CORONARY ANGIOGRAPHY AND NEUROLOGICALLY INTACT SURVIVAL IN OUT-OF-HOSPITAL CARDIAC ARREST PATIENTS WITH RETURN OF SPONTANEOUS CIRCULATION

By

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Abstract

**Introduction:** Acute Coronary Syndrome (ACS) is prevalent in out-of-hospital cardiac arrest (OHCA) patients but only a minority receives coronary angiography. Also, evidence for the effectiveness of coronary angiography in this population is conflicting.

**Objectives:** 1) To describe the patient and hospital-level factors that are associated with receiving coronary angiography 2) To determine if receiving coronary angiography is associated with survival to hospital discharge with favorable neurologic outcome.

**Methods:** This was a population-based retrospective cohort study of 2578 consecutive cases of adult OHCA transported to and treated at 28 hospitals in Southern Ontario between March 1\(^{st}\), 2010 and December 31\(^{st}\), 2014. We included patients with atraumatic OHCA, who achieved return of spontaneous circulation (ROSC), and survived to at least six hours after hospital arrival. Multilevel logistic regression was used to explore the association between exposure variables and outcome variables, while accounting for clustering of patients (level 1) within hospitals (level 2) and adjusting for potential confounders.

**Results:** Coronary angiography use varied from 13% to 70% across the hospital sites. Overall, 33\%(n=863/2578) of patients received coronary angiography, 42\%(n=1082/2578) survived to hospital discharge and 38\%(n=960/2552) survived to hospital discharge with favorable neurologic outcome. Multilevel analysis revealed that factors positively associated with receiving coronary angiography included patient age, STEMI status, being conscious at hospital arrival, having a shockable initial cardiac rhythm, an EMS witnessed arrest, initiation of therapeutic hypothermia, receiving bystander defibrillation, and being admitted directly to a PCI center. Receiving coronary angiography was associated with neurologically intact survival (OR=2.03, CI\(_{95}\) 1.47-2.80, p<.0001) and survival to hospital discharge (OR=1.86, CI\(_{95}\) 1.36-2.55, p<.0001). Similar associations were observed in the subgroup of
patients without ST-elevation myocardial infarction (STEMI) (OR=2.90, CI₉₅ 1.90-4.43 and OR=2.44, CI₉₅ 1.62-3.69, respectively).

Conclusions: There is significant variability in receipt of coronary angiography after cardiac arrest. We identified several patient and hospital-level factors that contribute to this variability. Neurologically intact survival amongst post cardiac arrest patients may be improved with coronary angiography, particularly for patients without STEMI. Future work should determine which post arrest patients will benefit most from urgent angiography, and our findings should be confirmed with randomized controlled trials.
Co-Authorship

This thesis was written by Tasha Hanuschak. Guidance throughout the process was provided by Tasha’s primary supervisor, Dr. Steven Brooks, Tasha’s secondary supervisor, Dr. Paul Peng, and Andrew Day who provided support for statistical analysis procedures. Feedback concerning content and wording were provided by Dr. Steven Brooks and Dr. Paul Peng.

The study was designed by Tasha Hanuschak with guidance from Dr. Steven Brooks and guidance on data analysis strategies by Dr. Paul Peng and Andrew Day. Tasha Hanuschak cleaned and prepared the data for analysis, analyzed the data and interpreted the findings. Dr. Steven Brooks and Dr. Paul Peng assisted with interpretation of findings. Assistance was also provided by co-investigators of the Strategies for Post-Arrest Resuscitation Care (SPARC) Network: Dr. Laurie Morrison and Dr. Cathy Zhan. Dr. Zhan, a database analyst with the Rescu program at St. Michael’s Hospital, provided the dataset and data dictionary with data abstraction instructions.
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List of Abbreviations

ACLS ........................................................................................................ Advanced cardiac life support
ACS ......................................................................................................... Acute coronary syndrome
AED ......................................................................................................... Automated external defibrillator
AHA ......................................................................................................... American Heart Association
AMI ....................................................................................................... Acute myocardial infarction
CABG ................................................................................................. Coronary artery bypass grafting
CAD ....................................................................................................... Coronary artery disease
CPC ......................................................................................................... Cerebral Performance Category
CPR ......................................................................................................... Cardiopulmonary resuscitation
DNR ......................................................................................................... Do not resuscitate
ECG ........................................................................................................ Electrocardiogram
EMS ....................................................................................................... Emergency Medical Services
GCS ......................................................................................................... Glasgow Coma Scale
ICC ......................................................................................................... Intraclass correlation coefficient
ILCOR ................................................................................................. International Liaison Committee on Resuscitation
LBBB ................................................................................................. Left bundle branch block
MOR ....................................................................................................... Median odds ratio
MRS ......................................................................................................... Modified Rankin Scale
OHCA ................................................................................................. Out-of-hospital cardiac arrest
PCI ......................................................................................................... Percutaneous coronary intervention
PEA ......................................................................................................... Pulseless electrical activity
PROCAT .............................................................................................. Parisian Region Out of Hospital Cardiac Arrest
ROC ....................................................................................................... Resuscitation Outcomes Consortium
ROSC ................................................................................................. Return of spontaneous circulation
SAS ......................................................................................................... Statistical Analysis Software
SPARC ................................................................................................. Strategies for Post Arrest Resuscitation Care
STEMI ................................................................................................. ST-elevation myocardial infarction
VF ......................................................................................................... Ventricular fibrillation
VT ......................................................................................................... Ventricular tachycardia
Chapter 1

Introduction

1.1 Purpose

The purpose of this thesis was to identify opportunities to improve the consistency and quality of care received by out-of-hospital cardiac arrest (OHCA) patients in Southern Ontario and beyond. We were interested in aspects of care related to the urgent assessment and treatment of acute coronary syndrome (ACS) in the post-cardiac arrest patient with return of spontaneous circulation (ROSC). To accomplish this, we measured variability in emergency cardiovascular care provided to post-cardiac arrest patients in a collaborative network of hospitals in Southern Ontario. More specifically, we examined the association between patient demographic and clinical features, hospital features and a key element of post-resuscitation care, specifically diagnostic coronary angiography.

Previous studies have suggested an association between coronary angiography and improved outcomes amongst post cardiac arrest patients, however, findings have conflicted, especially in particular subgroups of OHCA patients. Secondly, we measured the consequences of the observed variability with respect to clinical outcomes. We determined the relationship between receipt of coronary angiography within 72 hours of hospital arrival, and patient survival to hospital discharge with favorable neurologic outcome, as well as survival to hospital discharge.

1.2 Background

Each year, 11% of all deaths in Canada are due to sudden cardiac arrest.¹ The case-mortality rate for out-of-hospital cardiac arrest (OHCA) is approximately 95%,²,³ making it the third most common cause of death in North America⁴. Unfortunately, only 37% of patients who are admitted to a hospital will survive to hospital discharge.⁵ A significant proportion of the survivors will suffer neurologic and cognitive deficits due to hypoxic ischemic brain injury.⁶,⁷ Since the majority of patients who are alive at
hospital admission do not survive to hospital discharge, it is evident that further research must focus on in-hospital post-resuscitation interventions that have the potential to improve outcomes.

The majority of patients resuscitated from cardiac arrest have acute coronary syndrome (ACS), however the treatment of cardiac arrest patients is controversial. A treatment which may be feasible for OHCA patients with suspected acute coronary syndrome (ACS) is coronary angiography, as it is able to identify the presence and/or location of coronary artery occlusions. Once identified, culprit lesions are amenable to treatment using additional procedures such as PCI and stent placement, or coronary artery bypass grafting (CABG). However, only a minority of post cardiac arrest patients receive coronary angiography. If the patient does not demonstrate ST-segment elevation myocardial infarction (STEMI) on the post-arrest electrocardiogram (ECG), the chances of receiving coronary angiography are even lower. Other factors influencing whether or not an OHCA patient receives coronary angiography are largely unknown.

Evidence for the effectiveness of coronary angiography in post cardiac arrest patients is conflicting. Though recent studies have demonstrated that coronary angiography and percutaneous coronary intervention (PCI) improve rates of survival to hospital discharge with good neurologic outcome, regardless of initial post-arrest ECG findings. These studies provide preliminary evidence that it may be beneficial to provide coronary angiography to all resuscitated cardiac arrest patients admitted to hospitals, but it is unclear whether this is true in the Canadian setting.

1.3 Rationale

For patients who have STEMI, but have not suffered a cardiac arrest, the recommended treatment is immediate coronary angiography, followed by PCI. Early coronary angiography and revascularization are also recommended for non-arrested patients with non-STEMI.

Meanwhile, the optimal treatment strategy for post cardiac arrest patients is controversial, as large randomized controlled trials have not been conducted in this patient population. The proportion of OHCA patients who receive coronary angiography in Canada is largely unknown and there is
disagreement in clinical practice as to which patients should undergo coronary angiography and PCI.\textsuperscript{12,14,26} It is important to describe clinical practice in Ontario hospitals to determine which factors influence whether or not an OHCA patient receives coronary angiography. An understanding of system and patient factors driving the variability in receipt of coronary angiography may identify targets for future interventions to improve the quality and consistency of post-cardiac arrest care in Ontario and beyond.

Only the minority of post cardiac arrest patients receive coronary angiography and definitive management with PCI,\textsuperscript{8,19} despite the fact that acute coronary syndrome (ACS) is thought to be the cause of OHCA in the majority of patients.\textsuperscript{10–13,27} In particular, clinicians do not agree upon the methods to select patients without STEMI for coronary angiography.\textsuperscript{14,26} Some research has demonstrated that coronary angiography is beneficial to OHCA patients with certain electrocardiogram (ECG) features such as STEMI or new left bundle branch block (LBBB),\textsuperscript{12,22,28–33} however considerable uncertainty exists for other ECG findings.\textsuperscript{12,13,20,26,34–37}

The majority of related studies have been conducted outside of North America with data that may not be generalizable to the Canadian healthcare setting. Previous studies have also been primarily single center studies with small sample sizes. There is no Canadian data on the association between STEMI status, receipt of coronary angiography and outcomes in OHCA patients. We were able to examine these associations in a large network of hospitals in Ontario, Canada. The results may support modifications to clinical practice, and methods of selecting patients for coronary angiography and PCI.

1.4 Objectives and Hypotheses

The objectives of this study were:

1) To quantify the association between patient demographic and cardiac arrest features, hospital characteristics and receipt of coronary angiography following an out-of-hospital cardiac arrest (OHCA) in a network of 28 hospitals across Southern Ontario.
To evaluate the association between receipt of coronary angiography and i) survival with favorable neurologic outcome and ii) survival to hospital discharge in patients with and without STEMI admitted to 28 Epistry network hospitals from 2010-2014. Receipt of percutaneous coronary intervention (PCI) was examined as a secondary exposure variable.

It was hypothesized that patients who received coronary angiography or PCI would be more likely to survive to hospital discharge and to survive with favorable neurologic outcome than patients who did not receive coronary angiography or PCI.

1.5 Study Design

This was a population-based retrospective cohort study of consecutive cases of adult OHCA treated at 28 hospitals in Southern Ontario between March 1st, 2010 and December 31st, 2014. For the first objective, the exposure variables were patient, cardiac arrest and hospital characteristics, which will be described in detail, and the primary outcome was receipt of coronary angiography. For the second objective, the primary exposure of interest was receipt of coronary angiography and the primary outcome of interest was survival with favorable neurologic outcome. For the third objective, the exposure of interest was receipt of PCI and the outcome of interest was survival with favorable neurologic outcome. Survival to hospital discharge was examined as a secondary outcome in the second and third objectives. The variables of interest are displayed in Figure 1.
1.6 Scientific and Public Health Relevance

Knowledge generated from the results of this study will be disseminated to key stakeholders and decision-makers in the resuscitation field. The results will enable well-informed decisions to be made concerning treatment of resuscitated cardiac arrest patients within the Canadian healthcare system. The goal is to ultimately improve survival rates for patients who are admitted to Canadian hospitals for post-arrest care. The analysis will specifically answer the question of whether or not all post-arrest patients admitted to a Canadian hospital (STEMI and no STEMI) for care will benefit from receiving coronary angiography. If the analysis demonstrates that coronary angiography is beneficial in both groups of patients, knowledge translation of these key study findings into clinical practice will be of utmost importance. Individuals involved in this study include members of the International Liaison Committee on Resuscitation (ILCOR), the American Heart Association (AHA) and the Heart and Stroke Foundation of Canada who take part in creating guidelines for the treatment of post-cardiac arrest patients. Having an influential group of individuals as team members, will ensure this evidence is included in future guideline development.
1.7 Thesis Organization

This thesis is divided into five chapters. The first chapter provides an overview of the study. Chapter Two begins with a review of background information on topics of relevance, including the epidemiology of cardiac arrest, cardiac arrest causes, acute coronary syndrome, coronary angiography and PCI. This is followed by a review of the relevant literature, including important limitations of previous studies. The third chapter reviews the methodology applied to accomplish the objectives. The study design, study population, databases, exposures and outcomes, covariates, effect modifiers and statistical analysis methods are discussed. Chapter Four presents the results from the analyses. Chapter Five provides a general summary of findings, discusses the findings and their implications, as well as further studies, and strengths and limitations of the study.
Chapter 2

Literature Review

2.1 Sudden Cardiac Arrest

Cardiac arrest occurs when the heart ceases to pump blood effectively, resulting in undetectable peripheral pulses.\textsuperscript{38} Without early resuscitative efforts including cardiopulmonary resuscitation (CPR) and in some cases, electrical defibrillation, cardiac arrest is uniformly fatal.\textsuperscript{38}

An out-of-hospital cardiac arrest (OHCA) occurs approximately once every 12 minutes in Canada, which equates to 40,000 cardiac arrests per year.\textsuperscript{1} Not only is the incidence of cardiac arrest high, but it also contributes to significant morbidity and mortality in society.\textsuperscript{39} In Canada, each year, 11\% of all deaths are due to sudden cardiac arrest\textsuperscript{1} and the case-mortality rate is nearly 95\%.\textsuperscript{2,3} The largest meta-analysis to date demonstrated that 23.8\% of cardiac arrest patients with a cardiac etiology of arrest survive to hospital admission, and only 7.6\% survive to hospital discharge.\textsuperscript{40}

In the Ontario Prehospital Life Support Trial, only 18\% of patients achieved return of spontaneous circulation (ROSC) after an OHCA\textsuperscript{3} and only about 37\% of post cardiac arrest patients admitted to a hospital, will survive to hospital discharge.\textsuperscript{5} However, the presence of particular cardiac arrest features significantly improve the chances of survival, and will be discussed shortly. Improving survival from sudden cardiac arrest is a clinical and public health problem that must be urgently addressed.

2.1.1 Causes

Approximately 80\% of cardiac arrests have a cardiac cause.\textsuperscript{41,42} Literature suggests that 60-80\% of cardiac arrests can be attributed to cardiovascular disease, such as coronary artery disease (CAD),\textsuperscript{10,30,34,41} and that cardiac arrests are generally triggered by acute coronary ischemia\textsuperscript{5,16,34} due to CAD.\textsuperscript{5,16} Individuals with CAD generally have atherosclerosis, which develops due to cholesterol deposits referred to as plaques, accumulating on the interior walls of arteries, and causing narrowing of
the arteries. Rupturing of coronary plaques, followed by thrombosis at the site of plaque rupture, often provide the trigger for sudden cardiac arrest.\textsuperscript{41,43}

Other cardiac causes of OHCA include non-atherosclerotic disease of coronary arteries, cardiomyopathies, conduction defects, valvular heart disease, myocardial infarction, infiltrative and inflammatory myocardial disease, congenital heart disease, and electrical abnormalities.\textsuperscript{35,41,44} Cardiomyopathy refers to diseased heart muscle, whereas valvular heart disease refers to a deficiency in the valves of the heart. Myocardial infarction can cause ventricular fibrillation (VF) and/or can result in cardiac scar tissue.\textsuperscript{41}

While the majority of out-of-hospital cardiac arrests have a cardiac etiology,\textsuperscript{41,42} non-cardiac causes of cardiac arrest may include trauma, excessive blood loss, pulmonary embolism, lung disease, malignancy, near drowning, suffocation, and drug overdose.\textsuperscript{41}

The two types of arrhythmias that are classified as shockable rhythms are ventricular fibrillation (VF) and ventricular tachycardia (VT). Ventricular fibrillation (VF) occurs when the ventricular cardiac muscle fails to contract in a coordinated manner.\textsuperscript{41} Ventricular tachycardia (VT) is rapid arrhythmia in the ventricles of the heart.\textsuperscript{41} Non-shockable rhythms include pulseless electrical activity (PEA) and asystole. Pulseless electrical activity is the lack of a pulse, even though electrical activity is present within the heart, while asystole is complete lack of electrical activity within the heart.\textsuperscript{41}

It is often difficult to determine the cause of cardiac arrest in the emergency setting because there is lack of reliable information, the patient is often unconscious, medical histories are seldomly available, and clinical and ECG findings are open to interpretation.\textsuperscript{35}

\textbf{2.1.2 Risk Factors for Cardiac Arrest}

The most important risk factor for cardiac arrest is heart disease.\textsuperscript{39} Rea and colleagues (2004) found that the incidence of OHCA was sevenfold greater in individuals with clinically established heart disease than individuals without clinically established heart disease. The incidence of OHCA was 5.98/1,000 person-years in individuals with heart disease, and only 0.82/1,000 person-years in individuals
without heart disease. However, individuals who suffered a myocardial infarction or who experienced heart failure, had even higher incidence rates of 13.69/1,000 person-years and 21.87/1,000 person years, respectively.

Additional risk factors include advanced age, male sex, family history, race, and lifestyle factors. Individuals who have a first-degree relative who suffered a cardiac arrest are twice as likely to have a cardiac arrest, and the incidence of OHCA was nearly two times greater among black individuals than among Caucasians, in a study conducted in New York City. Furthermore, the Nurses’ Health Study demonstrated that lifestyle factors including smoking, physical inactivity, poor diet and being overweight accounted for 81% of sudden cardiac deaths.

### 2.1.3 Factors Associated with Survival

The following factors have been widely established to be associated with improved survival from an OHCA; having an initial shockable cardiac rhythm (ventricular fibrillation or ventricular tachycardia), a public location of arrest, a bystander or EMS witnessed arrest, a shorter time to arrival of EMS, prehospital return of spontaneous circulation (ROSC), receiving bystander CPR or bystander defibrillation, and younger age.

For instance, one study involving patients who had a cardiac arrest in a casino, demonstrated that survival to hospital discharge was 53% for those individuals who received bystander defibrillation and had an initial cardiac rhythm of ventricular fibrillation (VF), and was even higher (74%) for individuals who received bystander defibrillation within three minutes of the arrest. These survival rates are much higher than the average.

Many of these factors are important determinants of whether or not a cardiac arrest patient survives because they are related to the speed at which resuscitation occurs. For instance, cardiac arrests that are witnessed, and/or occur in a public place, will often be responded to more quickly, allowing resuscitative efforts to begin sooner. Patients who receive bystander CPR or defibrillation also have resuscitation initiated more quickly than those who must wait for EMS to arrive. Post-cardiac arrest
treatment guidelines identify timely intervention to be a key component of post cardiac arrest treatment.\textsuperscript{5,16–18,24}

In patients who are successfully resuscitated and admitted to a hospital, a key factor associated with survival to hospital discharge is neurologic status.\textsuperscript{31–33,51} In-hospital treatment with therapeutic hypothermia also improves neurologically intact survival.\textsuperscript{14,52,53} Some hospital features may also be associated with improved survival rates including being admitted to a larger hospital,\textsuperscript{54} a hospital with teaching status,\textsuperscript{54} or a hospital capable of performing PCI.\textsuperscript{51,55,56}

2.1.4 Out-of-Hospital Cardiac Arrest (OHCA) Standards of Care

Survival rates are largely affected by both prehospital and in-hospital standards of care.\textsuperscript{37,57} The ‘Chain of Survival’ refers to the four sequential actions that should be performed with haste in the prehospital setting, in order to improve patient survival. These actions include early recognition of the cardiac arrest patient, early CPR, early defibrillation, and early advanced cardiac life support (ACLS).\textsuperscript{58,59} Improvements in short-term survival have resulted from emergency response teams implementing the ‘Chain of Survival’.\textsuperscript{60}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chain_of_survival.png}
\caption{The chain of survival.\textsuperscript{60}}
\end{figure}

Adapted from “The chain of survival” by Nolan et al., 2006, Resuscitation, 71, p.270.
However, clinical studies demonstrate that short-term survival does not correlate with long-term survival and survival with favorable neurologic outcome.\textsuperscript{60} The Ontario Prehospital Advanced Life Support Study demonstrated that performing early advanced cardiac life support increased survival to hospital admission for OHCA patients, however, did not increase survival to hospital discharge.\textsuperscript{3} In fact, the rate of survival to hospital discharge has not changed for over 50 years.\textsuperscript{5}

In order to improve this statistic, and more importantly, neurologically intact survival, optimized in-hospital post-cardiac arrest care is necessary.\textsuperscript{34,60,61} Sunde and colleagues (2007) found that effective treatment performed in hospitals is the single most influential way to improve survival after OHCA. Post-cardiac arrest treatment is important in preventing secondary injury and the effects of reperfusion injury.\textsuperscript{5} Unfortunately, post-cardiac arrest care practices are widely variable between regions and treatment centers.\textsuperscript{2,19,60}

An initial goal in post-cardiac arrest care is to achieve coronary reperfusion.\textsuperscript{62} The American Heart Association (AHA) recommend coronary angiography, followed by PCI as the preferred method of reperfusion for OHCA patients with STEMI, regardless of initial neurologic status.\textsuperscript{16} They also state that this strategy may be considered in patients without STEMI, since there are high rates of coronary artery ischemia in all post-cardiac arrest patients.\textsuperscript{16}

\subsection*{2.2 Post-cardiac Arrest Syndrome}

Mortality after return of spontaneous circulation (ROSC) is generally due to post-cardiac arrest syndrome.\textsuperscript{5} The components of post-cardiac arrest syndrome are brain injury, dysfunction of the myocardium, the response of the body to ischemia and reperfusion, and pre-existing pathologies that contributed to the cardiac arrest.\textsuperscript{5} The clinical facets of post cardiac arrest syndrome are the result of the original hypoxic injury caused by the cardiac arrest, and also reperfusion injury that occurs with ROSC.\textsuperscript{5} Two-thirds of resuscitated OHCA patients die in the hospital due to hypoxic-ischemic brain injury,\textsuperscript{63,64} while the others generally die from hemodynamic or myocardial failure.\textsuperscript{65}
2.3 Acute Coronary Syndrome

Acute coronary syndrome (ACS) is the clinical term used to describe acute myocardial ischemia and/or infarction, generally due to a sudden reduction in blood flow through the coronary arteries.\textsuperscript{25} Acute coronary syndrome includes unstable angina, non-ST-segment elevation myocardial infarction (non-STEMI) and ST-segment elevation myocardial infarction (STEMI).\textsuperscript{43} Unstable angina is chest pain caused by a decrease in blood flow through the coronary arteries, which is generally due to thrombus formation.\textsuperscript{43} Differentiation between these subtypes of acute coronary syndrome is made based on ECG findings and biochemical or angiographic evidence of cardiac tissue infarction.\textsuperscript{43}

In the patient who suffers from STEMI, the ECG will demonstrate ST-segment elevation, while in the patient who suffers from non-STEMI, the ECG generally demonstrates T-wave inversion, ST-segment depression, or a combination of these features.\textsuperscript{43} In non-arrested patients, non-STEMI is generally due to partial occlusion of the coronary artery, while STEMI results from complete occlusion of the coronary artery.\textsuperscript{43}

2.4 Coronary Angiography and Percutaneous Coronary Intervention

Coronary angiography is the procedure used to produce a coronary angiogram, which is an image of the coronary arteries that can indicate regions of occlusion. Prompt coronary angiography is recommended for patients with acute coronary syndrome (ACS),\textsuperscript{5,12,16,17,24} as it enables confirmation of coronary artery occlusion. In patients whose cardiac arrest is assumed to have a cardiac etiology, 37% to 70% of patients have acute coronary artery occlusion.\textsuperscript{10,12,22,35,66}

If the angiogram indicates arterial occlusion (thrombotic coronary occlusion or critical coronary stenosis),\textsuperscript{35} PCI is the primary treatment option.\textsuperscript{16,17,24,43} Balloon angioplasty is the most common form of PCI, which involves inserting a small, deflated balloon into the occluded section of the coronary artery and inflating the balloon to eliminate the occlusion.\textsuperscript{43} Stent implantation may be performed following PCI, if necessary.\textsuperscript{43} Coronary angiography and PCI must be performed in hospitals capable of performing these procedures, sometimes referred to as PCI centers, which are generally larger hospitals and/or
Academic Health Science Centers. If the patient has multiple occlusions or occlusions in particular anatomical positions, he/she may be referred for urgent coronary artery bypass grafting (CABG) (open heart surgery) rather than PCI.

2.4.1 Coronary Angiography for OHCA Patients

Some experts agree that coronary angiography is an important component of post-arrest care, as it may improve outcomes for some OHCA patients. The strongest evidence in support of coronary angiography in patients after cardiac arrest comes from a large Canadian study. Receiving invasive coronary intervention (coronary angiography +/- PCI) was a very strong predictor of survival to hospital discharge in over 13,000 OHCA patients (OR 21.98, 95% CI 17.62 – 27.42). Callaway and colleagues (2014) also conducted a large (n=3981) multicenter (n=151) study to examine outcomes in resuscitated OHCA patients. They found that both survival to hospital discharge and survival with good neurologic outcome (Modified Rankin Score [MRS] ≤ 3) were significantly higher (64.7% and 54% respectively) for OHCA patients who received early coronary angiography (less than 24 hours after hospital arrival) than for those who did not (27.1% and 18.4% respectively). The association between early coronary angiography and survival to hospital discharge remained significant after adjusting for all potential confounders (OR=1.69, 95% CI=1.06-2.70) as did the association between early coronary angiography and survival with good neurologic outcome (OR=1.87, 95% CI= 1.15-3.04).

Another multicenter study conducted in the United States also demonstrated that OHCA patients who received early coronary angiography (within 6 hours of hospital admission) had significantly higher rates of survival to hospital discharge than patients who received no, or later (after 6 hours from hospital admission), coronary angiography. However, neurologic outcome at hospital discharge did not differ between groups. A meta-analysis pooled the unadjusted odds ratios from ten studies that compared outcomes for cardiac arrest patients who received coronary angiography versus those who did not, which resulted in an unadjusted odds ratio of 2.78 (CI 1.89-4.10), with nine of the ten studies favoring the use of coronary angiography.
Bougouin and associates (2014) reached similar conclusions, namely that individuals who suffer from an OHCA and receive coronary angiography have 2.4 times the odds of surviving to hospital discharge than those who do not receive coronary angiography. Similarly, Reynolds and associates (2009) demonstrated that receipt of coronary angiography was associated with good neurologic outcome (discharge to home or acute rehabilitation facility) in OHCA patients, after adjusting for the likelihood of receiving coronary angiography, and for other factors that may be associated with improved outcomes (OR=2.16, 95%CI 1.12-4.19). Coronary angiography was associated with improved survival and neurologic outcomes, regardless of the presence of STEMI or new left bundle branch block (LBBB), neurological status, initial rhythm or arrest location. In the Parisian Region Out of Hospital Cardiac Arrest study, coined the ‘PROCAT’, the rate of survival to hospital discharge was 39% for OHCA patients who received immediate coronary angiography (at hospital admission). Of these survivors, 94% had a CPC level of 1 or 2 at hospital discharge, indicating favorable neurologic outcome.

The majority of previous literature suggests that coronary angiography is beneficial for OHCA patients when considered as a homogenous group, however previous studies have several limitations, which will be expanded upon shortly. Furthermore, some investigators have studied specific subgroups of OHCA patients, such as those with and without STEMI on the first post-arrest ECG, or those who were comatose versus conscious at hospital admission. In particular subgroups, investigators have found no association between coronary angiography and survival outcomes. These studies will be discussed momentarily.

2.4.2 Percutaneous Coronary Intervention for OHCA Patients

The literature generally indicates a positive association between percutaneous coronary intervention (PCI) and survival outcomes in OHCA patients. Spaulding and associates (1997) conducted the pioneering prospective study and demonstrated that successful PCI was a predictor of survival to hospital discharge for OHCA patients (OR=5.2, 95%CI 1.1-24.5). Since this time, several studies have confirmed these findings. Grasner and colleagues (2011) conducted a study in Germany involving 584
OHCA patients and found that receiving PCI increased the odds of survival with good neurologic outcome (CPC 1 and 2) by about 5.7 times and increased the odds of 24-hour survival by nearly four times. When they limited the patient population to those who did not receive therapeutic hypothermia (n=405), PCI was associated with 24-hour survival (OR=4.46, CI<sub>95</sub> 2.26-8.81) and good neurologic outcome at hospital discharge (OR=10.81, CI<sub>95</sub> 5.86-19.93).<sup>42</sup>

Callaway and colleagues (2014) found that receiving coronary reperfusion (either PCI or fibrinolysis) was associated with survival to hospital discharge (OR=1.94, 95%CI 1.34-2.82) and favorable neurologic outcome (Modified Rankin Score [MRS] < 3) (OR= 2.14, 95%CI 1.46-3.14) in nearly 4000 OHCA patients.<sup>19</sup>

Other investigators studied the association between PCI and outcomes in subgroups of OHCA patients such as those with STEMI,<sup>12,22,28,31-33,68</sup> those without STEMI,<sup>12,22</sup> and those who were comatose at hospital admission.<sup>32</sup> For instance, Cronier and colleagues (2011) and Dumas and colleagues (2010) conducted studies in France where all OCHA patients receive emergency coronary angiography, followed by PCI, if indicated. Both of these studies found that survival to hospital discharge was significantly higher for OHCA patients with and without STEMI who received PCI.<sup>12,22</sup> Findings from studies that investigated the influence of PCI in patients with specific cardiac arrest features will be expanded upon in Sections 2.9 and 2.10.

On the contrary, three studies have demonstrated that PCI was not a predictor of survival in OHCA patients.<sup>28,35,68</sup> Weiser and associates (2013) studied 249 OHCA patients with STEMI and found that receiving PCI was positively associated with 30-day survival with favorable neurologic outcome (CPC 1 and 2) in the univariate analysis (OR=2.52, CI<sub>95</sub> 1.42-4.48), however, the association became non-significant in the multivariate analysis (OR=1.40, CI<sub>95</sub> 0.53-3.70).<sup>28</sup> Anyfantakis and colleagues (2009) found no association between receiving PCI and survival to hospital discharge in 72 OHCA patients.<sup>35</sup> Garot et al. (2007) studied 186 patients who were resuscitated after cardiac arrest, had STEMI, and were given immediate PCI. The patients who had successful PCI, did not have better outcomes at one month or
six months post-cardiac arrest than patients whose PCI was unsuccessful, however, only 25 patients had unsuccessful PCI.  

2.5 Patient and Cardiac Arrest Features Associated with Coronary Angiography

Only a handful of studies have investigated factors associated with whether or not an OHCA patient receives coronary angiography, and have generally involved small sample sizes. Strote and colleagues (2012) conducted a study on 240 OHCA patients admitted to 11 hospitals throughout Seattle, Washington. They calculated a propensity score for the likelihood of undergoing acute coronary angiography and found that patients who received early coronary angiography (≤6 hours) were more likely to be male and less likely to have pre-existing cardiac conditions including congestive heart failure and/or stroke. Furthermore, patients who received bystander CPR, were younger, had ST-elevation on the first post-arrest ECG and who presented to the hospital during the day, were more likely to receive coronary angiography.  

In another study, conducted in 241 survivors of OHCA admitted to a single US hospital, the propensity-adjusted logistic regression analysis demonstrated that the only factor predicting whether or not an OHCA patient receives coronary angiography was STEMI status or new left bundle branch block (LBBB). Patients with STEMI or new LBBB on the post-arrest ECG had four times the odds of receiving coronary angiography than patients with other ECG patterns. Gorjup et al. (2007) studied 135 patients with STEMI, admitted to a single hospital in Slovenia after OHCA. They found that attending physicians were more likely to decide upon early coronary angiography for OHCA patients who were conscious following ROSC, had bystander resuscitation, had an initial shockable cardiac rhythm, had a shorter time between cardiac arrest and EMS response, and had received advanced cardiac life support (ACLS) for less than 30 minutes.  

Waldo et al. (2013) conducted a study aimed at evaluating the clinical characteristics of sudden cardiac arrest patients who do not receive coronary angiography. In this study, 110 patients had a sudden cardiac arrest and 26 of these patients did not receive emergency coronary angiography. Factors
associated with withholding coronary angiography in the adjusted analysis included absence of ST-segment elevation (OR=10.26), PEA as the initial cardiac rhythm (OR=13.27), female sex (OR=4.45), and older age (OR=1.10 per year).\textsuperscript{21}

2.5.1 Patient Cardiac Arrest Features

The literature demonstrates that cardiac arrest features may be associated with whether or not an OHCA patient with ROSC receives coronary angiography. However, there is uncertainty regarding the direction of associations. Also, the combined influence of many features, adjusting for potential confounders, has not been examined.

2.5.1.1 Initial Neurologic Status

Some patients are comatose after cardiac arrest, while others are awake. Coma in the post cardiac arrest patient may be caused by hypoxic neurologic insult or another contributing factor to the cardiac arrest (i.e. intracerebral hemorrhage or intoxication).\textsuperscript{5} Physicians tend to base their post-resuscitation care decisions on neurological function immediately following cardiac arrest.\textsuperscript{69–71} In the past, coronary angiography has generally only been considered in patients who had improvement in neurologic status.\textsuperscript{69} Patients in a coma following ROSC may be less likely to receive coronary angiography because of perceived poorer prognosis by attending physicians.\textsuperscript{69}

In fact, Gorjup and colleagues (2007) demonstrated that physicians were more likely to decide upon coronary angiography for OHCA patients who were conscious after ROSC.\textsuperscript{31} Likewise, Reynolds and colleagues (2009) found that low scores on the verbal, motor and eye categories of the Glasgow Coma Scale (GCS) were associated with decreased likelihood of receiving coronary angiography in an unadjusted propensity analysis.\textsuperscript{13}

Since a significant proportion of resuscitated cardiac arrest patients with initially low scores on the Glasgow Coma Scale (GCS) survive with favorable neurologic outcome,\textsuperscript{70,71} coma should not be a contraindication to coronary angiography. The 2010 International Consensus Statement for the Treatment
of Acute Coronary Syndromes stated that “Out-of-hospital cardiac arrest patients are often initially comatose but this should not be a contraindication to consider immediate angiography and PCI”.

2.5.1.2 Electrocardiogram (ECG) Findings

In patients who present to an emergency department (ED) with symptoms of coronary artery ischemia, clinicians use the findings from the 12-lead ECG to decide whether or not the patient requires immediate revascularization. Patients who demonstrate STEMI on the ECG are rapidly sent for coronary angiography, followed by PCI, while patients without STEMI generally do not receive immediate coronary angiography. Based on extrapolation of evidence for the benefit of coronary angiography in the non-arrested patient with STEMI, there is a general consensus that prompt coronary angiography should also be provided to cardiac arrest patients who present with STEMI on the first post-arrest ECG.

After adjusting for the propensity for receiving coronary angiography, Reynolds and colleagues (2009) found that patients with STEMI or new left bundle branch block (LBBB) on the immediate post-arrest ECG had four times the odds of receiving coronary angiography than patients without these ECG findings. Of the patients with STEMI or new LBBB, 91% received coronary angiography, whereas of the patients without STEMI or new LBBB, only 28% received coronary angiography. Likewise, Callaway and colleagues (2014) found that early coronary angiography was performed on 62.1% of STEMI patients and only 12.0% of patients without STEMI. Additional studies have confirmed these findings.

2.5.1.3 Initial Cardiac Rhythm

Waldo and colleagues (2013) found that the odds of withholding coronary angiography were 13 times higher for cardiac arrest patients with pulseless electrical activity (PEA) as the initial cardiac rhythm. Bro-Jeppesen et al. (2012) found that the only independent predictor of receiving emergency...
coronary angiography for OHCA patients without STEMI was having a shockable initial cardiac rhythm of ventricular fibrillation (OR=3.2, 95% CI=1.4-7.4).\textsuperscript{20}

Recently, Dankiewicz and colleagues (2015) demonstrated that the rate of early coronary angiography (within 6 hours of hospital admission) was significantly higher among OHCA patients with shockable initial cardiac rhythms.\textsuperscript{36} Results from the unadjusted analysis of another study showed that OHCA patients with initial rhythms of pulseless electrical activity (PEA), or asystole were less likely to receive coronary angiography.\textsuperscript{13} Physicians associate these initial rhythms with poor prognosis and thus may be less likely to engage in aggressive post-resuscitation treatments, such as coronary angiography and PCI.\textsuperscript{13}

2.5.1.4 Therapeutic Hypothermia

Therapeutic hypothermia is the application of cooling agents to reduce the core body temperature for a period of approximately 24 hours.\textsuperscript{52,74,75} Cooling post cardiac arrest patients to a temperature of 32-34 degrees Celsius has been demonstrated to be effective in markedly improving survival rates and neurologic outcomes.\textsuperscript{52,74} As a result, the International Liaison Committee on Resuscitation (ILCOR) have recommended mild therapeutic hypothermia for unconscious OHCA patients with ROSC, and an initial cardiac rhythm of ventricular fibrillation, since 2003.\textsuperscript{76}

There is limited research on the association between therapeutic hypothermia and coronary angiography. However, Callaway and associates (2014) studied nearly 4000 OHCA patients and demonstrated that being treated in higher volume hospitals was associated with receiving both therapeutic hypothermia and coronary angiography.\textsuperscript{19} Patients who receive therapeutic hypothermia may be more likely to receive coronary angiography because administration of therapeutic hypothermia is an indicator of more aggressive hospital care and adherence to recommended guidelines.\textsuperscript{19,26} On the other hand, Reynolds and colleagues (2009) demonstrated no difference in receipt of therapeutic hypothermia between cardiac arrest patients who received coronary angiography and those who did not.\textsuperscript{13}
2.5.1.5 Location of Arrest / Witnessed Arrest

Several studies have demonstrated that individuals who have a cardiac arrest in a public location have increased odds of survival.\textsuperscript{49,77–79} This is likely due to shorter time to resuscitation.\textsuperscript{77} Cardiac arrests that occur in a public place are witnessed, and as a result the individual may receive bystander CPR or bystander defibrillation prior to EMS arrival.\textsuperscript{77} Having a witnessed cardiac arrest is also independently associated with better outcomes for OHCA patients.\textsuperscript{3,40,49} Healthcare professionals tend to have a more positive outlook regarding outcomes in OHCA patients whose arrest was witnessed, and therefore may be more likely to send these patients for more aggressive treatments, such as coronary angiography.

2.5.1.6 Bystander Resuscitation

Bystander resuscitation generally consists of bystander defibrillation and bystander CPR. Bystander CPR and rapid defibrillation have been cited to be key factors in improving outcomes for OHCA patients.\textsuperscript{3,40,58} Patients who receive bystander automated external defibrillation (AED) have more rapid defibrillation than those who must wait for paramedics to provide these interventions. Stiell and colleagues (2004) found that OHCA patients who received bystander defibrillation had 3.7 times the odds of surviving to hospital admission than patients who did not.\textsuperscript{3} Individuals who receive bystander AED treatment or bystander CPR may be clinically judged to have a positive prognosis, and as a result may be more likely to be given particular diagnostic tests and treatments, such as coronary angiography.

In fact, Strote and colleagues (2012) found that OHCA patients who received bystander CPR were more likely to receive emergency coronary angiography.\textsuperscript{23} However, in a different setting with more routine use of angiograms after cardiac arrest, Spaulding and colleagues (1997) found that there was no difference in rate of bystander CPR administration between patients who received successful angioplasty and those who did not.\textsuperscript{10}
2.5.1.7 EMS Response Time

Several studies have demonstrated that OHCA patients who have a shorter time between initial cardiac arrest and ROSC are more likely to survive to hospital discharge and to attain neurologically intact survival. As EMS response time decreases, the time between initial cardiac arrest and ROSC should also decrease, since EMS attempt to restore circulation upon arrival. Healthcare professionals have a more pessimistic outlook toward cardiac arrest patients who have longer times to ROSC because it is well known that rapid access to, and treatment of the patient, is essential in the setting of cardiac arrest. Therefore, clinicians may be less inclined to treat patients with longer times to ROSC using more aggressive post-resuscitation therapies, such as coronary angiography and PCI. However, Larsen and Ravkilde (2012) found that time from cardiac arrest to ROSC did not influence rates of administration of early coronary angiography.

2.5.1.8 Prehospital Return of Spontaneous Circulation (ROSC)

Prehospital ROSC means achieving a pulse before hospital arrival. Patients with prehospital ROSC and a shorter time to ROSC are more likely to survive and to survive with favorable neurologic outcome compared to patients who have longer resuscitation times and achieve ROSC after arriving to the hospital. Healthcare professionals may attribute poor prognoses to patients who did not achieve prehospital ROSC, since those without prehospital ROSC were likely without circulatory and cardiac activity for a substantial period of time. As such, clinicians may be inclined to withhold more aggressive therapies, such as coronary angiography, from patients who did not achieve prehospital ROSC.

2.5.1.9 Daytime Presentation

Research has demonstrated that aggressive, guideline-based care is performed less often during non-business hours (evenings, nights and weekends) than during business hours. Becker (2006) found that patients with acute myocardial infarction admitted to hospitals during the weekend were less likely to receive coronary angiography and angioplasty, than those admitted during the week. Likewise,
Strote et al. (2010) demonstrated that patients who had an OHCA during the daytime were more likely to receive acute coronary angiography than patients who had a cardiac arrest during the evening or night.²³

Magid and colleagues (2005) studied nearly 34,000 acute myocardial infarction patients with STEMI admitted to hospitals and treated with PCI, and found that time to receipt of PCI was substantially longer in patients who arrived to a hospital during off-hours (weekdays 5pm-7am and weekends) than patients who arrived during regular hours (weekdays, 7am – 5pm).⁸³

The resources required to perform coronary angiography and PCI are more readily available or more easily accessible during the daytime, since most hospitals have fewer staff in the cardiac catheterization laboratories during weekends, evenings and nights.⁸³,⁸⁵

2.5.2 Patient Demographic Characteristics

Some factors unrelated to cardiac arrest features may influence whether or not a patient receives coronary angiography following an out-of-hospital cardiac arrest (OHCA).

2.5.2.1 Sex

Several studies have demonstrated that male OHCA patients receive coronary angiography more often than female patients.¹²,¹³,²¹,²³ However, others have found no difference in receipt of coronary angiography between the sexes.²⁰,³¹

2.5.2.2 Age

Some studies have found that OHCA patients who are younger are more likely to receive coronary angiography²³,³⁶ and PCI.¹² However, others have found no difference in age between patients who received early coronary angiography and those who did not.²⁶ Healthcare professionals may be inclined to give a more positive prognosis to younger adults because they are more resilient and capable of recovering from bodily injuries than older adults. Accordingly, clinicians may treat younger cardiac arrest patients using more aggressive therapies, such as coronary angiography and PCI.
2.6 Hospital Characteristics and Coronary Angiography

Investigators have noted significant differences in OHCA patient survival between hospitals, after adjusting for prehospital factors that may influence survival rates.\textsuperscript{55,86–89} Wnent and colleagues (2012) found that patients who were admitted to hospitals with PCI capability had greater adjusted odds of survival to hospital discharge and survival with good neurologic status than patients admitted to hospitals without PCI capability.\textsuperscript{56} Stub and colleagues (2011) demonstrated similar findings, and Kumar et al. (2012) found that OHCA patients treated at Cardiac Receiving Centers, which provide comprehensive guideline-based post-resuscitation care, and 24/7 cardiac catheterization services, were more likely to survive to hospital discharge.\textsuperscript{90}

Hospital size, annual cardiac arrest volume and hospital type have also been demonstrated to be associated with survival. Callaway and colleagues (2014) found that as the number of cardiac arrest patients treated at a hospital per year increased by five, the odds of survival to hospital discharge and survival with favorable functional status increased by 6\% (OR=1.06, 95\%CI 1.04-1.08).\textsuperscript{19} Another study demonstrated that survival rates are better for OHCA patients treated at hospitals that admit more than 50 cardiac arrest patients per year compared to hospitals that admit fewer than 20.\textsuperscript{89} Ro and colleagues (2012) found that adjusted odds of survival to hospital discharge were 2.5 times higher for cardiac arrest patients admitted to high volume centers compared to low volume centers.\textsuperscript{91} Søholm and associates (2013) demonstrated that OHCA patients treated at specialized centers had lower mortality rates at 30 days post-discharge and beyond, than those treated at non-specialized centers.\textsuperscript{55}

This variability in survival has been attributed to differences in post-resuscitation care amongst hospitals.\textsuperscript{55,60,88} The hospital a patient is admitted to may influence whether or not he/she receives coronary angiography. Wnent et al. (2012) confirmed that the hospital an OHCA patient is initially transferred to is associated with the likelihood of receiving post-cardiac arrest therapies, such as coronary angiography and PCI.\textsuperscript{56} Patients initially admitted to PCI centers may be more likely to receive coronary angiography than patients admitted to non-PCI centers because if the results of coronary angiography indicate coronary artery occlusion, the treatment to remove the occlusion (i.e. PCI) is easily accessible
and available at PCI centers. Larger hospitals and hospitals with teaching status generally treat more OHCA patients per year than smaller hospitals. As a result, these hospitals may have staff with greater experience in treating medical emergencies, such as cardiac arrest, who may be more likely to adhere to recommended guidelines, such as providing coronary angiography to OHCA patients.\textsuperscript{19}

However, some investigators have found no association between hospital bed number, hospital cardiac arrest volume and survival outcomes in OHCA patients.\textsuperscript{51,92} It is possible that hospitals that admit a greater number of OHCA arrest patients have medical teams with high workloads who may be unable to provide the highest standards of post-resuscitation care, due to time and resource constraints.

### 2.7 Post-Resuscitation Care Guidelines

Post-resuscitation care is an essential component in improving survival from out-of-hospital cardiac arrest (OHCA).\textsuperscript{61} The 2013 American Heart Association (AHA) and American College of Cardiology (ACC) guidelines recommend that patients with STEMI who have acute coronary syndrome (ACS), but have not suffered a cardiac arrest, receive immediate coronary angiography, followed by PCI.\textsuperscript{24} The 2014 guidelines also recommended early coronary angiography and revascularization for non-arrested patients with non-STEMI.\textsuperscript{25} However, the latter recommendation was based on lower level evidence than the former. Refer to Appendix A for a description of how recommendations are classified.

Meanwhile, the optimal treatment strategy for post cardiac arrest patients is controversial.\textsuperscript{14,15} The 2010 AHA guidelines recommend coronary angiography, followed by PCI, as the preferred method of reperfusion for OHCA patients with STEMI, regardless of initial neurologic status.\textsuperscript{16} Likewise, the 2013 AHA/ACC guidelines recommend that “Immediate angiography and PCI when indicated should be performed in resuscitated out-of-hospital cardiac arrest patients whose initial ECG shows STEMI.”\textsuperscript{24} This recommendation was classified as Class 1, Level of Evidence B.\textsuperscript{24} Meanwhile, Class 1, Level of Evidence A, is the highest level recommendation (Appendix A). The 2010 International Consensus Statement has stated that “In OHCA patients with STEMI or new LBBB on ECG following return of spontaneous
circulation, early angiography and PCI should be considered. Generally, the presence of STEMI in the OHCA patient is a clinical indicator that the patient should be sent for coronary angiography and PCI if required.

The guidelines for the treatment of OHCA patients without STEMI are not as straightforward. The AHA states that coronary angiography followed by PCI if required, may be considered in patients without STEMI, since there are high rates of coronary artery ischemia in all post cardiac arrest patients. The International Liaison Committee on Resuscitation (ILCOR) have stated that “it is appropriate to consider immediate coronary angiography in all post cardiac arrest patients in whom ACS is suspected.” The 2010 International Consensus Statement stated “It is reasonable to perform early angiography and PCI in selected patients despite the absence of ST-segment elevation on the ECG or prior clinical findings, such as chest pain, if coronary ischemia is considered the likely cause on clinical grounds.” However, the strength and amount of evidence available to make these recommendations were limited. In sum, the 2010 International Consensus Statement advised that “It may be reasonable to include cardiac catheterization in a standardized post-cardiac-arrest protocol as part of an overall strategy to improve neurologically intact survival in this patient group.” The language used (i.e. ‘it may be reasonable’) acknowledges the low level of evidence available to make this recommendation.

2.7.1 Time to Receipt of Coronary Angiography and PCI

For patients who demonstrate STEMI, but have not suffered a cardiac arrest, the evidence overwhelmingly demonstrates that immediate coronary angiography and PCI are very important to improve survival and neurologic outcomes. As such, significant resources have been put into providing these patients with a “90-minute door to-reperfusion time” because non-cardiac arrest patients with STEMI benefit from early reperfusion therapies, such as PCI. However, the benefit may not be as clear in myocardial infarction patients without STEMI. Thiele and colleagues (2012) conducted a randomized controlled trial in approximately 600 patients who suffered a myocardial infarction and had...
non-STEMI. They found that patients who received immediate PCI (within 2 hours of hospital arrival) were not more likely to survive than those who received early (10-48 hours after arrival) or late PCI (greater than 48 hours after arrival).94

The evidence for providing immediate coronary angiography to cardiac arrest patients is not as strong as the evidence in the non-cardiac arrest population. However, to date, there have been a handful of observational studies demonstrating the benefit of early coronary angiography in post-cardiac arrest patients.19,23,26,95 As a result, several guidelines have recommended early coronary angiography and PCI for OHCA patients with STEMI5,16,24,73 and for patients without STEMI who have suspected acute coronary ischemia or acute coronary syndrome.5,17,18 However, the evidence to make these recommendations was not strong.

Some investigators have found no benefit of early compared to late coronary angiography and PCI.13,36 For instance, Reynolds and colleagues (2009) have found that early coronary angiography (within 24 hours of hospital arrival) is not superior to later coronary angiography in terms of improving survival to hospital discharge or good neurologic outcome.13 Likewise, Dankiewicz et al. (2015) found no survival benefit of early coronary angiography (within 6 hours of cardiac arrest) in OHCA patients without STEMI.36 Further studies need to be conducted that are randomized and examine survival outcomes associated with early compared to delayed coronary angiography and PCI.

2.8 Diagnosis of Acute Coronary Syndrome (ACS)

In OHCA patients with ROSC, there is a high prevalence of acute coronary syndrome (ACS).12,16,27 In patients who have ACS, but who have not had a cardiac arrest, the standard treatment is coronary angiography,24 followed by PCI for patients with STEMI, while patients without STEMI generally do not receive immediate coronary angiography.25,96 However, these guidelines for the treatment of patients with ACS were developed from randomized trials that did not include cardiac arrest patients.10,15,69
It is difficult to diagnose ACS in OHCA patients because the post arrest ECG findings can be misleading.\textsuperscript{10,23,26,35,63,97} Following cardiac arrest, some patients display nearly normal ECG patterns, despite having significant coronary artery disease.\textsuperscript{20} Spaulding and colleagues (1997) stated that “acute coronary-artery occlusion is frequent in survivors of out-of-hospital cardiac arrest and is predicted poorly by clinical and electrocardiographic findings…such as chest pain or ST-segment elevation.”\textsuperscript{10,34} In the 2010 update of the recommendations, the Acute Coronary Syndrome Task Force stated that “The history and physical examination, initial ECG, and initial serum biomarkers, even when used in combination, cannot be used to reliably exclude ACS in the prehospital and ED settings.”\textsuperscript{73} Consequently, it is difficult to determine which patients should receive coronary angiography, and PCI.

Many experts agree that ECG findings do not have adequate sensitivity and specificity to predict ACS in post cardiac arrest patients.\textsuperscript{10,34,63,97} A large study conducted in Paris (PROCAT), found that the positive predictive value of ST-segment elevation for predicting significant coronary lesions was 96\%, while the negative predictive value was only 42\%.\textsuperscript{12} Another Parisian study found nearly identical predictive values, with a positive predictive value of ST-segment elevation for predicting significant coronary disease of 95\%, and a negative predictive value of 44\%.\textsuperscript{35} These findings demonstrate that lack of ST-segment elevation does not eliminate coronary occlusion as the cause of arrest.\textsuperscript{10,12,20,34,35,98}

2.8.1 Coronary Artery Occlusion and Post Arrest ECG Findings

The most common trigger of cardiac arrest is acute coronary occlusion.\textsuperscript{11} Spaulding et al. (1997) found that over 70\% of patients resuscitated from OHCA had coronary artery disease and nearly 50\% had coronary artery occlusion.\textsuperscript{10} Likewise, Reynolds et al. (2009) discovered that nearly 52\% of OHCA survivors had significant coronary artery disease ($\geq$70\% stenosis of $\geq$1 coronary arteries),\textsuperscript{13} while Anyfantakis and associates (2009) reported a rate of 65\%.\textsuperscript{35} Likewise, the PROCAT study demonstrated that 70\% of OHCA patients had at least one significant coronary artery lesion.\textsuperscript{12} When autopsies were performed on individuals who had died after sudden cardiac arrest, findings demonstrated that 57\% of these individuals had active coronary lesions.\textsuperscript{99}
2.8.1.1 STEMI

It is well-established that patients with STEMI on the post-arrest ECG are more likely to have an occluded coronary artery than patients without STEMI.\textsuperscript{10,12,23,35,69,73,97} Strote and colleagues (2012) studied 186 patients who were resuscitated from sudden cardiac arrest, and found that those patients with ST-segment elevation had 4.5 times the odds of having acute coronary occlusion than patients with no evidence of ST-segment elevation.\textsuperscript{23}

Studies have demonstrated that 89-96\% of OHCA patients with STEMI have significant coronary artery lesions.\textsuperscript{12,20,66} However, in the cardiac arrest population, ST-segment elevation does not always indicate that the cardiac arrest was due to acute coronary syndrome (ACS).\textsuperscript{10} It can occur due to repolarization abnormalities as a result of electric countershock or electrolyte imbalances.\textsuperscript{35}

2.8.1.2 No STEMI

The absence of STEMI does not indicate the absence of acute coronary occlusion,\textsuperscript{34,35,69} as several studies have demonstrated that the rate of coronary artery occlusion is significant in patients without STEMI as well.\textsuperscript{12,13,20,23,26,34,66,98}

The strongest evidence for the presence of coronary artery occlusion in patients without STEMI comes from the PROCAT study in which 58\% of OHCA patients without ST-segment elevation had at least one coronary artery lesion, amenable to treatment with PCI.\textsuperscript{12} Similarly, Reynolds et al. (2009) demonstrated that of the patients who received coronary angiography, 57\% of those without “acute ischemic ECG changes” (i.e. STEMI) had significant coronary artery disease (≥70\% stenosis of ≥1 coronary arteries).\textsuperscript{13} Two other studies found that coronary angiography was able to identify significant coronary artery lesions in 52\% and 59\% of OHCA patients without STEMI.\textsuperscript{20,66} These findings indicate that more than half of OHCA patients presenting without STEMI may benefit from coronary angiography and PCI.

Meanwhile, acute coronary artery occlusion has been found in 24-27\% of OHCA patients without STEMI.\textsuperscript{26,66} It appears that 1 in every 2 to 4 cardiac arrest patients without STEMI would benefit from
coronary angiography. To identify one patient without STEMI to have coronary artery occlusion, between two to four patients without STEMI must receive coronary angiography.

In patients who do not display STEMI and did not suffer a cardiac arrest, rates of coronary artery occlusion are similar. Wang et al (2009) studied nearly 2000 patients presenting to an emergency department with non-STEMI and acute coronary syndrome (ACS) who did not suffer a cardiac arrest, and demonstrated that coronary angiography revealed that 27% of these patients had an occluded coronary artery that was responsible for the symptoms. Another study demonstrated that 31.4% of myocardial infarction patients with non-STEMI had a totally occluded coronary artery.

Since the frequency of acute coronary occlusion is high in OHCA patients, and the use of ECG findings to predict the presence of coronary artery occlusion are unreliable, many experts agree that early coronary angiography, followed by PCI, if required, should be provided to all OHCA patients without an obvious non-cardiac etiology for their arrest.

2.9 Coronary Angiography, PCI and Post Arrest ECG Findings

2.9.1 STEMI

For patients who demonstrate STEMI, but have not suffered a cardiac arrest, significant resources have been put into providing these patients with a “90-minute door to-reperfusion time” because non-cardiac arrest patients with STEMI benefit from early reperfusion therapies, such as PCI. As a result, the presence of STEMI in an OHCA patient is used as a clinical indicator that the patient should receive coronary angiography and PCI, if indicated. In a recent study including nearly 4000 OHCA patients, early coronary angiography (within 24 hours of hospital arrival) was provided to 62.1% of patients with STEMI, but only to 12% of patients with other ECG patterns.

Studies investigating the benefit of coronary angiography and/or PCI for OHCA patients with STEMI have generally demonstrated that these treatments improve survival and neurologic outcomes. Bendz and colleagues (2004) compared 2-year survival rates between OHCA patients with STEMI who received PCI (n=40) and non-arrested STEMI patients who received PCI (n=325) and
found no difference in mortality after hospital discharge between the groups.\textsuperscript{30} Gorjup and colleagues (2007) also reported that OHCA patients with STEMI who are conscious and receive PCI have rates of survival to hospital discharge that are comparable to rates in non-cardiac arrest patients.\textsuperscript{31} However, there were less than 50 OHCA patients included in each of the aforementioned studies and the comparison groups were inappropriate. Lettieri et al. (2009) found no difference in rates of death, myocardial infarction or revascularization from hospital discharge to six months post-arrest, between OHCA patients with STEMI who received emergency PCI compared to non-arrested patients with STEMI who received emergency PCI.\textsuperscript{33}

Other studies examined differences in survival outcomes between OHCA patients with STEMI who received PCI, compared to those who did not. Dumas et al. (2010) found that STEMI patients who had successful immediate PCI had better odds of surviving to hospital discharge, than patients who had no PCI or failed PCI\textsuperscript{12} and Cronier and colleagues (2011) studied STEMI patients with ventricular fibrillation, and found that receiving PCI was associated with decreased odds of mortality.\textsuperscript{22} Hosmane et al. (2009) demonstrated that in hospital mortality was lower for OHCA patients with STEMI who received revascularization therapy (PCI or CABG), than for those who did not (25% versus 76%, p<.0001).\textsuperscript{32} However, the sample size was only 98 patients and all patients were admitted to a single hospital. According to recent guidelines by the AHA, the ACC, and the ILCOR, out-of-hospital cardiac arrest patients with STEMI should either receive, or be considered for, early coronary angiography and PCI.\textsuperscript{5,16–18,24}

However, a handful of studies have demonstrated no benefit of early coronary angiography or PCI. Weiser et al. (2013) investigated differences in outcomes between OHCA patients with STEMI, who were sent for coronary angiography within 12 hours of sustained ROSC (n=197), compared to those who were not sent for coronary angiography within 12 hours (n=52). They found no difference in 30-day survival with favorable neurologic outcome (CPC 1 or 2) between groups (OR=1.17, 95% CI 0.45-3.04).\textsuperscript{28} There was also no association between receiving PCI and 30-day survival with favorable neurologic outcome (OR=1.40, 95% CI= 0.53–3.70). However, the sample size in the groups who did not
receive coronary angiography and PCI were small, and patients were admitted to a single tertiary care center.\textsuperscript{28} Similarly, Garot and colleagues (2007) found that OHCA patients with STEMI who had successful PCI, did not have better outcomes at one month or six months post-cardiac arrest than patients whose PCI was unsuccessful.\textsuperscript{68} This study was limited by small sample size, with only 25 of 186 patients having unsuccessful PCI and lack of a control group, since PCI was attempted in all patients.

\subsection{2.9.2 No STEMI}

The optimal management strategy for OHCA patients without STEMI is controversial.\textsuperscript{8,12,13,20,26,35,36,66} There is significant disagreement among healthcare professionals regarding whether or not to send these patients for coronary angiography\textsuperscript{12,26} because the prevalence of coronary artery occlusion in patients without STEMI is lower than in patients with STEMI.\textsuperscript{10,23,35,69,96,97} Clinical experience suggests that patients who have not suffered a cardiac arrest, and do not demonstrate STEMI, are unlikely to receive benefit from reperfusion therapies.\textsuperscript{34,66} As such, OHCA patients without STEMI generally do not receive coronary angiography and PCI\textsuperscript{19} because the benefit remains uncertain.\textsuperscript{34}

However, recent findings have demonstrated that coronary angiography and PCI may be beneficial for cardiac arrest patients without STEMI.\textsuperscript{12,13,22,26,34} Kern (2012) summarized the findings from four studies that investigated outcomes for resuscitated cardiac arrest patients with and without STEMI who received coronary angiography and PCI (if indicated). The combined unadjusted results of these studies demonstrated that survival to hospital discharge was 49\% for patients with STEMI who received coronary angiography and PCI, if indicated, compared to 45\% for patients without STEMI who received the same interventions (p=0.72).\textsuperscript{34} Similarly, survival with intact neurological function did not differ between patients with and without STEMI who received coronary angiography +/- PCI (79\% versus 82\%, p=0.66).\textsuperscript{12,22,34,66,75}

In the Parisian Out of Hospital Cardiac Arrest (PROCAT) study, early coronary angiography (performed at hospital admission) followed by successful immediate PCI was positively associated with survival to hospital discharge in OHCA patients with and without ST-segment elevation.\textsuperscript{12} There was no
significant difference in survival between patients with STEMI who had successful PCI and patients without STEMI who had successful PCI (54% versus 47%, p=0.42). Another study performed in France, compared outcomes between OHCA patients with ventricular fibrillation who received emergency coronary angiography and PCI, to patients who received emergency coronary angiography, but no PCI. They found that receiving PCI reduced the odds of mortality, regardless of initial ECG findings (OR=0.30, 95%CI 0.11-0.79).

Other studies have also found that coronary angiography is positively associated with survival outcomes, regardless of ECG findings in OHCA patients. Refer to Sections 2.4.1 and 2.4.2 for a summary of these studies. Hollenbeck and colleagues (2014) performed a study in comatose OHCA patients with ventricular arrhythmia and no STEMI, and found an association between receipt of early coronary angiography (within 24 hours of hospital arrival) and reduced odds of death (OR=0.35, 95%CI 0.18-0.70).

Based on the results of their studies, several investigators believe that immediate coronary angiography and PCI are two of the most important aspects of post-resuscitation care, and thus these therapies should be considered for all OHCA patients, regardless of post-arrest ECG findings. Even if diagnostic coronary angiography does not demonstrate arterial occlusion, coronary angiography is considered low risk in OHCA patients and a negative result can provide insight into the cause of the arrest and appropriate treatment. For instance, the results of the Arizona Saver Heart Center study, demonstrated that coronary angiography can identify coronary artery anomalies that may have caused the arrest. Patients without STEMI who are identified as not having coronary artery obstruction via coronary angiography, may also benefit from the procedure, through optimization of hemodynamics.

On the contrary, a handful of recent studies have demonstrated that coronary angiography and PCI do not improve outcomes in OHCA patients without STEMI. One such study involved OHCA patients without STEMI who were comatose at hospital admission. Mortality did not differ between those who received emergency coronary angiography (within 12 hours of hospital arrival) and PCI (if
indicated), compared to those who did not (HR=0.69, CI _95_ 0.4-1.2), nor did survival with good cerebral outcome (CPC 1 and 2) (OR= 1.50, CI _95_ 0.80-2.90). Likewise, Dankiewicz and colleagues (2015) assessed the association between early coronary angiography (within 6 hours of arrest) and survival to the end of the study, as well as neurologic outcomes (CPC score), in OHCA patients without ST-elevation. Of the 544 patients who did not demonstrate ST elevation, 46% received early coronary angiography, whereas 54% did not. The results of the propensity analysis and survival analysis, demonstrated no significant difference in survival or neurologic outcome between patients who received early coronary angiography and those who did not. 

### 2.10 Comatose Versus Conscious After OHCA

Unfortunately, the majority of survivors of OHCA are comatose at hospital admission. There is considerable confusion and uncertainty pertaining to the association between treatments and outcomes in comatose OHCA patients because findings from the literature have been conflicting. As a result, it is difficult for physicians to determine the best management strategy for this patient population.

Most of the studies investigating the association between coronary angiography or PCI, and survival outcomes have included both comatose and conscious OHCA patients. However, there is evidence that suggests these may be two very different groups of patients. The AHA and ILCOR, as well as several studies, indicate that OHCA patients who are comatose at hospital admission are less likely to receive coronary angiography and PCI than those who are conscious. However, recent AHA guidelines indicate that being comatose should not be a contraindication to receiving coronary angiography and PCI. Comatose OHCA patients also tend to be given a poorer prognosis and to have poorer outcomes.

A recent study compared immediate coronary angiography and PCI (if indicated) to no intervention in comatose OCHA patients with initial shockable cardiac rhythms. They found that the
association between immediate coronary angiography and PCI (if indicated), and neurologically intact survival (CPC 1 or 2) was positive, but non-significant (OR=1.32, 95% CI 0.26-7.87).\textsuperscript{7} Similarly, Batista et al. (2010) compared mortality between initially comatose OHCA patients who received therapeutic hypothermia, and PCI to those who received therapeutic hypothermia without PCI. They found no difference in survival rates or neurologic outcomes (MRS $\leq 3$) between groups, indicating that the addition of PCI to the treatment protocol did not decrease mortality rates.\textsuperscript{101} However, there were a very small number of patients ($n=20$) who received both PCI and therapeutic hypothermia. Some experts agree that performing routine coronary angiography and PCI in comatose patients who had out-of-hospital resuscitation, is questionable.\textsuperscript{102}

However other studies have demonstrated opposing findings. Zanuttini et al. (2012) recently demonstrated that emergency coronary angiography and emergency PCI were independently associated with survival to hospital discharge in 93 comatose OHCA patients.\textsuperscript{11} Mooney and colleagues (2011) found that comatose OHCA patients who received emergency coronary angiography without PCI had nearly four times the odds of surviving to hospital discharge compared to patients who did not receive emergency coronary angiography.\textsuperscript{75} Those who received emergency coronary angiography and PCI had about twice the odds of surviving than those who did not receive either intervention.\textsuperscript{75} However, they did not adjust for important confounders of these associations.

Two other important patient subgroups are those with and without STEMI on the post-arrest ECG. The association between coronary angiography and outcomes could potentially differ by both STEMI status and initial neurologic status. Bro-Jeppesen et al. (2012) recommend that studies investigating outcomes in comatose OHCA patients should stratify comatose patients by STEMI status.\textsuperscript{20} To date, only four such studies have been published.

Bro-Jeppesen et al. (2012) compared outcomes between 244 comatose OHCA patients without STEMI who received emergency coronary angiography (within 12 hours of hospital arrival) and PCI (if indicated) to those who did not undergo emergency coronary angiography and PCI (if indicated) and found no difference in one month or one year survival.\textsuperscript{20} Another study including 135 OHCA patients,
found that comatose patients with STEMI had significantly worse outcomes than conscious patients with STEMI, despite both groups of patients receiving aggressive reperfusion therapy with PCI. The success rate of PCI was 82% in patients who were comatose, and 94% in conscious patients.

The remaining two studies demonstrated positive associations in comatose patients with and without STEMI. Hollenbeck and colleagues (2009) compared the effect of receiving early coronary angiography (at hospital admission or during therapeutic hypothermia) to not receiving coronary angiography in OHCA patients without STEMI who were comatose at hospital admission and treated with therapeutic hypothermia. They found that having early coronary angiography was associated with decreased mortality (OR=0.14, 95%CI 0.06-0.32). Hosmane et al. (2009) demonstrated that OHCA patients with STEMI who are initially comatose benefit from revascularization, such that mortality was 42% in revascularized patients compared to 84% in non-revascularized patients (p=0.003). Consequently, some experts agree that coronary angiography and PCI may be beneficial to OHCA patients who are initially comatose as well.

2.11 Limitations of Previous Studies

Previous studies have methodological limitations and generalizability issues that we will attempt to eliminate. Please refer to Appendix B for a summary of the limitations of important previous studies. Many of the studies have been conducted outside of North America, where there are differences in many aspects of care for cardiac arrest patients. For instance, the PROCAT study was one of the largest cohort studies to examine the association between STEMI status, coronary angiography and PCI, and outcomes in OHCA patients. It was conducted in France, where response to and treatment of OHCA is more aggressive than in North America. As a result, the investigators stated that “Our findings therefore cannot be applied to all patients with OHCA.” In Paris, prehospital management of cardiac arrest is performed by physicians trained in emergency medicine. Also, all OHCA patients are dispatched to hospitals equipped with cardiac catheterization facilities, and all patients with presumed
cardiac cause of arrest are given emergency coronary angiography, despite ECG findings. Four other important studies were also conducted in France. The results of such studies are not generalizable to countries where post-cardiac arrest care practices and resources are quite different. Furthermore, these studies lacked a control group, since all patients presenting to a hospital with cardiac arrest in France receive coronary angiography. These studies were not able to specifically investigate if OHCA patients who receive coronary angiography have better outcomes than those who do not receive the intervention.

In addition, the majority of previous studies have been primarily single center studies, and/or have used small sample sizes. For instance, Nanjayya et al. (2012) studied outcomes of 70 OHCA who were initially comatose and received coronary angiography and PCI, if indicated, at a single center. Anyfantakis et al. (2009) studied only 72 OHCA patients admitted to a single center in France, and Gorjup and colleagues (2007) studied 135 patients admitted to a single hospital in Slovenia. Please refer to Appendix B for a summary of sample sizes and number of centers employed in important previous studies.

The results from single center studies or studies conducted in a handful of centers, reflect the management and treatment of patients in those specific centers, the patient population is relatively homogenous, and the results may not be applicable to patients treated in other centers. Some studies have been multicenter, however these studies had other important limitations. One multicenter study conducted at 11 sites in Seattle, Washington, and another conducted at 151 sites across North America, both investigated if there were differences in survival between OHCA patients who received early versus late or no coronary angiography, rather than comparing coronary angiography to no coronary angiography. Neither study investigated the association between early coronary angiography and PCI, and outcomes separately in patients with and without STEMI, or by initial neurologic status. Redpath et al. (2010) conducted a multicenter study in Canada and also failed to perform subgroup analyses by STEMI status and initial neurologic status.
These studies failed to adjust for several important confounders as well. In fact, Callaway et al. (2013) did not even adjust for initial neurologic status, which has been shown to be strongly associated with both the decision to send a patient for coronary angiography and survival.\textsuperscript{7,13,19,26,29,31} In the study conducted by Redpath and associates (2010) the only variables included in the multivariate model were invasive coronary artery management, age, gender, hospital size and type, patient address (rural or non-rural), patient comorbidities, province of arrest, and year of arrest.\textsuperscript{8}

Lastly, many previous studies had limited inclusion criteria and extensive exclusion criteria or have investigated specific patient populations. Reynolds and associates (2009) can attest to this statement, as they criticize prior studies for using “extensive exclusion criteria and highly selective patient populations.”\textsuperscript{13} For instance, Hollenbeck and associates (2014) investigated the association between early coronary angiography and survival to hospital discharge in OHCA patients with ROSC. However, the patient population was limited to patients who were comatose following ROSC, had an arrest caused by ventricular arrhythmia, did not display STEMI on the post-arrest ECG, and were treated with therapeutic hypothermia.\textsuperscript{26} Other studies included only OHCA patients with shockable cardiac rhythms,\textsuperscript{7,22,26} or studied only patients with STEMI,\textsuperscript{28,31,33,68} or without STEMI.\textsuperscript{36} Several investigators examined the association between coronary angiography and/or PCI and survival outcomes in comatose OHCA patients specifically.\textsuperscript{7,11,20,75} It is important to conduct studies with less stringent inclusion criteria, in order for the results to be widely generalizable.

Several of the limitations of previous studies can be overcome through use of the Rescu Epistry database, which was used for the purposes of this study. This database contains extensive and accurate data on nearly 3000 patients eligible for this study. Data are available on nearly all potential confounders identified in the literature. The database also enabled associations to be examined in subgroups of patients, including patients with and without STEMI on the first post-arrest ECG, and patients who were initially comatose versus initially conscious. The analysis included patients from 28 hospitals in Ontario, Canada, which enables generalizability of our study findings.
2.12 Rationale for Objective 1

The nature and prevalence of interventions received by post-cardiac arrest patients in hospitals across Canada are not well understood. More specifically, the proportion of OHCA patients who receive coronary angiography is largely unknown and practice patterns in the Canadian setting, specifically around factors driving the decision to pursue coronary angiography, have not been described. There is disagreement in clinical practice as to which patients should undergo coronary angiography and PCI (if indicated). Post-resuscitation guidelines do exist, however, there was limited evidence available to make these recommendations and clinician adherence to the guidelines is sub-optimal. The guidelines merely provide recommendations, leaving the final treatment decision to the discretion of the attending physician(s).

While studies have demonstrated associations between various factors and receipt of coronary angiography in OHCA patients, most have failed to perform adjusted analyses, and few have investigated a large number of factors potentially associated with receiving coronary angiography. It is important to describe clinical practice in Ontario hospitals to quantify variability in practice and to determine which factors drive the decision to send an OHCA patient for coronary angiography. An understanding of system and patient factors may enable the formation of a more complete representation of what is driving the variability in receipt of coronary angiography. This understanding may also result in the identification of targets for future interventions to improve the quality and consistency of post-cardiac arrest care in Ontario and beyond. Clinical practice must be described in order to understand where improvements can be made.

2.13 Rationale for Objective 2

Unfortunately, only about 37% of cardiac arrest patients who are successfully resuscitated, and admitted to a hospital will survive to hospital discharge, and a significant proportion of the survivors will suffer neurological and cognitive deficits. Furthermore, the rate of survival to hospital discharge has not changed for over 50 years. Currently, the majority of research on cardiac arrest focuses on improving
methods to achieve ROSC in the pre-hospital setting. However, given these dismal survival statistics, it is evident that further research must focus on improving outcomes following ROSC, through enhanced in-hospital post-resuscitation care.9,104

Several studies have demonstrated that OHCA patient survival following ROSC differs between hospitals, after adjusting for other factors that may influence survival.55,86–89 The variability in survival may be due to inconsistencies in the quality and nature of post-cardiac arrest care between receiving hospitals.55,88,104 Coronary angiography is the post-resuscitation procedure used to identify acute coronary artery occlusions, which are highly prevalent in OHCA patients, and are amenable to treatment with reperfusion therapies, such as PCI.10,12,22

However, it is the minority of patients who receive coronary angiography.8,19 This may be due to the fact that its’ efficacy in patients who are successfully resuscitated from a sudden cardiac arrest is questionable,23 and there are few clear guidelines that explicitly state how resuscitated OHCA patients should be treated.104 Coronary angiography and PCI are also costly to the healthcare system,105 and associated with complications such contrast media allergic reactions, bleeding complications, cerebral ischemia, stroke, coronary dissection, vascular injury, myocardial infarction, heart failure, cardiogenic shock, respiratory and renal complications, infection and even death.106,107 Receiving these procedures may also delay other important tests and therapies.69 It is important to understand whether the benefit of these treatments outweigh the associated risks and costs.

Recent research has demonstrated that coronary angiography and PCI are generally beneficial to OHCA patients with certain ECG features such as STEMI.12,22,28–33 However, uncertainty still exists for other ECG findings.12,13,20,26,35–37,66 Only a handful of studies have investigated the outcomes of providing early coronary angiography and PCI to OHCA patients with other ECG findings. However, these studies have had conflicting results, as well as several limitations and generalizability issues.13,20,26,28,35,36,66

Furthermore, there are no Canadian data on the association between STEMI status, coronary angiography, PCI and outcomes in OHCA patients. Further research must be performed to determine if it would be beneficial for coronary angiography and PCI to be administered to a broader group of patients.
with return of spontaneous circulation beyond those with STEMI following OHCA. Using the Rescu Epistry database, there is an opportunity to examine the association in a large and heterogeneous network of hospitals in Ontario, Canada. The Epistry database includes hospitals that are varied with respect to size, location (rural versus urban) and academic status, which will improve the generalizability of our findings. If coronary angiography is found to improve survival, and neurologically intact survival, in both groups of patients (STEMI and no-STEMI), this research may support modifications to clinical practice, and methods of selecting patients for coronary angiography and PCI.
Chapter 3

Methods

3.1 Study Design and Population

This study was a retrospective cohort study using data from consecutive OHCA patients who presented to one of the 28 participating Strategies for Post Arrest Care (SPARC) network hospitals between March 1st, 2010 and December 31st, 2014, and met the pre-specified inclusion and exclusion criteria.

3.2 Inclusion and Exclusion Criteria

A patient was included in the analysis if he/she was an adult (over the age of 18), had an OHCA that was treated by EMS personnel in the SPARC network region between March 1st, 2010 and December 31st, 2014, had a return of spontaneous circulation (ROSC), was admitted to one of the 28 participating SPARC Network hospitals, and survived for at least six hours following initial emergency department arrival.

Patients were excluded from the analysis if they were under the age of 18, had a pre-existing do not resuscitate (DNR) order, or if the etiology of the arrest was identified to be non-cardiac by treating paramedics or in-hospital staff. Non-cardiac causes of arrest included respiratory failure, airway obstruction, drug overdose, poisoning, stroke and traumatic causes such as hemorrhage.12,41

3.3 Data Sources

3.3.1 Rescu Epistry Database

The Strategies for Post Arrest Resuscitation Care (SPARC) dataset108 and the Resuscitation Outcomes Consortium (ROC) Epistry dataset109 have been previously combined into a single database termed Rescu Epistry, which was used for the purpose of this thesis. The Rescu Epistry database captures data for all individuals who had an OHCA in the SPARC network region of Southern Ontario (see Figure
The ROC Epistry component of the database provided all prehospital patient characteristics, cardiac arrest features, and treatments delivered by prehospital care providers, while the SPARC component provided data on all in-hospital cardiac arrest features and treatments.

Currently the Rescu Epistry database captures all individuals who have had a cardiac arrest or traumatic injury attended to by EMS in the City of Toronto and surrounding regions (Peel, York, Halton, Simcoe, Durham and Muskoka), which comprises a population of 6.6 million. The patients included in the Epistry database are admitted to hospitals that range in size and type from small community hospitals to large teaching hospitals. Data is entered into the Rescu Epistry database via a web-based data management system that links data from EMS call reports, defibrillators and monitors, as well as clinical data abstracted from patient charts. The electronic database has many automated features to minimize data entry errors such as built-in error checks and visibility rules (i.e. point of entry logic).

3.3.1.1 SPARC Dataset

The SPARC dataset contains in-hospital data on more than 40,000 OHCA patients admitted to 37 participating SPARC network hospitals located in Southern Ontario, since 2007. Refer to Figure 3 for geographic locations of the SPARC Network hospitals. The SPARC network project was originally initiated to increase the use of therapeutic hypothermia in resuscitated cardiac arrest patients. The hospitals in the network voluntarily participated in a knowledge translation intervention trial aimed at improving the care of resuscitated cardiac arrest patients, through observation, measurement and standardization of post cardiac-arrest care practices.

The study design was a stepped wedge cluster randomized controlled trial whereby the participating hospitals were each randomly assigned to no intervention, followed by passive intervention, followed by active intervention over a series of time periods. In this study design, each hospital acted as its’ own control. The passive intervention included identification of site nurse and physician champions, a site visit to educate healthcare providers about therapeutic hypothermia, and provision of a standard protocol for administration of therapeutic hypothermia. The active intervention included distribution of
a protocol for administering therapeutic hypothermia, education on therapeutic hypothermia (webinars, video teleconferences, expert speaker sessions), email notifications to site champions when a patient eligible for therapeutic hypothermia is at their site, and timely access to feedback pertaining to patient outcomes.\textsuperscript{110} A greater proportion of eligible patients received therapeutic hypothermia during the intervention periods compared to the control periods.\textsuperscript{111}

The SPARC dataset is a comprehensive dataset containing 454 variables, of which 400 variables are in the Ustein style,\textsuperscript{108} which is a validated and standardized data collection tool.\textsuperscript{108,112} Eligible OHCA cases were identified via paramedics calling a cardiac arrest notification hotline and through hand-searching of ambulance call reports.\textsuperscript{110} When a paramedic calls the hotline, this triggers an automated email to be sent to the in-hospital data abstractor, who then begins data entry for the case. A data dictionary was also developed to standardize data collection and quality assurance programs were also developed to improve data accuracy.\textsuperscript{108} For variables that had low agreement, the reasons for discrepancies in data entry were analyzed and modifications to the data dictionary abstraction instructions were made, where necessary.\textsuperscript{108} An internal audit found that 99\% of eligible OHCA cases are captured in the SPARC dataset (unpublished data).
Figure 3. The SPARC Network. Stars indicate the locations of participating hospitals. Regions that each EMS system operates within are indicated in grey.

3.3.1.2 Resuscitation Outcomes Consortium (ROC) Epistry Dataset:

Resuscitation Outcomes Consortium (ROC) is a network composed of ten Regional Clinical Centers, a Data Coordinating Center and satellite sites (see Figure 4). The network is responsible for conducting clinical trials related to prehospital cardiac arrest. The ROC satellite sites provide the infrastructure to conduct clinical trials aimed at improving outcomes in resuscitated cardiac arrest
patients.\textsuperscript{109} The ROC Epistry database is a large population-based registry containing data on over 100,000 OHCA patients who were assessed by EMS in 11 geographic areas throughout North America.\textsuperscript{109} Data for patients over the age of 18, who suffered an OHCA assessed by EMS, in the geographic region of Toronto, Ontario was used for this thesis.

Verified data collection procedures were used to collect data for each of the variables in the ROC database, and quality assurance programs were carried out to ensure accuracy of data entry.\textsuperscript{109} For instance, the Data Coordinating Center randomly selects patient records to ensure data for those patients were entered accurately, and conducts site visits to ensure quality assurance mechanisms are being implemented at all sites.\textsuperscript{109}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ROC_participating_sites.png}
\caption{Resuscitation Outcomes Consortium (ROC) participating sites.}
\end{figure}
3.4 Descriptive Variables

Due to the clustered nature of the data, descriptive variables were divided into patient level (Level-1) and hospital-level (Level-2) variables. The patient-level descriptive variables can be divided into four categories: patient demographic characteristics, cardiac arrest features, interventions, and outcomes (Table 1). Patient demographic characteristics included age and sex, and pre-existing comorbidities. Age was represented as a continuous variable and was determined by subtracting patient date of birth from date of hospital admission for the cardiac arrest.

Cardiac arrest features included initial cardiac rhythm (shockable, non-shockable), bystander witnessed arrest (yes, no/unknown), EMS witnessed arrest (yes, no), bystander resuscitation (yes, no/unknown), bystander cardiopulmonary resuscitation (yes, no/unknown), bystander automated external defibrillator (AED) use (yes, no/unknown), location of arrest (public, private), presentation during business hours (yes, no), EMS response time (minutes), prehospital return of spontaneous circulation (ROSC) (yes, no/unknown), neurologic function at ED arrival (comatose, conscious), emergency department status (pulse present, ongoing resuscitation, unknown), and initial electrocardiogram (ECG) findings (STEMI, no/unknown).

Shockable rhythms were defined as ventricular fibrillation (VF) or ventricular tachycardia (VT) and non-shockable rhythms were considered to be pulseless electrical activity (PEA) or asystole. Bystander resuscitation was defined as any CPR or AED use. Private locations of arrest included nursing homes, apartments/condo buildings, and houses/townhouses, while all other locations were considered public. Presentation during business hours was defined as initial ED arrival between 9am and 5pm Monday to Friday. Initial ECG findings were defined as the presence or absence of STEMI on the first post arrest in-hospital ECG that was performed. Patients classified as not having STEMI were those with all other ECG patterns, who did not demonstrate significant ST-segment elevation.20 All cardiac arrest features were categorical, except for EMS response time, which was a continuous variable defined as the number of minutes from the time of the emergency call to the time of arrival of EMS personnel to the scene.
Intervention variables included administration of echocardiography (yes, no/unknown), initiation of therapeutic hypothermia (yes, not noted), receipt of coronary angiography (yes, unknown/not noted), PCI (yes, unknown/not noted), or coronary artery bypass grafting (CABG) (yes, not noted), as well as receipt of fibrinolytic drugs (yes, no/unknown) and inotropic drugs (yes, no/unknown). Initiation of therapeutic hypothermia was defined as any in-hospital attempt to lower core body temperature.\textsuperscript{19} Coronary angiography was defined as the patient being taken to the catheterization laboratory to receive diagnostic catheterization (coronary angiography) within 72 hours of first emergency department (ED) arrival. PCI was defined as the patient receiving interventional catheterization within 72 hours of first ED arrival. Early coronary angiography was defined as receiving the procedure within 24 hours of ED arrival, while late coronary angiography was defined as receiving the procedure 24 to 72 hours after ED arrival. All treatment variables were categorical binary variables.

Clinical outcome variables included survival to hospital discharge (yes, no) and survival with favorable neurologic outcome (yes, no). Favorable neurologic outcome was defined as having a Modified Rankin Scale (MRS) score of 0-2 at hospital discharge and poor neurologic outcome was defined as having an MRS score of 3-5 at hospital discharge or being deceased.\textsuperscript{113–115} Refer to Appendix C for definitions of MRS scores. A MRS score of zero to two indicates that the patient has adequate neurologic function to perform daily activities independently.\textsuperscript{113} Cerebral Performance Category (CPC) scores can also be used to indicate neurologically intact survival with a CPC score of 1 or 2 indicating survival with favorable neurologic outcome, and a CPC score of 3-5 indicating survival with poor neurologic outcome.\textsuperscript{116} Refer to Appendix D for definitions of CPC scores. All outcome variables were categorical.

Hospital-level variables included the size of hospital (small <250 beds, medium 250-400 beds, large >400 beds),\textsuperscript{51,92} type of hospital (Academic Health Science Center, non-Academic Health Science Center), as designated by the Ontario Ministry of Health and Long-Term Care, whether or not the hospital was a PCI center (yes, no), and hospital cardiac arrest volume (arrests/year). PCI centers are hospitals that are capable of performing PCI. Patients were assigned to the hospital they first arrived to, despite the fact that transfers may have occurred afterwards. The hospital-level variables were obtained from a variety of
sources. Average hospital cardiac arrest volume was calculated from the study population by dividing the number of patients admitted to each participating hospital between 2010 and 2014 by five. The number of acute beds per hospital and hospital type were obtained from the Ontario Ministry of Health and Long Term Care (MOHLTC) and whether or not the hospital was a PCI center was obtained using a report published by the Cardiac Care Network of Ontario. All hospital-level variables were categorical. Refer to Table 1 for an overview of descriptive variables.

Table 1. Descriptive variables (patient-level and hospital-level)

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient demographic characteristics</strong></td>
<td>Sex</td>
<td>Categorical</td>
<td>Male, female</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>Continuous</td>
<td>Difference in years between the date of birth of the patient and the date of hospital admission for cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>Pre-existing comorbidities</td>
<td>Categorical</td>
<td>Yes, no/not noted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Refer to Table 4.</td>
</tr>
<tr>
<td><strong>Patient cardiac arrest features</strong></td>
<td>Initial cardiac rhythm</td>
<td>Categorical</td>
<td>Shockable (VF/VT), non-shockable (asystole/PEA)</td>
</tr>
<tr>
<td></td>
<td>Bystander-witnessed arrest</td>
<td>Categorical</td>
<td>Yes, no</td>
</tr>
<tr>
<td></td>
<td>EMS witnessed arrest</td>
<td>Categorical</td>
<td>Yes, no</td>
</tr>
<tr>
<td></td>
<td>Bystander resuscitation</td>
<td>Categorical</td>
<td>Any CPR or AED use, no CPR or AED use/unknown</td>
</tr>
<tr>
<td></td>
<td>Bystander CPR</td>
<td>Categorical</td>
<td>Yes, no/unknown</td>
</tr>
<tr>
<td></td>
<td>Bystander AED use</td>
<td>Categorical</td>
<td>Yes, no/unknown</td>
</tr>
<tr>
<td></td>
<td>Location of arrest</td>
<td>Categorical</td>
<td>Public, private</td>
</tr>
<tr>
<td></td>
<td>Presentation during business hours</td>
<td>Categorical</td>
<td>Initial ED arrival between 9am and 5pm on weekday, other time</td>
</tr>
<tr>
<td></td>
<td>EMS response time</td>
<td>Continuous</td>
<td>Number of minutes between time of 911 call and time of</td>
</tr>
</tbody>
</table>

48
<table>
<thead>
<tr>
<th>Event Description</th>
<th>Data Type</th>
<th>Data Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>arrival of EMS personnel to the scene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prehospital ROSC</td>
<td>Categorical</td>
<td>Yes, no/cannot obtain</td>
</tr>
<tr>
<td>Neurologic status at ED arrival</td>
<td>Categorical</td>
<td>Comatose, conscious</td>
</tr>
<tr>
<td>Emergency department status</td>
<td>Categorical</td>
<td>Pulse present, ongoing resuscitation, unknown</td>
</tr>
<tr>
<td>Electrocardiogram (ECG) findings</td>
<td>Categorical</td>
<td>STEMI, no/unknown/not noted</td>
</tr>
<tr>
<td>Patient interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Categorical</td>
<td>Yes, no/not noted</td>
</tr>
<tr>
<td>Initiation of therapeutic hypothermia</td>
<td>Categorical</td>
<td>Initiated, N/A or not recorded</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>Categorical</td>
<td>Coronary angiography within 72 hours of hospital arrival, unknown/not noted</td>
</tr>
<tr>
<td>Percutaneous coronary intervention (PCI)</td>
<td>Categorical</td>
<td>PCI within 72 hours of hospital arrival, unknown/not noted</td>
</tr>
<tr>
<td>Coronary artery bypass grafting (CABG)</td>
<td>Categorical</td>
<td>Yes, N/A or not recorded</td>
</tr>
<tr>
<td>Fibrinolytic drugs</td>
<td>Categorical</td>
<td>Yes, no/unknown</td>
</tr>
<tr>
<td>Inotropic drugs (epinephrine, dopamine)</td>
<td>Categorical</td>
<td>Yes, no/unknown</td>
</tr>
<tr>
<td>Patient outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>Categorical</td>
<td>Patient alive at hospital discharge, deceased</td>
</tr>
<tr>
<td>Survival with favorable neurologic outcome (MRS)</td>
<td>Categorical</td>
<td>Patient had a MRS score of 0-2 (favorable) at hospital discharge, MRS score of 3-5 (unfavorable)/deceased</td>
</tr>
<tr>
<td>Survival with favorable neurologic outcome (CPC)</td>
<td>Categorical</td>
<td>Patient had CPC score of 1 or 2 at hospital discharge (favorable), CPC score of 3-5 (unfavorable)/deceased</td>
</tr>
</tbody>
</table>
### Hospital characteristics

<table>
<thead>
<tr>
<th></th>
<th>Size of hospital</th>
<th>Academic Health Science Center</th>
<th>PCI center</th>
<th>Hospital cardiac arrest volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Categorical</td>
<td>Categorical</td>
<td>Categorical</td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td>Average number of acute care beds in operation (small &lt;250, medium 250-400, large &gt;400)</td>
<td>Yes, no</td>
<td>Yes, no</td>
<td>Average number of cardiac arrest patients admitted to hospital per year</td>
</tr>
</tbody>
</table>

Descriptive statistics were used to describe the study population using the individual patient as the unit of analysis. Means and standard deviations were reported for continuous variables. Counts, frequencies and proportions were used to describe characteristics that were classified as categorical variables.

Some variables had missing values or were recorded to be ‘unknown’ or ‘not noted’ in the Epistry database. ‘Unknown’ or ‘not noted’ value coding rules were established on the basis of input from clinicians experienced in emergency medicine and Rescu Epistry data collection. For instance, based on established practices in clinical record keeping, bystander CPR or bystander defibrillation is recorded as ‘yes’ in the clinical record if it is observed. Many times this space on the clinical record is left blank if it is not observed. Therefore, our coding rules for this variable grouped ‘no’ and ‘unknown’ as a single category. Similarly, STEMI is typically noted in the affirmative on the clinical record. When STEMI is not present, usual practice in clinical record keeping would not include a statement in the negative. Rather, the clinical note would make no mention of STEMI. Therefore, our coding rules grouped “no STEMI” with “unknown”.

Variables for which missing data was coded as ‘no/unknown’ were bystander CPR, bystander defibrillation, bystander-witnessed arrest, echocardiography, and pre-existing comorbidities. Refer to Table 1 for a list of variables for which ‘unknown’ or ‘not noted’ status, were classified as ‘no’.
3.5 Hospital Characteristics

Of the hospitals included in our study, there were a total of six PCI centers and six Academic Health Science Centers. The number of acute care beds staffed and in operation March 2013 at each hospital was used as a proxy measure of the average number of acute care beds during the entire study period at that hospital, as these figures change very little from year to year, and data was not available for each year. Table 2 provides a description of each hospital included in our study.

Table 2. Rescu Epistry network hospital characteristics

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Number of patients admitted from study population (2010-2014)</th>
<th>Average number of cardiac arrest patients admitted per year</th>
<th>PCI Center (yes/no)</th>
<th>Academic Health Sciences Center (yes/no)</th>
<th>Number of acute beds staffed and in operation (March 2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunnybrook Health Sciences Center</td>
<td>180</td>
<td>90.2</td>
<td>Yes</td>
<td>Yes</td>
<td>556</td>
</tr>
<tr>
<td>St. Michael’s Hospital</td>
<td>146</td>
<td>76.8</td>
<td>Yes</td>
<td>Yes</td>
<td>418</td>
</tr>
<tr>
<td>Scarborough Hospital - General site</td>
<td>106</td>
<td>76.0</td>
<td>No</td>
<td>No</td>
<td>277</td>
</tr>
<tr>
<td>Scarborough Hospital - Grace division</td>
<td>75</td>
<td>52.8</td>
<td>No</td>
<td>No</td>
<td>164</td>
</tr>
<tr>
<td>The Credit Valley Hospital</td>
<td>126</td>
<td>89.6</td>
<td>No</td>
<td>Yes</td>
<td>330</td>
</tr>
<tr>
<td>Trillium Health Center - Mississauga Site</td>
<td>263</td>
<td>143.6</td>
<td>Yes</td>
<td>No</td>
<td>495</td>
</tr>
<tr>
<td>St. Joseph’s Health Center</td>
<td>119</td>
<td>79.4</td>
<td>No</td>
<td>No</td>
<td>318</td>
</tr>
<tr>
<td>Humber River Regional Hospital – York - Finch</td>
<td>94</td>
<td>72.0</td>
<td>No</td>
<td>No</td>
<td>241</td>
</tr>
<tr>
<td>Humber River Regional Hospital – Humber Memorial</td>
<td>145</td>
<td>78.4</td>
<td>No</td>
<td>No</td>
<td>241</td>
</tr>
<tr>
<td>Orillia Soldiers Memorial Hospital</td>
<td>44</td>
<td>33.0</td>
<td>No</td>
<td>No</td>
<td>101</td>
</tr>
<tr>
<td>Mount Sinai Hospital</td>
<td>19</td>
<td>13.4</td>
<td>No</td>
<td>Yes</td>
<td>317</td>
</tr>
<tr>
<td>Health System</td>
<td>Code</td>
<td>Score</td>
<td>COVID-19</td>
<td>Influenza</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>------</td>
<td>-------</td>
<td>----------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Rouge Valley Health System - Centenary</td>
<td>138</td>
<td>72.8</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Rouge Valley Health System - Ajax</td>
<td>77</td>
<td>53.2</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lakeridge Health Corporation - Oshawa Site</td>
<td>162</td>
<td>103.8</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lakeridge Health Corporation - Bowmanville</td>
<td>15</td>
<td>22.6</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lakeridge Health Corporation - Port Perry</td>
<td>15</td>
<td>11.6</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Collingwood General and Marine Hospital</td>
<td>26</td>
<td>22.2</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>The Toronto East General Hospital</td>
<td>125</td>
<td>83.6</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>The Royal Victoria Hospital - Barrie</td>
<td>98</td>
<td>65.8</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>North York General Hospital</td>
<td>120</td>
<td>82.6</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Markham Stouffville Hospital</td>
<td>63</td>
<td>46.8</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Markham Stouffville Hospital - Uxbridge Site</td>
<td>10</td>
<td>9.6</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>William Osler Health System - Brampton Civic</td>
<td>228</td>
<td>176.4</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>William Osler Health System - Etobicoke</td>
<td>115</td>
<td>92.2</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>The Stevenson Memorial Hospital - Alliston</td>
<td>19</td>
<td>14.2</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>University Health Network - General Site</td>
<td>60</td>
<td>26.8</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>University Health Network - Western Site</td>
<td>79</td>
<td>52.4</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Muskoka Algonquin Health Care - Bracebridge Site</td>
<td>11</td>
<td>15.0</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>28</td>
<td>2578</td>
<td>Mean=89</td>
<td>Total=6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Mean=330</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.6 Analytic Approach

3.6.1 Multilevel Logistic Regression

When performing logistic regression on a dataset that contains both individual-level and group-level data, it is necessary to perform multilevel logistic regression, as opposed to traditional logistic regression. This is done in order to reduce the potential for bias and inaccurate results. Ordinary logistic regression is not appropriate for hierarchical data, as it does not take the hierarchical structure of the data into account. It ignores the potential correlation among individuals within a group by assuming that observations are independent, and therefore, can result in ecological fallacy. Ecological fallacy occurs when the individual-level association is confounded due to variability of covariates and exposure variables within groups. When dealing with hierarchical data, multilevel modeling results in more accurate and conservative estimates of effect than traditional modeling techniques.

Multilevel modeling techniques account for data that consist of units clustered into groups. For instance, in our study, patients are clustered by hospital. We assumed that some of the variability in our results would exist at the hospital level, so we adjusted for this clustering through the use of multilevel logistic regression. Multilevel models may consist of several levels. In this study, two-level models were developed, which took into account both patient- and hospital-level effects. We designated the patient level as “Level-1” and hospital level as “Level-2”. Hospital was treated as a random variable, and the patient-level and hospital-level variables were considered fixed variables in the multilevel models.

3.6.2 Multiple Imputation

Multiple imputation is a statistical procedure used to analyze incomplete datasets. It involves three steps; imputation, analysis and pooling. Statistical software imputes missing values by taking into account the association between a missing variable and variables that are correlated with the missing variable. During imputation, a specified number of datasets are created. Each dataset has slightly different imputed values for the missing data. By creating a number of datasets, the uncertainty of each
imputed value is taken into account. In our study, missing values were imputed using ten imputations. Each of the datasets are then analyzed using a chosen statistical procedure, and then the results of each analysis are pooled together using statistical software.

Multiple imputation was performed (PROC MI v 9.4, Cary, NC) using the exposure and outcome variables of interest, the covariates identified a priori from the literature, as well as coronary artery bypass grafting (CABG), administration of fibrinolytic drugs, etiology of arrest, ED status, and CPC score, to predict the missing values. Each of the ten imputed datasets were analyzed using multilevel logistic regression (PROC GLIMMIX v 9.4, Cary, NC) and then the results from the imputed datasets were merged (PROC MIANALYZE v 9.4, Cary, NC) to get a final set of parameter estimates, confidence limits and p-values. Multiple imputation was performed rather than eliminating cases with a missing value from the analysis, because these cases had data available on all other covariates of interest, as well as exposures and outcomes of interest. It would have been less efficient and more prone to bias to exclude patients who were missing data for a single variable.

One of the key assumptions that must be met in order to perform multiple imputation is the data is missing at random. In our study, the covariates that had missing data (EMS response time and initial cardiac rhythm) were recorded by EMS. Missing data is a known and recognized problem by patients seen by EMS because the scene is somewhat chaotic and clinical record keeping is less of a priority than treating the patient. These rates of missing data are not unexpected and there is no obvious reason these missing data are non-random. Multiple imputation is more efficient than other imputation methods because it uses all the available data to impute missing values, it takes the uncertainty of missing values into account, and it makes a weaker assumption regarding the missing data mechanism, and thus may be less biased than complete case analysis for example.

3.6.3 Intraclass Correlation Coefficient

An issue with this hierarchical data is that there is potential for patients admitted to the same hospital to be more alike in terms of exposures and outcomes, than patients admitted to other hospitals.
This is termed the intra-class correlation (ICC).\textsuperscript{124} If the intra-class correlation was not taken into account in our data analysis, the standard error of the regression coefficient of coronary angiography would have been underestimated,\textsuperscript{118} resulting in overestimation of the significance of the association between coronary angiography and the outcome of interest (i.e. survival to hospital discharge or survival with favorable neurologic outcome).

The intra-class correlation coefficient (ICC) can range from zero to one with zero indicating that none of the variability in individual outcomes can be attributed to the group or cluster that the individual belongs to, whereas an ICC of 1 indicates that all of the variability in individual outcomes is attributable to the cluster to which the individual belongs.\textsuperscript{124} For instance, an ICC of 0.10 in our study would mean that 10% of the variability in the primary outcome was due to the hospital the patient was initially admitted to. Generally, an ICC above 0.05 demonstrates that there is sufficient variability between clusters to use multilevel analysis strategies.\textsuperscript{124} However, when units are clustered into groups, it is advisable to use multilevel modeling regardless of the ICC attained from the empty model, because the ICC attained from more complex models may demonstrate considerable group-level variability.\textsuperscript{124} The formula to determine the intraclass correlation coefficient (ICC) is as follows;

\[
\text{ICC} = \frac{\text{between cluster variability}}{\text{between cluster variability} + \text{within cluster variability}}
\]

3.7 Objective 1

To quantify the association between patient demographic characteristics, cardiac arrest features, interventions, hospital characteristics and receipt of coronary angiography in a network of 28 hospitals across Southern Ontario.

3.7.1 Exposure Variables

*Patient characteristics, cardiac arrest features and interventions*: Age (years), sex, initial cardiac rhythm (shockable, non-shockable), bystander witnessed arrest (yes, no/unknown), EMS witnessed arrest (yes, no), bystander CPR (yes, no/unknown), bystander automated external defibrillator (AED) use (yes,
no/unknown), location of arrest (public, private), presentation during business hours (yes, no), prehospital ROSC (yes, no/unknown), EMS response time (minutes), neurologic status at ED arrival (comatose, conscious), initial electrocardiogram (ECG) findings (STEMI, no/unknown), and initiation of therapeutic hypothermia (yes, not noted). Age was separated into two continuous variables (age <55 and ≥ 55) based on the appearance of the Loess curve (see Appendix E). The curve demonstrated a positive linear association between age and coronary angiography before the age of approximately 55 and a negative linear association beyond the age of 55. Treating age as a single linear continuous variable would have resulted in inaccurate effect estimates.

Hospital characteristics: Size of hospital (small < 250 beds, medium 250-400 beds, large >400 beds), type of hospital (Academic Health Science Center, no), PCI center status (yes, no), and average annual hospital cardiac arrest volume (arrests/year).

3.7.2 Outcome Variable

The outcome of interest was receipt of coronary angiography (yes, no). Receiving coronary angiography was defined as receiving coronary angiography within 72 hours of emergency department arrival.

3.7.3 Statistical Analysis

Multilevel logistic regression was employed (PROC GLIMMIX v 9.4, Cary, NC), using ‘hospital’ as a random factor, in order to assess the association between each exposure variable and receipt of coronary angiography, while adjusting for potential confounders and accounting for potential heterogeneity in receipt of coronary angiography between hospitals. Patient-level and hospital-level data were considered fixed effects in all models.

First, empty regression models were built with only ‘hospital’ as a predictor of whether or not a patient received coronary angiography. Building the null model was used to assess the degree of
heterogeneity in receipt of coronary angiography across hospitals. Intraclass correlation coefficients (ICCs) were calculated. Next, several multilevel logistic regression models were developed to examine the independent association between each exposure variable and receipt of coronary angiography. As such, each model included only a single exposure variable, and hospital was included as a random effect to account for clustering.

A multilevel logistic regression model was then developed that included all exposure variables of interest to determine the association between each exposure variable and receipt of coronary angiography, after adjusting for the effect of other exposure variables on the outcome. Odds ratios and 95% confidence intervals were generated for exposure variables entered into the models to understand their association with receipt of coronary angiography. The association between a single predictor variable and receipt of coronary angiography was deemed significant if the 95% confidence interval did not cross the null value of one and the p-value was less than 0.05. All tests were two-sided and all analyses were conducted using SAS (v 9.4 Cary, NC).

3.8 Objective 2

The primary objective was to determine the association between receipt of coronary angiography and survival to hospital discharge with favorable neurologic outcome overall, and in patients with and without STEMI. The secondary objective was to examine the association between PCI and survival to hospital discharge with favorable neurologic outcome overall, and in patients with and without STEMI. Survival to hospital discharge was examined as a secondary outcome for both objectives.

3.8.1 Exposure Variables

Primary:

The primary exposure of interest was receipt of coronary angiography (yes, no) within 72 hours of emergency department arrival.
Secondary:

The secondary exposure of interest was receipt of percutaneous coronary intervention (PCI) (yes, no), within 72 hours of emergency department arrival.

3.8.2 Outcome Variables

Primary:

The primary outcome of interest was survival with favorable neurologic outcome (yes, no). Favorable neurologic outcome was defined as a Modified Rankin Scale (MRS) score of 0-2 and unfavorable neurologic outcome was defined as a MRS score of 3-5 or deceased (refer to Appendix C). This was chosen as the primary outcome because the purpose of post-cardiac arrest care is to discharge patients with pre-arrest functional status.16,114

Secondary:

The secondary outcome of interest was survival to hospital discharge (yes, no).

3.8.3 Hypotheses

1. There will be a positive association between receipt of coronary angiography and survival with favorable neurologic outcome overall, and in patients with and without STEMI on the first in-hospital post-arrest ECG.

2. There will be a positive association between receipt of coronary angiography and survival to hospital discharge overall, and in patients with and without STEMI on the first in-hospital post-arrest ECG.

3. In the secondary analysis, it is expected that PCI will be positively associated with survival to hospital discharge and survival with favorable neurologic outcome overall, and in both patients with and without STEMI.
3.8.4 Covariates

The covariates that will be discussed were adjusted for in several other studies, which examined the association between coronary angiography or PCI, and survival outcomes.12,13,19,22,23,26,28,33 None of the identified prehospital or in-hospital covariates have the potential to be on the causal pathway between exposures and outcomes. All of the following covariates identified from the literature were included in all primary adjusted models, regardless of statistical significance.

3.8.4.1 Prehospital Factors

Pre-hospital factors that have the potential to confound the association between receipt of coronary angiography and survival with favorable neurologic outcome or survival to hospital discharge include bystander CPR, bystander defibrillation (AED), whether or not the arrest was witnessed, time between initiation of CPR and return of spontaneous circulation (ROSC), prehospital ROSC, location of arrest (public/private), initial cardiac rhythm, age and sex. These factors have been demonstrated in the literature to be independently associated with survival to hospital discharge and survival with favorable neurologic outcome. They also have the potential to be independently associated with receipt of coronary angiography and PCI (see Sections 2.5.1 and 2.5.2). Physicians generally associate receipt of bystander CPR or bystander defibrillation, prehospital ROSC, a shorter EMS response time, shockable initial cardiac rhythm and younger age with a more positive prognosis.40,49,125,126 A patient who is believed to have a better prognosis, may be more likely to receive aggressive treatments, such as coronary angiography, and PCI.

Age: Numerous studies have demonstrated that OHCA patients who are younger are more likely to survive.8,12,32,35,42,57,78,87,127 Perhaps the strongest evidence for the association between age and survival in OHCA patients comes from a meta-analysis composed of 14 studies. The investigators found that increasing age was associated with a lower likelihood of survival.127 Likewise, Hosmane and colleagues (2009) found that for every five year increase in patient age, the odds of mortality increased by 34%.32
Two other studies demonstrated that age under 70 and age under 60 were strongly associated with long-term survival and neurologically intact survival, respectively, in OHCA patients.42,57

Both the likelihood ratio test, and the non-parametric Loess smoother demonstrated that the associations between age and survival outcomes were strongly non-linear (see Appendix E). For this reason, modeling age as a single linear continuous variable resulted in a poor model fit and inadequate adjustment. Therefore, age was modeled using a natural cubic spline with three equally spaced knots. This approach resulted in a better model fit and only added one additional degree of freedom to the model.

Sex: Results from studies investigating the association between gender and survival after OHCA are conflicting.128 However, Karlsson et al. (2015) found that male OHCA patients were more likely to survive to hospital discharge than female OHCA patients (OR=1.34, CI95 1.01-1.78.128 Other studies have demonstrated similar findings.8,32,51,78 In fact, Hosmane and associates (2009) found that the odds of dying for female OHCA patients were nearly six times greater than the odds for male patients in the adjusted analysis.32

Witnessed arrest: Studies have demonstrated that patients who suffered from an OHCA that was witnessed by a bystander are more likely to survive.3,40,49,78,79 In fact, in a meta-analysis including 79 studies and 143,000 OHCA patients, those with bystander or EMS witnessed arrest were more likely to survive to hospital discharge.40 Stiell and associates (2004) found that OHCA patients whose arrest was witnessed by a bystander had 4.4 times the odds of surviving to hospital discharge than patients whose arrest was not witnessed.3 Liu et al. (2008) also demonstrated that OHCA patients who had a witnessed arrest in a public location, had a greater odds of survival to hospital discharge.78

Location of Arrest (public, private): Eisenburger and colleagues (2006) found that OHCA patients who had a cardiac arrest in a public location had better outcomes.77 These patients were more likely to be alive upon hospital admission and to have good neurological function six months post-cardiac arrest. In other
studies, having a witnessed arrest in a public location was found to be associated with greater odds of survival to hospital discharge in OHCA patients in general,\textsuperscript{49,78,79} as well as in OHCA patients with STEMI.\textsuperscript{37}

\textit{Bystander Resuscitation:} A meta-analysis including nearly 143,000 OHCA patients demonstrated that survival to hospital discharge was higher for patients who received bystander CPR.\textsuperscript{40} Several other researchers also found that OHCA patients who received bystander CPR had significantly greater odds of survival to hospital discharge than those who did not.\textsuperscript{3,49,78,79} Stiell et al. (2004) found that the odds of surviving to hospital discharge were 3.7 times higher for OHCA patients who received bystander CPR than those who did not.\textsuperscript{3}

\textit{EMS response time:} Many studies have established that a shorter EMS response time or shorter time to resuscitation are associated with better survival rates.\textsuperscript{10,12,32,33,35,68,79} For instance, Garot and colleagues (2007) found that survival at six months post-arrest was higher in OHCA patients who were responded to more quickly by an EMS team member.\textsuperscript{68} Presumably, if EMS response time is longer, the time to initiation of resuscitative therapies will also be longer. Anyfantakis et al. (2009) found that the only predictor of hospital death in the adjusted analysis was an interval greater than ten minutes between cardiac arrest and return of spontaneous circulation (ROSC) (OR=14.6, CI\textsubscript{95} = 3.3-63.5).\textsuperscript{35} Likewise, Dumas et al. (2010) demonstrated that an interval between onset of cardiac arrest and basic life support of greater than five minutes was associated with a worse prognosis.\textsuperscript{12}

\textit{Prehospital ROSC:} Wampler and colleagues (2012) demonstrated a very strong association between prehospital ROSC and survival to hospital discharge in nearly 2,500 OHCA patients.\textsuperscript{81} Of the patients who achieved field ROSC, survival to hospital discharge was 17.2%, while only 0.69% of patients who did not achieve field ROSC survived. The meta-analysis including nearly 150,000 OHCA patients also
demonstrated that patients who achieved prehospital ROSC were more likely to survive to hospital discharge.\textsuperscript{40}

\textit{Initial cardiac rhythm:} A multitude of studies have identified that OHCA patients with ventricular fibrillation or ventricular tachycardia have better outcomes than patients with pulseless electrical activity (PEA) or asystole. In the large, previously mentioned meta-analysis, OHCA patients with ventricular fibrillation or ventricular tachycardia were more likely to survive to hospital discharge than patients with non-shockable rhythms\textsuperscript{40} Additional individual studies found that OHCA patients with shockable initial cardiac rhythms were more likely to survive to 24 hours,\textsuperscript{42} to hospital discharge,\textsuperscript{12,33,79} with good neurologic function,\textsuperscript{42} and to have higher rates of long-term survival.\textsuperscript{37} Herlitz and colleagues (2005) found that OHCA patients with ventricular fibrillation (i.e. shockable rhythm) had survival to hospital discharge rates more than five times higher than patients with non-shockable rhythms.\textsuperscript{79}

3.8.4.2 In-hospital Factors

In-hospital factors that have the potential to confound the relationships of interest include initial neurologic status, ECG findings (STEMI, other), initiation of therapeutic hypothermia, presentation during business hours, treatment at a PCI center, hospital cardiac arrest volume, academic status of hospital, and hospital size. Previous work has found that these factors are independently associated with survival and/or survival with favorable neurologic outcome. They also have the potential to be independently associated with receipt of coronary angiography and PCI (Refer to Section 2.5.1 and 2.6). For instance, studies have shown that patients with poor initial neurologic status are less likely to receive aggressive treatment such as coronary angiography and PCI\textsuperscript{13,31} because they are viewed as having a poor prognosis by attending physicians.\textsuperscript{60–71} Furthermore, OHCA patients who do not demonstrate STEMI on the post-arrest ECG are unlikely to receive coronary angiography\textsuperscript{13,19,20,23} and patients admitted to PCI centers may be more likely to receive coronary angiography and PCI than patients admitted to non-PCI centers.\textsuperscript{55,56,88}
Initial neurologic status: Several studies have found that worse outcomes for OHCA patients are positively associated with decreased levels of consciousness post-cardiac arrest. The most compelling evidence comes from a study performed by Hosmane and colleagues (2009). The adjusted analysis demonstrated that OHCA patients who were comatose at the time of coronary angiography had 47 times the odds of dying compared to conscious patients, and nearly 19 times the odds of having neurologic impairment.

ECG findings: Patients who demonstrate ST-segment elevation on the post-cardiac arrest ECG may have higher survival rates than patients with other ECG patterns. Pleskot and colleagues (2009) found that nearly 60% of OHCA patients with STEMI survived one year and about 54% survived three years, compared to 22% and 19.5% of patients without STEMI surviving to one year and three years, respectively. Patients with STEMI after cardiac arrest are viewed as clinically different from those without STEMI, in terms of cause of arrest, treatment course, and prognosis.

Therapeutic Hypothermia: Two large randomized controlled trials indicated that therapeutic hypothermia improved survival with favorable neurologic outcome and decreased mortality rates for OHCA cardiac arrest patients. In fact, mainly as a result of these trials, the AHA guidelines now recommend therapeutic hypothermia for comatose OHCA in an effort to improve patient outcomes (Class I, Level of Evidence B). Arrich and colleagues (2009) conducted a meta-analysis of randomized controlled trials investigating the benefit of therapeutic hypothermia in OHCA patients. They found that survival to hospital discharge (RR=1.35, CI95 1.10-1.65) and survival with favorable neurologic outcome (CPC 1 or 2) (RR=1.55, CI95 1.22-1.96) were higher among the patients who received therapeutic hypothermia than among those who did not.

Presentation during business hours: Stub et al. (2011) provided compelling evidence that OHCA patients who arrive to a hospital during the day have better outcomes. They performed a study that included
nearly 3000 OHCA patients admitted to 70 hospitals, and found that OHCA patients who were admitted to a hospital between 8am and 5pm were more likely to survive to hospital discharge (OR=1.34, p=0.004). Similarly, Lairez et al. (2009) demonstrated that hospitalized patients who received emergency PCI during night hours (12am-4am) or during weekend daytime hours had greater odds of mortality than patients who received PCI during weekday daytime hours. Martinez et al. (2012) summarized the evidence relating to factors associated with survival after cardiac arrest, and showed that having an arrest between midnight and 6am was associated with the lowest chance of survival.

**Hospital cardiac arrest volume:** Callaway and colleagues (2014) found that as the number of cardiac arrest patients treated at a hospital per year increased by five, the odds of survival to hospital discharge and survival with favorable functional status increased (OR=1.06, 95%CI 1.04-1.08). Other investigators found that adjusted survival rates are better in patients treated at hospitals which admit more than 50 cardiac arrest patients per year compared to hospitals which admit fewer than 20 cardiac arrests per year. Ro and colleagues (2012) found that adjusted odds of survival to hospital discharge were 2.5 times higher for cardiac arrest patients admitted to high volume centers compared to low volume centers.

**Hospital Size (number of beds):** In a national US study including nearly 110,000 OHCA patients admitted to many hospitals, Carr et al. (2009) found a significant association between size of hospital and in-hospital mortality, such that mortality was lower for patients admitted to larger hospitals (OR=0.55, p<.0001).

**Hospital Type:** Carr and colleagues (2009) demonstrated a significant association between mortality and hospital teaching status such that mortality was lower for OHCA patients admitted to teaching hospitals (OR=0.58, p<.0001). Other studies have demonstrated that OHCA patients treated at specialized centers have better outcomes. For instance, Kajino et al. (2010) studied more than 10,000 OHCA patients
and found that those who were transported to Critical Care Medical Centers (CCMCs) were more likely to survive to one-month post-hospital discharge with favorable neurologic status than those transported to non-critical care centers. Other investigators found that OHCA patients treated at Cardiac Receiving Centers, which provide comprehensive, guideline-based post-resuscitation care and 24/7 cardiac catheterization services, are more likely to survive to hospital discharge.

**PCI Center:** PCI capability is an important hospital feature that may improve survival for OHCA patients. Stub et al. (2011) performed a study that included nearly 3000 OHCA patients admitted to 70 hospitals and found that being treated at a hospital that had 24-hour cardiac interventional services was associated with survival to hospital discharge (OR=1.40, 95% CI 1.12-1.74). In another study, the results of the adjusted analysis demonstrated that OHCA patients initially admitted to PCI centers had more than three times the odds of surviving with favorable neurologic function (OR 3.14, 95% CI 1.51 – 6.56) and more than 2 times the odds of surviving to hospital discharge (OR=2.39, 95% CI 1.33-4.28) than patients admitted to non-PCI centers. Refer to Figure 5 for a review of confounders that were adjusted for in the primary models.
3.8.5 Effect Modifiers

We suspected that STEMI status, initial neurologic status, and whether or not the patient was initially admitted to a hospital with PCI capability, had the potential to be effect modifiers. Therefore, overall models were built, and then separate models were built by 1) STEMI status 2) initial neurologic status and 3) initial admission to a PCI center.
3.8.5.1 STEMI Status

It is well established that OHCA patients with STEMI are more likely to have an occluded coronary artery than patients without STEMI.\textsuperscript{10,12,23,35,69,96,97} Recent AHA, ACC and ILCOR guidelines recommend coronary angiography, followed by PCI as the preferred method of reperfusion for OHCA patients with STEMI.\textsuperscript{16,18,24} There is a general consensus among clinicians that prompt coronary angiography should be considered for OHCA patients with STEMI on the first post-arrest ECG.\textsuperscript{13,14,16,18,24,73}

On the contrary, there is considerable confusion regarding how to treat OHCA patients without STEMI.\textsuperscript{12–14,20,26,35–37,66} These patients are rarely sent for coronary angiography, as they are considered less likely to have an occluded coronary artery.\textsuperscript{12,13,19,23,35,37,97} Since OHCA patients with and without STEMI on the post-arrest ECG, are viewed as clinically distinct patient groups and treated as such, the associations between coronary angiography and survival outcomes are likely to differ between groups.

3.8.5.2 Initial Neurologic Status

Out-of-hospital cardiac arrest patients who are initially comatose are less likely to receive coronary angiography than those who are conscious.\textsuperscript{7,13,16,18,26,29,31} Comatose OHCA patients also tend to be given a poorer prognosis\textsuperscript{34,69} and to have poorer outcomes.\textsuperscript{31–33,51} There is uncertainty in clinical practice regarding whether comatose OHCA patients should receive coronary angiography\textsuperscript{7,11,20,26,32} and findings from studies investigating the benefit of coronary angiography and PCI in comatose OHCA survivors have conflicted.\textsuperscript{7,11,26,31,32,101,102} It will be beneficial to study the initially comatose subgroup of patients separately, to attempt to rectify these conflicting findings, and to provide recommendations for the clinical setting.

3.8.5.3 PCI Center Admission

In OHCA patients, there is variability in rates of survival to hospital discharge between hospitals, after adjusting for prehospital factors that may influence outcomes.\textsuperscript{55,86–89} Studies have demonstrated that
survival rates are higher in OHCA patients who are initially transported to hospitals equipped with cardiac catheterization facilities (i.e. PCI centers). The variability in survival may be due to disparities in provision of important post-resuscitation treatments, such as coronary angiography between PCI centers and non-PCI centers.

If the results of coronary angiography indicate coronary artery occlusion, the primary treatment option is PCI. A patient who initially arrives to PCI center may be more likely to receive coronary angiography because the treatment option (i.e. PCI) is accessible and readily available. On the other hand, patients initially admitted to non-PCI centers must be transported to receive PCI, which may be a complicated and potentially risky process. Taking into consideration the potential variability in both patient care and outcomes between PCI centers and non-PCI centers, there is reason to suspect that the associations of interest may differ between these types of hospitals.

3.8.6 Statistical Analysis

Multilevel logistic regression was employed (PROC GLIMMIX v 9.4, Cary, NC) using ‘hospital’ as a random factor, in order to determine the association between the exposures and outcomes of interest. The multilevel analysis strategy was used to account for clustering by hospital, which is the potential for patients treated at one hospital to have more similar exposures and outcomes than patients treated at another hospital. Patient-level and hospital-level data were considered fixed effects in all models.

First, empty regression models were developed with hospital as the only predictor variable. Building the null model was used to assess the degree of heterogeneity in patient outcomes across hospitals. Intraclass correlation coefficients (ICCs) were calculated. Next, unadjusted multilevel logistic regression models were developed to determine the crude association between exposures, and outcomes of interest. Models were then developed that included all the pre-selected covariates of interest, in order to determine the association between exposures and outcomes, while adjusting for covariates.
For the primary models, a priori selection of covariates based on the literature was used to select covariates, rather than model selection because we believed that the sample size was large enough to support a model that included all pre-selected covariates. In secondary models, we adjusted for a smaller set of covariates that were identified via expert opinion, to be important confounders of the relationships investigated. Tertiary models were built using backward stepwise selection, which resulted in an even smaller set of covariates to adjust for, and enabled identification of the most significant confounders of the associations.

Odds ratios and 95% confidence intervals were generated for exposure variables and covariates, to understand their association with survival to hospital discharge and survival with favorable neurologic outcome. The association between a variable and an outcome was deemed significant if the 95% confidence interval did not cross the null value of one, and the p-value was less than 0.05. All tests were two-sided and all analyses were conducted using SAS (v 9.4 Cary, NC).

3.8.6.1 Modeling Strategies

Three different types of models were built, with each model including a different set of covariates;

1) The primary models included all pre-specified covariates of interest identified from a review of the literature. These included age, sex, initial cardiac rhythm, initial neurologic status, STEMI status, initiation of therapeutic hypothermia, location of arrest, presentation during business hours, prehospital ROSC, EMS response time, bystander resuscitation, bystander AED use, bystander CPR, bystander witnessed arrest, EMS witnessed arrest. Hospital-level variables included hospital type (i.e. Academic Health Science Center), PCI center status, hospital size, and annual cardiac arrest volume. This model was chosen a priori to be the primary model because the large sample size for this study enabled adjustment for a large number of potential confounders.

2) The secondary models included covariates identified, via expert opinion, to be clinically important to adjust for. These included age, sex, initial cardiac rhythm, initial neurologic status, initiation of
therapeutic hypothermia, STEMI status, prehospital ROSC, bystander resuscitation, bystander witnessed arrest, EMS witnessed arrest, and PCI center status.

3) The tertiary models were developed using backward stepwise selection. Each covariate was excluded one at a time from the primary adjusted model, which included all covariates identified in the literature as important to adjust for. A variable was removed from the model if removing it resulted in the smallest percent change in the odds ratio for coronary angiography, and the change was less than 10%. Models differed according to associations being examined.

3.8.6.2 Power Considerations

For all power calculations, the alpha level was set to 0.05 (two-sided test) and the minimal power that we were willing to accept was 80%. Power calculations were performed manually using a standard formula to calculate power for two binomial proportions using a two-sided test with a significance level of alpha, and sample sizes of \( n_1 \) and \( n_2 \).\(^{130}\) It is important to examine the difference in survival with favorable neurologic outcome that would be considered the minimal clinically significant difference, however this is often difficult to ascertain. Therefore, power calculations were performed across a range of differences from 5% to 20% and a range of design effects from 1.0 to 2.0.\(^{131}\) Refer to Appendix F for details on the design effect.

First, we determined if we would have adequate power to examine the association between coronary angiography and survival with favorable neurologic outcome, as well as coronary angiography and survival to hospital discharge. We found that the power was greater than 80% to detect a 10% or greater difference in survival with favorable neurologic outcome and survival to hospital discharge, between patients who received coronary angiography and those who did not, at design effects ranging from one to two. Power calculations with PCI as the exposure, and power calculations in subgroups of patients with and without STEMI can be found in Appendix F.
3.8.6.3 Subgroup Analyses

Subgroup analyses were conducted by STEMI status. Exposures were coronary angiography and PCI and outcomes were survival with favorable neurologic outcome and survival to hospital discharge. Subgroup analyses were also conducted by initial neurologic status and by initial admission to a PCI center. For these analyses, coronary angiography was the exposure and survival with favorable neurologic outcome and survival to hospital discharge were the outcomes.

Multilevel logistic regression was employed (PROC GLIMMIX v 9.4, Cary, NC) using ‘hospital’ as a random factor in all models. Unadjusted multilevel models were developed to determine the crude association between coronary angiography or PCI and survival outcomes in subgroups of patients. Next, models were developed that included either all the pre-selected covariates of interest or covariates identified to be clinically important to adjust for, in order to determine the associations between exposures and outcomes, while adjusting for covariates.

Odds ratios and 95% confidence intervals were generated to determine the associations between coronary angiography or PCI and survival outcomes in subgroups of OHCA patients. The independent association between an exposure variable and an outcome variable was deemed significant if the 95% confidence interval did not cross the null value of one and the p-value was less than 0.05.
Chapter 4

Results

4.1 Eligible patients

From March 1\textsuperscript{st}, 2010 to December 31\textsuperscript{st}, 2014, there were 33,637 out-of-hospital cardiac arrest (OHCA) patients in the Rescu Epistry database. There were 177 cases, which were incomplete and were excluded. Of the complete cases, those patients who were not treated by EMS (n=14,426), since they were dead at the scene, were excluded. Of the 19,034 OHCA patients who were treated by EMS, 8846 individuals had resuscitation terminated in the field, and thus were excluded. Therefore 10,188 patients were transported to a hospital alive, however 1716 patients were excluded because they were not admitted to one of the 28 participating hospitals. Of the 8472 patients who were admitted alive to a participating hospital, 121 were excluded due to a pre-existing Do-Not-Resuscitate (DNR) order. Meanwhile, 323 patients who were under the age of 18 or whose age was unknown were excluded, as well as 1231 patients who had an obvious non-cardiac cause of arrest, 3411 patients who did not have sustained ROSC for more than twenty minutes in the emergency department (ED) and 668 patients who did not survive for at least six hours following initial ED arrival. After these exclusions were applied, there were 2718 eligible patients remaining, however, patients with unrecorded STEMI status (n=140) also had to be excluded, resulting in 2578 OHCA patients who were eligible for the study. Please see Figure 6 for a flow diagram of included and excluded patients.
48,096 patients in Epistry database

33,637 patients had arrest after March 1, 2010

14,459 patients had arrest prior to March 1, 2010

177 cases incomplete

14,426 not treated by EMS since dead at scene

8846 had resuscitation terminated in the field

19,034 treated by EMS

14,426 not treated by EMS since dead at scene

1716 not admitted to participating Epistry hospital

10,188 transported to a hospital

8472 admitted to participating Epistry hospital

3386 had sustained ROSC ≥20 minutes in ED

Excluded (n=5086) ➔ prehospital DNR (n=121) ➔ <18 years of age or age missing (n=323) ➔ obvious non-cardiac cause (n=1231) ➔ did not have ROSC ≥ 20 mins in ED (n=3411)

2718 survived for at least 6 hours

2578 patients eligible for study

668 did not survive for at least 6 hours

140 had missing STEMI status

Figure 6. Consort diagram
4.2 Description of Study Population

4.2.1 Patient and Cardiac Arrest Characteristics

Refer to Table 3 for an overview of descriptive statistics for the study population. The study population was predominantly male (69%) and the average age of a patient was 67 (+/- 15). Slightly more than half of the patients had their arrest witnessed by a bystander (54%), whereas 20% had their arrest witnessed by EMS. Nearly half of the study population had bystander resuscitation (43%), with bystander CPR being more common (35%) than bystander AED use (6%). The minority of the population had their arrest in a public location (27%) and it took approximately six minutes for EMS to respond to a cardiac arrest. Almost half of the population had a shockable initial cardiac rhythm (ventricular fibrillation or ventricular tachycardia) and the majority of patients achieved prehospital return of spontaneous circulation (ROSC) (89%) and had a pulse present upon arrival to the hospital emergency department (79%). However, most patients were in a coma upon hospital arrival (84%) and 34% arrived during business hours (9am-5pm Monday to Friday). The initial post-arrest ECG finding was STEMI for 31% of patients.
Table 3. Patient and cardiac arrest characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=2578 (28 hospitals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1772 (69%)</td>
</tr>
<tr>
<td>Age (years), mean (±SD)</td>
<td>67 (± 15)</td>
</tr>
<tr>
<td>Bystander witnessed arrest</td>
<td>1399 (54%)</td>
</tr>
<tr>
<td>EMS-witnessed arrest</td>
<td>516 (20%)</td>
</tr>
<tr>
<td>Bystander resuscitation</td>
<td>1099 (43%)</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>912 (35%)</td>
</tr>
<tr>
<td>Bystander AED use</td>
<td>154 (6%)</td>
</tr>
<tr>
<td>Public location</td>
<td>707 (27%)</td>
</tr>
<tr>
<td>EMS response time (minutes), mean (±SD)</td>
<td>6.25 (±2.71) (n=2419)</td>
</tr>
<tr>
<td>Prehospital ROSC</td>
<td>2295(89%)</td>
</tr>
<tr>
<td>Shockable initial rhythm</td>
<td>1219/2463 (49%)</td>
</tr>
<tr>
<td>Presentation during business hours</td>
<td>872 (34%)</td>
</tr>
</tbody>
</table>

**Emergency department status**

- Pulse present                      | 2035 (79%)             |
- Ongoing resuscitation               | 528 (20%)              |
- Unknown                              | 15 (0.6%)              |
| Coma at ED arrival                   | 2164 (84%)             |
| STEMI                                 | 799 (31%)              |

*Denominators represent the number of patients who had data available for the variable

4.2.2 Comorbidities

The proportion of patients with a variety of prior medical conditions and a history of cardiac disease were examined and summarized in Table 4. A significant proportion of patients had a history of cardiac disease (45%), and high blood pressure (52%) and a considerable proportion had a history of myocardial infarction (24%), coronary artery disease (27%), diabetes (28%) and respiratory conditions (21%). Thirty-five percent of the population was taking cardiac medications. These data provide a view of the health status of the population in general. However, these variables were not used in further analyses, as there were issues concerning completeness and quality of the comorbidity variables. Further discussion of this limitation is provided in Chapter 5.
### Table 4. Patient comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>N=2578 (28 hospitals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of myocardial infarction</td>
<td>606 (24%)</td>
</tr>
<tr>
<td>History of coronary artery bypass grafting (CABG)</td>
<td>236 (9%)</td>
</tr>
<tr>
<td>History of coronary artery disease (CAD)</td>
<td>708 (27%)</td>
</tr>
<tr>
<td>History of cardiac disease</td>
<td>1156 (45%)</td>
</tr>
<tr>
<td>History of chest pain</td>
<td>145 (6%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>165 (6%)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>222 (9%)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>355 (14%)</td>
</tr>
<tr>
<td>Cardiac medications</td>
<td>899 (35%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>260 (10%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>316 (12%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>727 (28%)</td>
</tr>
<tr>
<td>Heart surgery</td>
<td>265 (10%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1336 (52%)</td>
</tr>
<tr>
<td>Implantable cardioverter defibrillator (ICD)</td>
<td>40 (2%)</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>75 (3%)</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>252 (10%)</td>
</tr>
<tr>
<td>Recreational drug use</td>
<td>132 (5%)</td>
</tr>
<tr>
<td>Respiratory condition</td>
<td>535 (21%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>101 (4%)</td>
</tr>
<tr>
<td>Stroke/Transient Ischemic Attack</td>
<td>229 (9%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>82 (3%)</td>
</tr>
</tbody>
</table>

### 4.2.3 Hospital Characteristics

Selected hospital characteristics of the 28 hospitals were examined and the results are reported in Table 5. Six of the 28 hospitals were considered to be PCI centers and six hospitals were classified as Academic Health Science Centers. Three of the six hospitals were both PCI centers and Academic Health Science Centers (see Table 2). About one third of the study population was initially transported to a PCI center (34%) and about one quarter to an Academic Health Science Center (23%). There were an average...
of 330 acute care beds in a participating hospital, and an average of 88 cardiac arrests per year.

Approximately equal proportions of patients were admitted to large, medium and small hospitals.

Table 5. Hospital characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=28 hospitals</th>
<th>N=2578 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI center</td>
<td>6 (21%)</td>
<td>871 (34%)</td>
</tr>
<tr>
<td>Academic Health Science Center</td>
<td>6 (21%)</td>
<td>591 (23%)</td>
</tr>
<tr>
<td>Hospital size (acute care beds), mean (+/- SD)</td>
<td>330 (±146)</td>
<td></td>
</tr>
</tbody>
</table>

Hospital size (acute care beds)

- Large: 5 (18%) 929 (36%)
- Medium: 9 (32%) 838 (33%)
- Small: 14 (50%) 811 (31%)

Cardiac arrest volume, mean (+/- SD) 88 (±40) 

4.2.4 Interventions

Descriptive statistics on patient interventions are displayed in Table 6. Approximately 33% of the study population received coronary angiography, with the majority of patients receiving early coronary angiography (29%) than later coronary angiography (4%). Refer to Appendix G for the proportion of patients initially admitted to each hospital, who received coronary angiography and PCI. Twenty-three percent of patients received PCI and 3% received coronary artery bypass grafting (CABG). The majority of the population had therapeutic hypothermia initiated (64%).
Table 6. Patient interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>N=2578 (28 hospitals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary angiography</td>
<td>863 (33%)</td>
</tr>
<tr>
<td>Coronary angiography (early before 24 hours)</td>
<td>761 (29%)</td>
</tr>
<tr>
<td>Coronary angiography (later 24 ≥ 72 hours)</td>
<td>102 (4%)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention (PCI)</td>
<td>581 (23%)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting (CABG)</td>
<td>68 (3%)</td>
</tr>
<tr>
<td>Therapeutic hypothermia initiated</td>
<td>1653 (64%)</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>1434 (56%)</td>
</tr>
<tr>
<td>Fibrinolytic drugs</td>
<td>166 (6%)</td>
</tr>
<tr>
<td>Inotropic drugs (epinephrine)</td>
<td>1639 (64%)</td>
</tr>
<tr>
<td>Inotropic drugs (dopamine)</td>
<td>282 (13%)</td>
</tr>
</tbody>
</table>

4.2.5 Outcomes

The proportions of patients achieving favorable outcomes throughout the study period are displayed in Table 7. Overall, 42% of the patient population survived to hospital discharge and 38% of patients survived with favorable neurologic outcome, defined as having an MRS score of zero to two. If CPC scores are used to indicate neurologic outcome instead, 39% of the population survived with favorable neurologic outcome (CPC 1 or 2). In our study, overall survival to hospital discharge progressively increased in small increments from 2010 to 2013, and decreased slightly from 2013 and 2014. There was a general trend toward increasing survival with favorable neurologic outcome over the years of the study. Since this study used data beginning March 2010, data from the months of January and February of 2010 were not included in these statistics, which explains the smaller sample size in 2010. Survival to hospital discharge and survival to hospital discharge with favorable neurologic outcome are plotted in Figure 7.
### Table 7. Patient survival outcomes (2010-2014)

<table>
<thead>
<tr>
<th>Year</th>
<th>Survival to Hospital Discharge</th>
<th>Survival to Hospital Discharge with Favorable Neurologic Outcome (MRS 0-2)</th>
<th>Proportion of Survivors Discharged with Favorable Neurologic Outcome (MRS 0-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>144/363 (40%)</td>
<td>124/355 (35%)</td>
<td>124/144 (86%)</td>
</tr>
<tr>
<td>2011</td>
<td>190/476 (40%)</td>
<td>170/475 (36%)</td>
<td>170/190 (89%)</td>
</tr>
<tr>
<td>2012</td>
<td>242/568 (43%)</td>
<td>209/556 (37%)</td>
<td>209/242 (86%)</td>
</tr>
<tr>
<td>2013</td>
<td>259/593 (44%)</td>
<td>232/587 (40%)</td>
<td>232/259 (90%)</td>
</tr>
<tr>
<td>2014</td>
<td>247/578 (43%)</td>
<td>225/569 (40%)</td>
<td>225/247 (91%)</td>
</tr>
<tr>
<td>Entire study period</td>
<td>1082/2578 (42%)</td>
<td>960/2542 (38%)</td>
<td>960/1082 (89%)</td>
</tr>
</tbody>
</table>

#### Figure 7. Survival from 2010-2014

![Survival 2010-2014](image-url)
4.3 Missing Data

Variables used in the analyses, that had missing data were EMS response time (n=159), initial cardiac rhythm (n=115), and MRS score (n=26). These values were imputed using multiple imputation.\(^\text{123}\) Refer to Section 3.6.2 for a description of multiple imputation. Means and proportions of imputed variables were almost identical before and after imputation. Prior to multiple imputation, 49.5% of patients had a shockable cardiac rhythm, and after multiple imputation, 49.4% of patients had a shockable initial cardiac rhythm. Before imputation, 37.6% of patients had a favorable MRS score (0-2) and after imputation 37.7% of patients had a favorable MRS score. The mean EMS response time prior to imputation was 6.25 minutes and this value did not change after multiple imputation.

4.4 Objective 1

To quantify the association between patient demographic and cardiac arrest features, interventions, hospital characteristics and receipt of coronary angiography in a network of 28 hospitals across Southern Ontario.

4.4.1 Bivariate Analyses

The proportion of patients receiving coronary angiography varied markedly by first receiving hospital, ranging from 13% to 70%. The bivariate associations between each variable of interest and receipt of coronary angiography are displayed in Table 8. Nearly all the variables of interest were independently associated with coronary angiography. Patient characteristics that were associated with receiving coronary angiography in the unadjusted analyses included male sex and age. Cardiac arrest features associated with receiving coronary angiography included STEMI status, initial shockable cardiac rhythm, being conscious at hospital admission, having a bystander or EMS witnessed arrest, receiving bystander resuscitation, bystander CPR or bystander AED use, having prehospital ROSC, and a public location of arrest. In the unadjusted analyses, being admitted to a PCI center was associated with receiving coronary angiography. Patients admitted to large hospitals received coronary angiography more
often than those admitted to small hospitals, and patients admitted to medium hospitals received coronary angiography less often than those admitted to small hospitals. Odds ratios for average annual cardiac arrest volume are reported as the odds of receiving coronary angiography, per one unit increase in the number of cardiac arrest patients admitted to the hospital per year.

4.4.2 Empty Regression Model: Intraclass Correlation Coefficient

The intraclass correlation coefficient (ICC) was calculated from the empty regression model to quantify the amount of variability in receipt of coronary angiography that could be attributed to hospital-level factors. The ICC demonstrated that 10.5% of the variability in receipt of coronary angiography was attributed to the characteristics of the hospitals patients were initially admitted to. Since the ICC was greater than 0.05, multilevel logistic regression modeling was employed to account for clustering. Refer to Appendix H for intraclass correlation calculations.

4.4.3 Adjusted Analysis using Multilevel Logistic Regression

The final odds ratios from multilevel logistic regression model for the association between patient, cardiac arrest, intervention and hospital characteristics and receipt of coronary angiography are displayed in Table 8.

The most notable finding is that the adjusted odds ratio of receiving coronary angiography was over 22 times greater for patients with STEMI on the first post-arrest ECG, than for patients without STEMI (OR= 22.10, CI_{95} 16.67-29.29). In addition, patients who were conscious at hospital admission had more than six times the odds of receiving coronary angiography than patients who were comatose (OR=6.48, CI_{95} 4.16-10.1) and the odds of receiving coronary angiography was nearly five times greater for patients whose initial cardiac rhythm was shockable compared to non-shockable (OR=4.44, CI_{95} 3.32-5.95). Also, patients initially admitted to PCI centers had over three times the odds of receiving coronary angiography than those initially admitted to a non-PCI centers (OR= 3.29, CI_{95} 1.84-5.89).
For patients under the age of 55, the odds of receiving coronary angiography increased by 4% per year increase in patient age (OR=1.04, CI$_{95}$ 1.02-1.07). For patients above the age of 55, the odds of receiving coronary angiography decreased by 2% per year increase in patient age (OR=0.98, CI$_{95}$ 0.96-0.99). Other factors associated with receiving coronary angiography were bystander AED use (OR=1.93, CI$_{95}$ 1.13-3.28), EMS-witnessed arrest (OR=1.80, CI$_{95}$ 1.15-2.81), and initiation of therapeutic hypothermia (OR=1.88, CI$_{95}$ 1.31-2.70).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>p-value</th>
<th>Adjusted</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age under 55 (per year)</td>
<td>1.06(1.04-1.08)</td>
<td>&lt;.0001</td>
<td>1.04(1.02-1.07)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Age 55 and above (per year)</td>
<td>0.93(0.92-0.94)</td>
<td>&lt;.0001</td>
<td>0.98(0.96-0.99)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Male</td>
<td>2.53(2.07-3.10)</td>
<td>&lt;.0001</td>
<td>1.28(0.96-1.72)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Cardiac arrest features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial shockable cardiac rhythm</td>
<td>8.88(7.15-11.02)</td>
<td>&lt;.0001</td>
<td>4.44(3.32-5.95)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bystander witnessed arrest</td>
<td>1.44(1.21-1.70)</td>
<td>&lt;.0001</td>
<td>1.20(0.88-1.65)</td>
<td>0.26</td>
</tr>
<tr>
<td>EMS witnessed arrest</td>
<td>1.25(1.01-1.54)</td>
<td>0.04</td>
<td>1.80(1.15-2.81)</td>
<td>0.01</td>
</tr>
<tr>
<td>Bystander resuscitation</td>
<td>1.64(1.38-1.94)</td>
<td>&lt;.0001</td>
<td>1.24(0.75-2.05)</td>
<td>0.39</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>1.65(1.38-1.97)</td>
<td>&lt;.0001</td>
<td>0.97(0.59-1.57)</td>
<td>0.89</td>
</tr>
<tr>
<td>Bystander AED use</td>
<td>1.67(1.18-2.36)</td>
<td>0.004</td>
<td>1.93(1.13-3.28)</td>
<td>0.02</td>
</tr>
<tr>
<td>EMS response time (minutes)</td>
<td>0.98(0.95-1.01)</td>
<td>0.23</td>
<td>0.99(0.94-1.04)</td>
<td>0.72</td>
</tr>
<tr>
<td>Presentation during business hours</td>
<td>1.04(0.87-1.24)</td>
<td>0.68</td>
<td>1.22(0.93-1.60)</td>
<td>0.14</td>
</tr>
<tr>
<td>Public location of arrest</td>
<td>2.62(2.17-3.16)</td>
<td>&lt;.0001</td>
<td>1.09(0.81-1.48)</td>
<td>0.57</td>
</tr>
<tr>
<td>Prehospital ROSC</td>
<td>1.42(1.07-1.89)</td>
<td>0.02</td>
<td>1.34(0.89-2.02)</td>
<td>0.16</td>
</tr>
<tr>
<td>Comatose</td>
<td>0.22(0.18-0.28)</td>
<td>&lt;.0001</td>
<td>0.15(0.10-0.24)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>STEMI status</td>
<td>26.33(20.75-33.42)</td>
<td>&lt;.0001</td>
<td>22.10(16.67-29.29)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Initiation of therapeutic hypothermia</td>
<td>0.89(0.74-1.06)</td>
<td>0.19</td>
<td>1.88(1.31-2.70)</td>
<td>0.0006</td>
</tr>
<tr>
<td><strong>Hospital characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average annual cardiac arrest volume</td>
<td>1.00(0.99-1.01)</td>
<td>0.94</td>
<td>1.00(0.99-1.01)</td>
<td>0.71</td>
</tr>
<tr>
<td>Hospital size (large) vs. small</td>
<td>2.30(1.40-3.79)</td>
<td>0.002</td>
<td>1.30(0.41-4.10)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hospital size (medium) vs. small</td>
<td>0.48(0.29-0.80)</td>
<td>0.006</td>
<td>0.61(0.30-1.25)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hospital type (i.e. Academic Health Science Center)</td>
<td>1.38(0.72-2.62)</td>
<td>0.32</td>
<td>0.58(0.23-1.50)</td>
<td>0.26</td>
</tr>
<tr>
<td>PCI center</td>
<td>3.65(2.56-5.18)</td>
<td>&lt;.0001</td>
<td>3.29(1.84-5.89)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*Adjusted model included all the variables in the table. The variables were identified a priori from the literature to potentially be associated with receipt of coronary angiography.

*Age was a single continuous variable that was divided into two continuous variables (age < 55 and age ≥ 55)
### 4.4.4 Bivariate versus Multivariate Findings

Variables that were significantly associated with receiving coronary angiography in the bivariate analysis that were no longer associated with receiving coronary angiography in the multivariate analysis were sex, bystander witnessed arrest, bystander resuscitation, bystander CPR, location of arrest, prehospital ROSC, and hospital size. Interestingly, initiation of therapeutic hypothermia was not associated with receiving coronary angiography in the bivariate analysis, however it was in the adjusted analysis.

### 4.5 Objective 2

To examine the association between receipt of coronary angiography (primary exposure of interest) and survival with favorable neurologic outcome overall, and in patients with and without STEMI. Survival to hospital discharge was examined as a secondary outcome.

### 4.5.1 Description of Study Population by Coronary Angiography

#### 4.5.1.1 Hospital Characteristics

Hospital characteristics were compared between patients who received coronary angiography (n=863) and those who did not (n=1715). Please refer to Table 9 for a summary. Compared to patients who did not receive coronary angiography, patients who did receive the intervention tended to be much more likely to have been initially admitted to PCI centers (51% versus 25%) and large hospitals (50% versus 29%). They were slightly more likely to have been initially admitted to Academic Health Science Centers (26% versus 21%), and hospitals with higher cardiac arrest volumes (94 versus 86 arrests per year).
Table 9. Hospital characteristics by receipt of coronary angiography

<table>
<thead>
<tr>
<th>Hospital characteristic</th>
<th>Received coronary angiography (N=863)</th>
<th>Did not receive coronary angiography (N=1715)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted to PCI center</td>
<td>443 (51.3%)</td>
<td>428 (25.0%)</td>
</tr>
<tr>
<td>Admitted to Academic Health Science Center</td>
<td>229 (26.5%)</td>
<td>362 (21.1%)</td>
</tr>
<tr>
<td>Hospital size (average number of acute care beds)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Large</td>
<td>436 (50.5%)</td>
<td>493 (28.7%)</td>
</tr>
<tr>
<td>- Medium</td>
<td>180 (20.9%)</td>
<td>658 (38.4%)</td>
</tr>
<tr>
<td>- Small</td>
<td>247 (28.6%)</td>
<td>564 (32.9%)</td>
</tr>
<tr>
<td>Average annual cardiac arrest volume</td>
<td>94 (+/-44)</td>
<td>86 (+/-37)</td>
</tr>
</tbody>
</table>

4.5.1.2 Patient and Cardiac Arrest Characteristics

Please refer to Table 10 for a comparison of patient and cardiac arrest characteristics by receipt of coronary angiography. Compared to patients who did not receive coronary angiography, those who received coronary angiography were much more likely to have STEMI (72% versus 10%) and an initial shockable cardiac rhythm (84% versus 33%). They were also more likely to be male (81% versus 63%), to have had a bystander witnessed arrest (60% versus 51%), bystander resuscitation (51% versus 39%), and an arrest in a public location (42% versus 20%). Patients who did not receive coronary angiography were more likely to be older (69 versus 62), and to be in a coma at hospital admission (91% versus 69%).
<table>
<thead>
<tr>
<th>Patient or cardiac arrest characteristic</th>
<th>Coronary angiography (N=863)</th>
<th>No coronary angiography (N=1715)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>696(80.6%)</td>
<td>1076(62.7%)</td>
</tr>
<tr>
<td>Age (years), mean (±SD)</td>
<td>62(+/-13)</td>
<td>69(+/-16)</td>
</tr>
<tr>
<td>Bystander witnessed arrest</td>
<td>518(60.0%)</td>
<td>881(51.4%)</td>
</tr>
<tr>
<td>EMS-witnessed arrest</td>
<td>200(23.2%)</td>
<td>316(18.4%)</td>
</tr>
<tr>
<td>Bystander resuscitation</td>
<td>437(50.6%)</td>
<td>662(38.6%)</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>376(43.6%)</td>
<td>536(31.2%)</td>
</tr>
<tr>
<td>Bystander AED use</td>
<td>75(8.7%)</td>
<td>79(4.6%)</td>
</tr>
<tr>
<td>Public location of arrest</td>
<td>359(41.6%)</td>
<td>347(20.2%)</td>
</tr>
<tr>
<td>EMS response time (minutes), mean (±SD)</td>
<td>6.1(+/-2.9) (n=811)</td>
<td>6.3(+/-2.6) (n=1608)</td>
</tr>
<tr>
<td>Prehospital ROSC</td>
<td>786(91.1%)</td>
<td>1509(88.0%)</td>
</tr>
<tr>
<td>Shockable initial rhythm</td>
<td>682/816(83.6%)</td>
<td>537/1647(32.6%)</td>
</tr>
<tr>
<td>Presentation during business hours</td>
<td>299(34.6%)</td>
<td>573(33.4%)</td>
</tr>
<tr>
<td>Coma at ED arrival</td>
<td>599(69.4%)</td>
<td>1565(91.2%)</td>
</tr>
<tr>
<td>STEMI</td>
<td>619(71.7%)</td>
<td>180(10.5%)</td>
</tr>
</tbody>
</table>

*Denominators represent the number of patients who had data available for the variable

4.5.1.3 Interventions

For a summary of intervention rates please refer to Table 11. There was little difference in rates of therapeutic hypothermia initiation between patients who received coronary angiography and those who did not (61% versus 65%). Those who received coronary angiography were more likely to have received fibrinolytic drugs or CABG and less likely to have received inotropic drugs.
Table 11. Interventions by receipt of coronary angiography

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Coronary angiography (N=863)</th>
<th>No coronary angiography (N=1715)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation of therapeutic hypothermia</td>
<td>529(61.3%)</td>
<td>1124(65.5%)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting (CABG)</td>
<td>46(5.3%)</td>
<td>22(1.3%)</td>
</tr>
<tr>
<td>Fibrinolytic drugs</td>
<td>122(14.1%)</td>
<td>44(2.6%)</td>
</tr>
<tr>
<td>Inotropic drugs</td>
<td>442(51.2%)</td>
<td>1226(71.5%)</td>
</tr>
</tbody>
</table>

4.5.2 Description of Study Population by STEMI Status

4.5.2.1 Hospital Characteristics

Refer to Table 12 for a comparison of hospital characteristics between patients who displayed STEMI on the first post-arrest ECG (31%) and those who did not (69%). Compared to patients without STEMI, patients with STEMI were more likely to be initially admitted to a PCI center (46% versus 28%), or an Academic Health Science Center (27% versus 21%). Most STEMI patients were admitted to large hospitals (44%), whereas approximately equal proportions of patients without STEMI were admitted to small, medium and large hospitals.

Table 12. Hospital characteristics by STEMI status

<table>
<thead>
<tr>
<th>Hospital characteristic</th>
<th>STEMI (N=799)</th>
<th>No STEMI (N=1779)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted to PCI center</td>
<td>364(45.6%)</td>
<td>507(28.5%)</td>
</tr>
<tr>
<td>Admitted to Academic Health Science Center</td>
<td>219(27.4%)</td>
<td>372(20.9%)</td>
</tr>
<tr>
<td>Hospital size (average number of acute care beds)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Large</td>
<td>354(44.3%)</td>
<td>575(32.3%)</td>
</tr>
<tr>
<td>o Medium</td>
<td>220(27.5%)</td>
<td>618(34.7%)</td>
</tr>
<tr>
<td>o Small</td>
<td>225(28.2%)</td>
<td>586(32.9%)</td>
</tr>
<tr>
<td>Average annual cardiac arrest volume, mean (+/-SD)</td>
<td>89(+/-41)</td>
<td>88(+/-39)</td>
</tr>
</tbody>
</table>
4.5.2.2 Patient and Cardiac Arrest Characteristics

Refer to Table 13 for differences in demographic and cardiac arrest features between patients with and without STEMI. Compared to patients without STEMI, patients with STEMI were more likely to be male (79% versus 64%), to have had bystander resuscitation (48% versus 40%), specifically bystander CPR (42% versus 32%), and an arrest in a public location (38% versus 22%). They were much more likely to have a shockable initial cardiac rhythm (ventricular fibrillation or ventricular tachycardia) than patients without STEMI (77% versus 37%). Patients without STEMI were three years older on average, and more likely to be in a coma at hospital arrival (88% versus 75%) than patients with STEMI. EMS response times, rates of prehospital ROSC and rates of presentation during business hours did not differ between groups. Witnessed arrest status only differed slightly between patients with and without STEMI.

Table 13. Patient and cardiac arrest characteristics by STEMI status

<table>
<thead>
<tr>
<th></th>
<th>STEMI (N=799)</th>
<th>No STEMI (N=1779)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>634(79.4%)</td>
<td>1138(64.0%)</td>
</tr>
<tr>
<td>Age (years), mean (±SD)</td>
<td>64(+/-13)</td>
<td>67(+/-16)</td>
</tr>
<tr>
<td>Bystander witnessed arrest</td>
<td>470(58.8%)</td>
<td>929(52.2%)</td>
</tr>
<tr>
<td>EMS-witnessed arrest</td>
<td>177(22.2%)</td>
<td>339(19.1%)</td>
</tr>
<tr>
<td>Bystander resuscitation</td>
<td>384(48.1%)</td>
<td>715(40.2%)</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>338(42.3%)</td>
<td>574(32.3%)</td>
</tr>
<tr>
<td>Bystander AED use</td>
<td>43(5.4%)</td>
<td>111(6.2%)</td>
</tr>
<tr>
<td>Public location</td>
<td>307(38.4%)</td>
<td>399(22.4%)</td>
</tr>
<tr>
<td>EMS response time (minutes), mean (±SD)</td>
<td>6.2(+/-2.9) (n=748)</td>
<td>6.3(+/-2.6) (n=1671)</td>
</tr>
<tr>
<td>Prehospital ROSC</td>
<td>711(89.0%)</td>
<td>1584(89.0%)</td>
</tr>
<tr>
<td>Shockable initial rhythm</td>
<td>593/771(76.9%)</td>
<td>626/1692(37.0%)</td>
</tr>
<tr>
<td>Presentation during business hours</td>
<td>275(34.4%)</td>
<td>597(33.6%)</td>
</tr>
<tr>
<td>Coma at ED arrival</td>
<td>601(75.2%)</td>
<td>1563(87.9%)</td>
</tr>
</tbody>
</table>

*Denominators represent the number of patients who had data available for the variable
4.5.2.3 Interventions

Refer to Table 14 for differences in interventions received by patients with and without STEMI. Patients with STEMI were much more likely to have received coronary angiography than patients without STEMI (77% versus 14%). They were also much more likely to have received PCI (57% versus 7%) and more likely to have received coronary artery bypass grafting (CABG) (4% versus 2%) and fibrinolytic drugs (14% versus 3%). Initiation of therapeutic hypothermia did not differ between STEMI subgroups.

<table>
<thead>
<tr>
<th></th>
<th>STEMI (N=799)</th>
<th>No STEMI (N=1779)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Angiography</td>
<td>619(77.5%)</td>
<td>244(13.7%)</td>
</tr>
<tr>
<td>Initiation of therapeutic hypothermia</td>
<td>506(63.3%)</td>
<td>1147(64.5%)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention (PCI)</td>
<td>459(57.4%)</td>
<td>122(6.9%)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting (CABG)</td>
<td>33(4.1%)</td>
<td>35(2.0%)</td>
</tr>
<tr>
<td>Fibrinolytic drugs</td>
<td>113(14.1%)</td>
<td>53(3.0%)</td>
</tr>
<tr>
<td>Inotropic drugs</td>
<td>476(59.6%)</td>
<td>1192(67.0%)</td>
</tr>
</tbody>
</table>

4.6 Primary Exposure: Coronary Angiography

4.6.1 Descriptive Statistics for Patient Outcomes by Receipt of Coronary Angiography

Descriptive differences in outcomes between patients who received coronary angiography and those who did not are displayed in Table 15. Overall, 33% of patients received coronary angiography and 23% received PCI. Of the patients admitted alive to a participating hospital, 42% survived to hospital discharge and 89% of these patients survived with favorable neurologic outcome (MRS 0-2). Survival to hospital discharge with favorable neurologic outcome and survival to hospital discharge were much higher among patients who received coronary angiography than among patients who did not receive coronary angiography. In fact, there was a 40% absolute difference in survival with favorable neurologic outcome and a 39% absolute difference in survival to hospital discharge between patients who received coronary angiography and those who did not.
Of the 799 patients who had STEMI, 77% (n=619) received coronary angiography and 23% (n=180) did not. The probability of survival with favorable neurologic outcome was 61% for STEMI patients who received coronary angiography and 28% for those who did not. Similarly, STEMI patients who received coronary angiography had nearly a 65% probability of surviving to hospital discharge, whereas STEMI patients who did not receive the procedure had about a 31% chance of surviving to hospital discharge. Of the STEMI patients who received coronary angiography (n=619), 74% also (n=459) received PCI.

Of the 1779 patients who did not have STEMI, 14% (n=244) received coronary angiography and 86% (n=1535) did not. In contrast, 77% of the STEMI patients received coronary angiography. Remarkably, in patients without STEMI, 72% who received coronary angiography survived with favorable neurologic outcome, compared to about 24% of those who did not receive the procedure. A patient without STEMI who received coronary angiography also had a 75% probability of surviving to hospital discharge, compared to a 29% probability for those who did not receive the procedure. Of the patients without STEMI who received coronary angiography (n=244), approximately 50% (n=121) received PCI.

Descriptive data demonstrated that coronary angiography is beneficial to patients with and without STEMI, however, it appeared to be more beneficial to patients without STEMI. Factors that may influence these associations were adjusted for in subsequent analyses.
Table 15. Coronary angiography and survival outcomes

<table>
<thead>
<tr>
<th></th>
<th>Survival with favorable neurologic outcome n(%)</th>
<th>Survival to hospital discharge n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall (N=2578)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Angiography</td>
<td>553/861 (64.2%)</td>
<td>584/863 (67.7%)</td>
</tr>
<tr>
<td>No Coronary Angiography</td>
<td>407/1691 (24.1%)</td>
<td>498/1715 (29.0%)</td>
</tr>
<tr>
<td>Difference (%)</td>
<td>40.1%</td>
<td>38.7%</td>
</tr>
<tr>
<td><strong>STEMI (N=799)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Angiography</td>
<td>377/617 (60.9%)</td>
<td>401/619 (64.8%)</td>
</tr>
<tr>
<td>No Coronary Angiography</td>
<td>50/179 (27.9%)</td>
<td>56/180 (31.1%)</td>
</tr>
<tr>
<td>Difference (%)</td>
<td>33.0%</td>
<td>33.8%</td>
</tr>
<tr>
<td><strong>No STEMI (N=1779)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Angiography</td>
<td>176/244 (72.1%)</td>
<td>183/244 (75.0%)</td>
</tr>
<tr>
<td>No Coronary Angiography</td>
<td>357/1512 (23.6%)</td>
<td>442/1535 (28.8%)</td>
</tr>
<tr>
<td>Difference (%)</td>
<td>48.5%</td>
<td>46.2%</td>
</tr>
</tbody>
</table>

4.6.2 Empty Regression Models: Intraclass Correlation Coefficients

The ICC for the primary outcome of survival with favorable neurologic outcome demonstrated that 4.7% of the variability in this outcome was attributed to the characteristics of the hospitals the patients were initially admitted to. The ICC for the secondary outcome of survival to hospital discharge was 0.043, indicating that about 4.3% of the variability in patient survival was attributed to hospital-level factors. Refer to Appendix I for intraclass correlation and median odds ratio calculations.

4.6.3 Statistical Analyses using Multilevel Logistic Regression

Refer to Table 16 for presentation of unadjusted and adjusted findings. In the unadjusted analyses, receiving coronary angiography was positively associated with survival with favorable
neurologic outcome (OR=5.56, CI\textsubscript{95} 4.59-6.73) and survival to hospital discharge (OR=5.09, CI\textsubscript{95} 4.23-6.11). The primary adjusted models, adjusting for all covariates identified from the literature a priori, demonstrated that patients who received coronary angiography had about twice the odds of surviving to hospital discharge with favorable neurologic outcome (OR=2.03, CI\textsubscript{95} 1.47-2.80, p<.0001) and nearly twice the odds of surviving to hospital discharge (OR=1.86, CI\textsubscript{95} 1.36-2.55, p<.0001) than patients who did not receive coronary angiography.

When the significant interaction between coronary angiography and STEMI status was included in the primary adjusted model, the association between coronary angiography and survival with favorable neurologic was positive but non-significant in STEMI patients (OR=1.35, CI\textsubscript{95} 0.84-2.18) and significant in patients without STEMI (OR=2.62, CI\textsubscript{95} 1.74-3.95).

In the unadjusted models, the associations were much stronger, indicating that there are many important confounders that were adjusted for. Backward stepwise selection indicated that the most important confounders of these associations were initial cardiac rhythm, initial neurologic status, age, STEMI status, and bystander AED use. Refer to Appendix J for model building strategies.

The results from the secondary models, adjusting for clinically important covariates and using model building techniques, are also presented in Table 16. The odds ratios and significance levels derived from the secondary models were similar to the odds ratios derived from the primary adjusted models, indicating that the additional covariates included in the primary adjusted models were likely not important confounders of the associations. Several sensitivity analyses were also performed and findings can be located in Appendix K.
Table 16. Unadjusted and adjusted odds ratios: Coronary angiography and outcomes

<table>
<thead>
<tr>
<th>Model</th>
<th>Survival with favorable neurologic outcome</th>
<th>Survival to hospital discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (CI&lt;sub&gt;95&lt;/sub&gt;)</td>
<td>p-value</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>5.56(4.59-6.73)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Primary adjusted</td>
<td>2.03(1.47-2.80)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Secondary adjusted</td>
<td>2.16(1.57-2.96)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Tertiary adjusted</td>
<td>2.07(1.53-2.81)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*Primary models adjusted for covariates identified from literature *Secondary models adjusted for clinically important covariates *Tertiary models resulted from backward stepwise selection. Refer to Section 3.8.6.1 for covariates included in primary and secondary models and Appendix J for covariates in tertiary models.

4.6.4 Effect Modification

Effect modification of the relationships between coronary angiography and survival outcomes was investigated by STEMI status, initial neurologic status (comatose versus conscious) and initial admission to a PCI center. The results of the analyses for interaction are displayed in Table 17. In the unadjusted analysis, STEMI status significantly modified the association between coronary angiography and survival with favorable neurologic outcome (OR= 0.49, CI<sub>95</sub> 0.30-0.79), as well as survival to hospital discharge (OR= 0.53, CI<sub>95</sub> 0.32-0.85).

In the adjusted analysis, the impact of receiving coronary angiography on survival with favorable neurologic outcome differed between patients with and without STEMI (OR=0.52, CI<sub>95</sub> 0.28-0.95). However, the impact of receiving coronary angiography on survival to hospital discharge did not differ significantly between patients with and without STEMI (OR=0.60, CI<sub>95</sub> 0.33-1.08).

Initial admission to a PCI center and initial neurologic status did not appear to be effect modifiers in the unadjusted or adjusted analyses. However, these subgroup analyses were still performed, since they were planned a priori.
### Table 17. Effect modification of coronary angiography and outcomes

<table>
<thead>
<tr>
<th>Effect modifier</th>
<th>Survival with favorable neurologic outcome</th>
<th>Survival to hospital discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>CI&lt;sub&gt;95&lt;/sub&gt;</td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI status</td>
<td>0.49</td>
<td>0.30-0.79</td>
</tr>
<tr>
<td>PCI center</td>
<td>1.34</td>
<td>0.91-1.97</td>
</tr>
<tr>
<td>Initial neurologic</td>
<td>0.48</td>
<td>0.20-1.18</td>
</tr>
<tr>
<td><strong>Primary adjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI status</td>
<td>0.52</td>
<td>0.28-0.95</td>
</tr>
<tr>
<td>PCI center</td>
<td>1.17</td>
<td>0.72-1.90</td>
</tr>
<tr>
<td>Initial neurologic</td>
<td>1.00</td>
<td>0.40-2.58</td>
</tr>
</tbody>
</table>

*Primary model adjusted for covariates identified from literature. Refer to Section 3.8.6.1 for covariates included in this model.

*Effect modifier* coronary angiography = interaction term included in adjusted model

#### 4.6.5 A Priori Subgroup Analysis: STEMI Status

**4.6.5.1 Unadjusted Analyses**

Unadjusted odds ratios and confidence intervals and presented in Table 18. The unadjusted analysis demonstrated that coronary angiography was positively associated with survival with favorable neurologic outcome (OR=3.75, CI<sub>95</sub> 2.56-5.49) and survival to hospital discharge (OR=3.58, CI<sub>95</sub> 3.15-4.06) in STEMI patients. In patients without STEMI, coronary angiography was even more strongly associated with survival with favorable neurologic outcome (OR=8.83, CI<sub>95</sub>=6.40-12.19) and survival to hospital discharge (OR=8.29, CI<sub>95</sub> 7.47-9.20).

**4.6.5.2 Adjusted Analyses**

Analyses were conducted separately in patients with STEMI and in patients without STEMI. Table 18 displays adjusted odds ratios and confidence intervals. For patients with STEMI, the primary
adjusted models demonstrated no association between receiving coronary angiography and survival to hospital discharge with favorable neurologic outcome (OR= 1.04, CI$_{95}$ 0.62-1.74), or survival to hospital discharge (OR=1.09, CI$_{95}$ 0.66-1.81). The results from the secondary models, adjusting for clinically important covariates and using model building techniques, showed that the associations did not change considerably in strength or significance, when different sets of covariates were included in the models.

Model building techniques revealed that the most important confounders of the association between coronary angiography and survival with favorable neurologic outcome in STEMI patients were initial neurologic status, initial cardiac rhythm, age, location of arrest, prehospital ROSC, and hospital size (medium vs. small). Backward stepwise selection indicated that the most important confounders of the association between coronary angiography and survival to hospital discharge were those mentioned above, in addition to initiation of therapeutic hypothermia. Refer to Appendix J for model building strategies. In fact, these variables were such strong confounders of the unadjusted association that it no longer existed after adjusting for their influence.

For patients without STEMI on the first post-arrest ECG, the primary adjusted model demonstrated that patients who received coronary angiography had nearly three times the odds of surviving with favorable neurologic outcome (OR=2.90, CI$_{95}$ 1.90-4.43) and over two times the odds of surviving to hospital discharge (OR=2.44, CI$_{95}$ 1.62-3.69) than patients who did not receive coronary angiography. Adjusted odds ratios remained significant in the secondary models.

Model building techniques revealed that the most important confounders of the association between coronary angiography and survival outcomes in patients without STEMI were initial cardiac rhythm, initial neurologic status, and age (Appendix J). Several sensitivity analyses were also performed and findings can be located in Appendix K.
### Table 18. Unadjusted and adjusted odds ratios: Coronary angiography and outcomes by STEMI status

<table>
<thead>
<tr>
<th>Model</th>
<th>Outcome</th>
<th>STEMI (N=799)</th>
<th>No STEMI (N=1779)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Odds Ratio (CI$_{95}$)</td>
<td>p-value</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>Survival with favorable neurologic outcome</td>
<td>3.75(2.56-5.49)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Survival to hospital discharge</td>
<td>3.58(3.15-4.06)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Primary adjusted</td>
<td>Survival with favorable neurologic outcome</td>
<td>1.04(0.62-1.74)</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>Survival to hospital discharge</td>
<td>1.09(0.66-1.81)</td>
<td>0.73</td>
</tr>
<tr>
<td>Secondary adjusted</td>
<td>Survival with favorable neurologic outcome</td>
<td>1.15(0.70-1.89)</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>Survival to hospital discharge</td>
<td>1.20(0.74-1.95)</td>
<td>0.46</td>
</tr>
<tr>
<td>Tertiary adjusted</td>
<td>Survival with favorable neurologic outcome</td>
<td>1.09(0.67-1.79)</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>Survival to hospital discharge</td>
<td>1.15(0.71-1.87)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

*Primary models adjusted for covariates identified from literature *Secondary models adjusted for clinically important covariates *Tertiary models resulted from backward stepwise selection. Refer to Section 3.8.6.1 for covariates included in primary and secondary models and Appendix J for covariates in tertiary models.

### 4.6.6 A Priori Subgroup Analysis: Initial Neurologic Status

While the majority of OHCA patients are comatose at hospital admission, those who are initially comatose are less likely to receive coronary angiography than those who are conscious, and the literature has demonstrated conflicting findings concerning the benefit of coronary angiography and PCI in OHCA patients, but particularly in comatose OHCA patients.

In the unadjusted analyses, initially comatose patients (n=2164) who received coronary angiography had greater than four times the odds of surviving with favorable neurologic outcome.
(OR=4.22, CI₉⁵ 3.39-5.25) and nearly four times the odds of surviving to hospital discharge (OR=3.95, CI₉⁵ 3.69-4.22) than comatose patients who did not receive coronary angiography. In the unadjusted analysis, receiving coronary angiography was even more strongly associated with survival with favorable neurologic outcome (OR=8.88, CI₉⁵ 3.69-21.33) and survival to hospital discharge (OR=8.99, CI₉⁵ 6.57-12.32) in conscious patients (n=414). Refer to Table 19 for details.

The primary adjusted models did not converge in conscious patients because the number of patients who were conscious at hospital admission was too small to include all the covariates identified from the literature in the models. Therefore, secondary models are presented, which include the covariates that were identified to be clinically important to adjust for. Refer to Section 3.8.6.1 for covariates included in secondary models. Refer to Table 19 for odds ratios and confidence limits.

In patients who were comatose at hospital admission, those who received coronary angiography had approximately twice the odds of surviving to hospital discharge with favorable neurologic outcome (OR=2.09, CI₉⁵ 1.51-2.90) and surviving to hospital discharge (OR=1.95, CI₉⁵ 1.42-2.67). In patients who were conscious at hospital admission, those who received coronary angiography had over three times the odds of surviving to hospital discharge with favorable neurologic outcome (OR=3.08, CI₉⁵ 0.78-12.22), and over two times the odds of surviving to hospital discharge (OR=2.19, CI₉⁵ 0.51-9.48) than those who did not receive coronary angiography. However, these associations were not statistically significant likely due to the small number of patients who were conscious at hospital admission (16%). The wide confidence intervals demonstrate that there was insufficient power to claim that the associations were significant.

When the interaction term between initial neurologic status and coronary angiography was included in the primary adjusted models that included the entire study population, the findings demonstrated no effect modification by initial neurologic status (see Table 17). This indicates that the association between coronary angiography and survival with favorable neurologic outcome, as well as survival to hospital discharge did not differ by initial neurologic status. Likewise, the subgroup analysis indicated that the associations were positive, regardless of initial neurologic status.
Table 19. Unadjusted and adjusted odds ratios: Coronary angiography and outcomes by initial neurologic status

<table>
<thead>
<tr>
<th>Model</th>
<th>Outcome</th>
<th>Comatose (N=2164)</th>
<th>Conscious (N=414)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Odds Ratio (CI\textsubscript{95})</td>
<td>p-value</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>Survival with favorable neurologic outcome</td>
<td>4.22 (3.39-5.25)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Survival to hospital discharge</td>
<td>3.95 (3.69-4.22)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Secondary</td>
<td>Survival with favorable neurologic outcome</td>
<td>2.09 (1.51-2.90)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>adjusted</td>
<td>Survival to hospital discharge</td>
<td>1.95 (1.42-2.67)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*Secondary model adjusted for clinically important covariates, identified via expert opinion. Refer to Section 3.8.6.1 for covariates included in secondary models.

4.6.7 A Priori Subgroup Analysis: PCI Center

The observed variability in survival for OHCA patients admitted to hospitals equipped with catheterization laboratories compared to those without catheterization laboratories\textsuperscript{51,56,61,90} may be due to disparities in provision of important post-resuscitation treatments, such as coronary angiography, between PCI centers and non-PCI centers.

In the unadjusted analyses, for patients initially admitted to PCI centers (n=871), those who received coronary angiography had nearly seven times the odds of surviving with favorable neurologic outcome (OR= 6.82, CI\textsubscript{95} 4.99-9.31) and nearly six times the odds of surviving to hospital discharge (OR=5.76, CI\textsubscript{95} 5.24-6.32) than those who did not receive coronary angiography. Similar, yet slightly weaker unadjusted associations were observed in patients initially admitted to non-PCI centers (n=1707). Table 20 provides a summary of unadjusted and adjusted findings.

In the primary adjusted analyses, for patients initially admitted to PCI centers, receiving coronary angiography was positively associated with survival with favorable neurologic outcome (OR=1.75, CI\textsubscript{95} 1.01-3.04) and survival to hospital discharge (OR=1.59, CI\textsubscript{95} 0.93-2.71), however, the latter association
did not quite reach statistical significance (p=0.09). In patients initially admitted to non-PCI centers, those who received coronary angiography had more than two times the odds of surviving with favorable neurologic outcome (OR=2.11, CI\textsubscript{95} 1.41-3.14), and surviving to hospital discharge (OR=2.06, CI\textsubscript{95} 1.39-3.05) than those who did not receive coronary angiography.

When the interaction term between admission to PCI center and coronary angiography was included in the primary adjusted models that included the entire study population, the findings demonstrated no effect modification by admission to PCI center (see Table 17). Likewise, the subgroup analysis indicated that the associations between coronary angiography and survival outcomes were positive, regardless of whether patients were initially admitted to PCI centers or non-PCI centers.

The secondary models, adjusting only for covariates identified to be clinically important to adjust for, demonstrated similar findings, indicating that the additional covariates adjusted for in the primary models were not important confounders of the associations. Refer to Section 3.8.6.1 for covariates included in secondary models.
Table 20. Unadjusted and adjusted odds ratios: Coronary angiography and outcomes by PCI center

| Model          | Outcome                             | PCI center (N=871) |            | Non-PCI center (N=1707) |            |
|----------------|-------------------------------------|-------------------|--|------------------------|--|--|
|                |                                     | Odds Ratio (CI 95%) | p-value | Odds Ratio (CI 95%) | p-value |
| Unadjusted     | Survival with favorable neurologic  | 6.82 (4.99-9.31)  | < .0001 | 4.98 (3.90-6.36)     | < .0001 |
|                | outcome                              |                   |          |                        |          |
|                | Survival to hospital discharge       | 5.76 (5.24-6.32)  | < .0001 | 4.90 (4.53-5.30)     | < .0001 |
| Primary        | Survival with favorable neurologic  | 1.75 (1.01-3.04)  | 0.047   | 2.11 (1.41-3.14)     | 0.0003  |
| adjusted       | outcome                              |                   |          |                        |          |
|                | Survival to hospital discharge       | 1.59 (0.93-2.71)  | 0.09    | 2.06 (1.39-3.05)     | 0.0003  |
| Secondary      | Survival with favorable neurologic  | 1.87 (1.09-3.21)  | 0.02    | 2.28 (1.54-3.38)     | < .0001 |
| adjusted       | outcome                              |                   |          |                        |          |
|                | Survival to hospital discharge       | 1.61 (0.96-2.70)  | 0.07    | 2.21 (1.50-3.25)     | < .0001 |

*Primary models adjusted for covariates identified from literature *Secondary models adjusted for clinically important covariates. Refer to Section 3.8.6.1 for covariates included in primary and secondary models.

4.6.8 Summary of Findings

Refer to Table 21 for a summary of findings. In our study population receiving coronary angiography resulted in improved survival to hospital discharge and improved neurologically intact survival. This was also true in patients without STEMI, but not in patients with STEMI. Coronary angiography improved survival to hospital discharge with favorable neurologic outcome in OHCA patients, regardless of whether they were initially admitted to PCI centers or non-PCI centers. We observed positive associations between receiving coronary angiography and survival outcomes in comatose patients. The associations were also strong in conscious patients, however not statistically significant, likely due to inadequate power in this subgroup.
Table 21. Summary of adjusted odds ratios for the relationship between coronary angiography and survival outcomes for the entire study population and among select subgroups

<table>
<thead>
<tr>
<th>Survival with favorable neurologic outcome</th>
<th>Survival to hospital discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Odds (CI 95)</td>
</tr>
<tr>
<td>Overall (N=2578)</td>
<td>2.03(1.47-2.80)</td>
</tr>
<tr>
<td>STEMI (N=799)</td>
<td>1.04(0.62-1.74)</td>
</tr>
<tr>
<td>No STEMI (N=1779)</td>
<td>2.90(1.90-4.43)</td>
</tr>
<tr>
<td>Comatose (N=2164)</td>
<td>2.09(1.51-2.90)</td>
</tr>
<tr>
<td>Conscious (N=414)</td>
<td>3.08(0.78-12.22)</td>
</tr>
<tr>
<td>PCI center (N=871)</td>
<td>1.75(1.01-3.04)</td>
</tr>
<tr>
<td>Non-PCI center (N=1707)</td>
<td>2.11(1.41-3.14)</td>
</tr>
</tbody>
</table>

4.7 Secondary Exposure: Percutaneous Coronary Intervention (PCI)

4.7.1 Statistical Analyses using Multilevel Logistic Regression

The benefit of PCI for successfully resuscitated OHCA patients remains uncertain, as findings from the literature have been conflicting.\(^\text{10,12,19,22,28,32,35,42,68}\) It is important to determine whether this treatment improves survival outcomes for OHCA with and without STEMI.

Refer to Table 22 for odds ratios and confidence intervals. The unadjusted analysis demonstrated that patients who received PCI had nearly four times the odds of surviving with favorable neurologic outcome (OR=3.93, CI\(_{95}\) 3.20-4.83) and surviving to hospital discharge (OR=3.72, CI\(_{95}\) 3.03-4.56) than those who did not receive PCI. The results of the adjusted analyses demonstrated that receiving PCI was positively associated with survival with favorable neurologic outcome (OR=1.27, CI\(_{95}\) 0.93-1.75) and survival to hospital discharge (OR=1.22, CI\(_{95}\) 0.89-1.68), however these associations did not quite reach statistical significance.
Table 2. Unadjusted and adjusted odds ratios: PCI and outcomes

<table>
<thead>
<tr>
<th>Model</th>
<th>Survival with favorable neurologic outcome</th>
<th>Survival to hospital discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (CI_{95})</td>
<td>p-value</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>3.93(3.20-4.83)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Primary adjusted</td>
<td>1.27(0.93-1.75)</td>
<td>0.14</td>
</tr>
<tr>
<td>Secondary adjusted</td>
<td>1.32(0.96-1.80)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Primary model adjusted for covariates identified from literature *Secondary model adjusted for clinically important covariates, identified via expert opinion. Refer to Section 3.8.6.1 for covariates included in primary and secondary models.

4.7.2 Effect Modification

Effect modification by STEMI status was investigated. Refer to Table 23 for findings. In the unadjusted analysis, STEMI status modified the association between PCI and survival with favorable neurologic outcome (OR=0.42, CI_{95} 0.23-0.69), as well as survival to hospital discharge (OR=0.45, CI_{95} 0.27-0.75). In the primary adjusted analysis, the association between PCI and survival with favorable neurologic outcome also varied by STEMI status (OR=0.48, CI_{95} 0.26-0.91), such that the association was weaker in STEMI patients. However, the association between PCI and survival to hospital discharge did not differ by STEMI status (OR=0.56, CI_{95} 0.30-1.07).

When the statistically significant interaction between PCI and STEMI status (OR=0.48, p=0.02) was included in the primary adjusted model including the entire study population, the findings demonstrated no association between PCI and survival with favorable neurologic in STEMI patients (OR=0.99, CI_{95} 0.67-1.45) and a positive, significant association between PCI and survival with favorable neurologic outcome in patients without STEMI (OR=2.04, CI_{95} 1.20-3.45).
Table 23. Effect modification of PCI and outcomes by STEMI status

<table>
<thead>
<tr>
<th>Survival with favorable neurologic outcome</th>
<th>Survival to hospital discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>CI&lt;sub&gt;95&lt;/sub&gt;</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.42</td>
</tr>
<tr>
<td>Primary adjusted</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*Primary adjusted model adjusted for covariates identified from literature. Refer to Section 3.8.6.1 for covariates included in primary models.

4.7.3 A Priori Subgroup Analysis: STEMI Status

Analyses were also conducted separately in patients with STEMI and in patients without STEMI. The unadjusted analysis demonstrated a significant association between PCI and survival with favorable neurologic outcome, as well as survival to hospital discharge, in both patients with and without STEMI. Table 24 displays odds ratios and confidence limits.

In patients with STEMI, findings from the primary adjusted model demonstrated that PCI was not associated with survival to hospital discharge with favorable neurologic outcome (OR=0.81, CI<sub>95</sub> 0.53-1.23) or survival to hospital discharge (OR=0.86, CI<sub>95</sub> 0.57-1.31). The relationships remained non-significant when only those covariates identified to be clinically important via expert opinion, were included in the models.

On the contrary, the primary adjusted models showed that patients without STEMI who received PCI had more than twice the odds of surviving with favorable neurologic outcome (OR=2.22, CI<sub>95</sub> 1.30-3.81) and nearly twice the odds of surviving to hospital discharge (OR=1.83, CI<sub>95</sub> 1.07-3.14) than those who did not receive PCI.
### Table 24. Unadjusted and adjusted odds ratios: PCI and outcomes by STEMI status

<table>
<thead>
<tr>
<th>Model</th>
<th>Outcome</th>
<th>STEMI (N=799)</th>
<th>No STEMI (N=1779)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adjusted Odds</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ratio (CI&lt;sub&gt;95&lt;/sub&gt;)</td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td>Survival with favorable neurologic outcome</td>
<td>2.07(1.53-2.80)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Survival to hospital discharge</td>
<td>2.00(1.80-2.22)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Primary adjusted</strong></td>
<td>Survival with favorable neurologic outcome</td>
<td>0.81(0.53-1.23)</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Survival to hospital discharge</td>
<td>0.86(0.57-1.31)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Secondary adjusted</strong></td>
<td>Survival with favorable neurologic outcome</td>
<td>0.87(0.58-1.29)</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Survival to hospital discharge</td>
<td>0.89(0.60-1.34)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

*Primary model adjusted for covariates identified from literature *Secondary model adjusted for clinically important covariates, identified via expert opinion. Refer to Section 3.8.6.1 for covariates included in primary and secondary models.
Chapter 5
Discussion

5.1 Summary of Key Findings

Multilevel analysis revealed that factors associated with receiving coronary angiography included age, STEMI status, being conscious at hospital arrival, having a shockable initial cardiac rhythm, an EMS-witnessed arrest, initiation of therapeutic hypothermia, receiving bystander defibrillation, and being admitted directly to a PCI center. STEMI status was most strongly associated with receiving coronary angiography, followed by initial neurologic status and initial cardiac rhythm.

Receiving coronary angiography was positively associated with survival to hospital discharge and survival with favorable neurologic outcome in the entire study population, and in patients without STEMI. There was no association between angiography and survival outcomes in patients with STEMI. Patients who were comatose at hospital admission were more likely to achieve neurologically intact survival and survival to hospital discharge if they received coronary angiography. The relationship between coronary angiography and survival with favorable neurologic outcome was positive and significant, regardless of whether patients were initially admitted to PCI centers or non-PCI centers. Receiving PCI was positively associated with both survival to hospital discharge and survival with favorable neurologic outcome in patients without STEMI.

5.2 Characteristics of OHCA Patients in Southern Ontario

The study population was similar to OHCA patients described in other studies. However, the OHCA patients included in our study generally had more favorable cardiac arrest features than those included in other studies. Large proportions of the study population had an initial shockable cardiac rhythm (49%), had their arrest witnessed (74%), had bystander resuscitation (43%) and achieved prehospital ROSC (89%). In comparison, in a study involving approximately 4000 OHCA patients admitted to 151 hospitals in North America, 41% of patients had an initial shockable cardiac rhythm, 41%
received bystander resuscitation, 69% of arrests were witnessed, and 19% of the patients received early coronary angiography (within 24 hours of hospital arrival). Of the patients included in our study, 29% received early coronary angiography (within 24 hours of hospital admission).

The slightly higher observed rates in our study are likely due to the exclusion criteria applied in the study. Only patients who survived for at least six hours following ED arrival were included in the study, and therefore we selected a group of patients who had increased odds of survival, likely due to favorable cardiac arrest features.

5.3 Variability in Receipt of Coronary Angiography Between Hospitals

In this group of Ontario hospitals, there was considerable variability in administration of coronary angiography to OHCA patients, with rates ranging from 13% to 70%, demonstrating that post-resuscitation care practices and standards of care differ markedly amongst Ontario hospitals. Rates of PCI administration also varied amongst receiving hospitals from 5% to 50%. Moving forward, it will be important to standardize post-resuscitation care across Ontario, and to improve access to coronary angiography and PCI for post cardiac arrest patients, regardless of which hospital they are initially admitted to. Recall that patients initially admitted to non-PCI centers must be transferred to a PCI center in order to receive PCI. It is important that survival is a result of specific interventions, rather than the quality of care the post-cardiac arrest patient receives at the hospital he/she is treated at.50

5.4 Key Variables Associated with Receipt of Coronary Angiography

5.4.1 STEMI Status

In our study population, 31% of the patients had STEMI, while 69% did not. Dumas and colleagues (2010) also demonstrated that 31% of their population had STEMI, while 69% had other ECG patterns.12 In the non-cardiac arrest population, it is very well established that individuals with STEMI require immediate coronary angiography.24,42,72 In fact, the evidence is so strong that significant resources have been put into providing these patients with a “90-minute door to-reperfusion time.”24
Evidence for the optimal treatment of patients who present with STEMI after cardiac arrest suggests a similar association, however the evidence is not as strong, since no randomized controlled trials have been conducted in the cardiac arrest population. Nonetheless, based on extrapolation of evidence from the non-cardiac arrest population, and the lower level evidence in the cardiac arrest population, there is a general consensus that prompt coronary angiography should also be provided to cardiac arrest patients who present with STEMI on the first post-arrest ECG. The reasoning is that patients with STEMI have an increased probability of having acute coronary syndrome (ACS) and coronary artery occlusion, which is detected via coronary angiography, and treated with reperfusion therapies, such as PCI. Recent guidelines by the AHA, the ACC, and the ILCOR recommend that OHCA patients with STEMI should either receive, or be considered for, early coronary angiography and PCI.

In our study population, about 78% of STEMI patients received coronary angiography within 72 hours, with the majority of these patients (76%) receiving coronary angiography within 24 hours. The adjusted analysis demonstrated that OHCA patients with STEMI had over 22 times the odds of receiving coronary angiography than patients without STEMI. In general, Canadian clinicians are following recommended guidelines for the treatment of OHCA patients with STEMI, and appear to be treating cardiac arrest patients with STEMI in a similar manner to non-cardiac arrest patients who present to the emergency department with STEMI.

While coronary angiography was provided to 78% of STEMI patients, it was only provided to 14% of patients without STEMI. These findings are relatively consistent with the literature. For instance, a recent large study found that early coronary angiography (within 24 hours of hospital arrival) was provided to 76.3% of patients with STEMI and only 15.2% of patients without STEMI. Reynolds and colleagues (2009) found slightly higher rates. Of the patients with STEMI or new LBBB, 91% received coronary angiography, whereas of the patients without STEMI or new LBBB, 29% received coronary angiography. Similarly, Bro-Jeppesen (2012) demonstrated that coronary angiography was provided to all OHCA with STEMI in their study and to 34% of patients without STEMI.
The 2010 International Consensus Statement on Emergency Cardiovascular Care stated that “It is reasonable to perform coronary angiography and PCI in selected patients despite the absence of ST-segment elevation on the ECG” and the 2010 AHA guidelines stated that “It is reasonable to include cardiac catheterization and coronary angiography in standardized post-cardiac arrest protocols as part of an overall strategy to improve neurologically intact survival in this patient group.” However, the evidence used to make these recommendations was not the highest quality and quantity (Class 2a, Level of Evidence B). Refer to Appendix A for recommendation rating scale.

In our study population, coronary angiography was only provided to 14% of patients without STEMI. This low number may reflect the limited and controversial evidence in the cardiac arrest population compared to the non-arrest population, and also the fact that there are risks and high costs associated with providing coronary angiography. Since the evidence is so immature at this point, physicians may not be comfortable deciding that the benefit of coronary angiography and PCI outweigh the risks and costs for this patient population.

5.4.2 PCI Center

Our study demonstrated that patients initially admitted to PCI centers have 3.3 times the odds of receiving coronary angiography than those admitted to non-PCI centers. However, the association between other hospital-level factors such as hospital type, size and annual cardiac arrest volume were not related to receipt of coronary angiography.

For patients who demonstrate coronary artery occlusion(s) on an angiogram, PCI is the recommended method of reperfusion. Patients who require PCI must receive the procedure at a designated PCI center that is equipped with the facilities required to perform the procedure. Several researchers have demonstrated in adjusted analyses, that OHCA patients admitted to PCI centers are more likely to have favorable outcomes. It is plausible that the quality of general critical care may be superior at PCI centers compared to non-PCI centers. PCI centers tend to be heavily resourced larger centers with more specialty services.
Patients admitted to hospitals without coronary intervention facilities (i.e. a non-PCI centers) may be less likely to receive coronary angiography, because facility transfer is required to receive the procedure. Transfers are often complicated and risky procedures, which require the treating physician to find an accepting physician at the PCI center, and arrange critical care transport. There may be several barriers to transporting critically ill post cardiac arrest patients to PCI centers.

Based on our findings, it may be reasonable to transport all OHCA patients to the nearest PCI center to improve access to coronary angiography and PCI. However, there are significant and complex resource implications that would need to be considered prior to making this change to current practice. In addition, the risks associated with initially transporting all cardiac arrest patients to PCI centers must be weighed against the benefits of receiving coronary angiography. Transporting a patient to the nearest PCI center will often take more time than transporting the patient to the nearest hospital and may increase the likelihood of mortality. Further studies must be conducted to determine if regionalization of OHCA patients is a necessary and feasible strategy.

Our findings demonstrate that post-resuscitation treatment and quality of care vary between Ontario hospitals, such that less aggressive care is provided at non-PCI centers. There is the need to alter clinical practices in Ontario hospitals, such that OHCA patients are provided with quality, guideline-based care, regardless of the hospital to which they are initially admitted. Future studies may want to focus on implementation of a targeted knowledge translation intervention trial to increase the use of coronary angiography in non-PCI centers.

5.4.3 Initial Neurologic Status

Oftentimes, physicians will base their post-resuscitation care decisions on neurological function immediately following cardiac arrest. In fact, cardiologists in the United States tend to withhold coronary angiography from patients who are clinically judged to have a high risk of dying due to neurologic damage in order to improve publicly reported mortality statistics. There is the belief amongst the clinical community that resuscitated cardiac arrest patients who are in a coma at hospital
arrival, are less likely to survive. In the past, coronary angiography has generally only been considered in patients who had improvement in neurological status.\textsuperscript{69} Our findings were consistent with this. The odds of receiving coronary angiography were about 6.5 times greater for patients who were conscious at hospital arrival than for patients who were unconscious.

A few studies have revealed that patients with poor initial neurologic status are less likely to receive aggressive treatments such as coronary angiography and PCI because they are viewed as having a poor prognosis by attending physicians.\textsuperscript{69} In fact, Gorjup and colleagues (2007) demonstrated that physicians were more likely to decide upon coronary angiography for OHCA patients who were conscious after ROSC.\textsuperscript{31} Reynolds and colleagues (2009) found that low scores on the verbal, motor and eye categories of the Glasgow Coma Scale (GCS) were associated with a decreased likelihood of receiving coronary angiography in an unadjusted propensity analysis.\textsuperscript{13} Our findings confirm the results of these studies.

However, the neurological trajectory of a cardiac arrest patient may not be known until several days after return of spontaneous circulation (ROSC).\textsuperscript{70,71} Kern and colleagues (2012) explicitly stated that “Excellent long-term neurologically favorable outcomes can be achieved even in those comatose at the time of cardiac catheterization.”\textsuperscript{34} Lettieri et al. (2009) believe that neurologic status at hospital admission should not be used as a decision-making tool because their findings demonstrated that two-thirds of the OHCA patients who had poor neurologic status (GCS=3) at admission regained normal neurologic function.\textsuperscript{33} Furthermore, The AHA and ILCOR state that neurologic status following return of spontaneous circulation (ROSC) should not be a contraindication for consideration of coronary angiography and PCI.\textsuperscript{5,16–18} The 2010 AHA guidelines clearly state that outcomes of comatose cardiac arrest patients cannot be predicted within the first 24 hours after ROSC.\textsuperscript{16}

Unfortunately, in this Canadian population of OHCA patients, it appears that initial neurologic status is in fact, a key factor that determines whether or not an OHCA patient receives coronary angiography. Physicians in Ontario do not appear to be following recommendations, as only 28% of comatose patients received coronary angiography, despite the fact that coronary angiography improved
survival to hospital discharge and neurologically intact survival in this population of comatose OHCA patients.

This may be due to the fact that despite the evidence and guidelines,\textsuperscript{16,17} clinicians still attribute poor prognoses to comatose OHCA patients, perhaps based on clinical beliefs or previous experiences. Many physicians have the belief that initially comatose patients are unlikely to survive to hospital discharge. As a result, they may withhold coronary angiography because they believe it will not improve outcomes in a meaningful way.

Withholding coronary angiography may also be due to resource limitations. If resources are limited (i.e. access to coronary angiography and cardiac catheterization, staff to perform procedures), clinicians may decide to send those patients for coronary angiography who are clinically judged to be most likely to benefit from it (i.e. initially conscious patients with additional favorable features). Future studies should specifically investigate the reasons that clinicians cite for withholding coronary angiography from comatose resuscitated cardiac arrest patients.

5.4.4 Initial Cardiac Rhythm

Of the patients with an initial non-shockable cardiac rhythm, only 11% received coronary angiography, whereas 60% of those with an initial shockable rhythm received coronary angiography. In the adjusted analysis, patients with shockable cardiac rhythms had 4.4 times the odds of receiving coronary angiography, compared to patients with non-shockable rhythms. Of the patients who received coronary angiography, approximately 55% went on to receive PCI, regardless of whether the initial cardiac rhythm was shockable or non-shockable. This demonstrates that patients with shockable cardiac rhythms were not more likely to have an occluded coronary artery and therefore, should not be more likely to receive coronary angiography.

Other studies have also found that OCHA patients with initial shockable cardiac rhythms were more likely to receive coronary angiography.\textsuperscript{13,20,21,36} In fact, Waldo and colleagues (2013) demonstrated that the adjusted odds of withholding coronary angiography were 13 times higher for OHCA patients with
an initial cardiac rhythm of pulseless electrical activity (PEA), which is a non-shockable cardiac rhythm. Likewise, Bro-Jeppesen et al. (2012) found that the only independent predictor of receiving coronary angiography for OHCA patients without STEMI was initial shockable cardiac rhythm. Another recent study demonstrated that patients with an initial shockable rhythm were more likely to receive early coronary angiography (within 6 hours of hospital admission) than patients without shockable initial rhythms. Our findings confirm results from previous studies in a Canadian population of OHCA patients.

Unfortunately, physicians associate initial non-shockable rhythms with poorer prognosis and thus may be less likely to engage in aggressive post-resuscitation treatments, such as coronary angiography and PCI. Even though studies have demonstrated that patients with non-shockable rhythms are less likely to survive, this does not mean that their chances of surviving are so low that providing coronary angiography is futile. Perhaps future studies should investigate if providing coronary angiography to resuscitated OHCA patients with initial non-shockable cardiac rhythms will improve survival rates.

5.4.5 Bystander Defibrillation and EMS Witnessed Arrest

The ‘Chain of Survival’ refers to the four sequential actions that should be performed with haste in the prehospital setting, in order to improve patient survival. These actions include early recognition of the cardiac arrest patient, early CPR, early defibrillation, and early advanced cardiac life support (ACLS). Clinicians treating OHCA patients are likely well aware of key components of the ‘Chain of Survival’ and the fact that timely resuscitation is strongly related to all four components. Patients with an EMS witnessed arrest and patients who received bystander defibrillation will have received resuscitative attempts in a timely fashion. These patients will have a better chance of survival according to the ‘Chain of Survival’ model.

Accordingly, having an EMS witnessed arrest and receiving bystander defibrillation are considered by the medical community to be synonymous with better prognosis. Patients who are
considered to have positive prognoses may be more likely to receive invasive therapies, such as coronary angiography, that may improve their chances of survival and survival with favorable neurologic outcome. Our results were as expected, in that patients who had bystander defibrillation and EMS witnessed arrest had approximately 1.9 and 1.8 times the odds of receiving coronary angiography, respectively, compared with patients who did not receive bystander defibrillation or did not have an EMS witnessed arrest.

5.4.6 Initiation of Therapeutic Hypothermia

Overall, 61% of patients who received coronary angiography had therapeutic hypothermia initiated. In the adjusted analysis, patients who had therapeutic hypothermia initiated had nearly two times the odds of receiving coronary angiography than patients who did not. The association between therapeutic hypothermia and coronary angiography cannot be considered to be causal, since coronary angiography may be provided prior to therapeutic hypothermia in some cases.

Although the research is limited, Reynolds and colleagues (2009) demonstrated no difference in receipt of therapeutic hypothermia between cardiac arrest patients who received coronary angiography and those who did not,\textsuperscript{13} while another group of investigators found that OHCA patients treated in higher volume hospitals were more likely to receive both therapeutic hypothermia and coronary angiography.\textsuperscript{19} Induced hypothermia is known to be “a marker of protocolized, aggressive, hospital care.”\textsuperscript{19} Coronary angiography is also considered to be an indicator of more aggressive post-resuscitation care.\textsuperscript{19,26} Providing coronary angiography and therapeutic hypothermia to OHCA patients with ROSC are both components of recommended guidelines as well.\textsuperscript{5,16–18,73} We believe that the association between initiation of therapeutic hypothermia and coronary angiography exists because they are both associated with an aggressive approach to in-hospital post-resuscitation care.

5.4.7 Age

The association between age and receipt of coronary angiography varied depending on patient age. For patients between the ages of 18 and 55, as age increased by one year, the odds of receiving
coronary angiography increased by 4%. However, beyond the age of 55, the odds of receiving coronary angiography decreased by 2% per year. Refer to Appendix E for the Loess curve that demonstrates these associations. The curve demonstrates that the youngest patients (early twenties) and the oldest patients were least likely to receive coronary angiography.

Cardiac arrest is very unusual in young adults. The arrest may have a very different etiology than cardiac arrest in older individuals. Perhaps these patients had heart defects or abnormalities, or congenital heart disease that led to the arrest. It is unlikely for individuals in their twenties and thirties to have a cardiac arrest that is due to an occluded coronary artery. As such, coronary angiography, which detects the occlusion, would be unlikely to have any benefit. This may explain why the youngest patients in our study were least likely to receive coronary angiography.

On the other hand, very old individuals may be clinically judged to be more ill, or to be unlikely to survive a cardiac arrest based on factors that were not taken into account in our analysis, such as current patient comorbidities and medical history (i.e. stroke, myocardial infarction, heart failure, diabetes, cancer, etc.). This may be the reason why the oldest individuals in our study were also unlikely to receive coronary angiography, as the procedure may have been considered futile in these patients.

5.5 Outcomes of OHCA Patients in Southern Ontario

In our study population of OHCA patients, 42% survived to hospital discharge and 89% of these patients had favorable neurologic outcome at hospital discharge. Redpath and colleagues (2010) reported a 38% survival to hospital discharge rate in a Canadian population of about 13,000 OHCA survivors. In the PROCAT study, 39% of OHCA patients survived to hospital discharge and 94% of the survivors achieved a favorable neurologic outcome. Kern et al. (2012) combined the results from 19 studies conducted around the globe, and found that the overall survival rate for cardiac arrest patients who received coronary angiography and PCI (if indicated) was 60%, and of the survivors, 86% survived with favorable neurologic outcome. For patients in our study who received coronary angiography, the survival to hospital discharge rate was nearly 68%
and of these patients, 95% had favorable neurologic outcome at hospital discharge. For patients who received PCI, the survival to hospital discharge rate was 70% and of these survivors, 95% had favorable neurologic outcome at discharge. These statistics suggest that post-resuscitation care in this group of Ontario hospitals, may be slightly better than care provided at the average hospital. This may be due to the fact that the hospitals included in this study were involved in a knowledge translation trial aimed to improve post-resuscitation care for OHCA patients. An active attempt to improve post-resuscitation care should result in enhanced survival rates.

The scientific community and care providers often worry that as more aggressive care for post arrest patients is introduced, the proportion of survivors with poor neurologic function (i.e. minimally conscious, vegetative state) may actually increase. Some argue that improving survival rates without improving neurologically intact survival is essentially useless. There is also the concern that this aggressive care strategy will result in chronic care facilities being overloaded with neurologically impaired survivors. However, our findings are reassuring, as they contradict these concerns.

Descriptive statistics demonstrated that survival to hospital discharge and survival with favorable neurologic outcome were much higher among patients who received coronary angiography (67.7% and 64.2%, respectively) than among patients who did not receive coronary angiography (29.0% and 24.1%, respectively). Survival to hospital discharge and survival with favorable neurologic outcome were also much higher among patients who received PCI (70% and 63.5%, respectively) than among patients who did not receive PCI (34.7% and 29.6%, respectively). Other investigators demonstrated similar findings, such that survival to hospital discharge and survival with favorable neurologic outcome were higher among patients who received coronary angiography (64.7% and 54%, respectively) than among patients who did not receive the procedure (27.1% and 18.4%, respectively).
5.6 Coronary Angiography and Patient Outcomes

Receiving coronary angiography was associated with both survival to hospital discharge and survival with favorable neurologic outcome in this population of OHCA patients. These findings are consistent with the majority of previous literature.\textsuperscript{8,13,19,23,29,67} For instance, in a large study of nearly 13,000 Canadian OHCA patients, those who received coronary angiography and PCI (if indicated), had nearly 22 times the odds of surviving to hospital discharge than those who did not.\textsuperscript{8} A meta-analysis composed of ten studies also demonstrated that nine of the ten studies showed better outcomes for OHCA patients who received coronary angiography than those who did not.\textsuperscript{29} Callaway and colleagues also conducted a large (n=3981) multicenter (n=151) study and found that OHCA patients who received early coronary angiography (within 24 hours of hospital arrival) were more likely to survive to hospital discharge and to survive with good neurologic outcome than patients who received later or no coronary angiography.\textsuperscript{19}

5.7 Percutaneous Coronary Intervention and Patient Outcomes

Receiving PCI was positively associated with survival to hospital discharge and survival with favorable neurologic outcome in this population of OHCA patients, however the associations were not statistically significant. Previous literature has demonstrated inconsistent findings. Spaulding and associates (1997) conducted the pioneering prospective study of the association between PCI and OHCA patient outcomes, and found that successful PCI was a predictor of survival to hospital discharge.\textsuperscript{10} Similarly, Grasner and colleagues (2011) found that receiving PCI increased the odds of survival with good neurologic outcome (CPC 1 and 2) by about 5.7 times and increased the odds of 24-hour survival by nearly four times.\textsuperscript{42} Cronier and colleagues (2011) and Dumas and colleagues (2010) found that survival to hospital discharge was significantly higher for OHCA patients with and without STEMI who received PCI.\textsuperscript{12,22} Meanwhile, three studies found that PCI was not a predictor of survival in OHCA patients.\textsuperscript{28,35,68} However, these studies only included OHCA patients with STEMI. In fact, the findings from our study also demonstrated that PCI was not positively associated with survival outcomes in STEMI patients,
however we did find a significant positive association between PCI and survival outcomes in patients without STEMI. Randomized controlled trials should be conducted to rectify conflicting findings.

5.8 How Does Coronary Angiography Improve Outcomes?

Early coronary angiography may be associated with improved survival rates due to PCI. A significant proportion of patients who receive coronary angiography subsequently receive PCI. Since PCI is the procedure that removes the occlusion identified in the angiogram, it results in reperfusion of the vessel, and a decreased likelihood of further ischemic injury. However, there is the possibility that coronary angiography leads to improved survival via other mechanisms.

Receiving coronary angiography may be a part of a more comprehensive diagnostic examination that is taking place. We found that patients who received coronary angiography were also more likely to have therapeutic hypothermia initiated, which is generally considered to be evidence of more comprehensive and intensive care.  

Nanjayya et al. (2012) found that OHCA patients who received immediate coronary angiography also received more aggressive treatment in the form of intensive care unit (ICU) intervention therapies, which included vasoactive agents, renal replacement therapies and intra-aortic balloon pumps. The investigators concluded that there is a bias towards more aggressive treatment for patients who receive early coronary angiography.

In addition, patients treated with early coronary angiography often receive enhanced hemodynamic support, including administration of vasoactive medications in a timely manner, initiation of central venous access, and invasive monitoring of hemodynamics.  

Hollenbeck and associates (2014) remarked that patients who were treated with early coronary angiography were more likely to receive aggressive anticoagulation and mechanical support, and to have hypotension managed more effectively, which is not well tolerated after cardiac arrest. These hemodynamic support strategies may provide clues for the observed improved survival rates.

In general, receiving coronary angiography may be a part of a more comprehensive diagnostic examination that is being undertaken. Even in the case where the findings from the angiogram indicate
that the coronary arteries are clear, this information may prompt further investigation and diagnosis of other causes of cardiac arrest, leading to more effective treatment. Well-controlled randomized trials are required to further explore whether coronary angiography and PCI can lead to improved neurologically intact survival.

5.9 Subgroup Analysis: STEMI Status

5.9.1 Patients Without STEMI

When the significant interaction between coronary angiography and STEMI status was included in the primary adjusted model, the association between coronary angiography and survival with favorable neurologic outcome was positive and significant in patients without STEMI. Results of the subgroup analyses demonstrated similar findings. Patients without STEMI who did receive coronary angiography had adjusted odds of surviving with favorable neurologic outcome nearly three times greater than the odds for those who did not receive coronary angiography. They also had nearly 2.5 times greater odds of surviving to hospital discharge than those who did not receive coronary angiography. Patients without STEMI who received PCI also had more than twice the odds of surviving with favorable neurologic outcome and nearly twice the odds of surviving to hospital discharge, than those who did not receive PCI.

Previous studies have had conflicting findings as to whether or not coronary angiography and PCI improve outcomes for OHCA patients without STEMI. A recent study found no difference in survival to the end of the study or neurologic outcomes, for OHCA patients without STEMI who received early coronary angiography (≤6 hours) compared to patients who received later (≥ 6 hours) or no coronary angiography. However, in this study, 32% of the patients received later coronary angiography. Since those who received later coronary angiography were grouped with those who did not receive coronary angiography, this would have biased the association towards the null. The definition of early coronary angiography in this study was also quite strict, as other studies have defined early coronary angiography to be within 24 hours of cardiac arrest. Two other studies have also
demonstrated no association between coronary angiography and PCI (if indicated), and survival outcomes in OHCA patients without STEMI.\textsuperscript{20,35}

However, the majority of investigators have provided evidence that coronary angiography and PCI improve survival and survival with good neurologic outcomes for OHCA patients without STEMI.\textsuperscript{8,10,12,13,19,22,23,26,34,66} Several studies have found that coronary angiography and PCI benefit patients with and without STEMI equally. Kern (2012) summarized the findings from four studies and found no unadjusted differences in survival to hospital discharge or neurologically intact survival between OHCA patients with and without STEMI who received coronary angiography and PCI (if indicated).\textsuperscript{34} Parisian investigators also found no difference in survival to hospital discharge between patients with and without STEMI who had successful PCI. Cronier and colleagues (2011) found that receiving PCI reduced the odds of mortality, regardless of initial ECG findings, as did several other investigators.\textsuperscript{8,10,13,19,22,23} Refer to Section 2.4 for a summary of these studies.

Our study demonstrated that 50\% of patients without STEMI, who received coronary angiography, went on to receive PCI, indicating that half of patients without STEMI may have experienced an arrest caused by acute coronary ischemia, which was not recognized by ECG findings. Other investigators have also reported that significant proportions of patients without STEMI have coronary artery occlusion.\textsuperscript{12,13,20,23,26,34,66,98} Between 24-58\% of OHCA patients without electrocardiographic evidence of STEMI have significant coronary artery disease, coronary lesions or acute coronary occlusion.\textsuperscript{12,13,20,26,66}

Our findings indicate that the presence or absence of STEMI on the post-arrest ECG should not be used to decide whether or not OHCA patients receive coronary angiography. Since ECG findings cannot reliably predict acute coronary occlusion,\textsuperscript{10,23,26,73,97} many experts agree that all OHCA patients should be provided coronary angiography, regardless of initial post-arrest ECG findings.\textsuperscript{12,22,23,26,34,63,66} In fact, this has become routine practice in France and other European countries.\textsuperscript{12,22,35} Findings from our study support expert opinion, as well as the 2010 AHA and ILCOR guidelines, which state that
performing early angiography and PCI in OHCA patients without STEMI is reasonable, provided that coronary ischemia is suspected to be the cause of arrest.\textsuperscript{5,16–18} 

Although previous literature has been conflicting regarding the benefits of coronary angiography and PCI for resuscitated OHCA patients without STEMI, our findings demonstrate that this patient population may benefit substantially from receiving coronary angiography and PCI. If coronary angiography becomes a part of the standard of care, survival rates with good neurologic function could potentially triple for OHCA patients without STEMI. It will be important to distribute our findings to the larger scientific community.

However, our findings require confirmation with data from randomized controlled trials. Only about 14% of our study population without STEMI received coronary angiography and even fewer (7%) received PCI. Patients without STEMI who were selected for coronary angiography had more favorable cardiac arrest features than patients without STEMI who were not selected for coronary angiography. Refer to Appendix L for differences in cardiac arrest features. This demonstrates that clinicians select patients for invasive procedures based on perceived prognosis. The findings from our first objective indicated that patients with more favorable cardiac arrest features (i.e. initially conscious, shockable initial cardiac rhythm) receive coronary angiography more often than those with less favorable features.

While we adjusted for these cardiac arrest features, it is possible that statistical methods were not able to completely account for these differences, and hence a randomized controlled trial would be ideal. To our knowledge no randomized controlled trial has been performed to investigate the association between coronary angiography or PCI and outcomes in OHCA patients.\textsuperscript{14,15,34}

5.9.2 Patients With STEMI

For STEMI patients, the unadjusted analyses demonstrated significant positive associations between coronary angiography and PCI, and both survival outcomes of interest. However, after adjusting for potential covariates, the associations became non-significant. The strong unadjusted associations were likely due to selection bias. Physicians often select patients deemed to have a better prognosis, for more
aggressive therapies, such as coronary angiography.\textsuperscript{36} It is possible that receiving coronary angiography is a marker of ‘total patient prognosis,\textsuperscript{20} since it was significantly associated with neurologically intact survival and survival to hospital discharge in the unadjusted analyses, but not in the adjusted analyses.

The results that were attained in the STEMI subgroup were unexpected, as most studies have demonstrated that coronary angiography and PCI improve survival to hospital discharge and survival with favorable neurologic outcome in STEMI patients who have been resuscitated from an OHCA. Three different studies independently demonstrated that OHCA patients with STEMI who receive PCI have outcomes that are comparable to STEMI patients without cardiac arrest who receive PCI.\textsuperscript{30,31,33} However, there were less than 50 OHCA patients included in two of these studies and the other included just 99 OHCA patients. Also the comparison groups should have been OHCA patients with STEMI who did not receive PCI, in order to determine if PCI improves outcomes in this patient population.

Hosmane et al. (2009) used the appropriate comparison group, and found that in-hospital mortality was lower for OHCA patients with STEMI who received PCI or CABG, than for those who did not. However, PCI was not investigated independently and the sample size was small (n=98).\textsuperscript{32} Dumas et al. (2010) and Cronier and colleagues (2009) also found that receiving PCI was associated with improved survival rates for STEMI patients, however these studies were single center studies conducted in France.\textsuperscript{12,22} Other investigators have found that coronary angiography is positively associated with survival outcomes in OHCA patients, regardless of ECG findings.\textsuperscript{8,10,13,19,23}

On the contrary, Weiser et al. (2013) investigated differences in 30-day survival with favorable neurologic outcome (CPC 1 and 2) between OHCA patients with STEMI who were sent for coronary angiography within 12 hours of ROSC, compared to those who were not. They found no significant difference in outcomes between groups. There was also no association between receiving PCI and 30-day survival with favorable neurologic outcome.\textsuperscript{28} Garot and colleagues (2007) also found that OHCA patients with STEMI who had successful PCI, did not have better outcomes at one month or six months post-cardiac arrest than patients who did not have successful PCI.\textsuperscript{68}
It is important to note that in our analysis, both conscious and comatose patients with STEMI were included in the STEMI subgroup. This may have been problematic, because 75% of the STEMI patients were comatose at hospital admission. Initial neurologic status is a key factor in whether or not an OHCA patient survives with good neurologic outcome. Bulut and colleagues (2000) found that the strongest predictor of in-hospital death for OHCA patients was initial neurologic status, not lack of specific interventions, such as coronary angiography and PCI.

The results of our adjusted analyses also demonstrated that the associations between initial neurologic status and survival outcomes were much stronger than the associations between coronary angiography or PCI and survival outcomes in STEMI patients. In the tertiary models, initial neurologic status was the strongest confounder of the association between coronary angiography and survival outcomes in STEMI patients. In fact, the odds of surviving to hospital discharge and surviving with favorable neurologic outcome were about 98% lower for patients who were comatose at hospital arrival compared to those who were conscious. It is possible that the influence of initial neurologic status on survival outcomes was so strong, that statistical methods were unable to completely adjust for the influence of this variable. This may have resulted in the odds ratios being biased towards the null.

It is biologically plausible that comatose patients with STEMI are unlikely to benefit from coronary angiography and PCI because a patient who is comatose is much more likely to have numerous injuries that put them at a greater risk of dying, despite receiving coronary angiography and PCI. For instance, comatose OHCA patients generally have significant multisystem injury, and are also exposed to the risk of being on a ventilator and receiving critical care. The 75% of STEMI patients who were comatose in the study population could have resulted in poor survival rates in the STEMI group overall, due to the other injuries associated with being comatose that increase the risk of death, that were not adjusted for explicitly in the analyses.

Furthermore, if the comatose STEMI patients in our study were treated with substandard post-resuscitation care overall, due to poor prognosis often attributed to comatose patients, it is plausible that coronary angiography and PCI on their own may not improve survival outcomes, as they are only one
component of a package of optimized care that resuscitated OHCA patients should receive. In fact, in adjusted analyses, stratified by both STEMI status and initial neurologic status, the relationships between coronary angiography and survival outcomes were very weak and non-significant in comatose STEMI patients, however stronger in conscious STEMI patients. Refer to Appendix N.

Another explanation for the findings is that STEMI may be transient, so it is possible that some of the patients classified as having STEMI on the first-post arrest ECG may have demonstrated a different pattern prior to first measurement. This may have led to failure to find a benefit of angiography and PCI in patients classified as having STEMI. It is standard in clinical practice to send OHCA patients with STEMI for coronary angiography. In our study, only 22% of patients with STEMI on the first post-arrest ECG were not sent for coronary angiography within 72 hours of hospital arrival. The reasons that these patients were not sent for angiography are unclear. It is possible that the patients with STEMI who were not selected for angiography may have been different in some significant way from those who were selected for angiography, which may have led to the lack of association between angiography and outcomes. There is also the possibility of over adjustment of potential confounders. Some of the variables we adjusted for may have been working in tandem with coronary angiography to improve outcomes in STEMI patients.

The value of coronary angiography in the post arrest patient with STEMI is still unclear. However, selected groups of STEMI patients, namely those who are conscious at hospital admission are likely to derive greater benefit from the procedure than those who are comatose at hospital admission. We believe that it is important to consider both initial neurologic status and STEMI status in further investigations of the association between coronary angiography and survival.

5.10 Subgroup Analysis: Initial Neurologic Status

We found that receiving coronary angiography was positively associated with neurologically intact survival and survival to hospital discharge in comatose OHCA patients. We found that the associations between coronary angiography and survival to hospital discharge, as well as neurologically
intact survival, were positive in conscious OHCA patients, with odds ratios ranging from two to three. However, the confidence intervals were very wide, indicating lack of power and inability to claim the associations were statistically significant. Only 16% of the study population was conscious at hospital admission.

Some recent studies have also found that comatose OHCA patients benefit from coronary angiography and PCI. Zanuttini et al. (2012) demonstrated that emergency coronary angiography and emergency PCI were independently associated with survival to hospital discharge in 93 comatose OHCA patients.11 Another study found that early coronary angiography was associated with decreased mortality in comatose OHCA patients without STEMI26 and other investigators demonstrated that comatose OHCA patients with STEMI who were revascularized, had significantly lower mortality rates than those who were not.32

Currently, in Ontario hospitals, neurologic status at hospital admission is a primary factor in the decision to send a patient for coronary angiography, such that a patient with poor neurologic status at hospital admission is much less likely to undergo coronary angiography, after adjusting for other factors associated with receiving the procedure. However, our findings demonstrate that aggressive post-resuscitation strategies, such as coronary angiography, should be provided to comatose survivors of OHCA more often, since receiving this therapy is associated with higher rates of survival to hospital discharge and neurologically intact survival.

While not all experts believe sending comatose OHCA patients for coronary angiography is the optimal management strategy,7,20,31,101 recent guidelines and findings have demonstrated that it is reasonable to send comatose survivors of OHCA for coronary angiography.16–18 and that being comatose should not be a contraindication to receiving coronary angiography and PCI.7,13,16,17,26,29 Investigators have found that a significant proportion of resuscitated cardiac arrest patients with initial low scores on the Glasgow Coma Scale (GCS) survive with favorable neurologic outcome.70,71 Sunde et al. (2007) contend that delaying prognostication in comatose survivors of cardiac arrest is the best strategy, since it has been
demonstrated that neurologically intact survival is quite high, even in patients who are comatose at hospital arrival.\textsuperscript{9}

Our findings support these guidelines and recommendations. Going forward, it will be important to confirm our findings using randomized controlled trials and then to implement a targeted knowledge translation intervention trial to increase the use of coronary angiography in comatose OHCA patients admitted to Ontario hospitals. It may also be useful to conduct cost-benefit and cost-effectiveness analyses to determine the appropriate course of action.

\textbf{5.11 Subgroup Analysis: PCI Center}

The associations between coronary angiography and survival with favorable neurologic outcome were positive and significant, regardless of whether patients initially arrived to PCI centers or non-PCI centers. The association between coronary angiography and survival to hospital discharge was significant for patients admitted to non-PCI centers and nearly significant for patients admitted to PCI centers. Patients who arrive at non-PCI centers who require coronary angiography and potentially PCI, will be transferred to PCI centers for these procedures. Therefore, all patients will receive coronary angiography and PCI, if required, at a designated PCI center. Consequently, one may expect the association between coronary angiography and survival outcomes to be similar in both groups of patients.

While several researchers have noted that survival rates are higher for OHCA patients treated at PCI centers or specialized centers,\textsuperscript{51,56,61,90} none have specifically investigated the association between coronary angiography and outcomes stratified by hospital type (PCI center or non-PCI center). Our findings indicated that the association between coronary angiography and survival outcomes is similar for patients initially admitted to PCI centers and non-PCI centers. However, it is important to note that patients who initially arrive to non-PCI centers, who may benefit from receiving coronary angiography and PCI, will be less likely to receive these therapies than patients who are initially admitted to PCI centers. This is likely due to the added time, difficulty, and potential danger of transporting the patient. Findings from the first objective confirmed that OHCA patients who are initially admitted to PCI centers
have more than three times the odds of receiving coronary angiography than patients who are initially admitted to non-PCI centers.

## 5.12 Further Studies

Clifton Callaway asserted that, “The most exciting scientific progress occurs when new research challenges conventional wisdom. Even when a medical practice is founded on less-than-perfect scientific data, testing of an established therapy is nearly impossible to justify unless compelling new data lead to questioning of standard care.”

We believe that our research provides findings, which may lead to questioning the standard of care and potentially improving it. Currently OHCA patients with STEMI are generally provided with coronary angiography, while OHCA patients without STEMI are typically not. Our research demonstrates that patients without STEMI may benefit from coronary angiography and PCI more than expected, while OHCA patients with STEMI may benefit less than expected.

However, randomized controlled studies are urgently needed to confirm the role of coronary angiography in the post-cardiac arrest patient. To date, all of the studies in this area of research have been observational in design and the findings from these studies, and our study, have been conflicting. The associations that we investigated were strongly confounded by a few key variables such as initial neurologic status, initial cardiac rhythm and STEMI status. It is possible that statistical methods were not able to completely adjust for the influence of these strong confounders. There are likely other factors that confound the relationships as well, that are difficult to adjust for, such as perceived patient prognosis. Randomized controlled trials will eliminate these concerns, resulting in effect estimates free of bias and confounding.

Further studies should also determine which patient and cardiac arrest characteristics are associated with the greatest benefit from receiving coronary angiography. If the practice of undertaking angiography on all post arrest patients is not feasible, perhaps we can identify patient subgroups most likely to benefit. If other investigators can demonstrate that some factors are strongly associated with a very low likelihood of neurologically intact survival in this patient population, such as advanced age or a
long period of time between arrest and ROSC, these factors could be used to develop guidelines. These guidelines could be used to determine when it would be reasonable for OHCA patients to undergo coronary angiography and when it would be considered futile.

For instance, if patients over the age of 80 with pre-existing cardiac disease, a time to resuscitation longer than 10 minutes, and poor initial scores on the Glasgow Coma Scale, are found to have a 2% chance of surviving with favorable neurologic outcome, then it may be reasonable not to consider such a patient for coronary angiography, as it is unlikely to provide significant benefit. Ideally, in the future, we will be able to reliably predict whether or not a patient with a given set of characteristics has a reasonable chance of neurologically intact survival if he/she receives coronary angiography. Such a strategy would enable the most ideal use of hospital resources, while ensuring neurologically intact survival remains high.

In addition, it may also be of interest to determine if there is an effect of early versus late coronary angiography on the association between the procedure and outcomes in patients with and without STEMI on the post-arrest ECG. Strote and colleagues (2102) admit that it is difficult to ascertain not only if resuscitated sudden cardiac arrest patients should be given coronary angiography, but also within which time frame it should be provided. The relevant literature addressing this question is limited and has conflicting findings. 

5.13 Limitations

5.13.1 Administrative Data (Hospital Records)

The primary limitation with this data is that it was entered into the database retrospectively from hospital records. The use of administrative data for research studies is not ideal, as there is the possibility for errors in the patient records, missing records and/or data, and data entry errors. With administrative data, there is a lack of quality control over the data collection. Hospital records are not intended for the purposes of answering research questions.
If a variable of interest was not listed in a patient’s chart, it was recorded as ‘unknown’ or ‘not noted’. For most variables ‘no’ and ‘unknown or not noted’ were grouped together. However, if the presence of a variable was not recorded in a patient’s chart, this does not indicate that the patient certainly did not have the feature of interest or receive the intervention of interest. Perhaps the feature or intervention was simply not recorded. This feature of data collection likely resulted in the prevalence of interventions and outcomes being underestimated and effect estimates being biased toward the null hypothesis. However, if coronary angiography was performed within 72 hours, it is highly unlikely it was not recorded in the patient chart.

5.13.2 Uncontrolled/Unaddressed Confounding

The study design is retrospective, meaning that there is a possibility of uncontrolled or unaddressed confounding in the prehospital and/or hospital settings that could have influenced the findings. We attempted to lessen the possibility of confounding by adjusting for a wide range of variables that were identified from the literature to be associated with survival and neurologic outcomes. We also adjusted for differences in practice between hospitals through the multilevel analysis strategy. However, there is still the possibility that variables that could not be measured or were not accounted for influenced the findings.

One of the primary variables that we were unable to adjust for was troponin levels. Troponin is a cardiac biomarker that is released into the circulation when cardiac muscle dies as a result of cardiac ischemia. There is evidence that elevation in troponin levels is associated with poorer prognosis in patients who suffer a myocardial infarction. Antman and colleagues (1996) demonstrated that elevations in cardiac troponin are associated with worse outcomes in patients with acute coronary syndrome. Elevations in cardiac troponin are also an indicator of coronary artery occlusion and ischemia. Patients suspected of having coronary artery occlusion are undeniably more likely to be sent for coronary angiography. However, Anyfantakis and colleagues (2009) demonstrated that nearly 87% of their study population of OHCA patients, without a diagnosis of acute myocardial infarction, had elevated
levels of cardiac troponin. Hence, it is possible that failing to control for cardiac troponin levels was a trivial limitation, since the majority of OHCA patients may have had elevated troponin. Unfortunately these statistics were not available for our patient population.

Other variables that have may be associated with receiving coronary angiography include cardiogenic shock,\textsuperscript{26,33,36} use of aspirin, anti-thrombin agents and glycoprotein inhibitors,\textsuperscript{26,33,37} and pre-existing comorbidities.\textsuperscript{66} The literature has demonstrated that pre-existing medical conditions are related to patient outcomes following a cardiac arrest,\textsuperscript{8,39,45} and studies have demonstrated that cardiogenic shock and echocardiographic findings are associated with survival in OHCA patients.\textsuperscript{20,33,36} Medications that patients received during the course of treatment, as well as additional interventions, were also not accounted for in the analyses. These variables have the potential to be confounders of the associations examined. However, we were unable to adjust for these factors, since the appropriate data were not collected in the Rescu Epistry database, or the recording of data was insufficient. For instance, data collection methods for comorbidity data were not reliable in the Epistry database because a large proportion of patients were classified as having ‘other’ comorbidities. Since the nature of these other comorbidities was not explicitly stated, it was difficult to accurately adjust for patient comorbidities.

A prospective cohort study or randomized controlled trial would be most ideal in order to collect information on all variables of interest, however these types of studies would require considerable resources, and large expenses and time investments, and therefore were not feasible, especially for the scope of this thesis.

### 5.13.3 Confounding by Indication

Confounding by indication may be present in that patients were not randomly allocated to receive coronary angiography. Patients who have had an OHCA are a heterogeneous group,\textsuperscript{35} and as such they may have been selected for coronary angiography based on factors that were not taken into account in this study. The attending physician ultimately determined whether or not a patient was sent for coronary angiography, based on clinical judgment and the patient’s clinical presentation.\textsuperscript{26} These features were also
likely associated with survival outcomes. While we have attempted to adjust for all of the factors that may influence a physician’s decision of whether or not to send a patient for coronary angiography, we recognize that statistical methods cannot entirely eliminate selection bias. There is the possibility that the treating physicians may have considered factors in their decisions to perform coronary angiography, that have not or cannot, be adjusted for in the analysis. These factors may have been associated with survival. Perhaps future studies should focus on the specific decision making processes of healthcare professionals in the choice to send OHCA patients for important post-resuscitation therapies.

5.13.4 Misclassification Bias

Receipt of coronary angiography was only recorded if it occurred within 72 hours of hospital admission. A patient who received coronary angiography after 72 hours was recorded as not having received coronary angiography in the Rescu Epistry database. The result would be differential misclassification bias if one of the STEMI status groups, for instance, the patients without STEMI, received coronary angiography after 72 hours more often than the patients with STEMI. In this case, those without STEMI would be more likely to be misclassified with respect to receipt of coronary angiography, than patients with STEMI. The result would be non-differential misclassification bias if both groups of patients (STEMI and no STEMI) were equally likely to be misclassified with respect to receipt of coronary angiography. We believe that differential misclassification of patients without STEMI was more likely to have occurred than non-differential misclassification, because evidence in the non-arrest population demonstrates that it is important for STEMI patients to receive coronary angiography as quickly as possible.\(^2^{4}\) As a result, OHCA patients with STEMI are regularly sent for early coronary angiography as well. However, if patients who received angiography after 72 hours were included, this may have biased the odds ratios for the associations between angiography and survival outcomes away from the null. Those who survived to 72 hours were likely to survive to hospital discharge, regardless of whether they receive angiography.
The other issue pertaining to our exposure is that coronary angiography is generally considered to be early if it is given within 24 hours of hospital admission\textsuperscript{19} or earlier.\textsuperscript{23,36} Callaway and colleagues (2014) noted that patients who receive coronary angiography after 24 hours are likely to survive to hospital discharge because they survived for the first 24 hours after cardiac arrest, which is the period of time the majority of patients die.\textsuperscript{19} Patients included in our analysis who received coronary angiography after 24 hours could bias the odds ratio away from the null resulting in a stronger effect than that which truly exists. However, only 4\% of patients received coronary angiography after 24 hours, while 29\% received coronary angiography before 24 hours, so this aspect of the study is not likely to have significantly biased our findings, especially since we adjusted for many factors associated with survival.

5.13.5 Survival Bias

Survival bias occurs when those individuals who are more likely to survive from a life-threatening event or disease are more likely to be included in a study. In order to be included in our study, a patient had to be alive six hours after ED arrival to be eligible to be considered for coronary angiography. Therefore, we included those cardiac arrest sufferers who were the most likely to survive, since the majority of OHCA patients die prior to hospital admission, followed by the first few hours after being admitted to a hospital.\textsuperscript{8} As a result, rates of survival to hospital discharge and neurologically intact survival reported from our study may be high relative to the general population of OHCA patients.

5.13.6 Network of Hospitals

The group of hospitals included in the study were engaged in a knowledge translation intervention trial that aimed to optimize certain aspects of post-cardiac arrest care, with a primary focus on therapeutic hypothermia. Since these hospitals voluntarily agreed to participate in a trial aimed at improving post-cardiac arrest care, these hospitals may have been more similar to one another than hospitals outside of the network. However, the results demonstrated that there was variability in treatment
processes and outcomes even amongst these hospitals, suggesting that even more variability might exist outside of this network.

5.13.7 Study Design

The observational study design limits our ability to make causal inferences, since patients are not randomized to treatment and control arms. Large, randomized controlled trials should be conducted to confirm our findings and to provide more definitive evidence of the benefit of coronary angiography in OHCA patients, with and without STEMI.

5.13.8 Effect of Time to Coronary Angiography

Studies in the non-cardiac arrest population have demonstrated that timely coronary angiography is important, specifically for patients with STEMI. However, we were not able to compare the effect of early versus late coronary angiography on outcomes, because after applying the exclusion criteria to the patient population, the number of patients who received late coronary angiography (defined as more than 24 hours from hospital admission) was too small to have adequate power to achieve accurate effect estimates. However, the majority (85%) of patients who received coronary angiography in the study received the intervention within 24 hours of hospital arrival.

5.13.9 Long Term Follow-up

Data were not available on the patient population once discharged from the hospital. Time to event analysis was not conducted because we did not have data on time of death after hospital discharge. As such, we were not able to comment on the association between coronary angiography or PCI and longer-term outcomes. However, a much higher proportion of OHCA patients die during the hospital stay, compared to after hospital discharge, and studies have demonstrated that long-term survival rates remain relatively stable in survivors of OHCA. Hence, our study appears to have captured the most significant period of time, during which patients are at highest risk of mortality.
5.14 Strengths

5.14.1 First Canadian Study

This research has the potential to add valuable knowledge to previous post cardiac arrest research by describing which patient, cardiac arrest, and hospital characteristics are driving the variation in receipt of important post-cardiac arrest treatments, particularly coronary angiography and PCI, in Southern Ontario. Currently no Canadian studies have investigated these associations. It is necessary to describe clinical practice in order to determine where limitations exist and where improvements must be made. Similarly, no Canadian studies have investigated the association between receipt of coronary angiography and survival outcomes in a large population of OHCA patients, with and without STEMI.

5.14.2 Large Sample Size

Our study included 2578 OHCA patients admitted to 28 Ontario hospitals over a considerable time period of nearly five years (March 1st, 2010 and December 31st, 2014). Previous similar studies have included smaller sample sizes, ranging from 72 to 584 patients. A handful of large multicenter studies were conducted in this research area, however they had other limitations, such as being conducted outside North America, failing to adjust for important confounders, failing to investigate associations in important subgroups of OHCA patients, such as patients with and without STEMI (Appendix B), and use of inappropriate comparison groups. For instance, many studies compared early coronary angiography to late or no angiography. These issues were addressed with our methodology.

5.14.3 Multicenter Study

Most other studies investigating this area of research are limited to OHCA patients admitted to single hospitals or care centers. The limitation of this approach is that the sample sizes are relatively small, and variation in post-cardiac arrest care practices between hospitals cannot be captured. Furthermore, the results from these studies reflect the management and treatment of patients in those specific centers, and therefore the results may not be generalizable to patients treated at other centers. Our
study involved patients admitted to 28 Ontario hospitals of different sizes, types and geographic locations (rural vs. urban). This resulted in variation amongst patients and care processes, generalizability of findings, and the capacity to study differences in post-cardiac arrest treatments between hospital sizes and types.

5.14.4 Examination of Both Treatment Processes and Associated Outcomes

This was the first study to examine both the association between patient demographic and cardiac arrest features, hospital characteristics and receipt of coronary angiography and the association between coronary angiography and survival outcomes in OHCA patients. The examination of these associations enabled us to describe clinical practice for successfully resuscitated OHCA patients in Canadian hospitals, and to conclude that receiving coronary angiography itself, regardless of whether or not PCI follows, is associated with survival to hospital discharge and survival with favorable neurologic outcome.

5.14.5 Rescu Epistry Database

The database is of high quality as variables are in the Ustein style, and qualified data abstractors manually enter in-hospital data into the web-based database, which includes many automated features to minimize data entry errors. The electronic data dictionary ensures homogenous data collection across hospitals. Cases are identified prospectively in the Rescu Epistry database, ensuring that selection bias did not exist, and mechanisms were established to ensure a complete and unbiased sample.

5.14.6 Analysis Strategy

The use of multilevel logistic regression to analyze the data, enabled examination of both patient-level and hospital-level factors, while accounting for clustering by hospital, and adjusting for confounding variables. We adjusted for a wide variety of confounders identified through a thorough review of the literature, as well as those identified through expert clinical insight.
5.14.7 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria that were developed for this study ensured that only patients who were eligible to receive coronary angiography were included in the study. More specifically, only patients who survived for at least six hours following initial ED arrival were included in the analysis. The choice of six hours is conservative, however, it was chosen to ensure that patients survived for long enough to be considered for coronary angiography. As a result, the findings from this study are highly clinically relevant, since the study was performed in a group of patients who would be considered for coronary angiography in clinical practice, rather than all OHCA patients.

Furthermore, the inclusion and exclusion criteria for this study were much more lenient than the majority of previous related studies.\(^7,13,20,22,26,31,36\) We did not exclude patients by initial cardiac rhythm, neurologic status or post-arrest ECG findings. This allows the findings from our primary analyses to be generalizable to all OHCA patients who survive for at least six hours following hospital admission.

5.14.8 Subgroup Analyses

Patients with STEMI after OHCA differ in many significant ways from patients without STEMI, and patients who are initially comatose are unique from those who are initially conscious. Evidence has demonstrated that the association between coronary angiography and outcomes may differ by initial post-arrest ECG findings (STEMI, no STEMI),\(^14,16,17,24,73\) and by initial neurologic status (coma, no coma).\(^7,11,20,26,32\) We were able examine the associations of interest separately in comatose OHCA patients, in conscious patients, and in those with and without STEMI on the post-arrest ECG.

5.15 Conclusions

We have described clinical practice in Ontario hospitals, with regard to in-hospital post-resuscitation treatment of OHCA patients with return of spontaneous circulation. More specifically, we determined which patient demographic, cardiac arrest and hospital characteristics predict whether or not an OHCA patient receives coronary angiography.
We found that receipt of coronary angiography is associated with improved survival to hospital discharge and survival with favorable neurologic outcome in resuscitated OHCA patients. These associations were also observed in patients without STEMI, but not in patients with STEMI. It is important to remember that complex interactions exist between the factors that influence the decision to pursue coronary angiography, and the factors that influence survival outcomes.

Our research has also demonstrated that coronary angiography is beneficial to OHCA patients who are comatose at hospital admission. The benefit of coronary angiography and PCI in the patient subgroups that we examined was previously unclear. It will be important for large randomized controlled trials to be conducted in order to confirm our findings, and to definitively elucidate the associations between coronary angiography, PCI and outcomes in selected subgroups of OHCA patients.
References


Appendix A

Classification of Recommendations and Levels of Evidence

The American Heart Association (AHA) and the American College of Cardiology (ACC) detail best practice guidelines for the treatment of particular patient populations\textsuperscript{16-18,24,25} Each recommendation is assigned a level of evidence and a class. The level of evidence provides a rating of the scientific literature used to support the recommendation, in terms of quality, quantity and consistency\textsuperscript{25}. Level of Evidence ranges from A to C, with A being the highest level of evidence having data derived from several randomized controlled trials or meta-analyses\textsuperscript{25}. The class of the recommendation takes into account the magnitude and certainty of benefit over risk\textsuperscript{25}. Class I is the most favorable class, indicating that the benefit of the intervention in question greatly outweighs the risk.

Table 25. Classification of recommendations and levels of evidence

<table>
<thead>
<tr>
<th>Class</th>
<th>(Measure of the size of treatment effect)</th>
<th>Level of Evidence</th>
<th>(Estimate of certainty or precision of treatment effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I:</td>
<td>• Benefit of treatment greatly outweighs risk</td>
<td>Level A:</td>
<td>• Multiple populations are evaluated</td>
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<tr>
<td></td>
<td>• Treatment/procedure SHOULD be performed as it is useful/effective</td>
<td></td>
<td>• Data derived from multiple randomized clinical trials or meta-analyses</td>
</tr>
<tr>
<td>Class IIa:</td>
<td>• Benefit outweighs risk</td>
<td>Level B:</td>
<td>• Limited populations are evaluated</td>
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<td></td>
<td>• IT IS REASONABLE to perform procedure or give treatment as it is believed to be useful/effective</td>
<td></td>
<td>• Data derived from a single randomized clinical trial or nonrandomized studies</td>
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<td>Class IIb:</td>
<td>• Benefit is greater than or equal to the risk</td>
<td>Level C:</td>
<td>• Very limited populations are evaluated</td>
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<tr>
<td></td>
<td>• Treatment/procedure MAY BE CONSIDERED as it may be useful/efficacious</td>
<td></td>
<td>• Data derived from cases studies, consensus among experts or the standard of care</td>
</tr>
<tr>
<td>Class III: Benefit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III: Harm</td>
<td>• Recommendation that treatment/procedure is not beneficial and may be harmful</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from O’Gara et al. (2013)
### Appendix B

#### Limitations of Previous Studies

**Table 26. Limitations of previous studies**

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Population studied</th>
<th>Comparison population</th>
<th>Country and number of centers</th>
<th>Sample Size</th>
<th>Major limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anyfantakis et al. (2009)</td>
<td>- OHCA patients - Received PCI</td>
<td>- OHCA patients - Did not receive PCI</td>
<td>- Paris, France - Single center</td>
<td>72</td>
<td>- Single center - Conducted in Paris - Small sample size - Did not compare coronary angiography (CAG) to no CAG - No subgroup analyses</td>
</tr>
<tr>
<td>Gorjup et al. (2007)</td>
<td>- OHCA patients - Conscious - STEMI - 98% received PCI</td>
<td>- OHCA patients - Comatose - STEMI - 70% received PCI</td>
<td>- Slovenia - Single center</td>
<td>135</td>
<td>- Single center - Small sample size - Conducted outside North America - Restricted to OHCA patients with STEMI - Did not compare PCI to no PCI - Did not compare CAG to no CAG - Compared outcomes of OHCA patients to outcomes of patients without cardiac arrest also</td>
</tr>
<tr>
<td>Hollenbeck et al. (2014)</td>
<td>- Cardiac arrest patients - Ventricular arrhythmia - Without STEMI - Had therapeutic hypothermia - Comatose - Early CAG (≤24 h)</td>
<td>- Cardiac arrest patients - Ventricular arrhythmia - Without STEMI - Had therapeutic hypothermia - Comatose - Later (&gt;24 h) or no CAG</td>
<td>- USA - 6 centers</td>
<td>269</td>
<td>- Restrictive inclusion criteria - Small sample size - Did not compare CAG to no CAG</td>
</tr>
<tr>
<td>Strote et al. (2012)</td>
<td>- OHCA patients - Received early</td>
<td>- OHCA patients - Received later (&gt;6)</td>
<td>- USA - 11 centers</td>
<td>240</td>
<td>- Small sample size - Did not compare</td>
</tr>
<tr>
<td>Study</td>
<td>Population and Intervention</td>
<td>Controls and Outcomes</td>
<td>Number</td>
<td>Limitations</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>---------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| Hosmane et al. (2009)      | (≤6 h) CAG - Cardiac arrest patients - STEMI - Received revascularization (PCI or CABG)   | h) or no CAG - Cardiac arrest patients - STEMI - Did not receive revascularization (PCI or CABG) | 98      | - Small sample size  
- Single center  
- Did not compare PCI to no PCI  
- Did not compare CAG to no CAG  
- All patients had STEMI |
| Callaway et al. (2014)     | OHCA patients - Received early (≤24 h) CAG                                                | OHCA patients - Received later (>24 h) or no CAG                                       | 3981    | - Did not compare CAG to no CAG  
- Did not investigate association between CAG and outcomes in subgroups of OHCA patients (i.e. STEMI, no STEMI)  
- Failed to adjust for initial neurologic status |
| Redpath et al. (2010)      | OHCA patients - Received CAG +/- PCI                                                      | OHCA patients - Did not receive CAG +/- PCI                                             | 13,263  | - Did not investigate association between CAG and outcomes in subgroups of OHCA patients (i.e. STEMI, no STEMI)  
- Did not adjust for important confounders |
| Nanjayya et al. (2012)     | OHCA patients - Initially comatose - Shockable initial cardiac rhythm - Received immediate CAG +/- PCI | OHCA patients - Initially comatose - Shockable initial cardiac rhythm - Did not receive any CAG +/- PCI | 70      | - Small sample size  
- Conducted outside North America  
- Single center  
- All patients comatose with shockable cardiac rhythm |
| Bro-Jeppesen, et al. (2012)| OHCA patients - Initially comatose 1) STEMI patients (n=116) who received emergency CAG (≤12 h) +/- PCI 2) No-STEMI patients (n=244) | OHCA patients - Initially comatose 1) STEMI patients (n=116) who did not receive emergency CAG (≤12 h) +/- PCI 2) No-STEMI patients (n=244) | 360     | - Single center  
- Conducted outside North America  
- All patients were comatose |
<table>
<thead>
<tr>
<th>Study</th>
<th>OHCA patients</th>
<th>Non-OHCA patients</th>
<th>Europe and Australia</th>
<th>Italy</th>
<th>Small sample size</th>
<th>Single center</th>
<th>Conducted outside North America</th>
<th>All patients were comatose</th>
<th>Did not compare CAG to no CAG</th>
<th>Conducted outside North America</th>
<th>All patients with no STEMI</th>
<th>Did not compare CAG to no CAG</th>
<th>Did not compare CAG to no CAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zanuttini et al. (2012)</td>
<td>- OHCA patients - Initially comatose - Received emergency CAG +/- PCI</td>
<td>- OHCA patients - Initially comatose - Received delayed or no CAG +/- PCI</td>
<td>- Italy</td>
<td>Single center</td>
<td>93</td>
<td>- Single center</td>
<td>- Conducted outside North America</td>
<td>- All patients were comatose</td>
<td>- Did not compare CAG to no CAG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dankiewicz et al. (2015)</td>
<td>- OHCA patients - Without ST-elevation - Received early CAG (≤6 h)</td>
<td>- OHCA patients - Without ST-elevation - Received later (&gt;6 h) or no CAG</td>
<td>- Europe and Australia</td>
<td>36 centers</td>
<td>544</td>
<td>- 36 centers</td>
<td>- Conducted outside North America</td>
<td>- All patients with no STEMI</td>
<td>- Did not compare CAG to no CAG</td>
<td>- Conducted outside North America</td>
<td>- Did not compare CAG to no CAG</td>
<td>- Did not compare CAG to no CAG</td>
<td>- Did not compare CAG to no CAG</td>
</tr>
<tr>
<td>Lettieri et al. (2009)</td>
<td>- OHCA patients - STEMI - Received emergency PCI</td>
<td>- Non-OHCA patients - STEMI - Received emergency PCI</td>
<td>- Italy</td>
<td>Multicenter</td>
<td>2617 (99 OHCA and 2518 without OHCA)</td>
<td>- Multicenter</td>
<td>- Conducted outside North America</td>
<td>- All patients had STEMI</td>
<td>- Did not compare CAG to no CAG</td>
<td>- Compared OHCA patient outcomes to non-arrested patient outcomes</td>
<td>- Small number of OHCA patients</td>
<td>- Conducted outside North America</td>
<td>- All patients had STEMI</td>
</tr>
<tr>
<td>Reynolds et al. (2009)</td>
<td>- Cardiac arrest patients - Received CAG</td>
<td>- Cardiac arrest patients - Did not receive CAG</td>
<td>- USA</td>
<td>Single center</td>
<td>241</td>
<td>- Single center</td>
<td>- Included both OHCA and in-hospital cardiac arrest patients</td>
<td>- Small sample size</td>
<td>- Single center</td>
<td>- No subgroup analyses</td>
<td>- Small sample size</td>
<td>- Single center</td>
<td>- No subgroup analyses</td>
</tr>
<tr>
<td>Spaulding et al. (1997)</td>
<td>- OHCA patients aged 30-75 years - Received CAG and successful PCI</td>
<td>- OHCA patients aged 30-75 years - Received CAG but no PCI or unsuccessful PCI</td>
<td>- France</td>
<td>Single center</td>
<td>84</td>
<td>- Single center</td>
<td>- Restricted age range</td>
<td>- Older study</td>
<td>- Small sample size</td>
<td>- Single center</td>
<td>- Conducted outside North America</td>
<td>- Did not compare CAG to no CAG</td>
<td>- No subgroup analyses</td>
</tr>
<tr>
<td>Study Authors (Year)</td>
<td>Population Description</td>
<td>Intervention &amp; Procedure</td>
<td>Country</td>
<td>Sample Size</td>
<td>Notes</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cronier et al. (2011)</td>
<td>- OHCA patients - Shockable initial cardiac rhythm - Most had therapeutic hypothermia 1) STEMI patients who received emergency CAG and PCI 2) Patients without STEMI who received emergency CAG and PCI</td>
<td>- OHCA patients - Shockable initial cardiac rhythm - Most had therapeutic hypothermia 1) STEMI patients who received emergency CAG but no PCI 2) Patients without STEMI who received emergency CAG but no PCI</td>
<td>- France - 2 centers</td>
<td>111</td>
<td>- Small sample size - Conducted outside North America - All had shockable cardiac rhythm - Included cardiac arrest patients with cardiac and non-cardiac causes - Did not compare CAG to no CAG</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dumas et al. (2010)</td>
<td>- OHCA patients 1) STEMI patients who received early CAG and successful PCI 2) Patients without STEMI who received early CAG and successful PCI</td>
<td>- OHCA patients 1) STEMI patients who received early CAG with no or failed PCI 2) Patients without STEMI who received early CAG with no or failed PCI</td>
<td>- France - Single center</td>
<td>435</td>
<td>- Single center - Conducted outside North America - Since all patients received CAG, did not compare CAG to no CAG</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grasner et al. (2011)</td>
<td>- OHCA patients - Received PCI</td>
<td>- OHCA patients - Did not receive PCI</td>
<td>- Germany - Multicenter</td>
<td>584</td>
<td>- Conducted outside North America - Did not compare CAG to no CAG - No subgroup analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garot et al. (2007)</td>
<td>- OHCA patients - STEMI - Had immediate successful PCI</td>
<td>- OHCA patients - STEMI - Immediate PCI unsuccessful</td>
<td>- Paris, France - 5 centers</td>
<td>186</td>
<td>- Small sample size - Conducted outside North America - All patients had STEMI - Did not compare CAG to no CAG</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weiser et al. (2013)</td>
<td>- OHCA cardiac arrest - STEMI 1) Received early PCI 2) Received early CAG (≤12 h) +/- PCI</td>
<td>- OHCA cardiac arrest - STEMI 1) Did not receive early PCI 2) Did not receive early CAG (≤12 h) +/-PCI</td>
<td>- USA - Single center</td>
<td>249</td>
<td>- Single center - All patients had STEMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
## Modified Rankin Scale (MRS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms.</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability. Able to carry out all usual activities, despite some symptoms.</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability. Requires some help, but able to walk unassisted.</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability. Requires constant nursing care and attention, bedridden, incontinent.</td>
</tr>
<tr>
<td>6</td>
<td>Dead.</td>
</tr>
</tbody>
</table>

*Rankin (1957), Sulter et al. (1999)\(^{113,115}\)"
### Appendix D

**Cerebral Performance Categories (CPC) Scale**

<table>
<thead>
<tr>
<th>Cerebral Performance Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>“Conscious, alert, able to work and lead a normal life. May have minor psychologic or neurologic deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities)”</td>
</tr>
<tr>
<td>2</td>
<td>“Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dress, travel by public transportation, food preparation). May have hemiplegia, seizures, ataxia, dysarthria, or permanent memory or mental changes.”</td>
</tr>
<tr>
<td>3</td>
<td>“Conscious. Dependent on others for daily support (in an institution or at home with exceptional family effort). Has at least limited cognition. This category includes a wide range of cerebral abnormalities, from patients who are ambulatory but have severe memory disturbances or dementia precluding independent existence, to those who are paralyzed and can communicate only with their eyes, as in the “locked in” syndrome.”</td>
</tr>
<tr>
<td>4</td>
<td>“Unconscious. Unaware of surroundings, no cognition. No verbal and/or psychologic interaction with environment.”</td>
</tr>
<tr>
<td>5</td>
<td>“Brain dead, circulation preserved.”</td>
</tr>
</tbody>
</table>

*Rittenberger et al. (2011)*
Appendix E

Loess Curves for ‘Age’

Loess curves of age versus the outcomes of interest were created to ensure that it was appropriate to model age as a linear continuous variable. The curves for each outcome demonstrated that age was not a linear continuous variable and therefore modeling it as such would have been inappropriate. Statistical methods were applied to model age as two separate linear variables (Objective 1) and a non-linear continuous variable (Objectives 2 and 3). The Loess plots for each of the outcomes are plotted in the following figures.

![Loess plot for coronary angiography](image)

Figure 8. Loess plot for coronary angiography
Figure 9. Loess plot for survival with favorable neurologic outcome

Figure 10. Loess plot for survival to hospital discharge
Appendix F

Design Effect and Power Calculations

Design Effect

Patients who are initially admitted to a given hospital may be more likely to have both similar exposures and outcomes than patients who are admitted to other hospitals.\textsuperscript{118} For instance, OHCA patients who initially arrive at hospitals with PCI capability may be more likely to be treated with PCI, since the therapy is more readily accessible, and as a result may also be more likely to survive. The result is that patients are no longer independent, which results in a decrease in statistical power.\textsuperscript{118} Therefore, to perform appropriate power calculations, the sample size was deflated by the design effect, which is the factor by which the sample size must be decreased when data is clustered.\textsuperscript{131}

There are two formulas generally used to calculate the design effect. When all units within a cluster are exposed to the factor of interest, while all units in another cluster remain unexposed, the design effect is calculated using the following formula.\textsuperscript{131}

\[
\text{Design effect} = 1 + \rho (n-1), \text{ where } n \text{ is the average cluster size and } \rho \text{ is an estimate of the ICC}
\]

In our study this would be akin to saying that all patients admitted to one hospital received coronary angiography, while no patients admitted to another hospital received coronary angiography. However, when the distribution of exposed and unexposed units are exactly the same in each cluster, then the design effect is as follows;\textsuperscript{131}

\[
\text{Design effect} = 1 - \rho, \text{ where } \rho \text{ is an estimate of the ICC}
\]

This formula would be used to calculate the design effect in our study if the proportion of patients who received coronary angiography in each of the 28 hospitals was exactly the same (30% for instance). We suspected that the design effect would be somewhere between the design effect calculated using each of these formulae since neither of these conditions hold true. The proportion of patients who receive
coronary angiography is never 100% at hospital x and 0% at hospital y, nor is the proportion of patients who receive coronary angiography the same across all hospitals. Given our data, by applying the formulae of Vierron and Giraudeau (2009), we reasonably assumed that our design effect would be between 1.0 and 2.0. Therefore, power calculations were performed ranging the design effect from 1.0 to 2.0.

**Power Calculations**

Power calculations are displayed in the following table. The last column indicates that the power is 80% or greater to detect an $x$ percent absolute difference in outcomes between patients who were exposed to the exposure variable and those who were not. All power calculations were initially conducted by hand and then confirmed using SAS (v 9.4, Cary, NC).

<table>
<thead>
<tr>
<th>Exposure variable</th>
<th>Outcome</th>
<th>Subgroup</th>
<th>$n_1$</th>
<th>$n_2$</th>
<th>$p_1$</th>
<th>Power over 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary angiography</td>
<td>Survival with favorable MRS (0-2)</td>
<td>None</td>
<td>1715</td>
<td>863</td>
<td>0.241</td>
<td>$\geq 10%$ difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STEMI</td>
<td>180</td>
<td>619</td>
<td>0.279</td>
<td>$\geq 15%$ difference, except at design effects $\geq 1.8$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No STEMI</td>
<td>1535</td>
<td>244</td>
<td>0.236</td>
<td>$\geq 10%$ difference, except at design effects $\geq 1.4$</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>Survival to hospital discharge</td>
<td>None</td>
<td>1715</td>
<td>863</td>
<td>0.290</td>
<td>$\geq 10%$ difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STEMI</td>
<td>180</td>
<td>619</td>
<td>0.311</td>
<td>$\geq 15%$ difference, except at design effects $\geq 1.8$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No STEMI</td>
<td>1535</td>
<td>244</td>
<td>0.288</td>
<td>$\geq 10%$ difference, except at design effects $\geq 1.4$</td>
</tr>
<tr>
<td>PCI</td>
<td>Survival with favorable MRS (0-2)</td>
<td>None</td>
<td>1997</td>
<td>581</td>
<td>0.30</td>
<td>$\geq 10%$ difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STEMI</td>
<td>338</td>
<td>458</td>
<td>0.417</td>
<td>$\geq 15%$ difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No STEMI</td>
<td>1634</td>
<td>122</td>
<td>0.275</td>
<td>$\geq 15%$ difference, except at design effects $\geq 1.6$</td>
</tr>
</tbody>
</table>

*n$_1$ = number of individuals unexposed to the exposure variable
*n$_2$ = number of individuals exposed to the exposure variable
*p$_1$ = probability of achieving the outcome for individuals who were unexposed to the exposure variable
Appendix G

Receipt of Coronary Angiography and PCI by Receiving Hospital

Table 28. Proportion of study population receiving coronary angiography and PCI by receiving hospitals

<table>
<thead>
<tr>
<th>Hospital Initially Admitted To</th>
<th>Patients Receiving Coronary Angiography (%)</th>
<th>Patients Receiving PCI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarborough Hospital – General site</td>
<td>20/103 (19%)</td>
<td>10/103 (10%)</td>
</tr>
<tr>
<td>Scarborough Hospital – Grace division</td>
<td>13/72 (18%)</td>
<td>7/72 (10%)</td>
</tr>
<tr>
<td>St. Michael’s Hospital</td>
<td>71/146 (49%)</td>
<td>48/146 (33%)</td>
</tr>
<tr>
<td>The Credit Valley Hospital</td>
<td>18/124 (15%)</td>
<td>11/124 (9%)</td>
</tr>
<tr>
<td>The Royal Victoria Hospital - Barrie</td>
<td>26/90 (29%)</td>
<td>14/90 (16%)</td>
</tr>
<tr>
<td>St. Joseph’s Health Center</td>
<td>19/111 (17%)</td>
<td>8/111 (7%)</td>
</tr>
<tr>
<td>Humber River Regional Hospital – York-Finch</td>
<td>23/90 (26%)</td>
<td>19/90 (21%)</td>
</tr>
<tr>
<td>Trillium Health Center - Mississauga Site</td>
<td>131/256 (51%)</td>
<td>106/256 (41%)</td>
</tr>
<tr>
<td>Orillia Soldiers Memorial Hospital</td>
<td>11/38 (29%)</td>
<td>9/38 (24%)</td>
</tr>
<tr>
<td>Mount Sinai Hospital</td>
<td>6/18 (33%)</td>
<td>1/18 (6%)</td>
</tr>
<tr>
<td>Rouge Valley Health System - Centenary</td>
<td>63/137 (46%)</td>
<td>43/137 (31%)</td>
</tr>
<tr>
<td>Rouge Valley Health System – Ajax</td>
<td>30/73 (41%)</td>
<td>16/73 (22%)</td>
</tr>
<tr>
<td>Lakeridge Health – Bowmanville</td>
<td>8/15 (53%)</td>
<td>7/15 (47%)</td>
</tr>
<tr>
<td>Lakeridge Health – Oshawa Site</td>
<td>43/156 (28%)</td>
<td>26/156 (17%)</td>
</tr>
<tr>
<td>Lakeridge Health – Port Perry</td>
<td>3/15 (20%)</td>
<td>2/15 (13%)</td>
</tr>
<tr>
<td>Collingwood General and Marine Hospital</td>
<td>8/24 (33%)</td>
<td>4/24 (17%)</td>
</tr>
<tr>
<td>Sunnybrook Health Sciences Center</td>
<td>78/169 (46%)</td>
<td>58/169 (34%)</td>
</tr>
<tr>
<td>The Toronto East General Hospital</td>
<td>27/119 (23%)</td>
<td>13/119 (11%)</td>
</tr>
<tr>
<td>North York General Hospital</td>
<td>21/117 (18%)</td>
<td>13/117 (11%)</td>
</tr>
<tr>
<td>Markham Stoufville Hospital</td>
<td>8/61 (13%)</td>
<td>3/61 (5%)</td>
</tr>
<tr>
<td>William Osler Health System – Etobicoke</td>
<td>39/110 (35%)</td>
<td>31/110 (28%)</td>
</tr>
<tr>
<td>The Stevenson Memorial Hospital - Alliston</td>
<td>11/18 (61%)</td>
<td>5/18 (28%)</td>
</tr>
<tr>
<td>Humber River Regional Hospital – Humber Memorial</td>
<td>21/138 (15%)</td>
<td>11/138 (8%)</td>
</tr>
<tr>
<td>University Health Network – General Site</td>
<td>31/59 (53%)</td>
<td>20/59 (34%)</td>
</tr>
<tr>
<td>University Health Network – Western Site</td>
<td>25/75 (33%)</td>
<td>11/75 (15%)</td>
</tr>
<tr>
<td>Muskoka Algonquin Health Care – Bracebridge Site</td>
<td>7/10 (70%)</td>
<td>5/10 (50%)</td>
</tr>
<tr>
<td>Markham Stoufville Hospital – Uxbridge Site</td>
<td>2/10 (20%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>William Osler Health System – Brampton Civic</td>
<td>100/224 (45%)</td>
<td>79/224 (35%)</td>
</tr>
</tbody>
</table>
Appendix H

Intraclass Correlations (ICC) and Median Odds Ratios (MOR) Calculations for Objective 1

Median odds ratios (MOR’s) were calculated from the empty regression models for the outcomes of interest to quantify the amount of variability in outcomes that could be attributed to hospital-level factors and to express it in the odds ratio scale. The median odds ratio converts the hospital-level variation into the odds ratio scale, so that odds ratios can be easily compared.\textsuperscript{136} The median odds ratio can be directly compared to the odds ratios for patient and hospital-level variables.\textsuperscript{136}

For instance, assume there are two patients with the exact same covariates, one treated at hospital $x$ and the other treated at hospital $y$, where the patient at hospital $y$ has a higher propensity to receive coronary angiography.\textsuperscript{137} If the MOR was 1.20, this means that if the patient initially treated at hospital $x$ was transferred to hospital $y$, his/her odds of receiving coronary angiography would be 20\% higher than at hospital $x$.\textsuperscript{136} The larger the MOR, the larger the variation between hospitals.\textsuperscript{137} MOR’s were calculated to determine the between hospital variation in outcomes.

Objective 1

The median odds ratio attained from the empty model demonstrated that the median increase in the odds of receiving coronary angiography was 1.81 times greater if the patient was transferred to a hospital where he/she had a higher probability of receiving coronary angiography. The median odds ratio attained from the adjusted model was 1.67, indicating that even after adjusting for several variables, there are still other hospital-level factors influencing whether or not a patient receives coronary angiography.
Calculations

EMPTY REGRESSION MODEL

Coronary angiography:

Intraclass correlation:

\[ ICC = \frac{\sigma^2}{\sigma^2 + (\pi^2/3)} \]

\[ = \frac{0.3880}{0.3880 + (3.14^2/3)} \]

\[ = 0.105 \approx 10.5\% \]

Median odds ratio:

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

\[ = \exp \left( \sqrt{2} \times 0.3880 \times 0.6745 \right) \]

\[ MOR = 1.81 \]

FINAL MODEL

Coronary angiography:

Median odds ratio:

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

\[ = \exp \left( \sqrt{2} \times 0.2880 \times 0.6745 \right) \]

\[ MOR = 1.67 \]
Appendix I

Intraclass Correlations (ICC) and Median Odds Ratios (MOR) Calculations for Objective 2

Objectives 2 and 3

The median odds ratios attained from the empty models demonstrated that the median increase in the odds of survival with favorable neurologic outcome was 1.47 times greater if the patient was transferred to a hospital where he/she had a higher probability of surviving with favorable neurologic outcome. The median increase in the odds of survival to hospital discharge was 1.44 times greater if the patient was transferred to a hospital where he/she had a higher probability of surviving to hospital discharge.

The median odds ratios from the adjusted models where coronary angiography was the exposure variable, were 1.23 for both survival with favorable neurologic outcome and survival to hospital discharge, indicating that after adjusting for receipt of coronary angiography and other covariates, there are still other hospital-level factors influencing survival outcomes. The median odds ratios from the adjusted models where PCI was the exposure variable, were 1.22 for both survival with favorable neurologic outcome and survival to hospital discharge, indicating that after adjusting for receipt of PCI and other covariates, there are still other hospital-level factors influencing survival outcomes.

Calculations

EMPTY REGRESSION MODELS

Outcome: Survival with favorable neurologic outcome

*Intraclass correlation:*

\[
\text{ICC} = \frac{\sigma^2}{\sigma^2 + \left(\frac{\pi^2}{3}\right)}
\]

\[
= \frac{0.1619}{0.1619 + \left(3.14^2/3\right)}
\]

\[
= 0.047 \approx 4.7%
\]
Median odds ratio:

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

\[ \text{MOR} = \exp \left( \sqrt{2} \times 0.1619 \times 0.6745 \right) \]

\[ \text{MOR} = 1.47 \]

Outcome: Survival to hospital discharge

Intraclass correlation:

\[ \text{ICC} = \frac{\sigma^2}{\sigma^2 + (\pi^2/3)} \]

\[ = 0.1479/ [0.1479 + (3.14^2/3)] \]

\[ = 0.043 \approx 4.3\% \]

Median odds ratio:

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

\[ \text{MOR} = \exp \left( \sqrt{2} \times 0.0475 \times 0.6745 \right) \]

\[ \text{MOR} = 1.44 \]

FINAL MODELS

Coronary angiography and survival with favorable neurologic outcome:

Median odds ratio:

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

\[ \text{MOR} = \exp \left( \sqrt{2} \times 0.0475 \times 0.6745 \right) \]

\[ \text{MOR} = 1.23 \]
Coronary angiography and survival to hospital discharge:

Median odds ratio:

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

\[ \text{MOR} = \exp \left( \sqrt{2} \times 0.0479 \times 0.6745 \right) \]

MOR = 1.23

PCI and survival favorable neurologic outcome:

Median odds ratio:

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

\[ \text{MOR} = \exp \left( \sqrt{2} \times 0.04236 \times 0.6745 \right) \]

MOR = 1.22

PCI and survival to hospital discharge:

Median odds ratio:

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

\[ \text{MOR} = \exp \left( \sqrt{2} \times 0.04462 \times 0.6745 \right) \]

MOR = 1.22
Appendix J

Model Building

Coronary angiography and survival with favorable neurologic outcome:
The final model included the following covariates listed in order from strongest to weakest confounder of the association: initial cardiac rhythm, initial neurologic status, age, STEMI status, and bystander AED use.

Coronary angiography and survival with favorable neurologic outcome in STEMI patients:
The final model included the following covariates listed in order from strongest to weakest confounder of the association: initial neurologic status, location of arrest, initial cardiac rhythm, age, prehospital ROSC, hospital size (medium vs. small).

Coronary angiography and survival with favorable neurologic outcome in patients without STEMI:
The final model included the following covariates listed in order from strongest to weakest confounder of the association: initial cardiac rhythm, initial neurologic status, and age.

Coronary angiography and survival to hospital discharge:
The final model included the following covariates listed in order from strongest to weakest confounder of the association: initial cardiac rhythm, initial neurologic status, age, bystander AED use, and STEMI status.

Coronary angiography and survival to hospital discharge in STEMI patients:
The final model included the following covariates listed in order from strongest to weakest confounder of the association: initial neurologic status, age, initial cardiac rhythm, prehospital ROSC, location of arrest, hospital size (medium vs. small), therapeutic hypothermia.

Coronary angiography and survival to hospital discharge in patients without STEMI:
The final model included the following covariates listed in order from strongest to weakest confounder of the association: initial cardiac rhythm, initial neurologic status, and age.
Appendix K

Sensitivity Analyses

Several post hoc sensitivity analyses were conducted to explore the robustness of the results. Refer to Table 29 for results from sensitivity analyses. A small amount of data was missing in our study population. It was imputed using a multiple imputation procedure in SAS. Our primary analyses were conducted after imputing the missing data with multiple imputation. However, in a sensitivity analysis, the analysis was conducted before conducting multiple imputation (n=2289).

The analysis was also conducted using Cerebral Performance Category (CPC) score as the primary outcome, rather than MRS score. Favorable CPC score was defined as having a CPC score of 1 or 2 at hospital discharge and poor CPC score was defined as having a CPC score of 3-5 at hospital discharge (refer to Appendix D) or being deceased. A sensitivity analysis was also performed using a less conservative definition of survival with favorable neurologic outcome, in which a MRS score of 0-3 indicated favorable neurologic outcome, rather than an MRS score of 0-2. After conducting these sensitivity analyses, we found that the findings did not change meaningfully in strength or significance overall, or in either of the STEMI subgroups.
Table 29. Sensitivity analyses: Coronary angiography and outcomes overall and by STEMI status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Model</th>
<th>Overall</th>
<th>STEMI</th>
<th>No STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Odds Ratio (CI&lt;sub&gt;95&lt;/sub&gt;)</td>
<td>p-value</td>
<td>Odds Ratio (CI&lt;sub&gt;95&lt;/sub&gt;)</td>
</tr>
<tr>
<td>Survival with</td>
<td>Primary adjusted</td>
<td>1.89(1.37-2.59)</td>
<td>&lt;.0001</td>
<td>1.04(0.62-1.75)</td>
</tr>
<tr>
<td>CPC score 0-2</td>
<td>Secondary adjusted</td>
<td>2.00(1.47-2.73)</td>
<td>&lt;.0001</td>
<td>1.16(0.71-1.91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.73</td>
<td>1.91</td>
<td>4.21</td>
</tr>
<tr>
<td>Survival with</td>
<td>Primary adjusted (before imputation)</td>
<td>1.91(1.39-2.62)</td>
<td>&lt;.0001</td>
<td>1.04(0.62-1.75)</td>
</tr>
<tr>
<td>MRS 0-3</td>
<td>Secondary adjusted</td>
<td>2.03(1.49-2.77)</td>
<td>&lt;.0001</td>
<td>1.14(0.69-1.87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.62</td>
<td>1.74</td>
<td>4.03</td>
</tr>
<tr>
<td>Survival with</td>
<td>Primary adjusted (before imputation)</td>
<td>1.83(1.30-2.56)</td>
<td>0.0005</td>
<td>0.91(0.53-1.57)</td>
</tr>
<tr>
<td>MRS 0-2</td>
<td>Secondary adjusted (before imputation)</td>
<td>2.07(1.50-2.85)</td>
<td>&lt;.0001</td>
<td>1.13(0.68-1.87)</td>
</tr>
</tbody>
</table>

*Primary model adjusted for covariates identified from literature *Secondary model adjusted for clinically important covariates, identified via expert opinion. Refer to Section 3.8.6.1 for covariates included in each of the models.
Appendix L

Features of Patients Without STEMI by Receipt of Coronary Angiography

Table 30. Comparison of patient and cardiac arrest features for patients without STEMI by receipt of coronary angiography

<table>
<thead>
<tr>
<th>Patient and cardiac arrest features</th>
<th>Received coronary angiography (N=244)</th>
<th>Did not receive coronary angiography (N=1535)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>76.6%</td>
<td>70.0%</td>
</tr>
<tr>
<td>Age</td>
<td>61 (+/-13)</td>
<td>69 (+/-16)</td>
</tr>
<tr>
<td>Initial shockable cardiac rhythm</td>
<td>80.3%</td>
<td>30.6%</td>
</tr>
<tr>
<td>Bystander witnessed arrest</td>
<td>62.3%</td>
<td>50.6%</td>
</tr>
<tr>
<td>EMS witnessed arrest</td>
<td>18.8%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Bystander resuscitation</td>
<td>53.3%</td>
<td>38.1%</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>41.8%</td>
<td>30.8%</td>
</tr>
<tr>
<td>Bystander AED</td>
<td>16.8%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Public location of arrest</td>
<td>41.0%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Prehospital ROSC</td>
<td>92.6%</td>
<td>88.5%</td>
</tr>
<tr>
<td>EMS response time (minutes) (+/-SD)</td>
<td>6.0 (+/2.3)</td>
<td>6.3 (+/2.6)</td>
</tr>
<tr>
<td>Presentation during business hours</td>
<td>34.8%</td>
<td>33.4%</td>
</tr>
<tr>
<td>Comatose</td>
<td>66.8%</td>
<td>91.2%</td>
</tr>
<tr>
<td>Initiation of therapeutic hypothermia</td>
<td>59.0%</td>
<td>65.3%</td>
</tr>
<tr>
<td>Inotropic drugs</td>
<td>41.3%</td>
<td>71.1%</td>
</tr>
</tbody>
</table>
Appendix M

Features of Patients With STEMI by Receipt of Coronary Angiography

Table 31. Comparison of patient and cardiac arrest features for patients with STEMI by receipt of coronary angiography

<table>
<thead>
<tr>
<th>Patient and cardiac arrest features</th>
<th>Received coronary angiography (N=619)</th>
<th>Did not receive coronary angiography (N=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>82.2%</td>
<td>69.4%</td>
</tr>
<tr>
<td>Age</td>
<td>62(+/-12)</td>
<td>70(+/-15)</td>
</tr>
<tr>
<td>Initial shockable cardiac rhythm</td>
<td>84.8%</td>
<td>49.7%</td>
</tr>
<tr>
<td>Bystander witnessed arrest</td>
<td>59.1%</td>
<td>57.8%</td>
</tr>
<tr>
<td>EMS witnessed arrest</td>
<td>24.9%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Bystander resuscitation</td>
<td>49.6%</td>
<td>42.8%</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>44.3%</td>
<td>35.6%</td>
</tr>
<tr>
<td>Bystander AED</td>
<td>5.5%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Public location of arrest</td>
<td>41.8%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Prehospital ROSC</td>
<td>90.5%</td>
<td>83.9%</td>
</tr>
<tr>
<td>EMS response time (minutes) (+/- SD)</td>
<td>6.2(+/3.1)</td>
<td>6.3(+/-2.0)</td>
</tr>
<tr>
<td>Presentation during business hours</td>
<td>34.6%</td>
<td>33.9%</td>
</tr>
<tr>
<td>Comatose</td>
<td>70.4%</td>
<td>91.7%</td>
</tr>
<tr>
<td>Initiation of therapeutic hypothermia</td>
<td>62.2%</td>
<td>67.2%</td>
</tr>
<tr>
<td>Inotropic drugs</td>
<td>55.1%</td>
<td>75.0%</td>
</tr>
</tbody>
</table>
Appendix N

Post-Hoc Subgroup Analysis: STEMI Status and Initial Neurologic Status

Overall, in STEMI patients, there was no association between coronary angiography and survival with favorable neurologic outcome or survival to hospital discharge. When the STEMI patients were grouped by initial neurologic status (conscious versus comatose), there was a stronger association in conscious STEMI patients than in comatose STEMI patients. STEMI patients who were conscious at hospital admission and received coronary angiography had 84% greater odds of surviving with favorable neurologic outcome than those who did not receive coronary angiography, however, this finding was not statistically significant. Wide confidence intervals suggest that low power in this subgroup analysis likely played a role. On the contrary, the association in STEMI comatose patients was small and non-significant (OR=1.19, CI$_{95}$ 0.71-1.98).

Patients without STEMI who received coronary angiography had about three times the odds of surviving with favorable neurologic outcome, regardless of whether they were initially conscious or comatose. However, the association was non-significant in conscious patients likely due to the small sample size in this subgroup. Refer to the following table for odds ratios and confidence intervals.

<table>
<thead>
<tr>
<th></th>
<th>Survival with favorable neurologic outcome</th>
<th>Survival to hospital discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Odds Ratio (CI$_{95}$)</td>
<td>p-value</td>
</tr>
<tr>
<td>STEMI comatose</td>
<td>1.19(0.71-1.98)</td>
<td>0.51</td>
</tr>
<tr>
<td>STEMI conscious</td>
<td>1.84(0.09-39.44)</td>
<td>0.70</td>
</tr>
<tr>
<td>No STEMI comatose</td>
<td>2.92(1.90-4.47)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No STEMI conscious</td>
<td>3.32(0.56-19.49)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Adjusting for initial cardiac rhythm, initiation of therapeutic hypothermia, prehospital ROSC, age, sex, PCI center status, bystander resuscitation, bystander witnessed arrest, EMS witnessed arrest.
Appendix O

Variance Inflation Factor

The variance inflation factor (VIF) provides a measure of the amount of correlation between variables. A variable displaying a variance inflation factor above 10 indicates that it is highly correlated with another variable. In this case, perhaps one of the variables should be removed from the model, since the estimation results will be poor for variables with variance inflation factors above 10. If highly correlated variables are kept in the model, caution must be taken in interpreting estimates derived from these variables. However, none of the covariates were highly correlated with one another, except for age under 50 and age above 50, which had VIFs of 8.8 and 9.0. Covariates were not correlated with the primary exposure variable; coronary angiography or the secondary exposure variable; PCI. All of the variables had a variance inflation factor less than five, with most variables displaying a variance inflation factor closer to one. Variance inflation factors of variables included in each objective are provided in Table 32.

Table 33. Variance Inflation Factors

<table>
<thead>
<tr>
<th>Predictors of receiving coronary angiography (Objective 1)</th>
<th>Coronary angiography and covariates (Objective 2)</th>
<th>PCI and covariates (Objective 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>VIF</td>
<td>Variable</td>
</tr>
<tr>
<td>Medium hospital</td>
<td>1.95</td>
<td>Medium hospital</td>
</tr>
<tr>
<td>Large hospital</td>
<td>5.34</td>
<td>Large hospital</td>
</tr>
<tr>
<td>Hospital type</td>
<td>2.47</td>
<td>Hospital type</td>
</tr>
<tr>
<td>PCI center</td>
<td>2.21</td>
<td>PCI center</td>
</tr>
<tr>
<td>Hospital cardiac arrest volume</td>
<td>2.79</td>
<td>Hospital cardiac arrest volume</td>
</tr>
<tr>
<td>Age &lt; 55</td>
<td>8.79</td>
<td>Age</td>
</tr>
<tr>
<td>Age ≥ 55</td>
<td>9.05</td>
<td>Coronary angiography</td>
</tr>
<tr>
<td>Sex</td>
<td>1.08</td>
<td>Sex</td>
</tr>
<tr>
<td>Event</td>
<td>Bystander-witnessed</td>
<td>Bystander-witnessed</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>---------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>arrest</td>
<td>1.53</td>
<td>1.53</td>
</tr>
<tr>
<td>EMS-witnessed arrest</td>
<td>1.85</td>
<td>1.86</td>
</tr>
<tr>
<td>Bystander resuscitation</td>
<td>4.31</td>
<td>Bystander resuscitation</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>4.01</td>
<td>Bystander CPR</td>
</tr>
<tr>
<td>Bystander AED use</td>
<td>1.15</td>
<td>Bystander AED use</td>
</tr>
<tr>
<td>Location of arrest</td>
<td>1.28</td>
<td>Location of arrest</td>
</tr>
<tr>
<td>EMS response time</td>
<td>1.09</td>
<td>EMS response time</td>
</tr>
<tr>
<td>Initial neurologic status</td>
<td>1.61</td>
<td>Initial neurologic status</td>
</tr>
<tr>
<td>Initial cardiac rhythm</td>
<td>1.41</td>
<td>Initial cardiac rhythm</td>
</tr>
<tr>
<td>STEMI status</td>
<td>1.24</td>
<td>STEMI status</td>
</tr>
<tr>
<td>Initiation of therapeutic hypothermia</td>
<td>1.51</td>
<td>Initiation of therapeutic hypothermia</td>
</tr>
<tr>
<td>Presentation during business hours</td>
<td>1.05</td>
<td>Presentation during business hours</td>
</tr>
<tr>
<td>Prehospital ROSC</td>
<td>1.07</td>
<td>Prehospital ROSC</td>
</tr>
</tbody>
</table>

*VIF=variance inflation factor*
Appendix P

Research Ethics Board Approval

QUEEN’S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW
December 05, 2014

Miss Tasha Hanuschak
Department of Public Health Sciences
Queen’s University

Dear Miss Hanuschak

Study Title: EPID-491-14 Factors influencing administration of coronary angiography in patients with return of spontaneous circulation
File # 6014342
Co-Investigators: Dr. S. Brooks, Dr. Y.P. Peng

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 # 6014342 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 6014342 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 L. Clark

Chair, Health Sciences Research Ethics Board
December 05, 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 US 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: #FWA0000184, #IRB0000173

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. M. Evans, Community Member

Ms. J. Hudacin, Community Member

Mr. D. McNaughton, Community Member

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. M. Sawhney, Assistant Professor, School of Nursing, Queen's University

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

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

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

Dr. J. Whiteley, Community Member