ACCESS TO CARDIAC CATHERIZATION SERVICES IN A RURAL-URBAN SETTING IN NORTHERN BRITISH COLUMBIA: EXAMINING THE IMPACT OF TIME-DELAY TO PCI ON PATIENT OUTCOMES AND WHETHER THE SICKEST GO THE QUICKEST...

by

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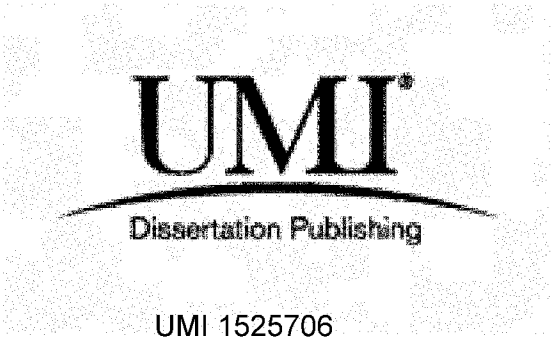

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Abstract

This thesis describes the results of a study exploring patient access to percutaneous coronary intervention (PCI) in a rural-urban setting in northern British Columbia, Canada. It specifically examines: 1) whether longer times to treatment (>120mins) are associated with higher adverse outcomes (death, re-infarction, heart failure, or stroke) in the UA, NSTEMI and STEMI groups within 30-days and 1-year of hospital admission and 2) whether patients most at risk using the Global Registry of Acute Coronary Events (GRACE) risk score receive PCI faster in the UA, NSTEMI and STEMI groups. Data were collected through retrospective medical chart reviews. Times to treatment and adverse outcomes data are provided although quantitative analysis of this association was not performed. It was determined that the only significant predictor of time to PCI was age and patients were not transferred according to their risk status. Thus it can be concluded that this exploratory study provided valuable real-time feedback for cardiac services in this region and is a basis for further longitudinal investigation in this area.

Keywords: percutaneous coronary intervention, thrombolysis, unstable angina, segment elevated myocardial infarction, non-segment elevated myocardial infarction, Global Registry of Acute Coronary Events, GRACE, risk score, GRACE risk score

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GLOSSARY

Acute coronary syndrome (ACS): umbrella terms for the clinical signs and symptoms of myocardial ischemia; unstable angina (UA), non-segment elevated myocardial ischemia (NSTEMI), and segment elevated myocardial ischemia (STEMI)

Acute myocardial infarction: chest pain due to the sudden reduction of blood flow to the heart

Atherogenic dyslipidemia: a metabolic risk factor characterized by the serum elevation of triglycerides, apo B and low density lipoproteins (LDL), as well as a decreased level of high density lipoproteins

Atherosclerosis: plaque buildup which can lead to the narrowing of coronary arteries

Angioplasty: also known as balloon angioplasty, percutaneous coronary intervention, balloon angiography, coronary angiography

Catheter: a small, narrow tube that can be inserted into a body cavity, duct or vessel

Congestive heart failure (CHF): condition that occurs when the heart is unable to provide sufficient blood flow to maintain the needs of the body and vital organs

Coronary artery bypass graft (CAGB): a type of open-heart surgery in which a vein is removed from an area such as the leg is stitched to the aorta and coronary artery to create a new path for the flow of oxygenated blood to the heart

Coronary heart disease (CHD): a disease of the coronary arteries in which plaque buildup obstructs the supply of oxygenated blood to the heart

Coronary heart disease: narrowing or blockage of the arteries which supply blood to the heart

Door-to-balloon time (d2b): the time elapsed between the patient presenting to the emergency department with ACS symptoms to the point of PCI initiation

Fibrinolysis: see thrombolysis

Global Registry of Acute Coronary Events (GRACE): a risk stratification tool used to predict both in-hospital and six month mortality post acute coronary syndrome presentation

Myocardial infarction: a heart attack

Myocardial ischemia: a sudden reduction in blood flow to the heart

Non-segment elevated myocardial ischemia (NSTEMI): the partial occlusion of a coronary artery

Percutaneous coronary intervention: a non-surgical procedure which uses a catheter to place stent to open blood vessels in the heart which were occluded by plaque

Peripheral vascular disease (PVD): the obstruction of arteries (other than coronary) from plaque buildup and thrombus formation among other causes

Segment-elevated myocardial ischemia (STEMI): usually indicative of a full occlusion of a coronary artery which can lead to the necrosis of the myocardium

Thrombolysis: the use of pharmacological agents to break up blood clots, often interchangeably used in the literature with the term, fibrinolysis

Thrombolysis in Myocardial Infarction (TIMI): a risk stratification tool used to predict mortality post acute coronary syndromes

Thrombus: a blood clot

University Hospital of Northern British Columbia (UHNBC): the largest regional hospital in Northern British Columbia, located in Prince George, also serves as a clinical teaching centre for the Northern Medical Program offered jointly through the University of British Columbia and the University of Northern British Columbia

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Finally I am grateful for the support of my family and friends. To my sisters and grandma for their unconditional support. To my mum, for being an invaluable source of strength and inspiration.

Dedication

To my father- J.S.K. I will never outgrow the feeling I get in knowing you are on my side. I know that if I need a little encouragement you will always be there just like when I was little. Thank you for giving me the strength to believe in myself and reach for the stars. T.G.N.

And to the patients of northern British Columbia, who despite the many associated with rural life, call this their home.

CHAPTER ONE: INTRODUCTION

Cardiovascular disease can be defined as a group of disorders that affect the heart and blood vessels (Public Health Agency of Canada, 2009). Cardiovascular disease is one of the leading causes of death for all Canadians (Statistics Canada, 2012). In fact it is estimated that every seven minutes, a Canadian dies due to heart disease or stroke (Heart and Stroke Foundation, 2012). Economically, CVD and stroke cost the Canadian economy over $20.9 billion annually in physician services, hospital costs, lost wages and decreased productivity (Charles River Associates, 2010; Heart and Stroke Foundation, 2012).

Coronary heart disease (CHD) is the most common form of CVD. CHD can lead to an acute myocardial infarction (AMI), or chest pain due to a sudden reduction in blood flow to the heart muscle. This restriction in blood flow results from a buildup of plaque deposits in the coronary arteries that are responsible for supplying oxygenated blood to the heart. It is estimated that there are nearly 70,000 AMIs a year in Canada 19,000 of which are fatal (Tu et al., 2003; Healthy People, 2010) and a large number of Canadians suffering from an AMI die before they are able to receive medical care.

Acute Myocardial Infarction most commonly presents in the form of acute coronary syndrome (ACS). Acute coronary syndrome is the umbrella term given for the clinical signs and symptoms of the following conditions associated with myocardial ischemia including: unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevated myocardial infarction (STEMI) (Overbaugh, 2009). These conditions represent a continuum of acuity and increasing

intensity from unstable angina to ST-segment myocardial infarction. Unstable angina and non-ST segment elevated myocardial infarction typically arise from a partially occluded coronary artery whereas ST-segment elevated myocardial infarction is indicative of a full occlusion of the artery and typically results in a full thickness infarction (Overbaugh, 2009).

Risk factors

There are a number of established cardiometabolic risk factors for CVD. These include: smoking, Type 2 diabetes mellitus, alcohol consumption, a lack of physical activity, elevated levels of serum cholesterol, and high blood pressure (Tanuseputra et al., 2003). According to recent statistics by the Heart and Stroke Foundation (2012) of Canada, at least nine out of ten Canadians have at least one or more of these risk factors. In addition to these factors, risk can also be increased due to certain influences such as sex (male), age (45 and over for males, 55 and over for females), family history, prior cardiac history (prior myocardial infarction, congestive heart failure (CHF), prior percutaneous coronary intervention (PCI), prior coronary artery bypass graft (CABG), a history of stroke and/or transient ischemic attack (TIA), atrial fibrillation (AF), and peripheral vascular disease (PVD)) and ethnic background. For example, research has shown that those of South Asian descent have much higher rates of cardiovascular disease when compared to other ethnic groups (Anand et al., 2000; Gupta et al, 2006; Joshi et al., 2007).

Geography and the link to cardiovascular disease

Canada is recognized by many around the world for the health care system and related services that it provides its citizens (Romanow, 2002). One of the core principles of the publically funded Canadian health care system is that of universal access to medically necessary care. While universal access to health services is perceived as one of the most important and underlying values of the system, the fact remains that not all Canadians are true recipients of universal and equal access to these services.

In Canada, the vast geography of the country makes it a challenge to deliver access to health care services and resources on a uniform basis. It is often seen that the larger, more urban centres are often equipped with highly advanced technology and a variety of specialized services and service providers. This is in stark contrast to Canada's rural and remote regions where health care services are often limited and hard to come by (Smith et al., 2008).

In situations like this, patients in rural settings needing more advanced health care services are often faced with the prospect of being transferred to larger centres to receive care. While medically necessary procedures including interventional cardiac services, are covered by provincial health care plans in Canada, the transfer of patients to these centres involves many variables that can affect patient outcomes (Pilote et al., 2004). These include, insufficient staffing levels, a lack of specialized services, and increased wait times to receive access to services (Ross et al., 2006).

One of the main concerns to health care providers is the impact of wait times on patient health outcomes. This is also true for higher-level life saving cardiac services

which are more often readily available in only the larger, more urban centres in Canada (Pilote et al., 2004; Patel et al., 2010). For example, primary percutaneous coronary intervention, is considered the reference treatment for patients suffering from acute coronary syndrome, in particular, STEMI (Zijlstra, 2003). It is considered to be superior to the pharmacological option of thrombolysis with respect to decreasing rates for both patient mortality and morbidity (Antman et al., 2008; Van de Werf et al., 2006; Keeley et al., 2003; Boersma et al., 2006). There are however major barriers to the implementation of widespread use of primary PCI (PPCI). These barriers include, the delay due to the lack of centres capable of performing PCI and long distances for transport required for access to the procedure (Sorensen et al., 2011).

Although not explicitly thought of as a risk factor, the concept of geography has been identified as a determinant of health. It can also have a profound influence on risk status for cardiovascular disease. Those living in rural areas are considered to be at higher risk for the development of cardiovascular disease. It is also a well-documented fact that those living in rural areas have poorer health status when compared to their urban counterparts (Romanow, 2002; Pong et al., 2009). Rural dwelling individuals have been documented to display a greater incidence of unhealthy lifestyle behaviors as compared to those in urban settings (DesMeules & Pongo, 2006; Pamplon et al., 2006). This often results in them having higher frequencies of the classical CVD risk factors such as diabetes, physical inactivity, and obesity.

In addition to increased levels of risk factors, risk is further exacerbated due to the unique challenges that rural individuals face when accessing health care services for their conditions. For example, it is a well-known fact that rural areas face challenges in the

recruitment of physicians and other allied health care professionals such as physiotherapists, and medical diagnostic technicians (Fleet et al., 2013). This often directly impacts the availability of diagnostic services and advanced level care procedures. As a result, rural patients are faced with the prospect of having to travel for their health care needs. This leads to the added burden of travel costs, and added wait times among other issues. As well there may be additional risk associated with moving to an urban centre (Sibley & Weiner, 2011). For example, the risk of travelling long distances in less than ideal weather conditions. Furthermore, patient outcomes are generally worse for those living in rural areas as highlighted by the increased mortality rates for cardiovascular disease in rural patient populations (Filate et al., 2003; DesMeules & Pongo, 2006).

Symptoms of acute coronary syndrome

Acute coronary syndrome, more commonly referred to in layperson's terms as a heart attack, presents with some common symptoms. These include: chest pain or discomfort, which is often described as involving a sense of crushing, tightness or pressure, pain or discomfort in one or both arms, neck, jaw, back or stomach, shortness of breath, a feeling of dizziness or lightheadedness, nausea and/or vomiting, and sweating. However, ischemia can also occur without any of these typical signs or symptoms. It is referred to in medical terms as 'silent ischemia' (Overbaugh, 2009). Silent ischemia is more common in the elderly (65 years and older), those with diabetes, and the female sex. The outcomes for silent ischemia are often worse as the absence of symptoms results in delays for seeking treatment. This delay in treatment seeking often leads to lower rates of recovery and higher rates of mortality (Maron & Hochman, 2013).

Diagnosis and management of acute coronary syndrome

The protocol for ACS diagnosis at hospitals in British Columbia is based on the guidelines established by British Columbia's provincial government. These provincial guidelines are based on those developed jointly by both the American Heart Association (AHA) and the American College of Cardiology (ACC). These guidelines split patients into the following categories namely, definite ACS and possible ACS.

When a patient presents to the emergency department with symptoms of ACS such as chest pain or difficulty breathing, there is a set of steps performed to determine whether it is ACS. These steps are established by the BC Medical Association and are presented in Figure 1. (pg. 10). ACS is essentially a working diagnosis and there are a series of tests and procedures performed to pinpoint the diagnosis and specifically define the type of ACS.

These patients are triaged according to the Canadian Triage Acuity Scale (CTAS). If the patient complains of typical ACS symptoms, and more specifically chest pain, they are triaged as a 1 (resuscitation required), 2 (emergent care required), or sometimes a 3 (urgent care required). These patients are given high priority and are evaluated on an urgent basis. Diagnostic test for ACS involve two preliminary tests including a blood test, and a 12-lead electrocardiogram (ECG) and also involves evaluation by a physician.

Diagnosis of an acute myocardial infarction is based upon the following criteria being met: detection of a rise and/or fall of cardiac biomarkers, specifically troponin. At least one value should be above the 99th percentile, plus at least one of the following: symptoms of ischemia, ECG changes indicating new ischemia; ST elevation; new left

bundle branch block, new pathological Q waves in the ECG, and /or imaging showing a new loss of viable myocardium or new regional wall motion abnormality.

Myocardial ischemia causes tissue damage and myocardial cell death resulting in the release of cardiac biomarkers in the blood, specifically troponins, TnT and TnI, and CK-MB). Testing for these biomarkers is perfomed alongside a 12-lead ECG and physician evaluation to diagnose ACS. The cardiac troponins are considered to be more sensitive and more specific in the detection of myocardial damage, and they are measured upon patient presentation and six to eight hours post chest pain onset.

A diagnosis of STEMI is made when cardiac biomarkers are elevated and electrocardiography reveals that there is ST-segment elevation or new left-bundle branch block whereas a diagnosis of NSTEMI is made when cardiac biomarkers are elevated and electrocardiography reveals there is ST-segment depression or T-wave inversion. Unstable angina is diagnosed when cardiac biomarkers are not elevated and electrocardiography findings reveal ST-segment depression or T-wave inversion.

Management of STEMI

Patients with STEMI are treated with the intent of reperfusing the ischemic muscle. The reference treatment for STEMI is PCI while thrombolysis is now only used in hospitals without PCI capabilities or in instances when PCI cannot be delivered in the target 'door-to-balloon' (d2b) times of 90 minutes or less (Levine et al., 2011). The ACC/AHA guidelines recommend that patients who receive thrombolytic therapy are transferred to a PCI capable centre following the treatment. Patients with STEMI presenting to UHNBC are transferred via British Columbia (BC) air ambulance, a flight

with duration of about an hour to one of the five cardiac catherization labs in the province. These include: Vancouver General Hospital (VGH) or St. Paul's Hospital (SPH) in Vancouver, Royal Jubilee Hospital (RJH) in Victoria, Kelowna General Hospital (KGH) in Kelowna, or Royal Columbian Hospital (RCH) in New Westminster (Figure. 2). This inter-hospital transfer of patients to provincial cardiac catherization labs is overseen by BC Bedline, formerly known as the Patient Transfer Network (PTN).

Management of NSTEMI/UA

Patients with NSTEMI or UA are treated for acute myocardial ischemia (British Columbia Medical Association, Guidelines and Protocols Advisory Committee, 2008). This treatment involves: bed rest with continuous ECG monitoring, oxygen for patients with respiratory distress or oxygen levels of less than 90%, sublingual nitrates for those experiencing continuous pain or intravenous nitrates for those with stable blood pressure readings or those unresponsive to sublingual nitrates or beta-blockers (Fitchett et al., 2011; Wright et al., 2011). Percutaneous coronary intervention (PCI) may also used for NSTEMI/UA patients though less frequently than those with STEMI (Fitchett et al., 2011; Wright et al., 2011). An alternative and more frequently used approach for NSTEMI and UA patients is the use of low molecular weight heparin, aspirin and anti-platelets agents such as clopidogrel, as well as statins and ace inhibitors. Along with beta-blockers these have been shown to decrease mortality in these patients (Wong et al., 2003). However, if considered suitable candidates for PCI, patients with NSTEMI or UA are also transferred to provincial cardiac labs like those with STEMI. Although the optimal time frame for maximum therapeutic benefit from PCI for these patients has not

been well-defined however early or immediate catherization is recommended (Jneid et al., 2012).

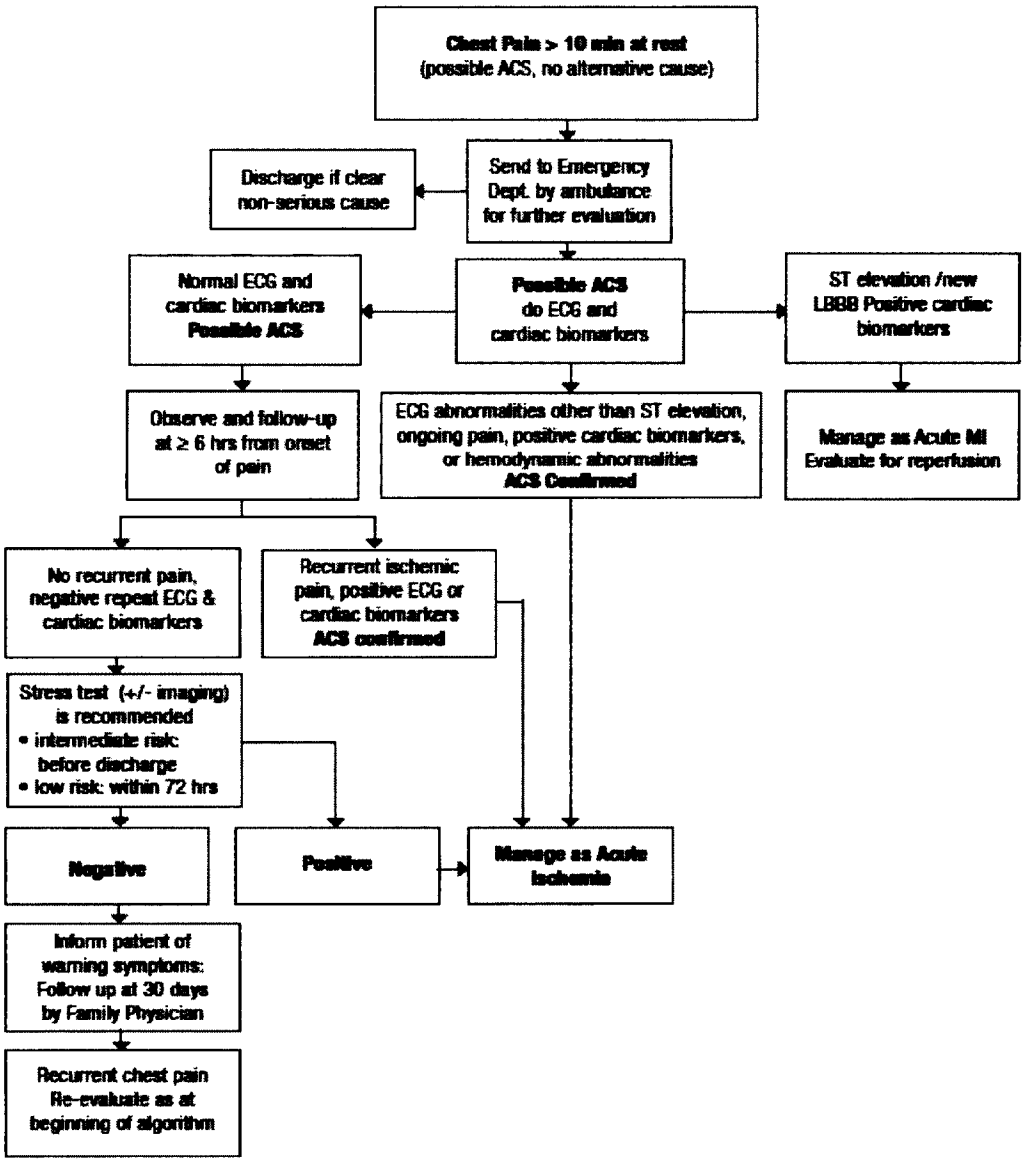

Figure 1. Management of suspected ACS algorithm (reprinted with permission from the British Columbia Medical Association, Guidelines & Protocols Advisory Committee 2014)

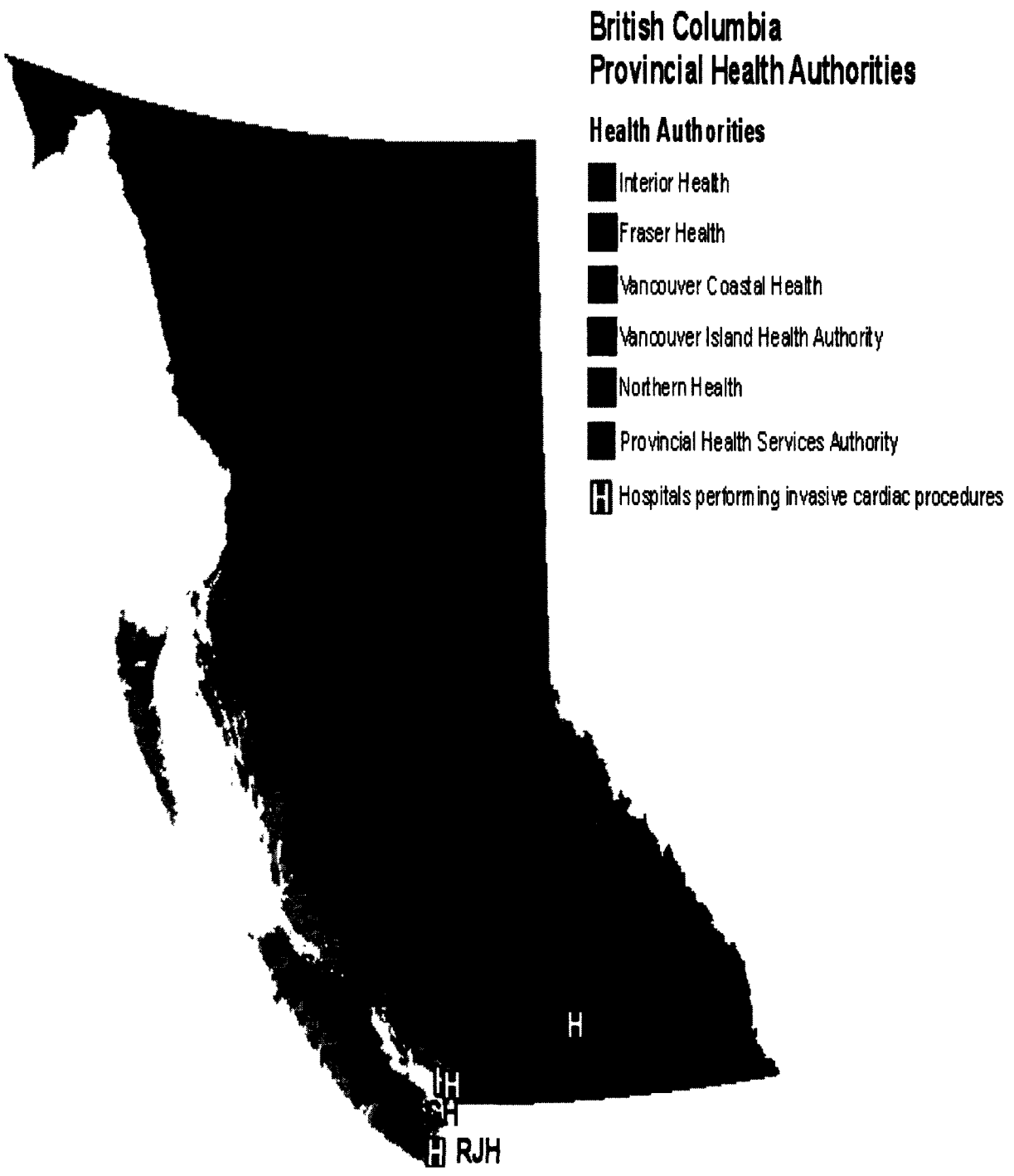

Figure 2. Provincial cardiac catherization labs in British Columbia (reprinted with permission from Cardiac Services BC [CSBC], 2014)

Treatment options

The current 'gold standard' for treatment of ACS is percutaneous coronary intervention (PCI) with respect to decreasing rates for both patient mortality and morbidity (Antman et al., 2008; Van de Werf et al., 2006; Keeley et al., 2003; Boersma et al., 2006). It is also known as balloon angioplasty, coronary angioplasty, coronary balloon angioplasty, coronary transluminal angioplasty and coronary artery angioplasty. Percutaneous coronary intervention (PCI) is a non-surgical procedure that is used to widen coronary arteries occluded by plaque deposits. It is performed through the use of a thin catheter. The catheter is inserted through the femoral or radial artery and is used to place a stent in the occluded blood vessel. When the stent tip is in place, a balloon on the end of the stent is inflated. The inflation of the balloon compresses the plaque and expands the stent. When the plaque has been compressed and the stent has fully expanded into place, the balloon is deflated and withdrawn (Heart and Stroke Foundation, 2012). Current ACC/AHA guidelines consider primary PCI (PPCI) to be most effective when delivered in the 'door to balloon' time of 90 minutes. In centres where primary PCI is not feasible, a 'door to balloon' time of 120 minutes is recommended.

Not all hospitals have on-site cardiac catherization labs. In fact some hospitals do not have access to catheriztion labs in their region and require patient transportation across large distances to receive required care. For hospitals not equipped with catherization facilities to perform PCI, pharmacological measures are the next best option. These measures, vary depending on diagnosis of STEMI or NSTEMI/UA. For patients with STEMI, thrombolysis or fibrinolysis, is the preferred treatment and it commonly involves the administration of tissue plasminogen activators (tPAs) for the

purpose of dissolving the artery obstructing clot. According to guidelines developed by the American Heart Association, thrombolytics are most effective when received within the first 90 minutes of presentation and greatly increase the patient's chances of survival and recovery if administered within 12 hours of symptom presentation (Levine et al., 2011).

Thrombolytics are used only in instances when not countra-indicated. Such countra-indicative factors are usually present in high-risk patients where the risk of administering treatment outweighs the potential for benefit to the patient. Such factors include: recent head trauma, bleeding problems, ulcers, pregnancy, recent surgery, uncontrolled high blood pressure and whether the patient is on blood thinning agents.

For patients suffering from NSTEMI or UA, pharmacological options include: low molecular weight heparin, aspirin and anti-platelets agents (eg. clopidogrel) as well as statins and ace inhibitors. Along with beta blockers these have been shown to decrease mortality and the anti-platelet agents and heparin are probably the most important therapies. There is no documented benefit in the literature from thrombolysis in these types of ACS (Levine et al., 2011). However, pretreatment with intensive antithrombotic therapy may diminish thrombus burden and "passivate" unstable plaques, improving the safety of percutaneous revascularization and reducing the risk of peri-procedural ischemic complications (Jneid et al., 2012).

Knowledge gaps

While recent advances in pharmacology and revascularization procedures have dramatically improved health outcomes for patients with ACS both the incidence and

prevalence of ACS is increasing and is further expected to increase (Grundy et al., 2004). This increase is thought to be in large part due to the exponential increases in obesity and Type 2 diabetes mellitus expected worldwide (Lakka et al., 2002; Malik et al., 2004; Booth et al., 2006; Donahoe, et al., 2007; Fox et al., 2007). This phenomenon is occurring in both, developed and developing countries alike. Rural and northern areas are being the most impacted due to poorer health status and health care resource limitations (Arcury et al., 2005). With the rise in incidence there is an increased stress on the health care system and resources. In such instances it is crucial to find ways to maximize the effectiveness of these resources and to use them in the most efficient manner possible. To date, there is a scarcity of research that has been conducted on this topic area.

The University Hospital of Northern British Columbia

The University Hospital of Northern British Columbia (UHNBC) is located in Prince George, the capital of northern British Columbia. It is a health care facility with over 200 acute care beds, and is the largest hospital in the entire northern region of the province (Northern Health Community Health Information Portal, 2013). It falls under the jurisdiction of the Northern Health Authority, one of the six regional health authorities in the province of British Columbia (Figure 3.). The hospital serves as a regional hub for health services and serves a city population of 80,000 and an estimated 300,000 that live in the more rural areas of the north (Rural Coordination Centre of British Columbia, 2013).

The UHNBC provides services that are not readily available in smaller community hospitals including: a variety of diagnostic services, radiology, neonatal

intensive care, trauma care, as well as clinics for chronic ailments and maternity services. Patients from other areas within the Northern Health Authority boundaries can be sent to UHNBC for evaluation, stabilization or further treatment. Furthermore, some may be transferred from other community hospitals to UHNBC to await transfer to a larger facility in the Lower Mainland for services not available in the north. In addition to providing health care services, the hospital serves as a clinical teaching campus for students in health professions such as physiotherapy, medical laboratory technology and medicine.

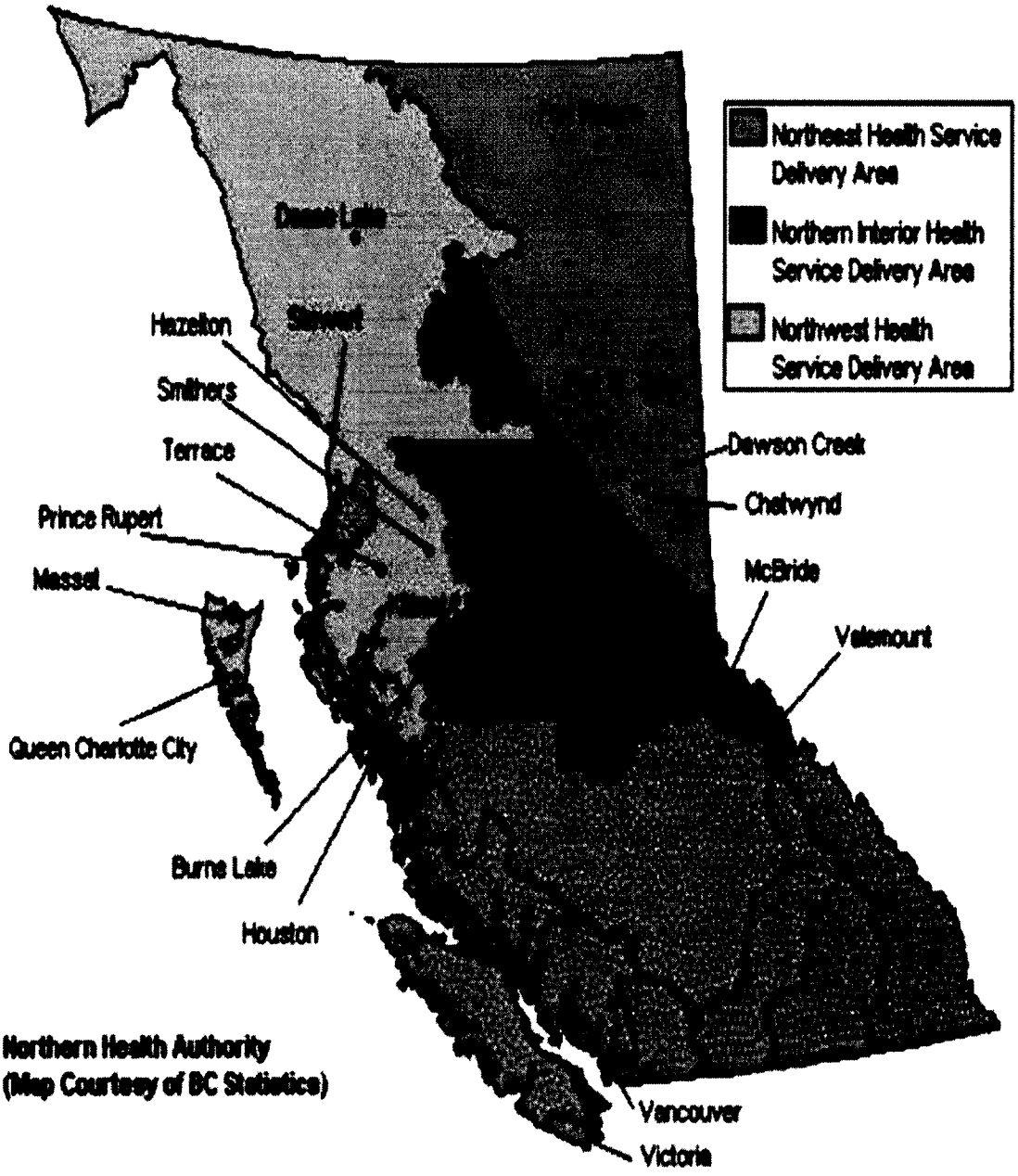

Figure 3. Areas served by the Northern Health Authority (reprinted with permission from UBC Faculty of Medicine, 2014)

Rationale for the study

This study aims to address the issue of access to cardiac catherization services, specifically PCI for patients in northern British Columbia. It responds to an important health care need in this part of the province. This study aims to explore the issue of access to PCI with a high-risk population with unique geography and health needs. Patients presenting to UHNBC are transferred for care to hospitals equipped with cardiac catherization labs. While most catherization centres recognize the urgency for treatment of patients with ACS, there is lack of a standardized or formal process for assigning patient priority. Instead this is done most often through either a formal or informal triage process. It is a process that often relies highly on physician judgement and can lead to some centres allocating the next 'available slot' to patients with ACS requiring the procedure. In fact there is little evidence to support that any centre risk stratifies patients for the urgency of transfer or has a system to ensure appropriate and timely triage of patients with ACS (Patel et al., 2010).

The rationale for studying patients presenting to UHNBC with ACS varies. To begin with, ACS is a fairly common presentation at the emergency department at UHNBC. In fact, northern BC has the highest AMI hospitalization rate and highest CVD related mortality rate in all of British Columbia (Cardiac Services British Columbia, 2010).

Secondly, based on prior estimates of ACS data for UHNBC, it was expected that the sample size would be adequate for this study. It was estimated that there would be

approximately 250 patients presenting to UHNBC with ACS for the one year time period of January 2012 through to December of 2012.

Thirdly, the population of northern British Columbia is considered to be a high-risk group for ACS. Higher rates of traditional risk factors, geographical barriers, and limited health care resources all contribute to this heightened risk status. It is therefore important to study this population and it is safe to assume that carrying out this project will help to inform cardiac care for future ACS patients at UHNBC.

Fourth, UHNBC currently has no facilities for PCI or angiography, which the literature regards as the 'gold standard' treatment for ACS STEMI (D'Souza et al., 2011). Patients with ACS who require this treatment are sent down to the hospitals in the Lower Mainland namely, Vancouver General or St. Paul's. This is in contradiction to the literature as the literature states that to be the most effective, PCI should be delivered in the 'door to balloon' time of 90 minutes (D'Souza et al., 2011). However, it is obvious by just the flight duration from Prince George to Vancouver of over just over an hour that achieving this target time is effectively impossible. Therefore research on this topic will help determine the impact of those wait times and allow for insight into areas of potential improvement in current practices.

Finally, it is important to note that given a Canadian context, the vast geography and population dispersion, we cannot justify the creation of PCI centres in every hospital. The primary objective here was to see whether when thrombolysed (or not), longer times to treatment for PCI are associated with worse patient outcomes and to determine

whether patients are transferred according to their risk status. This will help to provide direction for the future.

Research objectives

The proposed study has the following research objectives. They include: 1) to determine through multiple linear regression whether longer door-to-balloon times (>120mins) are associated with higher rates of adverse outcomes (death, re-infarction, heart failure, or stroke) in the UA, NSTEMI and STEMI groups within 30-days and one-year of hospital admission and 2) to determine through multiple linear regression whether the patients most at risk using the GRACE score receive PCI faster in UA, NSTEMI or STEMI groups

Significance of the research

This research responds to an important health issue of cardiac care in a setting with a high-risk population and limited access to evidence-based treatment. It also has the potential to drive changes in the clinical setting that may aid in improving patient outcomes. There is no doubt that there has been much research into the importance of rapid access to PCI, as well as the risk stratification of ACS patients using GRACE risk scores. Despite all this research, there remains a gap in the literature when it comes to studying these topics from a rural point of view. In fact the available research is often focused on centres where access to PCI is readily attainable. Furthermore, the study populations in this research are often urban dwelling and have a better overall health status as well as a different set of risk factors than their rural dwelling counterparts. This

is of significance as this limits the generalizability of the findings of these studies to the rural population.

Patients living in rural settings face unique health care challenges. These challenges can be in the form of poorer health status and health outcomes or limitations in access to health care services (Romanow, 2002; DesMeules et al., 2006). Addressing the aforementioned research aims from a rural standpoint will offer a relevant perspective to the issues faced by patient with acute coronary syndrome in a rural health care setting with particular health care needs.

A northern perspective

Northern British Columbia is a resource rich area of the province with an abundance of thriving forests, lakes, rivers and wildlife. This region is a major driving force behind the provincial economy. Northern BC is highly industry based with a heavy focus on forestry, mining and fishing. The northern region covers 2/3 of the northern part of the province, equivalent to area the size of France (de Leeuw, 2011). It is home to a population of approximately 350,000, most of which live in rural or remote areas. This combination of a vast geographical landscape coupled with an unevenly distributed rural population makes it difficult for efficient health care service delivery. In addition to this, the high-risk lifestyle associated with industry jobs that are dominant in this region can have additional negative impacts on the health status of this subset of the population (Pamplon et al., 2006).

The population in northern British Columbia is considered to be at high-risk for ACS. Factors contributing to this increased risk include high rates of obesity, diabetes,

smoking, alcohol consumption and physical inactivity. According to a recent report by Cardiac Services British Columbia (2011), northern British Columbia has the highest diabetes, obesity and smoking rates in the entire province. This region comes second highest for physical inactivity, and third highest for hypertension and heavy alcohol consumption (Cardiac Services British Columbia, 2011). This part of the province has a large concentration of First Nations people. This is of significance as heart disease is the leading cause of death among First Nations people (Heart and Stroke Foundation, 2012). Thus this makes it all the more important to study this topic from a northern point of view.

In addition to the effects of a northern and rural geography, there are additional factors that can impact the health of northern dwelling populations (University of Northern British Columbia, 2013). These factors include: physical and emotional isolation, a transient population, and seasonal employment alongside the fluctuation of a resource based economy, and a harsh climate. Additionally, the use of population, which is low and dispersed, can work to further disadvantage this community when it is used determine public investment in services as well as resource allocation, including health care services for this area.

This thesis is organized into six chapters. The next section of this thesis reviews existing literature on the use of PCI and the concept of risk stratifying patients with ACS using the Global Registry of Acute Coronary Events (GRACE) risk score. The approach used to risk stratify patients is described. Findings related to time to PCI and risk status of patients are summarized. The review of existing literature is followed by a description of the methodological and analytic procedures as well as a presentation of the results of this

research. Following this a discussion of the findings is presented and the thesis concludes with a discussion of implications, recommendations and directions for future research.

CHAPTER TWO: LITERATURE REVIEW

A review of the literature was conducted in relation to the two research questions that will be examined in this study. These include; the importance of timely access to percutaneous coronary intervention (PCI) for patients with ACS, and value of performing the risk stratification of patients with acute coronary syndrome using the Global Registry of Coronary Events (GRACE) risk scores. (see Appendix G/H for summary tables).

It begins with a discussion of the importance of timely access to primary percutaneous coronary intervention (PPCI) and moves onto discuss options in the event that PPCI is not available or cannot be conducted in the recommended time frame. Finally the GRACE risk score is introduced and its use for ACS patients is discussed. This is followed by a discussion on validation studies conducted on the use of the GRACE risk score for ACS patients and their findings.

Search strategy

A review of the literature was conducted through electronic health databases. For both research questions the databases used included: CINHAL, Medline Ovid, PubMed, and Cochrane Reviews. These databases were used as they were found to be most relevant to the research in question and evidence-based medical practice trials. In addition to this, an examination of grey literature available through Google Scholar was conducted to identify any missed relevant literature. Searches were limited to 2002-2013, trials involving humans, and publications in the English language, For the first research question, search words included: percutaneous coronary intervention, coronary

intervention, balloon angioplasty, transluminal coronary angioplasty, angioplasty, thrombolysis, fibrinolysis, time to treatment, door to balloon time, primary PCI, facilitated PCI, rescue PCI. Searches were filtered using the restriction of randomized control trials. For the second research question search terms included: Global Registry of Acute Coronary Events, GRACE, GRACE risk score, risk score, risk stratification, acute coronary syndrome(s).

Importance of timely access to percutaneous coronary intervention

Percutaneous coronary intervention (PCI) is a non-surgical procedure that helps to restore blood flow to the affected artery. It is essentially used to widen coronary arteries occluded by plaque deposits. It is performed through the use of a thin catheter that is used to place a stent in the occluded blood vessel. When the stent tip is in place, a balloon on the end of the stent is inflated. The inflation of the balloon compresses the occluding plaque and expands the stent. When the plaque has been compressed and the stent is in place and has fully expanded, the balloon is deflated and withdrawn (Heart and Stroke Foundation, 2012).

Current ACC/AHA guidelines consider PCI to be most effective when delivered in the 'door to balloon' time of 90 minutes. However, this target time is rarely achieved, especially in hospital settings without on-site cardiac catherization labs (De Luca et al., 2004). Instead facilitated, PCI post thrombolysis, or rescue PCI in the event of failed thrombolysis, is performed in such cases. ACC/AHA guidelines consider a 'door to balloon' time of less than 120 minutes acceptable in such conditions (Levine et al., 2011). Still this recommended target time can be hard to achieve given the real-life context (McNamara et al., 2006; Rathore et al., 2009). Futhermore, the generalizability of these

guidelines may be limited in Canadian context as they are reflective of the American landscape. The United States has a different geography, a much larger and more distributed population as well as a health care system that is very distinct from the publicly funded system in Canada thus expecting strict adherence to one set of guidelines for both nations is unfair and unrealistic.

Primary PCI has shown to offer more benefits as compared to fibrinolysis for many patients presenting with STEMI (Keeley et al., 2003). These benefits however are only sustained within 2 to 3 hours of door-to-balloon times (Levine et al., 2011). Given the current context, a rural urban setting without PCI capable facilities, the recommended target d2b times of less than 120 minutes are often a difficult feat to achieve. One of the greatest barriers to achieving target time is the inter-hospital transfer process (Scheller et al., 2003). This process can significantly increase times to treatment. This can be due to certain factors including; unsafe weather conditions for the air ambulance transfer, a lack of beds at the tertiary receiving centre as well a numerous other health care resource limitations which indirectly can affect transfer times. Therefore the current review of the literature will focus specifically on the results of randomized trials comparing fibrinolysis with transfer to another hospital for PCI and outcomes associated with facilitated or rescue PCI.

Facilitated PCI-use with fibrinolytics versus PCI alone

A study conducted by Widimisky et al. (2000), referred to as the PRAGUE study (*PR*imary *A*ngioplasty in patients transferred from *G*eneral community hospitals to specialized PTCA *U*nits with or without *E*mergency thrombolysis) compared three different reperfusion strategies in patients with AMI, presenting within six hours of

symptom onset at community hospitals without a catheterization laboratory and related PCI capabilities. Patients were randomized into one of the three treatment groups namely; *group A* (thrombolytic therapy in community hospitals (n=99)), *group B* (thrombolytic therapy during transportation to angioplasty (n=100)), and *group C* (immediate transportation for primary angioplasty without pre-treatment with thrombolysis (n=101)). The transport distance to the specialized PCTA units varied between 5 and 74 kilometers. There were no complications during transportation in group C. However, complications occurred during transfer for group B involving two instances of ventricular fibrillation. Median admission-reperfusion time in transported patients was as follows; group B 106 minutes and group C 96 minutes. These times compared favorably with the anticipated 90 minutes time in group A. The combined primary end-point, death or reinfarction and/or stroke at 30 days, was less frequent in group C (8%) compared to both groups B (15%) and A (23%, $p < 0.02$). The incidence of reinfarction was markedly reduced by transport to primary angioplasty (1% in group C vs 7% in group B vs 10% in group A, $p < 0.03$). Therefore, Widimisky and collegues (2000) concluded that transferring patients from community hospitals to a tertiary angioplasty centre, in the acute phase of myocardial infarction, was both feasible and safe. Furthermore this strategy was found to be associated with a significant reduction in the incidence of reinfarction and the combined clinical end-point of death, reinfarction, and stroke at 30 days (group C 8% and group B 15%) when compared to standard thrombolytic therapy at the community hospital (23%, $p < 0.02$).

Three years later there was a follow-up study conducted to the PRAGUE trial, entitled the PRAGUE-2 trial by Widimisky et al. (2003). The PRAGUE-2 study involved

the randomization of 850 patients with acute ST elevation myocardial infarction presenting within 12 hours to the nearest community hospital without a catheter laboratory to either thrombolysis in this hospital (TL group, n=421) or immediate transport for primary percutaneous coronary intervention (PCI group, n=429). The primary end-point was defined as 30-day mortality while the two secondary end-points included; death, reinfarction, and /or stroke at 30 days, a combined end-point, and 30-day mortality among patients treated within 0-3 hours and 3-12 hours after symptom onset. The maximum transport distance to catheter laboratories was 120 kilometres. There were five unspecified complications (1.2%) that occurred during patient transport. Randomization-balloon time in the PCI group was between 70 and 124 minutes, and randomization-needle time in the TL group was between 2 to 22 minutes. Mortality at 30 days was 10.0% in the TL group compared to 6.8% mortality in the PCI group ($p = 0.12$, intention-to-treat analysis). Mortality of 380 patients who actually underwent PCI was 6.0% versus 10.4% mortality in 424 patients who finally received thrombolysis, TL group ($p < 0.05$). Among the 299 patients randomized more than 3 hours after the onset of symptoms, the mortality of the TL group reached 15.3% compared to 6% in the PCI group ($p < 0.02$). Patients randomized within 3 hours of symptom onset (n=551) had no difference in mortality whether treated by TL (7.4%) or transferred to PCI (7.3%). A combined end-point occurred in 15.2% of the TL group versus 8.4% of the PCI group ($p < 0.003$). Widimisky et al. (2003) thus concluded that long distance transport from a community hospital to a tertiary PCI centre in the acute phase of AMI is safe as this strategy was associated with marked decreases in mortality in patients presenting more than 3 hours after symptom onset. However for patients presenting within 3 hours of

symptom onset, TL results were similar to the results in long distance transport for PCI.

The Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) study by Ellis et al. (2004) was a prospective, multicenter, randomized, double-blind, placebo-controlled trials involving 3000-patients. The study compared the efficacy and safety of early administration of reduced-dose reteplase and abciximab combination therapy or abciximab alone followed by PCI with abciximab alone administered just before PCI for AMI. Patients were randomized to one of these two facilitated PCI treatments, reduced-dose reteplase and abciximab combination therapy or abciximab alone followed by PCI with abciximab alone, or primary PCI in a 1:1:1 fashion. The primary end point was the composite of all-cause mortality or post-MI complications within 90 days of randomization. The primary safety outcome assessment was made through the use of the Thrombolysis In Myocardial Infarction (TIMI) score for the outcome of major bleeding. One-year mortalities in the three groups, reduced-dose reteplase and abciximab combination therapy or abciximab alone followed by PCI with abciximab alone, or primary PCI, were 6.3%, 7.4%, and 7.0%, respectively (p = NS), representing 1.1%, 1.9%, and 2.5% increments since the 90-day outcome (p = 0.053 for combination treatment vs. primary PCI). A favorable trend with combination treatment was seen for patients with anterior MI (p = 0.09), but no other specified groups were shown to benefit. Independent baseline correlates of 1-year mortality were systolic blood pressure less than100 mm Hg, prior myocardial infarction, age, Killip class greater than 1, anterior MI, body mass index less than or equal to 25 kg/m^2, heart rate greater than100 beats/min, and no statin use. Based on the results Ellis et al. (2004) concluded that widespread utilization of the facilitated approaches tested could not be justified, but that

high-risk patient groups such as patients with anterior MI deserve further study.

The GRACIA-2 trial (2007) was a randomized controlled trial that evaluated whether lytic-based early routine angioplasty represents a reasonable reperfusion option for victims of STEMI irrespective of geographic or logistical barriers, more specifically in cases where PPCI was not possible within the recommended guideline times. The trial involved a total of 212 AMI STEMI patients which were randomized to either the full tenecteplase followed by stenting within 3-12 hours of randomization (early routine post-fibrinolysis angioplasty; n=104), or to undergo primary stenting with abciximab within 3 hours of randomization (primary angioplasty; n=108). The primary endpoints were defined as epicardial and myocardial reperfusion, and the extent of left ventricular myocardial damage, determined by means of the infarct size and six-week left ventricular function. The secondary endpoints were defined as the acute incidence of bleeding and the six-month composite incidence of death, reinfarction, stroke, or revascularization. Results indicated that early routine post-fibrinolysis angioplasty resulted in higher frequency (21 versus 6%, p = 0.003) of complete epicardial and myocardial reperfusion (TIMI 3 epicardial flow and TIMI 3 myocardial perfusion and resolution of the initial sum of ST-segment elevation > or = 70%) following angioplasty. Both groups were similar regarding infarct size (area under the curve of CK-MB: 4613 +/- 3373 versus 4649 +/- 3632 microg/L/h, p= 0.94); 6-week left ventricular function (ejection fraction: 59.0 +/- 11.6 versus 56.2 +/- 13.2%, p= 0.11; end systolic volume index: 27.2 +/- 12.8 versus 29.7 +/- 13.6, p = 0.21); major bleeding (1.9 versus 2.8%, p = 0.99) and six month cumulative incidence of the clinical endpoint (10 versus 12%, p = 0.57; relative risk: 0.80; 95% CI: 0.37-1.74). Thus Fernández-Avilés et al. (2007) concluded that early

routine post-fibrinolysis angioplasty safely results in better myocardial perfusion than primary angioplasty as despite its delayed application, this approach was seen to be equivalent to primary angioplasty in limiting infarct size and preserving left ventricular function.

Transfer for PPCI vs. Immediate thrombolysis in AMI

The AIR-PAMI study by Grines et al. (2002) involved high-risk AMI patients (aged 70 years or older, anterior MI, Killip class II/III, heart rate greater than 100 beats/min or systolic blood pressure less than 100 mm Hg) who were eligible for thrombolytic therapy. Patients (n= 138) were randomized to either of two treatment arms, transfer for primary PTCA (n=71) or on-site thrombolysis (n=67). The time from arrival to treatment was delayed in the transfer group (155 versus 51 min, $p< 0.0001$), largely due to the initiation of transfer (43 min) and transport time (26 min). Patients randomized to transfer had a reduced hospital stay (6.1 +/- 4.3 versus 7.5 +/- 4.3 days, $p= 0.015$) and less ischemia (12.7% versus 31.8%, $p = 0.007$). At 30 days, a 38% reduction in major adverse cardiac events was observed for the transfer group however, because of the inability to recruit the necessary sample size, this did not achieve statistical significance (8.4% versus 13.6%, $p = 0.331$). Grines et al. (2002) concluded that high-risk patients with AMI at hospitals without a catheterization laboratory may have an improved outcome when transferred for primary PTCA versus on-site thrombolysis and suggested that the marked delay in the transfer process suggests a role for triaging patients directly to specialized heart-attack centers.

The DANAMI-2 (2003) trial randomly assigned 1572 patients with AMI to treatment with angioplasty or accelerated treatment with intravenous alteplase; 1129

patients were enrolled at 24 referral hospitals and 443 patients at five invasive-treatment centers. The primary study end point was a composite of death, clinical evidence of reinfarction, or disabling stroke at 30 days. Among patients who underwent randomization at referral hospitals, the primary end point was reached in 8.5% of the patients in the angioplasty group, as compared with 14.2% of those in the fibrinolysis group ($p=0.002$). The results were similar among patients who were enrolled at invasive-treatment centers: 6.7% of the patients in the angioplasty group reached the primary end point, as compared with 12.3% in the fibrinolysis group ($p=0.05$). Among all patients, the better outcome after angioplasty was driven primarily by a reduction in the rate of reinfarction (1.6% in the angioplasty group versus. 6.3% in the fibrinolysis group, $p<0.001$); no significant differences were observed in the rate of death (6.6 % versus 7.8 %, $p=0.35$) or the rate of stroke (1.1 % versus 2.0 %, $p=0.15$). Ninety-six % of patients were transferred from referral hospitals to an invasive-treatment center within two hours. Andersen et al. (2003) concluded that a strategy for reperfusion involving the transfer of patients to an invasive-treatment center for primary angioplasty is superior to on-site fibrinolysis, provided that the transfer takes two hours or less.

The ASSENT-4 trial (2006) investigated whether the administration of full-dose tenecteplase before a delayed PCI could mitigate the negative effect of this delay. ASSENT-4 was a randomized study in which patients with STEMI of less than six hours in duration were (scheduled to undergo primary PCI with an anticipated delay of 1-3 hours) to standard PCI (n=838) or PCI preceded by administration of full-dose tenecteplase (n=829). All patients received aspirin and a bolus, without an infusion, of unfractionated heparin. The primary endpoint was death or congestive heart failure or

shock within 90 days.

It is important to note that the initial plan was to enroll 4000 patients, but the premature cessation of enrollment was recommended by the data and safety monitoring board because of a higher in-hospital mortality in the facilitated than in the standard PCI group (6% [43 of 664] versus 3% [22 of 656], p=0.0105). Of those enrolled, six were lost to follow-up in the facilitated PCI group and seven in the other group. Median time from randomization to first balloon inflation was similar in both groups. The median time from bolus tenecteplase to first balloon inflation was 104 min. The primary endpoint was 19% (151 of 810) of patients assigned facilitated PCI versus 13% (110 of 819) in those randomized to primary PCI (relative risk (RR): 1.39, 95% CI 1.11-1.74; p=0.0045). It was also found that during the hospital stay, significantly more strokes (1.8% (15 of 829) versus 0, p<0.0001), but not major non-cerebral bleeding complications (6% (46 of 829) versus 4% [37 of 838], p=0.3118), were reported in patients assigned facilitated rather than standard PCI. Furthermore more ischemic cardiac complications, such as reinfarction (6% (49 of 805) versus 4% (30 of 820), p=0.0279) or repeat target vessel revascularization (7% (53 of 805) versus 3% (28 of 818), p=0.0041) within 90 days in this study group. Van der Werf et al. (2006) concluded that the strategy of full-dose tenecteplase with antithrombotic co-therapy, as used in this study and preceding PCI by one to three hours, was associated with more major adverse events than PCI alone in STEMI and cannot be recommended.

A follow-up study to the DANAMI-2 trial was conducted by Nielsen et al. in 2010. The study involved the randomization of 1572 patients with STEMI to primary angioplasty or intravenous alteplase; 1129 patients were enrolled at 24 referral hospitals

and 443 patients at five angioplasty centres. Ninety-six percent of inter-hospital transfers for angioplasty were completed within two hours and no patients were lost to follow-up. The composite endpoints primarily, death, clinical re-infarction, or disabling stroke, were reduced by angioplasty when compared with fibrinolysis at 3 years (19.6% versus 25.2%, p= 0.006). For patients transferred to angioplasty compared with those receiving on-site fibrinolysis, the composite endpoint occurred in 20.1% versus 26.7% (p= 0.007), death in 13.6 versus 16.4% (p= 0.18), clinical re-infarction in 8.9% versus 12.3% (p= 0.05), and disabling stroke in 3.2% versus 4.7% (p= 0.23). The benefit of transfer for primary angioplasty based on the composite endpoint was sustained after three years. Nielsen et al. (2010) concluded that for patients with characteristics such as those in DANAMI-2, primary angioplasty should be the preferred treatment strategy provided that inter-hospital transfer can be completed within two hours.

The LIPSIA-STEMI (2011) multicenter trial sought to assess the merits of facilitated percutaneous coronary intervention (PCI) versus primary PCI in an ST-segment elevation myocardial infarction (STEMI) network with long transfer distances in patients presenting early after symptom onset. Patients with STEMI presenting less than 3 hours after symptom onset, were randomized to either pre-hospital-initiated facilitated PCI using tenecteplase (Group A; n = 81) or primary PCI (Group B; n = 81) plus optimal antithrombotic co-medication. The primary endpoint was infarct size assessed by delayed-enhancement magnetic resonance imaging. Secondary endpoints included microvascular obstruction and myocardial salvage, early ST-segment resolution, and a composite of death, repeated myocardial infarctions, and congestive heart failure within 30 days. The median time from symptom onset to randomization was 64 min

(interquartile range (IQR): 42 to 103 min) in Group A versus 55 min in Group B (IQR: 27 to 91 min; p = 0.26). Despite better pre-interventional TIMI (Thrombolysis In Myocardial Infarction) flow in Group A (71% versus 35% TIMI flow grade 2 or 3; p < 0.001), the infarct size tended to be worse in Group A versus Group B (17.9% of left ventricle IQR: 8.4% to 35.0%) versus 13.7% IQR: 7.5% to 24.0%); p = 0.10). There was also a strong trend toward more early and late microvascular obstruction, (p = 0.06 and 0.09) and no difference in ST-segment resolution (p = 0.26). The combined clinical endpoint showed a trend toward higher event rates in Group A (19.8% versus 13.6%; p = 0.13, relative risk (RR): 0.52, 95% CI: 0.23 to 1.18). Thiele et al. (2011) concluded that in STEMI patients presenting early after symptom onset with relatively long transfer times, a fibrinolytic-based facilitated PCI approach with optimal antiplatelet co-medication does not offer a benefit over primary PCI with respect to infarct size and tissue perfusion.

Early PCI when PPCI is not feasible

The Southwest German Interventional Study in Acute Myocardial Infarction (SIAM-III trial) (2003) investigated potentially beneficial effects of immediate stenting after thrombolysis as opposed to a more conservative treatment regimen. The SIAM III study was a multicenter, randomized, prospective, controlled trial in patients receiving thrombolysis in AMI (less than12 hours). Patients of group I were transferred within six hours after thrombolysis for coronary angiography, including stenting of the IRA. Group II received elective coronary angiography two weeks after thrombolysis with stenting of the IRA. A total of 197 patients were randomized, 163 patients fulfilled the secondary (angiographic) inclusion criteria (82 in group I, 81 in group II). Immediate stenting was

associated with a significant reduction of the combined end point after six months (ischemic events, death, reinfarction, target lesion revascularization 25.6% versus 50.6%, p = 0.001). Bohmer et al. (2003) concluded that immediate stenting after thrombolysis leads to a significant reduction of cardiac events compared with a more conservative approach including delayed stenting after two weeks.

The GRACIA-1 trial (2004) was designed to reassess the benefits of an early post-thrombolysis interventional approach in the era of stents and new antiplatelet agents. The study involved 500 patients with thrombolysed STEMI, with recombinant tissue plasminogen activator. Patients were randomly assigned to angiography and intervention if indicated within 24 hours of thrombolysis, or to an ischaemia-guided conservative approach. The primary endpoint was the combined rate of death, reinfarction, or revascularisation at 12 months. Invasive treatment included stenting of the culprit artery in 80% (199 of 248) patients, bypass surgery in six (2%), non-culprit artery stenting in three, and no intervention in 40 (16%). Pre-discharge revascularisation was needed in 51 of 252 patients in the conservative group. By comparison with patients receiving conservative treatment, by 1 year, patients in the invasive group had lower frequency of primary endpoint (23 (9%) versus 51 (21%), relative risk 0.44 (95% CI 0.28-0.70), p=0.0008), and they tended to have reduced rate of death or reinfarction (7% versus 12%, 0.59 (0.33-1.05), p=0.07). Index time in hospital was shorter in the invasive group, with no differences in major bleeding or vascular complications. At 30 days both groups had a similar incidence of cardiac events. In-hospital incidence of revascularisation induced by spontaneous recurrence of ischaemia was higher in patients in the conservative group than in those in the invasive group. Fernandez-Avilés et al. (2004) concluded that in

patients with STEMI, early post-thrombolysis catheterization and appropriate intervention is safe and might be preferable to a conservative strategy since it reduces the need for unplanned in-hospital revascularization, and improves 1-year clinical outcomes.

The CARESS-in-AMI trial (2008) involved the randomization of patients with STEMI treated by thrombolysis and abciximab at a non-interventional hospital to immediate transfer for PCI, or to standard medical therapy with transfer for rescue angioplasty. 600 patients aged 75 years or younger with one or more high-risk features including; extensive ST-segment elevation, new-onset left bundle branch block, previous myocardial infarction, Killip classification of greater than two, or left ventricular ejection fraction < or =35%) in various hospitals in France, Italy, and Poland were treated with half-dose reteplase, abciximab, heparin, and aspirin, and randomly assigned to immediate transfer to the nearest interventional centre for PCI, or to management in the local hospital with transfer only in case of persistent ST-segment elevation or clinical deterioration. The primary endpoint was a composite of death, reinfarction, or refractory ischaemia at 30 days. Of the 299 patients assigned to immediate PCI, 289 (97.0%) underwent angiography, and 255 (85.6%) received PCI. Rescue PCI was done in 91 patients (30.3%) in the standard care/rescue PCI group. The primary outcome occurred in 13 patients (4.4%) in the immediate PCI group compared with 32 (10.7%) in the standard care/rescue PCI group (hazard ratio 0.40; 95% CI: 0.21-0.76, p=0.004). Major bleeding was seen in ten patients in the immediate group and seven in the standard care/rescue group (3.4% versus 2.3%, p=0.47). Strokes occurred in two patients in the immediate group and four in the standard care/rescue group (0.7% versus 1.3%, p=0.50). Di Mario et al. (2008) concluded that immediate transfer for PCI improves outcome in high-risk

patients with STEMI treated at a non-interventional centre with half-dose reteplase and abciximab.

The NORDISTEMI trial (2007) was done to compare a strategy of immediate transfer for percutaneous coronary intervention (PCI) with an ischemia-guided approach after thrombolysis in patients with very long transfer distances to PCI. A total of 266 patients with acute STEMI living in rural areas with more than 90-min transfer delays to PCI were treated with tenecteplase, aspirin, enoxaparin, and clopidogrel and randomized to immediate transfer for PCI or to standard management in the local hospitals with early transfer, only if indicated for rescue or clinical deterioration. The primary endpoint was a composite of death, reinfarction, stroke, or new ischemia at 12 months. The primary endpoint was reached in 28 patients (21%) in the early invasive group compared with 36 (27%) in the conservative group (hazard ratio: 0.72, 95% CI: 0.44 to 1.18, $p = 0.19$). The composite of death, reinfarction, or stroke at 12 months was significantly reduced in the early invasive compared with the conservative group (6% versus 16%, hazard ratio: 0.36, 95% CI: 0.16 to 0.81, $p = 0.01$). No significant differences in bleeding or infarct size were observed. Bohmer et al. (2007) thus concluded that immediate transfer for PCI did not improve the primary outcome significantly, but reduced the rate of death, reinfarction, or stroke at 12 months in patients with STEMI, treated with thrombolysis and clopidogrel in areas with long transfer distances.

The TRANSFER-AMI trial was conducted by Cantor et al. (2009) to determine the role and optimal timing of routine PCI after fibrinolysis. 1059 high-risk patients who had a myocardial infarction with ST-segment elevation and who were receiving fibrinolytic therapy at centers that did not have the capability of performing PCI were

randomly assigned to either standard treatment (including rescue PCI, if required, or delayed angiography) or a strategy of immediate transfer to another hospital and PCI within six hours after fibrinolysis. All patients received aspirin, tenecteplase, and heparin or enoxaparin; and concomitant clopidogrel was recommended. The primary end point was the composite of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days.

Cardiac catheterization was performed in 88.7% of the patients assigned to standard treatment a median of 32.5 hours after randomization and in 98.5% of the patients assigned to routine early PCI a median of 2.8 hours after randomization. At 30 days, the primary end point occurred in 11.0% of the patients who were assigned to routine early PCI and in 17.2% of the patients assigned to standard treatment (relative risk with early PCI, 0.64; 95% CI: 0.47 to 0.87; p=0.004). There were no significant differences between the groups in the incidence of major bleeding. Among high-risk patients who had a myocardial infarction with ST-segment elevation and who were treated with fibrinolysis, transfer for PCI within six hours after fibrinolysis was associated with significantly fewer ischemic complications than was standard treatment. Thus Cantor et al. (2009) concluded that transfer for PCI among high-risk STEMI patients is most effective provided the transfer occurs within six hours of fibrinolyctic treatment.

A real-world perspective

Some of the above listed clinical trials have documented that use of "facilitated" percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) may be harmful. McKay et al. (2009) examined in-

hospital outcomes in 1,553 consecutive patients with STEMI without cardiogenic shock who underwent PCI at a single tertiary center within six hours of presentation were analyzed. The study group included 767 patients who underwent primary PCI who initially presented to the tertiary center and were triaged for emergent PCI and 786 patients who underwent facilitated PCI who were pretreated at a community hospital with a glycoprotein IIb/IIIa platelet inhibitor and/or intravenous thrombolytic therapy before transfer for catheter-based therapy. Compared with patients who underwent primary PCI, the facilitated PCI group had longer door-to-balloon times (162 +/-57 versus 113 +/-61 minutes), higher baseline infarct-vessel TIMI 3 flow rates (52.8% versus 25.4%; p <0.001), and no increase in major adverse in-hospital outcomes. In patients treated with door-to-balloon times greater than 90 and less than150 minutes, patients who underwent facilitated PCI had fewer composite major adverse clinical events (combined mortality, recurrent myocardial infarction, emergent repeated PCI, hemorrhagic and non-hemorrhagic stroke, and non-intracranial TIMI major bleeding) compared with patients who underwent primary PCI (RR 0.50, 95% CI 0.26 to 0.96, p=0.034). McKay etl al. (2009) concluded that facilitated PCI can be safely used to increase pharmacologic reperfusion before catheter-based therapy in patients with STEMI without an increase in clinical hazard and with fewer major adverse clinical events in patients treated with door-to-balloon times greater than 90 and less than 150 minutes.

Overall the evidence from the literature suggests that PCI has the potential to significantly reduce morbidity and mortality post ACS provided the access occurs in a timely fashion (Di Mario et al., 2008; McKay et al. 2009). When compared to thrombolysis, primary PCI is considered to be the more effective strategy in reducing

rates of re-infarction and stroke (Bohmer et al., 2003). This being said, transfer for primary PCI was seen as an effective intervention provided the transfer time was within 2 hours after thrombolytic therapy (Grines et al., 2002; Andersen et al., 2003; Nielsen et al., 2010). However thrombolysis still remains the treatment of choice in ST-segment elevation myocardial infarction (STEMI) when primary PCI cannot be performed within 90 to 120 min (Levine et al., 2011). In some cases where primary PCI is not possible, or thrombolysis has failed, rescue or facilitated PCI is the next best option and timely access to these interventions is associated with improved patient outcomes such as lower risk of death, re-infarction, hospital re-admission rates and recurrent ER visits (Bohmer 2003; Fernandez-Avilés et al. 2004; Cantor et al., 2009).

GRACE risk stratification tool

There are a number of risk stratification tools used in emergency departments around the world for triaging, referring and decision-making purposes when it comes to resource allocation including the TIMI score, NERS, SYNTAX and GRACE score. The Global Registry of Acute Coronary Events (GRACE) score one of the more widely used and well-documented scores in the use of predicting both in-hospital and at discharge to six months mortality for patients who have experienced ACS. The GRACE risk stratification tool was used to determine which STEMI and NSTEMI/UA patients are at highest-risk for mortality upon admission and should be referred for and receive angiography and PCI services the fastest (Appendix F). It was used instead of the more commonly used TIMI score at UHNBC as variables for GRACE score calculation are better documented on patient files and because the GRACE risk score does not require information on the patient's aspirin use, which can often be misreported or missing from

charts. The score can be calculated for all ACS patients using the following information that can be found in their respective medical records including: patient age; heart rate (HR); systolic blood pressure (SBP); creatine levels; CHF (Congestive Heart Failure Classification); cardiac arrest at admission; ST-segment deviation; elevated cardiac enzymes/markers (specifically troponin).

Risk stratification of patients using the GRACE risk score

The Global Registry of Acute Coronary Event (GRACE) risk score was developed in a large multinational registry to predict in-hospital mortality across the broad spectrum of acute coronary syndromes (ACS). The GRACE risk score will be used to determine which STEMI and NSTEMI/UA patients are at highest-risk upon admission and therefore should theoretically be referred for and receive angiography and PCI the fastest. While it is one of many risk stratification tools for ACS available in today's market, the GRACE risk score has been accepted as a fast and valid method to assess a patient's cardiovascular risk and can be used in complement to clinical evaluation to help guide patient care due to the simplicity in calculation (Tang et al., 2007; Fox et al., 2006). Current ACC/AHA guidelines promote the use of either TIMI or GRACE risk scores for the risk stratification of ACS patients (Wright et al., 2011).

Validation of the use of GRACE to risk-stratify ACS patients

The Global Registry of Acute Coronary Events (GRACE) was established in 1999 with the purpose of resolving major uncertainties into what ACS is comprised of, defining the treatment of ACS patients, and to aid in the characterizing of outcomes for

ACS patients (Fox et al., 2010). The GRACE risk models have been derived and validated in large unselected cohorts of patients worldwide. These models have been tested and have shown to be valid for all forms of ACS, including STEMI, NSTEMI and UA (Alter et al., 2006; de Araujo et al., 2005; Bradshaw et al., 2006; Gale et al., 2009; Tang et al., 2007; Yan et al., 2004; Yan et al., 2007). The use of GRACE risk models is widespread and their usefulness in providing modern day cardiac care is echoed through guidelines put forth by the European Society of Cardiology (Bassand et al., 2007), NICE (NICE, 2010) and the ACC/AHA (Kushner et al., 2009).

GRACE vs. other risk scores

Overall, the literature is indicative of the fact that GRACE risk prediction models are valid and robust predictors of both in-hospital and six month post hospital discharge mortality for all forms of ACS. Some studies have even demonstrated GRACE as an effective risk prediction model for long-term mortality of ACS patients for up to five years (Kozieradzka et al., 2011). However further studies to validate these findings are warranted. For the purposes of the current study, in-hospital and to six month mortality prediction models are of particular interest as it is this version which has been most widely applied in clinical settings for the purposes of risk estimation for patients with ACS (Fox et al., 2006).

Generally speaking, the findings from the literature demonstrate the effectiveness and appropriateness of using the GRACE risk score for risk stratification purposes of patients with unselected ACS. The GRACE risk score has been well documented in the use of predicting mortality rates for patients who have experienced ACS and can be used

to determine both in-hospital and six months post hospital discharge ACS mortality rates (Aragam et al. 2009; Elabrouni et al., 2009; Abu-Assi et al., 2010; Stracke et al., 2010;). It has been found to have superior prognostic capacity when compared to the Thrombolysis in Myocardial Infarction (TIMI) score (Correia et al., 2010, Elbarouni et al., 2009, Fox et al., 2006). In addition to this, GRACE risk stratification is seen as being more applicable in hospital settings as it can be used for a wider age range of patients in comparison to the TIMI risk score (Ramsay et al., 2007) and it does not require there to be documentation on a patients use of aspirin (Fox et al., 2006). Furthermore, risk stratification using either TIMI or GRACE risk scores has been argued to be superior versus electrocardiograms and detection of troponin markers at presentation in the prediction of significant coronary events (Ramsay et al., 2007).

Gaps in the literature

There are certain limitations to consider when interpreting these results. These studies represent randomized-control trials, which occurred in conditions not always reminiscent of the real world. For example, current real world hospital transfer times vary greatly and in most cases can more than two fold of those times eluded to in these trials (Angeja et al., 2002; Nallamothu et al., 2005).

After extensive searches of the literature it can be said that there have been no previous studies conducted on this particular topic from a rural northern perspective. It is therefore important to note that this work will serve as a starting point to investigate this area of cardiac services in the region of northern British Columbia. Furthermore, current practice guidelines for cardiac care are based on those developed by the ACC/AHA. While these guidelines are invaluable in both clinical work and research, it is important to

note that they may not always reflect the realities of a Canadian landscape. The structure of the American health care system coupled with the more dense and disperse American population has resulted in the existence of more higher-level health care facilities including catherization labs than in Canada. What is possible in terms of access to services and transfer times in the United States can be at times in stark contrast to that Canada due to a number of differences in the national context. This study will aim to explore these issues from a northern and rural perspective and provide directions for future research as well as recommendations for improvements to current cardiac care for patients presenting with ACS at UHNBC.

Summary

There has been much research into the importance of rapid access to PCI, as well as the risk stratification of ACS patients using GRACE risk scores. Despite all this research, there remains a gap in the literature when it comes to studying these topics from a rural point of view. It is a well acknowledged fact that patients living in rural settings face unique health care challenges. These challenges can be in the form of poorer health status and health outcomes or limitations in access to health care services. Addressing the aforementioned research aims from a rural standpoint will offer a relevant perspective to the issues faced by those with acute coronary syndrome in a rural health care setting.

CHAPTER THREE: METHODS

This chapter provides an outline of the methods employed in the study. A retrospective approach was used. A medical records chart review was conducted to obtain patient data of interest. The use of PowerChart, a computer database for patient medical information, was used to locate any missing data points and validate the data collected from patient charts.

Study Design

This is a population-based study encompassing a retrospective analysis of all ACS admissions to the UHNBC emergency department was performed. Descriptive statistics on selected patient data were used to determine; patient baseline characteristics, patient residence, classification of ACS cases, average length of hospital stay, average length of hospital stay prior to transfer, and classification of patients given thrombolytics by diagnosis. GRACE risk scores for admission to in-hospital and admission to six months probability of death or re-infarction were also calculated.

In the current study, rescue or facilitated PCI was of most interest considering that UHNBC lacks a catherization lab to perform PCI and patients requiring the procedure need to be sent to one of the five provincial catherization labs to receive it. This study was a retrospective review of medical records of patients presenting to UHNBC with ACS from January through to December of 2012. Medical records were obtained through the medical records department at UHNBC.

A medical record can be defined as a document containing patient focused medical information (Worster et al., 2004). There are currently no universally accepted

standards for reporting or conducting medical record reviews (Gilbert et al., 1996). Medical records hold information for the purpose of documenting a patient encounter with the medical system and patient data are typically not collected for research purposes. In fact medical records have certain important limitations when it comes to using them as data collection including; data not being recorded for research purposes, and the possibility of having missing or incomplete information.

Despite these shortcomings medical record review studies are an appropriate method for many situations and can be used for pilot studies, to inform prospective clinical trials, to determine disease patterns throughout extended periods of time and to investigate questions difficult to answer in prospective trials (Gilbert et al., 1996; Lerner et al., 2002; Worster et al., 2004). Today medical record review studies comprise over 25% of all scientific studies published in peer reviewed emergency medical journals and are used for data collection in 53% of emergency medical services studies (Worster & Haines, 2004). While there are limitations to using medical records for research purposes the importance and value of medical record reviews in emergency medical research cannot be underestimated. They provide a valuable and rich source of patient derived medical information which often cannot be found in other environments or captured through typical methods of data collection in research such as surveys or patient based reporting (Dunn et al., 2006). Furthermore, the information is documented by professionals in the medical field, making the data less prone to patient recall and reporting bias (Worster & Haines, 2004).

Study Population

The study population consisted of patients who presented to UHNBC with ACS during January 2012 through to December 2012. A total of 265 cases were identified. These cases represented 249 people as 16 patients presented to the emergency department more than once throughout the calendar year.

Community Profile

A community profile for Prince George was extracted from the 2011 census data and the community health information portal through Northern Health (Statistics Canada, 2012; Northern Health Community Health Information Portal, 2013). The profile of this community is discussed based on demographic characteristics, health status and health facilities in this community. The population for the city of Prince George was found to be approximately 84,232. The mean age of the population was 39.0 years. The annual number of births for women of childbearing age was 1,045. The annual death rate was 574. The average life expectancy was 79.3 years, lower than the provincial average of 82 years.

Data source and extrapolation

Medical records were obtained through the medical records department at UHNBC. A request for access to records was put in to the department requesting access to the records of those patients presenting to the emergency department of UHNBC with ACS from January 2012 through to December 2012. The patient charts were pulled by the medical records department staff.

Patient data was initially entered into an extraction sheet in an Excel workbook by the month of presentation to the emergency department. All variables, including demographic and lab-based values were determined from the patient visit to the emergency department for ACS. For example, there was no looking through past records of patient encounters to determine any variables whether missing or otherwise. This information was located though the initial admission paperwork, ambulance summary, hospital discharge form, hospital transfer summary, cardiac catherization lab referral form, physician notes, nurses notes, PharmaNet medication history, and lab reports. Patients were given a unique identifier different from their personal health number to protect their identity.

The variables extracted from the chart included: date and time of admission, area of residence, mode of arrival, triage code, sex, age, height, weight, heart rate (bpm), blood pressure, creatine, glomerular filtration rate (gfr), CHF Killip classification, whether there was a cardiac arrest at admission, whether there was ST-segment elevation, whether there was elevation of cardiac enzymes, whether the patients received thrombolysis, diagnosis, date and time of discharge (whether for transfer or otherwise), facility transfer or discharged to, procedure and previous cardiac history including the presence of risk factors for cardiovascular disease. From these variables there were a number of data points calculated including: total length of hospital stay regardless of discharge status was calculated, patient body mass index using the documented height and weight of patients who had these data points in their charts and GRACE risk scores.

Data collection and criterion

Data were collected for patients for the calendar year of 2012. The rationale for choosing a one year time period from January 2012 to December 2012, was that this reflected the most current and available data as well as provided a longer-term picture of the situation compared to a shorter time period. This was done to minimize the effect of confounding variables that may delay the patient transfer process. Such confounding variables may include: differences in seasonal patterns, and health care service levels. Data were collected through review of medical charts. Any missing data points of interest were located through PowerChart. A total of 344 cases were identified and of these 344 cases, 265 were found to fit the inclusion/exclusion criteria.

Patients were included in the dataset if they presented to the UHNBC ED with ACS and were found to have true ACS (UA, NSTEMI or STEMI). They were included:

- regardless of their hometown/origin
- each time they presented to the UHNBC ED in the year (i.e one time in May of 2012, another in July 2012 and so forth)
- if they presented directly to the UHNBC ED without being at another NHA facility
- if they were transferred from another NHA facility to UHNBC *and* the referral for the catherization lab was made at UHNBC
- if they were found to have a late-presenting STEMI regardless of whether they required transfer to the catherization lab

Patients were excluded from the dataset if any of the following was true:

- patient was admitted in 2011 but was transferred in 2012 (i.e admitted in Dec of 2011 and transferred in Jan 2012)
- patient was admitted in 2012 but was transferred in 2013 (i.e admitted in Dec of 2012 and transferred in Jan 2013)
- patient presented to the UHNBC ED as an inpatient (inpatient transfers are not captured in the same way as outpatient as vitals and stats are not taken upon presentation)
- patients coming to UHNBC from another NHA facility for further evaluation (referral for PCI has already been made and tracking would be done at the respective hospital of origin)
- patients coming to UHNBC awaiting transfer to the catherization lab (referral for PCI has already been made and tracking would be done at the respective hospital of origin)
- patient presented to ED and was coded as ACS initially but was found to not be true ACS (i.e had elevated blood pressure, exacerbation of COPD)
- patient presented to ED with ACS complaint but left against medical advice (AMA) before investigations were completed

Measures and analytic procedures

Once it was determined that the data collection in the Excel workbook was complete, data were coded for use in IBM SPSS version 21.0. Dichotomous variables for cardiac enzyme elevation, for example, were coded as one for yes and two for no. Males

were coded as a one and females as a two. All nominal variables such as age or heart rate were coded as exact values. Baseline characteristics for the study population were determined. They included; age, gender, height, weight, area of residence, and risk factors as documented in their respective medical records (smoking history/status, family history of CVD, hypertension, diabetes, dyslipidemia, obesity, age, and prior cardiovascular history). Body Mass Indexes (BMIs) for patients were also calculated for those with both height and weight documented in their charts (Table 1.).

Study patients were divided into three groups according to the diagnostic and referral methods. Group 1 comprised of patients presenting with UA. Group 2 consisted of patients presenting with either NSTEMI. Group 3 consisted of patients presenting with STEMI. Baseline characteristics were determined through descriptive statistics. Analysis through crosstabs and one-way analysis of variance (ANOVAs) were conducted to determine time to PCI differences between patients presenting with STEMI compared to those with NSTEMI or UA. Data analysis was conducted using multivariate logistical regression through IBM SPSS version 21.0.

Risk stratification was performed through the use of the GRACE web-based calculation tool available through the GRACE website at, http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html. Patient data entered included; patient age, heart rate (bpm), systolic blood pressure (mmHg), creatine (umol/L), CHF Killip class as per Parakh et al., 2008 (Table 1.), and whether or not the patient had a cardiac arrest at admission, ST-segment deviation (as per ECG results), and the presence of elevated cardiac enzymes/markers (as per the pathology report) (Table 2.). Risk scores were determined and a breakdown of probability of mortality for both admission to in-

hospital and admission to six months for STEMI and NSTEMI/ UA is provided below (Table 3. and Table 4.).

Table 1.

Body Mass Index Classification

Classification	**Principal Cutoff Points**
Underweight	<18.5
Normal	18.5-24.99
Overweight	25.0-29.99
Obese	≥ 30.0
Class I	30.0-34.99
Class II	35.0-39.99
Class III	≥40.0

(Source: Health Canada. Canadian Guidelines for Body Weight Classification in Adults. Ottawa: Minister of Public Works and Government Services Canada; 2003.)

Table 2.

Killip Classification for GRACE

Killip Class	Clinical Features
I	No evidence of CHF
II	Crackles in ≤50% of lung fields or third heart sound or SBP >90mmHg
III	Pulmonary oedema and SBP >90mmHg
IV	Cardiogenic shock with crackles, SBP, <90mmHg and evidence of tissue hypoperfusion

CHF; congestive heart failure
SBP; systolic blood pressure

Table 3.

Troponin Elevation Criteria for GRACE

Value	Result
<14	Normal
14-50	Borderline
≥50	Positive
>50% from baseline	Significant

**Note:* these criteria are based on the high-sensitivity troponin scale

Table 4.

GRACE risk categories for UA/NSTEMI

Risk Category (tertile)	Grace risk score	In-hospital mortality (%)	Grace risk score	To 6 month mortality (%)
Low	≤108	<1	≤88	<3
Intermediate	109-140	1-3	89-118	3-8
High	<140	>3	≥118	>8

**Note:* scores can range from 2-372
(Abu-Assi et al. 2010 and European Society of Cardiology, 2012)

Table 5.

GRACE risk categories for STEMI

Risk Category (tertile)	Grace risk score	In-hospital mortality (%)	Grace risk score	To 6 month mortality (%)
Low	≤25	<1	27-99	<3
Intermediate	126-154	1-3	100-127	3-8
High	≤155	>3	≥128	>8

**Note:* scores can range from 2-372
(Abu-Assi et al. 2010 and European Society of Cardiology, 2012)

Ethical considerations and confidentiality

The study design and procedures for this study were submitted and were approved by both the *University of Northern British Columbia Research Ethics Board* (UNBC REB) and the *Northern Health Research Ethics Board* (NH REB) in May of 2013. Certificates of ethical approval from both research ethics boards can be found in the appendices (Appendix I. and Appendix J.).

Confidentiality of the patient data was strictly maintained throughout all phases of the study. Patients were given a unique identifying number unrelated to their Personal Health Number (PHN) or Northern Health Encounter Number (NH ENC #) to avoid the possibility of patient tracking. All electronic data files were password protected and stored on a password-protected computer and the data collected from patient records did not contain any identifiable information. The electronic files were further placed in a folder that required a username and password for login purposes that only the author of this thesis had access to. It was also ensured that the final deliverable, the thesis, did not include any patient identifiable information.

CHAPTER FOUR: RESULTS

This chapter presents the results from the data analyzed for this thesis. A descriptive analysis of patient baseline characteristics is provided. Second, statistical differences using crosstabs and one-way ANOVAs between patient area of residence, classification of cases by diagnosis, and length of hospital stay are presented. This is followed by statistical analyses using multiple linear regression of whether longer time to PCI was associated with adverse patient outcomes (death, stroke, reinfarction) and whether patient time to PCI treatment was correlated with GRACE risk status.

Preliminary data analysis

Preliminary data analyses identified a total of 344 cases. Those not fitting the inclusion criteria such as being diagnosed as not having true ACS (i.e. chronic obstructive pulmonary disease exacerbation or elevated blood pressure) or being inpatients were eliminated. A total of 265 patient cases were identified after the data were cleaned and coded. Of these patients 65.6% (n=174) were male, and 34.4% (n=91) were female. Ages for the patients ranged from 33 years to 94 years old with the average patient age of 64.1 years. The length of stay prior to transfer for the catherization lab ranged from 1 day to 47 days with the average length of stay being 4.9 days across all diagnostic categories.

Table 5.

Patient Baseline Characteristics

	UA (n=87)	NSTEMI (n=113)	STEMI (n=65)	p
Median Age (years)	64.0	65.4	61.9	0.140
Male (%)	58.6	82.3	80.0	0.099
Risk Factors				
Age (Males 45+, Females 55+)	90.8	90.3	89.2	0.949
Family History	30.0	31.9	29.2	0.381
Smoking	33.3	42.5	52.3	0.063
Diabetes mellitus	27.6	29.2	21.5	0.531
Hypertension	65.5	65.5	46.2	0.021
Dyslipidemia	51.7	48.7	36.9	0.715
Obesity	40.6	32.7	16.1	0.215
Prior Cardiovascular History	48.3	46.0	38.5	0.464
MI	20.7	12.4	16.9	
CHF	3.5	6.2	6.2	
PCI	19.5	19.5	16.9	
CABG	18.4	8.9	4.4	
Stroke/TIA	3.5	8.9	4.6	
AF	2.3	8.0	3.1	
PVD	15.0	11.5	4.4	

**Note*: For obesity UA n=32, NSTEMI n=49 and STEMU n=31
MI, myocardial infarction; CHF, congestive heart failure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AF, atrial fibrillation; PVD, peripheral vascular disease

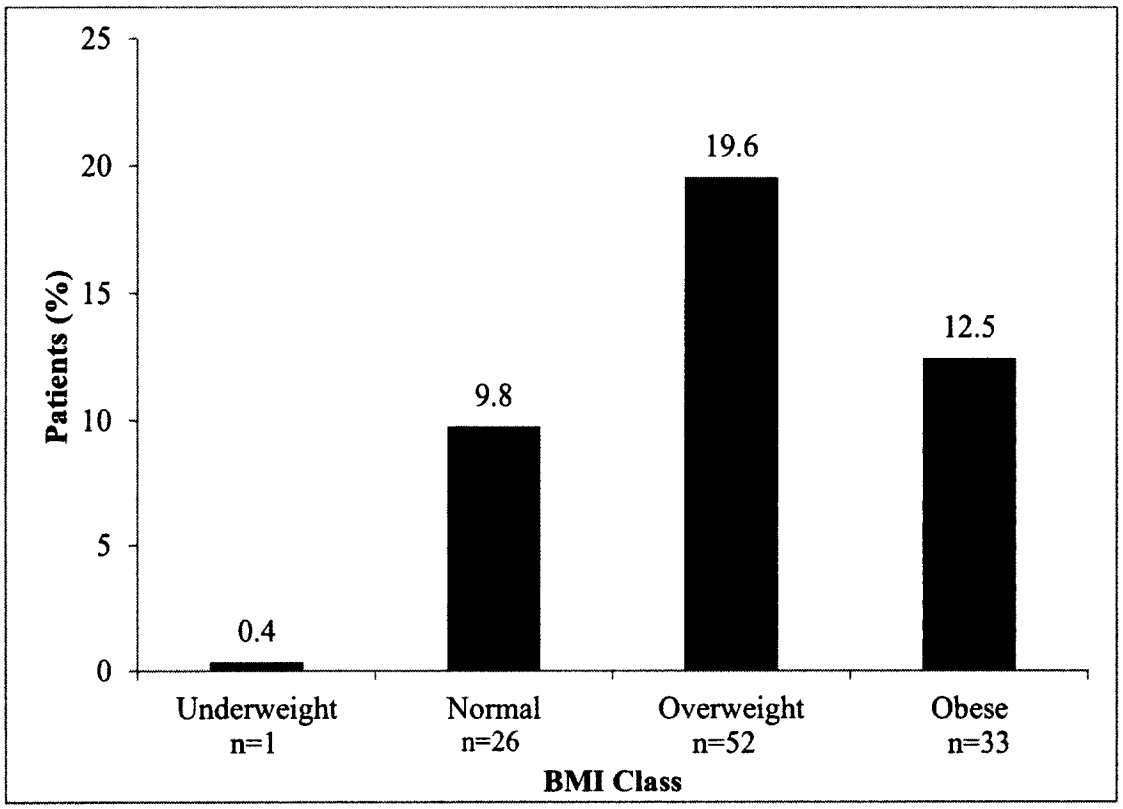

Figure 4. Classification of patients by body mass index (BMI)

Patients with documented height and weight data in their medical charts (n=112) were classified according to their BMI. It was found that 0.4% of patients (n=1) were underweight (BMI <18.5), 9.8% of patients (n=26) were within normal range (BMI 18.5-24.9), 19.6% of patients (n=52) were overweight (BMI 25.0-29.9) and 12.5% of patients (n=33) were obese (BMI $\geq$ 30.0).

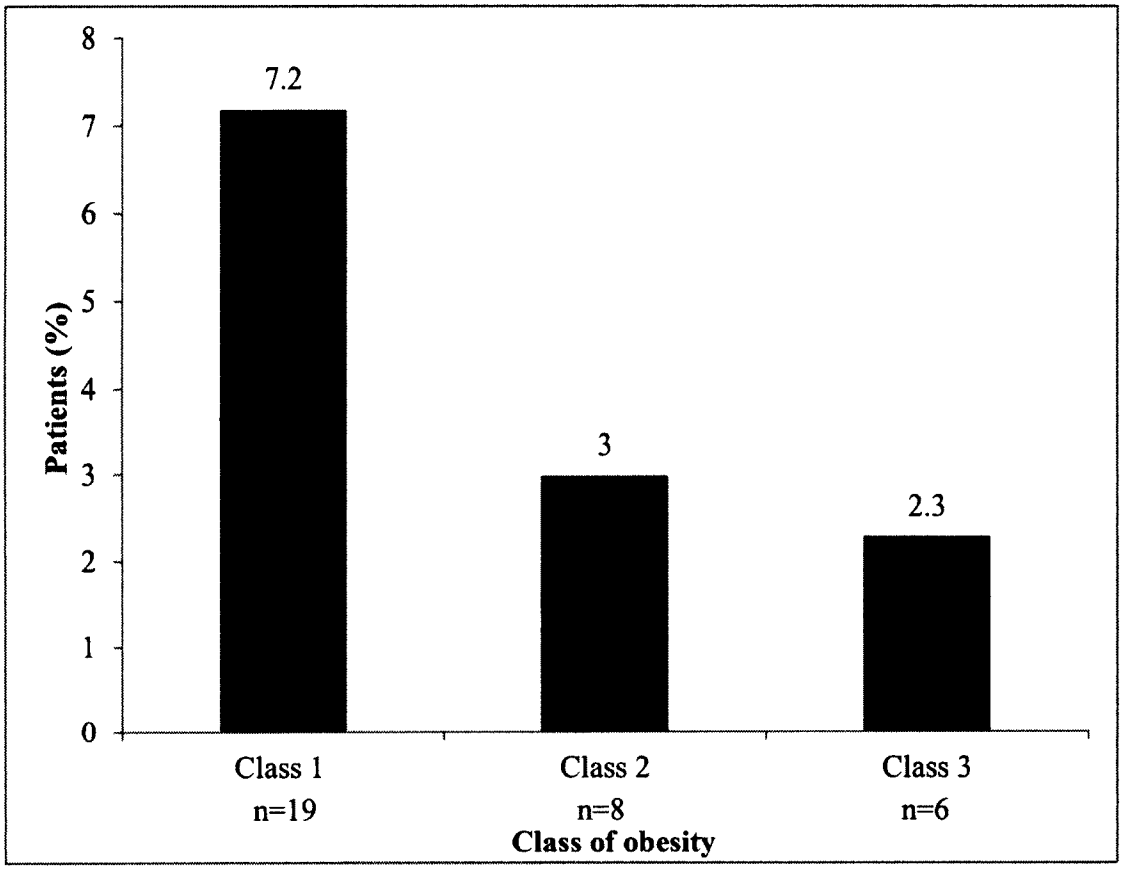

Figure 5. Classification of obese patients

Patients were classified into classes of obesity if their BMI was ≥30.0. There was a total of (n=33) 12.5% of patients which were found to be obese (BMI > 30.0). Of the 12.5%, 7.2% of patients (n=19) were classified as class I obese (BMI 30.0-34.9), 3.0% of patients (n=8) were classified as class II obese (BMI 35.0-39.9) and 2.3% of patients (n=6) were classified as class III obese (BMI ≥ 40.0).

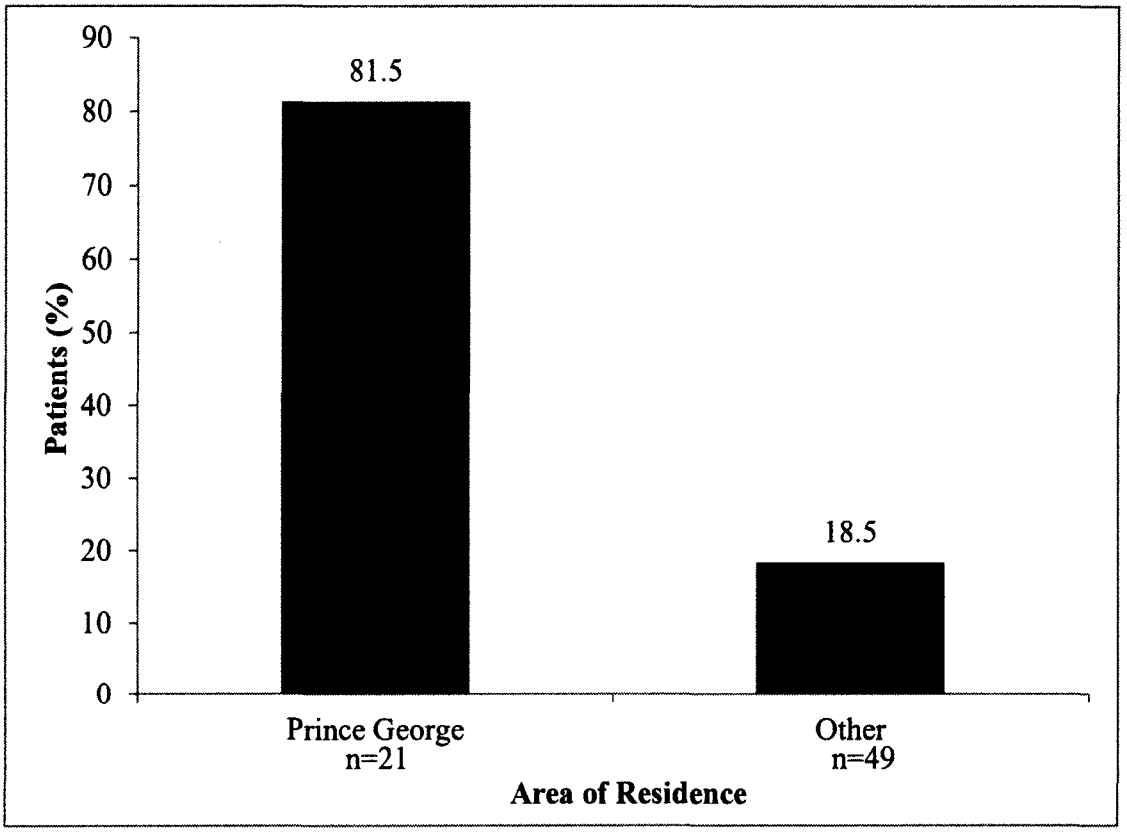

Figure 6. Classification of patients by area of residence

Patients (n=265) were classified according to area of residence. Of the 265 patients 81.5% (n=216) were Prince George residents. Of the remaining 18.5% of patients (n=49) 57.1% of these patients (n=28) were transferred from other hospitals within the Northern Health Authority including; Kitimat, Fort St. James, Fort St. John, Valemount, Vanderhoof, Burns Lake, Quesnel, Fort Fraser, Mackenzie and Dunster. The remaining 42.9% of patients (n=21) were in Prince George visiting or for work-related purposes from cities including: Surrey, Edmonton, Burnaby, Kelowna, and Hixon.

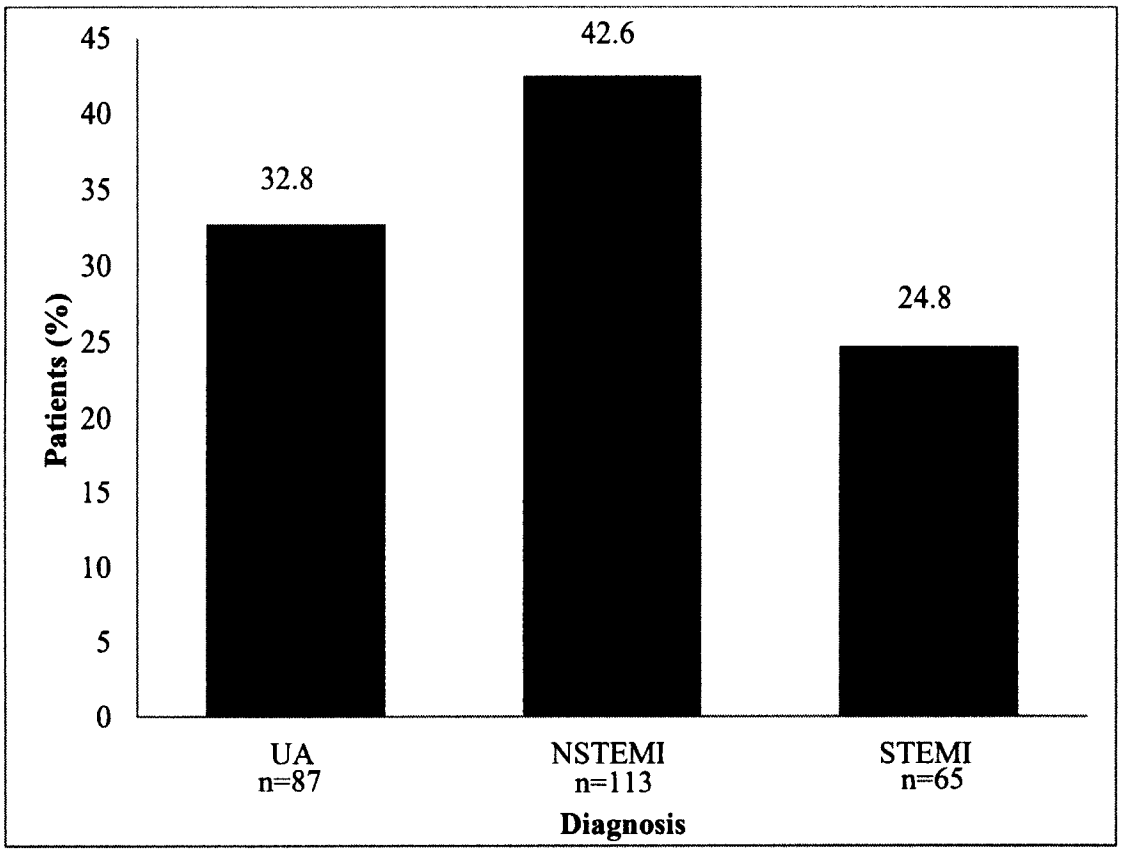

Figure 7. Classification of Patient Cases

Classification of patient cases by diagnosis is presented. The most common category of ACS was NSTEMI representing 42.6% of the total ACS cases (n=113). Unstable angina cases came in second with 32.8% of patients (n=87) and STEMI cases comprised the remaining 24.8% of patient cases (n=65).

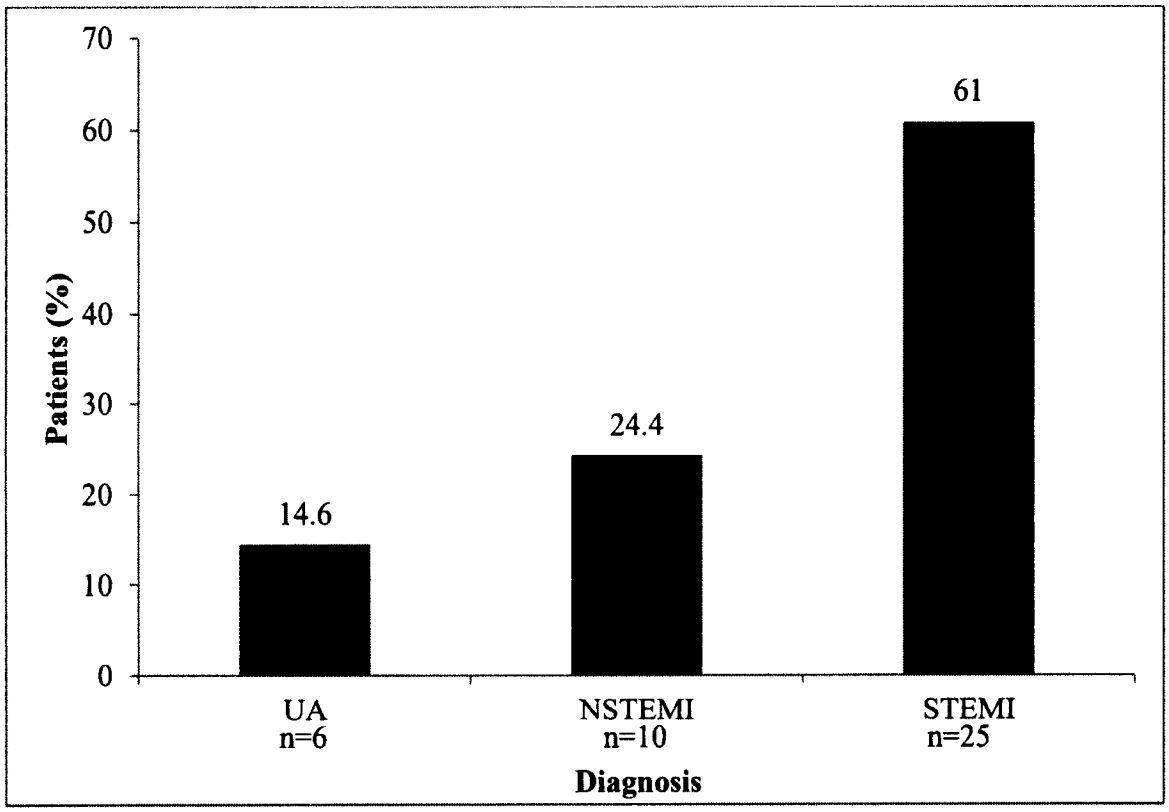

Figure 8. Classification of Patients given thrombolytics by diagnosis

A total of 15.5% of patients (n=41) across all diagnostic categories were administered thrombolytic therapy. Of these 15.5%, 14.6% of patients (n=6) were diagnosed as UA, 24.4 % of patients (n=10) were NSTEMI and 61% of patients (n=25) were STEMI.

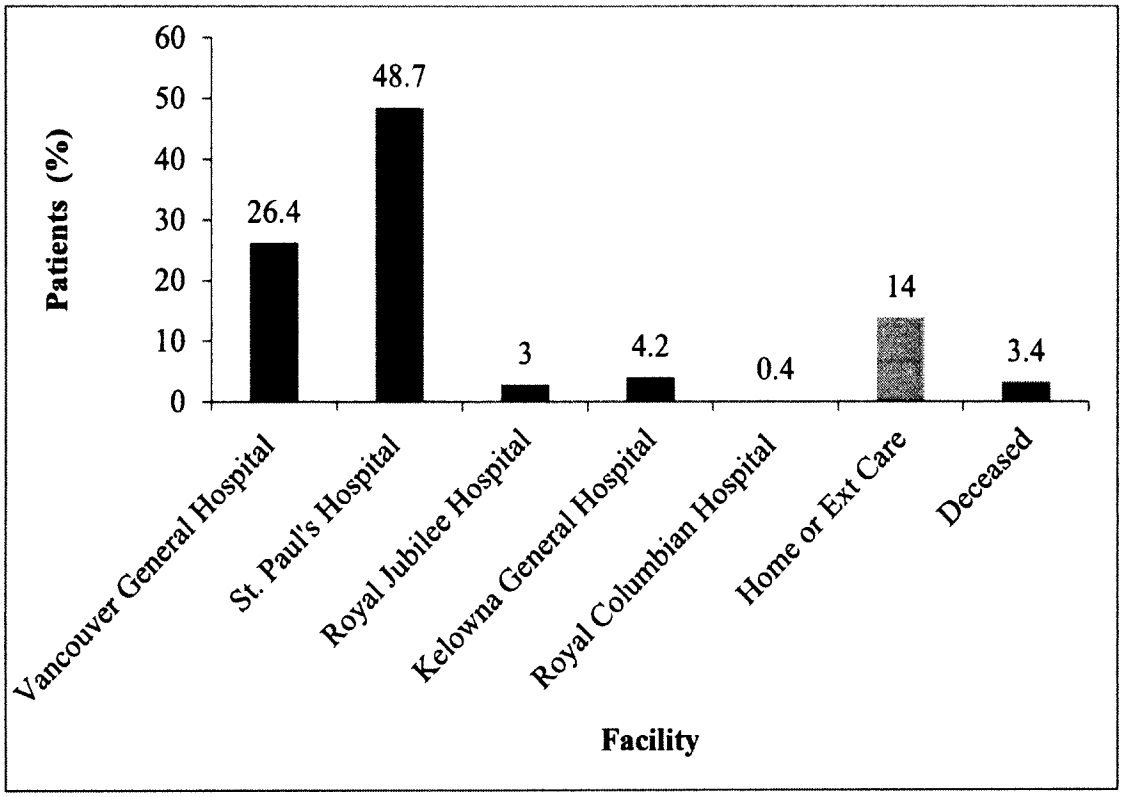

Figure 9. Patient Discharge Status from UHNBC

Roughly 50% (n=124) of patients presenting to UHNBC with ACS were transferred to St. Paul's Hospital (SPH). Over a quarter of patients (n=70) were sent to Vancouver General Hospital (VGH). 14% of patients (n=37) were deemed unsuitable candidates for PCI and were either sent home or to an extended care facility. There were 3.4% (n=9) of patients presenting to UHNBC with ACS that died from the condition, of which 22.2% (n=2) died while waiting for transfer to the cardiac catherization lab.

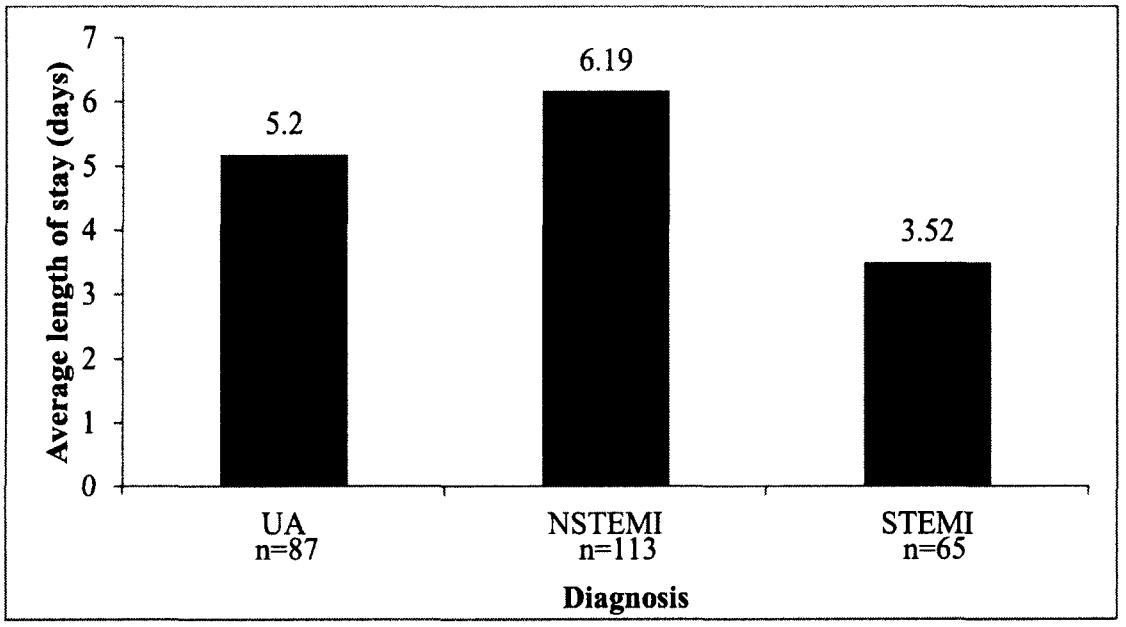

Figure 10. Average length of hospital stay according to diagnosis

The length of hospital stay among all patients with ACS regardless of transfer to a catherization lab was found to be the highest among patients with NSTEMI at an average of 6.19 days. Unstable angina came in second with an average of 5.2 days while STEMI patients remained in hospital for an average of 3.52 days. The two STEMI patients that died from cardiac events while awaiting transfer waited 14-48 hours before death.

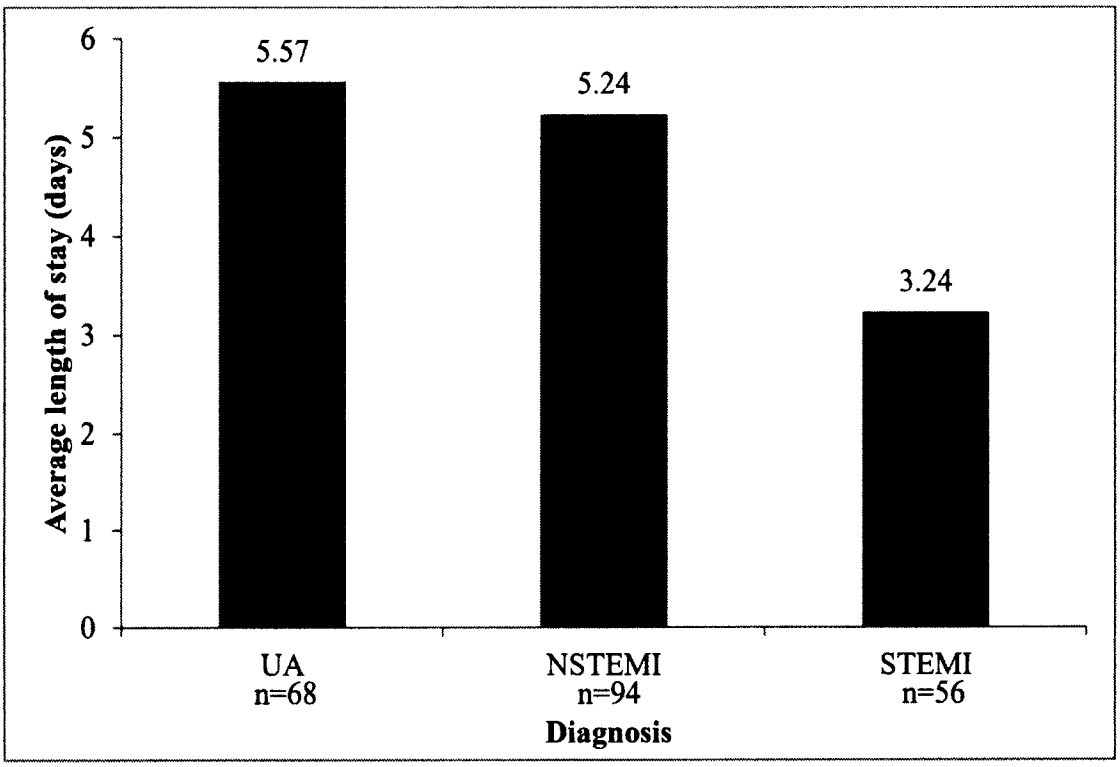

Figure 11. Average length of hospital stay prior to transfer according to diagnosis

The average length of stay prior to transfer to the catherization lab was 4.91 days. It found to be the highest among patients with unstable angina at an average of 5.57 days. NSTEMI came in second with an average of 5.24 days while STEMI patients waited an average of 3.54 days prior to transfer.

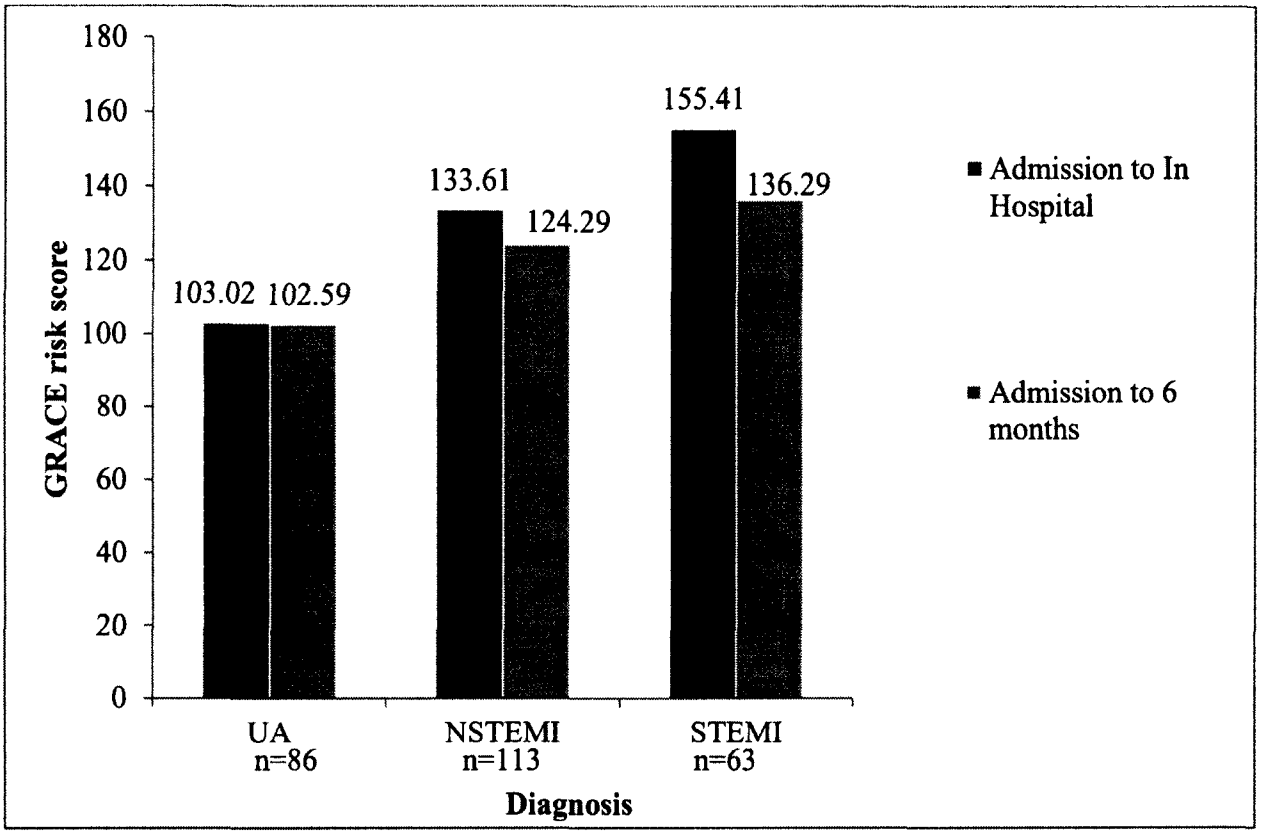

Figure 12. GRACE risk score by diagnosis

The GRACE risk score for both admission to in-hospital and admission to six months was the lowest among patients with unstable angina at an average score of 103.02 and 102.59 respectively. NSTEMI cases had an average GRACE risk score of admission to in-hospital score of 133.61 and an admission to six months score of 124.26. STEMI cases had the highest GRACE risk score of 155.41 and 136.29 for in admission to in-hospital and admission to six months respectively. The largest decrease in risk status from admission to in-hospital to admission to six months was seen among patients with STEMI and the smallest decrease was among those with UA.

Adverse outcomes for patients were determined at 30 days and one year of admission. The primary clinical endpoint was a combined measure of death, re-infarction, heart-failure, or stroke. It was found that a total of 6.04% of patients (n=16) suffered from adverse outcomes within 30-days of hospital admission for ACS. Of these patients 37.5% (n=6) belonged to the UA group, 25% (n=4) to the NSTEMI group and the remaining 37.5% of patients (n=6) were STEMI patients. At the one-year mark, 12.1% of patients were found to have suffered adverse outcomes. Of these patients 50% (n=16) were from the UA group, and 25% each (n=8) were NSTEMI and (n=8) were STEMI patients. Due to the number of patients suffering from adverse outcomes being less than 50 as required for the statistical significance for the software, IBM SPSS v. 21.0, multiple logistical linear regression analyses for this objective was not possible, however a scatterplot was created to display this data (Figure 13.).

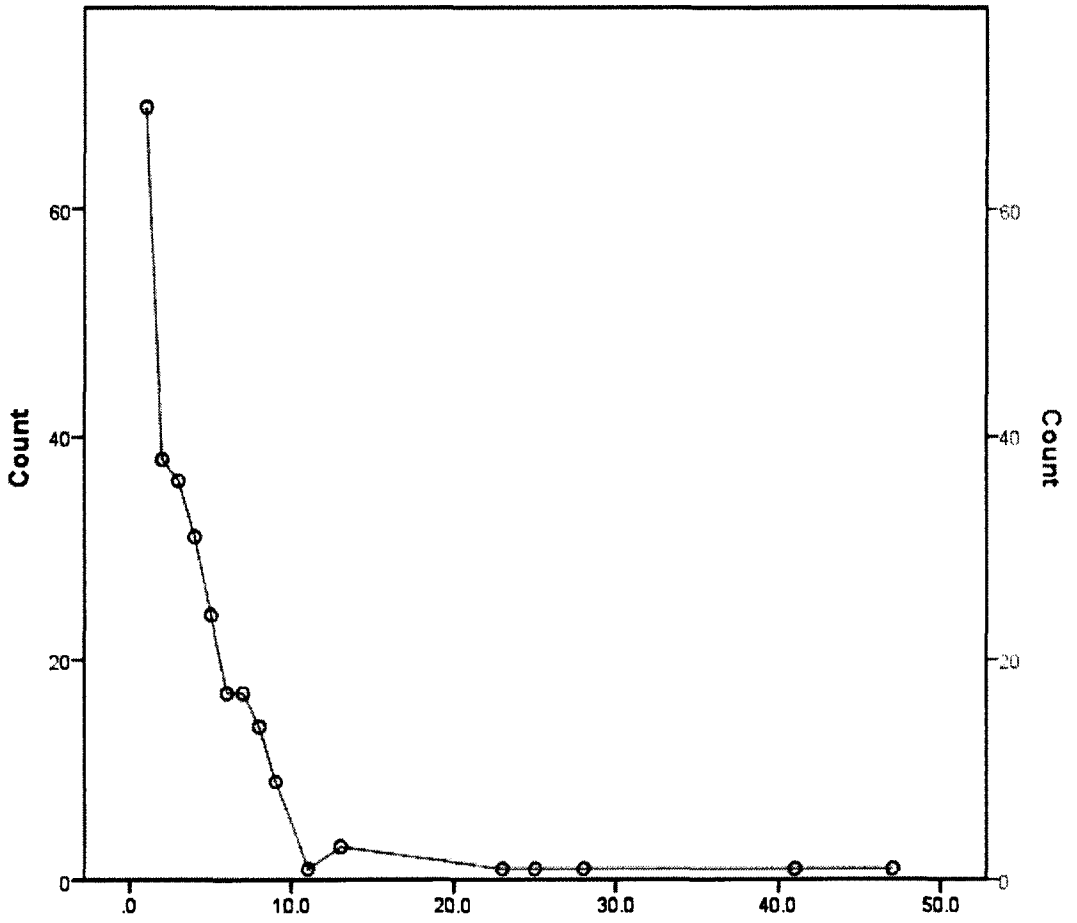

Figure 13. Adverse outcomes for 30-day (circles) and 1-year (line) post-ACS admission as per length of hospital stay (x-axis)

Table 6. Multiple linear logistical regression analysis of predictors for time to PCI

Model	Non-standardized Coeffiecients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	-4.947	6.261		-.790	.432
GRACE InHosp	.044	.045	.546	.977	.331
GRACE6mos	-.047	.065	-.438	-.724	.471
Age	.157	.077	.347	2.056	.043
Sex	-1.531	1.089	-.152	-1.405	.164
BMI	.093	.106	.095	.876	.384
Htn	1.560	1.117	.160	1.396	.166
Diabetes	-1.031	1.330	-.091	-.775	.440

a. Dependent Variable: PCI

b. Predictors: (Constant), Diabetes, Gender, BMI, Age, Hypertension, GRACEInHosp, GRACE6mos

Multiple logistical linear regression analysis was used to test if the patients were transferred for and received PCI according to their GRACE risk score of combined probability of death or reinfarction both from admission to course in hospital and from admission to 6 months. The results of the multiple linear regression indicated that patient age was the only significant predictor of time to PCI. Age explained 5.7 % of the variance in the outcome of time to PCI (R^2=0.131, F(1.772), p <0.43). The other predictors including: diabetes mellitus, gender, BMI, hypertension and GRACE risk score (both admission to in-hospital and admission to six months) were found to be insignificant predictors of when patients received their PCI treatment.

CHAPTER FIVE: DISCUSSION & CONCLUSION

The primary objective of the present study was to examine the issue of access to percutaneous coronary intervention (PCI) among patients presenting to the emergency department at the University Hospital in Northern British Columbia in Prince George. Specifically, this study aimed to determine whether the time delay to PCI was associated with more adverse outcomes, namely stroke, death or re-infarction at 30 days and whether the sickest patients, as risk stratified using the GRACE risk score, received care in the least amount of time.

The following chapter will interpret the results of the aforementioned research objectives and will discuss strengths and limitations of the study. Implications for future research, policy and practice will be presented in some detail. Finally, recommendations arising from the findings of this study will be made alongside concluding remarks.

Hypothesis 1: Longer times to treatment for PCI are associated with higher rates of adverse outcomes including stroke, death and re-infarction.

The first objective of this study was to explore associations among longer times to PCI treatment and adverse patient health outcomes, including a) stroke, b) death and/or c) re-infarction. Due to statistical software limitations, the sample size for adverse outcomes was insufficient, as was required for SPSS to run multiple linear regression analysis, therefore it was not possible to determine this association quantitatively. However, times to PCI and occurrences of stroke, death or re-infarction were calculated.

The average time to PCI across all diagnostic categories was determined to be 5.9 days. The average time to PCI for each type of ACS was 6.5, 6.2 and 3.8 days for UA, NSTEMI and STEMI respectively. The shortest length of stay prior to transfer was among the highest-acuity patients with STEMI, however the GRACE scores did not necessarily reflect this as the only significant predictor of patient transfer was age. A plausible explanation to this could be that length of stay was presented as an average thus may not accurately reflect the range of days STEMI patients waited for transfer. Furthermore, transfer may be strictly based on symptoms, diagnostic findings and clinical evaluation which depending on time of patient presentation may not accurately reflect patient risk status.

Furthermore, these results reveal an important discrepancy between the current best-practice guidelines and patients in a real-world setting. As previously mentioned in the first chapter, ACC/AHA guidelines recommend PPCI with 90 minutes and rescue or facilitated PCI within 120 minutes. The average times for PCI patients are clearly not meeting these guidelines primarily due to large distance required for transport of patients for care. Furthermore, the Canadian Cardiovascular Society (CCS) position statement on benchmarks as outlined in the first chapter for access to treatment state that diagnostic catherization and PCI for inpatients should be conducted within five days (Canadian Cardiovascular Society, 2011). Upon examination of the current times to treatment, it is evident that there is clear need for further improvements to reducing this delay in the population studied. Additionally, it is worth noting that two STEMI patients died from cardiac events while awaiting transfer to the cardiac catherization lab.

While there were no documented reasons for this delay in patient charts, there are several plausible explanations for this delay as it may result in part in relation to the long-distance transport required for access to the procedure (Sorenson et al., 2010). First, there are many organizational factors including delayed triage, and evaluation and diagnosis, which can delay a patient's transfer such as understaffed emergency departments. In addition, patients presenting to rural hospitals may be cared for by physicians other than cardiologists, thus may not receive the latest evidence-based care (Pesut et al., 2013). To the same effect, patients may present with symptoms not typical of ACS that would require further diagnostics tests to reach a concrete diagnosis which can delay treatment. Second, the receiving hospital with catherization lab capability may also have organizational factors contributing to delay. These include: lack of available beds, their own patient populations within catchment areas, patient transfers from other community hospitals and operational restrictions of a Monday to Friday eight hour time-frame. Third, for patients requiring PCI in the winter months, the harsh northern winter climate can make for unsafe travelling conditions. In such circumstances, there is little that can be done to make conditions more favorable. Fourth, a patient may have one or more comorbid conditions, which can make them less than desirable for immediate transfer thus increasing times to treatment. Fifth, BC Air Ambulance is operational on a 8am-8pm basis which restricts the time frame of patient transfer (BC Ambulance Service, 2013). Furthermore, this may be complicated by a number of other factors external to the health care environment. For example, there may be presentation delay by patients post-symptom onset while other patients may be adamant that they wish to receive care at a

specific centre based on their prior experience either personally or otherwise (Henry et al., 2014).

A recent study by Nallamothu et al. (2006) found that patients with comorbidities, absence of chest pain, delayed presentation after initial symptom onset, less specific ECG findings or presentation to hospital during off-hours were found to have longer times to treatment. Additional studies have found that patients presenting to rural teaching hospitals also waited longer than those in urban teaching and non-teaching hospitals as well as rural non-teaching hospitals (Aguirre et al., 2008; Sorensen et al., 2011). The increased wait times may be due in part to the effects of working environments seen in rural, often understaffed and resource limited, hospitals that can affect workload and can be further exacerbated due to the additional demands of instruction.

Some studies have examined ways to reduce this delay. While the focus of these strategies has been examined at facilities with PCI capabilities a small number of recommendations can also apply to transfer hospitals. Rezaee et al. (2010) found that initiating pre-hospital care including pre-hospital ECGs and pre-cardiac catherization lab activation by EMS led to an average of a 24-minute reduction. A study by Bradley et al. (2006) examined effective strategies to reduce delays in time to treatment for PCI. These strategies included having emergency medicine physicians activate the catheterization laboratory, having a single call to a central page operator activate the laboratory, having the emergency department activate the catheterization laboratory while the patient is en route to the hospital, expecting staff to arrive in the catheterization laboratory within 20 minutes after being paged, having an attending cardiologist always on site, and having

staff in the emergency department and the catheterization laboratory use real-time data feedback.

Adverse outcomes, namely a combined clinical endpoint resulting in death, re-infarction, heart failure or stroke, were 7.3% and 14.6% at 30-days and 1-year post-discharge respectively. Some studies have found that increased times to treatment have little effect on mortality (Brodie et al., 2001) while others have found that increased time to treatment not only increases mortality but infarct size as well (Angeja, 2002; Cannon et al., 2000). Therefore the results mortality due to delayed PCI remain inconclusive however best practice guidelines still stress that PCI should be carried out in a timely fashion. Timely care has been shown to improve overall patient outcomes including morbidity, stroke risk and re-infarction (Antman et al., 2008; Van de et al., 2008; Boersma et al., 2006; Ross et al., 2006; Keeley et al., 2003; Nallamothu et al., 2003). This is of relevance to the current study as results reveal UHNBC is not meeting provincial benchmarks therefore there is an urgent need to reduce this delay to treatment to avoid potential negative impacts on patient health.

Hypothesis 2: Patients are not transferred according to their risk status.

The second objective of this research was to explore the association between order of patient transfer and patient risk status. Patient time to PCI was not found to be associated with patient risk status. The only significant predictor of time to treatment is patient age. This finding was consistent with the literature as there has been repeated calls for there to be a formalized system to directly triage patients to cardiac catherization centres in order to reduce this time to treatment (Patel et al., 2010; Grines et al., 2002).

Current practice in Canada remains that patients requiring PCI are transferred on a 'next suitable' spot basis (Patel et al., 2010). Moreover, a risk-averse strategy seems to be in place when patient priority for transfer is assigned.

There are several plausible explanations for this current practice. First, the patient is required to be clinically stabilized before he or she is deemed safe for transfer via air ambulance. This stabilization may or may not correspond with the risk status of a patient. Additionally while this high-risk unstable patient is being stabilized, an opening at the receiving center may become available thus an already stable, yet lower-risk patient may be transferred first. Second, the current transfer of patients is based largely on ECG findings and clinical evaluation. Third, there tends to be a clinician bias as documented in the literature concerning the hesitation of clinicians to transfer overweight or obese patients due to risk of bleeding or other post-operative complications. This however is not always a correct assumption as several studies on the 'obesity paradox' have demonstrated that overweight or obese patients tend to have a lower incidence of post-operative complications when compared to their lean counterparts (Hastie et al., 2010; Lancefield et al., 2010; Diercks et al., 2006; Gruberg et al., 2002). Furthermore high BMI has been found to be an insignificant predictor of short and long-term mortality, demonstrated by an inverse relationship between high BMI and patient mortality (Schenkeveld et al., 2012).

Regardless of these considerations the GRACE risk score provides a valid alternative to aid in the risk stratification of patients. It is a readily available tool on mobile devices and can become part of a clinician's bedside tool kit to inform the triage and transfer processes (Stracke et al., 2010; Fox et al., 2006). Furthermore it is important

to note that while there is a perception that current practice involves the use of the TIMI risk score at UHNBC to risk stratify patients with ACS, there was little evidence of its use in patient charts reviewed for this study and use of it was sporadic at best. A potential barrier to this could be that the score requires there to be documentation of patient aspirin use for risk calculation (Yan et al., 2004). This information may or may not be documented in patient medication history and sometimes may be patient reported. In contrast, the GRACE risk score uses pre-collected basic clinical information which can be located in patient charts and does not require any information of patient drug use yet provides an equally if not superior risk prediction model (Fox et al., 2006; Ramsay et al., 2007) with a higher degree of discrimination and predictive accuracy (Correira et al., 2010; Elabarouni et al., 2009; Fox et al., 2006).

Secondary findings

The examination of demographics and cardiovascular history of the study population led to some important findings. First, the majority of patients presenting to UHNBC with ACS were from Prince George, however there were also patients from smaller community hospitals transferred to UHNBC for care. This finding speaks to the importance of having a regional hospital that is able to provide this level of care not available in the surrounding and more rural community hospitals.

The literature also highlights the importance of thrombolytic therapy in the absence of PPCI availability for patients with STEMI (Mckay et al., 2009; Nallamothu et al., 2003; Zijlstra et al., 2003). In this study, less than quarter of all patients received thrombolytic therapy, while 38.4% were patients with STEMI. A possible explanation to

this may be that since thrombolytic therapy is not recommended in high-risk patients, this patient population represents a high-risk group. However, the fact that not all STEMI patients (excluding high-risk, contra-indicated patients) received thrombolysis requires further investigation. Furthermore, thrombolytic therapy was administered to patients with all types of ACS, albeit less frequently then STEMI. This practice, for which there were no documented reasons in patient charts, is in contradiction to the ACC/AHA guidelines which state that there is no benefit from thrombolysis for patients with NSTEMI or UA (Levine et al., 2011).

STEMI patients on average were two to three years younger than those with NSTEMI or UA. Furthermore, males were over-represented in each ACS category comprising over half of the patient population. Major risk factors were present in more than half of the patients and included age, hypertension, dyslipidemia. Other significant risk factors included obesity and prior cardiovascular history.

As mentioned in the first chapter, a report by Cardiac Services BC (2011) highlights the presence of traditional risk factors in the northern population. This is also echoed in recent statistics published by Statistics Canada (2012). Traditional risk factors including obesity, diabetes, hypertension, smoking, physical inactivity and dyslipidemia are highly prevalent in northern residing populations. Furthermore, provincial prevalence of cardiovascular disease has remained stable over the last decade, but the NHA is the only health authority to see an increase during this time along with the higher than average provincial mortality rates (Cardiac Services BC, 2011).

Study strengths and limitations

Research involving patient sensitive data and outcome analysis based on the current practices can be a challenging undertaking. The success of this research can depend on the acceptance and participation of organizations and professional groups who may be at varying levels of readiness to explore this area of investigation. Therefore this study strived to be collaborative in nature and sought input from academics, clinicians, organizations and other relevant stakeholders.

In addition to this, this study examined patients for a one-year duration. This allowed for a complete analysis of access to PCI for northern patients and accounted for any variability in access times influenced any uncontrollable factors. Factors such as adverse weather conditions affecting transport to the hospitals with catherization centres, or a larger-scale emergency such as a workplace accident or other disaster which can use resources and may take precedence over the immediate transfer of ACS patients.

Thirdly this study was the first of its kind to explore this issue for northern patients. It focused on exploring access for rural-dwelling patients, addressing a very important knowledge gap in the research domain as the majority of literature centered around large urban settings. It focused on the issue of access in both a unique geographical setting as well as on a distinct rural population.

There are certain limitations to keep in mind when considering this study. First, this study was limited to patients presenting to UHNBC and therefore may not be fully representative of the smaller, more remote community hospitals in northern BC. Second, the study population was limited to patients presenting directly to the emergency

department at UHNBC. This excluded patients who experienced ACS as inpatients as well as patients transferred from smaller community hospitals who had already had their cardiac catherization lab referral process initiated prior to transfer to UHNBC. Third, data was collected from medical records, which typically do not contain data collected for research purposes so there is a possibility of some variation or inaccuracies in the dataset.

Key findings and contributions

To our knowledge, this study is the first of its kind to be conducted in northern BC on this topic. It uses an exploratory approach to respond to an important and pressing health care issue. It offers insights that cannot be provided through the experience of large-scale randomized control trials that are centered in larger urban centres as the generalizability of these studies is limited in rural settings. It aimed to address this knowledge gap and to identify this population, their risk status and their access to PCI services.

Keeping in line with this, a strong effort will be made to disseminate the findings from this study using a knowledge translation (KT) strategy. The KT plan includes: a briefing summary to Northern Health, a webinar, conference presentations and manuscript publications. This will ensure that the results are made available to key decision makers, stakeholders and health care practitioners.

Recommendations

There are certain recommendations that can be made from the results of this study. This study was focused on ACS patients presenting to one centre within the Northern Health Authority region. Therefore, a larger scale study covering the entire

Northern Health Authority region can be warranted. This would provide a complete picture of access to cardiac services in all of the north. It would enable a look into access to PCI for all northern patients and provide information concerning risk status, length of patient hospital stay among other factors. It would be beneficial to compare these trends among different areas of the north to see differences and similarities within the northern context. Furthermore, a larger scale study would allow for meaningful logistical regression analysis to study the relationship between adverse outcomes and length of stay prior to transfer for PCI.

Second, a look into all factors which can influence wait times for PCI is valid. Factors such as the process for transferring patients via BC Air Ambulance, the respective catherization labs procedures and their respective processes, and the referral process for each of the catherization labs. This would allow for the determination of possible areas of improvement as well as the identification of a standardized process of 'best practices' for transfer patients. Alongside this a look into the feasibility of a dedicated network for patient transfer to reduce transport related delay is also warranted.

Third, an exploration of developing a formal triage process for all ACS patients should be explored. This process should be standardized across all provincial cardiac catherization labs to ensure equitable access to treatment. Furthermore, in hospitals without cardiac catherization labs the development of a provincial patient priority system could potentially ensure that the sickest and highest risk patients would receive their care the fastest.

Fourth, it is worthwhile to examine the aspect of having a regional catherization

lab in Prince George. There are two reasons to this. Patients receiving PCI typically receive same day discharge from the hospital after their procedure. Therefore having a regional catherization lab for the north could potentially reduce length of stay for patients resulting in a cost savings for the health authority related to the number of 'bed days' used for patients awaiting transfer as well as the cost of an air-ambulance transfer.

According to the Canadian Centre for Policy Alternatives (2012) the average cost of treating a patient in hospital ranges from $825-$1968 per day and can vary depending on the patient's individual circumstances including diagnosis, level of acuity and comorbid conditions. The cost of an air ambulance for transfer of patients at UHNBC is as follows. Due to UHNBC not having a rooftop helipad, patients are transferred to the Prince George International Airport, using a ground air ambulance at cost of $530 per patient (BC Ambulance Service, 2013). From the airport, air ambulance transfer of patients is costed at $2746 per hour of travel. Furthermore, obese patients may require the use of a bariatric plane which costs $7 per statue mile (BC Ambulance Service, 2013). Additionally a cardiac catherization lab would be able to perform procedures other than PCI, such as CABG which can result better long-term patient outcomes for certain patients such as those with complex lesions (Mohr et al., 2013). This would not only improve patient outcomes but would enable the triage of patients for medical treatment versus cardiac intervention (PCI or CABG) saving angiography times in the larger centres and resulting in lower costs to the overall health care system.

Given the results of this study, a large majority of the patients are high risk with multiple co-morbidities or are elderly which can result in an even larger expenditure related to cost of hospital stay. As well the bed utilization for patients awaiting transfer

may also impact services for other patients. According to the BC Medical Association (2008), this can result in the cancellation of scheduled procedures for other patients. Furthermore, UHNBC does not have a critical care unit (CCU) and high-risk cardiac patients such as those requiring telemetry beds are placed in the intensive care unit (ICU) which can potentially limit the number of beds and consequently level of care required for non-cardiac but acutely ill patients requiring ICU care. As well, there are also out-of pocket costs for patients associated with travelling for care. For example, the Medical Services Plan (MSP) does not cover travel costs associated with patient travel from the cardiac catherization centre back to Prince George unless the patient is medically unfit and requires repatriation to UHNBC (BC Ambulance Service, 2013).

Furthermore, having a catherization lab in Prince George could reduce costs associated with other northern patients. It would potentially save the smaller community hospitals from having to keep their patients in hospital prior to transfer. It may also reduce the burden of cost associated with patient transfer through BC Ambulance due to shorter travel distances from northern communities to Prince George as compared to the Lower Mainland. This is consistent with research done by Le May et al. (2003) who discovered that in Canadian centers in which facilities and experienced interventionists are available, primary stenting (n=62) was less costly and more effective than thrombolysis (n=61).

However this requires the consideration of a number of complex financial and health care service factors given the current context. A detailed analysis of the literature alongside an examination of the practicality and feasibility of such a facility is warranted as there is considerable debate concerning the creation of stand-alone PCI centres.

Concerns include the sustainability of the system in terms of staffing levels as they require continuous and/or on-call staffing, infrastructure and patient volumes. This is particularly relevant in rural communities where the recruitment and retention of health care professionals can be challenging at best.

Finally, an examination into patient experiences associated with treatment delay may also provide valuable insight into this issue. This would include an examination of factors associated with patient delays to seeking treatment as well as an exploration of the patient journey in the process including emotional, physical, psychological and financial constraints. The findings from this work could help to inform future initiatives and planning to improve current practices and procedures.

Implications for research

The findings from this study present several areas for future investigation. To build on the findings from this exploratory study, a longitudinal study encompassing all hospitals within the boundaries of the Northern Health Authority could examine transfer times, and patient health outcomes. In addition to this, a study exploring the organizational barriers both at the transfer and receiving hospitals is needed. Equally as important would be an exploration of the logistics of current patient transfer via air ambulance through the BC Ambulance Service.

Implications for policy and practice

For hospitals without on-site cardiac catherization facilities, using transfer strategies there is a need to be cognizant of their own times to transfer. Attention to this can aid in process improvements which in turn can reduce the overall delay from time of

presentation to balloon time. This information can also be incorporated into clinical decision making when selecting between reperfusion strategies.

As a starting point, more attention to documentation of cardiac patients would be ideal. For example, having the documentation of cardiac referral times for all patients would allow for the identification of referral to transfer time. This in turn would allow for indication as to the delay in time at the transfer hospital. Furthermore, it would allow for the opportunity to identify the time of delay from point of referral to transfer.

Second, this study presents an alternative to the current practice of TIMI risk score use at UHNBC. The GRACE risk score is a validated risk prediction tool for implementation in prioritizing patient transfer for cardiac intervention. The use of this tool may also assist physicians, who are less likely to be specialist internists, in smaller, more rural community hospitals with triaging and prioritizing patients for transfer. . Thus the implementation of this risk stratification tool can have immediate effects on assisting physicians in their clinical decision making.

Third, there may be scope to introduce pre-hospital thrombolytic therapy, and pre-hospital ECGs for eligible patients by ambulance paramedics, a method endorsed by the ACC/AHA (Levine et al., 2011). This is general practice in some parts of the world including Europe and is strongly encouraged by the European Society of Cardiology (ESC), despite the existence of a larger number of PCI-capable hospitals and shorter distances to them (Van der Werf et al., 2008). While it's implementation in North America is somewhat limited, certain Canadian cities including Houston (NS) and Edmonton (Alta) have managed to demonstrate some level of success in terms of

improved patient outcomes with its use (Huynh et al., 2011). This would allow for a potential reduction in infarct size, limiting myocardial damage. Furthermore, the more acute patients may then be eligible for faster transfer for PCI (Rezaee et al., 2010).

The findings from this research also present some important opportunities for public health strategies. These include targeted obesity reduction approaches, smoking cessation campaigns, and healthier lifestyle interventions for high-risk patients. These public health interventions could be tailored to the high-risk patients and potentially reduce repeat visits and consequently repeat admissions to UHNBC.

Conclusion

In summary age was the only significant predictor of time to treatment for PCI. Furthermore, it was evident that a risk-averse strategy was adopted and transfer of patients was largely based on factors including clinical presentation rather than risk status. While PCI remains the treatment of choice for patients with ACS, particularly STEMI, thrombolytic therapy still offers a reasonable alternative in hospitals without on-site cardiac catherization facilities. Furthermore, under certain conditions, transfer for PCI despite prolonged time to treatment may still be the best option as the research surrounding patient transfer for PPCI remains somewhat inconclusive. It is hoped that the results from this study will provide a baseline for further research and allow decision makers to understand the current transfer situation and risk profiles of northern patient populations.

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APPENDICES

Appendix A: Corresponding ICD-9 Codes

Disease Term	ICD Number
Angina Pectoris	120
Unstable Angina	120.0
Acute Transmural myocardial infarction of anterior wall	121.0
Acute Transmural myocardial infarction of other sites	121.2
Acute Transmural myocardial infarction of unspecified site	121.3
Acute subendothelial myocardial infarction	121.9
Subsequent myocardial infarction of anterior wall	122.0
Subsequent myocardial infarction of inferior wall	122.1
Subsequent myocardial infarction of other sites	122.8
Subsequent myocardial infarction of unspecified site	122.9
Post myocardial infarction angina as current complication following acute myocardial infarction	123.2
Other acute ischaemic heart disease	124
Coronary thrombosis not resulting in acute myocardial infarction	124.0
Other forms of acute ischaemic heart disease	124.8
Acute ischaemic heart disease, unspecified	124.9

Appendix B: STEMI Protocol

northern health

Prince George Regional Hospital
PHYSICIAN'S ORDERS

ST ELEVATION MYOCARDIAL INFARCTION

Date:_____ Patient Weight:_____ Door Time:_____ First ECG:_____

		Time	Initials
	1. Admit to CCU and implement Physician's Orders for Coronary Routine.		
☐	2. Morphine 2 - 5 mg IV prn for chest pain.		
☐	3. Chew 2 x 80 mg ASA stat (check allergies first).		
☐	4. Initiate 2 IV's (#18 - 20) in opposite arms.		
	5. CBC, SeCr, PT, PTT @ baseline, then CBC q3days.		
☐	6. Enteric Coated ASA 325 mg po daily.		
	7. Choose **one** of the following:		

☐	A. Tenecteplase (TNK) with Enoxaparin	Time	Initials
	Enoxaparin 30 mg IV bolus before TNK.		
	TNK weight adjusted bolus over 5 sec.		
	Enoxaparin 1 mg/kg (max 100 mg) SC now, then BID x 7 days.		

☐	B. Tenecteplase (TNK) with Unfractionated Heparin ** ** Recommended for patients > 75 years old OR CrCl < 30 mL/min OR weight less than 50 kg	Time	Initials
	TNK weight adjusted bolus over 5 sec.		
	Heparin nomogram on reverse with first aPTT 3 hours post TNK.		

TNK Dosage Chart

Patient Weight (kg)	TNK (mg)	Volume (mL)
< 60	30	6
60 - < 70	35	7
70 - < 80	40	8
80 - < 90	45	9
> 90	50	10

To use the Table: → Select age and gender to identify SeCr cut-off value. Values above cut-off indicate a CrCl < 30 mL/min & enoxaparin should not be used.

Creatinine Clearance Estimate

Male	Age	Female
300	40	255
285	45	242
270	50	230
255	55	216
240	60	204
225	65	191
210	70	178
195	75	165
180	80	153
165	85	140
150	90	127

☐ 7. If admission blood glucose > 11.0, initiate DIGAMI protocol.
☐ 8. Beta Blocker: Choose one of the following:
- ☐ IV Metoprolol 5 mg over 2 minutes & repeat q5min x 3 doses (total = 15 mg) (consider dosage reduction if patient already on beta blocker or calcium channel blocker).
- ☐ Oral Metoprolol _____ starting at_____hours

☐ 9. Clopidogrel 300 mg po stat and 75 mg po daily.
☐ 10. Lipitor 80 mg po daily or_____mg po daily. (No Substitutions)
☐ 11. ACE Inhibitor: _____ starting at_____hours
12. 12 - lead ECG 90 minutes post TNK
13. Cholesterol, triglycerides, HDL, LDL, fasting glucose within 24 hours of admission.
☐ 14. Smoking Cessation Initiate Nicotine Withdrawal Protocol.
15. Cardiac Rehab Coordinator referral (fax: 250-565-2084).
16. Pharmacist to review medications on day 4.
17. Dietitican Consult (fax: 250-565-2889).

Physician's Signature: _____ **Time:**_____ **Date:**_____

IFD Form #11-100-1049 REV 4/07pc

Appendix C: NSTEMI/UA Protocol

northern health

Prince George Regional Hospital

ACUTE CORONARY SYNDROME ORDERS FOR UA/NSTEMI

Patient Weight _____

Consider the following as per Risk Stratification (on reverse) Indicate with a check (✓) for YES

1. **Initiate Physician's Orders for Coronary Routine**
2. ○ **Telemetry OR**
   ○ **ICU**

☐ 3. **ASA (choose one)**
   ○ ECASA 81 mg po daily
   ○ ECASA 325 mg po daily

☐ 4. **Nitroglycerin**
   ○ Patch strength _____ apply qam and remove qhs
   ○ Infusion beginning at 5 mcg/min & titrate to pain and BP as per protocol (ICU / ER only)

☐ 5. **Beta Blocker**
   ○ Metoprolol
      ● IV 5 mg bolus x _____ doses at intervals of _____ minutes (max. 15 mg)
      ● Oral _____ mg po every _____ hours starting at _____ hours
   ○ Other Beta blocker _____ mg po every _____ hours starting at _____ hours

☐ 6. **Calcium Channel Blocker** _____ mg po - frequency _____

☐ 7. **Clopidogrel** 300 mg po stat and 75 mg po daily.

☐ 8. **Lipitor** 80 mg po daily or _____ mg po daily. (No Substitutions)

☐ 9. **Ramipril** _____ mg po qam

☐ 10. **Anticoagulants**
   ○ Enoxaparin 1 mg/kg q12h and CBC Mondays & Thursdays (if CrCl < 30 mL/min, use UFH)
   ○ Heparin (as per protocol)

☐ 11. **Eptifibatide (Internists only)**
   ○ For patients with CrCl > 30 mL/min
      ● Loading dose 180 mcg/kg = _____ mcg (max 22.6 mg) over 2 minutes
      ● Maintenance dose 2 mcg/kg/min = _____ mcg/min (max 15 mg/hour) x _____ **hours (max 72 hrs)**
   ○ For patients with CrCl < 30 mL/min
      ● Loading dose 180 mcg/kg = _____ mcg (max 22.6 mg) over 2 minutes
      ● Maintenance dose 1 mcg/kg/min = _____ mcg/min (max 7.5 mg/hour) x _____ **hours (max 72 hrs)**
   ● CBC 4 hours post initiation of Eptifibatide and daily thereafter x 4 days.

☐ 12. If chest pain unresponsive to Nitroglycerin spray given three times 3 - 5 minutes apart, give Morphine Sulphate _____ mg IV q _____ minutes prn, request STAT ECG and notify physician.

13. Cholesterol, Triglycerides, HDL, LDL, fasting sugar within 24 hours of admission.

☐ 14. Smoking Cessation NICC referral (fax: 250-612-0810) consider Nicotine Replacement.

15. Cardiac Rehab Coordinator referral (fax: 250-562-2084).

16. Pharmacist to review medications on day 4

17. Dietician consult (fax: 250-565-2889)

Physician's Signature: _____ Date: _____

CDR Form #11-100-1023 DRAFT #6 - 04/07pc

Appendix D: Cardiac Catherization Lab Referral Form

Cardiac Cath Lab Referral

ST. PAUL'S HOSPITAL

VANCOUVER HOSPITAL & Health Sciences Centre

Name:
Address:
DOB:
PHN:
Telephone:
Referral Date: _____

Fax: referral form, history, ECG, lab results, echo report, ETT, CXR, meds

Vancouver Hospital
Fax: 604-875-5142
Phone: 604-875-4669

St. Paul's Hospital
Fax: 604-806-8637
Phone: 604-806-8051

Referring MD: _____
Referring tel: _____
Referring fax: _____
First Available Cardiologist ☑
Specific Cardiologist: _____
Angiogram / PCI within the last year by Dr. _____

Urgency
- ☐ Inpatient Hospital:
- ☐ Emergent (done without delay)
- ☐ Ut (before hospital discharge) ☐ suitable for same day dschg
- ☐ Outpatient ☐ Elective
- ☐ Semi-urgent: reason _____

For emergent cases please discuss with the on-call interventionalist
VH: 604-875-4111 SPH: 604-682-2344

Procedure(s) Requested:
- ☐ Diagnostic Catheterization
- ☐ Cath & Possible PCI
- ☐ PCI (cath done)
- ☐ Right Heart Cath
- ☐ Pulmonary Resistance
- ☐ Renal angiogram
- ☐ Aortogram
- ☐ Carotid/4vessel study
- ☐ Biopsy
- ☐ Other _____

Indication: please provide single best indication and give details if this is an ACS

Acute Coronary Syndromes

STEMI:
If Fibrinolysis: date / time: _____
- ☐ Direct PCI (no fibrinolysis)
- ☐ Rescue (failed thrombolysis)
- ☐ Facilitated (thrombolysis + PCI)
- ☐ Post acute STEMI

NSTEMI or other ACS:
- ☐ troponin / marker+
- ☐ ischemic ECG change (ST or T)
- ☐ equivocal or no marker rise

ACS Onset date:
_____

ACS Pain or Ischemia:
- ☐ Ongoing (no complete relief)
- ☐ Recurrent (episodic events)
- ☐ Provokable (on stress test)
- ☐ None (acute event settled)

ACS Medications:
- ☐ GP IIb/IIIa Inhibitor
- ☐ Heparin IV or LMWH
- ☐ IV NTG

- ☐ Stable CAD
  CCS Angina Class:
  0 I II III IV
- Valve ☐ aortic ☐ mitral
- ☐ CHF NYHA Class: I II III IV
- ☐ Dilated CM
- ☐ Hypertrophic CM
- Arrhythmia VT/VF ☐ SVT ☐
- ☐ Congenital
- ☐ Post Transplant
- ☐ Research Protocol only

Other risk factors
- ☐ hyperlipidemia
- ☐ current smoker
- Height: _____
- Weight: _____

Prior non-invasive tests:
Not done ☐
- ☐ Pos
- ☐ Neg
- ☐ Unk
- ☐ indeterminate

Safety :
- ☐ ASA administered
- ☐ Plavix administered
- ☐ Contrast allergy
- ☐ Warfarin ☐ mechanical valve
- ☐ Metformin

Renal status Last creatinine _____

Complexity:
- ☐ None ☐ Diabetes
- ☐ PVD ☐ CHF (current)
- ☐ Prior MI ☐ Hypertension
- ☐ Prior PCI ☐ Prior CABG
- ☐ Shock
- ☐ Other disease limiting survival

CATHLAB USE ONLY

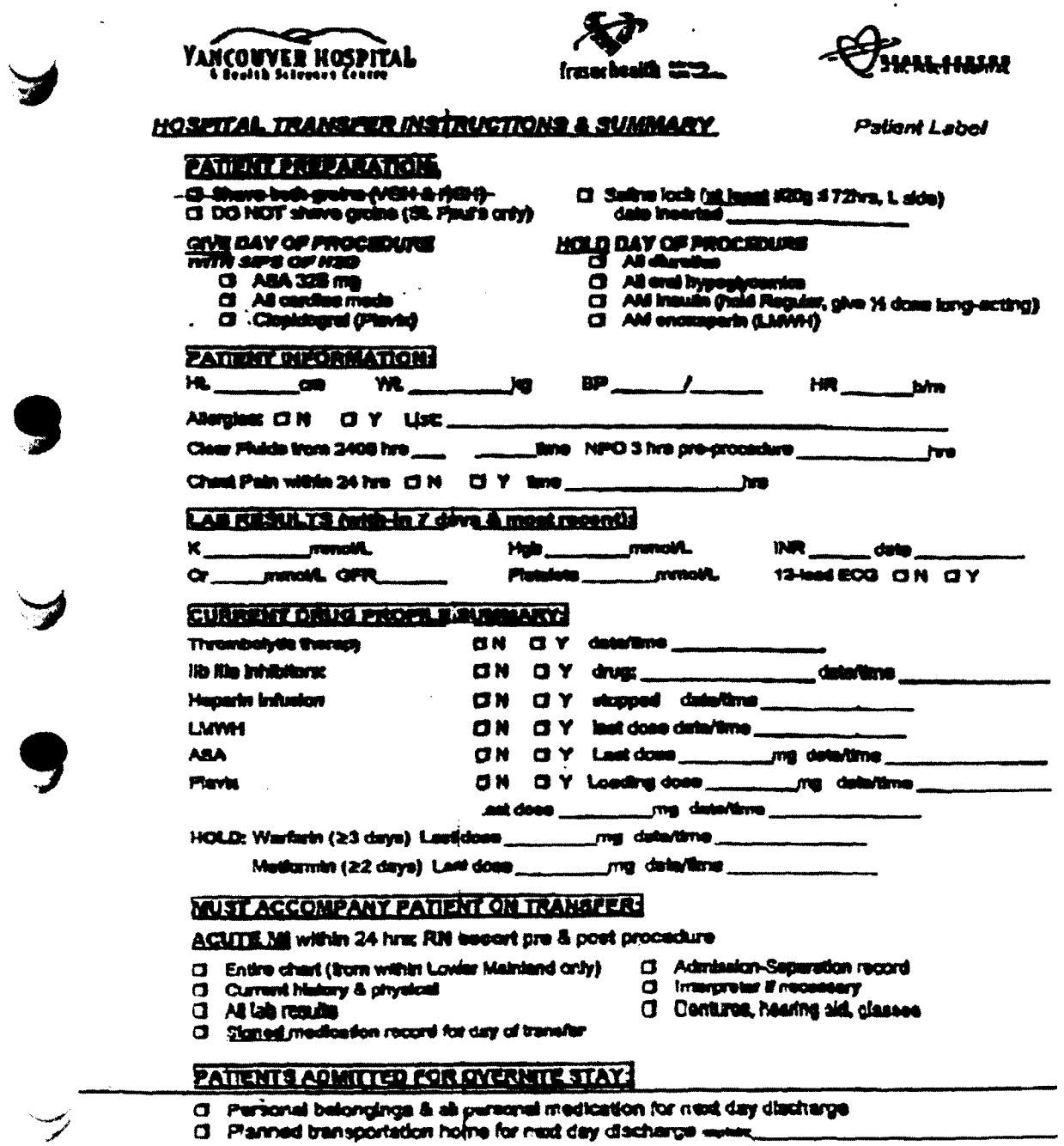
Anticoagulation Risk Low Intermediate High
Stop Warfarin 4-5 days pre-procedure
Bridge
DO NOT stop Warfarin

2nd Interventional opinion ☐
Surgical opinion ☐
Pe e Research Protocol
on Only ☐

Referring Physician History &Comments:

Referring Physician _____

Appendix E: Hospital Transfer Form



VANCOUVER HOSPITAL
& Health Sciences Centre

fraserhealth

HOSPITAL TRANSFER INSTRUCTIONS & SUMMARY

Patient Label

PATIENT PREPARATION:

~~☐ Shave bulk groins (VGH & RGH)~~
☐ DO NOT shave groins (St. Paul's only)

☐ Saline lock (at least #20g x 72hrs, L side)
date inserted _____

GIVE DAY OF PROCEDURE
WITH SIPS OF H2O
☐ ASA 325 mg
☐ All cardiac meds
☐ Clopidogrel (Plavix)

HOLD DAY OF PROCEDURE
☐ All diuretics
☐ All oral hypoglycemics
☐ AM insulin (hold Regular, give ½ dose long-acting)
☐ AM enoxaparin (LMWH)

PATIENT INFORMATION:

Ht. _____cm Wt. _____kg BP _____/_____ HR _____b/m

Allergies: ☐ N ☐ Y List: _____

Clear Fluids from 2400 hrs ___ _____time NPO 3 hrs pre-procedure _____/hrs

Chest Pain within 24 hrs ☐ N ☐ Y time _____hrs

LAB RESULTS (within 7 days & most recent):

K _____mmol/L Hgb _____mmol/L INR _____ date _____

Cr _____mmol/L GFR _____ Platelets _____mmol/L 12-lead ECG ☐ N ☐ Y

CURRENT DRUG PROFILE SUMMARY:

Thrombolytic therapy	☐ N ☐ Y	date/time _____
IIb IIIa inhibitors	☐ N ☐ Y	drug: _____ date/time _____
Heparin infusion	☐ N ☐ Y	stopped date/time _____
LMWH	☐ N ☐ Y	last dose date/time _____
ASA	☐ N ☐ Y	Last dose _____mg date/time _____
Plavix	☐ N ☐ Y	Loading dose _____mg date/time _____
		last dose _____mg date/time _____

HOLD: Warfarin (≥3 days) Last dose _____mg date/time _____

Metformin (≥2 days) Last dose _____mg date/time _____

MUST ACCOMPANY PATIENT ON TRANSFER:

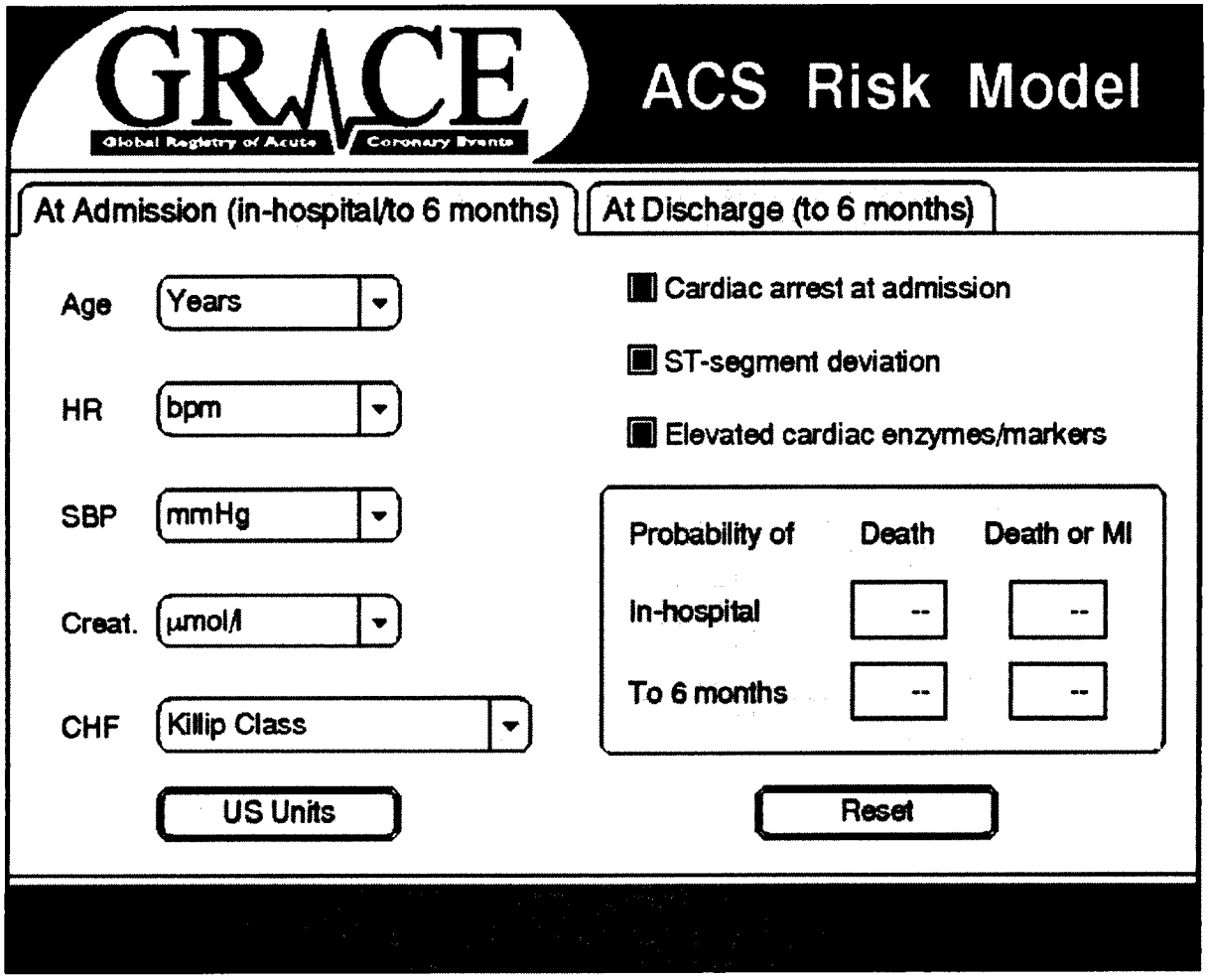
ACUTE MI within 24 hrs: RN escort pre & post procedure

☐ Entire chart (from within Lower Mainland only)
☐ Current History & physical
☐ All lab results
☐ Signed medication record for day of transfer
☐ Admission-Separation record
☐ Interpreter if necessary
☐ Dentures, hearing aid, glasses

PATIENT'S ADMITTED FOR OVERNITE STAY:

☐ Personal belongings & all personal medication for next day discharge
☐ Planned transportation home for next day discharge _____

Appendix F: Grace Risk Score ACS Models



Appendix G: PCI Studies Summarized

Study	Patient /Pop.	Intervention	Control	Outcome
Widimisky et al. (2000) PRAGUE TRIAL	N=300	Thrombolysis during transfer for PCI (group B) OR immediate transfer for PPCI (group C)	Thrombolysis at a community hospital (group A)	Combined primary end-point (death or reinfarction and/or stroke at 30 days) was less frequent in group C (8%) compared to both groups B (15%) and A (23%, $p<0.02$) Incidence of reinfarction was markedly reduced by transport to PPCI (1% in group C vs 7% in group B vs 10% in group A, $p<0.03$)
				The transfer of patients from a community hospital to a PCI centre in the acute phase of AMI is both safe and feasible and is associated with significant reduction in incidence of reinfarction and combined primary endpoint (death or reinfarction and/or stroke at 30 days)
Widimsky et al. (2003) PRAGUE-2 TRIAL	N=850	Immediate transfer for PPCI (PCI group)	Thrombolysis at a community hospital (TL group)	Mortality at 30 days was higher (10.0%) in the TL group compared to 6.8% mortality in the PCI group ($p=0.12$, intention-to-treat analysis). Mortality of 380 patients who actually underwent PCI was 6.0% vs 10.4% mortality in 424 patients who finally received thrombolysis, TL group ($p<0.05$). Among the 299 patients randomized >3 hours after the onset of symptoms, the mortality of the TL group was higher (15.3% compared to the PCI group (6%, $p<0.02$). Patients randomized $\leq$3 hours of symptom onset (n=551) had no difference in

				mortality whether treated by TL (7.4%) or transferred for PCI (7.3%). A combined end-point occurred was higher in the TL group (15.2%) vs the PCI group (8.4%, p<0/003)of the PCI group
				Long distance transport from a community hospital to a tertiary PCI centre in the acute phase of AMI is safe as this strategy was associated with marked decreases in mortality in patients presenting more than 3 hours after symptom onset. However for patients presenting within 3 hours of symptom onset, TL results were similar to the results in long distance transport for PCI
Ellis et al. (2004) FINESSE TRIAL	N=3000	PPCI	2 facilitated PCI treatments; reduced-dose reteplase and abciximab combination therapy OR abciximab alone followed by PCI with abciximab alone	One-year mortalities in the three groups, reduced-dose reteplase and abciximab combination therapy (6.3%) or abciximab alone followed by PCI with abciximab alone (7.4%), or PPCI, r (7.0, p = NS), representing 1.1%, 1.9%, and 2.5% increments since the 90-day outcome (p = 0.053 for combination treatment vs PPCI)
				Widespread use of facilitated PCI could not be justified among all ACS patients but high-risk (i.e with anterior AMI) deserve further study
Fernandez-Aviles et al. (2007) GRACIA-2	N=212	PPCI with abciximab ≤3 hours of randomization	Full tenecteplase followed by stenting within 3-12 hours of randomization	Early routine post-thrombolysis PCI resulted in higher frequency (21 versus 6%, p = 0.003) of complete epicardial and myocardial reperfusion (TIMI 3 epicardial flow and TIMI 3 myocardial perfusion and resolution of the initial sum of ST-segment

TRIAL			(early routine post-thrombolysis PCI	elevation > or = 70%) following angioplasty. Both groups were similar regarding infarct size (area under the curve of CK-MB: 4613 +/- 3373 vs 4649 +/- 3632 microg/L/h, p= 0.94); 6-week left ventricular function (ejection fraction: 59.0 +/- 11.6 vs 56.2 +/- 13.2%, p= 0.11; end systolic volume index: 27.2 +/- 12.8 vs 29.7 +/- 13.6, p = 0.21); major bleeding (1.9 vs 2.8%, p = 0.99) and 6-month cumulative incidence of the clinical endpoint (10 vs 12%, p = 0.57; RR: 0.80; 95% CI: 0.37-1.74)
				Early routine post-fibrinolysis angioplasty safely results in better myocardial perfusion than primary angioplasty as despite its delayed application, this approach was seen to be equivalent to primary angioplasty in limiting infarct size and preserving left ventricular function
Grines et al. (2002) AIR-PAMI TRIAL	N=138	Transfer for PPCI	On-site thrombolysis	Patients randomized to transfer had a reduced hospital stay (6.1 +/- 4.3 vs 7.5 +/- 4.3 days, p= 0.015) and less ischemia (12.7% vs 31.8%, p = 0.007). At 30 days, a 38% reduction in major adverse cardiac events was observed for the transfer group however, because of the inability to recruit the necessary sample size, this did not achieve statistical significance (8.4% vs 13.6%, p = 0.331)
				High-risk patients with AMI at hospitals without a catheterization laboratory may have an improved outcome when transferred for primary PCI versus on-site thrombolysis. This suggests that the marked delay in the

				transfer process suggests a role for triaging patients directly to specialized heart-attack centers
Andersen et al. (2003) DANAMI-2 TRIAL	N=1572	PPCI	Thrombolysis	The primary study end point was a composite of death, clinical evidence of reinfarction, or disabling stroke at 30 days. Among patients who underwent randomization at referral hospitals, the primary end point was reached in 8.5% of the patients in the PCI group, as compared with 14.2% of those in the thrombolysis group (p=0.002). The results were similar among patients who were enrolled at invasive-treatment centers: 6.7% of the patients in the PCI group reached the primary end point, as compared with 12.3% in the thrombolysis group (p=0.05). Among all patients, the better outcome after PCI was driven primarily by a reduction in the rate of reinfarction (1.6% in the PCI group vs 6.3% in the thrombolysis group, p<0.001); no significant differences were observed in the rate of death (6.6 % vs 7.8 %, p=0.35) or the rate of stroke (1.1 % vs 2.0 %, p=0.15)
				A strategy for reperfusion involving the transfer of patients to an invasive-treatment center for PPCI is superior to on-site thrombolysis, provided that the transfer takes two hours or less
Van der Werf et al. (2006)	N=1667	PPCI with 6 hours of STEMI	PCI preceded by administration of full-dose	Primary endpoint (death, CHF, or shock) in 19% (151 of 810) of patients assigned facilitated PCI versus 13% (110 of 819) of those

ASSENT-4 TRIAL			tenecteplase	randomised to PPCI (relative risk 1.39, 95% CI 1.11-1.74; p=0.0045). During hospital stay, significantly more strokes (1.8% [15 of 829] vs 0, p<0.0001), but not major non-cerebral bleeding complications (6% [46 of 829] vs 4% [37 of 838], p=0.3118), were reported in patients assigned facilitated rather than standard PCI. We also noted more ischaemic cardiac complications, such as reinfarction (6% [49 of 805] vs 4% [30 of 820], p=0.0279) or repeat target vessel revascularisation (7% [53 of 805] vs 3% [28 of 818], p=0.0041) within 90 days in this study group
				A strategy of full-dose tenecteplase with antithrombotic co-therapy, as used in this study and preceding PCI by 1-3 h, was associated with more major adverse events than PCI alone in STEMI and cannot be recommended.
Nielsen et al. (2010) Follow-up to the DANAMI-2 TRIAL	N=1572	PPCI	Thrombolysis	The composite endpoints primarily, death, clinical re-infarction, or disabling stroke, were reduced by PCI when compared with thrombolysis at 3 years (19.6% vs 25.2%, p= 0.006). For patients transferred to PCI compared with those receiving on-site thrombolysis, the composite endpoint occurred in 20.1% vs 26.7% (p= 0.007), death in 13.6 vs 16.4% (p= 0.18), clinical re-infarction in 8.9% vs 12.3% (p= 0.05), and disabling stroke in 3.2% vs 4.7% (p= 0.23)

				The benefit of transfer for primary PCI based on the composite endpoint was sustained after 3 years. Nielsen et al. (2010) concluded that for patients with characteristics such as those in DANAMI-2, primary PCI should be the preferred treatment strategy provided that inter-hospital transfer can be completed within 2 hours
Thiele et al. (2011) LIPSIA-STEMI TRIAL	N=162	PPCI (group B)	Pre-hospital-initiated facilitated PCI (group A)	Despite better pre-interventional TIMI (Thrombolysis In Myocardial Infarction) flow in Group A (71% versus 35% TIMI flow grade 2 or 3; $p < 0.001$), the infarct size tended to be worse in group A vs group B (17.9% of left ventricle IQR: 8.4% to 35.0%) vs 13.7% IQR: 7.5% to 24.0%); $p = 0.10$). There was also a strong trend toward more early and late microvascular obstruction, ($p = 0.06$ and 0.09) and no difference in ST-segment resolution ($p = 0.26$). The combined clinical endpoint showed a trend toward higher event rates in group A (19.8% vs 13.6%; $p = 0.13$, RR: 0.52, 95% CI: 0.23- 1.18)
				STEMI patients presenting early after symptom onset with relatively long transfer times, a thrombolytic-based facilitated PCI approach with optimal antiplatelet co-medication does not offer a benefit over primary PCI with respect to infarct size and tissue perfusion
Bohmer et al. (2003)	N=197	Transfer $\leq$6 hours after thrombolysis	Elective PCI two weeks after	Immediate stenting was associated with a significant reduction of the combined end point after six months

SIAM-III TRIAL		for PCI	thrombolysis	(ischemic events, death, reinfarction, target lesion revascularization 25.6% vs 50.6%, p = 0.001)
				Immediate stenting after thrombolysis leads to a significant reduction of cardiac events compared with a more conservative approach including delayed stenting after two weeks
Fernandez-Aviles et al. (2004) GRACIA-1 TRIAL	N=500	PPCI	Angiography or PCI within 24 hours of thrombolysis	By comparison with patients receiving conservative treatment, by 1 year, patients in the invasive group had lower frequency of primary endpoint (23 (9%) vs 51 (21%), relative risk 0.44 (95% CI 0.28-0.70), p=0.0008), and they tended to have reduced rate of death or reinfarction (7% vs 12%, 0.59 (0.33-1.05), p=0.07). Index time in hospital was shorter in the invasive group, with no differences in major bleeding or vascular complications. At 30 days both groups had a similar incidence of cardiac events. In-hospital incidence of revascularisation induced by spontaneous recurrence of ischaemia was higher in patients in the conservative group than in those in the invasive group
				In patients with STEMI, early post-thrombolysis catheterization and appropriate intervention is safe and might be preferable to a conservative strategy since it reduces the need for unplanned in-hospital revascularization, and improves 1-year clinical outcomes

Di Mario et al. (2008) CARESS-in- AMI TRIAL	N=600	Thrombolysis and immediate transfer for PCI	Thrombolysis and transfer for rescue PCI	The primary endpoint was a composite of death, reinfarction, or refractory ischaemia at 30 days. Of the 299 patients assigned to immediate PCI, 289 (97.0%) underwent angiography, and 255 (85.6%) received PCI. Rescue PCI was done in 91 patients (30.3%) in the standard care/rescue PCI group. The primary outcome occurred in 13 patients (4.4%) in the PPCI group compared with 32 (10.7%) in the standard care/rescue PCI group (hazard ratio 0.40; 95% CI: 0.21-0.76, p=0.004). Major bleeding was seen in ten patients in the immediate group and seven in the standard care/rescue group (3.4% vs 2.3%, p=0.47). Strokes occurred in two patients in the immediate group and four in the standard care/rescue group (0.7% vs 1.3%, p=0.50)
				Immediate transfer for PCI improves outcome in high-risk patients with STEMI treated at a non-interventional centre with half-dose reteplase and abciximab
Bohmer et al. (2007) NORDSTE MI TRIAL	N=266	Immediate transfer for angiography OR PPCI	Thrombolysis in the community hospitals, with urgent transfer only for a rescue indication or with clinical deterioration	The primary endpoint was a composite of death, reinfarction, stroke, or new ischemia at 12 months. The primary endpoint was reached in 28 patients (21%) in the early invasive group compared with 36 (27%) in the conservative group (hazard ratio: 0.72, 95% CI: 0.44 to 1.18, p = 0.19). The composite of death, reinfarction, or stroke at 12 months was significantly reduced in the early invasive compared with the

				conservative group (6% vs 16%, hazard ratio: 0.36, 95% CI: 0.16 to 0.81, p = 0.01). No significant differences in bleeding or infarct size were observed
				Immediate transfer for PCI did not improve the primary outcome significantly, but reduced the rate of death, reinfarction, or stroke at 12 months in patients with STEMI, treated with thrombolysis and clopidogrel in areas with long transfer distances
Cantor et al. (2009) TRANSFER -AMI TRIAL	N=1059	Immediate transfer to PCI capable hospital within 6hrs post-thrombolysis	Thrombolysis with rescue PCI or delayed angiography	The primary end point was the composite of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days. Cardiac catheterization was performed in 88.7% of the patients assigned to standard treatment a median of 32.5 hours after randomization and in 98.5% of the patients assigned to routine early PCI a median of 2.8 hours after randomization. At 30 days, the primary end point occurred in 11.0% of the patients who were assigned to routine early PCI and in 17.2% of the patients assigned to standard treatment (relative risk with early PCI, 0.64; 95% CI: 0.47 to 0.87; p=0.004). There were no significant differences between the groups in the incidence of major bleeding. Among high-risk patients who had a myocardial infarction with ST-segment elevation and who were treated with thrombolysis, transfer for PCI within

				6 hours after thrombolysis was associated with significantly fewer ischemic complications than was standard treatment.
McKay et al. (2009) ----------	N=1553	PPCI	Facilitated PCI	Compared with patients who underwent primary PCI, the facilitated PCI group had longer door-to-balloon times (162 +/-57 vs 113 +/-61 minutes), higher baseline infarct-vessel TIMI 3 flow rates (52.8% vs 25.4%; p <0.001), and no increase in major adverse in-hospital outcomes. In patients treated with door-to-balloon times greater than 90 and less than150 minutes, patients who underwent facilitated PCI had fewer composite major adverse clinical events (combined mortality, recurrent myocardial infarction, emergent repeated PCI, hemorrhagic and non-hemorrhagic stroke, and non-intracranial TIMI major bleeding) compared with patients who underwent primary PCI (RR 0.50, 95% CI 0.26 to 0.96, p=0.034)
				Facilitated PCI can be safely used to increase pharmacological reperfusion before catheter-based therapy in patients with STEMI without an increase in clinical hazard and with fewer major adverse clinical events in patients treated with door-to-balloon times greater than 90 and less than 150 minutes

Appendix H: GRACE Risk Score Studies Summarized

Study	Patient/ Pop.	Measure	Result	Conclusion
Yan et al. (2004)	4627	Examined the relationship between in-hospital revascularization and 1-year outcome among patients with non–ST-elevation ACS, stratified by the GRACE risk score	In-hospital mortality rates were 2.4% overall and 1.5% among the patients with non-ST-elevation ACS (n = 2925; 63.2%) in our validation cohort. Both the in-hospital PURSUIT and GRACE risk models showed similar and good prognostic discrimination (57.8% CI: 0.84 and 0.83, respectively; p = .69 for difference). The GRACE model also demonstrated good calibration (Hosmer-Lemeshow P = .40). In contrast, calibration in the PURSUIT model was poor (Hosmer-Lemeshow p < .001), with consistent overestimation of risks	High-risk patients with ACS appear to benefit from, but are less likely to undergo, early PCI. Used with sound clinical judgment, the GRACE risk stratification tool can facilitate an evidence-based approach that tailors treatment appropriately to the individual patient
Araujo et al. (2005)	460	Compared the prognostic value of three ACS risk scores (RSs) and their ability to predict benefit from myocardial revascularization performed during	460 consecutive patients admitted to coronary care unit with an ACS [age: 63±11 years, 21.5% female, 55% with myocardial infarction (MI)]. For each patient, the Thrombolysis In	The GRACE risk score demonstrates good predictive accuracy for death or MI at 1 year and enabled the identification of high-risk subsets of patients who will benefit most from myocardial revascularization performed during initial hospital stay

		initial hospitalization	Myocardial Infarction (TIMI), Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (PURSUIT), and Global Registry of Acute Coronary Events (GRACE) RSs were calculated using specific variables collected at admission. Their prognostic value was evaluated by the combined endpoint of death or MI at 1 year. The best cut-off value for each RS, calculated with receiver operating characteristic curves, was used to assess the impact of myocardial revascularization on the combined incidence of death or MI. Death or MI at 1 year was 15.4% (32 deaths/49 MIs). The best predictive accuracy for death or MI at 1 year was obtained by the GRACE risk score (CI: 0.672–0.756) but the performance of the PURSUIT risk score (CI: 0.584–0.674), and TIMI risk score (CI: 0.539–0.631) was also good. A statistically significant interaction	

			between the risk stratified by the best cut-off value for the GRACE and PURSUIT risk scores and myocardial revascularization, with a better prognosis for the high-risk patients was found. The high-risk patients represented the population as follows; GRACE (36.7%), PURSUIT (28.7%), and TIMI (57.8%)	
Alter et al. (2006)	3500	To validate the Global Registry of Acute Coronary Events (GRACE) risk-adjustment index for 6-month all-cause mortality across socioeconomic strata	Predicted and observed mortality rates were significantly higher among patients of lower incomes and education (ie, observed 6-month mortality: 5.1 % vs 1.8% among low income vs high income patients, respectively, p<.0001; 4.6% vs 2.9% among low-educated vs highly educated patients, respectively, p=.02). The predicted 6-month mortality as derived using GRACE closely mirrored observed mortality rates with strong accuracy and precision (CI: 0.80 for the overall cohort and within each income and education strata;	The GRACE risk score for 6-month all-cause mortality is an accurate, well-calibrated, and robust predictor across socioeconomic strata and can be used as a valid risk-adjustment index when examining socioeconomic-mortality differences after acute MI

			Hosmer-Lemeshow goodness-of-fit test was not significant within each income and education strata)	
Bradshaw et al. (2006)	12875	To determine the validity of the GRACE prediction model for death six months after discharge in all forms of acute coronary syndrome in an independent dataset of a community based cohort of patients with acute myocardial infarction (AMI)	Post-discharge crude mortality at six months for the EFFECT study patients with AMI was 7.0%. The discriminatory capacity of the GRACE model was good overall (CI: 0.80) and for patients with ST segment elevation AMI (STEMI) (0.81) and non-STEMI (0.78). Observed and predicted deaths corresponded well in each stratum of risk at six months, although the risk was underestimated by up to 30% in the higher range of scores among patients with non-STEMI	In an independent validation the GRACE risk model had good discriminatory capacity for predicting post-discharge death at six months and was generally well calibrated, suggesting that it is suitable for clinical use in general populations
Fox et al. (2006)	24189	To determine whether revascularisation is more likely to be performed in higher-risk patients and whether the findings are influenced by hospitals adopting more or less	Overall, 32.5% of patients with a non-ST elevation ACS underwent percutaneous coronary intervention (PCI; 53.7% in ST segment elevation myocardial infarction (STEMI) and 7.2% underwent coronary artery bypass	A risk-averse strategy to angiography appears to be widely adopted. Proceeding to PCI relates to referral practice and angiographic findings rather than the patient's risk status. Systematic and accurate risk stratification may allow higher-risk patients to be selected for revascularisation

		aggressive revascularization strategies	grafting (CABG; 4.0% in STEMI). The cumulative rate of in-hospital death rose correspondingly with the GRACE risk score (variables: age, Killip class, systolic blood pressure, ST-segment deviation, cardiac arrest at admission, serum creatinine, raised cardiac markers, heart rate), from 1.2% in low-risk to 3.3% in medium-risk and 13.0% in high-risk patients (c statistic = 0.83). PCI procedures were more likely to be performed in low- (40% non-STEMI, 60% STEMI) than medium- (35%, 54%) or high-risk patients (25%, 41%). No such gradient was apparent for patients undergoing CABG. These findings were seen in STEMI and non-ST elevation ACS, in all geographical regions and irrespective of whether hospitals adopted low (4.2233.7%, n = 7210 observations), medium (35.7251.4%, n = 7913 observations) or high rates (52.6277.0%, n =	procedures, in contrast to the current international practice

			8942 observations) of intervention	
Ramsay et al. (2007)	347	To determine the predictive accuracies of the GRACE risk score, the TIMI risk score and clinical evaluation in unselected patients with suspected cardiac pain	Overall 54 patients (15.6%) experienced a major cardiac event (16 deaths, seven myocardial infarctions (MIs), one emergency revascularization) or emergency re-admission (n=30) within 3 months. Both GRACE ($p< 0.001$) and TIMI scores ($p< 0.001$) predicted death/MI/revascularization (and the composite including re-admission), but the GRACE score was superior to the TIMI score for predicting major cardiac events (z. 2.05), and both scores were superior to clinical evaluation (ROC areas 0.82, 0.74 and 0.55 respectively). The GRACE score predicted an ACS discharge diagnosis ($p< 0.001$) and duration of hospital stay ($p< 0.001$)	In unselected patients presenting with suspected cardiac pain, the GRACE risk score is superior to the TIMI risk score in predicting major cardiac events, and both risk scores are superior to using ECG and troponin findings at presentation

Tang et al. (2007)	1143	To determine whether GRACE is a validated risk model to predict mortality beyond 6 months	39% had ST-elevation myocardial infarction, 39% had non–ST-elevation infarction, and 22% had unstable angina. The mortality was 7.5% during index admission, 12.1% at 6 months, 14.8% at 1 year,18.7% at 2 years, 25.0% at 3 years, and 39.2% at 4 years. The GRACE hospital discharge risk score calculated for 1057 hospital survivors discriminated survival from death at 6 months (CI: 0.81), 1 year (C index, 0.82), 2 years (CI: 0.81), 3 years (CI; 0.81), and 4 years (CI: 0.80). The risk score worked for all 3 subsets of ACS at all time points, with CI: 0.75 in all analyses. A separate multivariable mortality model for these 1057 patients over the 4-years follow-up period identified 10 independent predictors of mortality. Seven were in the GRACE risk model (age, history of ischemic heart disease, heart failure, increased heart rate on admission, serum	The GRACE post-discharge risk score contains relevant prognostic factors and was found to accurately discriminate survivors from non-survivors over the longer term (up to 4 years) in all subsets of ACS patients

			creatine level, evidence of myonecrosis, not receiving in-hospital PCI).	
Yan et al. (2007)	4144	To examine the use of in-hospital cardiac catheterization and medications in relation to risk across the broad spectrum of non–ST elevation ACSs	Although in-hospital mortality rates were similar, the in-hospital use of cardiac catheterization increased significantly over time (38.8% in the ACS 1 Registry vs 63.5% in the ACS 2 Registry; p=.001). The rates of cardiac catheterization in the low-, intermediate-, and high-risk groups were 48.0%, 41.1%, and 27.3% in the ACS 1 Registry, and 73.8%, 66.9%, and 49.7% in the ACS 2 Registry, respectively (p=.001 for trend for both). After adjusting for other confounders, intermediate-risk (adjusted odds ratio, 0.75; 95% CI: 0.63-0.90; p=.001) and high-risk (adjusted odds ratio, 0.35; 95% CI: 0.28-0.45; p=.001) patients remained less likely to undergo cardiac catheterization compared with low-risk patients. Furthermore, there existed a similar	Despite temporal increases in the use of cardiac catheterization and revascularization in the management of non–ST elevation ACS, evidence-based invasive and pharmacological therapies remain paradoxically targeted toward low-risk patients. Strategies to eliminate this treatment-risk paradox must be implemented to fully realize the benefits and optimize the cost effectiveness of invasive management

			inverse relationship between risk and the use of in-hospital revascularization	
Aragam et al. (2009)	3451	To compare the discriminative abilities of the TIMI and GRACE risk scores in a broad-spectrum, unselected ACS population and to assess the relative contributions of model simplicity and model composition to any observed differences between the two risk models	UA/NSTEMI (n = 2753) and STEMI (n = 698) The predictive abilities of the TIMI and GRACE scores for in-hospital and 6-month mortality were assessed by calibration and discrimination. There were 137 in-hospital deaths (4%), and among the survivors, 234 (7.4%) died by 6 months post-discharge. In the UA/NSTEMI population, the GRACE risk scores demonstrated better discrimination than the TIMI UA/NSTEMI score for in-hospital (C = 0.85, 95% CI: 0.81–0.89, vs 0.54, 95% CI: 0.48–0.60; p=0.01) and 6-month (C = 0.79, 95% CI: 0.76–0.83, vs 0.56, 95% CI: 0.52–0.60; p=0.01) mortality. Among STEMI patients, the GRACE and TIMI STEMI scores demonstrated comparably excellent discrimination for in-hospital (C = 0.84, 95% CI: 0.78–0.90 vs 0.83,	The GRACE scores provided superior discrimination as compared with the TIMI UA/NSTEMI score in predicting in-hospital and 6-month mortality in UA/NSTEMI patients, although the GRACE and TIMI STEMI scores performed equally well in STEMI patients. The observed discriminative deficit of the TIMI UA/NSTEMI score likely results from the omission of key risk factors rather than from the relative simplicity of the scoring system

			95% CI: 0.78–0.89; p = 0.83) and 6-month (C = 0.72, 95% CI: 0.63–0.81, vs 0.71, 95% CI: 0.64–0.79; p = 0.79) mortality. An analysis of refitted multivariate models demonstrated a marked improvement in the discriminative power of the TIMI UA/NSTEMI model with the incorporation of heart failure and hemodynamic variables	
Elbaroun et al. (2009)	12242	To validate the GRACE risk score in a contemporary Canadian population with ACS	A total of 12,242 Canadian patients with ACS were included; the median GRACE risk score was 127 (25th and 75th percentiles were 103 and 157, respectively). Overall, the GRACE risk score demonstrated excellent discrimination (c statistic 0.84, 95% CI 0.82-0.86, p= .001) for in-hospital mortality. Similar results were seen in all the subgroups (all c statistics ≥0.8). However, calibration was suboptimal overall (Hosmer-Lemeshow p= .06) and in various subgroups	GRACE risk score is a valid and powerful predictor of adverse outcomes across the wide range of Canadian patients with ACS. Its excellent discrimination is maintained despite advances in management over time and is evident in across all patient subgroups. However, the predicted probability of in-hospital mortality may require recalibration in the specific health care setting and with advancements in treatment.

Gale et al. (2009)	100886	To compare the discriminative performance of the PURSUIT, GUSTO-1, GRACE, SRI and EMMACE risk models, assess their performance among risk supergroups and evaluate the EMMACE risk model over the wider spectrum of acute coronary syndrome (ACS)	The C-indexes were: PURSUIT C-index 0.79 (95% CI 0.78 to 0.80); GUSTO-1 0.80 (0.79 to 0.81); GRACE in-hospital 0.80 (0.80 to 0.81); GRACE 6-month 0.80 (0.79 to 0.80); SRI 0.79 (0.78 to 0.80); and EMMACE 0.78 (0.77 to 0.78). EMMACE maintained its ability to discriminate 30-day mortality across different ACS diagnoses Recalibration of the model offered no notable improvement in performance over the original risk equation. For all models the discriminative performance was reduced in patients with diabetes, chronic renal failure or angina	The five ACS risk models (PURSUIT,GUSTO-1, GRACE, SRI, EMMACE) maintained their discriminative performance in a large unselected English and Welsh ACS population, but performed less well in higher-risk sub groups. Simpler risk models had comparable performance to more complex risk models

Abu-Assi et al. (2010)	N=1183	To assess the validity of the GRACE risk score in a contemporary cohort of patients admitted to a Spanish hospital	In total, 459 (38.8%) patients were admitted for ST-elevation myocardial infarction (STEMI) and 724(61.2%) for non-ST-elevation myocardial infarction (NSTEMI). PCI was performed in 846 (71.5%). The median GRACE risk score was 121[IQR, 96-144]. Mortality 6 months after discharge was 4.4%. The calibration of the GRACE risk score was acceptable (Hosmer-Lemeshow, P>.2) and its discriminatory capacity was excellent: the area under the curve was 0.86 (95% CI: 0.807-0.916) for all patients, 0.9 (95% CI: 0.829-0.975) for those with STEMI and 0.86 (95% CI: 0.783-0.927) for those with NSTEMI	The GRACE risk score for predicting death within 6 months of hospital discharge was validated and can be used in patients with ACS. It would be wise to include the GRACE risk score in the medical records of these patients
Stacke et al. *2010)	N=1014	To evaluate the relationship between the GRACE risk score and in-hospital mortality in patients presenting to the ED with chest pain of all	A total of 94 patients died during the stay in the hospital, 83 patients with high risk, 9 with medium risk, and 2 with low risk. The risk of in-hospital death was 24.5% for high-risk patients, 2.6% for medium-risk patients,	This study shows that the GRACE risk score accurately stratifies risk of intra-hospital mortality in patients presenting to the ED with chest pain and can help guide patient triage and management

		causes	and 0.6% for patients with low risk. The correlation between the GRACE risk score and in-hospital mortality is strongly positive (p=0.01).	
Koziera dzka et al. (2011)	N= 505	To test the of GRACE risk score prognosis of 5-year survival in a "real-life" population of patients with ST-elevation myocardial infarction (STEMI) treated with PPCI	32 patients died during the first 30 days (6.3%) and an additional 74 within 5 years (15.6%). PCI was successful in 95.2%(n = 481). Prognostic values (c statistics) for predicting 5-year mortality equaled: 0.742 (CI: 0.69–0.79) for the GRACE risk score, 0.727 (CI 0.67–0.78) for TIMI, 0.72 (CI: 0.67–0.77) for Zwolle, and 0.687 (CI 0.63–0.74) for CADILLAC. Univariate analysis all the scores were associated with the 5-year outcome.	GRACE, TIMI, and Zwolle risk scores predicted well 5-year all-cause mortality in patients with STEMI treated with PPCI. The data show that the usefulness of initial bedside risk assessment can be further extended for long-term follow-up