospitals in Southern Ontario, the Strategies for Post-Arrest Resuscitation Care (SPARC) Network, from 2007 to 2013.
2) To evaluate the association between hospital volume of cardiac arrest (average number of OHCA patients eligible for TTM received per year) and: i) successful induction of TTM; ii) cooling initiated; iii) premature termination of life sustaining therapy on the basis of

neuroprognostication; and iv) survival to hospital discharge with good neurologic function for post -cardiac arrest patients received by SPARC Network hospitals from 2007 to 2013.

It is hypothesized that the quality of care (e.g., the number of eligible patients that receive recommended treatments) will differ based on the experience of a given hospital with out-of-hospital cardiac arrest patients. Specifically, among adult populations with atraumatic, OHCA, those patients admitted to hospitals that see more OHCA patients per year will be more likely to receive successful therapeutic hypothermia, less likely to have life-sustaining therapy withdrawn within 72 hours on the basis of neuroprognosis, and be more likely to survive with a good neurologic status when compared to patients admitted to hospitals that see fewer cardiac arrest patients per year.

1.4 Study Design

This is a retrospective cohort study using consecutive OHCA cases presenting to SPARC Network hospitals. The exposure of interest is hospital experience with OHCA patients eligible for recommended therapies, measured by average annual emergency department volume of patients eligible for targeted temperature management (TTM). The primary outcome is successful TTM, with secondary outcomes including having cooling initiated, having life support withdrawn prematurely on the basis of neuroprognostication, and survival with good neurologic function. Figure 1 shows the schema of the study.

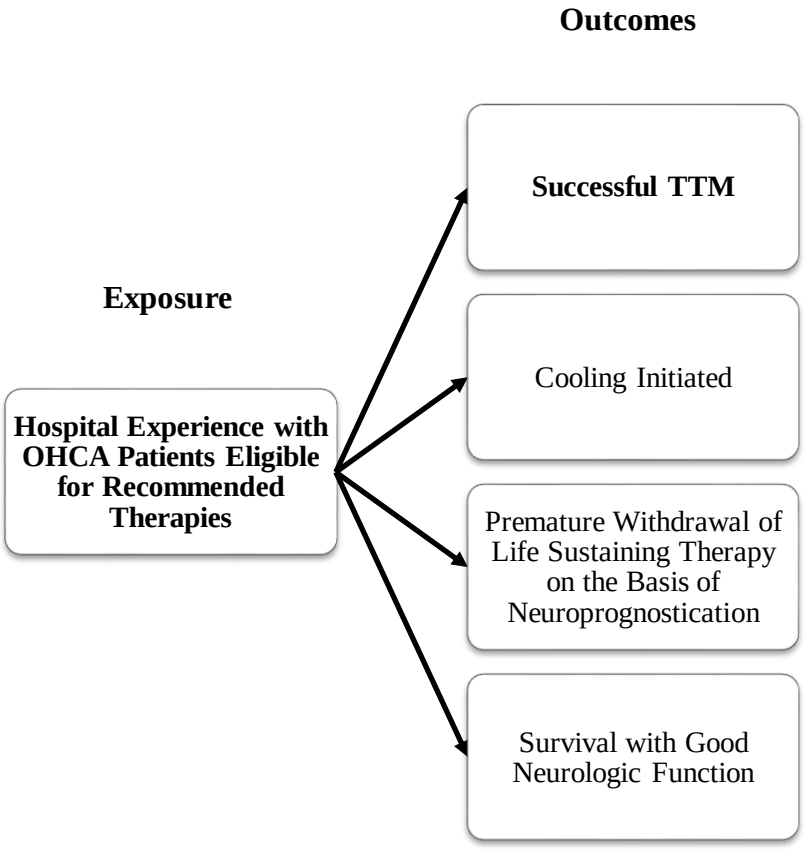

Figure 1. Schema of exposure and outcomes of the study

1.5 Scientific and Public Health Relevance

Results of the analyses will be distributed to stakeholders and decision-makers in the field, and presented in traditional peer-review outlets. Evidence generated from this study will provide guidance for decision-makers within the Canadian health care system who aim to improve post-cardiac arrest care and survival for patients after suffering OHCA. Our data will specifically apply to the question of whether post-arrest care might improve if regionalized towards high-volume centres. Members of the study team have membership on the International Liaison Committee on Resuscitation (ILCOR), the Heart and Stroke Foundation of Canada, and the American Heart

Association committees that undertake evidence synthesis and guideline creation. Therefore we will ensure this evidence is included in future synthesis activities including international guideline development.

1.6 Thesis Organization

This thesis is divided into five chapters. Chapter Two reviews the literature that is relevant to the context of the study, which includes a discussion of cardiac arrest, post-cardiac arrest syndrome, the present state of post-cardiac arrest care, the use of patient volume as a proxy for health care quality/experience, and the state of the evidence for regionalizing post-cardiac arrest care. Chapter Three describes the methodology used to meet the two study objectives. The study design, study population, data sources, exposure, outcomes, covariates, and analysis strategy will be discussed. The results of the study are presented in Chapter Four. Chapter Five discusses the key findings of this thesis in context, methodological considerations, as well as the strengths, limitations, and contributions of the study.

Chapter 2

Literature Review

2.1 General Overview

The variability of post-out-of-hospital cardiac arrest (OHCA) care and patient outcomes has been recognized as a clinical and public health concern. The American Heart Association and the International Liaison Committee on Resuscitation recommend that there should be regionalized systems of post-cardiac arrest care, with patients directly transported to higher volume, more "experienced" centres.[5,11] However, there is little evidence to support this recommendation. Current evidence on this topic is extremely varied, and no study has yet been able to examine the relationship between hospital volume of post-cardiac arrest patients and the delivery of specific post-cardiac arrest therapies.

This chapter begins with a discussion of the background information on OHCA. This will be followed with an overview of post-cardiac arrest syndrome and its treatment recommendations. Post-cardiac arrest therapies, including targeted temperature management (TTM), will be discussed in detail as well as the importance of avoiding premature neuroprognostication in this patient population. Next, the variability in post-cardiac arrest treatments and outcomes reported in the literature will be discussed. The use of hospital volume as a measure of hospital experience will be discussed. Then, the proposed remedy to the variability in post-cardiac arrest care and outcomes, the regionalization of post-cardiac arrest care, and the current evidence for this will be outlined. To conclude, the rationale for objectives one and two will be stated.

2.2 Sudden Cardiac Arrest

Normally, the sinus node in the right atrium of the heart generates electrical impulses that flow in an orderly manner through the heart to synchronize heart rate and coordinate the pumping of blood to the rest of the body.[18] Sudden cardiac arrest occurs when this process is disrupted causing the heart stop beating unexpectedly.[18] The cessation of cardiac mechanical function results in the disturbance of normal circulation and unconsciousness.[18] Death is certain if cardiac arrest is not treated immediately.[18]

2.2.1 Causes

There are several underlying physiologic conditions that can lead to sudden cardiac arrest, as well as possible non-cardiac causes.[19] Cardiac arrest patients are a heterogeneous patient population due to the wide variety of conditions and events that can precipitate cardiac arrest, making standardized treatments difficult.[20] Pre-existing cardiac conditions that can precipitate a cardiac arrest include: coronary artery disease, myocardial infarction, cardiomyopathy, valvular heart disease, and primary heart rhythm abnormalities.[20] Coronary artery disease can lead to cardiac arrest when arteries become blocked with cholesterol and other deposits, which reduces blood flow to the heart making it difficult for the heart to conduct coordinated electrical impulses.[20] A myocardial infarction can lead to cardiac arrest in multiple ways: it can trigger ventricular fibrillation (VF) that in turn leads to heart arrest, or areas of scar tissue left behind from a myocardial infarction can cause electrical short circuits leading to abnormalities in heart rhythm.[20] Cardiomyopathy can lead to cardiac arrest because the abnormality in the muscle of the heart leads to heart tissue damage and potential arrhythmias.[20] Valvular heart disease can lead to cardiac arrest by the leaking or narrowing of the valves of the heart causing stretching or thickening of the heart muscle, which increases the risk of developing

an arrhythmia.[20] Primary heart rhythm abnormalities can lead to cardiac arrest.[20] External triggers can also lead to cardiac arrest.[20] These include such triggers as electrical shock, the use of illegal drugs, drowning, or trauma to the chest (*commotio cordis*).[20,21]

Common to all of these conditions are the changes in the electrical activity of the heart (arrhythmias) that cause the pumping disruptions that lead to cardiac arrest.[19] Ventricular fibrillation (VF) is uncoordinated contraction of the cardiac muscle in the ventricles of the heart.[19] Asystole, where there is no electrical activity, is the most common rhythm observed in cardiac arrest victims.[19] Pulseless electrical activity (PEA) occurs when the a normal electrical impulse continues without any mechanical cardiac output.[19] Pulseless ventricular tachycardia (VT), is a very rapid arrhythmia originating from cells in the ventricle of the heart which is not associated with any mechanical output from the heart.[19] Arrhythmias are classified as shockable or not shockable, depending on whether they can be treated by defibrillation or synchronized cardioversion.[19] VF and VT are shockable rhythms, whereas asystole and PEA are not.[19]

2.2.2 Epidemiology of Out-of-Hospital Cardiac Arrest (OHCA)

There are wide variations in reported incidence and outcomes for OHCA.[1] This is due in part to differences in the definition and how cardiac arrest data are obtained, as well as differences in post-cardiac arrest treatments.[1]

The reported incidence of EMS-assessed OHCA in North America is 126.4 per 100,000.[1] Sixty percent of OHCAs are treated by EMS personnel.[22] It is reported that 25% of EMS-treated OHCA cases have no symptoms prior to the onset of the arrest.[23] The incidence of cardiac arrest with an initial rhythm of VF is decreasing, but the overall incidence of cardiac arrest is not.[24]

Identified risk factors for sudden cardiac arrest include: race, prior heart disease, family history, and lifestyle factors.[25–29] The age-adjusted incidence of OHCA per 10,000 adults was

reported to be 10.1 among blacks, 6.5 among Hispanics, and 5.8 among whites in a study done in New York City.[25] The incidence of OHCA is 6.0 per 1,000 person-years among patients with any clinically recognized heart disease, in contrast to 0.8 per 1,000 person-years among those without heart disease.[26] The incidence of OHCA is even higher in subgroups of patients with past myocardial infarction and heart failure.[26] Having a first-degree relative who suffered a cardiac arrest is associated with a 2-fold increase in the risk of cardiac arrest.[27,28] The Nurses' Health Study found that the population attributable risk of sudden death associated with the four lifestyle factors: smoking, physical activity, diet, and weight, was 81%.[29]

In Canada, approximately 40,000 people suffer sudden cardiac arrest annually equating to one every 12 minutes.[30] Sudden cardiac death that occurs as a direct consequence of cardiac arrest has been estimated to account for 11% of all deaths in Canada annually.[30] Studies have shown that greater than 70% of cardiac arrests occur out-of-hospital, and only 8.4% of patients who suffer out-of-hospital cardiac arrest survive to hospital discharge.[30] Clearly, OHCA is a significant clinical and public health concern in North America, and in Canada specifically.

2.2.3 Factors Associated with Survival

A systematic review and meta-analysis of predictors of survival from OHCA found that survival to hospital discharge was more likely among cardiac arrests that: were witnessed by a bystander, were witnessed by EMS, received bystander cardiopulmonary resuscitation (CPR), were found in VF/VT, or achieved return of spontaneous circulation (ROSC).[31]

Cardiac arrests that are witnessed by a bystander, witnessed by EMS, or receive bystander CPR all have improved outcomes because of the short time interval between the cessation of cardiac mechanical activity and resuscitation attempts. Early treatment of cardiac arrest is extremely important in improving the chances of restarting the heart and returning

circulation. Due to this, timely intervention has been deemed very important in post-cardiac arrest treatment guidelines.[19]

A patient's initial cardiac rhythm has a strong influence on outcome. The likelihood of survival is relatively high (up to 60%) if the initial rhythm is shockable (particularly if the VF-arrest is witnessed, and prompt CPR and defibrillation are provided).[32] If the initial rhythm is not shockable, survival is typically <5% in most reported case-series.[32] Asystolic patients whose cardiac arrest is not witnessed rarely survive neurologically intact to hospital discharge.[32] The only common exceptions are witnessed cardiac arrest patients whose initial asystole is a result of increased vagal tone or other relatively easily correctible factors, such as hypoxia of brief duration.[32]

Patients who have a ROSC have improved outcomes because they have been resuscitated from the cardiac arrest. Clearly, patients whose spontaneous circulation is restored will fare better than those who are not successfully resuscitated.

2.2.4 Treatments

In order to optimize a cardiac arrest victim's chance of surviving the event emphasis has been placed on early access to care, early CPR, early defibrillation, and early advanced cardiac life support.[19] This has been deemed the "Chain of Survival" in recent guidelines (see figure 2).[19]

Figure 2. The chain of survival. Adapted from "The chain of survival" by Nolan et al., 2006, Resuscitation, 71, p.270[33]

The early access link in the chain of survival involves getting the patient help as quickly as possible.[34] This includes having people recognize when a cardiac emergency is occurring, the decision to contact EMS, time spent locating a phone and making the call, the call itself, and call processing time.[34] Ambulance response time is then the interval from the time the call is received to the arrival of personnel on the scene.[34] More time may elapse before the emergency responder can actually examine the patient.[34] These steps of recognition, call processing, and ambulance response time add precious seconds to the critical interval between when the arrest occurs and emergency treatment.[34]

Early CPR should be initiated immediately after the cardiac arrest is recognized. The body of evidence supporting that CPR has helped return pulseless, non-breathing patients to spontaneous respiration and cardiac perfusion is vast and spans over 5 decades.[35] The value of CPR occurring early is in buying time for the cardiac arrest patient by maintaining enough blood flow to the central nervous system and the myocardium to keep the patient viable for a time.

Early defibrillation is an important link in the chain of survival because it is needed to re-establish a normal spontaneous heart rhythm.[34] It has been shown that approximately 85% of

people with ambulatory, OHCA experience ventricular tachyarrhythmias (VF or VT) during the early minutes after collapse.[36] These rhythms are shockable, meaning that an electrical impulse can be used to stop the heart momentarily and cease the disordered electrical activity to allow the heart to reset.[34] The earlier a cardiac arrest patient with a shockable rhythm can be defibrillated or cardioverted, the better. Studies have demonstrated that cardiac arrest survival rates are highest when the arrest is witnessed by a medical professional and electrical shock is performed within minutes.[34]

Early advanced cardiac life support is necessary because in many cases CPR and defibrillation or cardioversion on their own do not achieve or sustain resuscitation.[34] Advanced cardiac life support involves interventions such as endotracheal intubation and intravenous medication.[34]

2.2.5 Static Survival

Many in- and out-of-hospital emergency response systems have made improvements in the immediate management of cardiac arrest including public education in CPR, the optimization of EMS for rapid response to OHCA, enhanced and broadly accessible defibrillator technology, and emphasis on the quality of CPR, to improve the links in the chain of survival.[37] Despite these attempts to optimize a cardiac arrest victim's chance of surviving the event, it has been difficult to discern any significant increase in the proportion of admitted patients who survive to hospital discharge in recent years.[3] Several recent interventional studies have demonstrated significant improvements in short-term survival with novel CPR protocols, drugs, and devices, however these have not translated into improvements in neurologically intact, long-term survival.[37–39] In Canada, only 38% of people admitted to hospital after suffering out-of-hospital cardiac arrest survive to hospital discharge.[3] Redpath et al. reported that survival was static between the years

of 1993 and 2004.[3] A meta-analysis was not able to distinguish any significant differences in survival over the past 3 decades.[31] This is all despite significant advances in the treatment of post-cardiac arrest patients that clinical trials have demonstrated improve survival after cardiac arrest.[37]

2.3 Post-Cardiac Arrest Syndrome

The high in-hospital mortality rate of admitted post-cardiac arrest patients is due to post-cardiac arrest syndrome.[4] Post-cardiac arrest syndrome is a sepsis-like condition that is associated with multi-organ dysfunction secondary to the initial anoxic insult caused by the cardiac arrest and subsequent reperfusion injury.[4] Brain injury, myocardial dysfunction, systemic inflammatory response and any persisting underlying pathology that precipitated the cardiac arrest are components of post-cardiac arrest syndrome.[4]

Brain injury presents as coma, seizures, cognitive dysfunction, myoclonus (involuntary muscle twitching), stroke, persistent vegetative state, or brain death.[4] The myocardial dysfunction in post-cardiac arrest syndrome patients may result from myocardial stunning (a contractile abnormality) or an acute coronary syndrome.[4] Systemic inflammatory response manifests as ongoing tissue ischemia, hypotension, cardiovascular collapse, fever, hyperglycemia, multi-organ failure and infection.[4] Acute myocardial infarction, cardiomyopathy, pulmonary disease, cerebrovascular accidents, thromboembolic disease, toxicological conditions, infection or hypovolemia can be part of persisting precipitating pathology.[4]

The phases of post-cardiac arrest syndrome begin immediately after the patient has achieved a ROSC (see figure 3).[4] Treatment goals depend on what phase of the syndrome the patient is in.[4] Initially, the goal is to limit ongoing injury and support organs, which includes therapies such as TTM.[4] Prognostication should not take place until the recovery phase.[4]

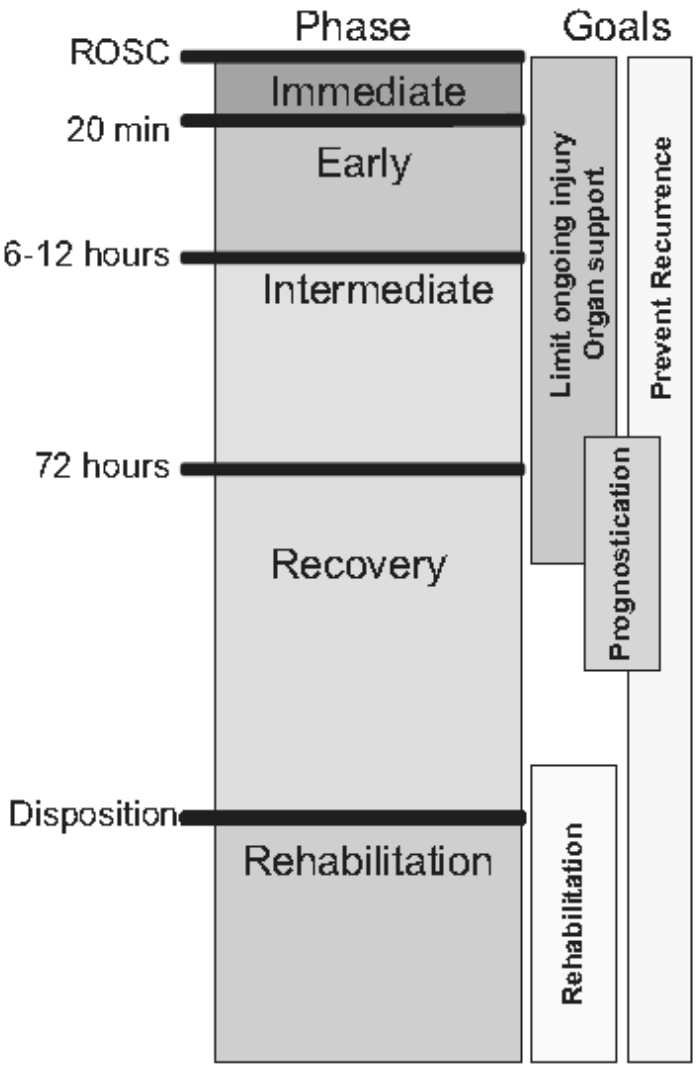

Figure 3. Phases of post-cardiac arrest syndrome. Adapted from "Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication", by Neumar R. et al., 2008, p.4[4]

2.3.1 Treatment Recommendations

The American Heart Association and the International Liaison Committee on Resuscitation have developed and published best practices for patients with post-cardiac arrest syndrome.[5,11] The components of these best practices include a multidisciplinary post-cardiac arrest care treatment plan, early therapeutic hypothermia (a.k.a. TTM), early percutaneous

coronary intervention (PCI), reliable early prognostication of functional outcome and implantable cardioverter defibrillator (ICD) placement.[5,11]

2.3.2 Targeted Temperature Management (TTM) or Therapeutic Hypothermia

Some of the destructive processes of post-cardiac arrest syndrome can be mitigated when core body temperature is reduced (32 to 34 degrees Celsius).[40] Therapeutic hypothermia acts in multiple ways to reduce the amount of cell death in the brain.[40] It inhibits the biosynthesis, release and uptake of several catecholamines and neurotransmitters, which prevents tissue damage.[40] It preserves the blood-brain barrier as well as protects adenosine triphosphate (ATP) reserves.[40] It also helps to restore cerebral microcirculation and decreases intracranial pressure.[40]

Several randomized studies have shown that the induction of mild therapeutic hypothermia to a core body temperature of 32-34 degrees Celsius maintained for 12-24 hours in comatose survivors of VF cardiac arrest is associated with increased survival and neurologic recovery.[41,42] A Cochrane review of hypothermia for neuroprotection in adults after cardiac arrest included four trials and one abstract, and found that patients in the hypothermia group were more likely to survive with good neurologic function (RR 1.55; CI_{95} 1.22-1.96) and were more likely to survive to hospital discharge (RR 1.35; CI_{95} 1.10-1.65).[40]

Subsequent observational studies in patients presenting with VF, VT as well as non-shockable initial rhythms (asystole and PEA) in both the out-of-hospital and in-hospital settings have also demonstrated a benefit with therapeutic hypothermia.[43–46] Observational data have shown that therapeutic hypothermia can provide a small but clinically significant improvement in hospital survival and favourable neurologic outcome in post-resuscitation out-of-hospital cardiac arrest patients who presented with any of the four initial rhythms, where prior studies had only included patients with VF of VT as the initial rhythm.[47] A review of therapeutic hypothermia

after cardiac arrest in clinical practice confirmed the findings from randomized controlled trials, finding that therapeutic hypothermia was associated with an increase in survival in post-cardiac arrest patients with an odds ratio of 2.5 (CI_{95} 1.8-3.3).[48] This finding may be an over-estimate of relative risk as the outcome, survival, is not rare. However it does provide evidence of the positive direction of the association in clinical practice.

Recently, Nielsen et al. conducted a randomized study of TTM at 33 versus 36 degrees Celsius after cardiac arrest.[49] The study found no evidence that cooling to 33 degrees Celsius was better than cooling to 36 degrees Celsius with respect to clinical outcomes.[49] There have been several hypothesized reasons for the lack of benefit of a lower temperature.[50] The first possible reason is that the Nielsen trial included a more heterogeneous patient population than the previous trials, including patients with both shockable and non-shockable initial rhythms.[50] The second possible reason is that due to the vast improvements in intensive care over the last few years, it may be difficult to discern the incremental benefit of a single intervention.[50] The third possible reason is that because the severity of post-cardiac arrest syndrome varies vastly within post-cardiac arrest patients, there may be subgroups of patients that do benefit from cooling to a lower temperature, but they were not distinguished in the study.[50] Though the study results do raise questions about what the target temperature in TTM should be, it is important to consider that though this trial did not find a benefit of cooling to the lower temperature of 33 degrees, it did not disprove any cooling as beneficial. The study did not include a control group where there was no cooling, and it is believed that even in the higher 36 degree group, the avoidance of hyperthermia was an important factor in the recovery of the patients.[49]

Based on this body of evidence, the practice of therapeutic hypothermia for post-cardiac arrest patients has been recommended by International Liaison Committee on Resuscitation and

incorporated into the guidelines of many national resuscitation councils around the world.[5] Generally, these guidelines state that unconscious adult patients with spontaneous circulation after out-of-hospital or in-hospital cardiac arrest should be cooled to 32-34 degrees Celsius for 12 to 24 hours.[5]

2.3.3 Coronary Angiography

Patients presenting with myocardial stunning and hypotension after cardiac arrest often require volume resuscitation and the use of vasopressor medications.[4] This hemodynamic compromisation is added to by acute coronary syndrome and cardiac ischemia.[6] In patients with cardiac arrest without obvious non-cardiac cause, several studies have found upwards of 50% of patients had angiographic evidence of an acute coronary occlusion.[4,51] Post-cardiac arrest patients with acute coronary occlusion may be amenable to PCI, but identifying them is challenging because the absence of ST-elevation on the 12-lead electrocardiogram (ECG) is not strongly predictive of the absence of coronary occlusion on angiogram.[51] Prior studies have shown that in post-cardiac arrest patients with ST-elevation on ECG, PCI was associated with angiographic success rates of 78% to 95% and overall survival to discharge rates of 44% to 75%.[52–55]

As the feasibility and efficacy of primary PCI in the post-cardiac arrest patient has been well established, the American Heart Association recommends that all patients with ST-elevation on the post-cardiac arrest ECG and all others without obvious non-cardiac cause for cardiac arrest be assessed with coronary angiography within 90 minutes of collapse.[11] PCI can only be done in centres equipped for the procedure, usually academic or large referral community hospitals.

2.3.4 Avoidance of Premature Neuroprognostication

The most common immediate cause of death in the intensive care unit (ICU) is withdrawal of life sustaining therapy by care providers.[56,57] The neurological prognosis for a patient may be poor due to a cerebral vascular accident, a long downtime prior to CPR being initiated, or another medical condition, and thus a decision is made to either withdraw or limit care (such as antibiotics, pressors, etc.) resulting in death. This highlights the importance of accuracy when determining prognosis and medical futility in this patient population. Most of the data that have traditionally guided prognostication practices in the post-cardiac arrest patient population are from before the era of therapeutic hypothermia.[46,58,59] Many patients who appear to have a poor prognosis initially by traditional markers can improve after treatment with hypothermia.[58,59] For example, motor responses no better than extension at day 3 in patients resuscitated from cardiac arrest was formerly considered a reliable predictor of very poor outcome.[60] However, post-cardiac arrest patients treated with therapeutic hypothermia can recover motor responses 6 days or more after the arrest and regain awareness.[60] In a study of timing of neuroprognostication in post-cardiac arrest therapeutic hypothermia patients it was found that 29% of patients documented as poor prognosis 72 hours post-arrest survived to hospital discharge.[60] In general, it is now agreed that neuroprognostication to identify patients appropriate for withdrawal of life sustaining therapy should not take place until at least 72 hours after cardiac arrest and this is reflected in current post-cardiac arrest treatment guidelines.[58,59]

2.3.5 Electrophysiological Assessment and Implantable Cardioverter Defibrillators (ICDs)

It is sometimes the case that the main cause of a patient's cardiac arrest is an arrhythmia. These patients are identified when no treatable cause is determined after appropriate investigation. ICDs have been shown to decrease mortality rates in post-cardiac arrest patients

when treatable causes are not identified.[61–63] ICD assessment and insertion is done by electrophysiologist sub-specialists in cardiology, and these specialists typically only practice in academic or large referral community hospitals.

2.4 Variability in Post-Cardiac Arrest Treatments and Outcomes

Despite publications of best practices for the management of post-cardiac arrest syndrome by the American Heart Association[11] and the recommendations from International Liaison Committee on Resuscitation[5] that promote the use of the previously discussed practices, they are not always implemented for eligible patients resulting in many patients receiving suboptimal care.[6] Many studies have suggested that survival to hospital discharge varies greatly between countries, regions, and hospitals.[7–9,64] One study revealed that within 21 hospitals in Sweden during the same time period, the survival rate, defined as alive at one month post-cardiac arrest, varied between 14 and 41 percent.[7] There is at least 5-fold regional variation in survival after OHCA among sites participating in the Resuscitation Outcomes Consortium (ROC) in North America.[64] Among the 10 sites of the ROC, with a total catchment population of 21.4 million, survival after EMS-treated cardiac arrest ranged from 3.0% to 16.3%.[64] This extreme variability in outcome is unlikely to be entirely explained by patient characteristics. In the Swedish study, there were still marked differences in survival rates between hospitals after adjusting for known patient characteristics.[7]

It is not currently clear how specific care processes differ between receiving hospitals that might explain these extreme differences in mortality rates. In the current system, EMS protocols for post-cardiac arrest patients usually involve transportation to the nearest hospital.[65] Many hospitals will see very few post-cardiac arrest patients per year and attending staff in those hospitals may have difficulty becoming experienced with this patient population due to the lack

of patient volume due to the modest catchment area of each hospital and the incidence of cardiac arrest in that region.[6]

There are data from around the globe that suggest therapeutic hypothermia is delivered inconsistently, incompletely, and delayed beyond the recommended time frames. A survey of physicians in the United States and Canada revealed that only 26% of physicians regularly institute therapeutic hypothermia.[66–69] In Germany, only 24% of ICUs used therapeutic hypothermia in 2006.[67] Also in 2006, only 28% of ICUs in the United Kingdom reported using therapeutic hypothermia.[70] An Australian study from 2012 revealed that only 27% of post-cardiac arrest cases received treatments consistent with guidelines.[68] Several barriers to knowledge translation have been identified including lack of awareness of recommended practice, perceptions of poor prognosis, too much work required to cool, and staffing shortages.[71] Despite recent efforts to overcome these barriers, therapeutic hypothermia is not being used as often as it should be.[72] There is a need to explore this on-going process variability, particularly in the Canadian context.

Despite the recommendation that neuroprognostication should not take place until at least 72 hours post-cardiac arrest, premature withdrawal of life-sustaining therapy occurs frequently.[73] This is likely the result of providers who are unfamiliar with current approaches to the assessment of post-cardiac arrest prognosis after therapeutic hypothermia treatment. In a study of over 14,000 in-hospital adult cardiac arrest patients from hospitals across the United States, the average length of stay after cardiac arrest for those patients who died was only 2 days.[73]

2.5 Hospital Volume as a Measure of Experience

Hospital volume is often used as a proxy measure of quality of care.[74] A conceptual framework of factors involved in the volume-health outcome relationship was developed by the

Committee on Quality in Health Care in America (see figure 4).[74] How patients are selected for hospital treatment depends on the surgical or medical services required. In the case of cardiac arrest, there is little time and choice, but for procedures and non-emergent care very different mechanisms of patient selection can be at play. Whatever the case, in order to draw meaningful conclusions about differences between hospitals and not just in the patient populations attending them, one must adjust for differences in the patient populations. Measuring the severity of a condition and any comorbidities are essential components of the validity of comparing outcomes of high and low volume centres.[74]

After the patient population, it is necessary to determine what treatments the patients receive. Better outcomes are not produced directly by volume of services. The association between volume and outcome must be explained by differences in the components of care or skill with which the treatments are provided.[74] Emphasis on whether specific treatment processes are adhered is an area of volume-health outcomes research that is often neglected.[74] In only 4 of the 135 studies reviewed in a systematic review of volume-health outcome studies did the authors examine differences in processes of care.[75] If patients at different institutions undergo the same treatment processes but have differing outcomes, it can be assumed that the skill level of the treating physicians and the hospital are playing a role in influencing certain outcomes.[74]

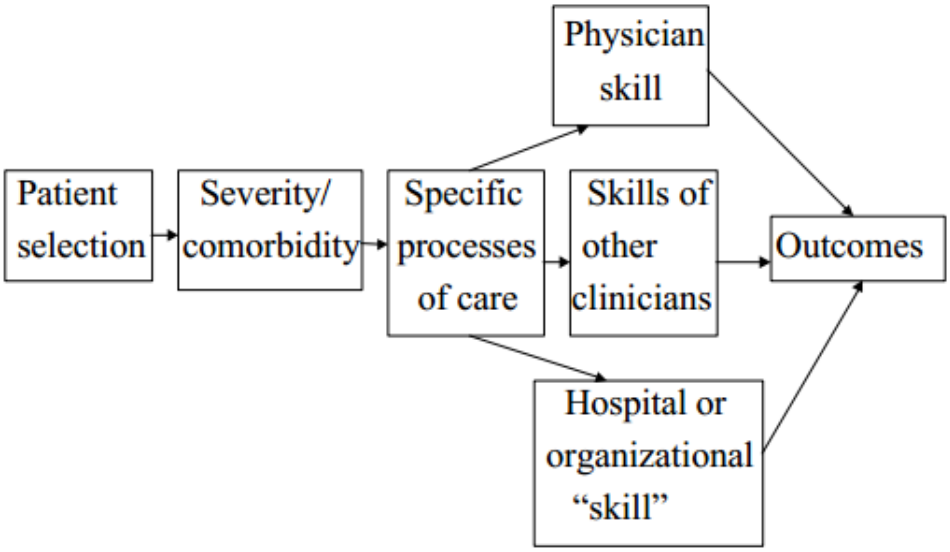

Figure 4. Conceptual framework for volume-outcome relationships in health care. Adapted from "Interpreting the Volume-Outcome Relationship in the Context of Health Care Quality", by Hewitt M., 2000, p.3[74]

It has been demonstrated that higher patient volume is associated with better health outcomes for a wide variety of surgical procedures and medical conditions.[74] The evidence for this is quite convincing, with 77% of studies systematically reviewed finding statistically significant associations between higher volume and better health outcomes, and no study demonstrating a significant association in the opposite direction.[75] Importantly, all 16 studies that were deemed of the highest quality by the review found statistically significant associations.[75] However, the magnitude of the association varies greatly between health outcomes.[75] For example, the volume-outcome association was strongest for high risk procedures and conditions including pancreatic cancer, esophageal cancer, abdominal aortic aneurysms, and pediatric cardiac problems, whereas the magnitude of the volume-outcome association was much more modest for more common procedures such as coronary artery bypass grafts, coronary angioplasty, and carotid endarterectomy.[75]

2.6 Conflicting Evidence for the Regionalization of Post-Cardiac Arrest Care

There is ample evidence of regional variation in post-cardiac arrest patient mortality rates as well as documented variation in post-cardiac arrest treatment practices due to administrative, resource and logistical barriers. Regionalization of post-cardiac arrest care in such a way that EMS systems bring OHCA patients to specialized cardiac arrest centres has been suggested as a potential solution to this situation.[11] As previously discussed, there is evidence for improved health outcomes at higher volume centres for many surgical procedures and medical condtions.[75] Regionalization and higher volume specialized centres have resulted in improved outcomes for other emergent patient types including those suffering severe trauma, ST-elevation myocardial infarction and stroke.[11] In 2010, the American Heart Association released a recommendation that post-cardiac arrest care be regionalized in such a way[11], however there is no consensus in the literature as to whether this would be effective in increasing survival of post-cardiac arrest patients.

Kajino et al. reported that transport of out-of-hospital cardiac arrest patients to hospitals certified as critical care centres in Japan resulted in better survival and overall neurological outcomes.[76] However, it is not clear what factors related to in-hospital care influenced the outcomes because data on specific treatments received during hospitalization were not captured in the study. Additionally, there may have been selection effects influencing the results as there was no pre-specified protocol dictating whether to transport patients to a critical care centre or a non-critical care hospital. The decision was made by the individual Emergency Medical Technician, fire department, or region medical control committee.[76]

A study in South Korea found that higher survival to discharge of OHCA patients with non-cardiac etiology was associated with high-volume hospitals (odds ratio 2.58, 95% CI: 1.90 –

3.52).[77] Yet this Korean study focused exclusively on OHCA patients of non-cardiac etiology. Furthermore, there were some inconsistencies in the data that could not be explained such as a relatively high rate of emergency department defibrillation in conjunction with a much lower rate of patients with an initial shockable rhythm.[77]

Positive evidence in support of regionalization of post-cardiac arrest care is contradicted by the findings of a study in the United States that found increasing hospital volume was not associated with improved survival in out-of-hospital cardiac arrest of cardiac etiology (odds ratio 1.04, 95% CI: 0.83 – 1.28).[78] However it was not known how often the therapies available at a hospital, such as therapeutic hypothermia and cardiac catheterization, were actually applied to individual patients. Additionally, though the study did not find a relationship between hospital volume and survival in OHCA, the study did find significant variation in survival between hospitals, the volume measure used was just unable to explain it. The study created the volume exposure variable by the number of OHCA patients that arrived to the emergency department per year, which would result in a heterogeneous patient population and may have impacted the study's findings.

There is also evidence from the United States that suggests the opposite is true; survival is higher at hospitals that treat higher volumes of cardiac arrest patients independent of patient characteristics.[79] Yet the differences in the process of care between high and low volume hospitals are not well understood.[79]

2.7 Rationale for Objective 1

Objective: To quantify the variability in post-cardiac arrest syndrome patient characteristics, processes, and outcomes by average annual hospital volume of OHCA patients eligible for TTM

received across a network of 37 hospitals in Southern Ontario, the Strategies for Post-Arrest Resuscitation Care (SPARC) Network, from 2007 to 2013.

Marked variability in post-cardiac arrest patient outcomes have been observed around the world.[7–9] In Canada, the variability in survival after OHCA has been characterized for sites that participate in the Resuscitations Outcomes Consortium (ROC),[80] but the variability in other outcomes such as those related to processes of care have not been examined. There is a need to determine any differences in care processes that exist to get a more complete picture of what is driving this variation in outcomes in Canadian hospitals. Establishing how specific care processes differ between receiving hospitals may help to explain the observed variability in mortality rates for post-cardiac arrest patients that have been observed globally. This study will inform researchers, policy-makers, and health care professionals about the regional variation in post-cardiac arrest care delivery and clinical outcomes in Southern Ontario. This information is important to guide the development of an optimal regional model for post-cardiac arrest care organization and associated knowledge translation efforts.

2.8 Rationale for Objective 2

Objective: To evaluate the association between hospital volume of cardiac arrest (average number of OHCA patients eligible for TTM received per year) and: i) successful induction of TTM; ii) cooling initiated; iii) premature termination of life sustaining therapy on the basis of neuroprognostication; and iv) survival to hospital discharge with good neurologic function for post -cardiac arrest patients received by SPARC Network hospitals from 2007 to 2013.

There have been several studies exploring the concept of regionalized cardiac arrest care with centres of excellence from various countries[34-37], but as previously discussed, there has yet to be a consensus on whether this strategy is actually beneficial for the patient. No study has been sufficiently designed and powered to investigate the nature of post-cardiac arrest treatments received at hospitals and to measure variability across different hospitals based on their experience with cardiac arrest. Thus far studies have only been able to look at associations between hospital volume and survival, not at cardiac arrest patient volume and specific types of post-cardiac arrest care received.[34-37]

This thesis is designed to conduct analyses on individual post-cardiac arrest treatment practices. At present, it is not clear exactly how the delivery of these important best practice care processes vary by hospital in Canadian settings. Identifying if an association exists between hospital experience (average annual volume of eligible post-cardiac arrest patients) and post-cardiac arrest quality of care is important. The presence of significant variability in processes based on hospital experience would mean that there is inequity based on geography. The health system would then need to decide whether to focus more knowledge translation efforts on inexperienced hospitals or whether the system should be reorganized to transfer post-cardiac arrest patients to larger, more experienced Centres of Excellence.[7] If no or minimal variability is observed, this will provide rationale to maintain the status quo where EMS vehicles deliver post-cardiac arrest patients to the closest hospital.

Chapter 3

Methods

3.1 Study Design

This was a retrospective cohort study using consecutive out-of-hospital cardiac arrest (OHCA) cases that presented to Strategies for Post-Arrest Resuscitation Care (SPARC) Network hospitals.

3.2 Study Population

The study population was patients with post-cardiac arrest syndrome (i.e., eligible for targeted temperature management (TTM)) who arrived at one of the 37 SPARC Network hospitals of Southern Ontario from September 1, 2007 to December 31, 2013. Ultimately, 2,723 patients (ranging from 5 to 236 per hospital) were eligible for the primary analysis.

3.3 Inclusion and Exclusion Criteria

The study included patients who sustained an OHCA in the SPARC region from September 1, 2007 to December 31, 2013 who had a completed case in the database, who were treated by emergency medical services (EMS), and who were transported and admitted to a SPARC Network hospital. Of those patients admitted to a SPARC Network hospital, patients who had a prehospital Do-Not-Resuscitate (DNR) order, who were less than 18 years old or whose age was missing, or who had a cardiac arrest of an obvious cause were excluded from the analysis. From those eligible patients admitted to hospital, those who were comatose as well as those who had a sustained return of spontaneous circulation (ROSC) in the emergency department (≥20 minutes) were included. Final exclusions were made if patients had any of the following within six hours of emergency department arrival: a DNR order, withdrawal of life

sustaining therapy, intracranial bleeding, severe bleeding, or death. These criteria are consistent with previous SPARC studies in identifying patients eligible for TTM. For the secondary analysis of premature withdrawal of life-sustaining therapy, from this population patients who died less than 72 hours after emergency department arrival with a diagnosis of brain death or despite full life sustaining therapy in place were excluded as they were not at risk for premature withdrawal of life-sustaining therapy.

3.4 Data Sources

This thesis used data from several pre-existing sources. The primary data source was the SPARC Network database.[72] These data were supplemented with linked data from the Resuscitations Outcome Consortium (ROC).[81] Hospital-level data were obtained from the Ontario Ministry of Health and Long-Term Care, and a report from the Cardiac Care Network of Ontario.[82]

3.4.1 Strategies for Post-Arrest Resuscitation Care (SPARC) Network Database

The SPARC Network is a collaborative network of hospitals, involving local emergency departments, and intensive care unit (ICU) physician and nursing leaders who participate in a comprehensive program designed to standardize, monitor, and improve the care of patients resuscitated from out-of-hospital and in-hospital cardiac arrest. The network represents all destination hospitals for six regional EMS systems and serves a population of 8.8 million (see figures 5 and 6). The SPARC Network database contains in-hospital data from all OHCA patients received at 37 hospitals in Southern Ontario.[83] Patient characteristics, cardiac arrest characteristics and detailed information about in-hospital treatments and processes of care are captured in this database. The SPARC Network hospitals are diverse, ranging from small rural community hospitals such as Collingwood, to large urban teaching hospitals such as St. Joseph's Toronto. The SPARC

Network has been in existence since 2007 and has collected data from more than 40,000 post-cardiac arrest patients.

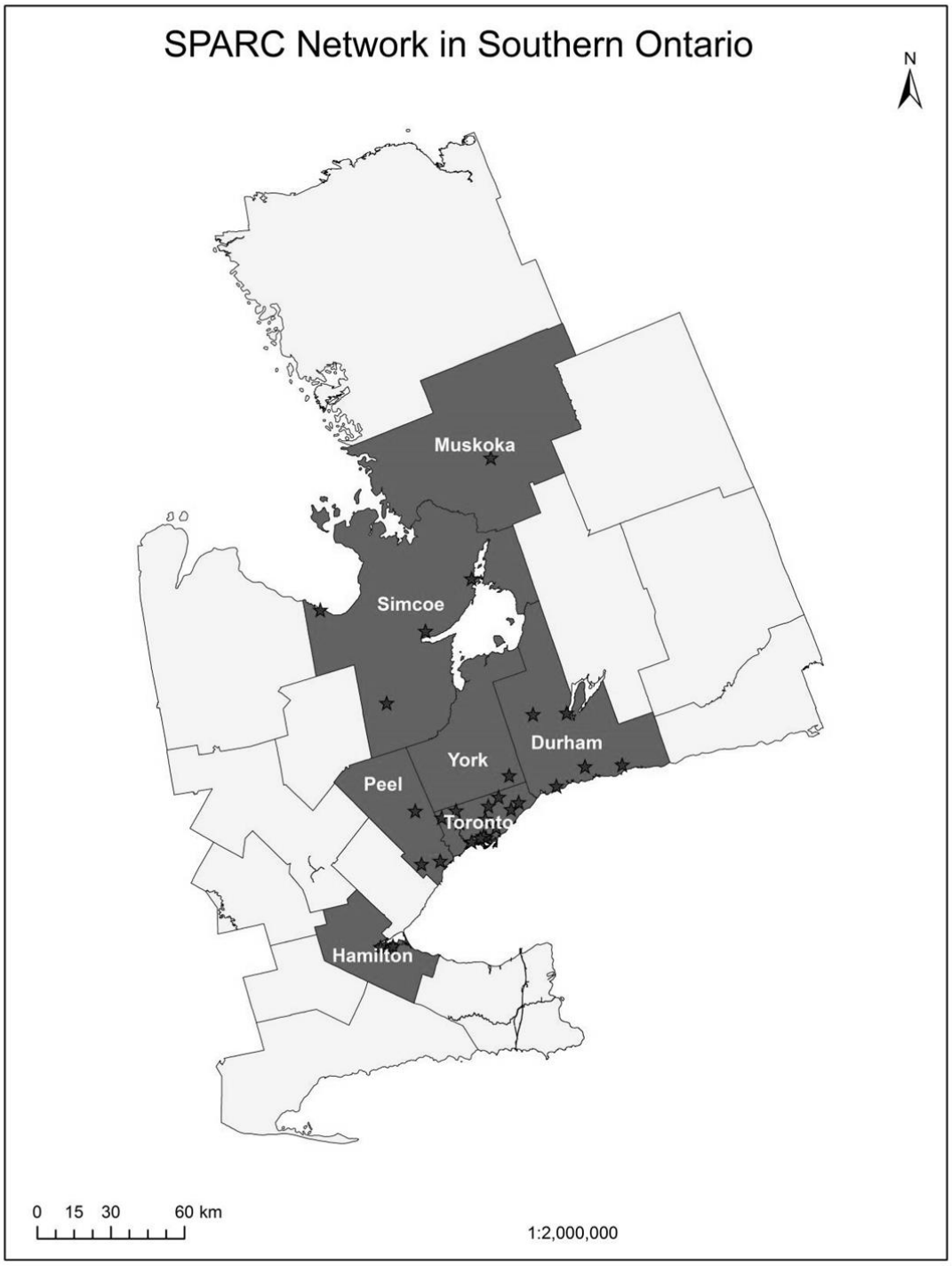

Figure 5. The SPARC Network. EMS regions are outlined and labelled. Participating hospitals are indicated by a star.

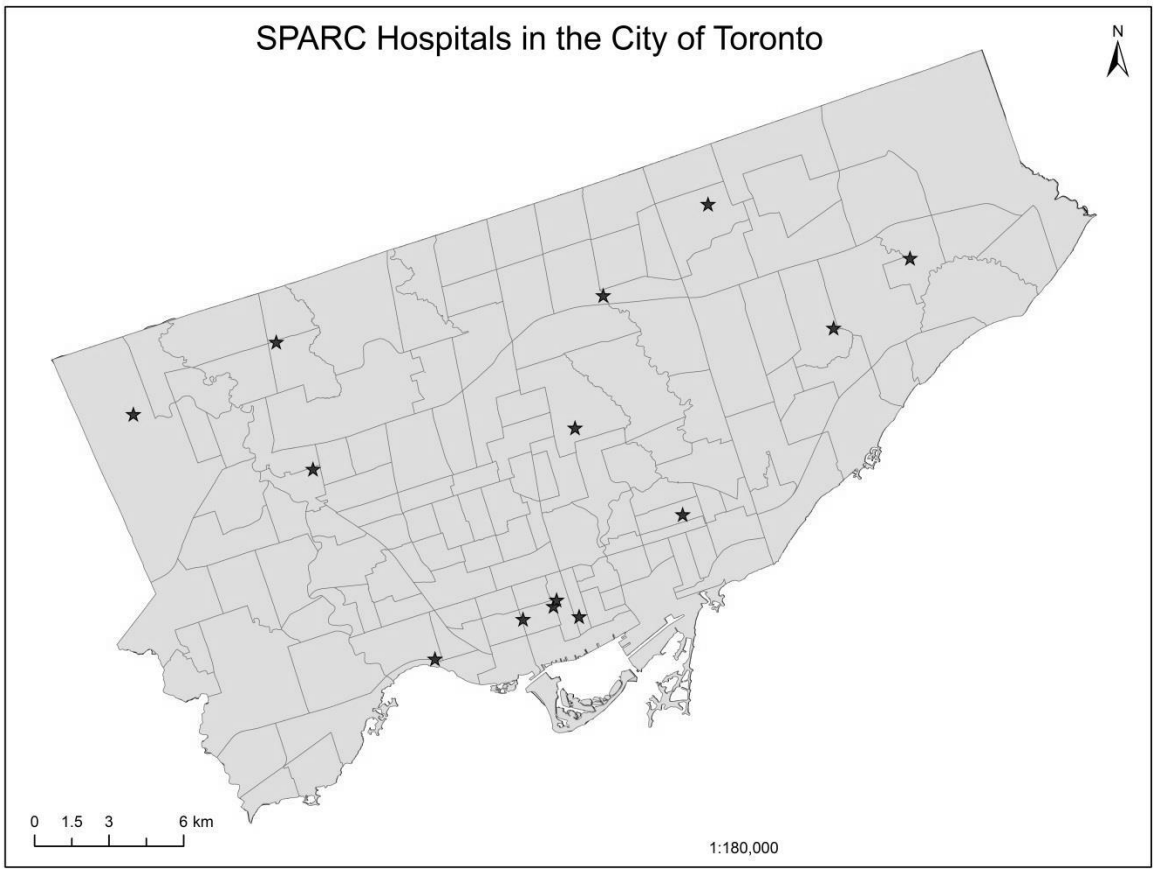

Figure 6. SPARC hospitals in the city of Toronto. Hospitals are indicated by a star.

Primary data collection occurs on all patients who arrive at a participating hospital following OHCA. Case identification of all potentially eligible cases is strengthened with two procedures. Paramedics in the region are instructed to call a cardiac arrest notification line using a 1-800 number to allow live notification of a cardiac arrest case at a participating SPARC hospital. This practice, related to previous cardiac arrest clinical trials in the region, has been incorporated into their standard operating procedures. Patient and receiving hospital details are used to open a new case in a web-based data collection tool. The in-hospital data abstractor for that hospital is notified by auto-email of a new case requiring data collection. A secondary mechanism currently

in place to ensure capture of all eligible cases involves the hand searching of all ambulance call report forms from the EMS services within the SPARC network region. If cases are identified during hand search, patient and hospital information from the ambulance call report are entered into a web interface to open a new case and the hospital data abstractor is automatically notified of a new case requiring data abstraction. The SPARC Network has achieved a 99% case capture rate based on an internal audit (unpublished data).

In addition to the built-in visibility rules and error checks of the web-based system, the SPARC Network conducts periodic quality audits of abstracted data.[83] Twenty percent of all charts undergo double data entry by core research staff for quality assurance.[83] This is done in a random fashion across all in-hospital data abstractors.[83] Data quality feedback is provided to all data entry personnel on systematic errors and personalized error rates are monitored.[83] The most recent audit looking at the percent of charts having agreement with the auditor for each of 260 key variables found the average percentage of correct responses across all variables was 90%.[83] Variables where average agreement is poor are systematically evaluated by exploring potential reasons for discrepancies and misinterpretation by the data abstractors.[83] Results of this type of review inform changes to the data abstraction instructions and future educational updates for the data abstractor network.[83]

Hospitals in the SPARC Network underwent a pragmatic, stepped-wedge cluster randomized controlled trial that involved active and passive knowledge translation interventions aimed at increasing the number of eligible patients who received TTM.[72] Each hospital was randomly assigned to one of 4 wedges, which in turn received quality improvement interventions according to a stepped-wedge implementation schedule. The stepped-wedge intervention schedule involved an initial baseline period of at least 7 months with no intervention, followed by a passive

(education, generic protocol, physician order set, and recruitment of local champions) intervention period of at least 9 months, followed by an active (clinical nurse specialist providing site-specific interventions, monthly audit-feedback, network educational events, internet blog) intervention period of at least 4 months (see figure 7). In this way, the hospital served as its own control. This trial found that there was a significant increase in the number of eligible patients who received TTM for the interventions versus the control group, but did not find a significant difference between the passive and active knowledge translation interventions (unpublished data).

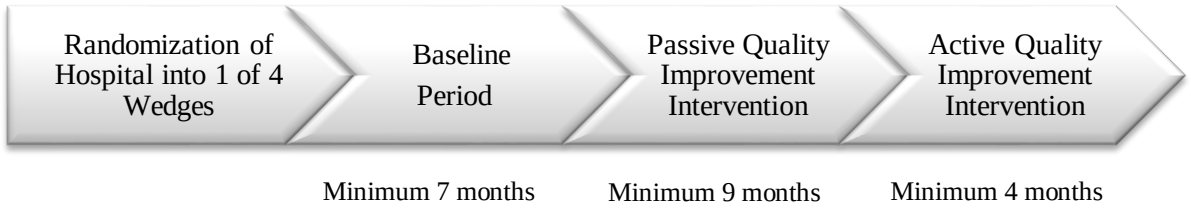

Figure 7. Study phases of the SPARC stepped wedge trial

3.4.2 Resuscitation Outcomes Consortium (ROC) Epistry Database

ROC is a clinical trial network focusing on research in the area of pre-hospital cardiopulmonary arrest and severe traumatic injury. ROC consists of 10 Regional Clinical Centers, satellite sites, and a Data and Coordinating Center that provide the necessary infrastructure to conduct multiple collaborative trials to aid rapid translation of promising scientific and clinical advances to improve resuscitation outcomes (see figure 8). Trials evaluate existing or new therapies (such as pharmacologic immune modulators) as well as clinical management strategies (such as new resuscitative fluids, novel hemorrhage control strategies, the use of cerebral protection and

neurologic preservation, metabolically directed therapies, and alternative methods of delivering CPR or defibrillation).

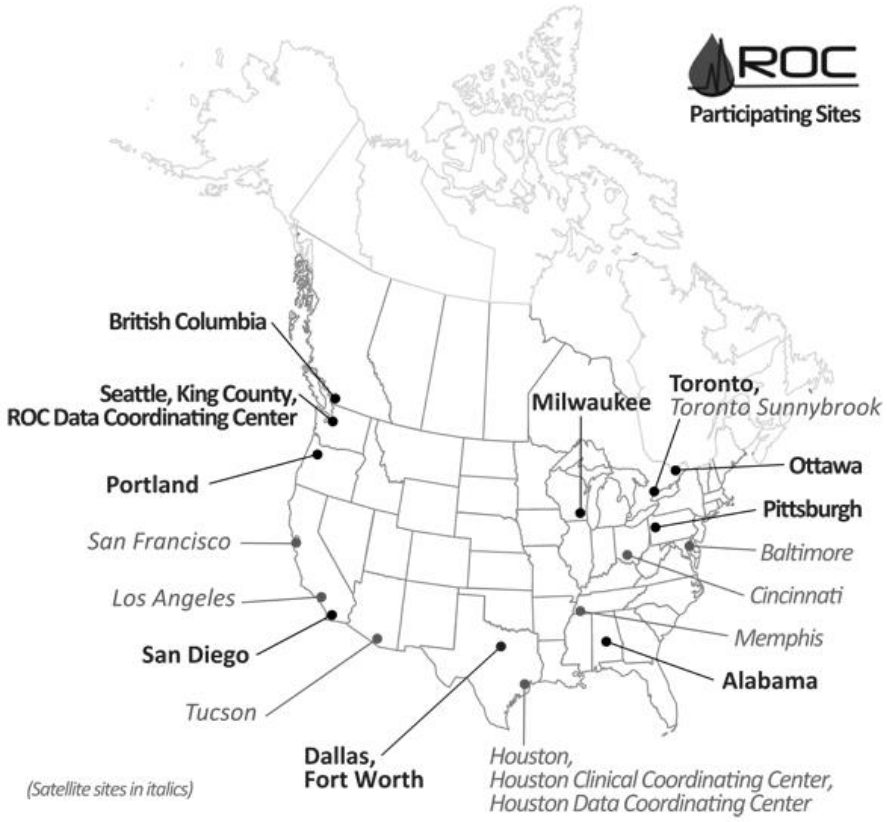

Figure 8. Sites of the Resuscitation Outcomes Consortium (ROC)

As Toronto is a Regional Clinical Center, the ROC Epistry database captures data on all OHCA patients in the SPARC region.[38] Epistry provided all prehospital cardiac arrest characteristics and treatment provided to patients identified in the SPARC database.

3.5 Study Variables

3.5.1 Descriptive Variables

There were a number of key descriptive variables used in this study (see table 1). These included both patient-level (Level 1) and hospital-level (Level 2) variables due to the clustered

nature of the data, with patients attending one of the thirty-seven hospitals in the SPARC Network. Patient-level descriptive variables were of four categories: patient characteristics (demographics), cardiac arrest characteristics, treatment processes, and patient outcomes.

Patient characteristic variables included sex and age. Age was a continuous variable, defined as the difference in years between the date of birth of the patient and the date of hospital admission for the cardiac arrest event. Comorbidity data were explored, and not considered beyond exploratory analyses as they were not well recorded in the database. The implications of excluding these variables are discussed in the limitations section of Chapter Five.

Cardiac arrest characteristic variables included: initial rhythm (shockable or not shockable/unknown), bystander witnessed arrest (yes or no/unknown), emergency medical services (EMS) witnessed arrest (yes or no/unknown), location of arrest (public or private/unknown), bystander resuscitation (yes or no/unknown), bystander cardiopulmonary resuscitation (CPR) (yes or no/unknown), bystander automated external defibrillator (AED) use (yes or no/unknown), EMS response time (seconds), ROSC in the field (yes or no/unknown), emergency department status (pulse present, ongoing resuscitation, or unknown), and SPARC stepped-wedge trial group (intervention or control). Bystander resuscitation was defined as any CPR or AED use. SPARC stepped-wedge trial group was assigned based on the date the patient was treated at hospital in relation to whether or not that hospital had yet undergone the knowledge translation initiative at that time. This was done to account for any differences in patient care that may have resulted from the knowledge translation-initiative as the study found that the intervention significantly increased the use of therapeutic hypothermia. All variables were categorical except EMS response time, which was continuous and defined as the number of seconds from the time of the 911 call to the time of arrival of EMS personnel on scene.

Treatment process variables included: whether or not the patient had cooling initiated, whether or not the patient achieved successful TTM, whether or not the patient received angiography, whether or not the patient had an electrophysiologist consult, and whether or not the patient received an implantable cardioverter defibrillator (ICD). Treatment process variables were defined according to the recommendations put forth by the American Heart Association and the International Liaison Committee on Resuscitation for the treatment of patients with post-cardiac arrest syndrome.[4,5] Cooling initiated was defined as any indication that cooling was done in the emergency department, hospital, or both. Doctor's orders had to be validated by nursing notes stating that cooling therapy was given, e.g., 2 litres of cold saline, ice pack applied, cooling blanked applied, therapeutic hypothermia initiated. Achieving successful TTM was defined as having a core body temperature of 32 to 34 degrees Celsius within 6 hours of emergency department arrival. Angiography was defined as the patient being taken to the catheterization lab for a diagnostic catheterization (angiography) within 72 hours of first emergency department arrival. Electrophysiologist consult was defined as documentation of the patient receiving their first electrophysiologist consultation after arrival in the emergency department and within 72 hours after emergency department arrival at the first hospital. ICD placement was defined as the patient having an ICD implanted at any time during hospitalization. All of these treatment process variables were categorical, either the procedure was done or it was not (or it was not recorded as being done in the chart).

Patient outcome variables were withdrawal of life sustaining therapy on the basis of premature neuroprognostication, survival, and survival with good neurologic function. Having life sustaining therapy withdrawn on the basis of premature neuroprognostication was defined as a patient who was deemed to have poor neurological prognosis, and had care withdrawn or

limited resulting in death within 72 hours of hospital arrival. Survival was defined as the patient being alive at the time of hospital discharge. Survival with good neurologic function was defined as being discharged with a cerebral performance category (CPC) score or 1 or 2, indicating "good" neurologic function (see appendix A). Those patients who had a CPC score of 3 or 4, or who were missing the CPC at discharge variable, were defined as "not good" neurologic function. CPC scores are valid in indicating gross functional states of cardiac arrest survivors and are useful for clinical and research applications such as this study.[84]

Hospital-level variables included the average number of patients eligible for TTM per year, number of beds, teaching status, and whether or not the hospital was a percutaneous coronary intervention (PCI) centre. Patients were assigned the first hospital at which they arrived, regardless of any transfers that may have occurred afterwards. This was done because the aim of this study was to evaluate the current system where patients are initially brought to the nearest hospital. With this aim in mind, it was not important where the patients eventually received treatment, only where they were initially brought. Hospital-level variables were obtained from several sources: average annual number of patients eligible for TTM was calculated from the study population, bed number and teaching status were obtained from the Ontario Ministry of Health and Long Term Care, and PCI centres were identified from a report from the Cardiac Care Network of Ontario.[82] Average annual number of patients eligible for TTM and bed number were continuous variables, and teaching and PCI status were categorical (yes, no).

Table 1. Patient and hospital-level descriptive variables

Category	Variable	Origin	Type	Definition
Patient-level				
Patient	Sex	ROC epistry	Categorical	Male or female

characteristics				
	Age	ROC epistry	Continuous	Difference in years between the date of birth of the patient and the date of hospital admission for the cardiac arrest event
Cardiac arrest characteristics	Initial rhythm	ROC epistry	Categorical	Shockable (VF/VT) or not shockable (asystole/PEA)/ unknown
	Bystander witnessed arrest	ROC epistry	Categorical	Yes or no/unknown
	EMS witnessed arrest	ROC epistry	Categorical	Yes or no/unknown
	Location of arrest	ROC epistry	Categorical	Public or private/unknown
	Any bystander resuscitation	ROC epistry	Categorical	Any CPR or AED use or no/unknown
	Bystander CPR	ROC epistry	Categorical	Yes or no/unknown
	Bystander AED use	ROC epistry	Categorical	Yes or no/unknown
	EMS response time	ROC epistry	Continuous	Number of seconds from the time of the 911 call to the time of arrival of EMS personnel on scene
	ROSC in the field	ROC epistry	Categorical	Yes or no/unknown
	Emergency department status	SPARC database	Categorical	Pulse present, ongoing resuscitation, or unknown
	SPARC trial group	SPARC database	Categorical	Intervention (patient attended a hospital past the point in time at which the passive intervention began) or control
Treatment Processes	Cooling initiated	SPARC database	Categorical	Any indication that cooling was done in the emergency department, hospital, or both or no/unknown

	Successful TTM	SPARC database	Categorical	Core body temperature of 32 to 34 degrees Celsius within 6 hours of emergency department arrival or no/unknown
	Any angiography	SPARC database	Categorical	Angiography within 72 hours of hospital arrival or no/unknown
	Electrophysiologist consult	SPARC database	Categorical	Documentation of patient receiving first electrophysiologist consultation within 72 hours after emergency department arrival or no/unknown
	ICD placement	SPARC database	Categorical	Patient had an ICD implanted any time during hospitalization or no/unknown
Outcomes	Withdrawal of life sustaining therapy on the basis of neuroprognostication	SPARC database	Categorical	Patient deemed to have poor neurological prognosis, and care withdrawn or limited resulting in death within 72 hours of hospital arrival or no/unknown
	Survival to hospital discharge	SPARC database	Categorical	Patient alive at time of hospital discharge or no/unknown
	Survival with good neurologic function	SPARC database	Categorical	Patient discharged with a CPC score or 1 or 2 or no/unknown
Hospital-level				
	Average number of patients eligible for TTM per year	SPARC database	Continuous	Total number of patients eligible for TTM seen for each hospital over the study period divided by the years of the

			study (5.33)
Number of beds	MOHLTC	Continuous	Hospital average number of beds staffed and in operation
Teaching status	MOHLTC	Categorical	Academic hospital or not
PCI centre	CCNO	Categorical	Yes or no

Average annual number of patients eligible for TTM was categorized into three categories for description of the study population: low (less than 15 patients eligible for TTM per year), moderate (between 15 and 25 patients eligible for TTM per year), and high (greater than 25 patients eligible for TTM per year). These categories were determined post-hoc taking into consideration what was considered to be meaningful cut-points in volume based on the opinion of clinical collaborators (DS, LM, SCB), while maintaining an adequate number of hospitals and patients in each category for sufficiently powered analyses.

3.5.2 Exposure Variable

The exposure of interest in this study was the average annual volume of patients with post-cardiac arrest syndrome, i.e., eligible for therapeutic hypothermia. This variable was calculated using the total number of eligible patients that attended each hospital over the entire study period, divided by the total number of years of the study period. This variable was then assigned to each patient as a level 2 variable based on the hospital at which they were first received.

3.5.3 Outcome Variables

3.5.3.1 Primary Outcome Variable: Successful TTM

The primary outcome of successful TTM was defined as achieving a core body temperature of 32 to 34 degrees Celsius within 6 hours of emergency department arrival.

3.5.3.2 Secondary Outcome Variable: Cooling Initiated

Cooling initiated was defined as any indication that cooling was done in the emergency department, hospital, or both. Doctor's orders had to be validated by nursing notes stating that cooling therapy was given, e.g., 2 litres of cold saline, ice pack applied, cooling blanked applied, therapeutic hypothermia initiated.

3.5.3.3 Secondary Outcome Variable: Premature Withdrawal of Life Sustaining Therapy on the Basis of Neuroprognostication

Having life sustaining therapy withdrawn on the basis of premature neuroprognostication was defined as a patient who was deemed to have poor neurological prognosis, and had care withdrawn or limited resulting in death within 72 hours of hospital arrival.

3.5.3.4 Secondary Outcome Variable: Survival with Good Neurologic Function

Survival with good neurologic function was defined as being discharged with a cerebral performance category (CPC) score or 1 or 2, indicating "good" neurologic function (see appendix A). Those patients who had a CPC score of 3 or 4, or who were missing the CPC at discharge variable, were defined as "not good" neurologic function.

3.5.4 Covariates

Several potential patient-level covariates were identified from previous studies that examined the relationship between volume of OHCA patients and survival. These included: age, sex, presenting rhythm (shockable or not shockable), EMS response time, witnessed arrest, bystander CPR, bystander AED use, location of arrest (public or private), and medical history.[78,79,85] These variables had the potential to confound the relationship between annual volume of eligible post-cardiac arrest patients and survival because all have been established as predictors of survival after cardiac arrest,

as well as have the potential to be associated with specific hospitals (and thereby specific hospital volumes), and are not on the causal pathway. For example, a hospital in a rural area that sees a low annual volume of post-cardiac arrest patients may have also experienced a patient population that is older, where the average EMS response time is lower due to the rurality of the area, and where there are fewer witnessed arrests and lower bystander CPR rates because of the lower population density of the area. These factors could have confounded the relationship between volume of post-cardiac arrest patients and survival because they are independently associated with both the exposure and outcome. As there are already important predictors of survival after cardiac arrest established, clinically important and statistically significant covariates were retained in the models of the patient outcomes: premature withdrawal of life sustaining therapy on the basis of neuroprognostication and survival with good neurologic function.

Most of these potential covariates also had the potential to confound the relationship between annual volume of post-cardiac arrest patients and the primary outcome, successful induction of therapeutic hypothermia. For example, it is conceivable that older, more co-morbid patients may be transported preferentially to larger hospitals (based on EMS destination hospital choices made by paramedics or the geographic distribution of demographics around particular hospitals) and may also be cooled in different ways or with different efficiency when compared to other patients with different demographics. Because of the exploratory nature of the potential confounders of the volume-target temperature relationship, the change in estimate method was used to identify confounders for outcomes related to TTM. This is described further in the statistical analysis section.

Hospital-level factors such as the availability of specialty services (local angiography, etc.), teaching status, and total number of beds that had been identified in the literature as potential covariates were also considered.[77–79] These factors had the potential to be independently associated

with both volume of post cardiac arrest patients and the outcomes of interest. Larger hospitals tend to see more cardiac arrest cases and are also more likely to offer specialty services, be academic hospitals, and have a higher total number of beds than smaller hospitals. Patients who were treated at hospitals with specialty services may have had better outcomes than patients who were treated at hospitals that do not offer those services. Academic hospitals could have been more likely to implement newer treatments such as therapeutic hypothermia.

Figure 9 represents a conceptual framework of how patient and hospital-level variables were considered as potential confounders to the relationship between average annual hospital volume of post-cardiac arrest patients eligible for TTM and the outcomes of interest.

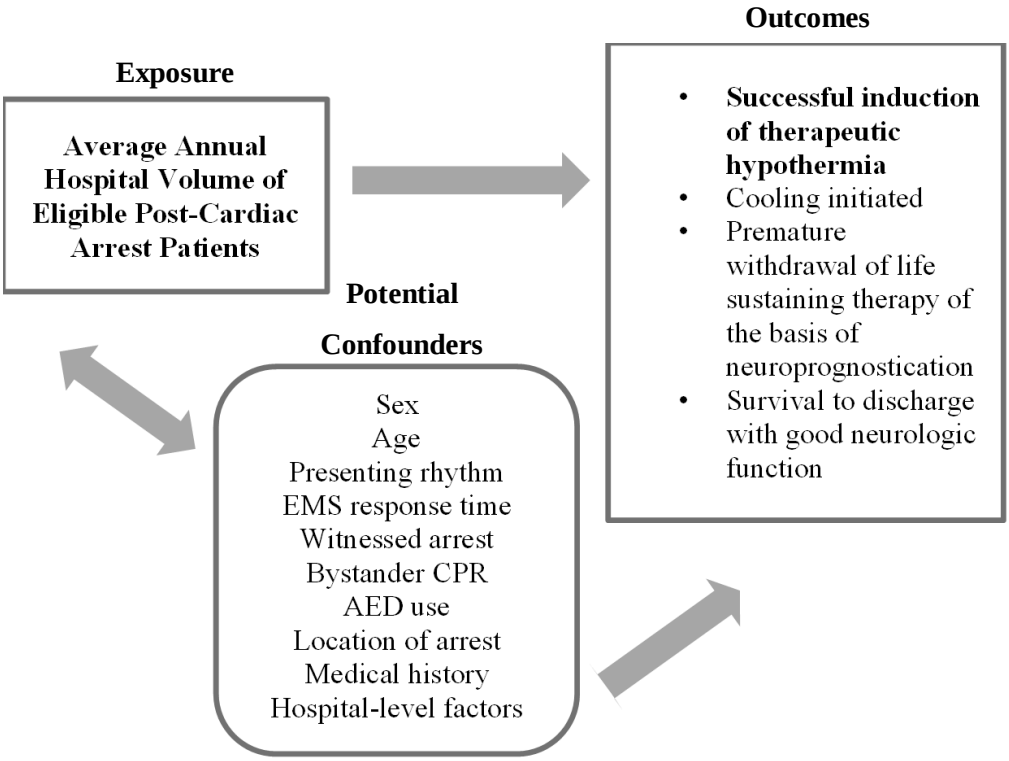

Figure 9. Conceptual framework of potential confounders

3.6 Statistical Analyses

All analyses were conducted using SAS (v 9.4 Cary, NC). For all analyses a *p*-value <0.05 was considered significant.

3.6.1 Objective 1: To quantify the variability in post-cardiac arrest syndrome patient characteristics, processes, and outcomes by average annual hospital volume of OHCA patients eligible for TTM received across a network of 37 hospitals in Southern Ontario, the SPARC Network, from 2007 to 2013.

Descriptive statistics were used to assess the study population. The unit of analysis was the individual patient. Standard measures of central tendency (means, medians, estimates of variability) and proportions were calculated to describe patient characteristics, cardiac arrest characteristics, treatment process, and outcome data within the SPARC region, then within the three previously described hospital volume categories. Statistical comparisons of any observed variations in mean/median values by hospital volume category, and proportions by hospital volume category, were based upon Rao-Scott chi-square and repeated measures one-way analysis of variance tests, which have adjustments for clustering. The patient-level variables assessed included sex, age, initial rhythm, bystander witnessed arrest, EMS witnessed arrest, location of arrest bystander resuscitation, bystander CPR, bystander AED use, EMS response time, ROSC in the field, ROSC at emergency department arrival, SPARC trial group, successful TTM, cooling initiated, premature withdrawal of life sustaining therapy on the basis of neuroprognostication, angiography, electrophysiologist consult, ICD placement, survival, and survival with good neurologic function. Survival and survival with good neurologic function were then stratified by year and described. The Cochrane-Armitage Chi-square test for trend was used to determine any trends in survival and survival with good neurologic function over the study period.

The hospitals in the population were described using standard measures of central tendency (means, medians, estimates of variability) and proportions. Hospital-level variables assessed included average number of patients eligible for TTM per year, number of beds, teaching status, and whether or not the hospital was a PCI centre.

3.6.2 Objective 2: To evaluate the association between hospital volume of cardiac arrest (average number of OHCA patients eligible for TTM received per year) and: i) successful induction of TTM; ii) cooling initiated; iii) premature termination of life sustaining therapy on the basis of neuroprognostication; and iv) survival to hospital discharge with good neurologic function for post -cardiac arrest patients received by SPARC Network hospitals from 2007 to 2013.

Several multi-level logistic regression models were built to assess the relationship between each of the outcomes of interest and average annual hospital volume of patients eligible for TTM (Proc GLMMIX, SAS v 9.4, Cary, NC). Data at the patient-level were considered fixed effects and data at the hospital-level were considered random effects. First, empty regression models were constructed with only hospital as a predictor and intraclass correlations (ICCs) and median odds ratios (MORs) were calculated. Second, multivariate multi-level regression models were constructed for each of the outcomes of interest adjusting for covariates as appropriate and MORs were calculated to assess the unexplained between hospital variation by the model.

For the clinical process outcomes, successful TTM and cooling initiated, the change in estimate approach with a 10% cutoff was used in model building to assess any potential confounders.[86] For the patient outcomes, life sustaining therapy withdrawn on the basis of premature neuroprognostication and survival to hospital discharge with good neurologic function, all variables with a $p<0.10$ or felt to be clinically significant based on published evidence were included in the final models.[31] We selected covariates a-priori based on

knowledge of association from previous literature or well-recognized risk factors from the clinical setting in order to increase the precision of the estimates.

The relationships between volume and the outcomes were assessed by modelling volume as a continuous variable, as a categorical variable using the categories defined in the descriptive analysis, and as a fractional polynomial using a standard algorithm to select the best fit term (*%mfp8*[87] macro in SAS) in case volume had a non-linear relationship with any of the outcomes of interest. Overall fit of the models was assessed by Akaike Information Criteria (AIC) and the best fit models are presented in Chapter Four (see appendix C for other models).

Chapter 4

Results

4.1 Eligible Patients

From September 1st, 2007 to December 31st, 2013, there were 40,573 out-of-hospital cardiac arrest (OHCA) patients in the Strategies for Post-Arrest Resuscitation Care (SPARC) region. After the exclusion criteria were applied, 2,723 patients in the 37 hospitals were eligible for the main analysis. For the secondary outcome of premature withdrawal of life sustaining therapy on the basis of neuroprognostication, 1,571 patients were deemed "at risk" and therefore eligible for analysis. At risk patients included all patients except those who died less than 72 hours after emergency department arrival with a diagnosis of brain death or despite full life sustaining therapy in place. A flow diagram of the inclusions and exclusions that lead to the patients included in the final analyses is shown in figure 10.

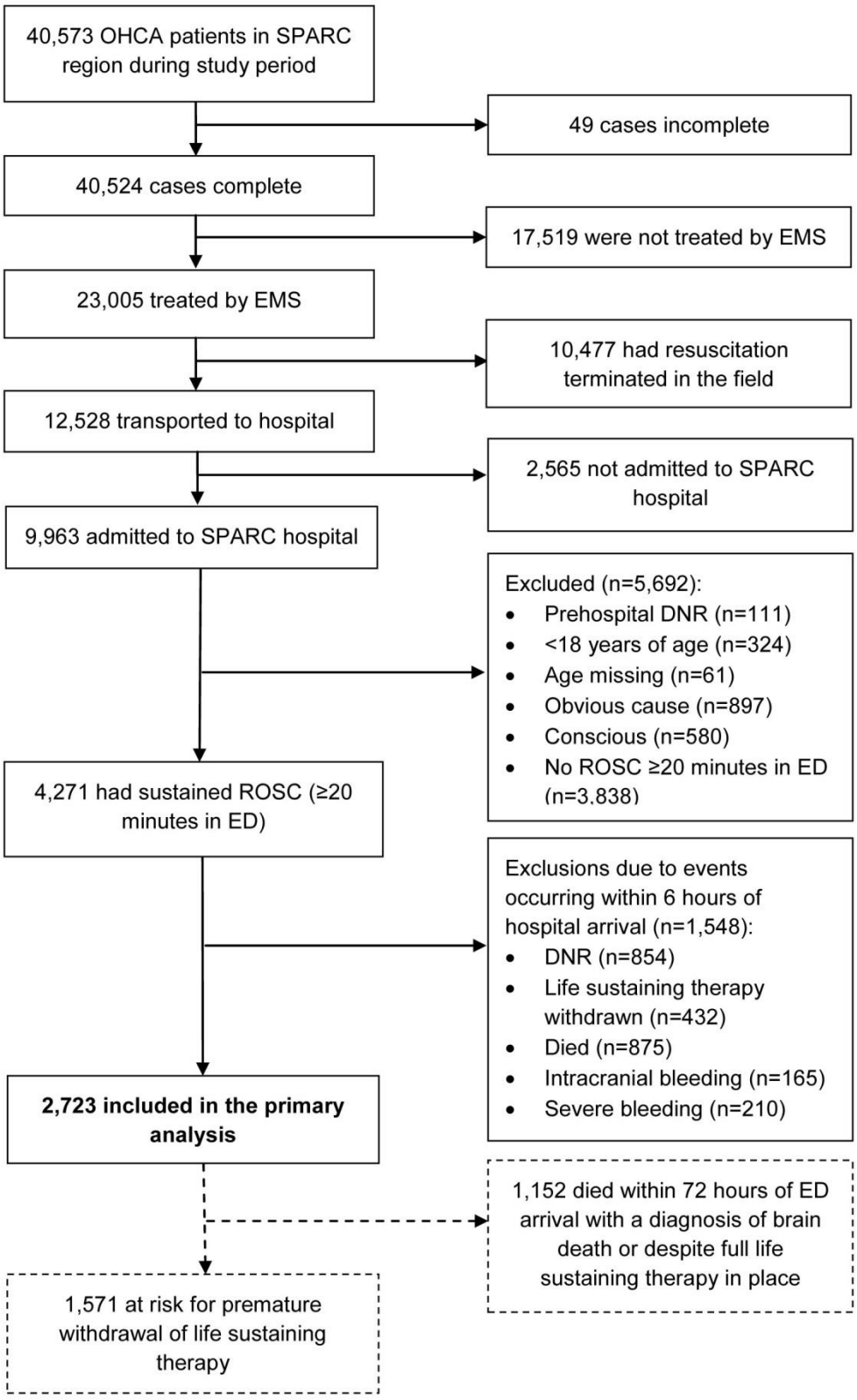

Figure 10. Flow diagram of patients included in the analyses

4.2 Overall Description of Study Population

4.2.1 Patient and Cardiac Arrest Characteristics

The average age of the post-cardiac arrest syndrome patient in the study population was 65. The population was predominantly male (69%). Most patients had a bystander witnessed arrest (58%). Approximately half of the patients had a shockable initial rhythm (ventricular fibrillation (VF) or ventricular tachycardia (VT)). A quarter of the patients had an arrest in public. 42% of patients had cardiopulmonary resuscitation (CPR) attempted by a bystander and only 5% had any indication of bystander automated external defibrillator (AED) use. It took an average of 6 minutes for emergency medical services (EMS) to respond to the cardiac arrests in the population. Almost all patients in the study population had a return of spontaneous circulation (ROSC) in the field (87%), and most had a pulse present in the emergency department (78%). Table 2 describes the patient demographics and cardiac arrest characteristics of the study population.

Table 2. Patient demographics and cardiac arrest characteristics

Characteristic	*N*=2723 (37 hospitals)
Age, years (mean)	65 (± 16)
Male	1868 (69%)
Bystander witnessed arrest	1588 (58%)
EMS witnessed arrest	430 (16%)
Shockable initial rhythm	1379 (51%)
Public location	694 (25%)
Bystander resuscitation	1145 (42%)
Bystander CPR	1135 (42%)
Bystander AED	123 (5%)
EMS response time, seconds (mean)	375 (± 156)
ROSC in the field	2371 (87%)
Emergency department status	
Pulse present	2114 (78%)
Ongoing resuscitation	585 (21%)
Unknown	24 (1%)

4.2.2 Comorbidities

The proportions of patients with relevant prior medical conditions were examined. Many patients had a history of cardiac illness, high blood pressure, and diabetes. These data are presented in table 3 to demonstrate the general health status of the population. Further analyses of comorbidity data were not conducted as there were concerns over quality and completeness. This limitation is discussed further in Chapter Five.

Table 3. Patient comorbidities

Condition	*N*=2723 (37 hospitals)
Alcohol abuse	194 (7%)
Atrial fibrillation/flutter	261 (10%)
Cancer	208 (8%)
Cardiac medications	657 (24%)
Chest pain/angina	132 (5%)
Congestive heart failure	224 (8%)
Coronary artery bypass graft	144 (5%)
Coronary artery disease	509 (19%)
Diabetes	516 (19%)
Gastrointestinal disorders	114 (4%)
Heart surgery	211 (8%)
Hypertension	1006 (37%)
Implantable cardioverter defibrillator	37 (1%)
Myocardial infarction	363 (13%)
Pacemaker	53 (2%)
Psychiatric	219 (8%)
Recreational drugs	155 (6%)
Respiratory	415 (15%)
Seizure	72 (3%)
Stroke/Transient Ischemic Attack	154 (6%)
Syncope	70 (3%)

4.2.3 Hospital Characteristics

Overall hospital characteristics of the 37 hospitals in the SPARC Network were examined. The mean average annual volume of eligible patients across the 37 hospitals, number of beds, teaching status, and percutaneous coronary intervention (PCI) centre status of the hospitals are reported in table 4.

Table 4. Hospital characteristics

Characteristic	*N*=37 hospitals
Patients eligible for TTM/year, mean (±SD)	13.8 (±10.8)
Hospital beds, median (IQR)	393 (150.5-597)
Academic hospital	11 (30%)
PCI centre	7 (19%)

4.2.4 Treatment

Seventy percent of eligible patients had cooling initiated, and less than half of these patients actually reached target temperature. Of those patients at risk for premature withdrawal of life sustaining therapy on the basis of neuroprognostication, 8% had care withdrawn prematurely. Twenty-seven percent of patients had some kind of angiographic procedure, 7% of patients had a consultation with an electrophysiologist, and 9% had an implantable cardioverter defibrillator (ICD) placed. These results are presented in table 5.

Table 5. Proportion of patients achieving treatment outcomes

Treatment Outcome	*N*=2723
Successful TTM	895 (33%)
Cooling initiated	1918 (70%)
Life sustaining therapy withdrawn on the basis of premature neuroprognostication (for those at risk)	120/1571 (8%)
Angiography	728 (27%)
Electrophysiologist consult	192 (7%)
Implantable cardioverter defibrillator placement	253 (9%)

4.2.5 Survival

Overall survival to hospital discharge for patients in the study was 43%, and 70% of those who survived did so with good neurologic function (cerebral performance category (CPC) score of 1 or 2). Survival was stratified by year (for the years the study had data for a complete calendar year, so the 4 months of 2007 were excluded) to determine any changes in survival over the study period. In 2008, 35% of eligible patients survived to hospital discharge and only 47% of those who survived did so with good neurologic function. In 2013, 51% of patients survived to hospital discharge and 78% of those who survived did so with good neurologic function. Each year of the study, survival to hospital discharge increased. The Cochrane-Armitage Chi-square test for trend revealed this increasing trend in the proportion of patients who survived to hospital discharge over the years of the study to be significant ($Z=5.36$, $p<0.01$). The Cochrane-Armitage Chi-square test for trend also revealed the increasing trend in the proportion of surviving patients who did so with good neurologic function over the years of the study to be significant ($Z=8.05$, $p<0.01$). The proportions of patients surviving to hospital discharge across the study period are shown in table 6.

Table 6. Proportion of patients surviving to hospital discharge from 2008-2013

Year	Proportion of Patients Surviving to Hospital Discharge	Proportion of Surviving Patients with Good Neurologic Function (CPC 1 or 2)
2008	109/313 (35%)	51/109 (47%)
2009	124/326 (38%)	59/124 (48%)
2010	187/459 (41%)	130/187 (70%)
2011	215/503 (43%)	181/215 (84%)
2012	232/503 (46%)	184/232 (79%)
2013	274/535 (51%)	214/274 (78%)
Entire Study period	**1179/2723 (43%)**	**828/1179 (70%)**

Survival to hospital discharge and survival with good neurologic function are plotted in figure 11 to demonstrate the increasing trends over time. The difference between overall survival and survival with good neurologic function narrows between 2009 and 2011.

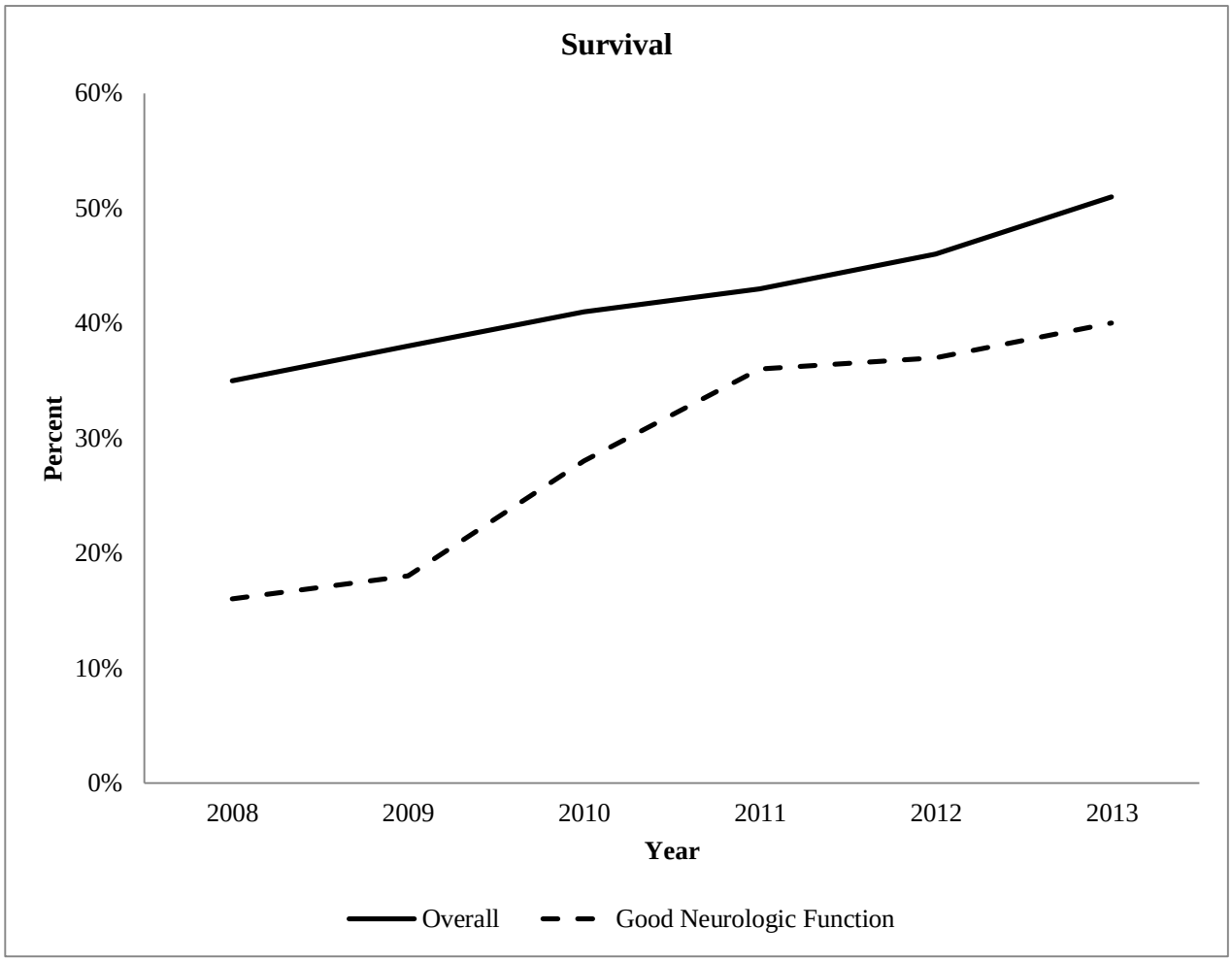

Figure 11. Survival from 2008-2013

4.3 Description of Study Population Stratified by Volume Category

The average annual volume of patients was calculated for each of the 37 hospitals from the study population. The hospitals of the SPARC Network were then classified into three different volume categories: low (less than 15 patients eligible for TTM per year), moderate

(between 15 and 25 patients eligible for TTM per year), and high (greater than 25 patients eligible for TTM per year). These categories were determined post-hoc taking into consideration what was considered to be an important difference in volume based on clinical experience, while maintaining a sufficient number of hospitals and patients in each category for meaningful analyses. There were 22 hospitals categorized as low volume, 9 hospitals categorized as moderate volume, and 6 hospitals classified as high volume. Table 7 lists the hospitals that were assigned to each of the three categories.

Table 7. Hospitals in volume categories

Low (<15 eligible TTM/year) (*N*=22)	**Moderate (15-25 eligible TTM/year) (*N*=9)**	**High (>25 eligible TTM/year) (*N*=6)**
Lakeridge Health – Port Perry Site	Humber – Memorial	Lakeridge Health – Oshawa Site
Markham Stouffville	North York General	Toronto East General Hospital
Mount Sinai Hospital	Richmond Hill Hospital	Sunnybrook Health Sciences Centre
Muskoka Algonquin Health Care – Bracebridge	Rouge Valley Health System – Centenary	Trillium Health Partners – Mississauga Hospital
Muskoka Algonquin Health Care - Huntsville Site	Scarborough – General	William Osler Health System – Brampton
Collingwood Hospital	Southlake Regional Health Centre	William Osler Health System – Etobicoke
Georgetown Hospital	St. Joseph's Health Centre Toronto	
Georgian Bay General Hospital	St. Michael's Hospital	
Milton District Hospital	Trillium Health Partners – Credit Valley Hospital	
Oakville Trafalgar Memorial Hospital		
Headwaters Health Care Centre		

Dufferin
Humber – York Finch
Joseph Brant Memorial Hospital
Lakeridge Health – Bowmanville Site
Orillia Soldiers Memorial Hospital
Rouge Valley Health System – Ajax Site
Scarborough – Grace
The Royal Victoria Hospital
The Stevenson Memorial Hospital
University Health Network – Toronto General Hospital
University Health Network – Toronto Western Hospital
Uxbridge Cottage

4.3.1 Hospital Characteristics

The characteristics of the hospitals within each volume category were then examined. Hospitals that received a higher volume of eligible post-cardiac arrest patients tended to have higher bed numbers, be academic centres, and be PCI centres. Only bed number was statistically significantly different between volume categories. This is shown in table 8.

Table 8. Characteristics of hospitals in 3 volume categories

	Low (*N*=22)	Moderate (*N*=9)	High (*N*=6)	*p*-value
Patients eligible for TTM/year, mean (±SD)	6.1 (±4.4)	21.3 (±2.5)	30.6 (±7.5)	<0.01
Hospital beds, median (IQR)*	231 (113-444)	444 (385-516)	843 (597-952)	0.04
Academic hospital	5 (23%)	3 (33%)	3 (50%)	0.42
PCI centre	2 (9%)	3 (33%)	2 (33%)	0.18

* $p<0.05$ for ANOVA, nonparametric ANOVA or chi-square tests

4.3.2 Patient and Cardiac Arrest Characteristics

The three hospital volume categories were compared on patient and cardiac arrest characteristics. Patients attending hospitals in each of the volume categories were comparable on most factors. Differences of note were that moderate and high volume hospitals tended to have lower rates of any bystander resuscitation and bystander CPR than low volume hospitals, and that EMS response time decreased with increasing hospital volume. A statistically significant difference between the volume categories was only detected for EMS response time. For this variable, repeated measures analysis of variance (ANOVA) demonstrated that patients at low volume hospitals had significantly higher EMS response times than patients at moderate volume hospitals, and patients at moderate volume hospitals had significantly higher EMS response times than patients at high volume hospitals. Table 9 shows the comparison of the three volume categories on patient and cardiac arrest characteristics.

Table 9. Patient and cardiac arrest characteristics by volume category

Characteristic	Low (*N*=721)	Moderate (*N*=1024)	High (*N*=978)	*p*-value
Age, (years), mean (±SD)	65 (±15)	65 (±16)	64 (±16)	0.44
Male	510 (71%)	684 (67%)	674 (69%)	0.36
Bystander witnessed arrest	428 (59%)	591 (58%)	569 (58%)	0.86
EMS witnessed arrest	97 (13%)	185 (18%)	148 (15%)	0.24
Shockable initial rhythm	382 (53%)	492 (48%)	505 (52%)	0.48
Public location	205 (28%)	242 (24%)	247 (25%)	0.47
Bystander resuscitation	340 (47%)	406 (40%)	399 (41%)	0.13
Bystander CPR	339 (47%)	402 (39%)	394 (40%)	0.10
Bystander AED	39 (5%)	42 (4%)	42 (4%)	0.40
EMS response time (s), mean (±SD)*	391 (±187)	379 (±152)	360 (±135)	<0.01
ROSC in the field	633 (88%)	893 (87%)	845 (86%)	0.32
Emergency department status				0.67
Pulse present	570 (79%)	787 (77%)	757 (77%)	
Ongoing resuscitation	144 (20%)	228 (22%)	213 (22%)	
Unknown	7 (1%)	9 (1%)	8 (1%)	
Intervention trial group	436 (60%)	666 (65%)	668 (68%)	0.45

*$p<0.05$ for Rao-Scott chi-square test or repeated measures ANOVA

4.3.3 Treatments

The treatment processes achieved at each of the tiers of volume were then examined. The only significant differences in treatment processes between the three hospital volume categories were in the proportion of patients who had cooling initiated and who achieved successful TTM. For these process outcomes, patients at high volume hospitals had cooling initiated 16% more than patients at low volume hospitals and had successful TTM 12% more than patients at low volume hospitals. Raw percentages of patients who had life sustaining therapy withdrawn on the basis of premature neuroprognostication increased with increasing hospital volume. Since the

outcome was limited to a subgroup of the population and only a small proportion of this subgroup had the outcome of interest, detecting differences in the rates of premature withdrawal of life sustaining therapy on the basis of neuroprognostication between volume categories was limited by statistical power. Table 10 shows the comparisons of the hospital volume categories in terms of treatment processes.

Table 10. Treatment processes achieved by volume category

	Low (*N*=721)	**Moderate (*N*=1024)**	**High (*N*=978)**	***p*-value**
Successful TTM*	184 (26%)	342 (33%)	369 (38%)	0.04
Cooling initiated*	460 (64%)	678 (66%)	780 (80%)	<0.01
Life sustaining therapy withdrawn on the basis of premature neuroprognostication (for those at risk)	27/454 (6%)	47/591 (8%)	46/526 (9%)	0.60
Angiography	199 (28%)	264 (26%)	265 (27%)	0.96
Electrophysiologist consult	51 (7%)	67 (7%)	74 (8%)	0.90
ICD placement	72 (10%)	83 (8%)	98 (10%)	0.38

*$p<0.05$ for Rao-Scott chi-square test

4.3.4 Survival

Table 11 compares survival to hospital discharge across the volume categories for the years of the study. Table 12 compares survival with good neurologic function across the volume categories for the years of the study. Overall survival to hospital discharge was highest among patients attending low volume hospitals (47%), as was survival with good neurologic function (34%). Though there were no statistically significant differences in survival to hospital discharge or survival with good neurologic function overall or in any year of the study, in 2009 the

differences in both survival and survival with good neurologic function across the volume categories almost reached significance (*p*-values of 0.09 and 0.05, respectively).

Table 11. Survival to hospital discharge by volume category, 2008-2013

	Low (*N*=721)	**Moderate (*N*=1024)**	**High (*N*=978)**	***p*-value**
Entire Study period	**339 (47%)**	**416 (41%)**	**424 (43%)**	**0.31**
2008	26/57 (46%)	35/113 (31%)	48/143 (34%)	0.17
2009	29/66 (44%)	39/122 (32%)	56/138 (41%)	0.09
2010	58/140 (41%)	63/167 (38%)	66/152 (43%)	0.68
2011	68/155 (44%)	73/178 (41%)	74/170 (44%)	0.89
2012	70/147 (48%)	89/197 (45%)	73/159 (46%)	0.93
2013	274/535 (51%)	83/142 (58%)	105/220 (48%)	0.17

*No $p<0.05$ for Rao-Scott Chi-Square test

Table 12. Survival with good neurologic function by volume category, 2008-2013

	Low (*N*=721)	**Moderate (*N*=1024)**	**High (*N*=978)**	***p*-value**
Entire Study period	**244 (34%)**	**297 (29%)**	**287 (29%)**	**0.51**
2008	9/57 (16%)	17/113 (15%)	25/143 (17%)	0.85
2009	10/66 (15%)	17/122 (14%)	32/138 (23%)	0.05
2010	46/140 (33%)	40/167 (24%)	44/152 (29%)	0.42
2011	58/155 (37%)	59/178 (33%)	64/170 (38%)	0.64
2012	54/147 (37%)	73/197 (37%)	57/159 (36%)	0.98
2013	67/142 (47%)	88/220 (40%)	59/173 (34%)	0.14

*No $p<0.05$ for Rao-Scott Chi-Square test

4.4 Hospital Variability in Treatment Processes and Outcomes

Individual hospital rates of treatment processes and outcomes varied markedly overall, but there was also wide variation within the volume categories. Cooling initiated varied from 25% to 88% with a median of 67% [IQR: 54%-79%]. Successful TTM varied from 0% to 61%

with a median of 27% [IQR 16%-38%]. Premature withdrawal of life sustaining therapy on the basis of neuroprognostication varied between 0% and 18% with a median of 3% [IQR 0%-6%]. Survival with good neurologic function varied from 15% to 64% with a median of 33% [IQR 23%-41%]. Within high volume hospitals (>25 patients eligible for TTM per year) specifically, cooling initiated varied from 68 to 87%, successful TTM from 25% to 55%, and premature withdrawal of life sustaining therapy from 2% to 8%, and survival with good neurologic function ranged from 21% to 35%.

4.4.1 Empty Regression Models: Intraclass Correlations (ICC) and Median Odds Ratios (MOR)

Intraclass correlation (ICC) statistics and median odds ratios (MOR) were calculated from the empty regression models for each of the outcomes of interest to quantify the variability attributable to hospital-level factors and express it in the odds ratio scale (see appendix B). The ICC for the primary outcome, successful TTM, demonstrated that 11% of the variability in successful TTM in the population was attributable to hospital-level factors. The MOR from the empty model for the primary outcome demonstrated that the median increase in the odds of successful TTM was 1.83-fold if a patient moved to another hospital with a higher probability of successful TTM. ICCs for the secondary outcomes of cooling initiated, premature withdrawal of life sustaining therapy on the basis of neuroprognostication, and survival with good neurologic function demonstrated that 13%, 13%, and 6%, respectively, of the variability in the outcome was attributable to hospital-level factors. Also for the secondary outcomes of cooling initiated, premature withdrawal of life sustaining therapy on the basis of neuroprognostication, and survival with good neurologic function, the median increase in the odds of the outcomes were 1.92, 1.97, and 1.52-fold if a patient moved to another hospital with a higher probability of the

outcomes, respectively. As all ICCs were greater than 0.05, there was a sufficient amount of variability at the hospital-level for multi-level modelling to be necessary to account for the correlations of the clustered data.[88] The ICCs and MORs from the empty regression models for each of the outcomes of interest are displayed in table 13.

Table 13. Intraclass correlations (ICC) and median odds ratios (MOR)

Outcome	Intraclass Correlation (ICC)	Median Odds Ratio (MOR)
Successful TTM	**0.11**	**1.83**
Cooling initiated	0.13	1.92
Life sustaining therapy withdrawn on the basis of premature neuroprognostication	0.13	1.97
Survival with good neurologic function	0.06	1.52

4.5 Multilevel Logistic Regression Modelling

4.5.1 Key Findings

Table 14 shows the final odds ratios from the multivariate multilevel logistic regression modelling for the association between average annual volume of post-cardiac arrest patients eligible for TTM and the four outcomes: successful TTM, cooling initiated, premature withdrawal of life sustaining therapy on the basis of neuroprognostication, and survival with good neurologic function.

The multilevel logistic regression models for the treatment process outcomes (successful TTM and cooling initiated) showed significant associations with average annual hospital volume

of patients eligible for TTM. For each 10 unit increase in annual volume of patients eligible for TTM, the adjusted odds for successful TTM were almost 30% higher (OR 1.29, CI_{95} 1.03-1.62). Similar to the primary outcome, but with a slightly larger effect size, the adjusted odds for cooling initiated for each 10 unit increase in annual volume of patients eligible for TTM were almost 40% higher (OR 1.38, CI_{95} 1.11 -1.72).

The models for the patient outcomes (premature withdrawal of life sustaining therapy on the basis of neuroprognostication and survival with good neurologic function) did not show statistically significant associations with average annual volume of patients eligible for TTM. Though not significant, the direction of the relationships demonstrated that the odds of having care withdrawn on the basis of premature neuroprognostication were slightly higher for each 10 unit increase in volume (OR 1.10, CI_{95} 0.80-1.51) and that the odds of surviving with good neurologic function were lower for each 10 unit increase in volume (OR 0.87, CI_{95} 0.74-1.02). The adjusted odds ratio for the outcome of survival with good neurologic function was marginally significant, with a *p*-value of 0.08 and a 95% confidence interval just barely on the upper side of 1.

Table 14. Adjusted Odds Ratios for Study Outcomes

Outcome	Adjusted* odds ratio (per 10 unit increase in volume)	95% CI	*p*-value
Successful TTM	**1.29**	**1.03-1.62**	**0.03**
Cooling initiated	1.38	1.12-1.72	<0.01
Premature withdrawal of life sustaining therapy on the basis of neuroprognostication	1.10	0.80-1.52	0.53
Survival with good neurologic function	0.87	0.74-1.02	0.08

*1° outcome adjusted for hospital, 2° outcome 1 adjusted for hospital, 2° outcome 2 adjusted for hospital, age, sex, EMS witnessed, bystander CPR, ROSC in the field, initial rhythm, 2° outcome 3 adjusted for hospital, age, sex, bystander witnessed, EMS witnessed, AED use, ROSC in the field, location, EMS response time, initial rhythm

4.5.2 Primary Outcome: Successful Targeted Temperature Management (TTM)

The final model for the primary outcome of successful TTM demonstrated that for each 10 unit increase in annual volume of patients eligible for TTM, the adjusted odds for successful TTM were almost 30% higher (OR 1.29, CI_{95} 1.03-1.62). When put in terms of comparing the mean of the high versus low categories of volume described in the previous section (6.1 versus 30.6), the odds of successful TTM were 1.87 times higher at the average high volume hospital versus the average low volume hospital (CI_{95} 1.08-3.25). The median odds ratio in this adjusted model was 1.78, indicating that after controlling for volume, there are still other hospital-level factors influencing the primary outcome. The exposure, average annual hospital volume of patients eligible for TTM, was modelled as a continuous variable in the final model because the AIC value was lowest and it was assessed that the relationship between the exposure and the log odds of successful TTM was approximately linear through a LOWESS curve (see appendix D).[89] The selection of covariates was done using the change in estimate method, which resulted in a final model for the primary outcome of successful TTM with no potential covariates. Sequential

removal of each variable from the model did not change the odds ratio estimate for the exposure of interest (average annual volume of patients eligible for TTM at receiving hospital) by greater than 10%. An alternate model retaining all variables with $p<0.1$ is presented in appendix E.

4.5.3 Secondary Outcome 1: Cooling Initiated

The secondary analysis of the outcome of having cooling initiated demonstrated that for each 10 unit increase in annual volume of patients eligible for TTM the odds of having cooling initiated were almost 40% higher (OR 1.38, CI_{95} 1.11 -1.72). When put in terms of comparing the mean of the high versus low categories of volume described in the previous section (6.1 versus 30.6), the odds of having cooling initiated were 2.20 times higher at the average high volume hospital versus the average low volume hospital (CI_{95} 1.29-3.78).The median odds ratio in the adjusted model was 1.78, demonstrating that after accounting for volume there are still other hospital factors that contribute to the variability in the outcome. As with the final model for the primary outcome, the final model for the secondary outcome cooling initiated contained no potential covariates and modelled the exposure of interest, average annual hospital volume of patients eligible for TTM, as a continuous variable. An alternate model retaining all variables with $p<0.1$ is presented in appendix E.

4.5.4 Secondary Outcome 2: Premature Withdrawal of Life Sustaining Therapy on the Basis of Neuroprognostication

Table 15 shows the final model for the secondary outcome of premature withdrawal of life sustaining therapy on the basis of neuroprognostication. The model demonstrated that for each 10 unit increase in annual volume of patients eligible for TTM, the adjusted odds for having care withdrawn prematurely on the basis of neuroprognostication were 10% higher (OR 1.10, CI_{95} 0.80-1.52). When put in terms of comparing the mean of the high versus low categories of

volume described in the previous section (6.1 versus 30.6), the adjusted odds of having life sustaining therapy prematurely withdrawn based on neuroprognostication were 1.27 times higher at the average high volume hospital versus the average low volume hospital (CI_{95} 0.58-2.77).This association was not statistically significant; however it is important to note that this secondary analysis was limited to a subset of the population. The median odds ratio of the adjusted model was 1.82, demonstrating that much of the hospital-level variation was still unaccounted for after controlling for volume. The exposure, average annual hospital volume of patients eligible for TTM, was modelled as a continuous variable in the final model because the AIC value was lowest and it was assessed that the relationship between the exposure and the log odds of having care withdrawn prematurely on the basis of neuroprognostication was linear through a LOWESS curve (see appendix D). Covariates in the final model included those variables with a $p<0.10$ or felt to be clinically significant based on published evidence. The final model contained the covariates: age, sex, EMS witnessed, bystander CPR, ROSC in the field, and initial rhythm.

Table 15. Multilevel model for premature withdrawal of life sustaining therapy on the basis of neuroprognostication (N=1571)

	Odds Ratio	**95% CI**	***p*-value**
Average annual volume of patients eligible for TTM	1.10	0.80-1.52	0.53
Age	1.04	1.02-1.05	<0.01
Male	1.00	0.66-1.53	0.99
EMS witnessed	0.30	0.16-0.58	<0.01
Bystander CPR	0.65	0.42-0.99	<0.05
ROSC in the field	0.45	0.26-0.79	<0.01
Shockable initial rhythm	0.23	0.14-0.38	<0.01

4.5.5 Secondary Outcome 3: Survival with Good Neurologic Function

Table 16 shows the final model for the secondary outcome of survival with good neurologic function. The model demonstrated that for each 10 unit increase in annual volume of patients eligible for TTM, the adjusted odds of surviving with good neurologic function were 13% lower (OR 0.87, CI_{95} 0.74-1.02). When put in terms of comparing the mean of the high versus low categories of volume described in the previous section (6.1 versus 30.6), the adjusted odds of surviving with good neurologic function were 29% lower at the average high volume hospital versus the average low volume hospital (OR 0.71 CI_{95} 0.48-1.05).This association was marginally significant (p=0.08). The median odds ratio of the adjusted model was 1.39, demonstrating that much of the hospital-level variation was still unaccounted for after controlling for volume. As with the other clinical outcome, average annual hospital volume of patients eligible for TTM was modelled as a continuous variable in the final model and covariates in the final model included those variables with a p<0.10 or felt to be clinically significant based on published evidence. The final model contained the covariates: age, sex, bystander witnessed, EMS witnessed, AED use, ROSC in the field, location, EMS response time, and initial rhythm.

Table 16. Multilevel model for survival with good neurologic function (N=2723)

	Odds Ratio	**95% CI**	***p-value***
Average annual volume of patients eligible for TTM	0.87	0.74-1.02	0.08
Age	0.96	0.95-0.97	<0.01
Male	1.09	0.87-1.37	0.45
Bystander witnessed	1.61	1.25-2.06	<0.01
EMS witnessed	3.70	2.62-5.2	<0.01
AED use	1.55	0.99-2.41	0.05
ROSC in the field	4.01	2.77-5.82	<0.01
Public location	1.36	1.08-1.72	<0.01
EMS response time	0.99	0.98-0.99	<0.01
Shockable initial rhythm	4.65	3.66-5.92	<0.01

Chapter 5

Discussion

5.1 Summary of Key Findings

Patient and cardiac arrest characteristics of post-cardiac arrest syndrome patients received at hospitals in the region of Southern Ontario were comparable, yet there was wide variation in the proportion of patients who received recommended treatment processes as well as in the outcomes of patients attending different hospitals in the region. A significant proportion of the variation in treatment processes and outcomes were attributable to hospital-level factors. Patients received at high volume hospitals had significantly higher rates of treatment processes related to targeted temperature management (TTM).

Treatment processes related to TTM were shown to be more likely to occur at hospitals that received higher volumes of patients with post-cardiac arrest syndrome in this multi-centre, multi-city, observational study. However, this increased use of treatment processes did not translate to an increased likelihood of favourable patient outcomes at higher volume centres.

5.2 Context of Key Findings

5.2.1 Characteristics of Post-Cardiac Arrest Syndrome Patients in Southern Ontario

Patients examined in this study exhibited characteristics consistent with previous descriptions of the post-cardiac arrest patient population.[78] The characteristics of patients in this study were generally more favourable than described in similar studies, meaning there were higher percentages of patients with a shockable initial rhythm, with a witnessed arrest, with bystander resuscitation, and who had a return of spontaneous circulation (ROSC).[78] This is due to this study having eligibility criteria specific to the subset of post-cardiac arrest patients who

were eligible for in hospital therapeutic hypothermia treatment. These patients had to survive at least 6 hours after hospital arrival, and so many of the sicker patients who would have been included in the sample of the previous studies in this area were excluded from the study, which resulted in a study population with a set of cardiac arrest characteristics that are known to result in more favourable outcomes.

Most patient and cardiac arrest characteristics were not found to vary substantially across categories of volume. This, again, is consistent with a previous study examining patients attending hospitals of differing post-cardiac arrest patient volume.[78] The one difference in cardiac arrest characteristics that was found between the three categories of volume by the study was that higher volume hospitals had shorter emergency medical services (EMS) response time. This finding is logical as high volume hospitals tend to be in more urban areas where there is higher population density, which results in closer EMS dispatch locations and faster EMS response times.

5.2.2 Treatment Processes for Post-Cardiac Arrest Syndrome Patients in Southern Ontario

This study found that treatment processes related to TTM differed between categories of volume, but other in-hospital processes of care such as angiography did not. This finding seems counterintuitive as not all centres in the study had percutaneous coronary intervention (PCI) facilities, and yet everywhere should theoretically be able to implement therapeutic hypothermia. However, as the analysis assigned patients the first hospital at which they were received, patients that required specialized services like PCI and implantable cardioverter defibrillator (ICD) placement were likely transferred to facilities capable of these procedures very soon after they first arrived at the closest hospital. This resulted in no discernable differences in the proportions of patients receiving any angiography, electrophysiologist consults, and ICD implants between

categories of hospital volume. In contrast, it was very interesting that there were differences in the proportion of patients who had cooling initiated and who had successful TTM between volume categories. Patients are usually treated at the initial receiving hospital for TTM because this therapy does not require specialized equipment or expertise. This means that there are differences in processes of care for post-cardiac arrest syndrome patients based on hospital volume for theoretically universally implementable care processes. This finding points to an inequity in Southern Ontario's hospital system that needs to be addressed.

The subgroup analysis of patients at risk for premature withdrawal of life sustaining therapy did not find a statistically significant difference in the proportions of patients who had care withdrawn prematurely between volume categories, potentially due to limited power. However, a tendency for higher volume hospitals to have higher proportions of patients with premature withdrawal of life sustaining therapy on the basis of neuroprognostication was observed. We hypothesize that there is potentially increased pressure towards patient turnover at high volume centres versus low volume centres, which results in care providers making the decision to withdraw care earlier than they would have otherwise.

5.2.3 Outcomes for Post-Cardiac Arrest Syndrome Patients in Southern Ontario

Consistent with previous studies examining the variability in outcomes of post-cardiac arrest patients,[7–10] this study demonstrated marked variability in survival and survival with good neurologic function across hospitals in the region of Southern Ontario. Survival was higher overall than in these previous studies because post-cardiac arrest syndrome patients were selected from the overall post-cardiac arrest population. These patients have more favourable outcomes because they had to survive at least 6 hours after hospital arrival, among other factors.

Overall survival to hospital discharge as well as survival with good neurologic function increased over the 5 complete years of the study. This is a promising result as previous studies have not found discernable differences in overall rates of survival in post-cardiac arrest patients for several decades.[3] Looking specifically at those patients who could potentially benefit from therapies may have removed some of the variability in survival due to post-cardiac arrest patients who are not eligible for therapies, allowing survival improvements because of the implementation of therapies to be seen. Though it may just be that care improved over the study period due to the measurement, audit, and feedback associated with being a participating hospital in the SPARC Network (the Hawthorne Effect).[90]

The proportion of surviving patients who did so with good neurologic function increased from 2009 to 2011. This is a very interesting finding because the initial purpose of the Strategies for Post-Arrest Resuscitation Care (SPARC) Network was to increase the use of post-cardiac arrest therapies through a knowledge translation intervention, and the initial trial showed a significant increase in the proportion of patients achieving successful TTM after the intervention. This intervention began to be implemented in the hospitals in the network in 2009. So, the increase in the proportion of surviving patients doing so with good neurologic function could be due to an increase in therapeutic hypothermia use, which resulted in improved neurologic functioning of patients.

5.2.4 Associations between Hospital Volume and Key Features of Post-Cardiac Arrest Care

5.2.4.1 Targeted Temperature Management (TTM)

The main finding of TTM treatment processes being more likely to occur at hospitals that receive higher volumes of patients with post-cardiac arrest syndrome supports the prior

recommendation for the regionalization of post-cardiac arrest care with the aim of treating more eligible patients with available therapies. Yet based on the results of this study, the improvements to post-cardiac arrest care with a regionalized system based on volume may not be drastic. As the study found that volume does not account for much of the between-hospital variation, further research is needed to determine which hospital-based phenomena are driving the variability before an optimal system of care can be developed.

Similar results have been observed by other investigators, with some studies finding weak associations between hospital factors and survival and others not able to distinguish any effect. A previous study of the Resuscitation Outcomes Consortium (ROC) in the United States and Canada showed lower mortality of post-cardiac arrest patients in intensive care units (ICUs) that admit higher patient volumes [91]. In an Australian study, it was also shown that some hospital characteristics are associated with improved outcomes, but there was no independent association with hospital volume of out-of-hospital cardiac arrest (OHCA) patients and survival.[92] Cudnik et al. found no association between increasing hospital volume and improved survival.[78]

It is important to note that these previous studies were only able to look at the relationship between volume and survival, and so were not able to examine the relationship between volume and care processes as in this study. By determining that there is a volume-care process relationship, yet it is so weak that it does not translate to improved survival, is a possible explanation for why no study thus far has been able to conclusively demonstrate a volume-survival relationship. Though there are several other possible explanations as well. It may be that there are competing factors unrelated to the strength of the association such as general intensive care unit (ICU) care and injury severity that were not measured. Additionally, recent evidence

points to TTM not being associated with improvements in survival as strongly as was once thought.[49]

The study demonstrated a stronger effect of volume on whether or not patients had cooling initiated than it did for whether or not patients actually reached target temperature. Looking at this earlier indicator of differences in care provides stronger evidence for a volume-care process relationship. However it is important to take into consideration that it is much easier to start cooling than it is to get to target. The environment of a hospital which supports starting hypothermia (e.g., champions, education, awareness, protocol to initiate) may not be the same as required for actually reaching the target (e.g., constant physician support, frequent monitoring, protocols for trouble-shooting, adequate sedation/analgesia, invasive cooling techniques).

5.2.4.2 Premature Withdrawal of Life Sustaining Therapy on the Basis of Neuroprognostication

In the subgroup analysis, modelling the outcome of premature withdrawal of life sustaining therapy on the basis of neuroprognostication did not demonstrate an association with volume, yet it yielded some interesting secondary findings. Being younger, having an EMS witnessed arrest, bystander CPR, a ROSC in the field, and having a shockable initial rhythm all tended to protect against early withdrawal of care. These are novel findings about potential influences on prognostication. These associations may exist because of their impact on provider prognostic optimism and perceptions of futility, which may not be based on evidence but rather preconceived notions about important prognosticators. It is very difficult to prognosticate at all. Early prognostication has been consistently identified as dangerous, and it has been emphasized that early prognostication can result in inappropriate withdrawal of life sustaining therapy in a patient who would otherwise survive.[59] This impact of patient characteristics on a care provider's

decision to withdraw care early is evidence of an important inequity in the management of patients with post-cardiac arrest syndrome.

We identified a non-significant relationship between volume and premature withdrawal of life-sustaining therapy on the basis of neuroprognostication, yet this outcome had the highest intraclass correlation (ICC) of all the outcomes in the empty model procedures. This finding points to a large influence of hospital-level factors on differences in physician decisions about when to withdraw care, but that volume is not a major component of these factors. This finding may also be a marker of uncertainty and lack of standardization among clinicians because the guidelines have not yet penetrated. This is an area that warrants further investigation in future studies.

5.2.4.3 Survival with Good Neurologic Function

This study showed a tendency for higher volume hospitals to be associated with lower rates of survival with good neurologic function. Though this relationship did not reach statistical significance, the confidence interval was very skewed to the left side of the null value of one and only just crossed the null (CI_{95} 0.74-1.02). It is important to note that there was a substantial problem with missing data for this variable (22% of surviving patients). Patients with missing data for this variable were coded conservatively as "poor neurologic outcome". This may have biased our results such that categories with a higher proportion of missing data in this category may appear to have proportionately more patients with worse neurologic outcomes. However, despite this caveat, we considered several scenarios which may have contributed to the positive association between higher volume centres and worse neurologic outcomes as observed.

First, cardiac arrest is a heterogeneous disease, and so any treatment effects may be diluted if there is an impact only in one particular subgroup of patients. Recent evidence failed to

demonstrate a benefit in cooling to 33 versus 36 degrees Celsius in the heterogeneous post-cardiac arrest treatment population.[49] If this evidence reflects truth as it occurred in our study population, it would cause the association to tend towards the null. Second, though EMS protocols dictate that patients should be brought to the nearest hospital, there may already be some selection happening where 'sicker' patients are brought to larger centres at the discretion of the treating paramedics. In locales where there are several equidistant receiving hospitals, paramedics can choose which destination may be most appropriate for the patient based on their perceptions of severity of illness and the resources of the receiving hospital. This phenomenon has been observed when looking at hospital mortality rates in general; larger hospitals tend to serve sicker patients and therefore report higher mortality rates than smaller hospitals. This phenomenon may partially explain our observation of higher volume centres being associated with lower rates of survival. Third, due to the pressure of patient turnover at high volume centres as well as the presence of long-term care facilities in urban centres, patients may be discharged sooner at higher volume hospitals than they would be at a lower volume centre; thus making the high volume centres appear to have less favourable neurologic outcomes measured at the time of early discharge.[93] It would be interesting to evaluate whether this is occurring by looking at whether there are differences in the length of stay of patients attending low versus high volume centres, but unfortunately this variable is not available in the dataset. This finding of poorer neurologic outcomes at higher volume centres is consistent with a previous study.[78]

5.2.4.4 Hospital-Level Variation Explained by Volume

The relatively small reductions in the median odds ratios of all the models (full models versus empty) demonstrated that though there is some underlying phenomenon occurring at the hospital-level that results in differences in the outcomes, the volume variable used in this study

does not fully encompass it. Since this study was the first to use a more precise measure of hospital experience with post-cardiac arrest syndrome patients than previous studies, finding that this measure did not explain much of the variation in the outcomes provides more weight to the argument that volume may not be the best proxy measure for a hospital's overall experience with post-cardiac arrest patients. Previous work created a volume variable based on the average annual number of cardiac arrest patients received,[78,91] whereas this study used a volume variable based on the average annual volume of post-cardiac arrest patients eligible for TTM. This variable should have provided a better representation of a hospital's experience with the post-cardiac arrest syndrome patient population, and yet the majority of the hospital-level variation in outcomes remained unexplained. Other sources of variation could include staffing patterns, individual care provider experience among nurses, physicians and respiratory therapists, the availability of equipment to support hypothermia (e.g. surface or invasive cooling devices), best practices in critical care (e.g. prevention of ventilator-associated pneumonia, prevention of thrombosis, feeding practices in the critically ill, etc.). Further studies should work to create a variable (or set of variables) that explains more of the hospital-level variation in order to have a set of criteria that can be used to plan an optimal model of post-cardiac arrest care.

Although the volume variable used did not fully assess the hospital factors responsible for the variation in outcomes, there are indications of associations between hospital volume and these key care process and clinical outcomes despite that the hospitals in the sample are likely more similar than hospitals outside of the SPARC Network. Because the SPARC Network was established as a knowledge translation strategy, after the intervention all hospitals should have theoretically been brought to the mean of performance. The fact that there were still some

differences between the hospitals in this more homogenous sample alludes to a stronger impact of volume on the outcomes of interest in hospitals outside of the SPARC Network.

5.2.4.5 Possibility of a Threshold Volume Effect

Generally, the hospitals studied saw very few OHCA patients eligible for TTM annually. The average hospital studied saw only 13.8 eligible patients per year, or just over one per month. Because the volume of patients at these hospitals was quite low, it may have impacted the results of the study if there is a threshold effect of volume on quality of care.

A threshold volume is a minimum volume necessary for a hospital to become more experienced at treating a particular type of patient, and therefore able to deliver higher quality care. Volume thresholds have been observed in many studies of volume-outcome relationships.[94] An example of such a threshold is for percutaneous transluminal coronary angioplasty.[95] It was found that hospitals performing at least 200 percutaneous transluminal coronary angioplasties per year achieve a mortality rate that is 24% (95% CI 8-38%) lower than hospitals that perform less than 200.[95]

The presence of a volume threshold may aid in the explanation of why this study did not find a strong influence of volume on treatment processes and outcomes. It may be that even the high volume centres in this study (the highest of which saw an average of 4 patients eligible for TTM per month) do not receive enough post-cardiac arrest patients eligible for TTM to allow them to become more experienced and therefore better at delivering high quality care.

5.2.4.6 Considerations in Modelling Volume-Outcome Relationships

Hospital-level covariates were not included in the final models because the average annual volume variable was meant to serve as a measure of overall hospital experience in order

to evaluate the current system. It was reasoned that hospital-level covariates are therefore a part of this measure and should not be additionally controlled for in the models. There were also concerns over collinearity with other hospital factors if it was decided to look just at volume on its own instead of using it as a proxy for hospital experience. For example, hospital volume and bed number are highly correlated.

Because of the obvious differences in ICD placement and PCI between hospitals (as only certain centres have these facilities) the association between volume and these processes of care were not evaluated. As previously discussed, patients who require these centre-specific procedures are already transferred to centres that can provide the appropriate treatment. This is likely why the descriptive aspect of this study did not find any differences in the rates of angiography, electrophysiologist consult, and ICD placement between the three volume categories (since this study assigned hospital by the first institution where the patient received treatment).

5.3 Methodological Considerations

5.3.1 Selection Bias

This study analyzed cases identified prospectively, so selection was unlikely to be related to the outcomes of interest. Because of this, classic forms of selection bias in terms of their effects on risk estimates are not of concern. Also, as this study enrolled all eligible patients within a geographic region, selection effects should be minimal.

5.3.2 Information Bias

There was the potential for information bias in this study. Case identification occurred prospectively, but as data were abstracted retrospectively by chart review it is possible that more effort was put into finding out the treatments received by patients who died compared to patients

who survived. Therefore there would be a more accurate representation of outcome in deceased patients than in those who survived (differential misclassification).

Non-differential misclassification was also possible in this study. Because the SPARC Network database relies on hospital records data, only if a patient had a characteristic, treatment, or outcome of interest recorded in their chart were data abstractors able to record it in the database. For most variables, patients had to be grouped into yes or no/unknown categories because it could not be assumed that just because a patient did not have a variable recorded in their chart that the variable was not truly present. Any misclassification of this kind would be non-differential in the assessment of outcomes by levels of the exposure as the recording of these variables occurred before recording the patient's outcomes. This non-differential misclassification is likely to have caused some degree of bias towards the null for the associations studied.

5.3.3 Confounding

This study was able to evaluate and adjust for the majority of potential confounders of the relationships of interest. Variables detailing patient and cardiac arrest characteristics that may have played a role in confounding were readily available in the dataset. The change in estimate method did not find that any of the potential confounders examined changed the odds ratio estimates by more than 10%. This is likely because the exposure of interest was a hospital-level factor that was designed to be an all-encompassing measure of hospital experience with post-cardiac arrest syndrome patients, and so the relationships between this robust exposure and the outcomes of interest were resistant to confounding by individual patient factors.

Uncontrolled confounding by variables that have not been considered was a potential concern in this study. There were several variables that could potentially have been confounders

of the relationships of interest that were either not available in the dataset or deemed of poor quality. These variables include patient comorbidities and race, which have been adjusted for in previous studies of the volume-survival relationship because they are strongly associated with survival.[78]

Residual confounding due to incomplete adjustment for factors that have been considered could also have potentially influenced the results of the study. It is likely that there was some degree of measurement error in the assessment of the covariates. Some patients may have had the presence of covariates of interest, but they were not recorded in the chart and so recorded as no/unknown in the dataset. This could have resulted in incomplete adjustment for these potential confounders in the models.

5.3.4 Chance

For the primary outcome, the *p*-value was 0.03 and the 95% confidence interval (CI) for the odds ratio nearly crossed the null value of one (CI_{95} 1.03-1.62). This is not evidence of a particularly strong relationship, and when considered on its own may raise questions about whether this finding is true, or simply due to chance. However, for the secondary outcome of cooling initiated there was more convincing evidence of a volume-outcome relationship ($p<0.01$, CI_{95} 1.11 -1.72), so it follows that the relationship described for the primary outcome is also true. This is because successful TTM is a downstream effect of having cooling initiated. As there is strong evidence of a relationship between hospital volume and having cooling initiated it is logical that there is also a relationship between volume and successful cooling. Therefore it is unlikely that the association found between hospital volume and successful TTM is due to chance.

For the null results seen for the secondary outcome of premature withdrawal of life sustaining therapy on the basis of neuroprognostication it is possible that there is truly an effect but the study was too small to detect it. Only a subgroup of patients from the total study population was eligible for this analysis, meaning the analysis was limited by statistical power. The confidence interval fell more to the upper side of one (CI_{95} 0.80-1.52), which alludes to the possibility that a larger study may have been able to detect a significant association.

5.3.5 Synopsis of Internal Validity

As data from the SPARC Network hospitals are collected in a standardized way with primary data collection occurring for all OHCA patients arriving at one of the hospitals in the network, valid comparisons can be made within the network. Though there were some methodological limitations (residual confounding, measurement error) as discussed previously, these are not likely to have biased the results in a major way and it is believed that the results of the study are applicable to the post-cardiac arrest patient population in Southern Ontario.

5.3.6 External Validity

The population studied appeared to be representative of the overall post-cardiac arrest syndrome patient population on the basis of baseline characteristics. When the study population was compared to populations of previous studies, we found similar patient characteristics.[78]

Because the SPARC Network hospitals participated in a comprehensive program designed to standardize, monitor, and improve the care of patients resuscitated from out-of-hospital and in-hospital cardiac arrest, the hospitals may be more similar to each other than they would be if they were not united under the knowledge translation project. Therefore, the generalizability of the findings is less than ideal because the hospitals analyzed are not expected

to represent the variation in outcomes found amongst hospitals outside such a network. However, since the study found significant variability even within this special setting, it is safe to assume that variability outside the network is likely to be more.

In terms of biologic plausibility, the main finding that successful TTM is more likely to occur for patients received at more experienced centres is logical and consistent with evidence for many other health outcomes showing that more experienced centres have higher quality care than less experienced centres.[75] Because of this, it is assumed that the main finding of this study is generalizable to the overall post-cardiac arrest syndrome patient population that is received by hospitals of variable experience.

5.4 Limitations of the Study

5.4.1 Hospital Records Data

Administrative data has a number of limitations when used for research purposes. The lack of quality control over the data, the possibility of missing items or records, and the difference in the purpose of data collection are potential limitations to this study due to the use of hospital records data. As the SPARC Network database collects data from chart reviews the records that were kept were not specifically designed to address research questions. This means that for many of the variables of interest it was only known that a patient had the presence of a variable of interest if it was recorded in the chart. Patients who did not have variables recorded in their charts could have not had the event of interest, or it may have either not made it into the chart or not been noticed by data abstractors. This resulted in most categorical variables analyzed to be classified as yes or no/unknown. Because of this caveat of the database, for most variables it is unclear what percentage of data was actually missing.

5.4.2 Missing Data

As discussed in the previous section, due to the nature of the SPARC Network database the extent of missing data in the study is unknown for most in-hospital variables. This means that the proportions of patients who actually had the treatments and outcomes studied were likely underestimated by this investigation, and associations were likely biased towards the null. However, due to the nature of this investigation there were some 'harder' events where missing data were minimized. Survival is the best example of this. If a patient was deceased at the time of hospital discharge it was definitely recorded in the chart. This is in contrast to some of the 'softer' outcomes such as neurologic status or whether the patient received an electrophysiologist consult, which were more dependent on detailed note-taking in the chart by care providers and therefore more prone to the problem of non-recorded events.

For the primary outcome, the specific definition of having successful TTM (a core body temperature of 32 to 34 degrees Celsius within 6 hours of hospital arrival) may have caused the results to be biased towards the null. If a patient did not have appropriate time and temperature recordings in the chart during the therapy, the patient would have been missed by the coding algorithm used to define the variable. This may help explain the discrepancy between the strength of the association between hospital volume and cooling initiated versus hospital volume and successful TTM. Cooling initiated was a 'harder' variable, in that it was defined as any indication of cooling in the chart.

For the secondary outcome of survival with good neurologic function there was the opportunity to investigate the approximate amount of missing data. The 'harder' outcome of death made it so that the proportion of patients with missing neurologic status at discharge could be analyzed. It was found that 22% of patients surviving to hospital discharge had no cerebral

performance category (CPC) score recorded, and so were classified conservatively as 'not good' neurologic status in the analysis. This means that some patients who, in reality had good neurologic status were coded as 'not good' because the variable was not recorded in the patient chart. Misclassification of this kind would bias the study findings towards the null. This is of interest because of the marginal significance found for the association between hospital volume and survival with good neurologic function. If some of the 22% of patients missing neurologic function at discharge had a CPC score of 1 or 2 then the finding may have been statistically significant.

5.4.3 Uncontrolled Confounding

As discussed in a previous section, uncontrolled confounding may have influenced the findings of this study. There were several variables that could have confounded the relationships of interest that were either not available in the dataset or deemed of poor quality and so not included in the modelling procedures.

Patient comorbidities may have confounded the relationships of interest. The effects of prior medical conditions on patient outcomes post-cardiac arrest have been well established.[26–28] It is possible that due to the catchment area of a hospital and the medical history of the patients in that region, that hospital volume is also related to patient comorbidity status. This is of particular interest for the secondary outcome of survival with good neurologic function if the hypothesized selection of sicker patients to higher volume centres by EMS is happening. Being able to adjust for comorbidity status would have been interesting in this case to see if this hypothesis is accurate. Unfortunately, the comorbidity data collected in the SPARC database were not obtained in an ideal manner. An 'other' category was written in for almost half of the patients in the study, which resulted in loss of information related to comorbid conditions for

which there were no pre-determined categories. For example, hypertension was an optional category and often 'high blood pressure' had been written in. This made it difficult to account for comorbidities in an accurate way in the analysis.

Race and lifestyle factors may have also played a role in confounding the relationships of interest. These factors have been well-established as risk factors for cardiac arrest and it is also probable that they are related to hospital volume.[25,29] Racial demographics vary based on region, and so it is very likely that the racial distribution of patients attending Sunnybrook Hospital in Toronto is very different from those attending Georgetown Hospital in a more rural area of the province. Lifestyle factors also often vary by region, which may cause patients who are more active with lower BMIs to attend high versus low volume hospitals, or vice versa.

However, as none of the potential covariates investigated in this study were shown to greatly influence the relationships of interest it is likely the associations found are representative of true relationships. It appears that using the hospital volume variable as a proxy for overall hospital experience with the post-cardiac arrest syndrome patient population was too robust a measure for confounding by patient-level factors to be an issue.

5.4.4 Similarity of SPARC Network Hospitals

The SPARC Network hospitals may be more similar to each other than hospitals that are not united under a knowledge translation strategy. This similarity of the SPARC Network hospitals poses a threat to the generalizability of the study findings. However, the study found significant variability even within this special setting which has undergone a network-wide knowledge translation intervention, so it is safe to assume that variability outside the network is likely to be greater.

5.5 Strengths of the Study

5.5.1 SPARC database

The SPARC Network database is large and of high quality. Cases are identified prospectively, which as previously discussed, avoids many of the potential biases that could be associated with retrospective data collection. Also, since the research was conducted with data compiled across a hospital network with homogenous data collection, valid comparisons could be made.

5.5.2 Volume Measure Specific to Patients with Post-Cardiac Arrest Syndrome

The use of patients with post-cardiac arrest syndrome for the creation of the volume variable allowed the study to be more specific than previous investigations by evaluating hospital experience with a particular patient type. Due to this, the results have very clinically relevant implications as they pertain to patients who are eligible for the treatments studied as opposed to all possible post-cardiac arrest patients.

5.5.3 First Study to Examine Treatment Processes as Well as Outcomes

This study was able to evaluate the relationship between volume and treatment processes as well as outcomes, whereas previous studies have only been able to look at associations between volume and survival.[77–79] Treatment processes are a step on the patient journey towards survival. Studying only survival and not the component processes may be overlooking important fundamental contributors driving the observed relationship. By having the ability to examine the relationships between hospital volume and specific treatment processes this study was able to find that volume does play a role in the quality of care provided by a hospital and may partially explain the association between volume and survival reported in previous studies.

5.5.4 Regional Multi-Centre Setting

The regional nature of this study population provided variation in hospital patient populations as well as variation in hospital characteristics that allowed for meaningful analyses. Additionally, we included consecutive cardiac arrest patients with robust patient capture mechanisms in place allowing for a complete sample with misrepresentation minimized.

5.6 Study Implications and Future Directions

We observed a weak relationship between increasing hospital volume of post-cardiac arrest syndrome patients and use and quality of TTM therapy. This finding supports the prior recommendation for the regionalization of post-cardiac arrest care with the aim of treating more eligible patients with available therapies. However, the analysis revealed that volume on its own does not account for the majority of between-hospital variation, and so further research is needed before a fully evidence-informed and optimized system of care can be developed.

The evidence in support of the regionalization of post-cardiac arrest care generated by this study is not sufficient to endorse changing policy at the time being. This study has shown that regionalizing post-cardiac arrest care could mildly increase the number of patients who receive recommended treatment practices. Yet there are possible negative implications on post-cardiac arrest patient care due to regionalization that must also be considered. Regionalizing care would mean that some patients would have longer travel times to a regional cardiac arrest centre compared to transport to the closest hospital. Post-cardiac arrest patients are a vulnerable population requiring complex care and constant monitoring, which is much better provided in hospital than in an ambulance. It is possible that prolonged transport could have a negative impact on a patient's outcome. However, a study conducted in Arizona examined more than

1100 cardiac arrest patients transported to hospital via ambulance and discovered that ambulance transport time was not associated with adverse effects or worse clinical outcomes.[96]

It will be necessary to conduct further studies to determine what hospital factors are driving higher quality post-cardiac arrest care in order to develop an optimal post-cardiac arrest care model. Factors such as general features of ICU care (thrombosis management, sepsis prevention, ventilator-associated pneumonia prevention, and nutrition practices, etc.), standardized protocols, and local champions may have a strong impact on whether or not a hospital provides recommended care to post-cardiac arrest patients regardless of volume. If this is found to be true, developing a system where all hospitals are brought to match the best performers in these aspects would be the most effective approach to optimize care.

5.7 Conclusions

Marked variation exists in care processes and outcomes of patients with post-cardiac arrest syndrome between hospitals within the same region of Southern Ontario. Patients who had cooling initiated and who reached target temperature were more likely to have arrived at hospitals with more experience in post-OHCA patients. However, patients who arrived at hospitals with more experience with post-OHCA patients were not less likely to have premature withdrawal of life sustaining therapy or more likely to survive with good neurologic function. Hospital volume of post-cardiac arrest patients did not explain the majority of the variation in treatment processes and outcomes between centres. The results of this study represent an important health inequity in the quality of care provided at the level of the hospital in Southern Ontario. Future work is required to explore other sources of variability at the level of the hospital and apply our findings to the development of a regional strategy to standardize and optimize care for this complex, but salvageable patient population.

References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 2013;127(1):e6-e245. doi:10.1161/CIR.0b013e31828124ad.

2. Nadkarni VM, Larkin GL, Peberdy MA, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA* 2006;295(1):50-7. doi:10.1001/jama.295.1.50.

3. Redpath C, Sambell C, Stiell I, et al. In-hospital mortality in 13,263 survivors of out-of-hospital cardiac arrest in Canada. *Am. Heart J.* 2010;159(4):577-583.e1. doi:10.1016/j.ahj.2009.12.030.

4. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, . *Circulation* 2008;118(23):2452-83. doi:10.1161/CIRCULATIONAHA.108.190652.

5. Morrison LJ, Deakin CD, Morley PT, et al. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation* 2010;122(16 Suppl 2):S345-421. doi:10.1161/CIRCULATIONAHA.110.971051.

6. Toma A, Bensimon CM, Dainty KN, Rubenfeld GD, Morrison LJ, Brooks SC. Perceived barriers to therapeutic hypothermia for patients resuscitated from cardiac arrest: a qualitative study of emergency department and critical care workers. *Crit. Care Med.* 2010;38(2):504-9. doi:10.1097/CCM.0b013e3181cb0a02.

7. Herlitz J, Engdahl J, Svensson L, Angquist K, Silfverstolpe J, Holmberg S. Major differences in 1-month survival between hospitals in Sweden among initial survivors of out-of-hospital cardiac arrest. *Resuscitation* 2006;70(3):404-9. doi:10.1016/j.resuscitation.2006.01.014.

8. Liu JM, Yang Q, Pirrallo RG, Klein JP, Aufderheide TP. Hospital variability of out-of-hospital cardiac arrest survival. *Prehosp. Emerg. Care* 2008;12(3):339-46. doi:10.1080/10903120802101330.

9. Langhelle a, Tyvold SS, Lexow K, Hapnes S a, Sunde K, Steen P a. In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway. *Resuscitation* 2003;56(3):247-63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12628556.

10. Hasegawa K, Tsugawa Y, Camargo C a, Hiraide A, Brown DFM. Regional variability in survival outcomes of out-of-hospital cardiac arrest: the All-Japan Utstein Registry. *Resuscitation* 2013;84(8):1099-107. doi:10.1016/j.resuscitation.2013.03.007.

11. Nichol G, Aufderheide TP, Eigel B, et al. Regional systems of care for out-of-hospital cardiac arrest: A policy statement from the American Heart Association. *Circulation* 2010;121(5):709-29. doi:10.1161/CIR.0b013e3181cdb7db.

12. Lurie KG, Idris A, Holcomb JB. Level 1 cardiac arrest centers: learning from the trauma surgeons. *Acad. Emerg. Med.* 2005;12(1):79-80. doi:10.1197/j.aem.2004.11.010.

13. Lick CJ, Aufderheide TP, Niskanen R a, et al. Take Heart America: A comprehensive, community-wide, systems-based approach to the treatment of cardiac arrest. *Crit. Care Med.* 2011;39(1):26-33. doi:10.1097/CCM.0b013e3181fa7ce4.

14. Stub D, Bernard S, Smith K, et al. Do we need cardiac arrest centres in Australia? *Intern. Med. J.* 2012;42(11):1173-9. doi:10.1111/j.1445-5994.2012.02866.x.

15. Apps A, Malhotra A, Mason M, Lane R. Regional systems of care after out-of-hospital cardiac arrest in the UK: premier league care saves lives. *J. R. Soc. Med.* 2012;105(9):362-4. doi:10.1258/jrsm.2012.120165.

16. Heffner AC, Pearson D a, Nussbaum ML, Jones AE. Regionalization of post-cardiac arrest care: implementation of a cardiac resuscitation center. *Am. Heart J.* 2012;164(4):493-501.e2. doi:10.1016/j.ahj.2012.06.014.

17. Donnino MW, Rittenberger JC, Gaieski D, et al. The development and implementation of cardiac arrest centers. *Resuscitation* 2011;82(8):974-8. doi:10.1016/j.resuscitation.2011.03.021.

18. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resusci. *Circulation* 2004;110(21):3385-97. doi:10.1161/01.CIR.0000147236.85306.15.

19. Waien S, Stiell I. Cardiac arrest care and emergency medical services. In: Naylor D, P S, eds. *Cardiovascular Health & Services in Ontario: An ICES Atlas*.; 1999:284-300.

20. Paradis NA, Halperin HR, Kern KB, Wenzel V, Chamberlain DA, eds. *Cardiac Arrest: The Science and Practice of Resuscitation Medicine*. 2nd ed. Cambridge University Press; 2007.

21. Maron BJ, Estes N a M. Commotio cordis. *N. Engl. J. Med.* 2010;362(10):917-27. doi:10.1056/NEJMra0910111.

22. Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *J. Am. Coll. Cardiol.* 2004;44(6):1268-75. doi:10.1016/j.jacc.2004.06.029.

23. Müller D, Agrawal R, Arntz H-R. How sudden is sudden cardiac death? *Circulation* 2006;114(11):1146-50. doi:10.1161/CIRCULATIONAHA.106.616318.

24. Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing Incidence of Out-of-Hospital Ventricular Fibrillation, 1980-2000. *JAMA* 2002;288(23):3008-3013.

25. Galea S, Blaney S, Nandi a, et al. Explaining racial disparities in incidence of and survival from out-of-hospital cardiac arrest. *Am. J. Epidemiol.* 2007;166(5):534-43. doi:10.1093/aje/kwm102.

26. Rea TD, Pearce RM, Raghunathan TE, et al. Incidence of out-of-hospital cardiac arrest. *Am. J. Cardiol.* 2004;93(12):1455-60. doi:10.1016/j.amjcard.2004.03.002.

27. Friedlander Y, Siscovick DS, Weinmann S, et al. Family History as a Risk Factor for Primary Cardiac Arrest. *Circulation* 1998;97(2):155-160. doi:10.1161/01.CIR.97.2.155.

28. Jouven X, Desnos M, Guerot C, Ducimetiere P. Predicting Sudden Death in the Population : The Paris Prospective Study I. *Circulation* 1999;99(15):1978-1983. doi:10.1161/01.CIR.99.15.1978.

29. Chiuve SE, Fung TT, Rexrode KM, et al. Adherence to a low-risk, healthy lifestyle and risk of sudden cardiac death among women. *JAMA* 2011;306(1):62-9. doi:10.1001/jama.2011.907.

30. Vaillancourt C, Stiell IG. Cardiac arrest care and emergency medical services in Canada. *Can. J. Cardiol.* 2004;20(11):1081-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15457303.

31. Sasson C, Rogers M a M, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ. Cardiovasc. Qual. Outcomes* 2010;3(1):63-81. doi:10.1161/CIRCOUTCOMES.109.889576.

32. Piktel JS. Cardiac Rhythm Disturbances. In: Tintinalli J, Stapczynski J, Ma O, Cline D, Cydulka R, Meckler G, eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*. 7e ed. New York, NY: McGraw-Hill; 2011. Available at: http://accessmedicine.mhmedical.com.proxy.queensu.ca/content.aspx?bookid=348&Sectionid=40381483.

33. Nolan J, Soar J, Eikeland H. The chain of survival. *Resuscitation* 2006;71(3):270-1. doi:10.1016/j.resuscitation.2006.09.001.

34. Cummins RO, Ornato JP, Thies WH, Pepe PE. Improving survival from sudden cardiac arrest: the "chain of survival" concept. A statement for health professionals from the Advanced Cardiac Life Support Subcommittee and the Emergency Cardiac Care Committee, American Heart Association. *Circulation* 1991;83(5):1832-1847. doi:10.1161/01.CIR.83.5.1832.

35. Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed-Chest Cardiac Massage. *JAMA* 2014;173(10):1064-1067.

36. Bayés de Luna a, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am. Heart J.* 1989;117(1):151-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2911968.

37. Peberdy MA, Ornato JP. Post-resuscitation care: is it the missing link in the Chain of Survival? *Resuscitation* 2005;64(2):135-7. doi:10.1016/j.resuscitation.2004.09.015.

38. Iwami T, Nichol G, Hiraide A, et al. Continuous improvements in "chain of survival" increased survival after out-of-hospital cardiac arrests: a large-scale population-based study. *Circulation* 2009;119(5):728-34. doi:10.1161/CIRCULATIONAHA.108.802058.

39. Yannopoulos D, Kotsifas K, Lurie KG. Advances in cardiopulmonary resuscitation. *Heart Fail. Clin.* 2011;7(2):251-68, ix. doi:10.1016/j.hfc.2011.01.003.

40. Arrich J, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation (Review). 2012;(9).

41. Bernard SA, Gray TW, Buist MD, et al. Induced Hypothermia after Out-of-Hospital Cardiac Arrest: Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Inducted Hypothermia. 2002;346(8):557-563.

42. Holzer M, Cerchiari E, Martens P, Roine R, Sterz F. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N. Engl. J. Med.* 2002;346(8):549-56. doi:10.1056/NEJMoa012689.

43. Arrich J. Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit. Care Med.* 2007;35(4):1041-7. doi:10.1097/01.CCM.0000259383.48324.35.

44. Belliard G, Catez E, Charron C, et al. Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. *Resuscitation* 2007;75(2):252-9. doi:10.1016/j.resuscitation.2007.04.014.

45. Castrejón S, Cortés M, Salto ML, et al. Improved prognosis after using mild hypothermia to treat cardiorespiratory arrest due to a cardiac cause: comparison with a control group. *Rev. española Cardiol.* 2009;62(7):733-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19709508.

46. Holzer M, Müllner M, Sterz F, et al. Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. *Stroke.* 2006;37(7):1792-7. doi:10.1161/01.STR.0000227265.52763.16.

47. Don CW, Longstreth WT, Maynard C, et al. Active surface cooling protocol to induce mild therapeutic hypothermia after out-of-hospital cardiac arrest: a retrospective before-and-after comparison in a single hospital. *Crit. Care Med.* 2009;37(12):3062-9. doi:10.1097/CCM.0b013e3181b7f59c.

48. Sagalyn E, Band R a, Gaieski DF, Abella BS. Therapeutic hypothermia after cardiac arrest in clinical practice: review and compilation of recent experiences. *Crit. Care Med.* 2009;37(7 Suppl):S223-6. doi:10.1097/CCM.0b013e3181aa5c7c.

49. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N. Engl. J. Med.* 2013;369(23):2197-206. doi:10.1056/NEJMoa1310519.

50. Rittenberger JC, Callaway CW. Temperature management and modern post-cardiac arrest care. *N. Engl. J. Med.* 2013;369(23):2262-3. doi:10.1056/NEJMe1312700.

51. Spaulding C, Joly L-M, Rosenberg A, et al. Immediate Coronary Angiography in Survivors of Out-of-Hospital Cardiac Arrest. *N. Engl. J. Med.* 1997;336(23):1629-1633.

52. Garot P, Lefevre T, Eltchanioff H, et al. Six-month outcome of emergency percutaneous coronary intervention in reuscitated patients after cardiac arrest complicating ST-elevation mycoardial infarction. *Circulation* 2007;115:1354-1362.

53. Keelan P, Bunch T, White R, Packer D, Holmes DJ. Early direct coronary angioplasty in survivors of out-of-hospital cardiac arrest. *Am. J. Cardiol.* 2003;91(A1466):1461-1463.

54. Bendz B, Eritsland J, Nakstad A, et al. Long-term prognosis after out-of-hospital cardiac arrest and primary percutaneous intervention. *Resuscitation* 2004;63:49-53.

55. Larsen JM, Ravkilde J. Acute coronary angiography in patients resuscitated from out-of-hospital cardiac arrest--a systematic review and meta-analysis. *Resuscitation* 2012;83(12):1427-33. doi:10.1016/j.resuscitation.2012.08.337.

56. Cook D, Rocker G, Marshall J, et al. Withdrawal of mechanical ventilation in anticipation of death in the intensive care unit. *N. Engl. J. Med.* 2003;349(12):1123-32. doi:10.1056/NEJMoa030083.

57. Perman SM, Kirkpatrick JN, Reitsma AM, et al. Timing of neuroprognostication on postcardiac arrest therapeutic hypothermia. *Crit. Care Med.* 2013;40(3):719-724. doi:10.1097/CCM.0b013e3182372f93.Timing.

58. Wijdicks EFM, Hijdra a, Young GB, Bassetti CL, Wiebe S. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;67(2):203-10. doi:10.1212/01.wnl.0000227183.21314.cd.

59. Young GB. Neurologic Prognosis after Cardiac Arrest. *N. Engl. J. Med.* 2009;361(6):605-611.

60. Al Thenayan E, Savard M, Sharpe M, Norton L, Young B. Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. *Neurology* 2008;71(19):1535-7. doi:10.1212/01.wnl.0000334205.81148.31.

61. Wyse DG, Friedman PL, Epstein AE. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N. Engl. J. Med.* 1997;337:1576-1583.

62. Kuck K-H, Cappato R, Siebels J, Ruppel R. Randomized Comparison of Antiarrhythmic Drug Therapy With Implantable Defibrillators in Patients Resuscitated From Cardiac Arrest : The Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;102(7):748-754. doi:10.1161/01.CIR.102.7.748.

63. Connolly SJ, Gent M, Roberts RS, et al. Canadian Implantable Defibrillator Study (CIDS) : A Randomized Trial of the Implantable Cardioverter Defibrillator Against Amiodarone. *Circulation* 2000;101(11):1297-1302. doi:10.1161/01.CIR.101.11.1297.

64. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008;300(12):1423-31. doi:10.1001/jama.300.12.1423.

65. Labinaz M, Swabey T, Watson R, et al. Delivery of primary percutaneous coronary intervention for the management of acute ST segment elevation myocardial infarction: summary of the Cardiac Care Network of Ontario Consensus Report. *Can. J. Cardiol.* 2006;22(3):243-50. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2528927&tool=pmcentrez&rendertype=abstract.

66. Abella BS, Rhee JW, Huang K-N, Vanden Hoek TL, Becker LB. Induced hypothermia is underused after resuscitation from cardiac arrest: a current practice survey. *Resuscitation* 2005;64(2):181-6. doi:10.1016/j.resuscitation.2004.09.014.

67. Wolfrum S, Radke PW, Pischon T, Willich SN, Schunkert H, Kurowski V. Mild therapeutic hypothermia after cardiac arrest - a nationwide survey on the implementation of the ILCOR guidelines in German intensive care units. *Resuscitation* 2007;72(2):207-13. doi:10.1016/j.resuscitation.2006.06.033.

68. Boyce R, Bures K, Czamanski J, Mitchell M. Adherence to therapeutic hypothermia guidelines for out-of-hospital cardiac arrest. *Aust. Crit. Care* 2012;25(3):170-7. doi:10.1016/j.aucc.2012.02.006.

69. Laver SR, Padkin A, Atalla A, Nolan JP. Therapeutic hypothermia after cardiac arrest : a survey of practice in intensive care units in the United Kingdom. *Anaesthesia* 2006;61:873-877. doi:10.1111/j.1365-2044.2006.04552.x.

70. Laver SR, Padkin A, Atalla A, Nolan JP. Therapeutic hypothermia after cardiac arrest : a survey of practice in intensive care units in the United Kingdom. *Anaesthesia* 2006;61:873-877. doi:10.1111/j.1365-2044.2006.04552.x.

71. Bigham BL, Dainty KN, Scales DC, Morrison LJ, Brooks SC. Predictors of adopting therapeutic hypothermia for post-cardiac arrest patients among Canadian emergency and critical care physicians. *Resuscitation* 2010;81(1):20-4. doi:10.1016/j.resuscitation.2009.09.022.

72. Dainty KN, Scales DC, Brooks SC, et al. A knowledge translation collaborative to improve the use of therapeutic hypothermia in post-cardiac arrest patients: protocol for a stepped wedge randomized trial. *Implement. Sci.* 2011;6(1):4. doi:10.1186/1748-5908-6-4.

73. Peberdy MA, Kaye W, Ornato JP, et al. Cardiopulmonary resuscitation of adults in the hospital: A report of 14 720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. *Resuscitation* 2003;58(3):297-308. doi:10.1016/S0300-9572(03)00215-6.

74. Hewitt M. *Interpreting the Volume – Outcome Relationship in the Context of Health Care Quality: Workshop Summary*.; 2000. Available at: http://www.nap.edu/catalog/10005.html.

75. Halm E a, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann. Intern. Med.* 2002;137(6):511-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12230353.

76. Kajino K, Iwami T, Daya M, et al. Impact of transport to critical care medical centers on outcomes after out-of-hospital cardiac arrest. *Resuscitation* 2010;81(5):549-54. doi:10.1016/j.resuscitation.2010.02.008.

77. Ro YS, Shin S Do, Song KJ, et al. A comparison of outcomes of out-of-hospital cardiac arrest with non-cardiac etiology between emergency departments with low- and high-resuscitation case volume. *Resuscitation* 2012;83(7):855-61. doi:10.1016/j.resuscitation.2012.02.002.

78. Cudnik MT, Sasson C, Rea TD, et al. Increasing hospital volume is not associated with improved survival in out of hospital cardiac arrest of cardiac etiology. *Resuscitation* 2012;83(7):862-8. doi:10.1016/j.resuscitation.2012.02.006.

79. Carr BG, Goyal M, Band R a, et al. A national analysis of the relationship between hospital factors and post-cardiac arrest mortality. *Intensive Care Med.* 2009;35(3):505-11. doi:10.1007/s00134-008-1335-x.

80. Callaway CW, Schmicker R, Kampmeyer M, et al. Receiving hospital characteristics associated with survival after out-of-hospital cardiac arrest. *Resuscitation* 2010;81(5):524-9. doi:10.1016/j.resuscitation.2009.12.006.

81. Morrison LJ, Nichol G, Rea TD, et al. Rationale, development and implementation of the Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. *Resuscitation* 2008;78(2):161-9. doi:10.1016/j.resuscitation.2008.02.020.

82. Oakes GH, Ko DT, Guo H. *Report on Adult Percutaneous Coronary Interventions (PCI) in Ontario*.; 2013.

83. Lin S, Morrison LJ, Brooks SC. Development of a data dictionary for the Strategies for Post Arrest Resuscitation Care (SPARC) network for post cardiac arrest research. *Resuscitation* 2011;82(4):419-22. doi:10.1016/j.resuscitation.2010.12.006.

84. Stiell IG, Nesbitt LP, Nichol G, et al. Comparison of the Cerebral Performance Category score and the Health Utilities Index for survivors of cardiac arrest. *Ann. Emerg. Med.* 2009;53(2):241-248. doi:10.1016/j.annemergmed.2008.03.018.

85. Kim JY, Shin S Do, Ro YS, et al. Post-resuscitation care and outcomes of out-of-hospital cardiac arrest: a nationwide propensity score-matching analysis. *Resuscitation* 2013;84(8):1068-77. doi:10.1016/j.resuscitation.2013.02.010.

86. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

87. Meier-Hirmer C, Ortseifen C, Sauerbrei W. *Multivariable Fractional Polynomials in SAS: An Algorithm for Determining the Transformation of Continuous Covariates and Selection of Covariates*.; 2003.

88. Merlo J, Chaix B, Yang M, Lynch J, Råstam L. A brief conceptual tutorial of multilevel analysis in social epidemiology: linking the statistical concept of clustering to the idea of contextual phenomenon. *J. Epidemiol. Community Health* 2005;59(6):443-9. doi:10.1136/jech.2004.023473.

89. Jacoby WG. Loess : a nonparametric , graphical tool for depicting relationships between variables. *Elect. Stud.* 2000;19:577-613.

90. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J. Clin. Epidemiol.* 2014;67(3):267-77. doi:10.1016/j.jclinepi.2013.08.015.

91. Carr BG, Kahn JM, Merchant RM, Kramer A a, Neumar RW. Inter-hospital variability in post-cardiac arrest mortality. *Resuscitation* 2009;80(1):30-4. doi:10.1016/j.resuscitation.2008.09.001.

92. Stub D, Smith K, Bray JE, Bernard S, Duffy SJ, Kaye DM. Hospital characteristics are associated with patient outcomes following out-of-hospital cardiac arrest. *Heart* 2011;97(18):1489-94. doi:10.1136/hrt.2011.226431.

93. Rittenberger JC, Raina K, Holm MB, Kim YJ, Callaway CW. Association between Cerebral Performance Category, Modified Rankin Scale, and discharge disposition after cardiac arrest. *Resuscitation* 2011;82(8):1036-40. doi:10.1016/j.resuscitation.2011.03.034.

94. Gandjour A, Bannenberg A, Lauterbach KL. Threshold Volumes Associated With Higher Survival in Health Care: A Systematic Review. *Med. Care* 2003;41(10):1129-1141.

95. Hannan EL, Racz M, Ryan TJ, et al. Coronary Angioplasty Volume-Outcome Relationships for Hospitals and Cardiologists. *JAMA* 1997;279:892-898.

96. Spaite DW, Bobrow BJ, Vadeboncoeur TF, et al. The impact of prehospital transport interval on survival in out-of-hospital cardiac arrest: implications for regionalization of post-resuscitation care. *Resuscitation* 2008;79(1):61-6. doi:10.1016/j.resuscitation.2008.05.006.

Appendix A

Cerebral Performance Category (CPC) Scale

Cerebral Performance Categories Scale

CPC Scale

Note: If patient is anesthetized, paralyzed, or intubated, use "as is" clinical condition to calculate scores.
CPC 1. Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.
CPC 2. Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
CPC 3. Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
CPC 4. Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
CPC 5. Brain death: apnea, areflexia, EEG silence, etc.

Safar P. Resuscitation after Brain Ischemia, in Grenvik A and Safar P Eds: Brain Failure and Resuscitation, Churchill Livingstone, New York, 1981; 155-184.

Appendix B

Intraclass Correlation (ICC) and Median Odds Ratio (MOR) Calculations

EMPTY REGRESSION MODELS

Successful TTM:

Intraclass correlation calculation:

ICC = σ^2 / [σ^2 + (π^2/3)]

= 0.4039 / [0.4039 + (π^2/3)]

= 0.109

Median odds ratio calculation:

MOR = $\exp\left(\sqrt{2 \times \sigma^2} \times \Phi^{-1}(0.75)\right)$

= $\exp\left(\sqrt{2 \times 0.4039} \times \Phi^{-1}(0.75)\right)$

= exp [$\sqrt{2 \times 0.4039}$ x 0.6745]

= 1.83

Cooling initiated:

Intraclass correlation calculation:

ICC = σ^2 / [σ^2 + (π^2/3)]

= 0.4679 / [0.4679 + (π^2/3)]

= 0.125

Median odds ratio calculation:

MOR = $\exp\left(\sqrt{2 \times \sigma^2} \times \Phi^{-1}(0.75)\right)$

= $\exp\left(\sqrt{2 \times 0.4679} \times \Phi^{-1}(0.75)\right)$

= exp [$\sqrt{2 \times 0.4679}$ x 0.6745]

= 1.92

Life sustaining therapy withdrawn on the basis of premature neuroprognostication:

Intraclass correlation calculation:

ICC = σ^2 / [σ^2 + (π^2/3)]

= 0.5017 / [0.5017 + (π^2/3)]

= 0.132

Median odds ratio calculation:

MOR = $\exp\left(\sqrt{2 \times \sigma^2} \times \Phi^{-1}(0.75)\right)$

= $\exp\left(\sqrt{2 \times 0.5017} \times \Phi^{-1}(0.75)\right)$

= exp [$\sqrt{2 \times 0.5017}$ x 0.6745]

= 1.97

Survival with good neurologic function:

Intraclass correlation calculation:

ICC = Covariance estimate / [covariance estimate + (π^2/3)]

= 0.1950 / [0.1950 + (π^2/3)]

= 0.056

Median odds ratio calculation**:**

MOR = $\exp\left(\sqrt{2 \times \sigma^2} \times \Phi^{-1}(0.75)\right)$

= $\exp\left(\sqrt{2 \times 0.1950} \times \Phi^{-1}(0.75)\right)$

= exp [$\sqrt{2 \times 0.1950}$ x 0.6745]

= 1.52

FINAL MODELS

Successful TTM:

Median odds ratio calculation:

MOR = $\exp\left(\sqrt{2 \times \sigma^2} \times \Phi^{-1}(0.75)\right)$

= $\exp\left(\sqrt{2 \times 0.3682} \times \Phi^{-1}(0.75)\right)$

= exp [$\sqrt{2 \times 0.3682}$ x 0.6745]

= 1.78

Cooling initiated:

Median odds ratio calculation:

MOR = exp $\left(\sqrt{2 \times \sigma^2} \times \Phi^{-1}(0.75)\right)$

= exp $\left(\sqrt{2 \times 0.3665} \times \Phi^{-1}(0.75)\right)$

= exp [$\sqrt{2 \times 0.3665}$ x 0.6745]

= 1.78

Life sustaining therapy withdrawn on the basis of premature neuroprognostication:

Median odds ratio calculation:

MOR = exp $\left(\sqrt{2 \times \sigma^2} \times \Phi^{-1}(0.75)\right)$

= exp $\left(\sqrt{2 \times 0.3931} \times \Phi^{-1}(0.75)\right)$

= exp [$\sqrt{2 \times 0.3931}$ x 0.6745]

= 1.82

Survival with good neurologic function:

Median odds ratio calculation**:**

MOR = exp $\left(\sqrt{2 \times \sigma^2} \times \Phi^{-1}(0.75)\right)$

= exp $\left(\sqrt{2 \times 0.1179} \times \Phi^{-1}(0.75)\right)$

= exp [$\sqrt{2 \times 0.1179}$ x 0.6745]

= 1.39

Appendix C

Model Building Strategies

For each of the outcomes of interest, the exposure was modelled 3 different ways (categorical, continuous, and as a fractional polynomial) and the model where the AIC was minimized was selected as the best model and presented in the results section.

The following tables show the modelling with the categories of volume established in the descriptive section of the thesis.

Table 17. Multilevel model for successful TTM with average annual volume modelled as a categorical variable

	Odds Ratio	**95% CI**
Low (<15 eligible TTM/year)	Reference	Reference
Moderate (15-25 eligible TTM/year)	1.454	0.828-2.553
High (>25 eligible TTM/year)	1.887	0.999-3.563

Table 18. Multilevel model for cooling initiated with average annual volume modelled as a categorical variable

	Odds Ratio	**95% CI**
Low (<15 eligible TTM/year)	Reference	Reference
Moderate (15-25 eligible TTM/year)	1.186	0.678-2.076
High (>25 eligible TTM/year)	2.296	1.209-4.360

Table 19. Multilevel model for premature withdrawal of life sustaining therapy on the basis of neuroprognostication with average annual volume modelled as a categorical variable

	Odds Ratio	95% CI
Low (<15 eligible TTM/year)	Reference	Reference
Moderate (15-25 eligible TTM/year)	1.182	0.534-2.616
High (>25 eligible TTM/year)	1.317	0.566-3.064
Age	1.031	1.016-1.047
Male	1.008	0.651-1.560
EMS witnessed	0.244	0.119-0.500
Bystander CPR	0.716	0.454-1.128
ROSC in the field	0.401	0.224-0.717
Shockable initial rhythm	0.254	0.150-0.430

Table 20. Multilevel model for survival with good neurologic function with average annual volume modelled as a categorical variable

	Odds Ratio	95% CI
Low (<15 eligible TTM/year)	Reference	Reference
Moderate (15-25 eligible TTM/year)	0.776	0.521-1.156
High (>25 eligible TTM/year)	0.730	0.474-1.122
Age	0.962	0.955-0.968
Male	1.091	0.867-1.373
Bystander witnessed	1.610	1.254-2.068
EMS witnessed	3.724	2.613-5.306
Bystander CPR	1.001	0.800-1.251
AED use	1.562	0.998-2.446
ROSC in the field	4.008	2.762-5.817
Public	1.362	1.080-1.717
EMS response time	0.999	0.998-0.999
Shockable initial rhythm	4.67	3.676-5.917

The SAS macro[87] that modelled the exposure as a fractional polynomial yielded that the 1st power was the best fit for all outcomes. This further supported the presentation of the exposure as a continuous variable in the final models.

Appendix D

Linearity in the Logit

As the models presented in this thesis model average annual hospital volume of patients eligible for TTM as a continuous variable, lowess curves of volume versus the outcomes of interest were created to ensure it was appropriate to model the exposure as a continuous variable. The curves for each of the outcomes showed a logistic relationship and so it was deemed that modelling the exposure as a continuous variable was appropriate. The LOWESS plots for each of the outcomes are presented in the following figures.

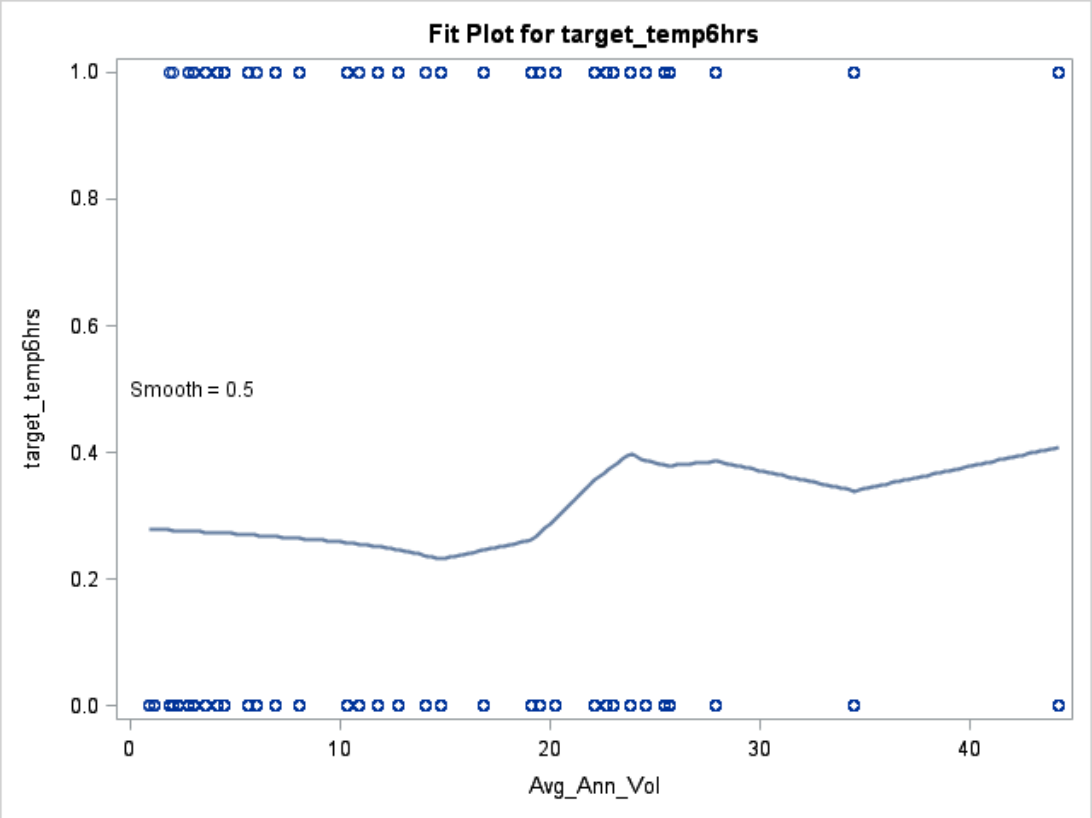

Figure 12. LOWESS curve for successful TTM

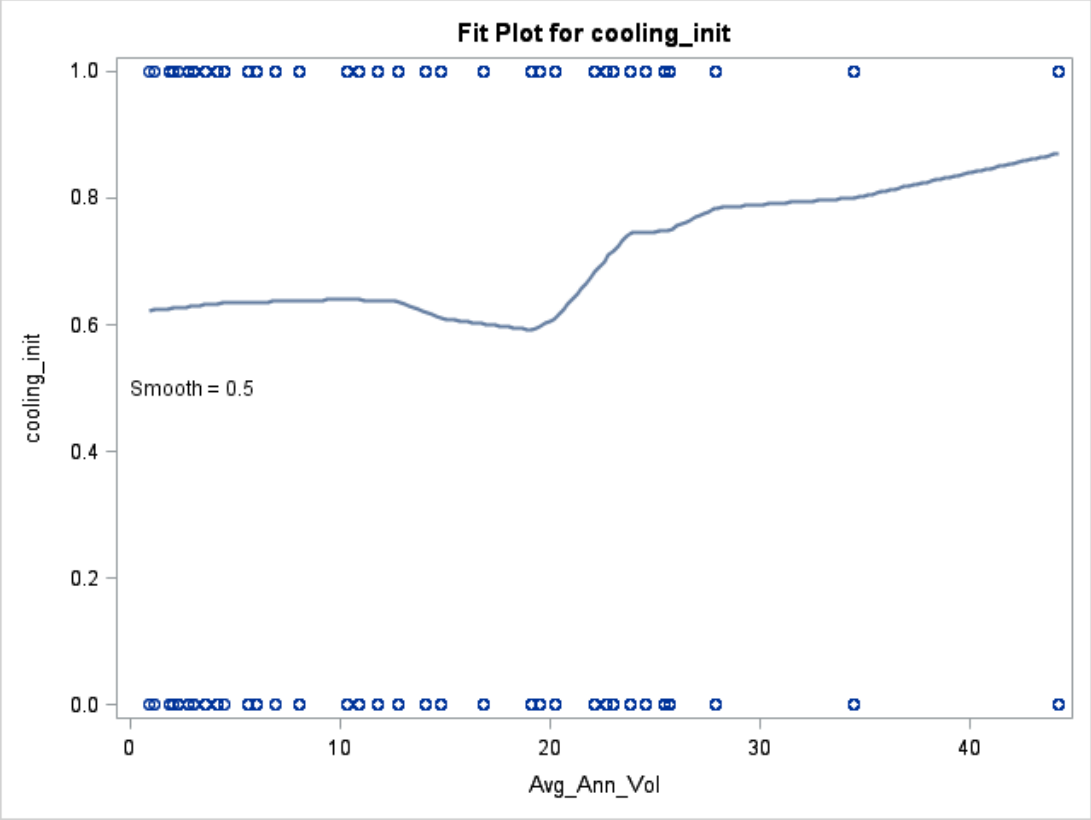

Figure 13. LOWESS curve for cooling initiated

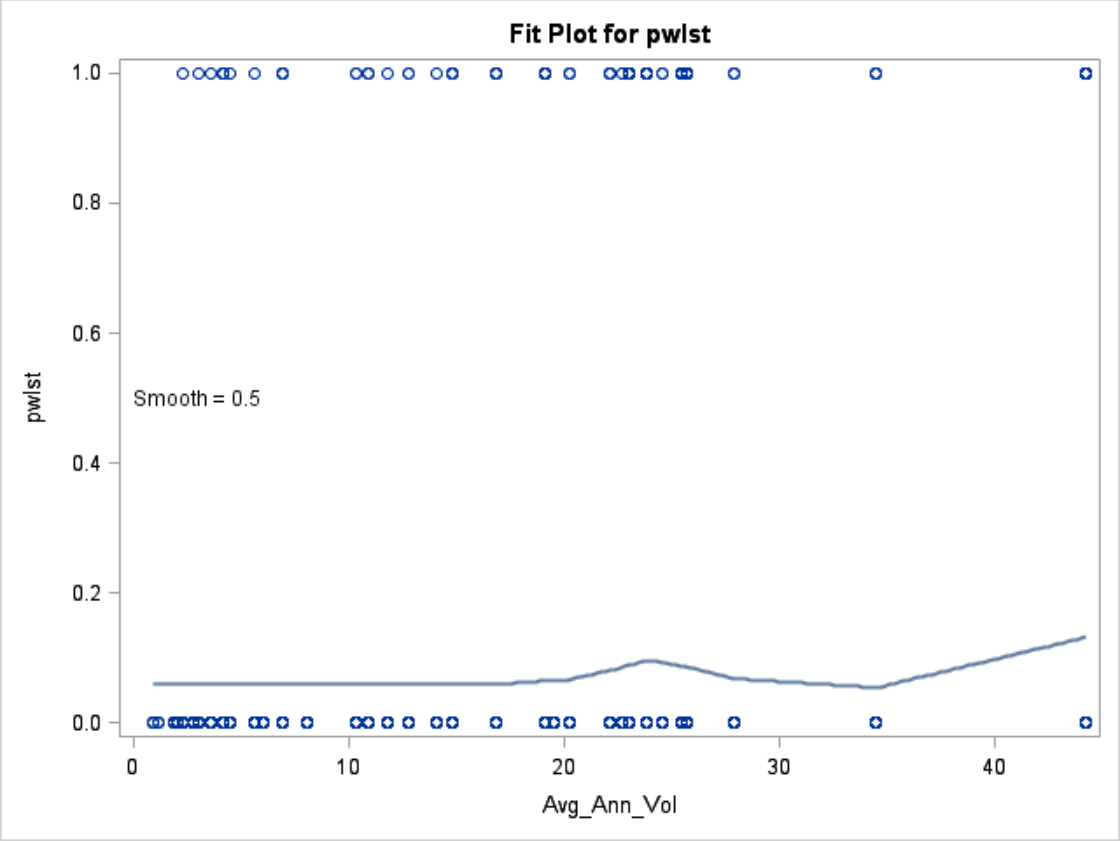

Figure 14. LOWESS curve for premature withdrawal of life sustaining therapy on the basis of neuroprognostication

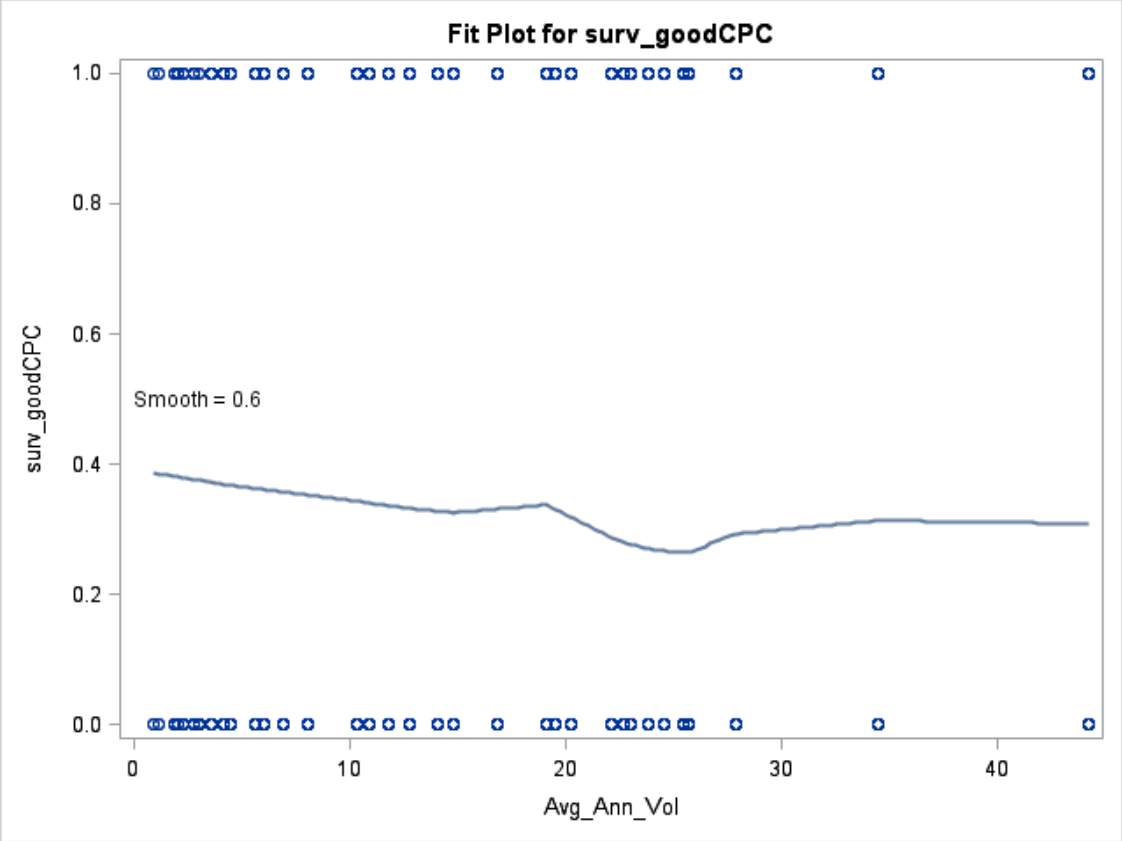

Figure 15. LOWESS curve for survival with good neurologic function

Appendix E

Alternate Treatment Process Models

These models include all variables with a $p<0.10$ or felt to be clinically significant. As the covariates included in these models did not change the odds ratio of interest by more than 10%, they were not presented in the final models in sections 4.5.2 and 4.5.3.

Table 21. Alternate multilevel model for successful TTM

	Odds Ratio	95% CI	*p*-value
Average annual volume of patients eligible for TTM	1.30	1.04-1.63	0.03
Age	1.01	1.01-1.02	<0.01
Male	1.11	0.86-1.33	0.52
Shockable initial rhythm	1.41	1.14-1.73	<0.01

Table 22. Alternate multilevel model for cooling initiated

	Odds Ratio	95% CI	*p*-value
Average annual volume of patients eligible for TTM	1.49	1.17-1.90	<0.01
Age	0.99	0.98-0.99	<0.01
Male	1.41	1.16-1.70	<0.01
Shockable initial rhythm	2.54	2.08-3.13	<0.01

Appendix F

Research Ethics Board Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW
February 06, 2014

Ms. Heather Worthington
Department of Public Health Sciences
Queen's University

Dear Ms. Worthington
Study Title: EPID-463-14 Hospital Post Cardiac Arrest Patient Volume and Key Features of Post Cardiac Arrest Care with a Focus on Therapeutic Hypothermia
File # 6011836
Co-Investigators: Dr. S. Brooks

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file **# 6011836** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file **6011836** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

Albert J. Clark.
Chair, Health Sciences Research Ethics Board
February 06, 2014

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards and operates in compliance with the Tri-Council Policy Statement; Part C Division 5 of the Food and Drug Regulations, OHRP, and U.S DHHS Code of Federal Regulations Title 45, Part 46 and carries out its functions in a manner consistent with Good Clinical Practices.

Federalwide Assurance Number: #FWA00004184, #IRB00001173

Current 2014 membership of the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board:

Dr. A.F. Clark, Emeritus Professor**,** Department of Biomedical and Molecular Sciences, Queen's University (Chair)

Dr. H. Abdollah, Professor**,** Department of Medicine, Queen's University

Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University

Dr. C. Cline, Assistant Professor, Department of Medicine, Director, Office of Bioethics, Queen's University, Clinical Ethicist, Kingston General Hospital

Dr. M. Evans, Community Member

Ms. J. Hudacin, Community Member

Mr. D. McNaughton, Community Member

Ms. P. Newman, Pharmacist, Clinical Care Specialist and Clinical Lead, Quality and Safety, Pharmacy Services, Kingston General Hospital

Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute

Dr. A. Singh, Professor, Department of Psychiatry, Queen's University

Dr. J. Walia, Assistant Professor and Clinical Geneticist, Department of Paediatrics, Queen's University and Kingston General Hospital

Ms. K. Weisbaum, LL.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)