THE PROVINCIAL GUIDELINES EFFECT ON RISK-BASED ACCESS TO CARDIAC CATHETERIZATION IN PATIENTS WITH NON-ST ELEVATION ACUTE CORONARY SYNDROMES IN NOVA SCOTIA (2003 – 2013)

By

Sanja Jovanovic

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Abstract

Background: For patients with Non-ST Elevation Acute Coronary Syndrome (NSTEACS), observational studies have found cardiac catheterization being utilized more in patients at lower risk compared to their higher risk counterparts, contrary to the recommendations of clinical practice guidelines. This study seeks to evaluate to what extent catheterization practices in Nova Scotia align with the provincial guideline recommendations for ACS.

Methods: We conducted a retrospective cohort study between 2003 and 2013. The primary outcome was utilization and timing of catheterization. The secondary outcome was one-year mortality. Multivariable logistic regression models were fit to estimate predictors of catheterization and mortality.

Results: While catheterization rates increased, higher risk patients were less likely to receive the procedure. One-year mortality was lower for those receiving catheterization, especially for patients at intermediate to high risk.

Conclusions: Targeting catheterization to higher risk patients would be more consistent with recommendations, and has potential to result in improved outcomes.

List of Abbreviations Used

ACS	=	Acute Coronary Syndromes
AMI	=	Acute Myocardial Infarction
CAD	=	Coronary Artery Disease
CHF	=	Congestive Heart Failure
CKD	=	Chronic Kidney Disease
CPG	=	Clinical Practice Guidelines
CVHNS	=	Cardiovascular Health Nova Scotia
DBP	=	Diastolic Blood Pressure
ECG	=	Electrocardiogram
LVEF	=	Left Ventricular Ejection Fraction
GRACE	=	Global Registry of Acute Coronary Events
HR	=	Heart Rate
NS	=	Nova Scotia
NSTEACS	=	Non-ST Elevation Acute Coronary Syndrome
NSTEMI	=	Non-ST Elevation Myocardial Infarction
PURSUIT	=	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
RCT	=	Randomized Clinical Trial
SBP	=	Systolic Blood Pressure
STEMI	=	ST Elevation Myocardial Infarction
TIMI	=	Thrombolysis In Myocardial Infarction
UA	=	Unstable Angina

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Chapter 1: Introduction

Access to health care presents an important indicator of health system performance (1). The Institute of Medicine committee (IOM) defines access as "the timely use of personal health services to achieve the best possible health outcomes"(2). Ensuring that health services are prioritized toward patients at highest risk of experiencing adverse outcomes (equitable care)(3), based on best available scientific evidence (appropriate care)(4), and delivered within the recommended time frames so optimal benefits could accrue (timely care)(5), largely contributes to improving the quality of care that patients receive.

Access issues have been long recognized in acute coronary syndrome (ACS). As ACS presents the most frequent manifestations of coronary artery disease (CAD) and is the second leading cause of death in Canada, ensuring equitable and timely access to appropriate health care in patients with ACS is important (6). Acute coronary syndrome includes ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA), with the last two conditions commonly referred to collectively as non-ST elevation acute coronary syndrome (NSTEACS)(7). Patients with NSTEACS account for around 75% of the ACS population; they are older and often have more comorbidities than STEMI patients (7). While they have lower in-hospital mortality rates compared to patients with STEMI, NSTEACS patients frequently develop recurrent ischemic events, resulting in similar or (often) higher 1-year mortality rates (8). Research evidence indicates that there is often less attention given to quality improvement initiatives in NSTEACS patients (9) compared to those developed for patients with STEMI(10).

Large randomized clinical trials (RCTs) support the use of an early invasive strategy, based on the findings that this strategy improves outcomes in the NSTEACS patient population when compared to an initial approach with medical management in this patient group (11-13). Furthermore, it was observed that this strategy conveys the greatest benefits in NSTEACS patients at higher risk of experiencing adverse events (11-13). Importantly, the benefits from the early invasive strategy have also been confirmed by observational studies as well several meta-analyses(14, 15). Clinical practice guidelines (CPGs) have incorporated the research evidence, and recommend an early invasive strategy as a preferred treatment approach in eligible high-risk NSTEACS patients (16-18).

Measuring the extent to which a clinical practice adheres to guideline recommendations, may help identify issues related to quality of care, as well as challenges in guideline implementation (19-21). Process of care measures are quality of care measures assessing the care patients receive (22). When based on research evidence showing a strong association between recommended care and patient outcomes, process of care measures can be used as performance measures to evaluate the extent to which received care adheres to the guideline recommendations (23) . When included in CPGs, performance measures improve both guideline effectiveness and patient outcomes (24).

However, the increase in utilization of cardiac catheterization in the NSTEACS patient population in the last decade has not been accompanied by improvements in patient outcomes such as in-hospital and 1-year mortality rates (25). Observational studies in Canada and worldwide have shown that despite the evidence-based guideline recommendations to perform early cardiac catheterization in high risk NSTEACS patients, the procedure has been utilized more in patients

at lower risk of adverse events compared to their higher risk counterparts (26-28). The findings suggested that guideline recommendations were not incorporated into actual clinical practice, a discrepancy termed the “treatment-risk paradox”(29, 30).

The NSTEACS population continues to experience 1-year mortality rates that are more than twice the rates in STEMI patients (31). The province of Nova Scotia has a considerable number of ACS hospitalizations annually, representing significant burden for the province. There is also evidence of variations in care across the province. To help alleviate the burden and improve the consistency and quality of care delivered across the province, Cardiovascular Health Nova Scotia (CVHNS), a provincial program under the auspices of the Department of Health and Wellness, developed guidelines for ACS in 2008 (32). The provincial guidelines explicitly outlined recommendations for both STEMI and NSTEACS patients based on patient risk category(32). Referral for cardiac catheterization (with intent to perform PCI, if possible) was recommended within 24-48 hours for the highest risk NSTEMI patients; the highest risk STEMI patients were recommended to receive the procedure on an emergent basis (32).

Following the development and dissemination of the 2008 Nova Scotia Guidelines for ACS, the extent of an adherence to the guideline risk-based recommendations for cardiac catheterization in NSTEACS patients is unknown. While utilization rates of catheterization in NSTEACS patients in Nova Scotia have been reported as progressively increasing over the past decade, it is unknown whether the increased rates of cardiac catheterization reflect increased utilization of the procedure among higher risk patients, who are most likely to benefit from it. Given that the rationale behind the provincial guidelines development was to improve the quality of care in

NSTEACS patients, it is important to know whether the guidelines had the intended effect on risk-based delivery of cardiac catheterization.

This study aimed to address whether the utilization and timing of cardiac catheterization in NSTEACS patients in Nova Scotia during the study period 2003-2013 was based on patient need, i.e., targeted toward high risk patients who are expected to gain the most benefit from receiving this procedure. In particular, the findings will be compared between the pre-guideline (2003-2008) and post-guideline (2009-2013) periods.

Chapter 2: Literature review

The literature was reviewed to identify relevant studies on the importance of access to health care, in terms of health system performance and quality of care. More specifically, the literature review included studies evaluating risk-based utilization of cardiac catheterization in NSTEACS patients, and articles on clinical practice guidelines and their impact on improving quality of care.

2.1 Access to Health Care

2.1.1 Access as an aspect of the quality of care

Access to care is one aspect of quality of care and represents an important indicator of health system performance. The quality of care is defined as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge"(2). Quality of care is concerned with ensuring patients receive care associated with receiving optimal benefits based on best available research evidence.

Access is a complex concept, traditionally described as having five components or dimensions -- availability, accessibility, affordability, accommodation, and acceptability (33). Each of the dimensions describes the relationships between characteristics of the providers and the patients, and each has the potential to act as a barrier to accessing adequate care. Availability of health care refers to the extent to which a health system has an adequate supply of health providers and technology (a supply factor) to meet patients' health needs (a demand

factor)(33). Accessibility is concerned with a physical or geographic aspect of accessibility, i.e., the possibility to physically reach the provider's location (33). Affordability is described in terms of the costs of accessing services, i.e., a patient's financial ability to access care, while acceptability refers to meeting patient needs and care preferences in a way that is acceptable to the patient (33). Accommodation is concerned with the way services are organized to meet patients' needs, including office hours and availability of appointment times, which affect wait times to receive care (33).

More recently, increased attention has been given to aspects of access such as equity, appropriateness, and timeliness of delivered care. Ensuring that accessed health services are prioritized toward patients at highest risk of adverse outcomes (equitable care)(3), based on the best available scientific evidence (appropriate care)(4), and within the recommended time frames so optimal benefits could accrue (timely care)(5) largely contribute to improving quality of care and ultimately, patient outcomes. Health care delivery should be based on the patient's health status-related need, in which case is said that health care services are fairly, or equitably accessed. In an equitable health system, those with equal need will have equal access to care (horizontal equity) and those who have more need should be prioritized in receiving health care (vertical equity)(34, 35). The majority of research on equity in receiving care uses an analytical approach based on horizontal equity and assumes that vertical equity was satisfied (36). However, if patients at higher risk are not accessing a service that would make a difference for their health status, the horizontal analytical approach of equal access for equal need in measuring equity will not identify unmet needs in those patients (37).

Appropriate care is related to several important aspects of access to care, including evidence-based, need-based, and timely delivered care, and has a substantial impact on effectiveness and efficiency of health system performance (38, 39). It is central to the increasing challenge of delivering optimal health outcomes for a given amount of health care spending. By measuring adherence of delivered care to clinical practice guidelines' recommendations, it may be possible to identify potentially inappropriate care (e.g., under- or over-use), with significant health quality and cost implications (40, 41). As stated in the Canadian Institutes of Health Research (CIHI) Mapping a Strategic Research Agenda for Timely Access to Quality Health Care Report, "Failure to address appropriateness greatly reduces the likelihood of reaching durable and sustainable solutions to access issues"(42).

Access is often concerned with timely utilization of health services so that optimal health outcomes can be achieved (43). Timely access to care does not necessarily mean immediate access, nor is the issue of timely access limited to acute or life-threatening situations. Timely access means that care is being provided within the timeframe that the health service is beneficial, based on the best available scientific evidence (44). Timeliness of accessed care is therefore an important aspect of an evaluation of delivered access. Research has shown that when care is received within recommended timeframes, it leads to achieving optimal clinical outcomes (45-47). Often used measures of timely access are median wait times from presentation to receiving care/procedure, median time between identifying a need for a specific service and receiving the service, and percentage of procedures completed within the recommended time.

Improving access to health care has long been a recognized problem in Canada. The last report of Euro-Canada Health Consumer Index in 2010 analyzing health system performance on a number of measures or quality indicators in 34 countries, placed Canada in 25th position overall (48). The main reasons for obtaining this low ranking were related to access to health services and medications. The results indicated that care was either not delivered to all individuals with health needs, or not accessed in a timely manner. Importantly, the conclusion was that considering the high levels of health expenditure in Canada, "Canada's ineffective performance cannot be attributed to inadequate funding but rather to the way how care is delivered"(48). In a recent Commonwealth Fund 2014 report comparing health care systems in 11 countries on a number of health care indicators, including health care quality and access, Canada was ranked 10th overall (ahead of only the United States)(49).

2.1.2 Measuring access

Access is often measured by calculating the overall service use, i.e., per total patient population of interest. However, overall utilization rates do not provide information on utilization based on health needs (50). This distinction is important because overall utilization rates do not necessarily imply that health care has been received by patients who are expected to derive the greatest absolute benefit from the delivered care (37). More than four decades ago, Aday and Anderson recognized important concerns related to the measurement of access, suggesting that "it is perhaps most meaningful to consider access in terms of whether those who need care get into the system or not" (51). Since patients differ in severity of symptoms and signs, access is most meaningfully assessed in terms of whether the patients with the greatest need are prioritized in receiving the care (51, 52).

Some stakeholders are more interested in measuring outcomes of care rather than processes of care, as a way of identifying potential care gaps (22). The rationale is that inadequate care is reflected in poor outcomes, so optimal outcomes provide evidence of delivery of high quality care. On the other hand, process of care measures capture the care patients actually receive, i.e., the accessed care (53). They can provide clear direction for potential improvements by measuring the practice adherence to guideline-recommended care, so that actions to address deficiencies can be initiated rapidly (54). Process of care measures are therefore commonly considered the best measures of the quality of delivered care. For example, guidelines recommend use of beta-blockers during admission and after discharge in acute myocardial infarction (AMI) patients, based on strong evidence that beta-blockers decrease mortality after AMI (55). Measuring the proportion AMI patients receiving beta-blockers during admission and at discharge quickly provides information about the quality of delivered care. By contrast, reliance on outcome measures can mean considerably more time to conclude with certainty that poor outcomes are associated with deficiencies in care (56).

2.2 Access to cardiac catheterization in non-ST elevation acute coronary syndromes

2.2.1 Acute coronary syndromes

The term acute coronary syndromes (ACS) refers to a group of life-threatening cardiac disorders requiring a prompt diagnosis, and it comprises ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA) (7). All three conditions are manifestations of coronary atherosclerosis, i.e., plaque buildup in the heart blood vessels. ST-elevation myocardial infarction is defined by presence of symptoms of myocardial ischemia

such as chest pain in association with persistent electrocardiographic (ECG) ST elevation and subsequent release of biomarkers of myocardial necrosis (e.g., cardiac-specific troponins, cTnT or cTnI) (57). The biomarkers of myocardial necrosis are released in blood when myocardial ischemia, i.e., blockage in a heart vessel obstructing blood flow, is sufficiently severe to cause myocardial damage (7). While chest pain and a positive troponin value are characteristics of NSTEMI as well, the ECG changes in NSTEMI are ST-segment depression or prominent T-wave inversion, therefore there is an absence of ST-segment elevation (7, 16). In the case of UA, no such biomarker can be detected in the circulation; ECG changes are consistent with those seen in NSTEMI (7). Non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA) are commonly referred to collectively as non-ST elevation acute coronary syndromes (NSTEACS) (31).

Acute coronary syndromes represent the most frequent manifestation of coronary artery disease (CAD), which is the second leading cause of death in Canada (after cancer) (58). Yet patients with ACS face long-recognized issues with access to care. Of the patient population with ACS, about 75% have NSTEACS. A diagnosis of NSTEACS is associated with an increased risk of cardiac-related mortality and recurrent MI, and it represents a major cause of emergency medical care and hospitalization in Nova Scotia and across Canada (6).

The pathophysiology is initially different in STEMI compared to NSTEACS, which results in different clinical presentations and different in-hospital patient outcomes. In-hospital mortality rates in STEMI patients are 50%, which is higher than for NSTEACS patients (6). These differences have led to different early treatment strategies. In STEMI, an urgent re-opening of the completely occluded artery needs to be performed as a life-saving procedure, known as a

primary percutaneous coronary intervention (PPCI) (59). In NSTEACS, the treatment is generally somewhat less urgent, with a management goal of preventing thrombus progression to total occlusion and recurrent infarction (60). However, the risk of further cardiovascular complications including recurrent myocardial infarction (MI), sudden cardiac death, heart failure, and stroke in NSTEACS patients surviving an initial event, particularly those with higher risk features is substantial (61). These high longer-term risks of adverse outcomes in NSTEASC patients subsequently result in 1-year mortality being as high as or higher than in STEMI patients (31).

2.2.2 Guidelines recommended risk-based invasive management for NSTEACS patients

The most current AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes outlines three invasive strategy approaches in NSTEACS patients (62). These are: an urgent/immediate invasive (within 2 hours of admission to a hospital), an early invasive (within 24 hours), or delayed invasive strategy (within 25-72 hours) (62). The indications for selection of these invasive strategies remained largely unchanged, compared to the earlier guidelines (16). An urgent/immediate invasive strategy is recommended in patients who have refractory angina (no improvement of angina despite optimal medical therapy), symptoms or signs of heart failure, hemodynamic instability (most commonly associated with very low blood pressure causing inadequate perfusion to support normal organ function) or electrical instability (ongoing changes on ECG indicative of myocardial ischemia), or life-threatening arrhythmias (Class IA recommendation)(62). An early invasive strategy is recommended in NSTEACS patients who have elevated troponin levels, new changes on ECG indicative of NSTEMI, or none of the characteristics described for immediate strategy but GRACE risk score >140 (Class IB recommendation)(62). A delayed invasive strategy is recommended for

patients who do not have any of the above described clinical characteristics, but have diabetes mellitus, renal insufficiency indicated by GFR <60 mL/min/1.73 m2 (creatinine >133µmol/L) or left ventricular dysfunction (depressed resting LV function; i.e., LVEF < or equal 0.40) on noninvasive study (Class IIa, Level of Evidence B)(62).

In the earlier version of the ACC AHA Guidelines for NSTEACS management in 2007, the invasive strategy was described as either urgent/immediate or deferred (but still early) cardiac catheterization (within 12 to 48 hours) followed by revascularization, if appropriate (16). An early invasive strategy is recommended for NSTEACS patients who have evidence of recurrent angina despite optimal medical therapy, or an evidence of hemodynamic or electric instability (Class I; Level of Evidence: B) or an elevated risk for clinical events based on clinical characteristics, including elevated cardiac biomarkers (TnT or TnI), or electrocardiographic abnormalities (e.g., new ST-segment depression) (Class I; Level of Evidence: A)(16). The invasive approach is also recommended in patients presenting with signs or symptoms of HF, high-risk findings from noninvasive testing, hemodynamic instability, sustained ventricular tachycardia, high risk score (e.g., TIMI, GRACE), or reduced left ventricular function (LVEF less than 40%)(16).The invasive approach is to be considered if the patients were without serious comorbidities or contraindications, defined as severe hepatic, pulmonary, or renal failure, or active or inoperable cancer (16, 62).

The recommendation of an early invasive strategy in high risk NSTEACS patients was based on the findings of three large RCTs comparing an early invasive strategy to a conservative approach in treating NSTEACS patients (11-13). The FRISC II trial (Fragmin and Fast Revascularization during Instability in Coronary Artery Disease) showed reduced risk of death or MI by 40% (13.2%

vs. 22.1%, *p* =0.001) at 1-year in patients at high risk (determined by cTnT levels and the presence of ST depression on the admission ECG) who received an early routine invasive strategy, compared to a group receiving a routine noninvasive strategy (11). Revascularization was done within the first 10 days in 71% of the invasive group and 9% of the non-invasive group; revascularization was done within the first year in 78% and 43%, respectively (11). At 1 year, the mortality rate was 2.2% in patients in the invasive group and 3.9% in the non-invasive group (risk ratio 0.57 [95% CI 0.36-0.90], p=0.016) (11).

The TACTICS-TIMI 18 trial (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction) showed reduced rates of mortality or myocardial infarction at 6 months (7.3% vs. 9.5%, $p < 0.05$) with the benefit observed in intermediate- and high-risk patients (defined by an increased TnT, the presence of ST-segment deviation, or a TIMI risk score > 3 (12). In contrast with FRISC II, patients in the TACTICS-TIMI 18 trial were randomized to an early invasive strategy with routine cardiac catheterization within 48 hours (a mean of 22 hours) followed by revascularization, if appropriate, or were treated conservatively (12).

The RITA-3 trial (Third Randomized Intervention Treatment of Angina) reported a reduction in the combined end point of death, nonfatal MI, and refractory angina that was 14.5% in the patients treated with an early invasive strategy compared to 9.6% in those randomized to receiving conservative treatment (13). Patients were randomized to receive either cardiac catheterization or conservative management within 48 hours of the occurrence of angina (cardiac chest pain) (13). The benefit seen in the trial with invasive strategy was mostly influenced by a reduction in refractory angina. Contrary to the FRISC-II and TACTIC-TIMI 18

trials, the reduction in mortality and myocardial infarction was still seen at 5-year follow-up in the group receiving early invasive strategy (63).

The ICTUS trial (Invasive versus Conservative Treatment in Unstable coronary Syndromes) evaluated outcomes in the patients randomized to routine invasive (early invasive strategy) versus selective invasive management (initially treated medically) (64). Patients randomized to the routine invasive approach received cardiac catheterization within 24 to 48 hours after randomization and percutaneous coronary intervention, when appropriate (64). The trial reported no significant difference in the combined rate of cardiovascular mortality, MI, and angina between groups at 1 year (22.7% in the early invasive group compared to 21.2% in the selective invasive group (relative risk, 1.07; 95% CI 0.87 to 1.33; P=0.33) (64). A strategy of selective invasive therapy was therefore recommended initial approach in the management of NSTEACS patients (64).

An analysis of individual patient data from the FRISC-II trial, ICTUS trial, and RITA -3 trial, reported 5-year outcomes in patients receiving a routine invasive strategy versus ischemia-guided strategy (65). Cardiovascular mortality or recurrent MI was experienced in 14.7% of patients randomized to former group compared to 17.9% of patients in the group randomized to receiving ischemia-guided strategy (HR: 0.81; 95% CI 0.71 to 0.93; p=0.002), with the effect primarily driven by the reduction in recurrent MI (18). However, the trends for fewer cardiovascular deaths (HR: 0.83; 95% CI: 0.68 to 1.01; p=0.068) and all-cause mortality (HR: 0.90; 95% CI 0.77 to 1.05) were consistent throughout the study period (18). Importantly, there was an 11.1% absolute risk reduction in cardiovascular mortality or MI among the highest risk

patients while much smaller effects were observed in the low- and intermediate-risk groups (2.0% and 3.8%, respectively) (18).

The TIMACS trial (Timing of Intervention in Acute Coronary Syndrome) showed a lower composite six-month rate of death, MI, or refractory ischemia in high-risk patients treated with early (≤24 hours) compared to delayed invasive strategy (≥36 hours) (66). While the early invasive strategy was not associated with reduction in mortality, the trial reported that reduction in refractory ischemia with the early invasive approach was associated with more than four times decreased likelihood of subsequent MI (66).

The evidence from large randomized clinical trials show that benefits of an immediate invasive and an early invasive strategy are greatest in NSTEACS patients at the highest risk, while patients at lower risk gain little advantage in terms of mortality. In addition, NSTEACS patients at higher risk treated with an invasive strategy had reduced risk of adverse cardiac events, compared to patients treated with an initial conservative strategy. As clinical trials findings are considered a gold standard of care for a variety of medical conditions, their findings are incorporated in clinical practice guidelines. The guidelines for management of NSTEMI/UA patients therefore recommend an early invasive strategy in treatment of high risk NSTEACS patients.

The finding of improved patient outcomes in higher risk NSTEACS patients receiving invasive strategies was confirmed by several observational studies. Importantly, these studies (28, 29, 67-71) analyzed outcomes in relation to the utilization of invasive and non-invasive strategies' outcomes in high risk patients. They reported that cardiac catheterization was underutilized in

higher risk NSTEACS patients, and that the patients not receiving early invasive treatment had a significantly increased risk for in-hospital as well long-term adverse outcomes (72, 73).

As mentioned earlier, observational research also reported that despite temporal increases in the use of cardiac catheterization and revascularization, medical and invasive therapies, including an early invasive strategy, continued to be targeted toward lower-risk patients. Furthermore, delaying cardiac catheterization and subsequent revascularization was found to be associated with significantly increased short-, and long-term mortality in high-risk patients, and adverse outcomes among intermediate and high-risk patients (74). The findings of cardiac catheterization being more often utilized in patients at lower risk compared to their higher risk counterparts who may derive greater absolute benefit from invasive management, suggest that the recommendations of clinical practice guidelines have not been incorporated into actual clinical practice, a discrepancy termed the "treatment-risk paradox" (29, 30).

Several observational studies reported that increased age, and comorbidities such as chronic renal disease (CKD), diabetes, and congestive heart failure were predictive of limited access to cardiac catheterization. This was despite the evidence that older patients gain larger absolute benefits compared to younger patients, and that the comorbidities are well-established coronary artery disease risk factors and powerful predictors of mortality after NSTEACS (70, 75). Similarly, observational studies analyzing use of guideline-recommended therapies in patients with CKD and diabetes, reported underutilization of cardiac catheterization in patients with comorbidities despite evidence that those patients could potentially gain the largest benefit from invasive treatment (76-78).

It is interesting that previous work on the management practices and the longer-term mortality in NSTEACS patients in Nova Scotia reported that despite temporal increases in use of medical and invasive therapies, one-year mortality rates remained strikingly high in NSTEMI patients (79).

2.2.3 Invasive strategy in NSTEACS patients with comorbidities

Chronic kidney disease (CKD) and diabetes mellitus represent risk factors for CVD as well as for adverse outcomes after MI (16). Patients with renal disease and diabetes are underrepresented in in randomized controlled trials of treatments for CVD. Importantly, it has been postulated that a higher risk of complications related to the invasive strategy contributes to reported underuse of cardiac catheterization and other invasive cardiac interventions in people with in patients with comorbidities such as CKD and diabetes.

Invasive cardiac procedures could induce contrast induced nephropathy (80), resulting in acute kidney injury; in addition to the renal damage associated with adverse outcomes such as recurrent cardiovascular events, this further injury could result in end stage renal disease and mortality (81). The decision to perform an invasive cardiac procedure in NSTEACS patients with prior history of renal insufficiency (as documented by history as well as increased creatinine values at the time of hospital admission) (82) requires careful balancing of associated risks while at the same time knowing that benefits in those patients are less certain. The most current AHA ACC guidelines recommend an invasive strategy in NSTEACS patients with mild (stage 2) and moderate (stage 3) CKD (Class IIa (Level of Evidence B) (62). A systematic review of ten cohort studies including the meta-analysis of the individual level data of five RCTs representing data on

147,908 NSTEACS patients from 1989 to 2010 supported an early invasive approach in patients with CKD as it was associated with reduced long term mortality (83).

It has been documented that a greater proportion of NSTEACS patients with diabetes (compared to those without diabetes) are not receiving guideline-recommended treatment (78, 84). It is possible that underutilization of recommended treatment is contributing to adverse outcomes for patients with diabetes and ACS.

2.2.4 Risk stratification in NSTEACS

The decision to consider a patient for one of the invasive approaches depends on their clinical presentation, including symptoms, physical findings, as well as presence or development of higher risk clinical features (16, 62). Early during the time of initial presentation, NSTEACS patients need to be risk stratified based on these factors (16, 62). Early risk stratification is recommended to facilitate triage of patients, i.e., whether the patients are to receive either the ischemia-guided approach (formerly called “initial conservative management”), or diagnostic cardiac catheterization followed by coronary revascularization, if indicated (16, 62). In the ischemia-guided strategy, patients are initially treated with medical treatment; cardiac catheterization is performed only if a patient develops recurrent symptoms despite optimal medical management. Importantly, if the decision is made to treat a patient with the ischemia-guided strategy, this treatment decision needs to be confirmed with noninvasive evaluation to ensure that no severe ischemia (i.e., impaired blood flow through the heart) would occur at a low threshold of stress(16, 62). If a severe ischemia is detected, the patient is to have performed cardiac catheterization followed by revascularization if indicated.

The international guidelines for the management of NSTEACS including those developed by the American College of Cardiology/American Heart Association (ACC/AHA) (16, 62)and the European Society of Cardiology (ESC) (18)emphasize risk stratification as a critical step in management of ACS patients. The ACC/AHA guidelines recommend that early risk stratification in patients with symptoms suggestive of ACS should focus on history, physical examination, ECG findings, assessment of renal function, and biomarkers of cardiac injury measurements (Class I, Level of evidence: C). As estimating a patient risk level requires simultaneous consideration of several prognostic factors, the guidelines recommend using the validated risk algorithms that allow for optimal risk stratification, such as the Thrombolysis In Myocardial Infarction (TIMI) or Global Registry of Acute Coronary Events (GRACE) or the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) (Class II Level of Evidence: B). All three risk scores use variables from initial clinical history, ECG, and laboratory results collected on admission, and assist clinical judgment in identifying high-risk patients. The American and European guidelines for NSTEACS management emphasize urgent invasive management of higher risk patients, such as defined by a Global Registry of Acute Coronary Events (GRACE) score for death or MI at 6 months greater than 140, ongoing ischemia and/or hemodynamic instability, with early (less than 24 h) or immediate invasive management (16, 18, 62).

The Thrombolysis In Myocardial Infarction, or TIMI score is derived from the Thrombolysis in Myocardial Infarction (TIMI)-11B trial, a multinational, randomized clinical trial with 1957 patients, comparing unfractionated heparin to enoxaparin (85). The components of the TIMI risk score are age of 65 years or older, at least three risk factors for coronary artery disease, prior coronary stenosis of 50% or more, elevation in serum cardiac markers, ST-segment deviation on

electrocardiogram, recent severe angina (equal or more than two episodes within 24 hours), and aspirin use in the past 7 days (85). Each of the factors can be assigned either 0 or 1 point, with a total possible score ranging from 0 to 7 (85). The TIMI score predicts the risk of all-cause mortality as well as adverse events such as recurrent MI and severe ischemia requiring urgent revascularization within 14 days after admission (85).

The PURSUIT score was developed from patient data in Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) multinational randomized clinical trial of 9,461 patients, comparing eptifibatide (Integrilin) to placebo in the management of UA or NSTEMI (86). The predictive model, developed using multivariate regression analysis, identified several factors predictive for risk of mortality and MI: higher age, sex (male or female), worst Canadian Cardiovascular Society (CCS) class of angina, signs of heart failure, and ST-segment depression on the index ECG. The investigators did not include tachycardia and low systolic blood pressure in the final risk score (86). Each of the five elements were assigned a score with a possible total score ranging from 1 to 18. The PURSUIT score predicts the risk of all-cause mortality as well as mortality from MI at 30 days after admission (86).

In contrast to TIMI and PURSUIT risk scores developed from RCT data, the GRACE score was developed by using patient data collected in the Global Registry of Acute Coronary Events (GRACE) multinational registry of 11,389 ACS patients (87). Using a multivariate logistic regression method, eight independent risk factors for in-hospital and 6-month mortality were identified. They are related to clinical, laboratory, and ECG findings: Killip class for congestive heart failure (CHF), systolic blood pressure at presentation (SBP), heart rate at presentation

(HR), age, creatinine level, cardiac arrest at admission, ST-segment deviation on the index ECG and elevated cardiac enzyme levels (87). With each factor having been assigned a score, a combined GRACE score can range from 1 to 372 (87). The GRACE score has shown a high predictive value for assessing the severity of coronary artery stenosis in patients with NSTEACS (88).

These risk scores are risk stratification tools validated in various clinical trial and registry patient populations. They are useful in predicting patient risk of adverse outcomes including mortality, and consequently are recommended for routine use in clinical practice. Importantly, several studies analyzed the process of risk assessment by physicians, comparing the results with and without use of risk scores (68, 87, 89, 90). The findings of these studies showed that risk scores had better discriminative performance compared to risk assessment by physicians in predicting long-term outcome. The population used for these comparative analyses was that in the Canadian ACS 2 Registry. While risk scores cannot replace clinical judgment, the results demonstrated that risk scores were valuable additions to clinical judgment in medical decision making (68, 91).

Risk scores are useful in identifying high risk NSTEACS patients, and they facilitate appropriate targeting of early cardiac catheterization toward patients who are expected to derive the largest benefit from an early invasive strategy (16, 62). The key role that risk stratification plays in ensuring the evidence-based management of NSTEASC patients is reflected by the fact that the recommendation to use validated risk algorithms for patient risk stratification received the highest class and level of evidence (Class I, Level of Evidence: A) (16, 18, 62).

2.3 Clinical practice guidelines for NSTEACS management

Clinical practice guidelines are defined as "systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances" (92). The driving force behind guidelines development is often concern about quality of care, lack of consistency in practice, and variations in clinical outcomes. The goal is to assist clinicians in their decision-making by summarizing the best available research evidence for the diagnosis and management of a certain condition. When clinical trials report improved outcomes with new treatments, guidelines incorporate the advances and recommend the new treatment strategies. While the expectations are that health providers will follow the recommendations (93, 94), guidelines cannot replace clinical judgment (94). There are multiple factors a treating physician needs to consider in the decision making, and guidelines are to assist in that process. Research evidence suggests that practice adherence to evidence-based guideline recommendations has been associated with improved quality of care and patient outcomes (24, 95, 96).

Given the rationale, efforts, and high costs of guideline development, it is important to know whether the guidelines had the intended impacts on quality of care. Measuring the extent to which delivered care adheres to evidence-based processes of care, or processes of care agreed by professional consensus, helps provide information on the quality of delivered care and on the effect of guidelines on practice (94, 97). In turn, information on quality of care can help explain effects of delivered care on patient outcomes, as well as potential opportunity/need for quality improvement (54, 98).

In addition to information about the quality of delivered care, process of care measures can provide important insight into health care costs. For example, there may be costs that could have been avoided by adhering to guideline recommendations (99). Canada's publicly funded health care system has been increasingly challenged to achieve optimal health outcomes with limited health care funds. A key concern is that cost trends may not be sustainable for health care budgets.

It is common that uptake of guideline recommendations occurs slowly, resulting in guidelines having little effect on practice improvement (99). Gaps between guideline recommendations and medical care have been recognized across many medical disciplines; it is not rare to find substantial proportions of patients not receiving appropriate (guideline-recommended) care (93, 100-102). The reasons for the slow uptake of guideline recommendations have been extensively researched. The greatest barriers to adoption of guideline recommendations are lack of awareness, lack of agreement, lack of outcome expectancy, and unwillingness to change established practices, often called inertia of previous practice (103, 104).

While lack of awareness is best addressed by educational initiatives, lack of outcome expectancy is best addressed by providing continuous feedback on guideline adherence and patient outcomes data. Interventions such as printed materials have little impact on improving physician adherence to the guideline recommendations (105, 106). On the other hand, critical care pathways or computerized support programs, for instance risk scores on palm devices, and the use of local opinion leaders are strategies shown to improve adherence to practice guidelines (107). Importantly, there is evidence that when feedback was provided to physicians about their care in relation to recommendations, their subsequent adherence improved (108).

2.3.1 Performance measures in measuring and reporting access to care

As mentioned earlier, measuring the care patients receive enables knowing to what extent clinical practice adheres to guideline recommendations. Process of care measures are quality of care measures assessing the care patients actually receive and are thus well suited to evaluate the extent to which received care adheres to guideline recommendations (23). When based on research evidence showing a strong association between recommended care and patient outcomes, processes of care are used as performance measures (56). Performance measures are based on the evidence-based recommendations relevant to clinical practice and consequently, can be used for quality improvement purposes (56). As mentioned earlier, performance measures can provide valuable information about possible relationships of received care with patient outcomes.

In 1999, the American Heart Association/American College of Cardiology First Scientific Forum on Assessment of Healthcare Quality in Cardiovascular Disease and Stroke released a report on quality measurement of health care in AMI, heart failure, and stroke recognizing that assessing healthcare quality required the development and implementation of performance measures (109). The Forum defined performance measures as "explicit standards of care against which actual clinical care is judged" (109). It was acknowledged that while clinical practice guidelines present a valuable tool in promoting healthcare quality, their recommendations do not constitute a standard of care. Performance measures, however, are defined as the standard of care to which a practicing physician is required to comply. In addition to informing about the quality of delivered care, performance measures can provide important insight into health care costs and could help inform future directions in health system spending and health policy (110).

When performance measures are included in guidelines, the rationale for using the performance measures must be provided, and the measure denominator (patient population of interest eligible for the assessment of use of a diagnostics/treatment) and nominator (the subset of patient population of interest with documented use of the diagnostics/treatment) clearly defined. Performance measures greatly improve effectiveness of guidelines. Performance measures provide the tools for monitoring incremental progress in practice adherence to guideline recommendations, thereby helping to document the guidelines' potential effect on the quality of delivered care (96, 111). Importantly, performance measures can identify potential underuse, overuse, or misuse of health services, helping to improve both appropriateness and effectiveness of delivered care (112).

Physicians actively participate in guidelines development as opinion experts, and provide input on what processes of care can be used as performance measures (113). Since physicians have knowledge of factors at the patient, provider, organization, and health system level impacting an access to health services, the performance measures included in CPGs are based on the recommendations that are most relevant, measurable, and appropriately chosen for quality improvement purposes (109). To help ensure feasibility of the performance measures, the expert panel confirms that sufficient data exist, or provides direction on what data need to be collected (114).

2.3.2 Performance measures in NSTEACS care

ACC/AHA 2008 Performance Measures for Adults With ST-Elevation and Non–ST-Elevation Myocardial Infarction Report did not include performance measures to evaluate the use of an

early invasive strategy in NSTEACS patients (113). While considered, no measure was endorsed at that time because of "the complexity of the guideline recommendations and the challenges in translating these recommendations into a measure that can be implemented feasibly". In addition, there were concerns about "identifying high-risk clinical characteristics reliably from abstracted data, particularly with respect to the accurate classification of ECG abnormalities" (113). There were two important things acknowledged at that time. The importance of considering potential overuse of cardiac catheterization was recognized. The hope was expressed that the quality improvement initiatives, especially through registries (e.g., ACTION or the National Cardiovascular Data Registry CathPCI) "may be valuable in exploring feasible approaches to identifying the 'eligible' population for early invasive strategy and to inform the construction of a quality or performance measure on this topic in the future" (113, 115).

2.3.3 Quality improvement initiatives in NSTEACS

Quality improvement initiatives enable comparing and evaluating the care patients receive with guideline-recommended care. They are defined as "systematic and continuous actions that lead to measurable improvement in health care services and the health status of targeted patient groups" (116). For example, a study evaluated adherence to NSTEACS guidelines-recommended medications and lifestyle modification interventions in high-risk NSTEACS patients from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) Quality Improvement Initiative (involving around 140,000 patients) (95). This study found significant improvements in the use of guideline-recommended therapies (use of aspirin, heparin, beta-blockers, and platelet inhibitors) during the first four years of the CRUSADE initiative. This quality improvement initiative includes a registry of high risk NSTEACS patients (defined as the patients having

positive cardiac markers, ST-segment depression, or transient ST segment elevation), and is aimed toward improving compliance with the ACC/AHA guidelines recommended care. The study reported a 10%-15% increase in the use of acute medications, 18%-25% increase in discharge medications, 25% increase in the use of lifestyle modification interventions, and 7% increase in the utilization of PCI (95). Furthermore, a study by Peterson *et al.* analyzed utilization of nine ACC/AHA class I guideline-recommended acute and discharge medications used in care of close to 65,000 NSTEACS patients enrolled in CRUSADE from 2001-2003 (24). They found that improvement in compliance with guideline recommendations was associated with improved patient outcomes. Specifically, every 10% increase in adherence with guidelines-recommended treatment was associated with 10% decrease in likelihood of in-hospital mortality (24).

The GRACE (Global Registry of Acute Coronary Events) multinational quality initiative for ACS reported temporal increases in the use of guidelines-recommended medications and invasive procedures in patients with NSTEACS and STEMI from 1999 to 2006, as well as reductions in mortality in both patient groups since the start of the quality initiative (96). Use of class I guideline-recommended medications significantly increased, as did recommended cardiac interventions. Primary PCI use in STEMI patients increased by 37%, and rates of cardiac catheterization and PCI among NSTEACS patients increased by 21 % and 18%, respectively (96).

Another quality improvement initiative successfully engaging cardiovascular providers in collecting and monitoring data for the quality of care improvements, is the ACTION registry (117). The ACTION registry is one of ten registries of the National Cardiovascular Data Registry (NCDR) under the umbrella of the American College of Cardiology (ACC). It comprises

eight hospital registries of in-patients and two outpatient registries. By participating in one of the registries, physicians measure and contribute improving the quality of delivered care. The ACTION registry collects data on STEMI and NSTEMI patient demographics, provider and facility characteristics, and adverse event rates. Importantly, the registry also collects AMI performance measures and selected quality measures and outcomes, as well as compliance with ACC/AHA clinical guideline recommendations (118).

The 2017 American Heart Association/American College of Cardiology Clinical Performance and Quality Measures for Adults With ST-Elevation (STEMI) and Non–ST-Elevation Myocardial Infarction (NSTEMI) Report recommends an early invasive strategy in high risk NSTEMI patients as a quality measure (119). An early invasive strategy was defined as a diagnostic cardiac catheterization with intent to perform revascularization, if appropriate based on coronary anatomy within 24 hours of admission. Use of an objective risk score is recommended, to identify patients at high risk -- e.g., patients with GRACE risk score >140 or TIMI risk score >4 are defined as high-risk NSTEMI patients (88) .

It was acknowledged that the impact of an early invasive strategy in high-risk NSTEACS patients is more prominent on reducing recurrent ischemia, length of stay, and costs, than on reducing events of recurrent MI or death. These benefits were deemed sufficient to recommend monitoring its use in appropriate patients. Similar to the earlier ACC/AHA report on performance measures in 2008 (113), the 2017 report states that since “objective risk stratification by risk scores is usually not available in current registries thus, ascertaining which patients benefit from early invasive strategy may not be readily feasible”, the recommendation is to monitor an early invasive strategy utilization in high risk NSTACS patients as a quality rather

than a performance measure (119). The ACC/AHA Task Force on Performance Measures (Task Force) therefore distinguishes quality measures from performance measures by stating that "quality measures are those metrics that may be useful for local quality improvement but are not yet appropriate for public reporting or pay for performance programs (uses of performance measures)" (119).

Importantly, the report emphasizes the role of registry-related initiatives in contributing to developing approaches to identifying the "eligible" population for an early invasive strategy (119). Results of such initiatives would then help to set a performance measure for this problem, for which resolution is long overdue. However, while patient registries document uses of certain care, they do not necessarily collect data needed for performance measurement, so identifying a subset of NSTEACS patients who are to derive largest benefit might be problematic. The 2017 American Heart Association/American College of Cardiology Clinical Performance and Quality Measures for Adults With ST-Elevation (STEMI) and Non–ST-Elevation Myocardial Infarction (NSTEMI) Report offered a similar explanation as to why the measure could not be included in the report (113). While the ACC/AHA 2008 Performance Measures for Adults With ST-Elevation and Non–ST-Elevation Myocardial Infarction report considered a performance measure for the use of an early invasive strategy for high-risk NSTEMI patients, a measure was not included in the report due to the complexity of the guideline recommendations for an early invasive strategy. Particular concern was about "identifying high-risk clinical characteristics reliably from abstracted data, particularly with respect to the accurate classification of ECG abnormalities" (113).

2.4 Nova Scotia Guidelines for Acute Coronary Syndromes (2008)

The province of Nova Scotia has a considerable number of ACS hospitalizations annually (~4,500), with a majority of ACS patents managed by physicians other than cardiologists. One of the CVHNS initiatives has been the development of the Nova Scotia Guidelines for Acute Coronary Syndrome in 2008 (32), which consists of two parts, The Nova Scotia Guidelines for NSTEACS, and The Nova Scotia Guidelines for STEMI. The guidelines and the related implementation strategies have been developed with the goal to reduce variations in practice and to ensure consistent access to appropriate interventions and care for ACS across Districts in Nova Scotia (32). The guidelines development had two main principles, to "address key issues in ACS management" and to "indicate areas of uncertainty or controversy" (32).

These evidence-based guidelines recommendations are designed to assist clinicians in providing appropriate and effective care in a timely manner, and ultimately to improve the consistency and quality of care (54, 100). The Nova Scotia guidelines for ACS therefore explicitly outline recommendations for cardiac catheterization for both STEMI and NSTEACS patients based on patient risk. To assist health providers with risk stratification, the guidelines provide clinical features that place patients at high-, intermediate-, or low-risk of adverse outcomes, as well as time frames when each risk stratified group is to receive procedures (32). Similar to the international guidelines for NSETACS, the Nova Scotia guidelines for ACS recommend considering the following high risk features in determining the need for cardiac catheterization followed by PCI, if indicated within 24 to 48 hours (consensus based recommendation): hypotension or definite evidence of heart failure, recurrent ventricular arrythmias, transient ST elevation, new ST depression equal or more than 2mm in 3 or more leads, recurrent or

refractory ischemia despite initial therapy, or TIMI score 5-7 (32). Following the release of the guidelines in 2008, the cardiac catheterization referral form was updated in March 2009 to include time frames for performing the procedure, based on presenting clinical features.

The Nova Scotia guidelines recommended the TIMI risk score to be used for risk stratification purposes. By providing the risk-stratification criteria and the corresponding time frames within which to receive cardiac catheterization, the Nova Scotia guidelines for ACS have sought to standardize care for ACS patients. These initiatives aimed to target cardiac catheterization toward patients with the strongest indications as well as to facilitate timely referral of ACS patients for this procedure. Adherence to recommended times for cardiac catheterization is critically important in enabling patients to derive the most benefit from this procedure.

The CVHNS quality improvement strategies for receiving reperfusion therapies within guideline-recommended time[76] have resulted in significant improvements of the proportion of STEMI patients receiving this evidence-based treatment. Utilization rates of catheterization and revascularization in NSTEACS patients in Nova Scotia have increased progressively over the past decade. Whether the increased rates of cardiac catheterization have been appropriately targeted or clinically effective has not yet been determined. Specifically, the extent of current practice adherence to the guideline recommendations for cardiac catheterization use in NSTEACS patients, i.e., the guidelines' possible impact on improving the quality of care, is not known.

The study goal was to determine the temporal changes in utilization and timing of cardiac catheterization in NSTEACS population of Nova Scotia in the period from 2003 to 2013, using

data from Nova Scotia NSTEACS patients enrolled in the Cardiovascular Health Nova Scotia (CVHNS) registry. In particular, the study aimed to analyze utilization of cardiac catheterization in higher risk patients, as outlined in the Nova Scotia guidelines for ACS, and to analyze whether there was an impact of the guidelines on improving utilization and timing of cardiac catheterization in higher risk NSTEACS patients.

2.5 Rationale

To date, little is known about the extent to which NSTEACS clinical practice in Nova Scotia adheres to the provincial guideline recommendations on performance of cardiac catheterization, based on patient risk and within recommended time frames. This project was concerned with risk-based access to cardiac catheterization in NSTEACS in Nova Scotia. It sought to evaluate utilization and timing of cardiac catheterization based on risk-based clinical characteristics, as per the Nova Scotia guideline for ACS. To the best of our knowledge, this was the first study in Nova Scotia and one of the few in Canada to characterize patterns of cardiac catheterization use in NSTEACS patients in follow-up to the development and implementation of provincial guidelines for ACS.

The study aimed to address whether the delivery of cardiac catheterization during the study period was based on patient need, i.e., targeted toward high risk patients who are expected to gain the most benefits from receiving this procedure. This study had potential to identify underutilization (i.e., failing to perform the procedure in patients who are most likely to benefit from it) and/or overutilization (i.e., performing the procedure in patients who are likely to gain

little advantage from it) of cardiac catheterization. The results could therefore contribute to further improvement in the care of NSTEACS patients and may help inform health policy.

Targeting service use toward those who are expected to benefit most improves efficacy and effectiveness of the service, improving the quality of care, and ultimately, optimizing patient outcomes. The economic costs of performing the service are justified by appropriate use of the procedure, i.e., using the procedure at the right time in the right patients.

Chapter 3: Objectives

For Nova Scotia patients with a first admission for a NSTEACS event between 2003 and 2013:

The primary objective is to analyze utilization and timing of cardiac catheterization

1. Over the period 2003 to 2013 (temporal analysis)
2. By clinical characteristics
3. By pre-guideline (2003-2008) vs. post-guideline (2009-2013) periods.

A secondary objective is to analyze one-year mortality outcomes for

1. Those who did vs. did not receive cardiac catheterization during hospitalization
2. Those who received cardiac catheterization early ($\leq$ 48 hrs) vs. later.

Chapter 4: Methods

4.1 Study Design

This study is a retrospective cohort study of all adult patients (aged 18 years and older) with a first admission to a hospital in Nova Scotia for NSTEACS (discharge diagnosis), in the period of 2003 to 2013. Patients with a cardiac event precipitated by severe trauma will be excluded. To help minimize patient selection bias, there will be no other specific exclusion criteria.

4.2 Data sources

This study will use retrospective data from NSTEACS patients in Nova Scotia enrolled in the Cardiovascular Health Nova Scotia (CVHNS) registry in the period from 2003 to 2013. Cardiovascular Health Nova Scotia is a provincial program under the auspices of the Nova Scotia Department of Health and Wellness whose mandate includes the development and dissemination of standards and service delivery models, monitoring, surveillance, and reporting of the process and outcomes of cardiovascular care throughout the province for the purposes of health care planning and quality improvement (120). The Registry is therefore well placed to document and promote evidence-based management and as such, can demonstrate potential improvements in guidelines adherence. The Nova Scotia guidelines for ACS outlined clinical characteristics to be used in risk stratifying NSTEACS patients as well as the time frames when to perform cardiac catheterization based on patient risk (32). Delivery of cardiac catheterization based on patient clinical characteristics as well as time when the procedure was performed were used as performance measures to document utilization and timing of receiving the procedure among NSTEACS patients.

Cardiovascular Health Nova Scotia uses trained abstractors to collect retrospective data on demographics, baseline clinical characteristics, use of acute medications within 24 hours of hospital arrival, use and timing of cardiac investigations and invasive cardiac procedures, laboratory results, clinical outcomes, and discharge medications for all patients admitted to hospital with AMI, UA and congestive heart failure throughout the province (121). This provincial population-based registry allows studying an unbiased representation of patients with NSTEACS who presented and were subsequently admitted at any Nova Scotia hospital and will be used to identify study participants. The registry collects patient and hospital factors previously shown to be related to the receipt of cardiac catheterization during admission for NSTEACS event such as patient demographics, comorbidities, cardiac risk factors, and type of an admitting hospital, as well other important data elements such as new events during hospitalization, time to cardiac catheterization during admission for event, utilization of PCI and CABG during hospitalization, and patient outcomes - cardiac death during hospitalization, mortality at 1 year, and at 3 years since index hospitalization.

4.3 Study population

The study included all patients with a discharge diagnosis of NSTEACS during the time of their first hospitalization for either NSTEMI or UA who were enrolled in CVHNS registry between January 2003 and December 2013. Acute MI is defined according to the universal definitions of MI[79] by characteristic symptoms, ECG changes, and cardiac marker elevation (troponin I or T above individual hospital cut-off levels for MI). Unstable angina is diagnosed by presence of symptoms or ECG changes compatible with ACS and cardiac marker levels lower than cut-off or normal levels.

Patients hospitalized with ACS across Nova Scotia and Prince Edward Island are referred by their treating physicians for cardiac catheterization at the Queen Elizabeth II Health Science Centre (QEIIHSC), the largest primary hospital for the Halifax Regional Municipality (HRM) with its population of over 300,000 as well as the only tertiary facility in the region with a capacity to perform this procedure. About 40% of patients referred to the catheterization laboratory present directly to the QEII HSC, while the rest of patients presenting at QEIIHSC are referred from other hospitals in the HRM, Nova Scotia and Prince Edward Island.

To receive cardiac catheterization, patients need to be referred for this procedure by their treating physicians. On the referral for cardiac catheterization, referring physicians are asked to assign a risk category (high-, intermediate-, or low-risk) to a referred patient based on risk stratifying criteria recommended by the Nova Scotia guidelines for ACS. Once received at QEII and accompanied by a complete required documentation, the referrals are reviewed by a QEII cardiologist. The referred patients are placed on a cardiac catheterization wait-list with the risk category assigned by their referring physician confirmed by the QEII cardiologist. If the referred patient doesn't have assigned risk category by its referring physician, the QEII cardiologist will assign a risk category based on received documentation. Based on physical examination, ECG, and required bloodwork including troponin performed upon the referred patient admission to QEII, the risk category is either confirmed or, if there are new findings related to the patient condition, the previously assigned risk category is updated based on admitting physician subjective risk assessment.

Cardiovascular Health Nova Scotia Registry does not collect data on NSTEACS patient risk category based on the TIMI risk score as the one of the Nova Scotia guidelines for ACS recommended options to risk stratify NSTEACS patients. Furthermore, not all data needed for

the TIMI risk score calculation are collected in CVHNS Registry. The CVIS registry of the Division of Cardiology Cardiac Catheterization Lab at QEII HSC collects data on risk category in NSTEACS patients referred to cardiac catheterization but based on a physician subjective risk stratification (not on risk scores as the objective risk stratification methods).

4.4 Urgency/timing of treatment

The Nova Scotia Guidelines for Acute Coronary Syndromes assist physicians with the risk stratification of ACS patients and recommend the evidence-based treatments. The Nova Scotia Guidelines for NSTEACS explicitly outline clinical characteristics to determine the patient need, or risk category to undergo cardiac catheterization, and corresponding time frames to undergo procedure. The time frames suggested by the Canadian Cardiovascular Society Access to Care Working Group expert committee in 2005 were adopted by the CVHNS guidelines.

The guidelines recommend determining the need for and the urgency (timing) of cardiac catheterization (followed by percutaneous coronary intervention - PCI, if indicated) based on outlined clinical characteristics. Patients recommended to undergo cardiac catheterization within 24-48 hours are those having one or more of the following high-risk features: hypotension (with other supportive evidence of ischemia) or definite evidence of CHF, recurrent ventricular arrhythmias, transient ST elevation, new ST depression equal or >2mm in 3 or more leads, recurrent or refractory ischemia despite initial therapy (with definite new or dynamic ST segment changes which are required to justify urgent status in patients with UA who have normal troponin level, or TIMI risk score 5-7 (32). Patients are to undergo cardiac catheterization within three to five days if they have any of the intermediate-risk features such as known LVEF less than 40% in the absence of high-risk features, or TIMI score 3-4 (32), and

within five to seven days in the presence of any of the low-risk features such as no high- or intermediate-risk features, suspected UA with recurrent symptoms but no ECG changes, UA with easily inducible (less than 3 METs) or widespread ischemia on non-invasive testing or some other marker of increased risk (hypotensive response, sustained ST depression, exercise-induced ventricular tachycardia (VT), large territory of reversible ischemia, multiple perfusion defects, low LVEF<40%), or TIMI score 1-2 (32).

4.5 Data analysis

4.5.1 – Primary objective: Utilization and timing – temporal analysis

Trends over the study period in the proportion of patients receiving cardiac catheterization and the proportion receiving early catheterization were described graphically and tested using the Cochran-Armitage trend test.

4.5.2 – Primary objective: utilization and timing – clinical characteristics and pre- and post-guideline periods

Patient baseline characteristics, type of admitting hospital (community vs QEII cohort), and guideline period (pre-guideline, 2003-2008 cohort vs post-guideline, 2009-2013 cohort) were described and compared between NSTEASC patients who received and those who did not receive cardiac catheterization during any time of first hospitalization. The same variables were also compared between patients who received and those who did not receive cardiac catheterization within 24-48 hours since first hospital admission per Nova Scotia guidelines recommended initial management approach in high risk NSTEACS patients. The patient risk characteristics used in the analyses were similar to those analyzed in the observational studies such as this one.

Medians with 25th and 75th percentiles were reported for continuous variables, while frequencies were reported for categorical variables. Proportions of patients with higher risk characteristics who received vs who did not receive cardiac catheterization were examined using frequency distribution tables, and differences between proportions were analyzed using chi-square statistics. Wilcoxon rank-sum tests were used to analyze a potential statistical difference between continuous variables.

To analyze the factors predicting the likelihood of receiving cardiac catheterization at any time during first hospitalization as well as the likelihood of receiving cardiac catheterization within 24-48 hours since first hospital admission, a multivariate logistic regression model was run using the variables that were shown from previous observational analyses to influence the utilization of cardiac catheterization[80]. The model also included high-risk clinical characteristics as outlined in the Nova Scotia guidelines for ACS. The predictive ability of the multivariate logistic regression model was analyzed using a C-index.

The Nova Scotia guidelines for ACS recommend using the TIMI score as a risk stratification method to guide a management approach in NSTEACS patients. However, since the CVHNS registry does not readily capture all variables needed for the TIMI risk score calculation, assigning the risk category to NSTEACS study population based on TIMI risk score from the variables available in CVHNS registry was not possible. The variables such as ST-segment deviation on electrocardiogram, number of severe angina episodes within 24 hours, and aspirin use in the past 7 days are not collected in the registry. Importantly, while troponin values are collected in the registry, they cannot be used in a meaningful way, i.e., to differentiate whether a patient had an elevation in serum cardiac markers because of a great variability in assays and reference ranges between and within districts in Nova Scotia. In addition, assays and reference

ranges are being changed in sites over time (120). We were also not able to use any of the other validated risk score such as the GRACE, or PURSUIT risk score to risk stratify out study population as the registry does not collect all needed variables to calculate these scores either.

To evaluate an impact of receiving cardiac catheterization on potential outcome benefit in higher risk NSTEASC population, we were however able to risk stratify the study population using a risk score developed by the team of QEII cardiologists in 2006. The Nova Scotia Non-ST Elevation Acute Coronary Syndrome Long Term Mortality Risk Score (122). The score is internally validated, and it predicts one-year mortality risk in a real-world Canadian setting (122). The score was derived from an analysis of 14142 patients admitted to hospital with either NSTEMI or UA event between 1998 and 2002 from the CVHNS registry [previously ICONS (Improving Cardiovascular Outcomes in Nova Scotia) database] (122). Ten variables were identified to independently predict 1-year mortality: age>70, prior diabetes or random glucose>11 mmol/L, prior CHF, prior MI, prior renal failure or Cr>133 umol/L, prior stroke, prior atrial fibrillation (AF), Hgb<100 g/L at admission, DBP< 50 mmHg or HR>100 bpm at admission, and diagnosis of NSTEMI[80]. All variables were readily collected in the CVHNS registry (122).

Based on a variable logistic regression coefficient, a score was assigned to each variable. Age>70, prior CHF, prior renal failure or Cr>133 umol/L, and diagnosis of NSTEMI received 3 points each; prior stroke, prior AF, presenting Hgb<100 g/L, DBP< 50 mmHg or HR>100 bpm at admission received 2 points each; and prior MI, and prior diabetes or random glucose>11 mmol/L received 1 point (122). A score was calculated for each patient based on variables present in each subject. The calculated scores for the study cohort ranged from 0 to 21. Based on number of patients with a same score and number of deaths corresponding to the score, the mortality risk for each score was calculated. Cut-off points were defined based on a mortality

risk, and the patients were assigned into five risk groups (mortality risk ranged from 2% to 58%). The predictive accuracy of NS score (C-statistic 0.83 ± 0.01) was found to be significantly greater than those published for the TIMI, GRACE or PURSUIT risk scores (122).

Given that the majority of NSTEACS patients in Nova Scotia are initially admitted to a community hospital and cared by a non-cardiologist, we analyzed the factors predicting the likelihood of receiving cardiac catheterization with a multivariate logistic regression model stratified by type of initially admitted hospital. The rationale for these analyses was based on the research findings suggesting that non-cardiologists might adhere to guideline recommendations to a lesser extent than cardiologists. The analyses were run to evaluate whether the factors predicting the likelihood of receiving cardiac catheterization differ by a hospital type hospital and then referred and transferred to QEII to receive cardiac catheterization. (community vs QEII cohort).

The effect size for each risk characteristic was estimated by odds ratios (OR) for cardiac catheterization derived first from univariate analysis. To determine the extent of association of various predictors shown by previous research to affect use of cardiac catheterization, a multivariable logistic regression model was developed. Odds ratios associated with patient clinical risk characteristics evaluated the probability of undergoing early catheterization relative to when the clinical characteristics was not present. Independent predictors of cardiac catheterization use were determined from obtained strength of association, namely, adjusted odds ratios (OR) and 95% confidence intervals (95% CI). The adjusted OR show predictors' relative contribution to the variability seen in utilization and timing of cardiac catheterization. Model discrimination (predictive ability of the model) are evaluated by the C statistic (C-index), and calibration by the Hosmer-Lemeshow goodness-of-fit test.

Demographics (age>75, sex, place of residence), presenting clinical characteristics (HR>100 bpm, SBP≤100 mmHg, DBP <60 mmHg), NSTEMI as discharge dg, CHF on presentation, prior CHF, higher creatinine (>133µmol/L) on presentation, patient medical history such as prior MI, prior CHF, prior stroke, prior atrial fibrillation (AF), prior peripheral vascular disease (PVD), type of initially admitting hospital (community vs. tertiary), EF <40%, Hgb <100, bleeding requiring transfusion, VT on admission, VF on admission, cardiogenic shock on admission, cardiac risk factors such as hypertension, diabetes mellitus, hyperlipidemia, current smoking, family history of CAD and guideline period (pre- vs post-guideline) were the variables used in the multivariable logistic regression model.

4.5.3 – Secondary objective: One-year mortality outcomes

The study analyzed 1-year mortality in NSTEACS patients receiving cardiac catheterization during the time of first hospitalization for event as well as in the patients receiving early cardiac catheterization using multivariate logistic regression. Unadjusted and adjusted one-year mortality was also analyzed according to patient risk category, calculated using the Nova Scotia Non-ST Elevation Acute Coronary Syndrome Long Term Mortality Risk Score.

The sensitivity analysis estimated the adjusted probability of 1-year mortality in patients initially admitted to QEII who had and who did not have cardiac catheterization during the time of first hospitalization for event as well as in the patients receiving early cardiac catheterization.

Chapter 5: Results

5.1 Temporal analyses

Temporal analyses showed an upward trend in the use of cardiac catheterization during the first hospitalization for a NSTEACS event, from 58.5% in 2008 to 67.6% in 2013. The trends in utilization of cardiac catheterization during first hospitalization were analyzed using the Cochran-Armitage Trend Test, which showed significant increases in the trend from 2008 to 2013 (58.5%, 63.5%, 63%, 66.1%, 64%, and 67.6%, respectively; $p<0.001$) (Figure 1).

For use of early cardiac catheterization, there were increases from 18.4% in 2005 to 23.8% in 2006 and 24.5% in 2007, followed by a sudden downward trend to 19.7% in 2008. Temporal analyses showed an upward trend from 19.7% in 2008 to 26.5% in 2013 (19.7%, 23.1%, 21.7%, 20.7%, 18%, and 26.5% respectively). The trends in utilization of early cardiac catheterization were analyzed using the Cochran-Armitage Trend Test. Despite some fluctuations, the increases in trend were significant for the period 2008-2013 ($p<0.001$) (Figure1).

5.2 Overall cardiac catheterization rates and characteristics of the study population

The study included 25463 patients who had been hospitalized for a first NSTEACS event from January 2003 to December 2013. The overall study population was significantly more likely to be male (61.4%), median age was 69 years, and majority of patients had an urban residence (Table 1). A significantly smaller proportion of patients was initially admitted to Queen Elizabeth II Health Sciences Centre (QEII) in Halifax, a quaternary care teaching hospital with the only cardiac catheterization and revascularization (percutaneous coronary intervention and cardiovascular surgery) facilities in the Province of Nova Scotia. Majority of patients had NSTEMI

as a discharge diagnosis. The patients were more likely to have hypertension and hyperlipidemia, and less likely to have diabetes, to be current smoker, or to j=have a family history of CAD. Approximately a third of the population had a history of prior MI, prior history of CHF was present in around 13% of patients, and renal insufficiency in close to 20% of the study population.

Of these patients, 14557 (57.2%) received cardiac catheterization at the QEII Health Sciences Centre (Table 1). Of the patients who received cardiac catheterization, 5107 (21%) received it early (within 48 hours of admission) (Table 1). Stratifying by guideline period, there were 13622 patients (53.5%) receiving early access in the pre-guideline period (2003-2008) and 11841 (46.5%) receiving it in the post-guideline period (2009-2013) (Table 2). Among patients in the pre-guideline period, 6974 (51.2%) received cardiac catheterization, compared to 7583 (64%) among patients in the post-guideline period ($p<0.001$). Of all the patients in the pre-guideline period who received cardiac catheterization, 2546 (36.5%) received the cardiac catheterization early; of patients in the post-guideline period who received cardiac catheterization, 2561 (33.8%) received it early ($p<0.001$) (Table 3).

In terms of patient characteristics, patients who received cardiac catheterization during hospitalization were younger, more often male, and more likely to be initially admitted to QEII (Table 2). At admission, the patients who received cardiac catheterization were less likely to have increased creatinine, low hemoglobin, low DBP, or low EF on ECHO. The patients who received cardiac catheterization also had a lower prevalence of previous MI, stroke, CHF, renal insufficiency, AF, or PVD. They were less likely to have prior HTN, or DM, but more likely to be smokers at the time of presentation, have hyperlipidemia, or have a family history of CAD. Unexpectedly, among those who received cardiac catheterization, there were more UA than

NSTEMI patients. All differences between patients who received and those who did not receive cardiac catheterization were statistically significant. The variables associated with receiving cardiac catheterization were similar in both the pre-guideline and the post-guideline period (Table 2).

Characteristics of patients who received early (vs. later) cardiac catheterization differed significantly. Patients who received early cardiac catheterization were younger, more often male, more likely to be initially admitted to the QEII, had a lower prevalence of previous MI, stroke, CHF, renal insufficiency, AF, or PVD, and were less likely to have a history of HTN or DM (Table 3). They were more likely to be smokers at the time of presentation, and to have hyperlipidemia. They were also less likely to have increased creatinine, low hemoglobin, low DBP, or low EF on ECHO. The variables associated with receiving early cardiac catheterization were similar in both the pre-guideline and the post-guideline period (Table 3).

5.3 Clinical characteristics and predictors of cardiac catheterization and early cardiac catheterization

5.3.1 Univariate predictors of cardiac catheterization during hospitalization

Univariate analysis showed that NSTEACS treatment in the post-guideline period was associated with increased odds of receiving cardiac catheterization during hospitalization (OR 1.70, 95% CI 1.61-1.79) compared to the pre-guideline period. Variables associated with receipt of cardiac catheterization during hospitalization were male sex, age < 75 years old, initial admission to QEII, being a smoker at the time of presentation, hyperlipidemia, and family history of CAD. Slower presenting HR, low SBP, low DBP, prior HTN, prior DM, MI, CHF, AF, stroke, renal insufficiency, or PVD, increased creatinine at admission, low presenting values of hemoglobin, and NSTEMI were all associated with reduced odds of receiving cardiac catheterization. The

variables associated with receiving cardiac catheterization were similar in both the pre-guideline and the post-guideline period. Notably, patients with NSTEMI had lower odds of receiving cardiac catheterization compared to UA patients in both the pre-guideline period (unadjusted OR 0.71, 95% CI 0.66-0.76) and the post-guideline period (unadjusted OR 0.82, 95% CI 0.76-0.89).

5.3.2 Univariate predictors of early cardiac catheterization

Univariate analysis showed that NSTEASC patients treated in the post-guideline period had higher odds of receiving early cardiac catheterization (OR 1.20, 95% CI 1.13-1.28) compared to patients in the pre-guideline period. Variables associated with receipt of early cardiac catheterization were similar to the variables noted in univariate analysis of (any) cardiac catheterization during hospitalization. Older age, female sex, initial admission to a community hospital, prior DM, MI, CHF, AF, stroke, renal insufficiency, or PVD, increased creatinine at admission, and low presenting values of hemoglobin were all associated with reduced receipt of early cardiac catheterization. Also, patients with NSTEMI had lower odds of receiving early cardiac catheterization (unadjusted OR 0.80, 95% CI 0.75-0.85) compared to UA patients (unadjusted OR 1.26, 95% CI 1.18-1.33). The variables associated with receiving early cardiac catheterization were similar in both the pre-guideline and the post-guideline periods. Again, patients with NSTEMI (compared to UA) had lower odds of receiving early cardiac catheterization in both the pre-guideline (OR 0.68, 95% CI 0.63-0.75) as well as the post-guideline periods (OR 0.87, 95% CI 0.79-0.94), although those odds were not as low in the post-guideline period.

5.3.3 Multivariate predictors of cardiac catheterization and early cardiac catheterization

Multivariate logistic regression models were fit to examine the variables associated with the odds of receiving (any) cardiac catheterization during hospitalization and the odds of receiving early catheterization. The strongest predictors of both any cardiac catheterization (Table 4) and early cardiac catheterization (Table 6) were younger age, male gender, lack of prior CHF, lack of prior stroke, lack of prior AF, normal values of creatinine at admission, normal presenting values of hemoglobin, and initial admission to QEII. Presence of hyperlipidemia and positive family history of CAD were also strong predictors of receiving cardiac catheterization.

The C-index for the cardiac catheterization predictive model was 0.82, and the Hosmer-Lemeshow P-value was 0.0033 while for early cardiac catheterization was 0.85 with the Hosmer-Lemeshow P-value <.0001. The results indicate good discrimination and calibration, respectively for both models.

Patients in the post-guideline period had nearly twice the odds of receiving cardiac catheterization at any point during hospitalization compared to patients in the pre-guideline period (OR 1.94, 95% CI 1.82-2.07) (Table 4). Also, NSTEACS patients treated in the post-guideline period had about 30% higher odds of receiving early cardiac catheterization, compared to patients treated in the pre-guideline period (OR 1.31, 95% CI 1.21-1.41) (Table 6). However, the independent predictors for receiving cardiac catheterization (Table 5) and for receiving early cardiac catheterization (Table 7) in the analysis stratified by guideline period were similar to the unstratified analysis. Older age, being female, having CHF, stroke, or AF, increased serum creatinine at admission, and low hemoglobin were strong predictors of not receiving cardiac catheterization during hospitalization.

Multivariate logistic regression models were also fit to examine the association of risk groups based on the NS risk score, with the odds of receiving (any) cardiac catheterization during hospitalization and the odds of receiving early catheterization (adjusted for gender, type of initially admitting hospital, place of residence, and guideline period). Multivariate logistic regression model examining the association of risk groups with the odds of receiving cardiac catheterization during hospitalization showed that compared to low-risk group, odds of receiving cardiac catheterization for intermediate-risk group was 0.76 (95% CI 0.69 – 0.85), for high-risk 0.31 (95% CI 0.27 – 0.34), for very high-risk 0.11 (95% CI 0.1 – 0.13), and for extremely high risk 0.05 (95% CI 0.05 – 0.06). When stratified by guideline period, the odds of cardiac catheterization remained unchanged in both the pre-guideline and the post-guideline period compared to the odds in unstratified analysis (Table 8). The model examining the association of risk groups with the odds of receiving early cardiac catheterization showed that compared to low-risk group, odds of receiving cardiac catheterization for intermediate-risk group was 0.85 (95% CI 0.76 – 0.94), for high-risk 0.41 (95% CI 0.36 – 0.46), for very high-risk 0.14 (95% CI 0.12 – 0.17), and for extremely high risk 0.07 (95% CI 0.05 – 0.09). When stratified by guideline period, the odds of early cardiac catheterization for intermediate group in the post-guideline period approached those of reference group (low-risk group) while odds for high-, very high-, and extremely high-risk group showed small increases compared to those in the pre-guideline period (Table 9).

5.4 Admitting hospital and cardiac catheterization

When stratified by type of the initially admitted hospital, there were 7200 patients initially admitted to the QEII and 18263 patients initially admitted to a community hospital. Cardiac

catheterization during the hospitalization occurred in 73.4% of patients initially admitted to QEII, compared to 51% of patients initially admitted to community hospitals.

The unadjusted OR for cardiac catheterization for patients initially admitted to a community hospital compared to those initially admitted to QEII (over the whole study period) was 0.37 (95% CI 0.35-0.40). After adjustment, patients initially admitted to a community hospital had 65% lower odds of receiving cardiac catheterization (OR 0.35 95% CI 0.32-0.37). The unadjusted OR for cardiac catheterization within 48 hours for patients initially admitted to a community hospital compared to those initially admitted to QEII (over the whole study period) was 0.097 (95% CI 0.091-0.104). After adjustment, patients initially admitted to a community hospital had 90% lower odds of receiving cardiac catheterization (OR 0.089 95% CI 0.082-0.097).

The same clinical characteristics were predictors of decreased odds of cardiac catheterization in patients initially admitted to a community hospital as for patients admitted to the QEII (Table 10).

Figure 2 shows the time from admission to cardiac catheterization for the QEII and community hospitals. Of the patients initially admitted to the QEII who received cardiac catheterization, 67% received early cardiac catheterization; only 17% of patients initially admitted to a community hospital received early catheterization.

Of the patients initially admitted to the QEII and receiving cardiac catheterization, 25.2% received it between 3 to 5 days, 4.4% received it between 6 to 7 days, and 3.5% received it between 8 to 30 days since admission. One patient received catheterization beyond 30 days (Figure 2).

Of the patients initially admitted to a community hospital and transferred to QEII to receive cardiac catheterization, 37.8% received it from 3 to 5 days, 18.9% received it from 6 to 7 days, and 26.2% received it from 8 to 30 days since admission. There were 18 patients who received catheterization beyond 30 days (Figure 2).

5.5. One-year mortality

5.5.1 Cardiac catheterization at some point during hospitalization

The one-year mortality was 5.3% % for patients who underwent cardiac catheterization at some point during hospitalization, compared with 31.7 % for patients who did not undergo cardiac catheterization (Figure 3).

When stratified by guideline period, the one-year mortality was 5.2% in patients who received cardiac catheterization during hospitalization in the pre-guideline period, compared with 5.4% in post-guideline period. The one-year mortality in patients who did not receive cardiac catheterization was 28.3% in the pre-guideline period compared with 36.9% in the post-guideline period (Figure 4).

The unadjusted OR for one-year mortality was 0.12 (95% CI 0.11-0.13) for patients who did (vs. did not) receive cardiac catheterization. The adjusted OR for one-year mortality was 0.3 (95% 0.27-0.33) for those who did (vs. did not) receive cardiac catheterization (Table 11). In other words, receiving cardiac catheterization reduced the odds of one-year mortality by 70%.

Multivariate logistic regression analysis of one-year mortality, stratified by guideline period, showed that the adjusted OR of one-year mortality in the pre-guideline period was 0.36 (95% 0.31-0.41) compared to OR 0.25 (95% CI 0.21-0.28) in the post-guideline period, for patients

who did (vs. did not) receive cardiac catheterization. Receiving cardiac catheterization reduced the odds of one-year mortality by 64% in the pre-guideline period, and by 75% in the post-guideline period. The adjusted association of guideline period on one-year mortality (with cardiac catheterization in the model) was not significant.

5.5.2 Early (within 48 hours) cardiac catheterization

The one-year mortality was 4.8% % for patients who underwent early cardiac catheterization, compared with 19.6% % for patients who underwent cardiac catheterization after 48 hours (Figure 3).

When stratified by guideline period, the one-year mortality for patients who received early cardiac catheterization was 4.3% in the pre-guideline period, and 5.3% in the post-guideline period. The one-year mortality in patients who received cardiac catheterization after 48 hours was 19.3% in the pre-guideline period, and 19.9% in the post-guideline period (Figure 5).

The unadjusted OR of one-year mortality was 0.21 (95% CI 0.18-0.24) for patients receiving early (vs. later) cardiac catheterization. The corresponding adjusted OR for one-year mortality was 0.48 (95% 0.41-0.57) (Table 12). In other words, receiving early cardiac catheterization reduced the odds of one-year mortality by approximately 50%.

A multivariate logistic regression model with the dependent variable of one-year mortality, and stratified by guideline period, showed that the adjusted OR for one-year mortality (for early vs. later catheterization) in the pre-guideline period was 0.482 (95% CI 0.379-0.613), with a virtually identical OR of 0.482 (95% CI 0.383-0.607) in the post-guideline period. In other words, receiving early cardiac catheterization reduced the odds of one-year mortality by approximately 50% in

both the pre-guideline and the post-guideline period. There was, however, no reduced risk of 1-year mortality in the post-guideline period after adjusting for patient demographic and clinical characteristics, type of admitting hospital, and receipt of early cardiac catheterization, as compared to the pre-guideline period (multivariate regression analysis not stratified by guideline period; OR 0.93, 95% CI 0.85-1.01) (Table 12).

5.5.3 Risk stratification using The Nova Scotia Non-ST Elevation Acute Coronary Syndrome Long Term Mortality Risk Score (NS risk score) – Impact of patient risk on one-year mortality

The study population was stratified into five categories or groups, based on pre-defined cut-points of the NS risk score. Of the patients studied, 10.6% were categorized as low-risk, 41.6% as low/intermediate-risk, 23.7% as high-risk, 17.2% as very high-risk, and 7% as extremely high-risk (Table 13). There was a significant trend of increasing one-year mortality rates across risk categories; from low- (1.3%), intermediate- (4.7%), and high- (18%), to very high- (38%), and extremely high-risk patients (53%) ($p<0.001$) (Table 13, Figure 6).

A multivariate logistic regression model, stratified by risk category, was fit to examine the relationship of cardiac catheterization at some point during hospitalization with one-year mortality. The model adjusted for variables such as patient sex, place of residence, type of initial admitting hospital, and guideline period.

Adjusted ORs of one-year mortality, for those receiving (vs. not receiving) cardiac catheterization were: 0.39 (95% CI 0.19-0.78) for the low-risk group, 0.22 (0.18 – 0.27) for the intermediate-risk group, 0.18 (0.16 – 0.22) for the high-risk group, 0.20 (0.17 – 0.24) for the very high-risk group, and 0.37 (0.29 – 0.49) for the extremely high-risk group (Table 13). The results show that the odds of one-year mortality were reduced most in the intermediate-, high-, and

very high-risk groups. Patients at extremely high risk of adverse outcomes as well as patients at low risk had smaller reductions in the odds of one-year mortality.

In contrast, the actual rates of cardiac catheterization were highest in the low-risk patients and the lowest in higher-risk patients. The rates of cardiac catheterization increased as patient risk decreased (Figure 7). When stratified by guideline period, the rates of cardiac catheterization during hospitalization improved in the post-guideline compared to the pre-guideline period across all risk groups but the rates in the higher-risk groups (i.e., above intermediate risk) were still significantly lower than for the low-risk group (Figure 8).

The rates of cardiac catheterization within 48 hours were similarly observed highest in the low-risk patients and the lowest in higher-risk patients. The rates of cardiac catheterization within 48 hours increased as patient risk decreased (Figure 7). When stratified by guideline period, the rates of cardiac catheterization within 48 hours improved in the post-guideline compared to the pre-guideline period across all risk groups but the rates in the higher-risk groups (i.e., above intermediate risk) were still significantly lower than for the low-risk group (Figure 9).

Adjusted ORs of one-year mortality, for those receiving (vs. not receiving) early cardiac catheterization were: 0.18 (95% CI 0.05-0.77) for the low-risk group, 0.54 (0.41 – 0.7) for the intermediate-risk group, 0.33 (0.25 – 0.42) for the high-risk group, 0.32 (0.23 – 0.44) for the very high-risk group, and 0.63 (0.37 – 1.06) for the extremely high-risk group (Table 14). The odds of one-year mortality were reduced most in the low-risk group, but the confidence interval was very wide. The odds of one-year mortality were significantly reduced in high-, and very high-risk group, and to a lesser extent in the intermediate-risk group. The benefit of early cardiac

catheterization was the smallest in the extreme-high risk group where the results were not significant (Table 14).

Table 1. Baseline characteristics of NSTEACS patients during the first hospitalization for event for the study period 2003-2013

Characteristics	N (%)
Age median (IQR), years	69 (59-79)
Female sex	9839 (38.6)
Urban residence	14881 (58.4)
QEII initially admitting hospital	7200 (28.3)
NSTEMI as discharge dg	14557 (57.2)
Hypertension	17252 (67.8)
Diabetes mellitus	8573 (33.7)
Hyperlipidemia	15419 (60.6)
Current smoking	6323 (24.8)
Family history of CAD	8226 (32.3)
Prior MI	7847 (30.8)
Prior stroke	1969 (7.7)
Prior CHF	3230 (12.7)
Prior renal insufficiency	2016 (7.9)
Prior AF	2541 (10.0)
Prior PVD	2807 (11.0)
Malignancy	3110 (12.2)
Presenting characteristics	
SBP, median (IQR), mmHg	140 (122-160)
HR, median (IQR), beats/min	80 (67-95)
Creatinine >133 µmol/L	4653 (18.3)
DBP <60 mmHg	2207 (8.7)
ECHO EF <40%	1380 (5.4)
Hgb <100 g/L	1746 (6.9)
Cardiogenic shock	201 (0.8)
CHF	751 (3.0)
Bleeding requiring transfusion	250 (1.0)
VT/VF	45 (0.2)/70 (0.3)
Treatment during hospitalization	
Cardiac catheterization at any time	14557 (57.2)
Cardiac catheterization within 48 hrs	5107 (20.1)

Table 2. Baseline characteristics of NSTEACS patients, by receipt of cardiac catheterization during the first hospitalization for event and by guideline period

Characteristics	Pre-guideline 2003 – 2008 N=13622			Post-guideline 2009 – 2013 N=11841		
	Cath N=6974 (51.2%)	**No Cath** N=6648 (48.8%)	**P-value**	**Cath** N=7583 (64%)	**No Cath** N=4258 (36%)	**P-value**
Demographics						
Age median (IQR), years	64 (55-73)	77 (66-84)	<0.001	64 (56-73)	80 (69-87)	<0.001
Female sex	2194 (31.5)	3062 (46.1)	<0.001	2486 (32.8)	2097 (49.3)	<0.001
Urban residence	4273 (61.3)	3809 (57.3)	<0.001	4464 (58.9)	2335 (54.8)	<0.001
Initially admitting hospital						
Tertiary	2748 (39.4)	1279 (19.2)	<0.001	2536 (33.4)	637 (15.0)	<0.001
NSTEMI as discharge dg	3109 (44.6)	3535 (53.2)	<0.001	4948 (65.3)	2965 (69.6)	<0.001
Risk factors						
Hypertension	4315 (61.9)	4397 (66.1)	<0.001	5353 (70.6)	3187 (74.9)	<0.001
Diabetes mellitus	2074 (29.7)	2400 (36.1)	<0.001	2432 (32.1)	1667 (39.2)	<0.001
Hyperlipidemia	4546 (65.2)	3424 (51.5)	<0.001	4951 (65.3)	2498 (58.7)	<0.001
Current smoking	2081 (29.8)	1252 (18.8)	<0.001	2276 (30.0)	714 (16.8)	<0.001
Family history of CAD	2919 (41.9)	1373 (20.7)	<0.001	3232 (42.6)	702 (16.5)	<0.001
Medical history						
Prior MI	2085 (29.9)	2559 (38.5)	<0.001	1702 (22.4)	1501 (35.3)	<0.001
Prior stroke	317 (4.6)	780 (11.7)	<0.001	332 (4.4)	540 (12.7)	<0.001
Prior CHF	441 (6.3)	1369 (20.6)	<0.001	447 (5.6)	973 (22.9)	<0.001
Prior renal insufficiency	240 (3.4)	744 (11.2)	<0.001	332 (4.4)	700 (16.4)	<0.001
Prior AF	381 (5.5)	939 (14.1)	<0.001	452 (6.0)	769 (18.1)	<0.001
Prior PVD	580 (8.3)	900 (13.5)	<0.001	669 (8.8)	658 (15.5)	<0.001
Presenting characteristics						
SBP, median (IQR), mmHg	141 (124-160)	140 (119-160)	NS	144 (127-162)	135 (116-155)	<0.001
HR, median (IQR), beats/min	75 (64-88)	82 (68-100)	<0.001	78 (66-92)	86 (72-103)	<0.001
Creatinine >133 µmol/L	720 (10.3)	1952 (29.4)	<0.001	646 (8.5)	1335 (31.4)	<0.001
DBP <60 mmHg	418 (6.0)	719 (10.8)	<0.001	400 (5.3)	670 (15.8)	<0.001
EF <40%	265 (3.8)	336 (5.1)	<0.001	438 (5.8)	341 (8.0)	<0.001
Hgb <100 g/L	176 (2.5)	661 (9.9)	<0.001	225 (3.0)	684 (16.1)	<0.001
Cardiogenic shock	46 (0.7)	70 (1.0)	0.013	48 (0.6)	37 (0.9)	0.144

Table 3. Baseline characteristics of NSTE-ACS patients, by receipt of cardiac catheterization within the first 48 hours since first admission for event and by guideline period

Characteristics	Pre-guideline 2003 – 2008 N=6960			Post-guideline 2009 – 2013 N=7578		
	Cath ≤ 48hrs N=2546 (36.6%)	**Cath ≥ 48hrs** N=4414 (63.4%)	**P-value**	**Cath ≤ 48hrs** N=2561 (33.8%)	**Cath ≥ 48hrs** N=5017 (66.2%)	**P-value**
Demographics						
Age median (IQR), years	61 (54-71)	65 (56-74)	<0.001	62 (54-71)	65 (57-74)	<0.001
Female sex	730 (28.7)	1463 (33.1)	<0.001	746 (29.1)	1739 (34.7)	<0.001
Urban residence	1686 (66.2)	2579 (58.4)	<0.001	1749 (68.3)	2710 (54.0)	<0.001
Initially admitting hospital						
Tertiary	1873 (73.6)	875 (19.8)	<0.001	1665 (65.0)	870 (17.3)	<0.001
NSTEMI as discharge dg	1048 (41.2)	2057 (53.4)	<0.001	1644 (64.2)	3301 (65.8)	<0.001
Risk factors						
Hypertension	1513 (59.4)	2792 (63.3)	0.002	1695 (66.2)	3654 (72.8)	<0.001
Diabetes mellitus	656 (25.8)	1412 (32.0)	<0.001	738 (28.8)	1692 (33.7)	<0.001
Hyperlipidemia	1710 (67.2)	2825 (64.0)	0.008	1613 (63.0)	3334 (66.5)	0.003
Current smoking	870 (34.2)	1208 (27.4)	<0.001	859 (33.5)	1414 (28.2)	<0.001
Family history of CAD	1163 (45.7)	1752 (39.7)	<0.001	1105 (43.2)	2124 (42.3)	0.499
Medical history						
Prior MI	685 (26.9)	1395 (31.6)	<0.001	487 (19.0)	1213 (24.2)	<0.001
Prior stroke	74 (2.9)	243 (5.5)	<0.001	82 (3.2)	249 (5.0)	<0.001
Prior CHF	91 (3.6)	349 (7.9)	<0.001	94 (3.7)	352 (7.0)	<0.001
Prior renal insufficiency	60 (2.4)	179 (4.1)	<0.001	79 (3.1)	253 (5.0)	<0.001
Prior AF	78 (3.1)	302 (6.8)	<0.001	94 (3.7)	358 (7.1)	<0.001
Prior PVD	136 (5.3)	440 (10.0)	<0.001	202 (7.9)	466 (9.3)	0.042
Presenting characteristics						
SBP, median (IQR), mmHg	136 (119-155)	144 (128-162)	<0.001	140 (123-160)	146 (129-163)	<0.001
HR, median (IQR), beats/min	72 (62-84)	76 (65-90)	<0.001	77 (65-91)	79 (68-93)	<0.001
Creatinine >133 µmol/L	177 (7.0)	540 (12.2)	<0.001	162 (6.3)	484 (9.7)	<0.001
DBP <60 mmHg	194 (7.6)	223 (5.1)	<0.001	155 (6.1)	245 (4.9)	0.031
EF <40%	97 (3.8)	168 (3.8)	0.994	183 (7.2)	255 (5.1)	<0.001
Hgb <100 g/L	51 (2.0)	125 (2.8)	0.034	62 (2.4)	162 (3.2)	0.05
Cardiogenic shock	26 (1.0)	20 (0.5)	0.005	38 (1.50)	10 (0.20)	<0.001

Table 4. Multivariable predictors of cardiac catheterization during first hospitalization for NSTEACS

Variable	Adjusted OR	95% CI	P-value
Female (vs Male)	0.70	0.66 - 0.74	<.0001
Age (per 10 y)*	0.56	0.54 - 0.58	<.0001
Presenting SBP (per 10 mm Hg)*	1.06	1.05 - 1.07	<.0001
Presenting HR (per 10/min)*	0.89	0.87 - 0.90	<.0001
NSTEMI	1.38	1.29 - 1.48	<.0001
Urban residence	1.05	1.00 - 1.12	0.1042
QEII	2.89	2.68 - 3.12	<.0001
Hypertension	1.14	1.06 - 1.22	0.0003
Hyperlipidemia	1.47	1.37 - 1.57	<.0001
Diabetes mellitus	0.92	0.86 – 0.99	0.0179
Current smoking	0.86	0.80 - 0.93	<.0001
Family history of CAD	1.51	1.41 - 1.62	<.0001
Prior MI	0.73	0.68 - 0.78	<.0001
Prior stroke	0.57	0.51 - 0.64	<.0001
Prior CHF	0.58	0.52 - 0.64	<.0001
Prior AF	0.74	0.67 - 0.82	<.0001
Prior PVD	0.86	0.78 – 0.95	0.0029
DBP < 60	0.84	0.74 – 0.94	0.0027
Echo EF < 40%	1.20	1.05 - 1.38	0.0070
Creatinine > 133 µmol/L	0.49	0.45 - 0.53	<.0001
Hgb < 100 g/L	0.36	0.31 - 0.41	<.0001
Guideline period	1.94	1.82 – 2.07	<.0001

*Continuous variables

Table 5. Multivariable predictors of cardiac catheterization during first hospitalization for NSTEACS by guideline period

	Pre-guideline period 2003 - 2008			Post-guideline period 2009 - 2013		
Variable	**Adjusted OR**	**95% CI**	**P-value**	**Adjusted OR**	**95% CI**	**P-value**
Female	0.72	0.66 - 0.78	<.0001	0.66	0.60 - 0.73	<.0001
Age (per 10 y)*	0.60	0.57 - 0.62	<.0001	0.51	0.48 - 0.53	<.0001
Presenting SBP (per 10 mm Hg)*	1.04	1.03 - 1.06	<.0001	1.09	1.07 - 1.11	<.0001
Presenting HR (per 10/min)*	0.89	0.88 - 0.91	<.0001	0.87	0.85 - 0.89	<.0001
NSTEMI	1.14	1.05 - 1.24	0.0030	1.89	1.69 - 2.11	<.0001
Urban residence	1.07	0.98 - 1.16	0.1288	1.04	0.94 - 1.15	0.4256
QEII	2.80	2.54 - 3.08	<.0001	3.05	2.68 - 3.46	<.0001
Hypertension	1.05	0.96 - 1.15	0.3014	1.33	1.18 - 1.50	<.0001
Hyperlipidemia	1.48	1.36 - 1.62	<.0001	1.48	1.33 - 1.66	<.0001
Diabetes mellitus	0.91	0.84 - 1.00	0.0480	0.93	0.84 - 1.03	0.1625
Current smoking	0.85	0.76 - 0.94	0.0012	0.89	0.78 - 1.01	0.0620
Family history of CAD	1.39	1.27 - 1.52	<.0001	1.74	1.55 - 1.94	<.0001
Prior MI	0.77	0.71 - 0.84	<.0001	0.65	0.58 - 0.72	<.0001
Prior stroke	0.61	0.52 - 0.72	<.0001	0.51	0.43 - 0.61	<.0001
Prior CHF	0.62	0.54 - 0.71	<.0001	0.53	0.46 - 0.62	<.0001
Prior AF	0.76	0.66 - 0.88	0.0002	0.73	0.63 - 0.85	<.0001
Prior PVD	0.89	0.78 - 1.01	0.0698	0.84	0.73 - 0.97	0.0210
DBP < 60	0.95	0.8 - 1.12	0.5513	0.74	0.62 - 0.88	0.0007
Echo EF < 40%	1.25	1.03 - 1.52	0.0262	1.19	0.99 - 1.44	0.0673
Creatinine > 133 µmol/L	0.56	0.49 - 0.61	<.0001	0.41	0.36 - 0.47	<.0001
Hgb < 100 g/L	0.44	0.36 - 0.54	<.0001	0.30	0.25 - 0.37	<.0001

*Continuous variables

Table 6. Multivariate predictors of cardiac catheterization within 48 hours since admission for NSTEACS

Variable	Adjusted OR	95% CI	P- value
Female	0.79	0.73 - 0.86	<.0001
Age (per 10 y)*	0.71	0.69 - 0.74	<.0001
Presenting SBP (per 10 mm Hg)*	1.00	0.98 - 1.01	0.8823
Presenting HR (per 10/min)*	0.88	0.86 - 0.9	<.0001
NSTEMI	1.28	1.17 - 1.39	<.0001
Urban residence	1.03	0.95 - 1.12	0.4254
QEII	11.18	10.30 - 12.14	<.0001
Hypertension	1.0	0.91 - 1.09	0.9533
Hyperlipidemia	1.16	1.08 - 1.27	0.0006
Diabetes mellitus	0.94	0.86 - 1.03	0.1893
Current smoking	1.09	0.99 - 1.19	0.0728
Family history of CAD	1.06	0.98 - 1.15	0.1642
Prior MI	0.73	0.67 - 0.8	<.0001
Prior stroke	0.56	0.46 - 0.68	<.0001
Prior CHF	0.42	0.35 - 0.51	<.0001
Prior AF	0.57	0.48 - 0.69	<.0001
Prior PVD	0.75	0.65 - 0.87	<.0001
DBP < 60	1.15	0.98 - 1.34	0.0864
Echo EF < 40%	1.28	1.07 - 1.52	0.0068
Creatinine > 133 µmol/L	0.44	0.38 - 0.51	<.0001
Hgb < 100 g/L	0.38	0.3 - 0.48	<.0001
Guideline period	1.31	1.21 - 1.41	<.0001

*Continuous variables

Table 7. Multivariate predictors of cardiac catheterization within 48 hours since admission for NSTEACS by guideline period

	Pre-guideline period 2003 - 2008			Post-guideline period 2009 - 2013		
Variable	**Adjusted OR**	**95% CI**	**P-value**	**Adjusted OR**	**95% CI**	**P-value**
Female	0.82	0.72 - 0.92	0.0007	0.76	0.67 - 0.85	<.0001
Age (per 10 y)*	0.72	0.68 - 0.76	<.0001	0.71	0.67 - 0.74	<.0001
Presenting SBP (per 10 mm Hg)*	0.99	0.97 - 1.01	0.3170	1.01	0.99 - 1.03	0.2427
Presenting HR (per 10/min)*	0.86	0.83 - 0.88	<.0001	0.91	0.88 - 0.93	<.0001
NSTEMI	1.11	1.0 - 1.25	0.0734	1.51	1.34 - 1.71	<.0001
Urban residence	0.87	0.78 - 0.98	0.0233	1.23	1.1 - 1.39	0.0004
QEII	12.92	11.49 - 14.52	<.0001	9.75	8.68 - 10.95	<.0001
Hypertension	0.98	0.87 - 1.10	0.7053	1.03	0.90 - 1.17	0.7025
Hyperlipidemia	1.24	1.1 - 1.4	0.0006	1.06	0.94 - 1.2	0.3575
Diabetes mellitus	0.89	0.79 - 1.01	0.0736	1.01	0.89 - 1.14	0.9379
Current smoking	1.15	1.01 - 1.31	0.0309	1.03	0.91 - 1.17	0.6193
Family history of CAD	1.13	1.01 - 1.27	0.0355	1.0	0.89 - 1.12	0.9861
Prior MI	0.75	0.66 - 0.85	<.0001	0.70	0.61 - 0.81	<.0001
Prior stroke	0.54	0.41 - 0.71	<.0001	0.60	0.46 - 0.79	0.0002
Prior CHF	0.43	0.34 - 0.56	<.0001	0.43	0.33 - 0.55	<.0001
Prior AF	0.58	0.44 - 0.76	<.0001	0.56	0.43 - 0.72	<.0001
Prior PVD	0.65	0.52 - 0.81	<.0001	0.87	0.71 - 1.05	0.1481
DBP < 60	1.18	0.95 - 1.46	0.1438	1.12	0.89 - 1.41	0.3201
Echo EF < 40%	1.15	0.87 - 1.53	0.3273	1.32	1.05 - 1.66	0.0162
Creatinine > 133 µmol/L	0.45	0.37 - 0.54	<.0001	0.43	0.35 - 0.53	<.0001
Hgb < 100 g/L	0.45	0.32 - 0.63	<.0001	0.33	0.24 - 0.46	<.0001

*Continuous variables

Table 8. Multivariable predictors of cardiac catheterization at any point during first hospitalization for NSTEACS based on NS risk score

Variable	Adjusted OR	95% CI		P- value
Female	0.59	0.56	0.62	<.0001
Urban residence	1.04	0.98	1.10	0.2104
QEII	2.78	2.6	2.98	<.0001
Intermediate risk (4-6)	0.76	0.69	0.85	<.0001
High-risk (7-9)	0.31	0.27	0.34	<.0001
Very-high risk (10-13)	0.11	0.1	0.13	<.0001
Extremely-high risk (14+)	0.05	0.05	0.06	<.0001
Guideline period	2.15	2.03	2.27	<.0001

Table 9. Multivariate predictors of early cardiac catheterization for NSTEACS based on NS risk score

Variable	Adjusted OR	95% CI		P- value
Female	0.70	0.65	0.76	<.0001
Urban residence	1.00	0.97	1.08	0.9765
QEII	10.94	10.1	11.80	<.0001
Intermediate risk (4-6)	0.85	0.76	0.94	<.0001
High-risk (7-9)	0.41	0.36	0.46	<.0001
Very-high risk (10-13)	0.14	0.12	0.17	<.0001
Extremely-high risk (14+)	0.07	0.05	0.09	<.0001
Guideline period	1.45	1.35	1.56	<.0001

Table 10. Multivariate predictors of cardiac catheterization during first hospitalization for NSTEACS by type of admitting hospital

	QEII			Community hospital		
Variable	**Adjusted OR**	**95% CI**	**P-value**	**Adjusted OR**	**95% CI**	**P-value**
Female	0.75	0.65 - 0.86	<.0001	0.69	0.64 - 0.74	<.0001
Age (per 10 y)*	0.50	0.47 - 0.54	<.0001	0.57	0.56 - 0.59	<.0001
Presenting SBP (per 10 mm Hg)*	1.05	1.03 - 1.08	<.0001	1.06	1.05 - 1.08	<.0001
Presenting HR (per 10/min)*	0.87	0.84 - 0.9	<.0001	0.89	0.88 - 0.91	<.0001
NSTEMI	0.92	0.79 - 1.06	0.2496	1.6	1.48 - 1.72	<.0001
Urban residence	0.67	0.56 - 0.79	<.0001	1.16	1.09 - 1.25	<.0001
Hypertension	1.03	0.87 - 1.22	0.7427	1.17	1.08 - 1.27	<.0001
Hyperlipidemia	1.28	1.1 - 1.49	0.0019	1.50	1.39 - 1.62	<.0001
Diabetes mellitus	0.97	0.84 - 1.13	0.7058	0.91	0.84 - 0.98	0.0186
Current smoking	1.09	0.91 - 1.30	0.3462	0.79	0.73 - 0.87	<.0001
Family history of CAD	1.38	1.19 - 1.6	<.0001	1.57	1.44 - 1.7	<.0001
Prior MI	0.62	0.53 - 0.72	<.0001	0.77	0.71 - 0.84	<.0001
Prior stroke	0.41	0.33 - 0.52	<.0001	0.65	0.57 - 0.74	<.0001
Prior CHF	0.52	0.43 - 0.64	<.0001	0.61	0.54 - 0.68	<.0001
Prior AF	0.75	0.6 - 0.95	0.0146	0.75	0.66 - 0.84	<.0001
Prior PVD	0.72	0.59 - 0.87	0.0007	0.96	0.86 - 1.07	0.4602
DBP < 60	0.99	0.79 - 1.25	0.9393	0.77	0.67 - 0.88	0.0002
Echo EF < 40%	1.47	1.15 - 1.88	0.0025	1.09	0.92 - 1.28	0.3159
Creatinine > 133 µmol/L	0.45	0.38 - 0.54	<.0001	0.51	0.46 - 0.56	<.0001
Hgb < 100 g/L	0.32	0.25 - 0.41	<.0001	0.37	0.32 - 0.44	<.0001
Guideline period	2.02	1.76 - 2.33	<.0001	1.90	1.77 - 2.04	<.0001

*Continuous variables

Table 11. Multivariate predictors of 1-year mortality during first hospitalization for NSTEACS (cardiac catheterization in the model)

Variable	Adjusted OR	95% CI	P- value
Female	0.94	0.86 - 1.03	0.1663
Age (per 10 y)*	1.72	1.65 - 1.80	<.0001
Presenting SBP (per 10 mm Hg)*	0.91	0.89 - 0.92	<.0001
Presenting HR (per 10/min)*	1.07	1.05 - 1.09	<.0001
NSTEMI	2.47	2.24 - 2.73	<.0001
Urban residence	1.04	0.96 - 1.14	0.3310
QEII	0.97	0.88 - 1.08	0.6213
Hypertension	0.94	0.85 - 1.03	0.1933
Hyperlipidemia	0.76	0.69 - 0.83	<.0001
Diabetes mellitus	1.29	1.18 - 1.41	<.0001
Current smoking	1.16	1.03 - 1.31	0.0128
Family history of CAD	0.81	0.72 - 0.91	0.0003
Prior MI	1.15	1.05 - 1.26	0.0025
Prior stroke	1.43	1.27 - 1.61	<.0001
Prior CHF	1.56	1.41 - 1.73	<.0001
Prior AF	0.98	0.88 - 1.10	0.7514
Prior PVD	1.47	1.31 - 1.64	<.0001
DBP < 60	1.1	0.97 - 1.25	0.1530
Echo EF < 40%	1.41	1.21 - 1.63	<.0001
Creatinine > 133 µmol/L	1.62	1.46 - 1.79	<.0001
Hgb < 100 g/L	1.62	1.43 - 1.84	<.0001
Cath during hospitalization	0.3	0.27 - 0.33	<.0001
Guideline period	1.03	0.94 - 1.12	0.5268

*Continuous variables

Table 12. Multivariate predictors of 1-year mortality during first hospitalization for NSTEACS (cardiac catheterization within 48 hours in the model)

Variable	Adjusted OR	95% CI	P- value
Female	1.00	0.92 - 1.09	0.9637
Age (per 10 y)*	1.96	1.88 - 2.05	<.0001
Presenting SBP (per 10 mm Hg)*	0.9	0.88 - 0.91	<.0001
Presenting HR (per 10/min)*	1.09	1.07 - 1.10	<.0001
NSTEMI	2.39	2.17 - 2.64	<.0001
Urban residence	1.04	0.96 - 1.13	0.3711
QEII	0.94	0.84 - 1.04	0.2339
Hypertension	0.90	0.82 - 0.99	0.0348
Hyperlipidemia	0.70	0.64 - 0.77	<.0001
Diabetes mellitus	1.30	1.2 - 1.42	<.0001
Current smoking	1.21	1.08 - 1.36	0.0012
Family history of CAD	0.72	0.64 - 0.80	<.0001
Prior MI	1.19	1.09 - 1.3	0.0002
Prior stroke	1.55	1.38 - 1.75	<.0001
Prior CHF	1.64	1.48 - 1.81	<.0001
Prior AF	1.02	0.91 - 1.14	0.7771
Prior PVD	1.49	1.33 - 1.67	<.0001
DBP < 60	1.14	1.00 - 1.29	0.0473
Echo EF < 40%	1.35	1.17 - 1.55	<.0001
Creatinine > 133 µmol/L	1.73	1.57 - 1.91	<.0001
Hgb < 100 g/L	1.82	1.61 - 2.06	<.0001
Cath within 48 hrs	0.48	0.41 - 0.57	<.0001
Guideline period	0.93	0.85 - 1.01	0.0751

*Continuous variables

Table 13. One-year adjusted mortality by cardiac catheterization per risk categories

NS risk score	Risk category	Number of patients	% of total study population	Mortality (N, %)[1]	Receiving catheterization (N, %)	Mortality (N) in those receiving catheterization	Adjusted[2] OR (95% CI)	P-value
0 - 3	Low	2701	10.6	35 (1.3)	2119 (78.5)	19	0.39 (0.19 – 0.78)	0.0083
4 - 6	Intermediate	10591	41.6	495 (4.7)	7726 (73)	207	0.22 (0.18 – 0.27)	<.0001
7 - 9	High	6026	23.7	1085 (18)	3133 (52)	237	0.18 (0.16 – 0.22)	<.0001
10 - 13	Very high	4370	17.2	1662 (38)	1274 (29.2)	203	0.20 (0.17 – 0.24)	<.0001
14 +	Extremely high	1775	7.0	947 (53)	305 (17.2)	104	0.37 (0.29 – 0.49)	<.0001

[1]Deaths within 1 year includes mortality within 1 year in patients who received catheterization and in those who did not

[2]Adjusted by sex (female vs male), place of residence (urban vs rural), type of hospital (QEII vs community hospital), and guideline period (post-guideline vs pre-guideline)

Table 14. One year adjusted mortality by early cardiac catheterization per risk categories

NS risk score	Risk category	Receiving cardiac catheterization within 48 hrs (N, %)	Mortality (N) in those receiving catheterization within 48 hrs	Adjusted[1] OR (95% CI)	P-value
0 - 3	Low	929	3	0.18 (0.05 – 0.77)	0.0105
4 - 6	Intermediate	2896	89	0.54 (0.41 – 0.70)	<.0001
7 - 9	High	935	74	0.33 (0.25 – 0.42)	<.0001
10 - 13	Very high	285	51	0.32 (0.23 – 0.44)	<.0001
14 +	Extremely high	62	27	0.63 (0.37 – 1.06)	0.0815

[1]Adjusted by sex (female vs male), place of residence (urban vs rural), type of hospital (QEII vs community hospital), and guideline period (post-guideline vs pre-guideline)

Figure 1. Temporal trends in utilization of cardiac catheterization during hospitalization, and early cardiac catheterization (within 48 hours) since admission for NSTEACS event

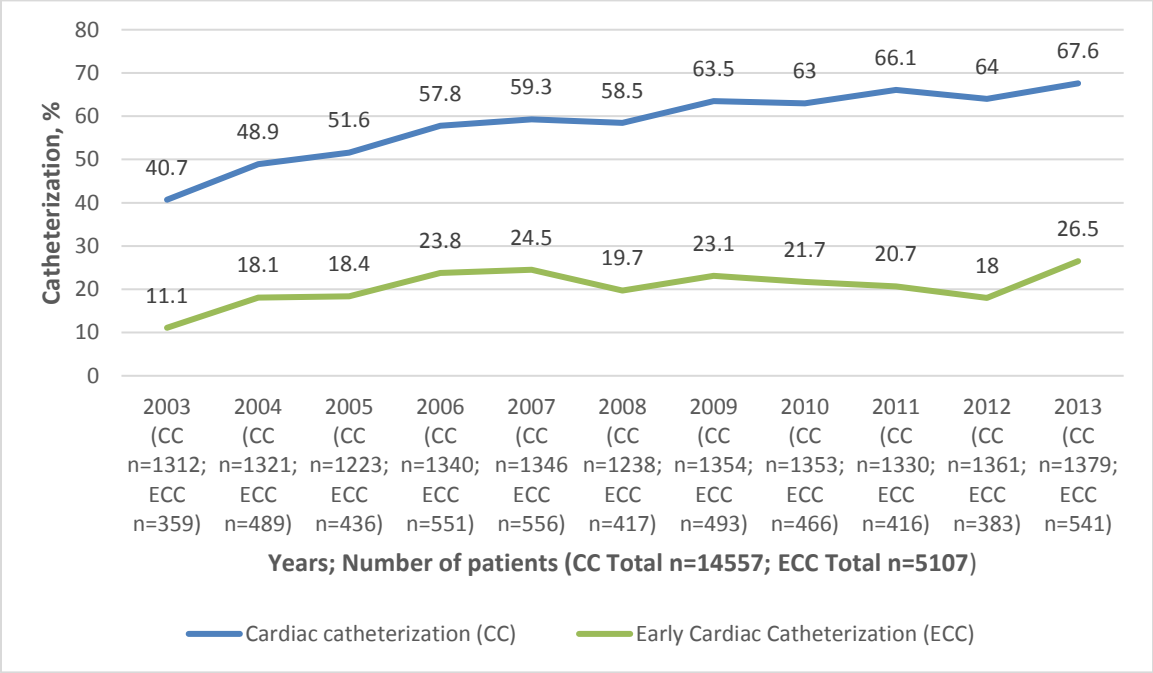


Figure 2. Time from NSTEACS admission to cardiac catheterization

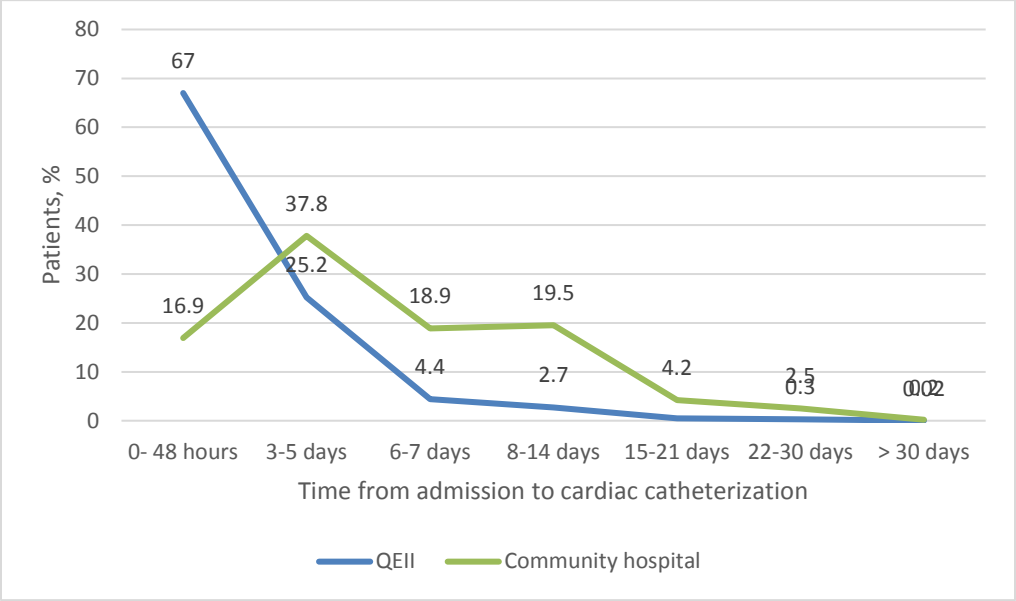


Figure 3. Unadjusted 1-year mortality rates by cardiac catheterization (during hospitalization and within 48 hours since admission) during entire study period (2003-2013)

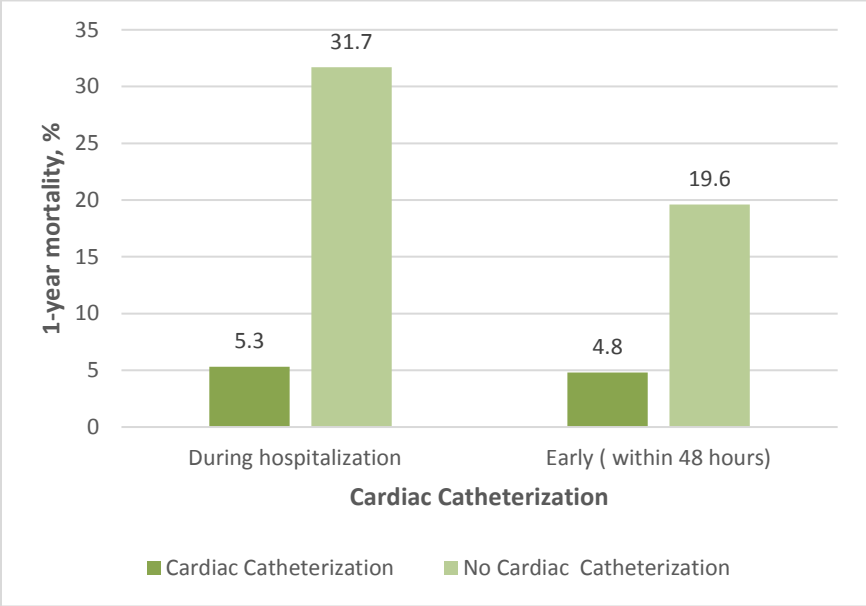


Figure 4. Unadjusted 1-year mortality rates by cardiac catheterization and guideline period

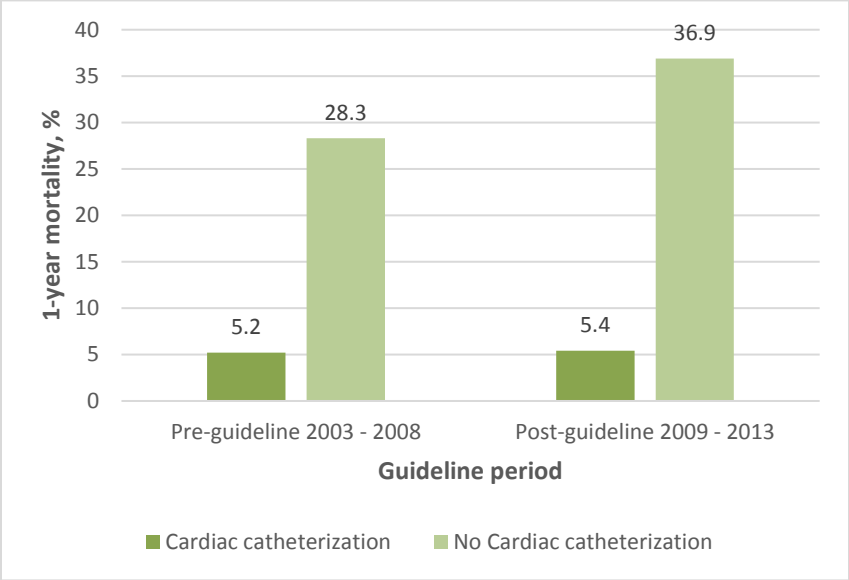


Figure 5. Unadjusted 1-year mortality rates by cardiac catheterization within 48 hours and guideline period

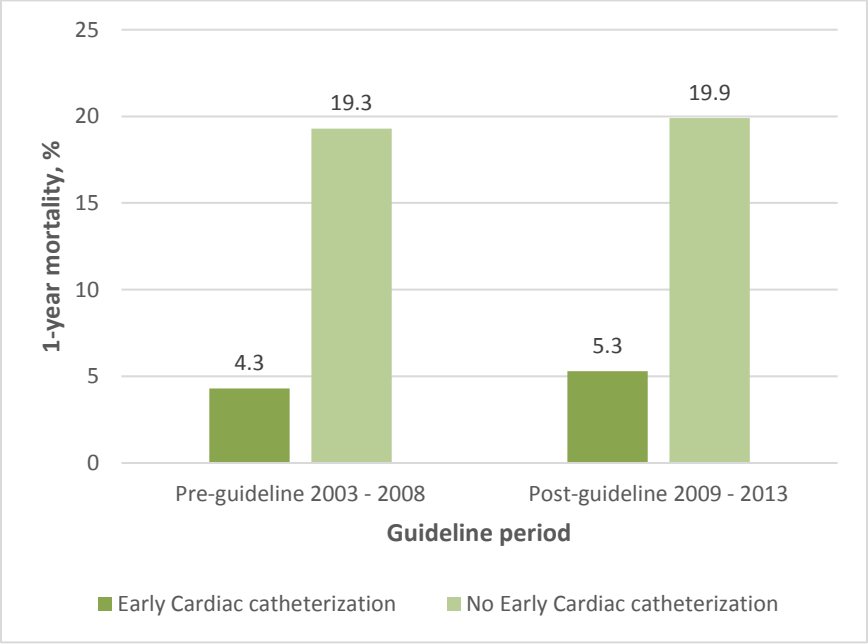


Figure 6. One-year mortality rates in NSTEACS patients stratified by risk (from lowest to highest risk group) as per NS risk score

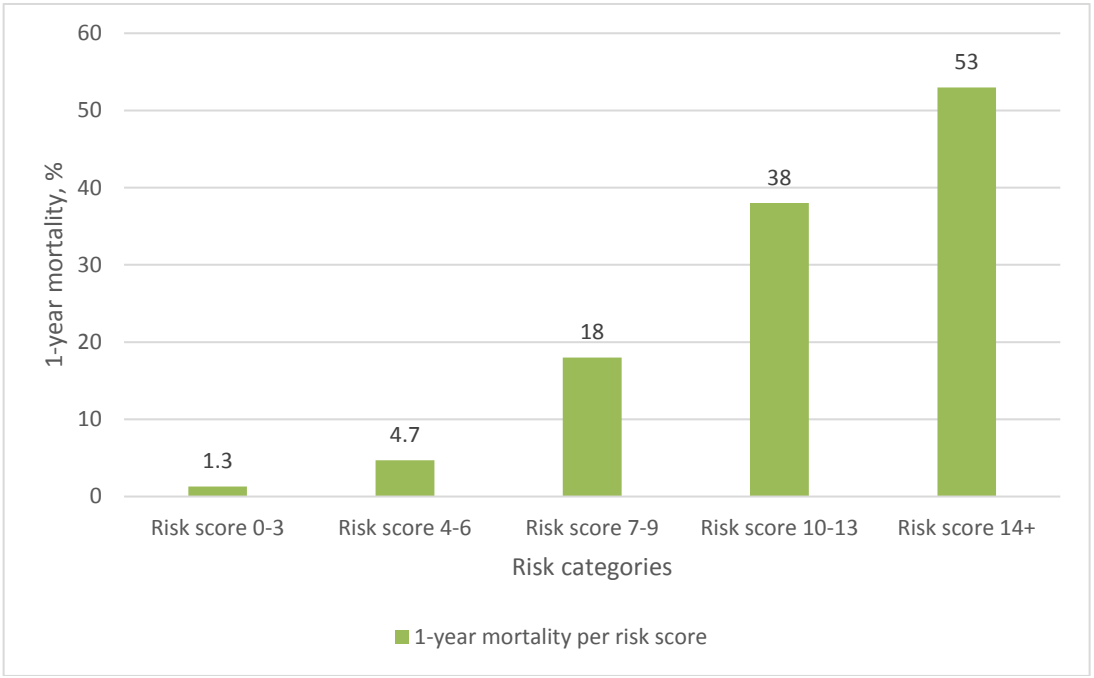


Figure 7. Utilization of cardiac catheterization and cardiac catheterization within 48 hours per risk category based on NS Risk Score

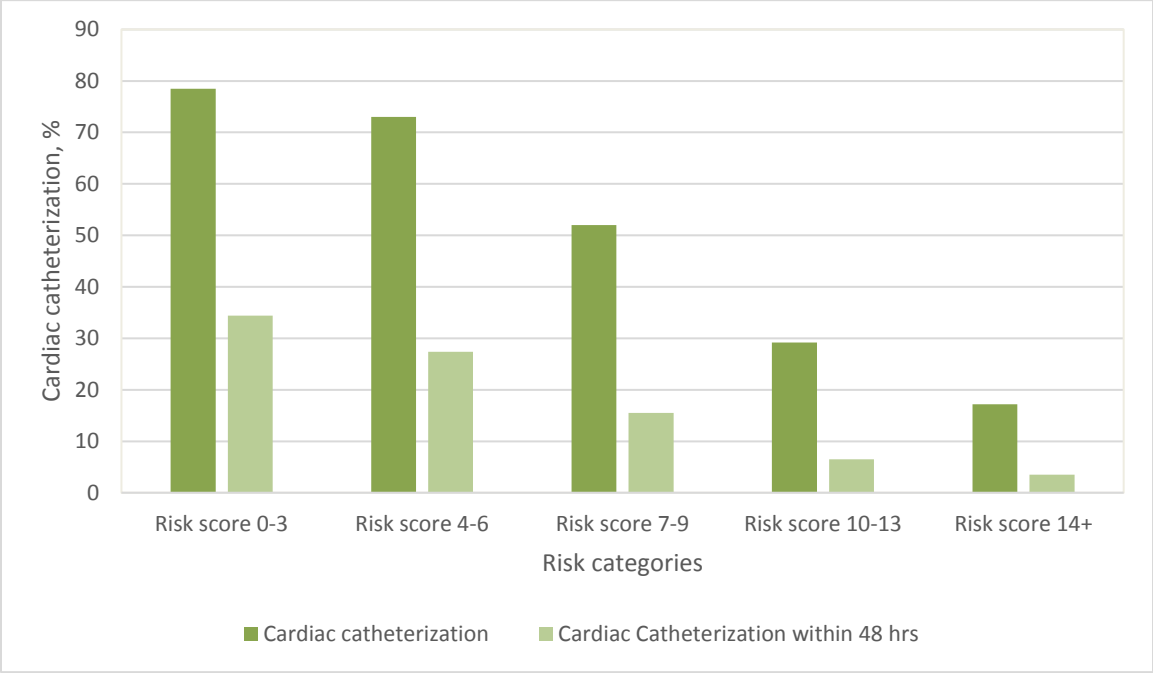


Figure 8. Cardiac catheterization rates in NSTEACS patients stratified by risk (from lowest to highest risk group) as per NS Risk Score, and by guideline period

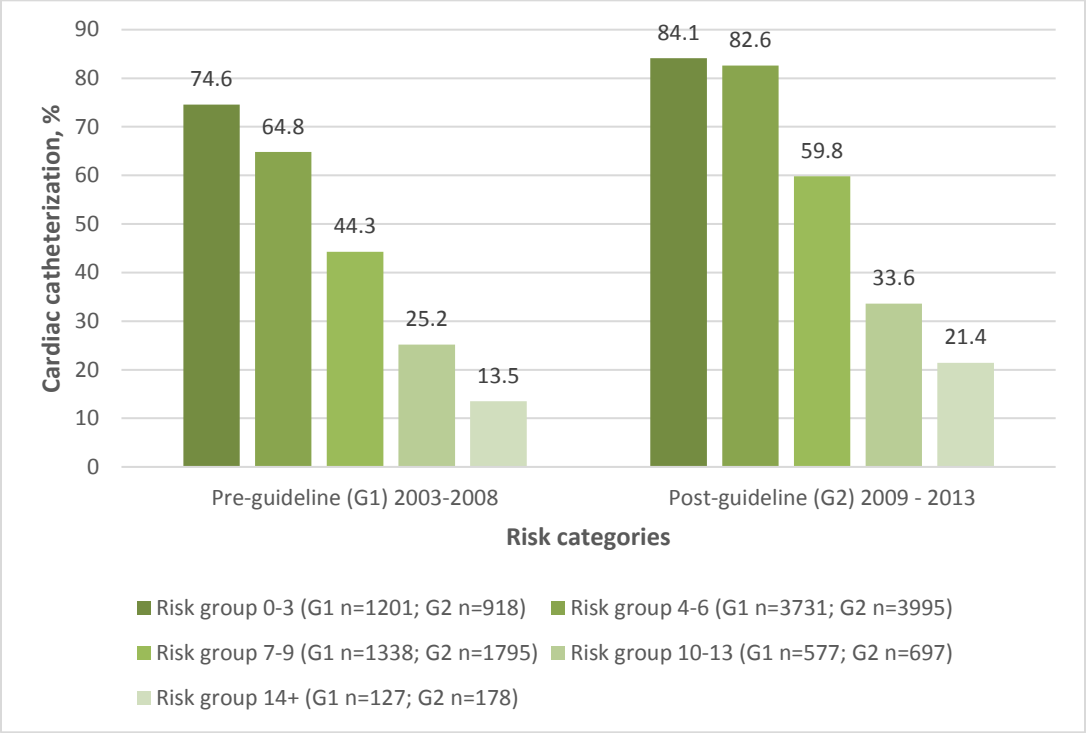


Figure 9. Rates of cardiac catheterization within 48 hours in NSTEACS patients stratified by risk (from lowest to highest risk group) as per NS Risk Score, and by guideline period

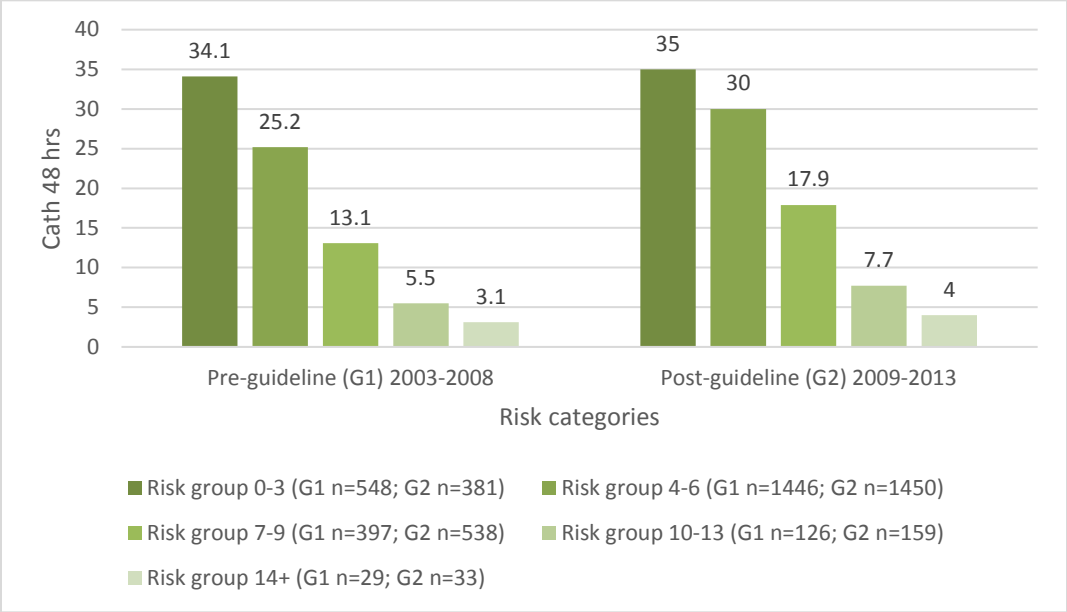
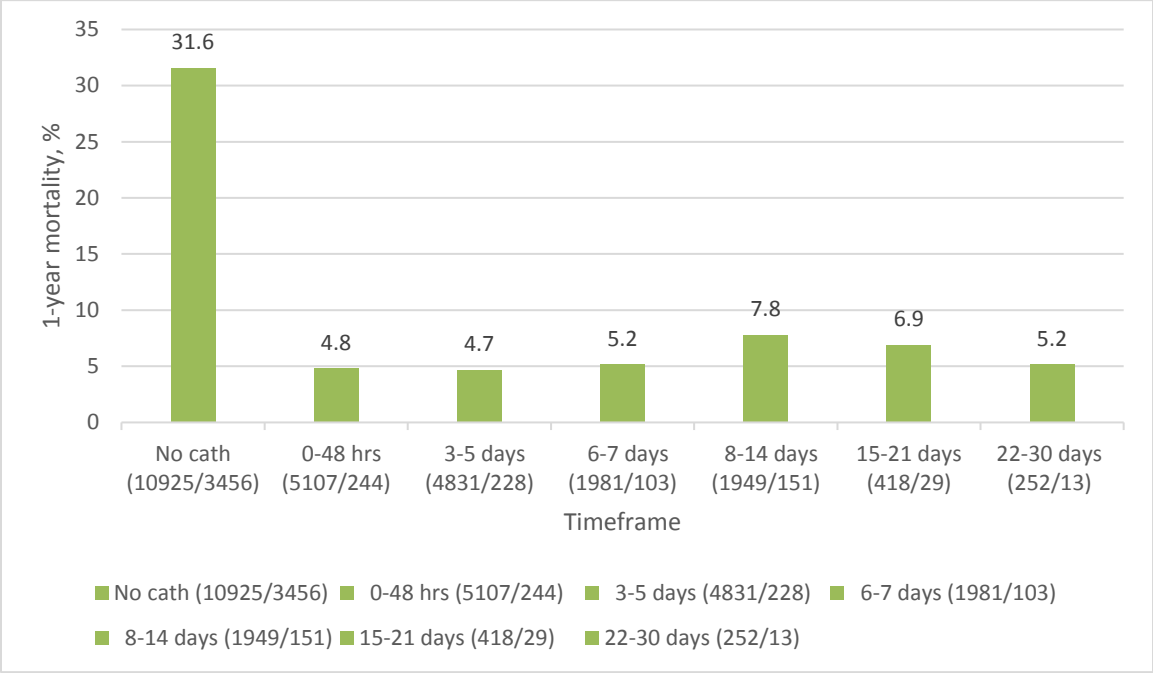


Figure 10. 1-year mortality per time to catheterization



Chapter 6: Discussion

The trends in utilization of both cardiac catheterization and early cardiac catheterization increased over the study period of 2003 to 2013. However, there was variability in the trends for early cardiac catheterization, including a decline or "dip" in 2008 (Figure 1). Some of the fluctuations are related to personnel changes among a relatively small group of interventional cardiologists.

It is perhaps not surprising that admission to a community hospital was associated with lower odds of cardiac catheterization and lower odds of early cardiac catheterization. NSTEACS patients admitted to community hospitals would be initially assessed and then referred as needed. However, depending on the location of the community hospital, assessment and transfer could take much of the first 48 hours. The issues associated with type of admitting hospital are important, given that the majority of NSTEACS patients in Nova Scotia initially present to a community hospital.

Patients' high-risk clinical characteristics, such as age 75 years or older, prior CHF, AF, stroke, decreased renal function, or lower Hgb at admission were significantly associated with decreased odds of receiving cardiac catheterization during hospitalization, or decreased odds of early receipt if the patients did receive cardiac catheterization. These findings seem potentially consistent with the "treatment-risk paradox" noted in the literature. Importantly, the pattern of cardiac catheterization (at any time as well early intervention) occurring more in lower risk patients persisted after stratifying by the type of admitting hospital, i.e., when the initial admitting hospital was a tertiary care facility providing cardiac catheterization and revascularization.

However, the treatment-risk paradox became even more clear after using the NS risk score to categorize patients into risk groups (low-, intermediate-, high-, very high- and extremely high-risk), based on clusters of risk characteristics. The adjusted odds of cardiac catheterization decreased across the categories of progressively higher risk.

While there was some improvement from the pre-guideline to the post-guideline period in cardiac catheterization rates for high-risk patients, the inverse relationship between patient risk and receipt of cardiac catheterization persisted. These findings suggest that despite evidence-based guideline recommendations for an invasive approach in NSTEACS high-risk patients, recent practice has continued to target patients at lower risk. This inverse relationship between patient risk, based on the NS risk score, and cardiac catheterization existed even when the initial admitting hospital was a tertiary care facility providing cardiac catheterization and revascularization.

From a clinical perspective, this practice may stem from understandable concerns about doing more harm than good by performing invasive procedures on older or sicker patients, especially those with multiple morbidities. Part of the problem is that clinical trials tend to exclude such patients, even though they represent a majority of patients seen in clinical practice. Practicing clinicians may therefore find the recommendations of the 2007 ACC/AHA Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction, which are based on the RCTs findings, not applicable to the real-world NSTEACS population. However, it should be noted that there is also risk-stratification evidence available from a number of observational studies, reflecting more representative patient populations.

The Nova Scotia Department of Health developed and implemented their own guidelines for ACS. Their risk-based recommendations regarding invasive strategies are the result of consensus among the province's experts in ACS care. In that context, one might expect that concerns about harm would be less problematic. It is also surprising that the inverse relationship between patient risk and cardiac catheterization was observed even when the initial admitting hospital was a tertiary care facility providing cardiac catheterization and revascularization. Some of the reviewed research studies' results suggested that specialists are more likely than non-specialists to adhere to guideline recommendations for specific conditions. In addition, since the champions of provincial ACS care and the clinical leads in guideline development were the senior cardiologists at the QEII, we expected to see greater adherence to the guideline recommendations for risk-based delivery of cardiac catheterization among these tertiary care hospital cardiologists.

The clinicians involved in NSTEACS care risk-stratify patients based on their subjective clinical judgment and experience. They are professionals with years of medical education and training, and their clinical judgment is executed on a daily basis in a variety of clinical scenarios. Furthermore, physicians are trained to consider each patient case individually, and tailor the treatment accordingly, therefore they might not see algorithms such as the risk scores as more trustworthy than their own experience. The benefits of risk scores are evaluated at the population level; they present a population-based risk stratification method developed on large numbers of patients and they convey mortality prognostication risk on a population level. It is a different perspective to see an individual in the Emergency Department, where the challenge is to make a timely decision. Some physicians might view the use of risk scores as unnecessarily time consuming.

Based on informal communication with some of the senior cardiologists at QEII, the TIMI risk score was apparently poorly used among cardiologists at QEII, and was likely hardly used among non-cardiologists at community hospitals. While the NS guidelines for ACS recommended using the TIMI risk score in a risk stratification process, the use of the TIMI risk score was not established as a process of care measure and therefore was not required to document in a patient chart. It is largely unknown what clinical factors physician consider in their subjective risk stratifying method, when referring a patient for cardiac catheterization vs. deciding to treat conservatively. The results from some observational studies suggest that the factors physicians consider most important in their decision makings were most often troponin levels, ischemic changes on the ECG, and presence of comorbidities. They are more likely to refer for cardiac catheterization a patient with elevated troponin levels and changes on ECG indicative of acute MI, and less likely to refer elderly patients, or patients with CHF, or RI. While there is evidence that older age, CHF, RI, or DM are clinical factors independently associated with risk of death at 1 year, the presence of any of these factors makes a decision on referral for cardiac catheterization in actual practice less likely. Given that numerous clinical factors are important to consider in appropriately risk-stratifying NSTEACS patients, weighing all factors simultaneously may present an overwhelming task in a busy clinical practice.

On the other hand, the risk scores facilitate accurate and simultaneous accounting for a number of clinical factors, and were developed exactly to assist physicians in their decision making when risk-stratifying their patient population (not to replace their clinical judgment). The TIMI, GRACE, and PURSUIT risk scores demonstrated good predictive accuracy for mortality and MI at 1 year, and were therefore recommended by both 2007 as well as 2014 ACC/AHA Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction to

accurately identify patients who could potentially benefit most from an invasive strategy, i.e., cardiac catheterization followed by revascularization, if appropriate.

In the current study, it is reassuring to examine the one-year mortality of patients who did vs. did not receive cardiac catheterization across the five risk categories. The reduction in the odds of one-year mortality was greatest (80%) for each of the intermediate-, high- and very high-risk groups, followed by the extremely high-risk group (63%) and the low-risk group (61%). A similar reduction was seen with early cardiac catheterization. These findings that the largest invasive treatment benefits are seen in patients at higher risk are consistent with results of observational studies that stratified patients into risk groups based on the GRACE risk score (68, 70, 90, 91). These results support the benefits of referring higher risk patients for cardiac catheterization, and help allay concerns about harms. Given that no overall improvement in one-year mortality was seen during the period from 2003 to 2013, it seems apparent that a risk-stratification based on a subjective physician decision making is not an ideal method of identifying higher risk patients who potentially benefit most from receiving cardiac catheterization. It is important to implement the use of risk scores to complement physicians' risk stratification decisions.

While it has been often suggested that increasing the number of catheterization labs is a strategy to overcome issues with access to cardiac catheterization, evidence suggests that it is important to first address treatment-risk mismatch issues. Otherwise, increasing the number of labs is likely to increase demand and sustain inequity in access to cardiac catheterization (123).

The strategy suggested by several observational studies is to incorporate risk scores into routine clinical practice, to assist physicians in their clinical decisions regarding management of NSTEASC patients. Ideally, programs incorporating appropriate algorithms could be run on a computer or

hand-held device. By simultaneously accounting for multiple clinical prognostic characteristics, the risk scores facilitate clinical judgment in predicting long-term outcomes and the patient groups who are most likely to benefit from a particular treatment.

System-level strategies could also support appropriate utilization of cardiac catheterization based on patient risk/need. For example, enhanced health service delivery management could involve development and implementation of evidence-based performance measures in daily treatment activities, regular data monitoring, and regular reporting to relevant stakeholders.

Strengths of this study include the size, unselected NSTEACS population enrolled in a population-wide registry, the long period of collected data to reveal changes in practice over time, and the fact that Nova Scotia is the only province with ACS provincial guidelines/treatment standards. These data represent virtually all of the identified first admission NSTEACS patients in Nova Scotia for the study period. Limitations of this study include both selection and information bias. This study's database did not include those NSTEACS patients who were not hospitalized, either because they were not recognized as requiring hospitalization, or because they died before they could be hospitalized. The study was restricted to the province of NS, potentially limiting generalizability to other areas. In terms of information or measurement bias, some types of information, such as history of conditions, were commonly coded as "negative" when they may have been "missing." The database did not contain information on biomarkers (e.g., cardiac enzymes) or ECG findings. In addition, while it was possible to determine a precise admission time, only the date (vs. the time) of the cardiac catheterization procedure was recorded in the database. Thus, the determination of "early" cardiac catheterization, meant to reflect that the procedure was carried out within 48 hours following admission, may actually be closer to within 72 hours in some cases. Finally, the one-year

mortality information did not include date/time of death. One-year mortality thus included in-hospital deaths – even those that occurred within the first 48-72 hours, before the patients could receive (and thus potentially benefit from) cardiac catheterization.

Implications for future practice and research

Analyzing possible barriers around the successful adoption of guidelines in Nova Scotia could contribute to improving quality of care and outcomes in NSTEACS patients. Despite a large clinical consensus (i.e. ACC/AHA guidelines) and observational studies reporting that the highest risk NSTEACS patients' receive the greatest survival benefit, lower risk patients in Nova Scotia were more likely to receive cardiac catheterization than their higher risk counterparts. Identifying barriers to implementing the NS guidelines, followed by the development of strategies to resolve those obstacles, have the potential to increase adherence to the guideline recommendations.

Subjective physician decision alone making does not appear to accurately identify higher risk patients. Since using the TIMI or GRACE risk score complements clinician judgment and leads to improving accuracy of risk stratification process, research on the best implementation strategies to ensure compliance and uptake of routine utilization of risk scores in clinical practice is needed. Clearly defining processes of care measures e.g., proportion of NSTEACS patients stratified by risk score (for treatment decision guiding purposes); proportion of high-risk patients receiving early procedure in the updated guidelines, monitoring them on a regular basis, and reporting results to all involved stakeholders may further improve risk-based delivery of cardiac catheterization among NSTEACS patients in Nova Scotia.

Chapter 7: Conclusions

The key findings in this retrospective observational study of the utilization and timing of cardiac catheterization for NSTEACS patients include:

(i) The rates of cardiac catheterization during the first hospitalization for a NSTEASC event, as well as early catheterization (within 24-48 hours of admissions) significantly increased over the period 2003-2013;

(ii) There was a significant increase between pre-guideline (2003-2008) and post-guideline (2009-2013) periods in rates of catheterization during hospitalization, but a slight decrease in the rates of early catheterization;

(iii) The rates of early cardiac catheterization were lower for patients initially admitted to a community hospital and transferred to the tertiary care center, compared to patients admitted directly to the tertiary care center;

(iv) Lower risk patients had greater odds of receiving cardiac catheterization and early cardiac catheterization, compared to their higher-risk counterparts, despite the higher risk of adverse outcomes after a NSTEASC event in the latter group. This pattern did not change between the pre- and post-guideline periods;

(v) Receipt of cardiac catheterization, especially early cardiac catheterization, was associated with significantly reduced odds of one-year mortality; and

(vi) After stratifying patients according to a previously developed NS risk score, there was a very large reduction in adjusted odds of one-year mortality with receipt of cardiac catheterization for the intermediate-, high- and very high-risk groups, and a moderately large reduction in adjusted odds of one-year mortality for the low-risk and extremely high-risk groups. A similar reduction but to a lesser degree was seen with early cardiac catheterization.

It appears that following implementation of the guidelines, there was an increase in the odds of cardiac catheterization for NSTEACS patients. While there was some improvement between the pre-and post-guideline periods in the proportion of intermediate- to high-risk patients receiving cardiac catheterization, this procedure was still more likely to be carried out on patients in the low-risk group. Throughout the study period, there was a reduction in the odds of one-year mortality among NSTEACS patients who received cardiac catheterization. This reduction in odds of one-year mortality was even greater for intermediate- to high-risk patients.

The implication is that, with improved targeting of intermediate- to very high-risk NSTEACS patients, there is potential for improved overall outcomes. These outcomes include substantially greater reduction in one-year mortality for the NSTEACS patient population in Nova Scotia.

Nova Scotia health providers are in a unique position to successfully implement the guideline recommendations for risk-based delivery of cardiac catheterization at the provincial level, given the small size of the province and limited number of health providers involved in NSTEACS care. It is time to identify potential issues and implementation barriers/facilitators regarding the

guideline risk-based recommendations, discuss and address concerns, and develop strategies to successfully implement the recommendations.

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