Identifying Predictors of Acute Myocardial Infarction Care Improvement by Inter-Jurisdictional Comparison of Outcome, Cost, and Resource Use

by

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ABSTRACT

Acute myocardial infarction (AMI) is a global health concern. Despite of a reduction in incidence and mortality in the last several decades, AMI is still the leading cause of mortality and morbidity in many parts of the world, especially high income countries including Canada. Because of continuing advancement in AMI care practice and change in patient risk profiles, continuing benchmark of AMI care practice, health outcomes as well as resource use and costs is needed to inform health policy and quality improvement initiatives.

We conducted four retrospective cohort studies using (1) the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) which contains acute care inpatient abstracts in all Canadian provinces except for Quebec between April 2004 and March 2014 and (2) the province of Alberta inpatient, outpatient, practitioner claims, pharmaceutical information network, population registry and vital statistic databases between April 2004 and March 2016. We examined temporal trends and provincial variations in the use of reperfusion strategies and associated in-hospital mortality, cardiac care quality indicators, resource use and health care costs of patients with AMI (International Classification of Diseases, 10th revision, codes I21 and I22). Canadian Classification of Health Interventions was used to identify relevant reperfusion and cardiac procedures, Alberta Interactive Health Data Application was used to provide dollar values for inpatient and outpatient services and Alberta Drug Benefit List was used to provide drug price.

Overall, there was a significant increase in the use of contemporary primary percutaneous coronary intervention (PCI) during the study period but there was generally no change in

health outcomes, except for a modest improvement in 30-day in-hospital mortality and 30-day readmission after coronary artery bypass grafting (CABG). The stable trend may reflect an avoided mortality and readmission when accounting for increased risk burden among patients with AMI over time. In addition, there were large variations in both the use of revascularization strategies and health outcomes across Canadian provinces. Patients with ST-segment elevation MI receiving fibrinolysis and followed by PCI in a systematic manner had the best outcomes compared with patients who underwent other alternative reperfusion strategies.

The health care costs for AMI are high. However, the annual costs for AMI decreased during the study period, possibly suggesting an efficiency improvement in AMI care. The combination of stable outcomes and decreased costs over time could indicate a success in AMI care in Canada. Resource use and costs in the long-term were modest compared with those during the first year after incident AMI. Hospitalization accounted for the largest share of total health care costs and the subgroup of non-ST-segment elevation MI patients appeared to be the biggest resource use and cost driver.

The large variation in care practice and outcomes across Canadian provinces could be a potential area for a pan-Canadian collaboration and coordination initiative to improve AMI care in Canada. In addition, a set of standard quality indicators specifically for AMI care should be developed. The methodology and findings in this thesis could be a starting point for a larger discussion on development of such a set of national quality indicators.

PREFACE

This thesis is an original work by Dat Tien Tran. This thesis received research ethics approval from the University of Alberta Research Ethics Board, No. Pro00066424, August 2, 2016.

Chapter 2 of this thesis has been published as “Tran DT, Welsh RC, Ohinmaa A, Thanh NX and Kaul P. Temporal Trends of Reperfusion Strategies and Hospital Mortality for Patients With STEMI in Percutaneous Coronary Intervention-Capable Hospitals. *Can J Cardiol.* 2017;33:485-492”. Chapter 3 of this thesis has been published as “Tran DT, Welsh RC, Ohinmaa A, Thanh NX, Bagai A, Kaul P. Quality of Acute Myocardial Infarction Care in Canada: A 10-Year Review of 30-Day In-Hospital Mortality and 30-Day Hospital Readmission. *Can J Cardiol.* 2017;33:1319-1326”. Chapter 4 of this thesis has been published as “Tran DT, Ohinmaa A, Thanh NX, Welsh RC, Kaul P. The Health Care Cost Burden of Acute Myocardial Infarction in Alberta, Canada. PharmacoEconomics – Open. 2017 (in press). DOI: 10.1007/s41669-017-0061-0”. I was responsible for data analyses and manuscript compositions. All other authors critically reviewed the manuscripts for intelectual contents and contributed to manuscript edits.

DEDICATION

For my wife, my parent and my amazing angels, Be and Nghe!

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AB	Alberta
ACS	Acute Coronary Syndrome
ADBL	Alberta Drug Benefit List
AMI	Acute Myocardial Infarction
ATC	Anatomical Therapeutic Chemical
BC	British Columbia
CABG	Coronary Artery Bypass Grafting
CACS	Comprehensive Ambulatory Classification System
CAN	Canada
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
CVD	Cardiovascular Disease
CMG	Case Mix Group
DAD	Discharge Abstract Database
FY	Fiscal Year
GLM	Generalized Linear Model
ICD	International Classification of Disease
IQR	Interquartile Range
LOS	Length of Stay
MB	Manitoba
NB	New Brunswick
NL	Newfoundland and Labrador
NS	Nova Scotia
NSTEMI	Non-ST-segment Elevation Myocardial Infarction
OECD	Organisation for Economic Co-operation and Development
ON	Ontario
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
SD	Standard Deviation
SK	Saskatchewan
STEMI	ST-segment Elevation Myocardial Infarction
UA	Unstable Angina

Chapter 1 : INTRODUCTION

1.1. Definition of Acute Myocardial Infarction

Acute myocardial infarction (AMI) or heart attack is a medically severe condition caused by a blockage of coronary arteries which supply blood for the heart muscle (myocardium) (Figure 1.1). As a consequence, heart myocardium deteriorates. The deterioration is not recoverable. Therefore, patients with AMI can die if blood flow is not restored in a timely manner.[1]

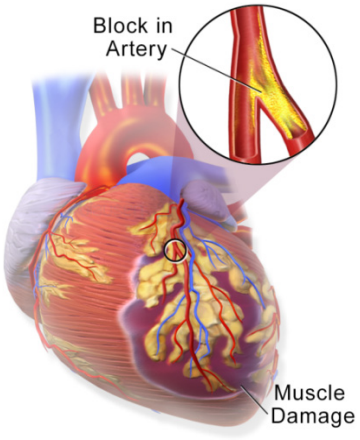

Figure 1-1: Heart Attack (from medicalexpress.com)

AMI belongs to the acute coronary syndromes (ACS) family, which describes a spectrum of atherothrombosis including unstable angina (UA), non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).[2] Most ACS with ST-segment elevation will lead to AMI with Q wave. ACS without ST-segment elevation will likely lead to AMI without Q wave or unstable angina.[3] In the International Classification of Diseases (ICD) 9th revision (ICD-9), AMI includes only one code of 410.[4] However, the next revision (ICD-10) includes more codes to better describe the condition. They are I21.0-I21.3 for STEMI; I21.4 for NSTEMI; I21.9 for undefined MI; and I22 for recurrent MI.[5]

The clinical definition of AMI has evolved over the last decades thanks to technology advancement that allows more tissue-specific biomarkers or more sensitive imaging techniques. The latest (2012) update of universal definition of AMI identifies five conditions

where a patient is diagnosed with AMI if any of the following five conditions is met.[6] They are detection of change in cardiac biomarker (Troponin), cardiac death with symptoms of myocardial ischemia, percutaneous coronary intervention (PCI) related MI, stent thrombosis associated MI, and coronary artery bypass grafting (CABG) related MI. Among them, detection of a rise and a fall of Troponin is an important indicator to diagnose acute MI. However, it is worthwhile to note that increase of Troponin biomarker's sensitivity may lead to decrease of its specificity. Therefore, electrocardiogram (ECG) should also remain a key diagnosis for AMI and should be frequently repeated if possible.[7]

1.2. Risk factor

Risk factors of AMI can include having an elevated amount of lipids in the blood, smoking, hypertension, diabetes, age, family history, male gender,[8, 9] obesity, metabolic syndrome, and chronic kidney disease.[8] Additional triggers include excessive alcohol intake, excessive physical activity, psychosocial conditions, bacteremia, nonsteroidal anti-inflammatory drug use, and use of illicit drugs, such as cocaine and amphetamines.[10-12]

1.3. Treatment and care for patients with AMI

Treatment for patients with AMI is complex and varied by MI subtype, comorbidity, and availability of health technologies. Revascularization is acknowledged as a key factor in the care for patient with AMI and should be provided as soon as possible to recover jeopardized myocardium.[13, 14]

The diagnosis and treatment of AMI has been improved significantly in the past several decades.[7] Contemporary primary PCI is a preferred mode of reperfusion for STEMI patients if there is an experienced team to perform the intervention in a timely manner. Both American and European guidelines recommend first medical contact (FMC) to device time within 90 minutes for STEMI patients at PCI-capable hospitals.[13-15] Thrombolytic therapy or fibrinolysis followed by PCI has been an alternative reperfusion strategy for STEMI patients if primary PCI cannot be provided in a timely manner, i.e., expected FMC to PCI time at a PCI-capable hospital is greater than 90 minutes. Clinical trials have shown that a pharmacoinvasive strategy, which includes either urgent catheterization and PCI following failed lysis (rescue PCI) or scheduled catheterization and PCI following successful lysis reperfusion in 24- 48 hours, has similar results to contemporary primary PCI; it is therefore recommended for patients with STEMI who could not undergo primary PCI within 90 minutes of presentation.[16-20] The European Society of Cardiology (ESC) also recommends early angiography and revascularization for high risk non-ST-segment elevation MI patients.[21] CABG can be indicated for AMI patients who are not eligible for PCI because of the coronary anatomy or those with selected clinical characteristics such as coexisting valvular heart disease or diabetes mellitus.[13, 14] The rate of revascularization among AMI patients has increased significantly over time.[22]

Post-hospitalization exercise-based cardiac rehabilitation has shown effective for patients with AMI and has been recommended by both American and European guidelines. The ESC also recommends additional specific lifestyle interventions and risk factor control after

hospitalization such as smoking cessation, physical activity, diet, weight, blood pressure and stress control.[13, 14]

1.4. Health and economic burdens of AMI

Globally, AMI accounts for half of 17 million annual deaths from cardiovascular diseases (CVD).[23] AMI is the leading cause of death and disability in many parts of the world.[24] The 30-day in-hospital mortality varies from 4% in Denmark to 22% in Mexico.[25] Thanks to the advancement in diagnosis and management of AMI in the last several decades,[7] patient outcomes have improved significantly. For example, 30-day in-hospital mortality in all Organisation for Economic Co-operation and Development countries has reduced from 8.1% in 2000 to 5.2% and 4.3% in 2005 and 2009, respectively.[25] Similarly, there has been a 24% relative decrease in sex- and age- adjusted incidence from 2000 to 2008 in California.[22] In Canada, even though there has been a reduction by 38% of sex- and age-standardized mortality between 1994 and 2004, AMI alone is still responsible for 84,000 hospitalizations and 18,000 deaths annually.[8, 26]

Although AMI has been an important condition of interest in determining overall population health[27], few evaluations of its economic burden exist. From the broadest and most preferable societal perspective[28], Heidenreich *et al.* estimated that total costs of CVD in the United States would triple from US $445 billion in 2010 to US $1,094 billion in 2030.[29] However, there was no separate estimate for AMI provided. Similarly, CVD is estimated to cost the Europeans €170 billion annually and there was also no estimate for AMI.[30] Recently, Seo *et al.* estimated that the total costs of AMI in South Korea in a single year of 2012 was US $1.2

billion.[31] From a narrower health care payer perspective, Soekhlal *et al.* reported average treatment costs of € 5,021 for an AMI patient in acute phase in the Netherlands.[32] Mantovani *et al.* reported a higher one-year health care costs of € 9,135 per patient after the first AMI event in Italy.[33] In a comparison of hospital costs for AMI, Tiemann *et al.* reported a significant variation of cost per case from € 396 in Hungary to € 5,916 in France.[34]

In Canada, it is estimated that CVD cost about $22 billion a year, in which ischemic heart diseases (including AMI) account for more than $8 billion. CVD is considered the second leading economic burden on the health care budget in Canada.[8] Currently, there is also a lack of up-to-date data on the cost burden of AMI for the nation.

1.5. Study objective and structure

The overall purpose of this thesis was to evaluate AMI care in Canada by inter-provincial comparison of health outcomes, resource use and costs to identify potential gaps for quality improvement. The findings of this thesis could be informative to health policies in AMI care, so patients with AMI could receive better care and associated health outcomes. Specifically, this thesis consisted of 4 studies (corresponding to chapters 2-5) looking at both health outcomes and cost burden of AMI.

The objective of the first study (chapter 2) was to examine temporal trends and provincial variations in the use of and outcomes associated with alternative reperfusion strategies among patients with STEMI presenting directly to PCI-capable hospital in Canada from 2009-2013. The second study (chapter 3) aimed to evaluate quality of AMI care in Canada by reviewing long-term trends and provincial variations in four PCI- and CABG- related cardiac

care quality indicators among patients with AMI in Canada from 2004-2013. The third (chapter 4) and the fourth (chapter 5) studies sought to benchmark resource use and cost burden of AMI in the province of Alberta, Canada. While the third study used the prevalence-based approach to calculate total annual health care costs (hereafter defined as summation of ambulatory care, hospitalization, practitioner claims and drug costs) for AMI, the fourth study used the incidence-based approach to calculate annual AMI related resource use and health care costs per patient from incident AMI between 2004-2013.

In chapters 2 & 3, the Canadian Institute for Health Information Discharge Abstract Database (DAD) which contains acute care hospitalization abstracts in all Canadian provinces except for Quebec was used. The DAD provides a broad range of information during a hospital stay including patient demographics, diagnoses, interventional procedures, and discharge disposition and uses an anonymous patient unique identifier to link multiple hospitalization records.[35] Chapters 4 & 5 used the province of Alberta administrative datasets including ambulatory care, hospital, practitioner claims, pharmaceutical information network, population registry and vital statistics databases.[36] Similar to the DAD, an anonymous patient unique identifier is used to link patient records both within and between Albertan administrative datasets. Canadian Classification of Health Interventions was used to identify interventional procedure, Alberta Interactive Health Data Application was used to provide inpatient and outpatient costs, and Alberta Drug Benefit List was used to provide drug price.[37-39]

In the last chapter (chapter 6), main results and key findings of the four studies were summarized and discussed. Strength and limitation of the thesis were also acknowledged.

Finally, a number of conclusions were drawn and potential topics for future investigation were presented.

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Chapter 2 : TEMPORAL TRENDS OF REPERFUSION STRATEGIES AND HOSPITAL MORTALITY FOR PATIENTS WITH STEMI IN PERCUTANEOUS CORONARY INTERVENTION-CAPABLE HOSPITALS IN CANADA

This chapter is based on the published article "Tran DT, Welsh RC, Ohinmaa A, Thanh NX and Kaul P. Temporal Trends of Reperfusion Strategies and Hospital Mortality for Patients With STEMI in Percutaneous Coronary Intervention-Capable Hospitals. *Can J Cardiol*. 2017;33:485-492"

2.1. Introduction

ST-segment elevation myocardial infarction (STEMI) requires expedited diagnosis and intervention. Despite a gradual decline in incidence over the past few decades[22], STEMI remains a global health concern. Primary percutaneous coronary intervention (pPCI) is a preferred mode of reperfusion for patients with STEMI if there is an experienced team to perform the intervention in a timely manner. Both American and European guidelines recommend first medical contact (FMC) to device time within 90 minutes for patients with STEMI at PCI-capable hospitals.[13-15]

Thrombolytic therapy or fibrinolysis (lysis) followed by PCI has been an alternative reperfusion strategy if pPCI cannot be provided in a timely manner, i.e., the expected FMC to PCI time is > 90 minutes. Clinical trials have shown that a pharmacoinvasive strategy, which includes either urgent catheterization and PCI after failed lysis (rescue PCI) or scheduled catheterization and PCI after successful lysis reperfusion in 24- 48 hours, has results similar

to those of contemporary pPCI.[16-19] Little is currently known about variations in practice and outcomes associated with different STEMI reperfusion strategies from a "real-world" perspective in Canada. Accordingly, we examined temporal trends and provincial variations in the use of and outcomes associated with alternative reperfusion strategies among patients with STEMI presenting directly to PCI-capable hospitals in Canada.

2.2. Methods

Study population

Data: We conducted a retrospective cohort study using the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) from April 2009 to March 2014 (fiscal years [FY] 2009-2013) to identify acute care hospitalizations with a primary diagnosis of STEMI (International Classification of Diseases, 10th revision, codes I21.0-I21.3). The CIHI DAD contains hospitalization data from all Canadian provinces except Quebec.[35] The CIHI DAD contains patient demographics, diagnoses, interventions (including type of intervention and timestamp), discharge disposition, and anonymously identified facility where patients receive services. It also uses unique anonymous patient identification number to link multiple hospitalizations of the same patient. FY 2009 was selected to coincide with the introduction of a Canadian Classification of Health Interventions (CCI) code for lysis.

Patient population: Patients were included in the study if they were 20 years of age or older and were admitted directly to a PCI-capable hospital. The unit of analysis was the STEMI episode. Therefore, if a patient had more than one STEMI during the study period, he/she was included multiple times. Consecutive hospitalizations within 24 hours of discharge from

the first or index STEMI hospitalization were considered as the same episode. Patients hospitalized with acute MI (all codes above plus I21.4 for non-ST segment elevation MI, I21.9 for undefined MI, and I22 for recurrent acute MI as the primary diagnosis) during the year before the index STEMI hospitalization were excluded to ensure that only new episodes were included in the analyses. STEMI episodes with (1) missing admission or PCI time stamps, (2) an extremely long lengths of stay (LOS) (> 90 days for index hospitalization or LOS > 365 days for entire episode), or (3) transfers between provinces were excluded.

Reperfusion strategy and in-hospital mortality

We used the CCI[37] to identify PCI (codes 1.IJ.50** and 1.IJ.57.GQ**) and lysis therapy (code 1.ZZ.35.HA-1C) in any of 20 intervention fields. Patients were categorized into the following mutually exclusive groups based on the primary treatment strategy they received: lysis, pPCI, or no reperfusion therapy. The lysis group was further categorized as (1) lysis only vs lysis plus PCI, when (2) PCI was performed ≤ 90 minutes after hospital arrival or (3) PCI was performed > 90 minutes after hospital arrival. The pPCI group was further categorized as (1) pPCI ≤ 90 minutes after hospital arrival or (2) pPCI > 90 minutes after hospital arrival. We defined all-cause, in-hospital mortality as death recorded in the hospital discharge abstracts within the index STEMI episode.

Statistical analysis

We summarized patient characteristics using means (± standard deviation), medians (interquartile ranges), counts and percentages, as appropriate. We used previously validated ICD codes to identify patient comorbidities (list of codes provided in Supplemental Table

S2.1).[40] Comorbidities were considered to be present if they were recorded in any hospitalization during the index STEMI episode or in any hospitalization in the year before the STEMI admission.

We used logistic regression to examine the univariate and multivariable association between reperfusion strategy and in-hospital mortality. Patient-level variables included in the multivariable model were patient age, sex, comorbidity, number of days in hospital during the year before the STEMI admission, admission during working hours (Monday-Friday, 7 AM to 6 PM), type of presentation (by ambulance or self-presentation), and median household income at the residential neighborhood (forward sortation area level). The latter was based on the 2006 Canadian census and was included as a categorical variable based on income quartiles (≤ CAD$47,616; $47,617 – $55,601; $55,602- $69,622; and ≥$69,623).[41] In addition to patient level variables, we included province, annual provincial health spending per capita[42], and FY. Reperfusion strategy was included as a categorical variable with pPCI ≤ 90 minutes as the reference category. Except for primary variables of interest (i.e., age, sex, province, FY, and reperfusion strategy), a variable remained in the final multivariate model if the likelihood ratio test was significant at a 5% level. There were very few patients aged 20-39 years; therefore, they were excluded from the multivariable mortality analysis.

All analyses were performed using Stata, version 14 (Stata Corp LC, College Station, TX); Two-sided *P* values < 0.05 were considered statistically significant.

2.3. Results

Between FY 2009 and FY 2013, there were 73,210 STEMI episodes of 71,651 patients in all Canadian provinces except Quebec (Figure 2.1). Of these episodes, 4,751 were in patients who had an AMI hospitalization in the year before the index STEMI hospitalization were excluded. In the remaining 68,459 STEMI episodes, 22,657 (33%) did not start at a PCI-capable hospital. After excluding LOS outliers, interprovincial transfers, and episodes with missing time data, the final study population included 44,650 STEMI episodes in 44,373 unique patients from the provinces of Alberta (AB), British Columbia (BC), New Brunswick (NB), Newfoundland and Labrador (NL), Nova Scotia (NS), Manitoba (MB), Ontario (ON), and Saskatchewan (SK). All patients (386 episodes in 382 patients) from Prince Edward Island were excluded as there were no PCI-capable hospitals in the province during the study period.

Reperfusion strategy

We identified 33 PCI-capable hospitals (Table 2.1). ON had the highest number of PCI-capable hospitals (18) and accounted for the largest proportion of STEMI episodes (56.3%). Overall, a majority of the patients received pPCI with the highest rates in BC (81.4%) and lowest rates in NB (30.2%). The provinces of AB, MB, NL, and NS had higher proportions of patients receiving no reperfusion than the Canadian average (14.8%). Specifically, NB had the fewest (5.3%) patients receiving no reperfusion, whereas MB had the most patients (49.8%). The proportion of patients receiving no reperfusion therapy was even higher (>40%) among patients presenting to non-PCI capable hospitals (Supplemental Table S2.2). Rates

of lysis in these patients ranged from 20.1% in MB to 59.7% in NS. The overall rate of pPCI was 28% and ranged from 15.1% in NS to 44.6% in BC.

Among patients presenting to PCI-capable hospitals, there was significant variation in the rate of pPCI over time across provinces (Figure 2.2), with increases observed in ON, SK, NL, and MB and decreases in AB, BC, NB, and NS. Overall, the proportion of patients receiving pPCI increased from 61.8% in FY 2009 to 68.9% in FY 2013 (7.8% relative annual increase, $p<0.001$), primarily as a result of increasing rates of pPCI ≤ 90 minutes (Figure 2.33). Correspondingly, the proportion of patients who did not receive reperfusion decreased from 17.2% in FY 2009 to 13.5% in FY 2013 ($p<0.001$). Median admission-to-PCI time was 14.3 hours (inter-quartile range [IQR]: 4.2-37.7 hours) for patients in the pPCI > 90 minutes group and 12.4 hours (IQR: 3.7-24.9 hours) for patients who received lysis + PCI > 90 minutes.

There were significant differences in baseline characteristics of patients receiving alternate reperfusion strategies (Table 2.2). Females were more likely to either receive lysis alone (30.5%) or to receive no reperfusion (35.6%). Patients receiving lysis and PCI ≤ 90 minutes were younger (median age, 59 years), whereas those receiving no reperfusion were oldest (median age, 66 years). Diabetes (22.1%) and heart failure (10.8%) were the most common comorbidities in this patient population, with highest rates observed in patients receiving no reperfusion. Overall, 76.2% of patients arrived by ambulance and this proportion was higher among patients who received lysis. The median LOS for patients who received pPCI in ≤ 90 minutes was 1 day less than for patients in the other reperfusion groups.

In-hospital mortality

Overall, 6.8% of patients died during the index episode. Unadjusted mortality was highest in patients receiving no reperfusion (16.3%) compared with those receiving pPCI (5.3%) and those receiving lysis (4.4%, p<0.001) (Table 2.3). Among treated patients, patients receiving lysis alone had the highest death rate (10.6%), followed by patients receiving pPCI ≤ 90 minutes (5.5%), patients receiving lysis + PCI ≤ 90 minutes (4.6%), patients receiving pPCI > 90 minutes (4.2%), and patients receiving lysis + PCI > 90 minutes (1.9%). Early hazard- i.e., death within the first day- was higher in patients who received no reperfusion (4.2%) or received lysis only (4.1%) (Table 2.2). In patients receiving lysis alone, the mortality rate was significantly higher in those who did not undergo catheterization (22.6%) than in those who underwent catheterization (4.8%) (p<0.001).

Overall unadjusted in-hospital mortality varied substantially across provinces, and was lowest in NB (4.6%) and highest in BC (8.9%) and NF (8.9%) (Table 2.3). Mortality rates for patients receiving pPCI were similar across provinces and there was no correlation between pPCI rate and in-hospital mortality rate (Pearson's correlation coefficient, 0.28; p=0.49). The highest degree of variability in mortality rates was found in patients who did not receive any reperfusion therapy and ranged from a low of 9.4% in AB to a high of 28.9% in BC. For comparison purposes, in-hospital mortality rates by province (overall and by treatment strategy) among patients presenting to non-PCI capable hospitals are provided in Supplemental Table S2.2.

After risk adjustment, there was no difference in in-hospital mortality over time (odds ratio [OR], 1.03; 95% confidence interval [CI], 0.99-1.06; p=0.091) (Table 2.4). Compared with patients who received pPCI ≤ 90 minutes, patients receiving lysis and routine PCI > 90 minutes had the best mortality outcome (OR, 0.42; 95% CI, 0.32, 0.55; p<0.001). Other patient factors associated with a higher likelihood of in-hospital mortality were female sex, older age, shock (both before and after hospitalization), and arrival by ambulance. Patients admitted during working hours had better outcomes than did those who were not (OR, 0.85; 95% CI, 0.77, 0.92; p<0.001). Inter-provincial differences in in-hospital mortality remained. NS was the only province that did not differ from AB during the study period (Table 2.4).

2.4. Discussion

We examined 44,650 STEMI episodes for 44,373 patients with STEMI presenting directly to PCI-capable hospitals in all Canadian provinces (except Quebec). Between FY 2009 and FY 2013, the proportion of patients receiving pPCI increased significantly, especially those receiving it within 90 minutes of hospital arrival. There was significant variation in the use of pPCI across provinces; highest rates were observed in BC and the lowest rates in NB. We observed no change in overall mortality outcomes over the period of the study.

Patients who did not receive any reperfusion therapy had the highest in-hospital mortality rate, followed by patients who received only lysis. However, these rates may be confounded by early hazard, with patients in these groups not surviving long enough to receive PCI. We observed the lowest mortality rate among patients who received lysis followed by PCI > 90 minutes. The findings of our large-scale, population-based study of real-world clinical practice

are consistent with those observed in the Strategic Reperfusion Early after Myocardial Infarction (STREAM) randomized clinical trial.[16] Patients in the STREAM trial who had a scheduled angiogram after lysis had the lowest 30-day mortality rate (2.1%) compared with patients who had lysis and rescue PCI (6.1%), and those who had pPCI (3.9%).[43] We believe that in our study, patients who received lysis + PCI > 90 minutes most closely approximate the patients who received lysis and scheduled angiography and PCI in the STREAM study. Although it must be noted that the trial included only patients presenting within 3 hours of symptom onset who could not undergo pPCI within 60 minutes of first medical contact.

Despite significant advances in the management of STEMI,[7] we found no temporal change in in-hospital mortality during the study period. These findings are similar to those reported previously. Yeh *et al.* [22] found a significant increase in PCI rates, but no change in mortality trends between 1999 and 2008 in the United States. Similarly, Fordyce *et al.*[44] reported no change in mortality despite an increase in pPCI between 2007 and 2015 in the Vancouver Coastal Health Authority hospitals. Mortality rates in our study were lower than those reported for Canadian provinces previously.[45] However, this might result from the fact that we restricted our analysis to patients with STEMI presenting only to PCI-capable hospitals. Consistent with previous studies, we found female sex, increasing age, ambulance use, and cardiogenic shock to be associated with higher mortality risk in this patient population.[45-50]

Although our study provides novel data on the use of and outcomes associated with alternative reperfusion strategies in Canada, it has certain limitations. First, we did not have access to data from Quebec, because the province submits hospitalization data in a format separate from the other provinces. Second, our examination was restricted to information

available during the hospitalization; therefore, we could not account for prehospital data, such as time from symptom onset to FMC. Third, we could not account for diagnostic misclassification (regarding STEMI and non-STEMI) or control for differences in provincial prehospital strategy regarding diagnosis, triage and treatment of STEMI patients, which is known to vary greatly across Canadian provinces.[51] The extent to which these factors may explain some of the observed variability (e.g., the low rate of reperfusion in MB) requires further examination. Fourth, we categorized patients according to the treatment they received and not the treatment that was planned. Therefore, some of the patients who were in the no-reperfusion group or in the lysis-only group may have been destined to receive PCI but did not survive long enough to do so. Finally, although Canadian administrative data have been shown to be valid relative to chart abstraction, these data may be affected by data entry errors, omissions, and inconsistencies.[52, 53]

2.5. Conclusion

The use of primary PCI in STEMI has increased significantly in Canada; however, significant interprovincial variation remains. Among patients with STEMI presenting directly at PCI-capable hospitals, changes in reperfusion strategies do not appear to have had an impact on in-hospital mortality rates. There was no correlation between rate of primary PCI and in-hospital mortality at the province level. Patients who underwent lysis followed by PCI in a systematic fashion had the lowest mortality compared with patients who received other reperfusion strategies.

2.6. References

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2.7. Tables

Table 2-1: Provincial distribution of study population

Variable N (%)	CAN	AB	BC	MB	NB	NL	NS	ON	SK
N PCI-capable hospitals	33	3	5	1	1	2	1	18	2
Episodes	44,650	6,798	4,990	1,555	1,647	687	1,368	25,158	2,447
Patients	44,373	6,754	4,971	1,546	1,640	679	1,358	25,004	2,421
Reperfusion strategy									
Lysis	8,431 (18.9)	1,814 (26.7)	399 (8)	232 14.9)	1,062 (64.5)	263 (38.3)	254 (18.6)	3,848 (15.3)	559 (22.8)
Lysis + PCI ≤ 90m	*3,177 (37.7)*	*494 (27.2)*	*161 (40.4)*	*52 (22.4)*	*355 (33.4)*	*44 (16.7)*	*86 (33.9)*	*1,686 (43.8)*	*299 (53.5)*
Lysis + PCI > 90m	*3,757 (44.6)*	*933 (51.4)*	*154 (38.6)*	*90 (38.8)*	*606 (57.1)*	*148 (56.3)*	*115 (45.3)*	*1,519 (39.5)*	*192 (34.3)*
Lysis only	*1,497 (17.8)*	*387 (21.3)*	*84 (21.1)*	*90 (38.8)*	*101 (9.5)*	*71 (27)*	*53 (20.9)*	*643 (16.7)*	*68 (12.2)*
Primary PCI	29,596 (66.3)	3,267 (48.1)	4,061 (81.4)	548 (35.2)	497 (30.2)	259 (37.7)	797 (58.3)	18,550 (73.7)	1,617 (66.1)
Primary PCI ≤ 90m	*24,429 (82.5)*	*2,257 (69.1)*	*3,426 (84.4)*	*281 (51.3)*	*307 (61.8)*	*116 (44.8)*	*568 (71.3)*	*16,201 (87.3)*	*1,273 (78.7)*
Primary PCI > 90m	*5,167 (17.5)*	*1,010 (30.9)*	*635 (15.6)*	*267 (48.7)*	*190 (38.2)*	*143 (55.2)*	*229 (28.7)*	*2,349 (12.7)*	*344 (21.3)*
No reperfusion	6,623 (14.8)	1,717 (25.3)	530 (10.6)	775 (49.8)	88 (5.3)	165 (24.0)	317 (23.2)	2,760 (11.0)	271 (11.1)

CAN: Canada; AB: Alberta; BC: British Columbia; MB: Manitoba; NB: New Brunswick; NL: Newfoundland and Labrador; NS: Nova Scotia; ON: Ontario; SK: Saskatchewan; PCI: percutaneous coronary intervention

Table 2-2: Characteristics and hospital outcomes of studied population

Variable	All	Fibrinolysis			Primary PCI		No reperfusion
		PCI ≤90m	PCI >90m	Lysis only	PCI ≤90m	PCI >90m	
Episode (N)	44,650	3,177	3,757	1,497	24,429	5,167	6,623
Females (%)	26.6	20.7	24.2	30.5	25	26.5	35.6
Age (mean/SD)	62.7 (13.1)	59.5 (11.5)	60.9 (11.6)	62 (13.7)	62.4 (12.9)	62.3 (12.7)	66.7 (14.9)
Age (median/IQR)	61 (53-72)	59 (51-67)	60 (52-69)	61 (52-71)	61 (53-71)	61 (53-71)	66 (56-79)
Age group (%)							
20-39 years	2.5	2.7	2.1	4.5	2.3	2.4	2.9
40-59 years	41.6	49.6	45.9	41.1	42.7	42.2	31.1
60-69 years	26.2	28.1	28.5	25.5	26.4	26.9	23.1
70-79 years	17	14	16.4	15.7	16.7	17.7	19.5
>=80 years	12.7	5.5	7	13.2	11.9	10.9	23.4
Household income ($, %)							
Missing	1.1	1.0	1.3	1.2	1.0	1.1	1.0
0-40,000	8.4	10.7	12.1	10.9	6.3	10.9	10.4
40,000-60,000	52.7	62.7	63.8	62.4	49.3	54.4	51.0
60,000-80,000	25.2	18.3	17.5	19.6	27.6	23.9	26.0
>80,000	12.6	7.2	5.4	5.9	15.8	9.8	11.6
Had catheterization during index episode (%)	88.8	98.5	99	67.5	98.6	98.6	39.5
Had coronary artery bypass grafting during index episode (%)	1.9	0.4	0.2	9.5	0.9	0.6	6.2
Selected comorbidities (%)							
Cancer	1.8	1.4	1	2.3	1.4	1.7	3.5
Cerebrovascular disease	1.9	1.4	1.2	3.9	1.5	1.9	3.6
Chronic pulmonary disease	3.8	3.7	3.6	5.4	2.9	4.5	6.0
Dementia	1.3	0.2	0.4	1.5	1	0.7	3.8
Diabetes	22.1	18.9	19.2	23.4	21.7	24.2	24.8
Heart failure	10.8	9.7	7.1	14.6	9.2	11.7	17.7
Peripheral vascular disease	2.1	1.5	1.5	2.4	1.8	2.1	3.3
Renal disease	2.3	1.1	1.5	3.1	1.8	2.8	4.3
Shock- preadmission	4.5	4.8	2	3.7	4.5	3.8	6.4
Shock- postadmission	1.3	1.4	0.7	1.4	1.3	1.5	1.5
Admit-in-work-hour (%)	42.4	42.5	28.7	36.7	45.2	36	46.1
Admit by ambulance (%)	76.2	93	90.7	86.3	74.5	70.5	68.9
Acute LOS (mean/SD)	5.5 (7.1)	5.1 (5.7)	4.7 (4.2)	6.7 (7.2)	5.1 (6.8)	6.0 (7.7)	6.8 (9.4)
Acute LOS (median/IQR)	4 (3-6)	4 (3-5)	4 (3-5)	4 (3-8)	3 (3-5)	4 (3-6)	4 (3-8)
In-hospital mortality (%)	6.8	4.6	1.9	10.6	5.5	4.2	16.3
In-hospital mortality within 1 day of admission (%)	1.7	1.2	0.4	4.1	1.4	0.4	4.2

Table 2-3: Unadjusted in-hospital mortality rate, overall and by reperfusion strategy

Variable	CAN	AB	BC	MB	NB	NL	NS	ON	SK
Episodes, N	44,650	6,798	4,990	1,555	1,647	687	1,368	25,158	2,447
Mortality (%)	6.8	5.7	8.9	7.9	4.6	8.9	5.7	6.7	7.2
Reperfusion strategy									
Lysis, n	8,431	1,814	399	232	1,062	263	254	3,848	559
Mortality (%)	4.4	3.3	9.0	6.0	3.1	6.5	5.1	4.7	3.4
Primary PCI, n	29,596	3,267	4,061	548	497	259	797	18,550	1,617
Mortality (%)	5.3	5.2	6.3	5.3	5.0	4.6	4.0	5.1	5.9
No reperfusion, n	6,623	1,717	530	775	88	165	317	2,760	271
Mortality (%)	16.3	9.4	28.9	10.3	20.5	19.4	10.4	19.6	22.5

CAN: Canada; AB: Alberta; BC: British Columbia; MB: Manitoba; NB: New Brunswick; NL: Newfoundland and Labrador; NS: Nova Scotia; ON: Ontario; SK: Saskatchewan; PCI: percutaneous coronary intervention

Table 2-4: In-hospital mortality during index STEMI episodes in Canada, 2009-2013

Variable	In-hospital mortality (%)	Univariate model		Multivariate model	
		OR (95% CI)	p	95% CI	p
Province					
Alberta	5.7	1.0		1.0	
British Columbia	8.9	1.60 (1.39- 1.84)	<0.001	1.49 (1.26-1.76)	<0.001
Manitoba	7.9	1.41 (1.14- 1.75)	0.001	0.74 (0.58-0.96)	0.024
New Brunswick	4.6	0.80 (0.62- 1.03)	0.080	1.38 (1.03-1.85)	0.032
Newfoundland and Labrador	8.9	1.60 (1.21- 2.13)	0.001	1.93 (1.39-2.68)	<0.001
Nova Scotia	5.7	0.99 (0.77- 1.27)	0.938	1.07 (0.80-1.43)	0.659
Ontario	6.7	1.17 (1.04- 1.31)	0.007	1.33 (1.16-1.52)	<0.001
Saskatchewan	7.2	1.27 (1.05- 1.53)	0.012	1.40 (1.12-1.74)	0.003
Sex					
Female	10.6	1.0		1.0	
Male	5.4	0.49 (0.45- 0.53)	<0.001	0.82 (0.75-0.91)	<0.001
Age group					
40-59 years	2.6	1.0		1.0	
60-69 years	4.9	1.92 (1.70- 2.17)	<0.001	1.57 (1.37- 1.80)	<0.001
70-79 years	10.4	4.33 (3.86- 4.87)	<0.001	3.12 (2.74- 3.57)	<0.001
>=80 years	20.4	9.54 (8.54- 10.66)	<0.001	6.37 (5.59- 7.27)	<0.001
Fiscal year		1.01 (0.98- 1.04)	0.483	1.03 (0.99- 1.06)	0.091
Reperfusion					
Primary PCI ≤ 90m	5.5	1.0		1.0	
Primary PCI > 90m	4.2	0.76 (0.66-0.88)	<0.001	0.76 (0.64-0.90)	0.001
Lysis & PCI ≤ 90m	4.6	0.82 (0.69-0.98)	0.030	0.92 (0.75-1.13)	0.440
Lysis & PCI > 90m	1.9	0.32 (0.25-0.41)	<0.001	0.42 (0.32-0.55)	<0.001
Lysis only	10.6	2.08 (1.74-2.47)	<0.001	2.51 (2.04-3.08)	<0.001
No reperfusion	16.3	3.38 (3.10-3.68)	<0.001	3.35 (3.01-3.73)	<0.001
Comorbidity					
Cancer	20.3	3.61 (3.02- 4.32)	<0.001	2.21 (1.78- 2.74)	<0.001
Cerebrovascular disease	27.2	5.46 (4.67- 6.38)	<0.001	2.97 (2.46- 3.58)	<0.001
Diabetes	9.6	1.65 (1.52- 1.79)	<0.001	1.25 (1.14- 1.38)	<0.001
Liver disease	27.3	5.13 (3.82-6.91)	<0.001	2.88 (1.93-4.31)	<0.001
Peripheral vascular disease	16.1	2.70 (2.25- 3.24)	<0.001	1.36 (1.08- 1.71)	0.008
Renal disease	20.9	3.79 (3.24- 4.43)	<0.001	1.42 (1.16- 1.73)	0.001
Shock- Pre-admission	46.1	16.51 (14.96- 18.22)	<0.001	18.67 (16.64- 20.94)	<0.001
Shock- Post-admission	58.5	21.63 (18.26- 25.62)	<0.001	28.53 (23.47- 34.69)	<0.001
LOS during previous year		1.04 (1.03- 1.04)	<0.001	1.01 (1.01- 1.01)	<0.001
Admit-in-work-hour	6.4	0.90 (0.83- 0.97)	0.006	0.85 (0.77- 0.92)	<0.001
Admit by ambulance	7.4	1.62 (1.46- 1.78)	<0.001	1.57 (1.39- 1.76)	<0.001

Supplemental Table S2-1: Comorbidity code

Comorbidities	ICD-10 code
Heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x–I69.x
Dementia	F00.x–F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Rheumatic disease	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	K25.x–K28.x
Liver disease	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Diabetes	E10.x-E14.x
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
Renal disease	I12.0, I13.1, N03.2–N03.7, N05.2– N05.7, N18.x, N19.x, N25.0, Z49.0– Z49.2, Z94.0, Z99.2
Cancer	C00.x–C26.x, C30.x–C34.x, C37.x– C41.x, C43.x, C45.x–C58.x, C60.x–C85.x, C88.x, C90.x–C97.x, D00.x-D09.x
Shock	R57.x

Supplemental Table S2-2: Reperfusion and in-hospital mortality among STEMI patients who did not admit directly to PCI-capable hospitals in Canada (except Quebec), 2009- 2013

Variable	CAN	AB	BC	MB	NB	NL	NS	ON	PEI	SK
Episodes, N	22,622	2,561	5,578	2,230	1,352	701	1,978	7,314	386	522
Mortality (%)	*8.9*	*6.3*	*8.0*	*7.6*	*9.5*	*8.3*	*6.5*	*11.5*	*6.0*	*12.6*
Patients, N	22,519	2,553	5,550	2,215	1,350	696	1,962	7,291	382	520
Reperfusion strategy										
Lysis, n (%)	6,949 (30.7)	698 (27.3)	1,521 (27.3)	449 (20.1)	450 (33.3)	377 (53.8)	1,181 (59.7)	1,920 (26.3)	191 (49.5)	162 (31)
Mortality (%)	*5.7*	*2.9*	*6.1*	*5.1*	*4.9*	*5.0*	*4.3*	*7.9*	*4.2*	*6.8*
Primary PCI, n (%)	6,344 (28.0)	724 (28.3)	2,490 (44.6)	602 (27)	348 (25.7)	116 (16.5)	299 (15.1)	1,590 (21.7)	66 (17.1)	109 (20.9)
Mortality (%)	*2.9*	1.8	3.3	2.7	2.6	0.9	1.3	3.4	1.5	3.7
No reperfusion, n (%)	9,329 (41.2)	1,139 (44.5)	1,567 (28.1)	1,179 (52.9)	554 (41)	208 (29.7)	498 (25.2)	3,804 (52.0)	129 (33.4)	251 (48.1)
Mortality (%)	*15.4*	*11.2*	*17.4*	*11.0*	*17.5*	*18.3*	*14.9*	*16.7*	*10.9*	*20.3*

CAN: Canada; AB: Alberta; BC: British Columbia; MB: Manitoba; NB: New Brunswick; NL: Newfoundland and Labrador; NS: Nova Scotia; ON: Ontario; PEI: Prince Edward Island; SK: Saskatchewan; PCI: percutaneous coronary intervention

2.8. Figures

Figure 2-1: Patient selection flowchart

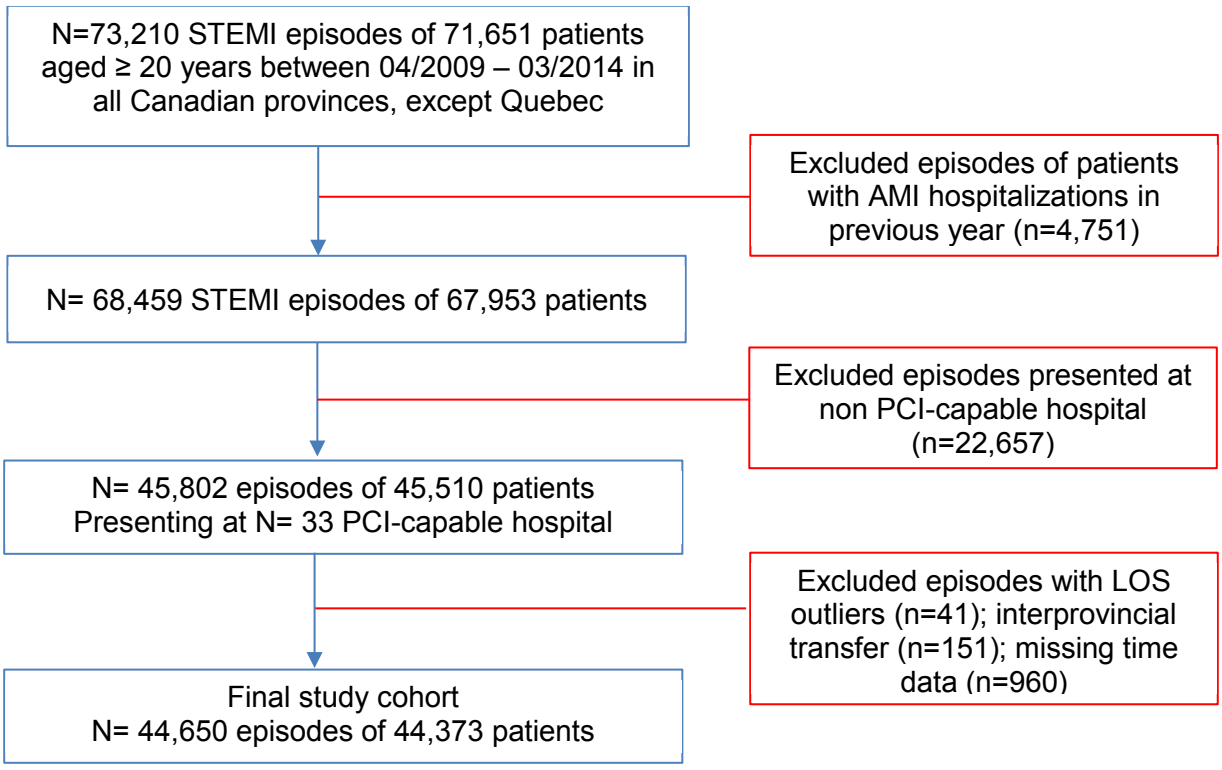
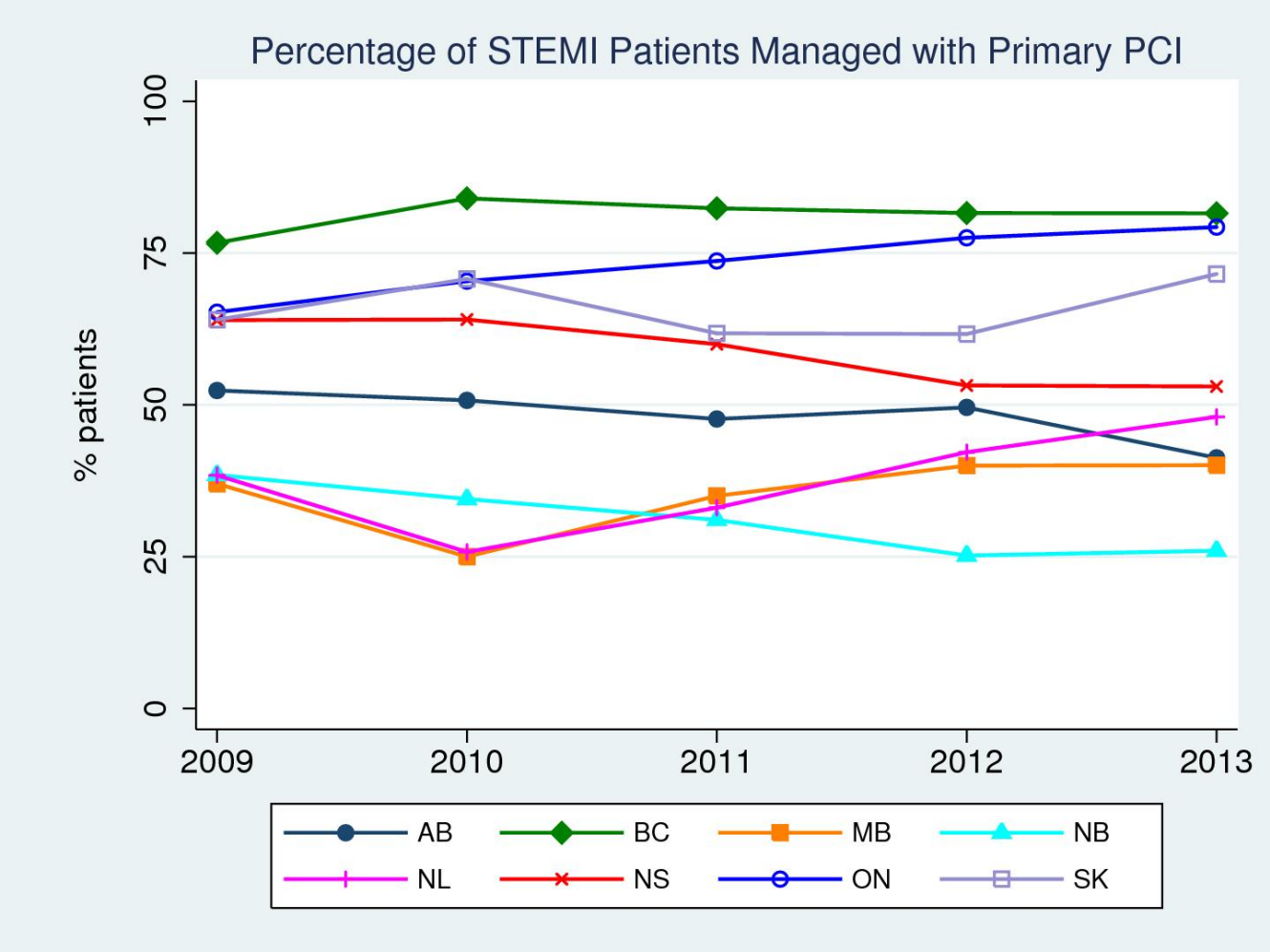
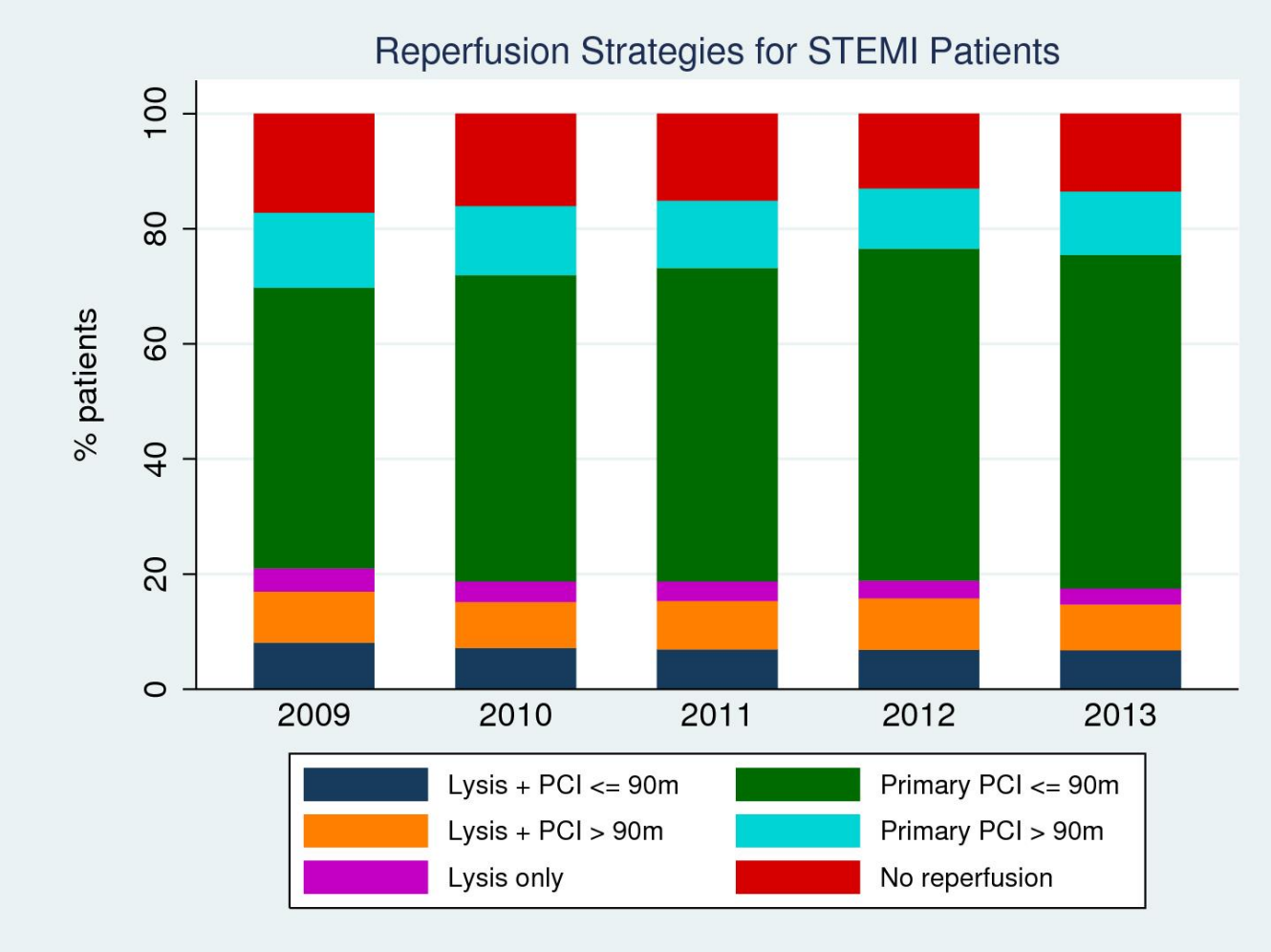


Figure 2-2: Percentage of STEMI patients at PCI capable hospitals managed with primary PCI by province in Canada, 2009- 2013. There was significant variation in the rate of primary PCI over time across provinces.



AB: Alberta; BC: British Columbia; MB: Manitoba; NB: New Brunswick; NL: Newfoundland and Labrador; NS: Nova Scotia; ON: Ontario; SK: Saskatchewan; PCI: percutaneous coronary intervention; STEMI: ST-segment Elevation Myocardial Infarction

Figure 2-3: Percentage of STEMI patients at PCI capable hospitals managed with indicated reperfusion strategy in Canada, 2009- 2013. Primary PCI increased from 61.8% in 2009 to 68.9% in 2013 (p<0.001).



STEMI: ST-segment Elevation Myocardial Infarction; PCI: percutaneous coronary intervention

Chapter 3 : QUALITY OF ACUTE MYOCARDIAL INFARCTION CARE IN CANADA: A 10-YEAR REVIEW OF 30-DAY IN-HOSPITAL MORTALITY AND 30-DAY HOSPITAL READMISSION

This chapter is based on the published article "Tran DT, Welsh RC, Ohinmaa A, Thanh NX, Bagai A, Kaul P. Quality of Acute Myocardial Infarction Care in Canada: A 10-Year Review of 30-Day In-Hospital Mortality and 30-Day Hospital Readmission. *Can. J. Cardiol.* 2017;33:1319-1326"

3.1. Introduction

Despite a gradual decline in both its incidence and mortality in the last decades, acute myocardial infarction (AMI) remains a key contributor to global and national population morbidity and mortality.[8, 23, 54] Thirty-day in-hospital case-mortality rates dropped from 8.1% in 2000 to 4.3% in 2009 in Organization for Economic Co-operation and Development countries.[25] Yeh *et al.* reported a 24% relative decrease in AMI incidence between 1999 and 2008 in California; and in Canada, Tu *et al.* reported a 38.1% reduction in AMI mortality between 1994 and 2004.[22, 26]

Revascularization is acknowledged as a key factor in the care of patients with AMI. Primary percutaneous coronary intervention (primary PCI) is a preferred mode of reperfusion for ST-segment elevation myocardial infarction (STEMI) patients and should ideally be performed in a timely manner.[13, 14] For those not receiving primary PCI, a pharmacoinvasive approach is typically applied with a large proportion subsequently receiving revascularization.[43]

International guidelines also recommend early angiography and revascularization for high risk non-ST-segment elevation myocardial infarction (NSTEMI) patients.[21] Coronary artery bypass grafting (CABG) can be indicated for AMI patients in whom the coronary anatomy precludes the use of PCI or among those with coexisting valvular heart disease or diabetes mellitus.[13, 14] The rate of revascularization with PCI or CABG among AMI patients has increased significantly over time.[22]

Recently, the Canadian Institute for Health Information (CIHI) and Canadian Cardiovascular Society (CCS), through consultation with key stakeholder groups, have defined a set of cardiac care quality indicators which include 30-day in-hospital mortality after PCI, 30-day in-hospital mortality after isolated CABG, 30-day readmission after PCI and 30-day readmission after isolated CABG.[55, 56] We examined long term trends and provincial variations in the four quality indicators in a contemporary population-based cohort of patients hospitalized with a primary diagnosis of AMI, overall, and by sub-type (ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI)). Our benchmarks provide novel data on quality of care to support improvements in care for AMI patients and in the health of Canadians.

3.2. Methods

Study population

We used the CIHI Discharge Abstract Database (DAD)[35] from April 2004 to March 2014 (fiscal year [FY] 2004 to 2013) to identify patients with a primary diagnosis of AMI for all provinces of Canada except Quebec. The CIHI DAD uses unique anonymous patient

identification number to link multiple hospitalizations of the same patient. The CIHI DAD does not contain hospitalization data from the province of Quebec, as the province submits hospitalization data in a separate format than the other provinces. In this study, we defined an index hospital admission as the admission in which the patient first presented at a hospital before any transfer. Consecutive hospitalizations within 24 hours of each other were considered to be the same hospital episode.[57]

Patients were included in the study if they were 18 years of age or older at the time of the index admission and had either STEMI (International Classification of Disease [ICD] 10th revision, codes I21.0-I21.3) or NSTEMI (ICD-10 code I21.4) listed as the primary diagnosis. The unit of analysis was an AMI hospital episode. A patient may have more than one episode during the study period, so s/he may be included multiple times. We excluded patients who had either a previous hospitalization with AMI as the primary diagnosis within 365 days prior to the index admission, or if the length of stay (LOS) of the index admission was longer than 90 days, or if the LOS of the index episode was longer than 365 days to reduce sample heterogeneity.[58] Patients who died during the index hospital episode were excluded from the readmission analyses. All patients discharged alive were followed-up for 30 days post-discharge to ascertain readmission.

Definition of variables

We used previously validated Canadian Classification of Health Interventions[37] codes to identify PCI (codes of 1.IJ.50** and 1.IJ.57.GQ**), CABG (code of 1.IJ.76**), catheterization (code of 3.IP.10.VX), and valve and other core concomitant procedures (for exclusions in 30-

day in-hospital mortality and 30-day readmission after isolated-CABG indicators; List of codes is provided in Supplemental Table S3.1) in any of the 20 intervention fields in the DAD record.[59-61] A 30-day in-hospital death after PCI or after isolated CABG was defined as death recorded in the hospital discharge abstracts within 30 days from the date of the respective procedure.[61] Similarly, a 30-day readmission after PCI or after isolated CABG was defined as an all-cause hospitalization within 30 days after discharge from the episode in which the procedure was performed.[61]

Statistical analysis

We summarized patient characteristics using means (±SD), medians (interquartile ranges), counts and percentages, as appropriate. We used previously validated ICD codes to identify patient comorbidities[40] (comorbidity codes are provided in Supplemental Table S3.2). Comorbidities were considered to be present if they were recorded in any hospitalization during the episode or in any hospitalization in the year prior to the episode.

We calculated invasive cardiac procedures (catheterization, PCI and CABG), 30-day in-hospital mortality and readmission rates for all AMI patients and for each of the STEMI and NSTEMI patient subgroups. We used multivariable logistic regression to examine risk-adjusted temporal trends and provincial variations of 30-day in-hospital mortality and 30-day readmission during the study period, accounting for patient characteristics and province. We developed two models to benchmark 30-day in-hospital mortality, one for after PCI and the other for after isolated CABG. Similarly, we used two models to benchmark 30-day readmission after PCI and after isolated CABG. Results are presented and expressed as

odds ratio (OR) and 95% confidence interval (CI). Variables included in the regression models were fiscal year, province, patient sex, age, and MI subgroups. We used the likelihood ratio (LR) test to examine the inclusion of additional risk adjustment factors. The factors were type of cardiac procedure (PCI, CABG and catheterization as binary variables), patient comorbidity, number of days in hospital during the year prior to the index admission, admission during working hours (Monday to Friday, 7 a.m. to 6 p.m.), arrival by ambulance or self-presentation, and sex/age interactions. In addition, we included two aggregate level economic variables: annual provincial health spending per capita[42] as a continuous variable and median household income quartiles at the residential neighborhood (forward sortation area level), based on 2006 Canadian census[41], as a categorical variable. We also examined the inclusion of acute LOS during the AMI episode in the readmission models. A variable remained in the final multivariate models if the LR test was significant at a 5% level. We excluded patients aged 18- 39 years due to low number of patients in this group (1.7%) and patients from Prince Edward Island (PEI) as there were no hospital facilities capable of PCI or CABG in the province during the study period in our multivariable analyses.

All analyses were performed using Stata version 14 (Stata Corporation, College Station, Texas); Two-sided P values < 0.05 were considered statistically significant.

3.3. Results

Characteristics of studied population

In total 341,001 AMI episodes of 323,862 unique patients from FY 2004-2013 in nine Canadian provinces (Alberta (AB), British Columbia (BC), New Brunswick (NB),

Newfoundland and Labrador (NL), Nova Scotia (NS), Manitoba (MB), Ontario (ON), PEI and Saskatchewan (SK)) were included in the analysis. A flow-chart depicting patient selection is presented in Figure 3.1.

Baseline characteristics of the study cohort, overall and by AMI type (STEMI or NSTEMI) are presented in Supplemental Table S3.3. NSTEMI patients accounted for 61.9% of the studied population. NSTEMI patients were significantly older (median age=71) than STEMI patients (median age=63, $p<0.001$) and more likely female (37.5% versus 29% in STEMI, $p<0.001$). In general, NSTEMI patients had higher rates of comorbidity than their STEMI counterparts. Patient characteristics by province are provided in Supplemental Table S3.4.

Invasive cardiac procedure use

Overall, 62%, 43.1% and 7% of patients received catheterization, PCI and CABG, respectively, during the index episode. Both catheterization and PCI utilization increased (11.6% relative annual increase, $p<0.001$, and 9.5% relative annual increase, $p<0.001$, respectively) while the use of CABG decreased during the study period (3.3% relative annual decrease, $p<0.001$). The rates of catheterization and PCI were both higher among STEMI patients (73.2% and 61.7%, respectively), while the rate of CABG was higher among NSTEMI patients (8.2%). Compared to the Canadian average, the rates of catheterization and PCI were both higher in BC (69.9% and 51.5%, respectively) and SK (69.3% and 53.3%, respectively) and lower in MB (43.6% and 28.6%, respectively) and NL (46.2% and 26.9%, respectively). Patients from PEI had higher rates (9.1%) while SK had lower rates (5.4%) of CABG (Supplemental Table S3.5).

30-day in-hospital mortality

Overall, 30-day in-hospital mortality rates after PCI and isolated CABG were 2.8% and 2.5%, respectively. Thirty-day in-hospital death after PCI and isolated CABG was higher in STEMI (4.1% and 3.0%, respectively) compared to NSTEMI (1.3% and 2.3%, respectively) patients (Figure 3.2 and Supplemental Table S3.6; p<0.001 for death after PCI; p=0.007 for death after CABG). Thirty-day in-hospital mortality after PCI (OR=1.01; 95% CI [0.99-1.02]; p=0.399) remained stable, while 30-day in-hospital mortality after isolated CABG (OR=0.96; 95% CI [0.93-0.99]; p=0.017) decreased during the study period.

Unadjusted 30-day in-hospital mortality rates after PCI varied across provinces and was lowest in PEI (1%) and highest in SK (3.7%) (p<0.001). Similarly, 30-day in-hospital mortality rates after isolated CABG ranged from a low of 1.9% in MB to a high of 6.3% in PEI (p<0.001). The observed interprovincial differences in in-hospital mortality remained after adjusting for differences in baseline characteristics of the patients. Compared to AB, 30-day in-hospital mortality after PCI (OR=0.72; 95% CI [0.56-0.92]; p=0.010) and after isolated CABG (OR=0.56; 95% CI [0.33-0.95]; p=0.031) were both lower in MB. Thirty-day in-hospital mortality after PCI was higher in ON (OR=1.30; 95% CI [1.15-1.45]; p<0.001) and SK (OR=1.32; 95% CI [1.12-1.57]; p=0.001) while 30-day in-hospital mortality after isolated CABG was higher in NL (OR=2.05; 95% CI [1.19-3.52]; p=0.010) and NS (OR=1.53; 95% CI [1.00-2.35]; p=0.052) (Table 3.1).

30-day hospital readmission

Approximately 9% and 11% of AMI patients who underwent PCI and isolated CABG were readmitted within 30 days of hospital discharge, respectively. While the readmission rate after PCI was higher among STEMI (9.2%) compared to NSTEMI (8.4%) patients (p<0.001), the readmission rate after CABG was the same among the two groups (STEMI: 10.8%; NSTEMI: 11.7%; p=0.087; Figure 3 and Supplemental Table S3.7).

Readmission for cardiac reasons accounted for 50.1% and 26.5% of readmissions after PCI and isolated CABG, respectively. Heart failure was the most frequent cardiac readmission after both PCI (11.8%) and isolated CABG (11.9%), while pain in throat and chest (17.1%) and infection following a procedure (11.4%) were the most frequent non-cardiac readmissions after PCI and CABG, respectively.

Thirty-day readmission after PCI (OR=1.06; 95% CI [1.03-1.08]; p<0.001) increased during the study period, while 30-day readmission after isolated CABG remained relatively stable (OR=0.99; 95% CI [0.97-1.00]; p=0.116). Unadjusted 30-day readmission rates after PCI varied from 6.3% in MB to 9.7% in SK (p<0.001) while 30-day readmission rates after isolated CABG ranged from 10.5% in MB to 16.1% in PEI (p=0.030). After risk adjustment, SK had highest rate of readmission after PCI (OR=1.24; 95% CI [1.13-1.37]; p<0.001), while NB had highest rate of readmission after isolated CABG (OR=1.49; 95% CI [1.16-1.90]; p=0.001) (Table 3.2).

3.4. Discussion

Our analysis of 341,001 AMI hospital episodes in all Canadian provinces except Quebec over a 10-year period showed no change in 30-day in-hospital mortality after PCI, slight increase in 30-day hospital readmission after PCI and modest improvement in 30-day in-hospital mortality after isolated CABG and 30-day hospital readmission after isolated CABG over time. There was significant inter-provincial variation in the rates of 30-day in-hospital mortality after PCI (1% in Prince Edward Island to 3.7% in Saskatchewan), 30-day in-hospital mortality after isolated CABG (1.9% in Manitoba to 6.3% in Prince Edward Island), 30-day hospital readmission after PCI (6.3% in Manitoba to 9.7% in Saskatchewan), and 30-day hospital readmission after isolated CABG (10.5% in Manitoba to 16.1% in Prince Edward Island). In addition, revascularization with PCI increased while revascularization with CABG decreased over time. There was also significant inter-provincial variation in utilization of catheterization (43.6% in Manitoba to 69.9% in British Columbia), PCI (26.9% in Newfoundland and Labrador to 53.3% in Saskatchewan), and CABG (5.4% in Saskatchewan to 7.5% in Ontario) during the index hospitalizations.

Despite recent advances in diagnosis and treatment of AMI[7] and availability of up-to-date international and Canadian guidelines in AMI care, we find no improvement in either 30-day in-hospital mortality rates or 30-day readmission rates among AMI patients and a large variation in both AMI care practice and health outcomes across Canadian provinces during the study period. However, it is important to note that PCI has been performing in older patients with greater comorbidity burden in recent years[62, 63], so the lack of improvement in risk-adjusted 30-day in-hospital mortality and 30-day readmission after PCI may actually reflect success in avoiding increasing complication with more severe cases. Nonetheless, our

findings signify a need to review and coordinate AMI care across the country, as well as a need for quality improvement initiatives to strengthen health service provision to patients with AMI. It has been shown that hospital outcomes can be affected by quality of care and hospital characteristics and patterns of practice[64] and that evidence-based and guideline-recommended treatment helps to improve health outcomes.[65] In addition, as CIHI/CCS has not set a target for its cardiac care indicators, our study could provide benchmarks for target-setting for overall PCI- and CABG-related cardiac care indicators as well as for AMI-specific care indicators, for which PCI is being used increasingly.

We found lower 30-day readmission rate after PCI for AMI patients in Canada (9%) than in the United States (17.5%).[66] However, the higher rate reported by Curtis *et al.* may be due to the fact that their study included Medicare patients aged ≥ 65 years while we selected patients aged ≥ 18 years. The association between older age and higher readmission was observed in our logistic regression model and has also been reported in the literature.[67, 68] Additionally, we cannot exclude the potential impact of variations in patterns of practice between the two nations.[69]

Significant provincial variations in in-hospital mortality have been previously reported.[45] Based on AMI hospitalization data from 1997/98 and 1999/2000, Tu *et al.* found age-sex standardized in-hospital mortality rate varied from a low of 10.5% in Prince Edward Island to a high of 13.1% in Quebec. In a more contemporary cohort of AMI patients who underwent PCI or CABG, we found that, although mortality outcomes have improved significantly, there continue to be differences across provinces.

Although the goal of the Cardiac Care Quality Indicators project is to provide "a comparable set of indicators and measures to support routine monitoring and quality improvement",[55] the interprovincial differences observed in our study need to be interpreted with caution and with the understanding that there may be other provincial-specific factors that could affect overall AMI patient outcomes. For example, we could not control for the time interval from symptom onset to first medical contact, as it is not recorded in the CIHI DAD. Similarly, we could not control for differences in provincial pre-hospital strategy regarding diagnosis, triage and treatment of STEMI patients, which is known to vary greatly across Canadian provinces.[51]

Our study has several strengths. First, it is among the first to provide pan-Canadian data for AMI quality indicators. Second, we used patient-level data and focused on episode of care, which facilitated adequate risk adjustments. However, in addition to the lack of data on time to treatment and pre-hospital care mentioned above, our study has some limitations. First, we did not have access to data from Quebec as the province submits hospitalization data in a separate format than the other provinces. Second, even though we considered the impact of comorbidities, we were not able to account for anatomical coronary disease severity or complexity. Furthermore, we were not able to correct for differences in physician knowledge, skills and attitudes between provinces that might affect AMI management and patient outcomes.

3.5. Conclusion

Our examination of cardiac care quality indicators for AMI population shows that there is no change in 30-day in-hospital mortality after PCI, slight increase in 30-day hospital

readmission after PCI and modest improvement in 30-day in-hospital mortality after CABG and 30-day hospital readmission after CABG among patients with AMI during the study period. The in-hospital mortality and readmission rates after PCI and CABG among patients with AMI differ considerably across Canadian provinces. We recommend a stronger focus on Pan-Canadian coordination in AMI care and the establishment of national benchmarks for AMI-specific PCI- and CABG-related quality indicators to foster the quality of care for Canadian AMI patients.

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3.7. Tables

Table 3-1: 30-day in-hospital mortality in AMI patients in Canada by multivariable analysis, 2004- 2013

Variable	30-day in-hospital mortality after PCI (N=142,947)		30-day in-hospital mortality after isolated CABG (N=20,532)	
	OR (95% CI)	p	OR (95% CI)	p
Province				
Alberta	1.0		1.0	
British Columbia	1.17 (1.02-1.34)	0.025	0.89 (0.61-1.28)	0.514
Manitoba	0.72 (0.56-0.92)	0.010	0.56 (0.33-0.95)	0.031
New Brunswick	1.07 (0.86-1.31)	0.577	1.24 (0.71-2.18)	0.447
Newfoundland and Labrador	1.16 (0.80-1.66)	0.433	2.05 (1.19-3.52)	0.010
Nova Scotia	0.95 (0.77-1.18)	0.637	1.53 (1.00-2.35)	0.052
Ontario	1.30 (1.15-1.45)	<0.001	0.89 (0.67-1.18)	0.417
Saskatchewan	1.32 (1.12-1.57)	0.001	1.03 (0.60-1.79)	0.906
Sex				
Female	1.0		1.0	
Male	0.85 (0.79-0.92)	<0.001	0.74 (0.60-0.90)	0.003
Age group				
40-59 years	1.0		1.0	
60-69 years	1.58 (1.41-1.76)	<0.001	1.60 (1.16-2.20)	0.004
70-79 years	3.16 (2.84-3.51)	<0.001	2.70 (2.00-3.66)	<0.001
>=80 years	5.96 (5.34-6.65)	<0.001	4.28 (3.04-6.04)	<0.001
Fiscal year	1.01 (0.99-1.02)	0.399	0.96 (0.93-0.99)	0.017
MI type				
STEMI	1.0		1.0	
NSTEMI	0.36 (0.33-0.39)	<0.001	0.89 (0.72-1.10)	0.264
Had catheterization during episode	0.77 (0.66-0.91)	0.001	--	--
Had PCI during episode	--	--	1.84 (1.29-2.62)	0.001
Had CABG during episode	1.31 (0.99-1.73)	0.057	--	--
Comorbidity				
Cancer	1.95 (1.61-2.36)	<0.001	--	--
Cerebrovascular disease	2.55 (2.18-2.99)	<0.001	2.06 (1.53-2.77)	<0.001
Diabetes	1.44 (1.34-1.56)	<0.001	--	--
Heart failure	1.49 (1.37-1.62)	<0.001	2.39 (1.96-2.92)	<0.001
Hemiplegia or paraplegia	1.56 (1.07-2.29)	0.021	--	--
Liver disease	3.80 (2.84-5.07)	<0.001	4.91 (2.81-8.56)	<0.001
Peripheral vascular disease	1.61 (1.38-1.89)	<0.001	2.18 (1.67-2.84)	<0.001
Peptic ulcer disease	0.58 (0.41-0.84)	0.004	--	--
Renal disease	1.69 (1.48-1.93)	<0.001	1.41 (1.08-1.84)	0.013
Rheumatic disease	0.64 (0.41-0.99)	0.044	--	--
Shock	23.13 (21.30-25.12)	<0.001	10.16 (8.03-12.87)	<0.001
LOS during previous year	1.01 (1.00-1.01)	0.008	--	--
Admitted by ambulance	1.49 (1.38-1.62)	<0.001	--	--

Table 3-2: 30-day readmission in AMI patients in Canada by multivariable analysis, 2004- 2013

Variable	30-day readmission after PCI (N=138,867)		30-day readmission after isolated CABG (N=19,897)	
	OR (95% CI)	p	OR (95% CI)	p
Province				
Alberta	1.0		1.0	
British Columbia	1.12 (1.02-1.24)	0.020	1.08 (0.91-1.28)	0.400
Manitoba	0.91 (0.80-1.03)	0.130	0.89 (0.70-1.14)	0.366
New Brunswick	1.15 (1.03-1.28)	0.010	1.49 (1.16-1.90)	0.001
Newfoundland and Labrador	1.09 (0.92-1.29)	0.309	1.10 (0.82-1.49)	0.530
Nova Scotia	0.85 (0.76-0.95)	0.004	0.99 (0.77-1.27)	0.910
Ontario	1.20 (1.11-1.30)	<0.001	1.04 (0.90-1.20)	0.604
Saskatchewan	1.24 (1.13-1.37)	<0.001	1.33 (1.02-1.72)	0.033
Sex				
Female	1.0		1.0	
Male	0.75 (0.69-0.81)	<0.001	0.73 (0.66-0.80)	<0.001
Age group				
40-59 years	1.0		1.0	
60-69 years	1.03 (0.94-1.14)	0.531	1.11 (0.98-1.25)	0.098
70-79 years	1.18 (1.07-1.29)	0.001	1.36 (1.21-1.53)	<0.001
>=80 years	1.47 (1.33-1.61)	<0.001	1.46 (1.24-1.73)	<0.001
Sex/Age interaction				
Male/ 60-69 years	1.07 (0.94-1.14)	0.231	--	--
Male/ 70-79 years	1.17 (1.05-1.31)	0.005	--	--
Male/ >=80 years	1.12 (0.99-1.26)	0.072	--	--
Fiscal year	1.06 (1.03-1.08)	<0.001	0.99 (0.97-1.00)	0.116
MI type				
STEMI	1.0		1.0	
NSTEMI	0.84 (0.81-0.87)	<0.001	1.00 (0.90-1.11)	0.988
Comorbidity				
Cancer	1.51 (1.33-1.71)	<0.001	1.40 (1.06-1.84)	0.016
Chronic pulmonary disease	1.34 (1.24-1.45)	<0.001	1.38 (1.20-1.59)	<0.001
Diabetes	1.22 (1.17-1.27)	<0.001	1.26 (1.15-1.38)	<0.001
Dementia	0.79 (0.64-0.98)	0.030	--	--
Heart failure	1.81 (1.71-1.91)	<0.001	1.27 (1.14-1.42)	<0.001
Liver disease	1.59 (1.24-2.05)	<0.001	2.27 (1.44-3.59)	<0.001
Peripheral vascular disease	1.21 (1.09-1.34)	0.001	--	--
Peptic ulcer disease	1.59 (1.30-1.94)	<0.001	--	--
Renal disease	1.52 (1.39-1.65)	<0.001	1.50 (1.29-1.75)	<0.001
Rheumatic disease	1.49 (1.22-1.80)	<0.001	--	--
Shock	1.36 (1.22-1.51)	<0.001	1.29 (1.00-1.68)	0.054
LOS during previous year	1.01 (1.01-1.01)	<0.001	1.02 (1.00-1.03)	0.005
Acute LOS of the index episode	1.01 (1.01-1.01)	<0.001	--	--
Admitted by ambulance	1.06 (1.02-1.10)	0.004	--	--
Provincial health spending per capita	0.75 (0.68-0.83)	<0.001	--	--

Supplemental Table S3-1: Exclusion criteria code for 30-day in-hospital mortality and 30-day readmission after isolated-CABG procedures

Description	CCI code
Valve procedure	
Therapeutic Interventions on the Tricuspid Valve	1.HS.^^
Therapeutic Interventions on the Pulmonary Valve	1.HT.^^
Therapeutic Interventions on the Mitral Valve	1.HU.^^
Therapeutic Interventions on the Aortic Valve	1.HV.^^
Therapeutic Interventions on the Annulus not elsewhere classified	1.HW.^^
Core concomitant procedures	
Excision partial, lobe of lung	1.GR.87.^^
Repair by decreasing size, lung not elsewhere classified	1.GT.78.^^
Repair, lung not elsewhere classified	1.GT.80.^^
Transplant, lung not elsewhere classified	1.GT.85.^^
Excision partial, lung not elsewhere classified	1.GT.87.^^
Destruction, cardiac conduction system	1.HH.59.^^
Therapeutic Interventions on the Atrium	1.HM.^^.^^
Division, interatrial septum	1.HN.71.^^
Repair, interatrial septum	1.HN.80.^^
Excision partial, interatrial septum no tissue used [e.g. excision alone] using open approach	1.HN.87.LA
Implantation of internal device, ventricle	1.HP.53.^^
Removal of device, ventricle	1.HP.55.^^
Division, ventricle	1.HP.71.^^
Repair by decreasing size, ventricle	1.HP.78.^^
Repair, ventricle	1.HP.80.^^
Reattachment, ventricle	1.HP.82.^^
Transfer, ventricle	1.HP.83.^^
Excision partial, ventricle	1.HP.87.^^
Division, interventricular septum	1.HR.71.^^
Repair, interventricular septum	1.HR.80.^^
Construction or reconstruction, interventricular septum	1.HR.84.^^
Excision partial, interventricular septum	1.HR.87.^^
Compression, heart not elsewhere classified	1.HZ.34.^^
Implantation of internal device, heart not elsewhere classified open	1.HZ.53.LA-KP
Removal of foreign body, heart not elsewhere classified	1.HZ.56.^^
Extraction, heart not elsewhere classified	1.HZ.57.^^
Destruction, heart not elsewhere classified	1.HZ.59.^^
Incision NOS, heart not elsewhere classified	1.HZ.70.^^
Repair, heart not elsewhere classified	1.HZ.80.^^
Transplant, heart not elsewhere classified	1.HZ.85.^^
Excision partial, heart not elsewhere classified	1.HZ.87.^^

Repair by increasing size, ascending aorta	1.IA.79.^^
Repair, ascending aorta	1.IA.80.^^
Excision partial, ascending aorta	1.IA.87.^^
Repair, arch of aorta	1.IB.80.^^
Excision partial, arch of aorta	1.IB.87.^^
Repair, thoracic [descending] aorta	1.IC.80.^^
Excision partial, thoracic [descending] aorta	1.IC.87.^^
Repair, aorta not elsewhere classified	1.ID.80.^^
Excision partial, aorta not elsewhere classified	1.ID.87.^^
Removal of device, coronary arteries	1.IJ.55.^^
Repair, coronary arteries	1.IJ.80.^^
Closure of fistula, coronary arteries	1.IJ.86.^^
Extraction, coronary veins	1.IK.57.^^
Repair, coronary veins	1.IK.80.^^
Excision partial, coronary veins	1.IK.87.^^
Occlusion, pulmonary artery	1.IM.51.^^
Extraction, pulmonary artery	1.IM.57.^^
Repair, pulmonary artery	1.IM.80.^^
Excision partial, pulmonary artery	1.IM.87.^^
Extraction, pulmonary vein	1.IN.57.^^
Repair, pulmonary vein	1.IN.80.^^
Excision partial, pulmonary vein	1.IN.87.^^
Dilation, carotid artery using percutaneous transluminal approach	1.JE.50.GQ-OA
Extraction, carotid artery	1.JE.57.^^
Bypass, carotid artery	1.JE.76.^^
Repair, carotid artery	1.JE.80.^^
Excision partial, carotid artery	1.JE.87.^^
Excision partial, brachiocephalic arteries	1.JJ.87.^^
Repair, subclavian artery	1.JK.80.^^
Excision partial, subclavian artery	1.JK.87.^^
Repair, thoracic vessels not elsewhere classified	1.JY.80.^^
Excision partial, thoracic vessels not elsewhere classified	1.JY.87.^^
Repair, abdominal aorta	1.KA.80.^^
Excision partial, abdominal aorta	1.KA.87.^^
Repair, abdominal arteries not elsewhere classified	1.KE.80.^^
Therapeutic Interventions on the Interventricular Septum with Interatrial Septum and Heart Valves	1.LC.^^.^^

Supplemental Table S3-2: Comorbidity code

Comorbidities	ICD-10 code
Heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x–I69.x
Dementia	F00.x–F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Rheumatic disease	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	K25.x–K28.x
Liver disease	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Diabetes	E10.x-E14.x
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
Renal disease	I12.0, I13.1, N03.2–N03.7, N05.2– N05.7, N18.x, N19.x, N25.0, Z49.0– Z49.2, Z94.0, Z99.2
Cancer	C00.x–C26.x, C30.x–C34.x, C37.x– C41.x, C43.x, C45.x–C58.x, C60.x–C85.x, C88.x, C90.x–C97.x, D00.x-D09.x
Shock	R57.x

Supplemental Table S3-3: Characteristics of studied population, 2004-2013

Variable	All patients	STEMI	NSTEMI
Episode, N	341,001	129,752	211,249
Females (%)	34.3	29	37.5
Age (mean/SD)	67.5 (14.1)	63.8 (13.7)	69.8 (13.8)
Age (median/IQR)	68 (57-79)	63 (54-74)	71 (59-81)
Age group (%)			
18-39 years	1.7	2.5	1.3
40-59 years	29.5	38.7	23.8
60-69 years	22.7	24.5	21.6
70-79 years	22.3	18.9	24.4
>=80 years	23.8	15.5	28.9
Household income ($, %)			
Missing	0.7	0.9	0.6
0-40,000	10.9	10.5	11.1
40,000-60,000	57.7	56.6	58.4
60,000-80,000	21.7	22.3	21.4
>80,000	9.0	9.7	8.5
Received catheterization during index episode (%)	62.0	73.2	55.1
Received PCI during index episode (%)	43.1	61.7	31.7
Received CABG during index episode (%)	7.0	5.2	8.2
Selected comorbidities (%)			
Cancer	2.9	2.1	3.4
Cerebrovascular disease	3.2	2.5	3.6
Chronic pulmonary disease	8.2	5.3	10.0
Dementia	2.9	1.8	3.6
Diabetes	28.5	22.6	32.0
Heart failure	19.1	14.1	22.2
Peripheral vascular disease	3.7	2.7	4.3
Renal disease	6.8	3.7	8.6
Shock	3.0	5.0	1.7
Charlson comorbidity score (%)			
1-2	76.7	84.5	72.0
3-4	17.5	12.3	20.7
>=5	5.8	3.1	7.4
Admit-in-work-hour (%)	41.8	42.3	41.6
Admit by ambulance (%)	53.9	61.4	49.3
Acute LOS (median/ IQR)	5 (3-9)	5 (3-8)	5 (3-10)

SD: standard deviation; IQR: interquartile range; LOS: length of stay; PCI: percutaneous coronary intervention; CABG: coronary artery by-pass grafting; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction.

Supplemental Table S3-4: Characteristics of studied population by province, 2004-2013

Variable	CAN	AB	BC	MB	NB	NL	NS	ON	PEI	SK
Episode, N	341,001	43,881	49,395	18,185	15,359	9,413	19,301	167,539	2,585	15,343
Females (%)	34.3	30.8	32.6	34.3	34.7	36.7	35.5	35.4	34.5	34.1
Age (mean/SD)	67.5 (14.1)	65.5 (14.0)	68.4 (13.7)	67.8 (14.0)	66.7 (13.9)	67.2 (13.6)	66.9 (13.8)	67.8 (14.2)	68.0 (13.4)	68.7 (14.1)
Age (median/IQR)	68 (57-79)	65 (55-77)	69 (58-79)	68 (57-79)	66 (56-78)	67 (57-78)	67 (57-78)	68 (57-79)	68 (58-78)	69 (58-80)
Age group (%)										
18-39 years	1.7	2.3	1.3	1.7	1.9	1.8	1.9	1.7	1.2	1.4
40-59 years	29.5	34.6	26.7	28.8	30.9	28.8	30.1	29.1	26.8	27.4
60-69 years	22.7	22.8	23.9	22.5	24.1	24.3	24.5	22.1	24.7	21.4
70-79 years	22.3	20.9	23.4	22.2	21.7	23.0	22.3	22.2	25.2	22.8
>=80 years	23.8	19.3	24.7	24.7	21.3	22.1	21.3	24.9	22.0	27.0
Household income ($, %)										
Missing	0.7	0.5	0.6	0.3	1.0	0.6	1.7	0.7	0.5	0.2
0-40,000	10.9	4.4	7.4	25.1	29.8	52.7	29.4	4.6	23.4	23.0
40,000-60,000	57.7	49.2	69.5	59.2	61.9	40.5	55.1	56.2	65.0	66.7
60,000-80,000	21.7	31.2	20.2	12.1	7.1	5.3	13.4	25.4	10.9	8.1
>80,000	9.0	14.7	2.3	3.4	0.1	0.9	0.5	13.1	0.2	1.9
Selected comorbidities (%)										
Cancer	2.9	3.1	2.0	2.9	2.3	2.3	2.7	3.2	3.5	2.9
Cerebrovascular disease	3.2	3.5	2.4	3.4	2.6	2.0	3.2	3.4	3.9	3.5
Chronic pulmonary disease	8.2	12.1	6.8	7.9	6.5	5.3	9.0	7.9	10.0	7.4
Dementia	2.9	3.2	2.3	2.8	2.0	1.5	2.6	3.3	2.0	2.4
Diabetes	28.5	26.9	25.9	30.2	28.8	30.4	30.8	29.0	29.2	29.2
Heart failure	19.1	16.3	17.0	20.7	17.4	15.6	19.2	20.7	19.7	18.1

Peripheral vascular disease	3.7	4.6	2.4	4.2	2.8	2.2	4.5	3.7	5.3	4.4
Renal disease	6.8	7.1	5.2	6.2	6.0	4.5	6.1	7.4	5.4	7.2
Shock	3.0	2.7	3.1	4.0	2.1	1.5	2.2	3.1	2.2	3.7
Charlson comorbidity score (%)										
1-2	76.7	75.9	81.2	76.1	79.8	80.8	75.8	75.3	75.7	76.6
3-4	17.5	17.7	14.8	18.4	15.2	15.6	18.5	18.4	18.6	17.3
>=5	5.8	6.4	4.0	5.6	5.0	3.7	5.7	6.3	5.8	6.1
Admit-in-work-hour (%)	41.8	40.7	41.7	46.8	44.9	41.5	44.7	41.0	44.9	41.8
Admit by ambulance (%)	53.9	62.2	52.2	38.2	58.2	47.5	55.7	53.7	38.5	56.6
Acute LOS (median/ IQR)	5 (3-9)	5 (3-9)	4 (3-8)	5 (3-9)	5 (3-9)	7 (5-13)	6 (4-10)	5 (3-9)	7 (5-12)	6 (4-10)

CAN: Canada; AB: Alberta; BC: British Columbia; MB: Manitoba; NB: New Brunswick; NL: Newfoundland and Labrador; NS: Nova Scotia; ON: Ontario; PEI: Prince Edward Island; SK: Saskatchewan.

Supplemental Table S3-5: Invasive cardiac procedure for AMI patients by province in Canada, 2004-2013

Variable N (%)	CAN	AB	BC	MB	NB	NL	NS	ON	PEI	SK
All episodes, N	341,001	43,881	49,395	18,185	15,359	9,413	19,301	167,539	2,585	15,343
Received catheterization during episode	*211,349 (62.0)*	*28,167 (64.2)*	*34,536 (69.9)*	*7,930 (43.6)*	*10,078 (65.6)*	*4,353 (46.2)*	*12,651 (65.5)*	*101,559 (60.6)*	*1,440 (55.7)*	*10,635 (69.3)*
Received PCI during episode	*146,901 (43.1)*	*20,067 (45.7)*	*25,418 (51.5)*	*5,208 (28.6)*	*7,155 (46.6)*	*2,535 (26.9)*	*7,750 (40.2)*	*69,761 (41.6)*	*827 (32)*	*8,180 (53.3)*
Received CABG during episode	*23,931 (7.0)*	*2,915 (6.6)*	*3,635 (7.4)*	*1,192 (6.6)*	*890 (5.8)*	*658 (7)*	*1,080 (5.6)*	*12,503 (7.5)*	*234 (9.1)*	*824 (5.4)*
STEMI	129,752 (38.1)	18,257 (41.6)	19,175 (38.8)	6,911 (38)	6,347 (41.3)	2,829 (30.1)	7,250 (37.6)	61,722 (36.8)	832 (32.2)	6,429 (41.9)
Received catheterization during episode	*94,948 (73.2)*	*13,241 (72.5)*	*15,069 (78.6)*	*3,081 (44.6)*	*4,542 (71.6)*	*1,691 (59.8)*	*5,090 (70.2)*	*46,493 (75.3)*	*553 (66.5)*	*5,188 (80.7)*
Received PCI during episode	*80,001 (61.7)*	*11,317 (62)*	*13,112 (68.4)*	*2,491 (36)*	*3,730 (58.8)*	*1,136 (40.2)*	*3,822 (52.7)*	*39,403 (63.8)*	*376 (45.2)*	*4,614 (71.8)*
Received CABG during episode	*6,700 (5.2)*	*790 (4.3)*	*1,107 (5.8)*	*341 (4.9)*	*278 (4.4)*	*205 (7.2)*	*305 (4.2)*	*3,345 (5.4)*	*61 (7.3)*	*268 (4.2)*
NSTEMI	211,249 (61.9)	25,624 (58.4)	30,220 (61.2)	11,274 (62)	9,012 (58.7)	6,584 (69.9)	12,051 (62.4)	105,817 (63.2)	1,753 (67.8)	8,914 (58.1)
Received catheterization during episode	*116,401 (55.1)*	*14,926 (58.3)*	*19,467 (64.4)*	*4,849 (43)*	*5,536 (61.4)*	*2,662 (40.4)*	*7,561 (62.7)*	*55,066 (52)*	*887 (50.6)*	*5,447 (61.1)*
Received PCI during episode	*66,900 (31.7)*	*8,750 (34.1)*	*12,306 (40.7)*	*2,717 (24.1)*	*3,425 (38)*	*1,399 (21.2)*	*3,928 (32.6)*	*30,358 (28.7)*	*451 (25.7)*	*3,566 (40)*
Received CABG during episode	*17,231 (8.2)*	*2,125 (8.3)*	*2,528 (8.4)*	*851 (7.5)*	*612 (6.8)*	*453 (6.9)*	*775 (6.4)*	*9,158 (8.7)*	*173 (9.9)*	*556 (6.2)*

CAN: Canada; AB: Alberta; BC: British Columbia; MB: Manitoba; NB: New Brunswick; NL: Newfoundland and Labrador; NS: Nova Scotia; ON: Ontario; PEI: Prince Edward Island; SK: Saskatchewan; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery by-pass grafting.

Supplemental Table S3-6: 30-day in-hospital mortality in AMI patients by province in Canada, 2004- 2013

Variable	CAN	AB	BC	MB	NB	NL	NS	ON	PEI	SK
After PCI										
All patients, N	146,901	20,067	25,418	5,208	7,155	2,535	7,750	69,761	827	8,180
Mortality, n (%)	*4,132 (2.8)*	*464 (2.3)*	*741 (2.9)*	*97 (1.9)*	*145 (2)*	*37 (1.5)*	*139 (1.8)*	*2,200 (3.2)*	*8 (1)*	*301 (3.7)*
STEMI, N	80,001	11,317	13,112	2,491	3,730	1,136	3,822	39,403	376	4,614
Mortality, n (%)	*3,248 (4.1)*	*401 (3.5)*	*579 (4.4)*	*76 (3.1)*	*99 (2.7)*	*28 (2.5)*	*92 (2.4)*	*1,750 (4.4)*	*5 (1.3)*	*218 (4.7)*
NSTEMI, N	66,900	8,750	12,306	2,717	3,425	1,399	3,928	30,358	451	3,566
Mortality, n (%)	*884 (1.3)*	*63 (.7)*	*162 (1.3)*	*21 (.8)*	*46 (1.3)*	*9 (.6)*	*47 (1.2)*	*450 (1.5)*	*3 (.7)*	*83 (2.3)*
After isolated CABG										
All patients, N	20,880	2,493	3,120	1,059	775	588	932	11,021	207	685
Mortality, n (%)	*524 (2.5)*	*71 (2.8)*	*67 (2.1)*	*20 (1.9)*	*17 (2.2)*	*20 (3.4)*	*40 (4.3)*	*256 (2.3)*	*13 (6.3)*	*20 (2.9)*
STEMI, N	5,849	669	927	304	239	188	265	2,988	55	214
Mortality, n (%)	*174 (3.0)*	*22 (3.3)*	*31 (3.3)*	*6 (2)*	*5 (2.1)*	*4 (2.1)*	*15 (5.7)*	*78 (2.6)*	*4 (7.3)*	*9 (4.2)*
NSTEMI, N	15,031	1,824	2,193	755	536	400	667	8,033	152	471
Mortality, n (%)	*350 (2.3)*	*49 (2.7)*	*36 (1.6)*	*14 (1.9)*	*12 (2.2)*	*16 (4)*	*25 (3.7)*	*178 (2.2)*	*9 (5.9)*	*11 (2.3)*

CAN: Canada; AB: Alberta; BC: British Columbia; MB: Manitoba; NB: New Brunswick; NL: Newfoundland and Labrador; NS: Nova Scotia; ON: Ontario; PEI: Prince Edward Island; SK: Saskatchewan; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery by-pass grafting.

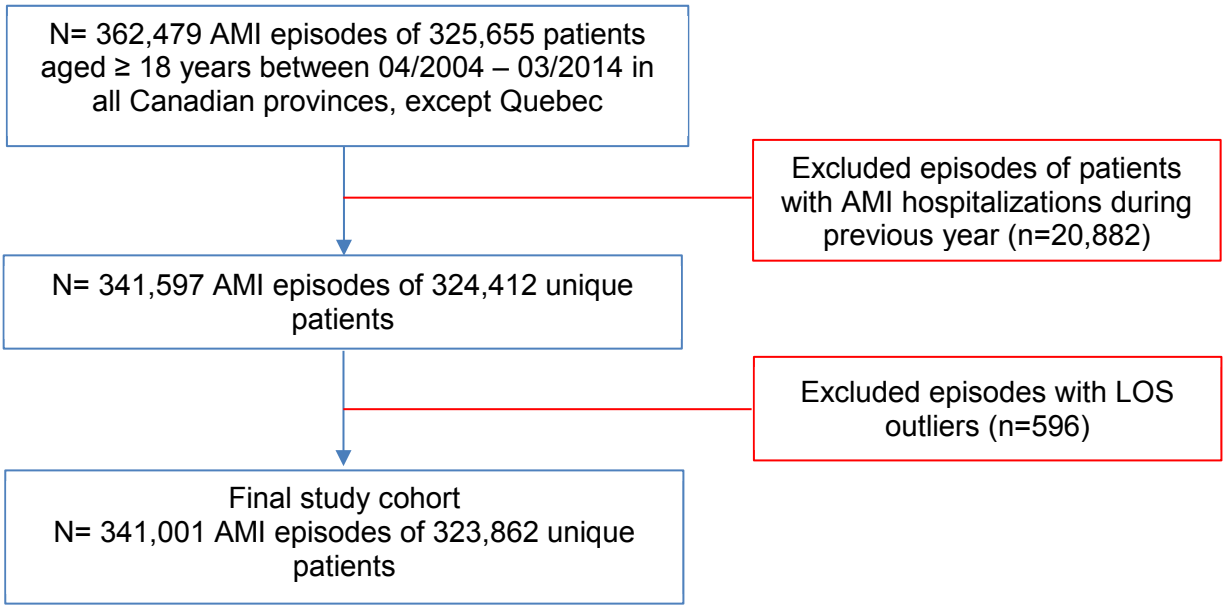
Supplemental Table S3-7: 30-day readmission of AMI patients after discharge by province in Canada, 2004- 2013

Variable	CAN	AB	BC	MB	NB	NL	NS	ON	PEI	SK
After PCI										
All patients, N	142,788	19,603	24,677	5,107	7,012	2,498	7,611	67,581	819	7,880
Readmission, n (%)	*12,567 (8.8)*	*1,415 (7.2)*	*2,256 (9.1)*	*324 (6.3)*	*616 (8.8)*	*179 (7.2)*	*485 (6.4)*	*6,466 (9.6)*	*64 (7.8)*	*762 (9.7)*
STEMI, N	76,724	10,915	12,520	2,411	3,631	1,108	3,729	37,649	371	4,390
Readmission, n (%)	7,021 (9.2)	827 (7.6)	1,196 (9.6)	162 (6.7)	335 (9.2)	88 (7.9)	253 (6.8)	3,709 (9.9)	30 (8.1)	421 (9.6)
NSTEMI, N	66,064	8,688	12,157	2,696	3,381	1,390	3,882	29,932	448	3,490
Readmission, n (%)	5,546 (8.4)	588 (6.8)	1,060 (8.7)	162 (6)	281 (8.3)	91 (6.5)	232 (6)	2,757 (9.2)	34 (7.6)	341 (9.8)
After isolated CABG										
All patients, N	20,229	2,402	3,034	1,032	756	566	871	10,714	193	661
Readmission, n (%)	*2,312 (11.4)*	*266 (11.1)*	*335 (11)*	*108 (10.5)*	*108 (14.3)*	*60 (10.6)*	*96 (11)*	*1,215 (11.3)*	*31 (16.1)*	*93 (14.1)*
STEMI, N	5,632	641	890	295	232	184	240	2,895	51	204
Readmission, n (%)	*609 (10.8)*	*61 (9.5)*	*90 (10.1)*	*32 (10.8)*	*33 (14.2)*	*23 (12.5)*	*24 (10)*	*320 (11.1)*	*6 (11.8)*	*20 (9.8)*
NSTEMI, N	14,597	1,761	2,144	737	524	382	631	7,819	142	457
Readmission, n (%)	*1,703 (11.7)*	*205 (11.6)*	*245 (11.4)*	*76 (10.3)*	*75 (14.3)*	*37 (9.7)*	*72 (11.4)*	*895 (11.4)*	*25 (17.6)*	*73 (16)*

CAN: Canada; AB: Alberta; BC: British Columbia; MB: Manitoba; NB: New Brunswick; NL: Newfoundland and Labrador; NS: Nova Scotia; ON: Ontario; PEI: Prince Edward Island; SK: Saskatchewan; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting

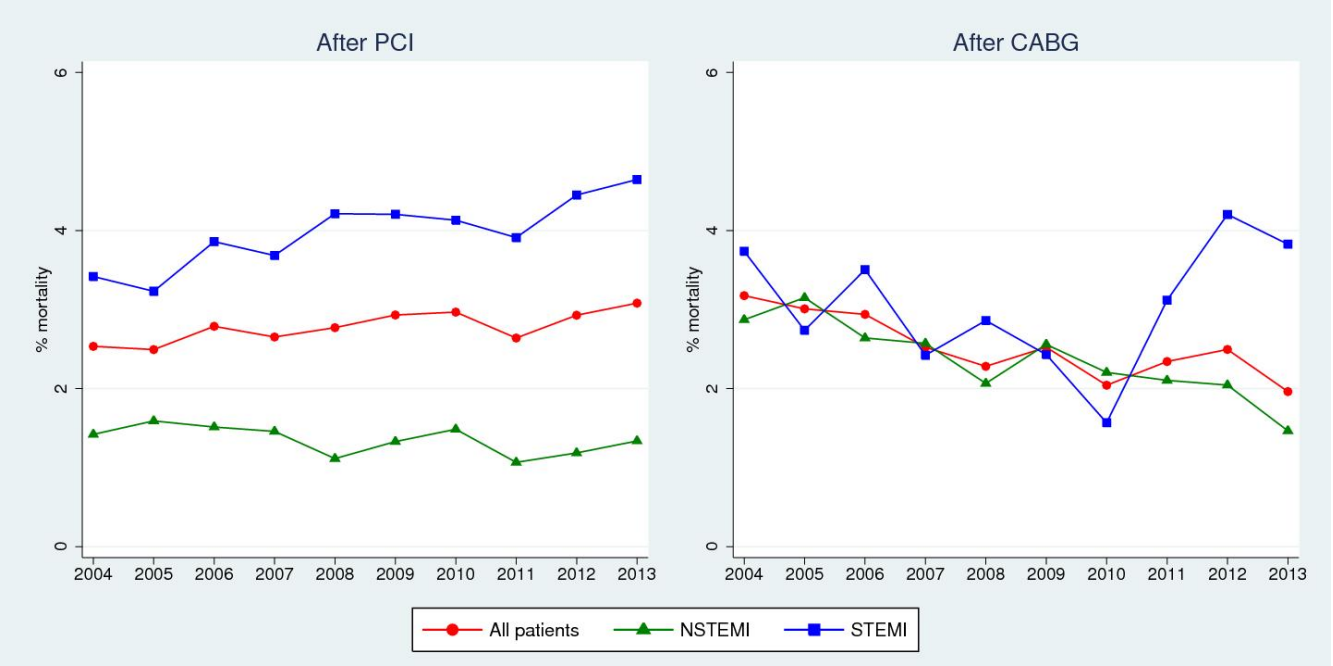
3.8. Figures

Figure 3-1: Patient selection flowchart



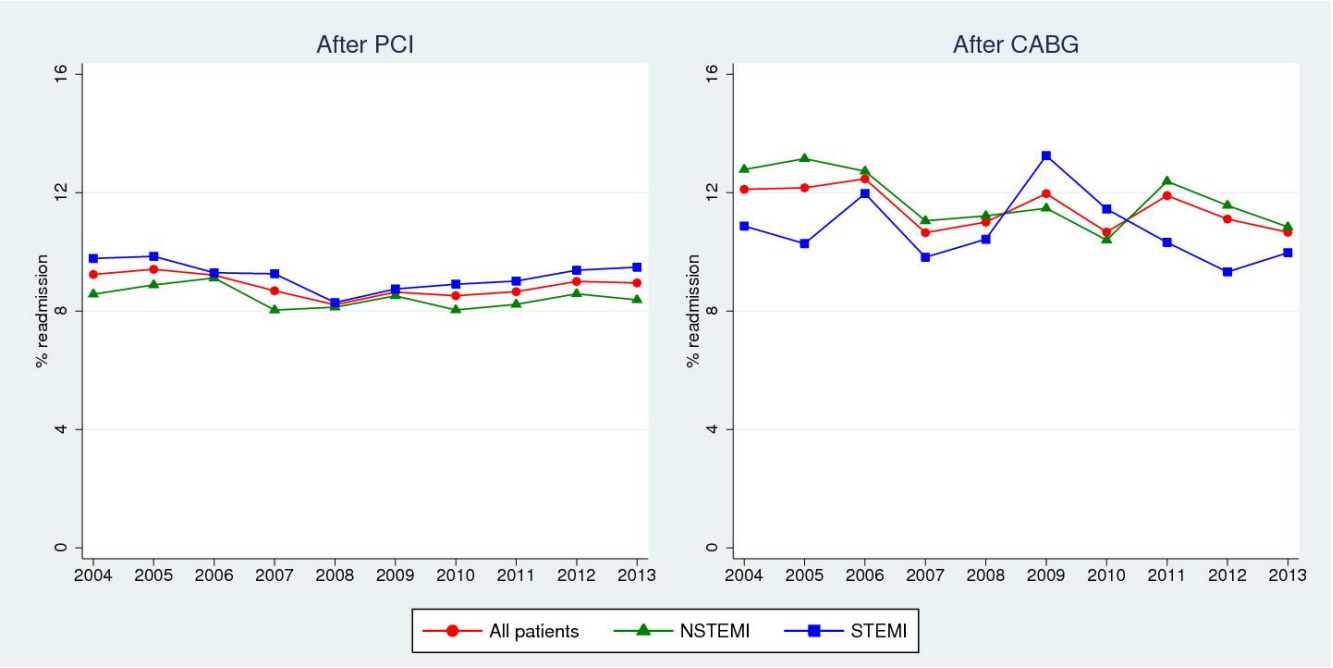
AMI: acute myocardial infarction; LOS: length of stay.

Figure 3-2: 30-day in-hospital mortality after PCI and after isolated CABG for AMI patients in Canada, 2004-2013. P for trend over time: after PCI=0.399; after isolated CABG=0.017



AMI: acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.

Figure 3-3: 30-day readmission after PCI and after isolated CABG for AMI patients in Canada, 2004-2013. P for trend over time: after PCI <0.001; after isolated CABG=0.116



AMI: acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.

Chapter 4 : THE HEALTH CARE COST BURDEN OF ACUTE MYOCARDIAL INFARCTION

This chapter is based on the published article "Tran DT, Ohinmaa A, Thanh NX, Welsh RC, Kaul P. The Health Care Cost Burden of Acute Myocardial Infarction in Alberta, Canada. PharmacoEconomics – Open. 2017 (in press). DOI: 10.1007/s41669-017-0061-0".

4.1. Introduction

Acute myocardial infarction (AMI) is an acute condition requiring expedited diagnosis and intervention. It is the leading cause of morbidity and mortality in many parts of the world[24] and accounts for half of the 17 million worldwide annual deaths from cardiovascular disease (CVD).[23] Hospital readmission is common among patients with AMI.[66] It is estimated that 37% of the United States population were living with a CVD in 2010 and the direct medical costs for CVD are predicted to triple from US$ 272.5 billion in 2010 to US$ 818.1 billion in 2030 while the productivity losses are projected to increase 61% during the same period.[29] In Canada, CVD is the second most expensive healthcare burden, costing $22 billion in 2000 (~$30 billion in 2016 dollars).[8] The higher prevalence of AMI associated with an aging population[70] and improved survival among patients with AMI[26] will likely increase its cost burden over time. However, little is known about the current cost burden of AMI on the health care systems, and how this cost burden is changing over time. In this study, we examined the health care costs associated with AMI between 2004 and 2013 in the province of Alberta, Canada.

4.2. Methods

Data source and study population

We conducted a retrospective cohort study using five linked administrative databases including Ambulatory Care Database, acute care inpatient records (Discharge Abstract Database [DAD]), Practitioner Claims, Pharmaceutical Information Network (PIN), and Population Registry in the province of Alberta, Canada.[36] Ambulatory Care Database contains all ambulatory care utilization (same-day surgery, day procedures, emergency department visits, and community rehabilitation services at publicly-funded facilities). It provides information on patient demographics, diagnoses, procedures, and Comprehensive Ambulatory Classification System (CACS) grouping identifying homogenous patient clusters.[71] DAD tracks all acute care hospitalizations in the province. It contains patient demographics, diagnoses, and Case Mix Group (CMG) classification (equivalent to CACS for hospitalized patients).[72] Practitioner Claims contains fee for service claims information for physicians and other providers for insured health services. PIN records information on drug dispensed for prescribed medications at almost all pharmacies in the provinces. Finally, Population Registry provide demographic and vital statistics for all inhabitants of Alberta.[36] The annual population of Alberta during 2004-2013 was used to calculate AMI prevalence over time.[73]

We first selected all ambulatory care visits and hospitalizations from April 1, 2004 to March 31, 2014 (fiscal years [FY] 2004- 2013) in which AMI (International Classification of Diseases [ICD], 10th revision, codes I21 or I22) was recorded as the primary diagnosis to create the study cohort. All practitioner claims relating to cohort members with a primary diagnosis of AMI (ICD, 9th revision, code 410) and AMI-related drug dispensing events to cohort members

that occurred during the study period were then retrieved. AMI related drugs were defined as: 1) antihypertensive agents, 2) diuretics, 3) peripheral vasodilators, 4) beta blockers, 5) calcium channel blockers, 6) agents acting on the renin-angiotensin system, 7) lipid modifying agents, and 8) antithrombotic agents. Anatomical Therapeutic Chemical (ATC) drug codes are presented in Supplemental Table S4.1.

Main outcomes

Main outcomes were total and annual costs for AMI. From a health care payer perspective, we defined annual costs as the annual summation of hospitalization, ambulatory care, practitioner claims, and drug costs incurred for all patients with AMI as the primary diagnosis. Other outcomes were distribution of health care costs by MI subtypes (ST-segment elevation MI [STEMI], non-ST-segment elevation MI [NSTEMI], and undefined/recurrent MI [Other MI]) and by sex and age (<50, 50-59, 60-69, 70-79, and ≥80 years).

Hospitalization costs

We used the Alberta Interactive Health Data Application (AIHDA) Hospital Inpatient Care Case Costs version 2013 to provide dollar values for each hospitalization based on its CMG classification.[74] The AIHDA CMG costs provide functional centre direct (e.g., nursing, diagnostic and therapeutic costs) and indirect costs (e.g., general administration and support services).[75] As the CMG codes were only available for FYs 2006-2012 in the DAD, we developed a generalized linear model (GLM) with gamma distribution and log link to estimate the average costs per hospitalization during this time period using a previously described algorithm.[76] The variables included in the model were FY, MI subtypes, patient sex and age

group. We used the model's coefficients to calculate average annual costs per hospitalization for FYs 2004, 2005 and 2013 for which CMG codes were not available. Annual total AMI hospitalization costs for each combination of sex, age group and MI subtype were derived by multiplying number of hospitalizations in each group by the costs per hospitalization in that group.

Ambulatory care costs

We used the AIHDA Ambulatory Care Case Costs version 2013 to provide dollar values for each ambulatory care visit based on its CACS code.[74] Similar to AIHDA CMG costs, the AIHDA CACS costs provide functional centre direct and indirect costs.[77] The CACS codes were only available for FYs 2006-2012 in the ambulatory care database. Therefore, we also developed a GLM model with gamma distribution and log link with FY, MI subtypes, patient sex and age group being independent variables to estimate the average costs per ambulatory visit during this time period and used the model's coefficients to calculate average costs per ambulatory care visits for FYs 2004, 2005, and 2013 for which the CACS codes were not available. Annual total AMI ambulatory care costs for each combination of sex, age group and MI subtype were derived by multiplying the number of visits in each group by the costs per visit in that group.

Practitioner claims costs

The practitioner claims database provides a paid amount and a system assessed amount to each claim. We used the paid amounts as costs for fee-for-service claims. For alternative relationship plan (ARP) claims (~10% of all claims) where the paid amounts were unavailable,

the system assessed amounts were used instead. We summed all claim costs in a year to determine annual practitioner claims costs.

Drug costs

We used the Alberta Drug Benefit List (ADBL)[38] to provide drug unit prices. If a drug price was not listed in the ADBL, we used the market price at Canada Drugs.[78] Drug costs of a dispensing event were then derived by multiplying the price of a dispensed unit by the number of units dispensed. We summed the costs of individual dispensing events per year to determine annual total drug costs.

Statistical analysis

We summarized patient characteristics using means (±SD), medians (interquartile ranges), counts and percentages, as appropriate. A patient was counted each year if s/he had either a hospitalization or an ambulatory care visit or a practitioner claim. As there is no indication of MI subtype in the practitioner claims and PIN databases, we assumed the MI subtype of the previous ambulatory care visit or hospitalization, whichever was closest, for a claim or drug dispensing event. We used previously validated ICD codes to identify patient comorbidities.[79] Comorbidities were considered to be present if they were recorded in any hospitalization or ambulatory care visit in each year of the study period. Univariate GLM regression was used to test for trends of costs over time. A non-parametric trend test was used for trend tests of medians and univariate linear regression was used for trend tests of means. All costs were converted to Canadian 2016 dollar values using the Bank of Canada inflation calculator.[80]

All analyses were performed using Stata version 14 (Stata Corporation, College Station, Texas); Two-sided P values < 0.05 were considered statistically significant.

4.3. Results

Study cohort descriptive statistics

Between FY 2004 and 2013, there were 55,384 hospitalizations, 75,309 ambulatory care visits, 524,238 practitioner claims, and 4,798,869 drug dispensing events involving 52,912 unique patients with AMI (Table 4.1). Patient characteristics by year are presented in Table 4.2. The number of patients increased from 6,031 in 2004 to 7,455 in 2013 ($p<0.001$), as did the number of hospitalizations (2004: 4,935; 2013: 6,071; $p<0.001$). However, population prevalence rates remained stable ($p=0.782$). The mean age of patients decreased over time ($p<0.001$), as did the proportion of females ($p<0.001$). The median hospital length of stay (LOS) decreased from 7 days in 2004 to 5 days in 2013 ($p<0.001$). Heart failure and diabetes mellitus were the most common comorbidities. The rates of heart failure decreased (2004: 16.4%; 2013: 12.7%; $p<0.001$) while the rates of diabetes mellitus increased over time (2004: 20.1%; 2013: 29.0%; $p<0.001$). However, the median Charlson score remained unchanged during the study period ($p=0.263$).

Total health care costs

Overall, AMI cost the Alberta health care system $1,033 million between 2004 and 2013. Of this, hospitalization costs accounted for the highest proportion ($716.4 million, 63.1% of total health care costs between FY 2008-2013 where ambulatory care, hospitalization, practitioner

claims and drug costs were all available), followed by drug costs ($147.2 million, 21.1%), ambulatory care costs ($94.5 million, 8.8%) and practitioner claims ($74.9 million, 7.0%) (Figure 4.1).

Both hospitalization (annual average=$71.6 million; p=0.141) and ambulatory care (annual average=$9.5 million; p=0.888) costs remained unchanged despite a decrease in costs per hospitalization during the study period (2004: $13,946; 2013: $11,397; p<0.001). Practitioner claims costs increased from $5.9 million in 2004 to $9.1 million in 2013 (p<0.001), primarily due to a 7.6% annual increase in the number of claims during the study period. In contrast, drug costs dropped from $28.6 million in 2008 to $18.3 million in 2013 (p<0.001) despite a constant increase of annual drug dispensing events (Table 4.1). As a result, total health care costs for AMI decreased from $124.6 million in 2008 to $108.6 million in 2013 (p=0.002).

Distribution of costs by MI subtype, sex and age, and drug class

Overall, care for STEMI was more costly than it was for other MI subtypes in both hospital and ambulatory care settings (Table 4.3 & 4.4). However, since NSTEMI occurred more frequently, it accounted for more than half of the total health care costs. While the proportion of STEMI costs (34.2%) remained stable during the study period (p=0.921), the NSTEMI contribution increased from 44.2% in 2004 to 54.7% in 2013 (p=0.006) and other MI costs decreased from 21.5% in 2004 to 10.8% in 2013 (p=0.006) (Figure 4.2). A detailed distribution of the costs by MI subtype in hospitalization, ambulatory care, practitioner claims, and drug domains are presented in Supplemental Figure 4.1.

The total AMI health care costs for males was double that for females. The most elderly groups (aged ≥70 years) accounted for more than half of total costs for females, but only 34.1% in males. In contrast, the youngest group (aged <50 years) accounted for 14.1% of total costs for males, about two times higher than did their female counterparts (Table 4.5).

Lipid modifying agents, antithrombotic agents and agents acting on the renin-angiotensin system accounted for the highest drug costs, while diuretics and peripheral vasodilators accounted for the lowest drug costs during the study period (Figure 4.3).

4.4. Discussion

Our study of health care costs for patients with AMI in the province of Alberta, Canada showed that AMI cost the province approximately $1 billion between 2004 and 2013 ($100 million per year, equaling 0.4% of provincial health expenditure in 2013[81]). Hospital services accounted for the greatest share and practitioner claims accounted for the smallest share of total AMI health care costs. During the study period, annual AMI health care costs decreased due to a reduction in drug costs and stable hospitalization and ambulatory care costs. NSTEMI was the main cost driver for patients with AMI in the province of Alberta.

In response to ever-increasing health care costs, cost containment efforts have been implemented in many countries, including Canada.[82] In addition, there have been significant advances in diagnosis and treatment of AMI in the last several decades which may lead to productivity improvements in AMI care.[7] For example, there have been a substantial increase in the use of PCI and decrease in the use of CABG which is far more costly and resource-intensive than PCI in AMI patients.[22, 83] The combination effect of cost containment efforts and

productivity improvements might explain the decrease in annual health care costs for AMI in Alberta. However, further investigation is needed to better understand this effect.

We found that the per capita cost of AMI in Alberta was $31.7 per capita in 2010 ($117.4 million for a population of 3.7 million[73]). This is lower than the cost of $131.2 per capita in the United States[29, 84] (converted to $2016 values using Federal Reserve System exchange rate[85] and Bank of Canada inflation calculator[80]). In addition, we observed a downward trend in health care costs while Heidenreich *et al.* forecasted the opposite to happen in the United States.[29] This may be due to the fact that the U.S. study included a broader population (AMI plus angina pectoris and other forms of chronic ischemic heart disease). Furthermore, variations in patterns of practice between the two countries may have an impact on medical costs[69, 86] and overall drug prices in the United States are approximately 2.9 times higher than in Canada.[87]

Our study confirmed that hospital services and drugs account for the majority of total health care costs for patients with AMI. While Seo *et al*. reported that hospitalization costs could account for 73% of total medical costs in Korea[31], Mantovani *et al*. reported a 77% and 15% attribution of inpatient care and drug costs, respectively, to the total medical costs in Italy.[33] In addition to opportunities to improve quality of care while controlling costs by preventative strategies[88], these findings emphasize the importance of cost saving strategies in hospital (i.e. utilizing the right procedure for the right patient and reduction of LOS). During the study period, we observed decreased costs per hospitalization which may be a composite effect of the reduction in costs for patients who underwent PCI[89] and decreased LOS during the study

period. It was reported previously that differences in procedure and LOS could contribute 34% and 53% to the variation in total hospital costs, respectively.[86]

Even though STEMI is an acute condition requiring expedited diagnosis and intervention and was more costly to treat, we found that NSTEMI was the biggest resource consumption and cost driver. Our findings are consistent with previously reported results which show a significant increase of the NSTEMI proportion from 52.8% in 2002 to 68.6% in 2011.[90] These findings suggest NSTEMI patients could be a potential target for future cost containment efforts. Recent studies have shown a high proportion of NSTEMI patients could be admitted to telemetry wards rather than resource-intensive and costly critical care units with no difference in clinical outcomes.[91, 92]

Although our study provides novel data on the health care costs of AMI in the province of Alberta, it has some limitations. First, we did not include productivity losses due to mortality and morbidity. Indirect costs for AMI could be equal to or higher than direct medical costs.[29, 31] Therefore, the true cost burden of AMI on Albertans is substantially higher than what we reported. Second, we did not have drug data for the years 2004-2007, so the drug costs could be significantly higher. Third, we could not account for any diagnostic errors and misclassification (in terms of MI subtype). Although Canadian administrative data have been shown to be valid relative to chart abstraction, these data may be affected by data entry errors, omissions and inconsistencies.[52, 53]

4.5. Conclusions

Health care costs for AMI are significant; however, they decreased slightly during the study period in the province of Alberta. Not surprisingly, hospital services accounted for the most of the AMI care costs. There are still opportunities to further improve cost saving efforts in AMI care. Our study suggests that further investigation is needed to better understand cost saving efforts in the province of Alberta and to explore possibility of replication to other jurisdictions.

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4.7. Tables

Table 4-1: Health services utilization for patients with AMI in Alberta, Canada, 2004- 2013

Variable	Total	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Hospital admissions, N	55,384	4,935	4,978	4,856	5,650	5,429	5,670	5,875	5,891	6,029	6,071
STEMI, n (%)	18,579 (33.6)	1,560 (31.6)	1,527 (30.7)	1,594 (32.8)	1,970 (34.9)	1,795 (33.1)	1,942 (34.3)	2,140 (36.4)	2,028 (34.4)	2,005 (33.3)	2,018 (33.2)
NSTEMI, n (%)	30,362 (54.8)	2,161 (43.8)	2,470 (49.6)	2,456 (50.6)	3,151 (55.8)	3,145 (57.9)	3,209 (56.6)	3,290 (56)	3,408 (57.9)	3,547 (58.8)	3,525 (58.1)
Other MI, n (%)	6,443 (11.6)	1,214 (24.6)	981 (19.7)	806 (16.6)	529 (9.4)	489 (9.0)	519 (9.2)	445 (7.6)	455 (7.7)	477 (7.9)	528 (8.7)
Ambulatory care visits, N	75,309	7,590	6,674	6,417	6,534	8,938	9,624	10,709	8,101	5,242	5,480
STEMI, n (%)	13,929 (18.5)	1,768 (23.3)	1,389 (20.8)	1,230 (19.2)	1,106 (16.9)	1,170 (13.1)	1,213 (12.6)	1,459 (13.6)	1,603 (19.8)	1,452 (27.7)	1,539 (28.1)
NSTEMI, n (%)	19,985 (26.5)	2,297 (30.3)	2,042 (30.6)	2,062 (32.1)	1,549 (23.7)	1,784 (20)	1,780 (18.5)	1,944 (18.2)	1,937 (23.9)	2,249 (42.9)	2,341 (42.7)
Other MI, n (%)	41,395 (55.0)	3,525 (46.4)	3,243 (48.6)	3,125 (48.7)	3,879 (59.4)	5,984 (67)	6,631 (68.9)	7,306 (68.2)	4,561 (56.3)	1,541 (29.4)	1,600 (29.2)
Practitioner claims, N	524,238	35,055	42,511	46,866	52,067	50,815	54,964	55,261	56,845	63,497	66,357
STEMI, n (%)	164,346 (31.4)	8,242 (23.5)	10,146 (23.9)	11,728 (25)	16,417 (31.5)	15,372 (30.3)	18,307 (33.3)	19,477 (35.2)	20,232 (35.6)	21,497 (33.9)	22,928 (34.6)
NSTEMI, n (%)	248,476 (47.4)	13,800 (39.4)	19,275 (45.3)	21,820 (46.6)	25,293 (48.6)	25,420 (50)	26,238 (47.7)	25,302 (45.8)	27,098 (47.7)	32,127 (50.6)	32,103 (48.4)
Other MI, n (%)	111,416	13,013	13,090	13,318	10,357	10,023	10,419	10,482	9,515	9,873	11,326

	(21.3)	(37.1)	(30.8)	(28.4)	(19.9)	(19.7)	(19)	(19)	(16.7)	(15.5)	(17.1)
Drug dispensing events, N	4,798,869					636,997	699,885	762,841	859,446	888,912	950,788
STEMI, n (%)	1,140,622 (23.8)					138,299 (21.7)	157,887 (22.6)	177,750 (23.3)	204,535 (23.8)	220,393 (24.8)	241,758 (25.4)
NSTEMI, n (%)	2,487,284 (51.8)					340,984 (53.5)	367,292 (52.5)	392,599 (51.5)	440,728 (51.3)	455,753 (51.3)	489,928 (51.5)
Other MI, n (%)	1,170,963 (24.4)					157,714 (24.8)	174,706 (25)	192,492 (25.2)	214,183 (24.9)	212,766 (23.9)	219,102 (23)
Hospital LOS, in day, median (IQR)		7 (4-10)	6 (4-10)	6 (4-9)	5 (4-9)	5 (4-8)	5 (3-8)	5 (3-7)	5 (3-7)	5 (3-7)	5 (3-7)

AMI: acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non- ST-segment elevation myocardial infarction; Other MI: combined group of undefined myocardial infarction and recurrent myocardial infarction; IQR: interquartile range; LOS: acute length of stay.

Table 4-2: Characteristics of study population

Variable	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Patients, N	6,031	6,487	6,741	6,872	6,972	7,102	7,347	7,517	7,419	7,455
Prevalence rate (/100,000 population)	186	195	197	196	194	193	197	198	191	186
Female (%)	33.3	33.8	33.3	32.6	32.6	32.3	31.0	30.9	33.0	31.2
Age in year, mean (SD)	67.1 (14.3)	67.1 (14.4)	66.9 (14.4)	66.4 (14.3)	66.3 (14.4)	66.5 (14.4)	66.0 (14.4)	66.3 (14.3)	66.6 (14.3)	66.4 (14.1)
Age in year, median (IQR)	68 (56-79)	68 (56-79)	67 (56-78)	66 (55-78)	66 (55-78)	66 (55-78)	65 (55-78)	66 (56-78)	66 (56-78)	66 (56-77)
Patient by age group (%)										
<50 years	12.2	11.8	12.4	12.8	12.8	12.3	12.6	12.2	11.6	11.0
50-59 years	20.3	21.0	21.0	21.7	22.2	22.0	23.0	22.2	22.3	22.6
60-69 years	20.5	20.1	20.9	22.2	21.5	22.2	23.0	24.6	24.0	24.8
70-79 years	23.8	24.0	23.6	22.2	22.3	21.5	20.2	19.4	20.0	20.4
≥80 years	23.2	23.2	22.2	21.0	21.2	22.0	21.1	21.6	22.0	21.2
Selected comorbidity (%)										
Heart failure	16.4	17.5	15.0	15.2	14.5	13.8	13.3	11.5	13.0	12.7
Peripheral vascular disease	4.2	3.9	3.3	3.9	3.1	3.1	3.0	2.8	3.1	2.9
CVD	3.3	2.7	2.7	3.2	2.4	2.2	2.2	2.2	1.9	1.5
Cancer	2.4	2.2	2.6	2.5	2.5	2.3	2.2	2.1	2.6	2.3
COPD	9.7	10.8	8.8	9.7	9.7	9.6	9.0	9.5	9.5	8.4
Diabetes	20.1	21.9	22.8	26.7	24.2	24.2	23.7	25.6	27.5	29.0
Dementia	2.9	3.2	2.8	2.9	2.7	2.7	2.7	2.8	2.9	2.3
Renal disease	7.6	8.5	6.9	7.2	7.4	5.5	4.4	4.2	5.0	4.1
Charlson score, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)

SD: standard deviation; IQR: interquartile range; LOS: acute length of stay; CVD: Cerebrovascular disease; COPD: chronic obstructive pulmonary diseases.

Table 4-3: Average costs per hospitalization with AMI in Alberta, Canada in CA$2016 dollars, 2004-2013

Fiscal Year	All	STEMI	NSTEMI	Other MI
2004	13,946	15,175	14,134	12,529
2005	13,637	14,839	13,820	12,251
2006	13,334	14,510	13,514	11,979
2007	13,039	14,188	13,214	11,714
2008	12,749	13,873	12,921	11,454
2009	12,467	13,566	12,635	11,200
2010	12,190	13,265	12,355	10,952
2011	11,920	12,971	12,081	10,709
2012	11,656	12,683	11,813	10,471
2013	11,397	12,402	11,551	10,239

Table 4-4: Average costs per ambulatory care visit with AMI in Alberta, Canada in CA$2016 dollars, 2004-2013

Fiscal Year	All	STEMI	NSTEMI	Other MI
2004	1,761	2,504	2,398	381
2005	1,756	2,496	2,390	380
2006	1,750	2,489	2,383	379
2007	1,745	2,481	2,376	378
2008	1,739	2,473	2,368	377
2009	1,734	2,465	2,361	375
2010	1,728	2,458	2,353	374
2011	1,723	2,450	2,346	373
2012	1,718	2,442	2,339	372
2013	1,712	2,435	2,331	371

AMI: acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non- ST-segment elevation myocardial infarction; Other MI: combined group of undefined myocardial infarction and recurrent myocardial infarction.

Table 4-5: Health care costs for AMI by sex and age in Alberta in CA$2016 dollars (millions), 2004- 2013

Group	Total	Hospitalization	Ambulatory care	Practitioner claims	Drug(*)
All patients	1,033.0	716.4	94.5	74.9	147.2
Female	317.5	221.6	26.9	22.2	46.9
< 50 years	23.8	17.1	2.6	1.8	2.3
50- 59 years	47.7	32.8	4.8	3.6	6.6
60- 69 years	63.6	42.5	5.9	4.6	10.6
70- 79 years	81.7	56.4	6.9	5.7	12.7
≥ 80 years	100.7	72.8	6.8	6.4	14.6
Male	715.4	494.8	67.6	52.8	100.3
< 50 years	101.0	72.1	11.9	7.8	9.2
50- 59 years	190.0	131.3	19.9	14.6	24.2
60- 69 years	180.7	121.4	17.1	13.4	28.8
70- 79 years	145.6	99.5	11.9	10.3	23.9
≥ 80 years	98.1	70.5	6.8	6.6	14.2

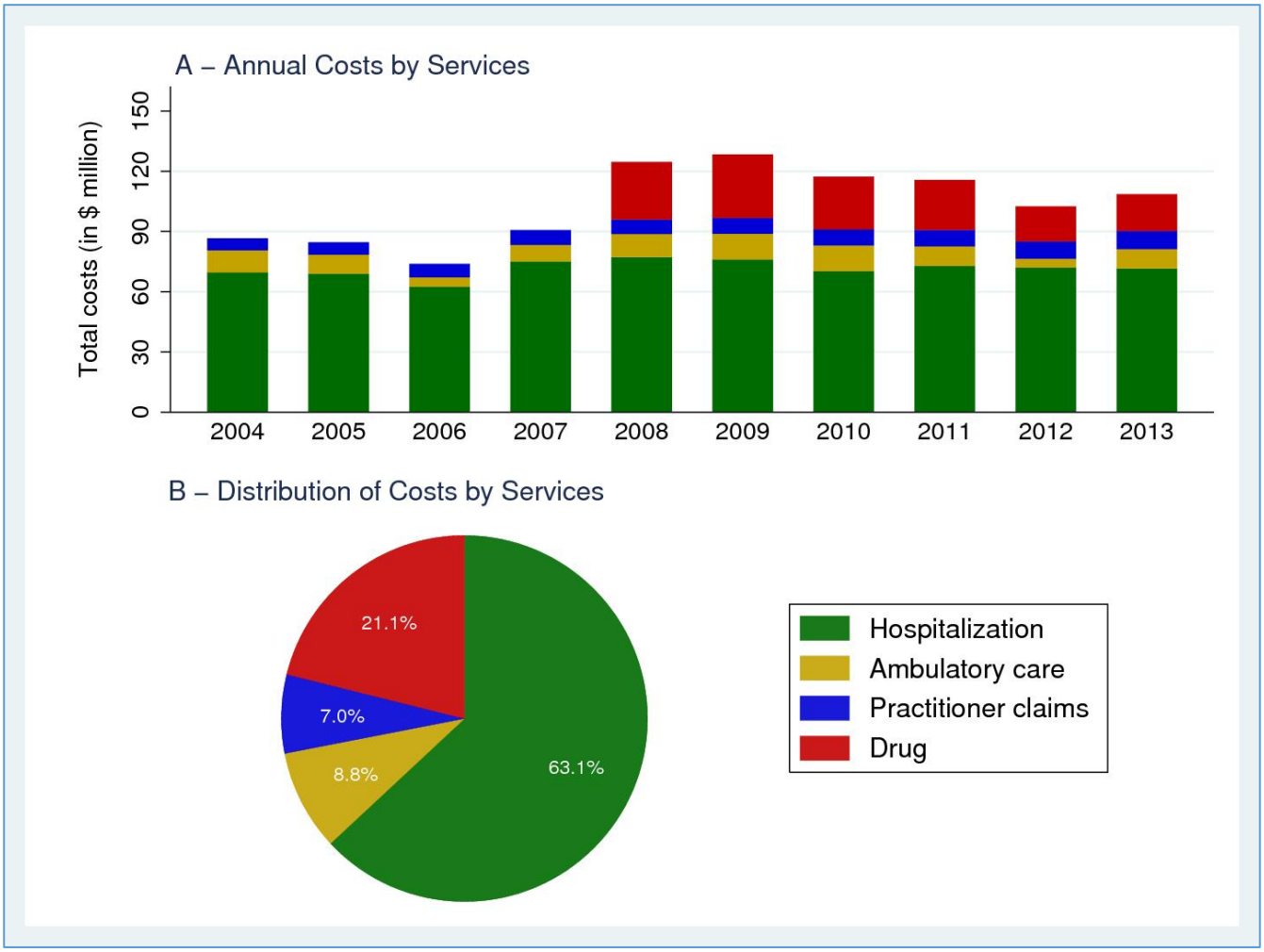
AMI: acute myocardial infarction. (*)Drug costs were available from FY2008-FY2013 only.

Supplemental Table S4-1: Anatomical Therapeutic Chemical (ATC) code of AMI drugs

Drug group	ATC codes
Antihypertensive agents	C02
Diuretics	C03
Peripheral vasodilators	C04
Beta blockers	C07
Calcium channel blockers	C08
Agents acting on the renin-angiotensin system	C09
Lipid modifying agents	C10
Antithrombotic agents	B01

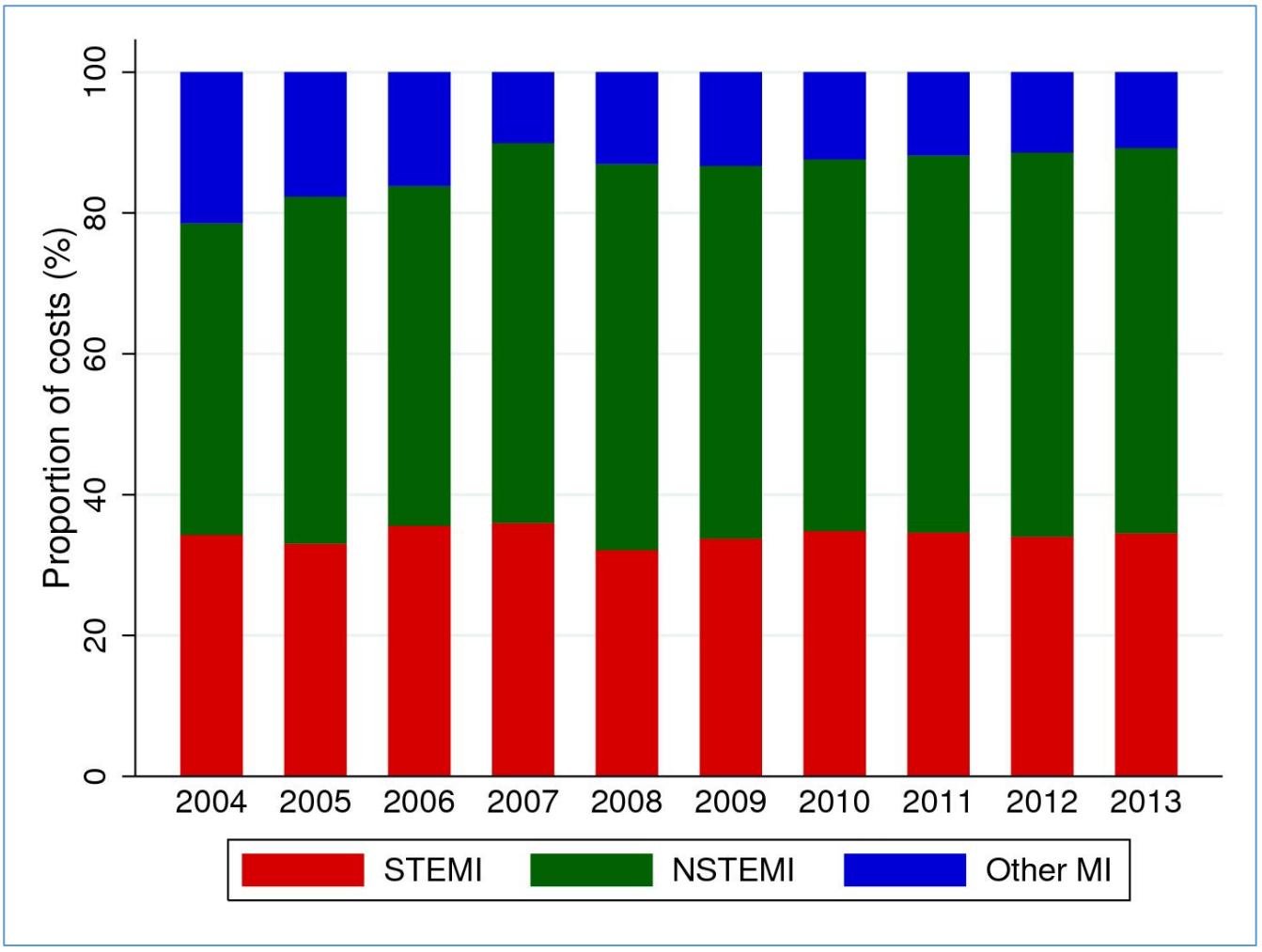
4.8. Figures

Figure 4-1: Healthcare costs for AMI in Alberta, Canada in 2016 dollars, 2004- 2013



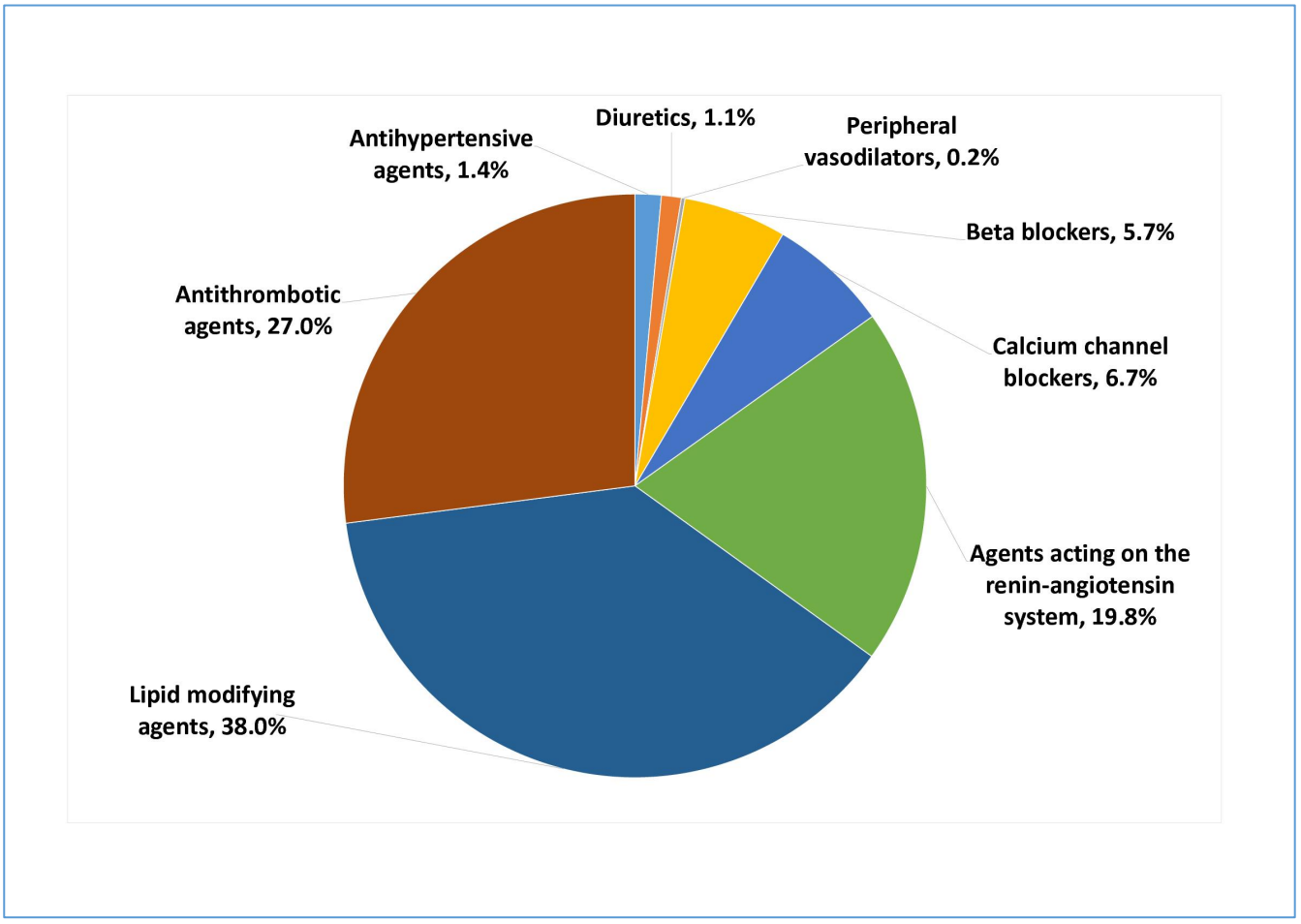
AMI: acute myocardial infarction

Figure 4-2: Distribution of health care costs by AMI subtype in Alberta, Canada, 2004-2013



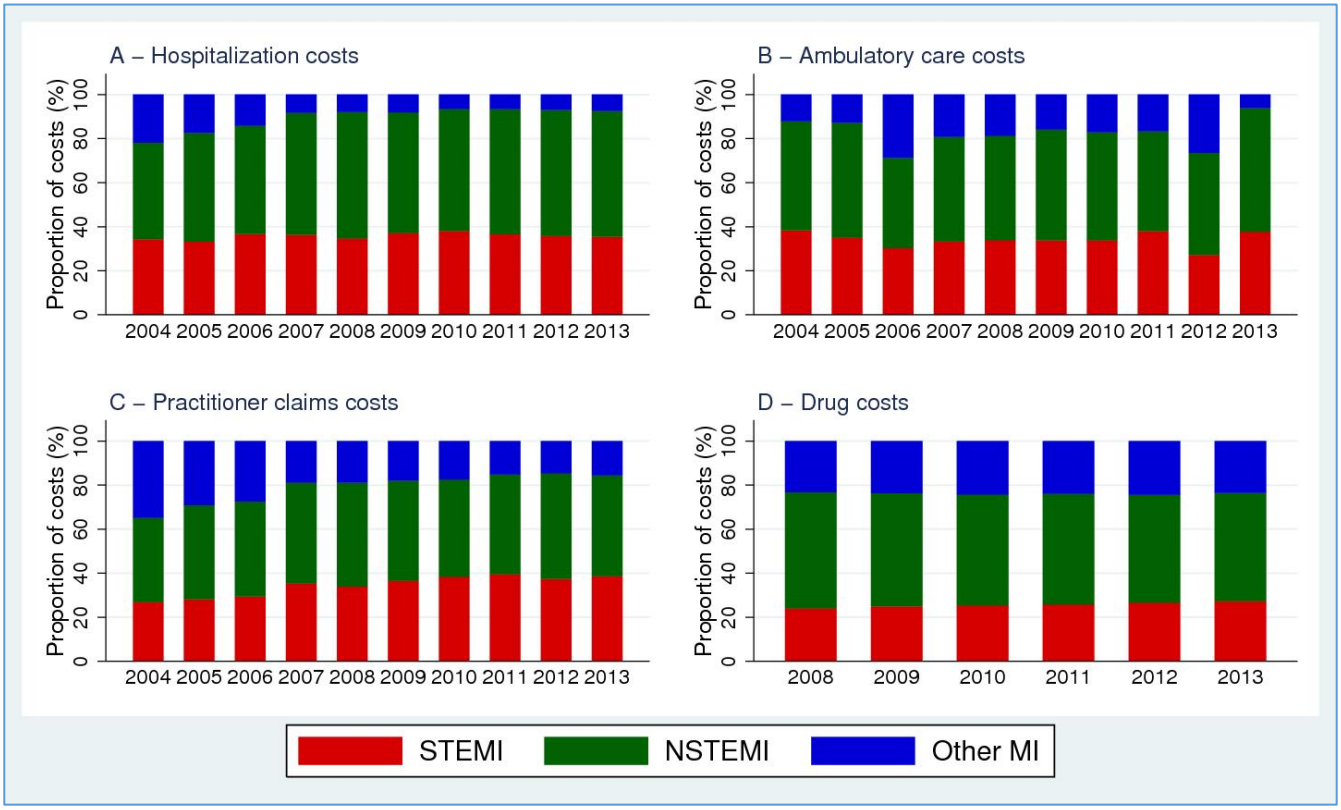
AMI: acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non- ST-segment elevation myocardial infarction; Other MI: combined group of undefined myocardial infarction and recurrent myocardial infarction

Figure 4-3: Drug costs distribution by main ATC groups



ATC: Anatomical Therapeutic Chemical

Supplemental Figure S4-1: Distribution of health care costs by AMI subtypes in Alberta, 2004-2013



AMI: acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non- ST-segment elevation myocardial infarction; Other MI: combined group of undefined myocardial infarction and recurrent myocardial infarction

Chapter 5 : RESOURCE USE AND RELATIVE BURDEN OF HOSPITALIZATION, OUTPATIENT, PHYSICIAN, AND DRUG COSTS IN THE SHORT- AND LONG-TERM AFTER ACUTE MYOCARDIAL INFARCTION

This chapter is based on the manuscript "Tran DT, Welsh RC, Ohinmaa A, Thanh NX and Kaul P. Resource Use and Relative Burden of Hospitalization, Outpatient, Physician, and Drug Costs in the Short- and Long-Term after Acute Myocardial Infarction" which will be submitted to The European Journal of Health Economics.

5.1. Introduction

Acute myocardial infarction (AMI) is an acute condition caused by a blockage of one or more coronary arteries which supply blood to the heart muscle. AMI has high mortality and morbidity burden.[23, 24] The age-sex standardized 30-day mortality after admission to hospital in Organization for Economic Co-operation and Development (OECD) countries ranged from 4.1% in Australia to 28.2% in Mexico in 2013.[93] Thirty-day hospital readmission among AMI patients who underwent percutaneous coronary intervention (PCI) could be as high as 17.5%.[66] Acute reperfusion with fibrinolytic therapy or primary PCI in ST-segment elevation MI (STEMI) and revascularization by PCI or coronary artery bypass grafting (CABG) are key factors in the care of patients with AMI.[13, 14, 21]

The topic of economic burden of cardiovascular disease (CVD) in general and AMI in particular has been of interest to many. From the broadest societal perspective[28], CVD could cost the United States as high as US$1,094 billion in 2030.[29] Likewise, the cost burden of

CVD in the Europe could also be as high as €170 billion per year.[30] For AMI specifically, Seo *et al.* estimated that the total costs of AMI in South Korea in 2012 was US$1.2 billion.[31] From a narrower health care payer perspective, Soekhlal *et al.* reported average treatment costs of €5,021 for an AMI patient in its acute phase in the Netherlands.[32] Mantovani *et al.* reported higher one-year health care costs of €9,135 per patient after the first AMI event in Italy.[33] In a comparison of hospital costs for AMI in the Europe, Tiemann *et al.* reported a significant variation of cost per case from €396 in Hungary to €7,450 in Italy.[34]

Currently, little is known about resource use and the cost burden of AMI beyond that of the index hospitalization. Accordingly, we examined resource use and the distribution of hospital, outpatient, physician, and drug costs during the first year, and in each subsequent year, among patients hospitalized with incident AMI in the province of Alberta, Canada. Our study could be informative for designing effective healthcare policies to alleviate the economic burdens of AMI.

5.2. Methods

Data source and study population

We conducted a retrospective cohort study using the following six linked administrative databases: Ambulatory Care Database, Discharge Abstract Database (DAD), Practitioner Claims, Pharmaceutical Information Network (PIN), Population Registry, and Vital Statistics in the province of Alberta, Canada[36] from April 1, 2004 to March 31, 2014 (fiscal years [FY] 2004-2013) to identify patients aged ≥ 18 years with an incident AMI (International Classification of Diseases [ICD], 10th revision, codes I21.0-I21.3 for ST-segment elevation

myocardial infarction [STEMI], I21.4 for non-ST-segment elevation myocardial infarction [NSTEMI], and I21.9 for undefined MI). Incident cases were defined as those without an AMI hospitalization in the previous 10 years. All ambulatory care visits, hospitalizations, and practitioner claims where AMI was coded as the primary diagnosis, and drug dispensing records from incident AMI to death or being censored by March 31, 2016 were then retrieved.

Variables of interest

The main variables included in this analysis are annual resource use (number of hospital days, number of ambulatory care visits, number of practitioner claims, and number of cardiac procedures including catheterization, PCI and CABG) and the average annual health care costs per patient from incident AMI. In this study, we defined health care costs as the summation of ambulatory care, hospitalization, practitioner claims, and drug costs where AMI was coded as the primary diagnosis incurred for an AMI patient. Other variables of interest were short- and long-term distribution of costs per patient by MI subtypes (STEMI, NSTEMI, and undefined MI) and by sex and age (<50, 50-59, 60-69, 70-79, and ≥80 years).

Cardiac procedure

We used Canadian Classification of Health Interventions codes to identify catheterization (code of 3.IP.10.VX), PCI (codes of 1.IJ.50** and 1.IJ.57.GQ**), and CABG (code of 1.IJ.76**) in any of the 10 intervention fields in the ambulatory care record or any of the 20 intervention fields in the DAD record.[37] If there were two identical procedures in a single ambulatory care visit or hospitalization, only the first procedure was counted.

Costing methods

a) Ambulatory care and hospitalization costs

We used the Alberta Interactive Health Data Application (AIHDA) to provide dollar values for each ambulatory care visit and hospitalization based on its Comprehensive Ambulatory Classification System (CACS) and Case Mix Group (CMG) codes, respectively.[74] The AIHDA CACS and CMG costs provide functional centre direct (e.g., nursing, diagnostic and therapeutic costs) and indirect costs (e.g., general administration and support services).[75, 77] As the CACS and CMG codes are both only available for FYs 2006-2012 and 2014-2015 in the ambulatory care and DAD, we developed two generalized linear models (GLM) with gamma distribution and log link to estimate the average costs per ambulatory care visit and hospitalization, respectively, during this time period using a previously described algorithm.[76] The variables included in the models were FY, MI subtypes, and patient sex and age group. We then used the models' coefficients to calculate average costs per ambulatory care visit and hospitalization for FYs 2004, 2005 and 2013 for which CACS and CMG codes were not available, respectively.

b) Practitioner claims costs

The practitioner claims database provides a paid amount and a system-assessed amount to each claim. We used the paid amounts as costs for fee-for-service claims. For alternative relationship plan claims (~10% of all claims) where the paid amounts were unavailable, the system-assessed amounts were used instead.

c) Drug costs

We only selected drugs that are closely related to AMI treatment.[13, 14, 21, 94] They are 1) antihypertensive agents, 2) diuretics, 3) peripheral vasodilators, 4) beta blockers, 5) calcium channel blockers, 6) agents acting on the renin-angiotensin system, 7) lipid modifying agents, and 8) antithrombotic agents. Anatomical Therapeutic Chemical drug codes are presented in Supplemental Table S5.1 in the Appendix. We used the Alberta Drug Benefit List (ADBL)[38] to provide drug unit prices. If a drug price was not listed in the ADBL, we used the market price at Canada Drugs.[78] Drug costs of a dispensing event were then derived by multiplying the price of a dispensed unit by the number of units dispensed.

Statistical analysis

Patient characteristics were summarized using means (±SD), medians (interquartile ranges), counts and percentages, as appropriate, and were compared across MI groups using Kruskal-Wallis tests for continuous and χ^2 tests for categorical variables. Previously validated ICD codes were used to identify patient comorbidities[79] which were considered to be present if they were recorded in hospitalization or ambulatory care visit at AMI incidence or during previous three years prior to the incidence. Trends of costs over time and costs between MI groups were compared using univariate GLM regression. Count data (i.e., number of hospital day) were compared across MI groups using negative binomial regression. All costs were converted to 2016 Canadian dollar values using Canadian Consumer Price Index.[80, 95]

All analyses were performed using Stata version 14 (Stata Corporation, College Station, Texas); Two-sided P values < 0.05 were considered statistically significant.

5.3. Results

Patient characteristics

Between FY 2004 and 2013, there were 55,186 hospitalizations and 25,313 emergency department (ED) visits with AMI as the primary diagnosis of 49,511 unique patients. After excluding those aged <18 years (n=10), those who were discharged home after the ED visit (n=1,985), those who were transferred from ED to hospital for reasons other than AMI (n=3,197), and those who had a hospitalization for AMI during the previous 10 years (n=3,109), the study cohort consisted of 41,210 patients with an incident AMI with a minimum follow-up of 2 years. A flow-chart depicting patient selection is presented in Figure 5.1.

Patient characteristics, overall and by MI subtypes, are presented in Table 5.1. NSTEMI accounted for 50.8% while STEMI and undefined MI contributed 36.8% and 12.5% of the study population, respectively. The median ages of NSTEMI (68 years) and undefined MI (72 years) patients were higher than that of STEMI patients (66 years, $p<0.001$) as were the proportions of females (NSTEMI: 35.5% and undefined MI: 36.1% versus STEMI: 26.9%, $p<0.001$). Hypertension (60.8%) and diabetes mellitus (26.5%) were the two most common comorbidities. NSTEMI (mean Charlson score: 2.8) and undefined MI (mean Charlson score: 2.9) patients had more co-morbidities than their STEMI (mean Charlson score: 2.1) counterparts ($p<0.001$). Seven percent of the study population died during the index event and the median survival time of ascertained deaths was 17.1 months from incidence.

Resource use

On average, an AMI patient visited ambulatory care services 1.2 times and spent 8.6 days in hospital during the first year. During each subsequent year, there were about 4 ambulatory care visits for every 100 AMI patients and each patient spent 0.2 days in hospital. AMI related ambulatory care visits and hospital stays during the first year decreased from 1.50 visits and 9.74 days in 2004 to 0.87 visits and 7.74 days in 2013, respectively (both $p<0.001$).

During the first year, STEMI patients visited ambulatory care (mean=1.64) more frequently than their NSTEMI (mean=0.99) and undefined MI (mean=0.87) counterparts ($p<0.001$). In contrast, NSTEMI (mean=9.23 days) and undefined MI (mean=8.5 days) patients spent longer time in hospital than STEMI (mean=7.72 days) patients ($p<0.001$). Due to higher number of patients and longer hospital stay, the NSTEMI group had substantially higher total hospital days than the other groups (193,189 days vs. 116,965 days in STEMI and 43,633 days in undefined MI) during the first year (Table 5.2).

Few patients underwent cardiac procedures beyond the first year after incidence, in which, catheterization, PCI and CABG were performed for 70%, 49.8% and 1.6% of patients, respectively. Of those, 24.6% and 18.8% had more than one catheterization and PCI during the first year, respectively (Table 5.3).

Health care costs

Overall, AMI cost $19,842 per patient during the first year and about $845 per year for the next 5 subsequent years. First year costs in STEMI patients ($21,060) were higher compared

to NSTEMI ($19,648) and undefined MI ($17,039) counterparts (p<0.001) but lower during 5 subsequent years (p<0.05). Males had higher costs than females during the first year ($20,329 vs $18,828, p<0.001) but there was no significant difference during subsequent years. The oldest group (≥80 years) cost least compared to younger age groups during the first year (Table 5.4).

Hospitalization costs accounted for the majority during the first year (81.1%) while drug costs did for the subsequent 5 years (on average 62.1%, Table 5.4 & Figure 5.2). Except for a decrease in the proportion of drug costs from 58.7% in year 2 to 55.3% in year 6 among NSTEMI patients (p=0.010), the proportions of hospitalization and drug costs remained stable in all MI groups after the first year (Figure 5.2).

The AMI care costs per patient for the first year decreased from $23,327 in 2008 to $16,943 in 2013 (p<0.001), primarily as a result of the reduction in ambulatory care costs ($2,275 in 2008 to $885 in 2013, p=0.003) and hospitalization costs ($18,157 in 2008 to $13,410 in 2013, p<0.001) (Figure 5.3).

5.4. Discussion

Our study of 41,210 patients with incident AMI in the province of Alberta, Canada showed that AMI consumed the most resources and costs during the first year. Overall, STEMI, male and younger patients were more costly to manage. However, NSTEMI consumed in total more resources than other MI groups. Hospital services accounted for the greatest cost share during the first year but drugs did so during the subsequent 5 years. Care costs during the

first year decreased during the study period, mainly as a result of the reduction in ambulatory care and hospitalization costs.

Our results were consistent with those reported earlier. Mantovani *et al.*[33] found that the health care cost during the first year in Italy was $22,692 per patient (converted to $2016 values using Canadian Foreign Exchange Services[96]). The slightly higher costs reported by Mantovani may be due to the fact that all hospitalizations and outpatient claims were included, while we selected only hospitalizations and outpatient visits where AMI was coded as the primary diagnosis. In addition, differences in pattern of practices and drug prices between jurisdictions may also have an impact on medical costs.[69, 86, 87] It was reported earlier that the costs of a hospitalization with AMI could vary from a low of $704 in Hungary to a high of $13,244 in Italy (in $2016 values) depending on type of hospital and procedure performed.[34] Our results, in agreement with other studies, also support hospitalization as being the major cost contribution.[31, 33]

Even though STEMI was more costly to treat, we found that NSTEMI patients consumed more resources, especially hospital length of stays, and had a greater total costs due to a higher population. This is consistent with current clinical practice, where STEMI patients require early invasive treatment strategies (i.e. primary PCI within 90 minutes of hospital presentation and timely cardiac catheterization following fibrinolysis), whereas both invasive and conservative treatment strategies (i.e. initial medical management, followed by catheterization and revascularization only if ischemia recurs) can be used for NSTEMI patients. Given an upward trend in the NSTEMI population over time in which its proportion of total AMI increases from 52.8% in 2002 to 68.6% in 2011[90] and likelihood of hospitalization as

a result of aging population and increased risk factors[62, 97, 98], it is expected that the NSTEMI group could be a significant resource consumption and cost driver and may be a focus to alleviate the burden of AMI cost in the foreseeable future.

We found the costs during the first year after incident AMI to be the most significant and they decreased during the study period, as did the number of ambulatory care visits and the hospital length of stays. Given a stable long-term trend in outcomes of AMI in the last decade in Canada[83, 99], the reduction in costs and health service encounters may be an indication of efficiency improvement and this may warrant further research in the era of increasing health care spending.[100]

While our study provides novel data on short- and long-term resource use and health care cost burdens of AMI from incidence, it has several limitations. First, our study was conducted using data from a single jurisdiction with jurisdiction-specific cost norms. It has been reported that AMI care practice (i.e. pre-hospital strategies regarding diagnosis, triage and treatment of STEMI patients) and health outcomes vary considerably between jurisdictions.[51, 83, 99] Therefore, the study results should be interpreted with caution. Second, we used administrative health data which may contain data entry errors, omissions and inconsistencies. However, Canadian administrative data have been shown to be valid relative to chart abstraction.[52, 53]

5.5. Conclusion

Resource consumption and health care costs during the first year after incident AMI account for most of the cost burden of AMI over time. While first year costs are dominated by

hospitalizations, pharmaceuticals account for the largest proportion of costs in the long-term. NSTEMI appears to be the driver of resource use and cost burden. First year resource use and cost burden decreases during the study period, possibly suggesting efficiency improvements in AMI care.

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5.7. Tables

Table 5-1: Characteristics of studied population

Variable	All patients	STEMI	NSTEMI	Undefined MI	p
Patients, N	41,210	15,154	20,922	5,134	
Females, n (%)	13,369 (32.4)	4,081 (26.9)	7,433 (35.5)	1,855 (36.1)	<0.001
Age (mean/SD)	66.3 (14.3)	62.6 (13.7)	67.9 (14.1)	70.7 (14.7)	<0.001
Age (median/IQR)	66 (55-78)	61 (53-73)	68 (57-79)	72 (59-83)	<0.001
Age group, n (%)					
<50 years	5,214 (12.7)	2,584 (17.1)	2,176 (10.4)	454 (8.8)	<0.001
50-59 years	9,445 (22.9)	4,328 (28.6)	4,247 (20.3)	870 (17.0)	<0.001
60-69 years	9,071 (22.0)	3,532 (23.3)	4,628 (22.1)	911 (17.7)	<0.001
70-79 years	8,597 (20.9)	2,669 (17.6)	4,719 (22.6)	1,209 (23.6)	<0.001
≥80 years	8,883 (21.6)	2,041 (13.5)	5,152 (24.6)	1,690 (32.9)	<0.001
Household income, $, n (%)					
Missing	70 (0.2)	23 (0.2)	43 (0.2)	4 (0.1)	0.110
0-40,000	1,498 (3.6)	566 (3.7)	839 (4)	93 (1.8)	<0.001
40,000-60,000	19,940 (48.4)	6,973 (46)	9,876 (47.2)	3,091 (60.2)	<0.001
60,000-80,000	13,230 (32.1)	4,976 (32.8)	6,769 (32.4)	1,485 (28.9)	<0.001
80,000-100,000	4,664 (11.3)	1,914 (12.6)	2,432 (11.6)	318 (6.2)	<0.001
>100,000	1,808 (4.4)	702 (4.6)	963 (4.6)	143 (2.8)	<0.001
Selected comorbidities, n (%)					
Hypertension	25,052 (60.8)	8,165 (53.9)	13,950 (66.7)	2,937 (57.2)	<0.001
Congestive heart failure	7,195 (17.5)	1,772 (11.7)	4,178 (20.0)	1,245 (24.3)	<0.001
Peripheral vascular disease	2,686 (6.5)	618 (4.1)	1,627 (7.8)	441 (8.6)	<0.001
Cerebrovascular disease	3,022 (7.3)	723 (4.8)	1,788 (8.6)	511 (10.0)	<0.001
Dementia	1,782 (4.3)	389 (2.6)	1,037 (5.0)	356 (6.9)	<0.001
Chronic pulmonary disease	6,979 (16.9)	1,815 (12.0)	3,988 (19.1)	1,166 (22.7)	<0.001
Rheumatoid disease	866 (2.1)	244 (1.6)	507 (2.4)	115 (2.2)	<0.001
Peptic ulcer disease	984 (2.4)	268 (1.8)	541 (2.6)	175 (3.4)	<0.001
Mild liver disease	472 (1.2)	134 (0.9)	272 (1.3)	66 (1.3)	0.001
Diabetes	10,916 (26.5)	3,241 (21.4)	6,234 (29.8)	1,441 (28.1)	<0.001
Hemiplegia or paraplegia	419 (1.0)	98 (0.7)	245 (1.2)	76 (1.5)	<0.001
Renal disease	3,363 (8.2)	654 (4.3)	2,128 (10.2)	581 (11.3)	<0.001
Cancer	2,269 (5.5)	638 (4.2)	1,264 (6.0)	367 (7.2)	<0.001
Metastatic solid tumor	556 (1.4)	169 (1.1)	296 (1.4)	91 (1.8)	0.001
Charlson score, mean (SD)	2.6 (2.1)	2.1 (1.8)	2.8 (2.3)	2.9 (2.4)	<0.001
Charlson score, n (%)					
1-2	25,509 (61.9)	10,723 (70.8)	11,900 (56.9)	2,886 (56.2)	<0.001
3-4	9,349 (22.7)	3,127 (20.6)	5,014 (24.0)	1,208 (23.5)	<0.001
>=5	6,352 (15.4)	1,304 (8.6)	4,008 (19.2)	1,040 (20.3)	<0.001
Died at incidence, n (%)	2,868 (7.0)	897 (5.9)	817 (3.9)	1,154 (22.5)	<0.001
Survival time, in month, median (IQR)	17.1 (0.8-49.8)	18.8 (0.3-56.2)	22.2 (3.9-50.8)	2.4 (0-34.9)	<0.001

Table 5-2: Service utilization in AMI patients by year from incidence in Alberta, Canada

Variable	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
All patients, N	41,210	35,462	34,028	29,150	24,579	20,456
Ambulatory care visit, n	50,104	2,086	1,338	804	566	489
Ambulatory care visit, mean (SD)	1.22 (2.97)	0.06 (.91)	0.04 (.64)	0.03 (.49)	0.02 (.41)	0.02 (.39)
Hospital day, n	353,787	7,840	5,622	4,348	3,511	2,502
Hospital day, mean (SD)	8.58 (10.45)	0.22 (2.82)	0.17 (2.13)	0.15 (1.92)	0.14 (2.25)	0.12 (1.39)
Practitioner claims, n	379,096	13,542	9,775	7,736	6,376	5,059
Practitioner claims, mean (SD)	9.20 (8.61)	0.38 (2.41)	0.29 (2.08)	0.27 (1.91)	0.26 (1.97)	0.25 (1.94)
STEMI, N	15,154	13,627	13,338	11,607	9,911	8,288
Ambulatory care visit, n	24,882	997	570	322	242	247
Ambulatory care visit, mean (SD)	1.64 (3.75)	0.07 (1.02)	0.04 (0.61)	0.03 (0.54)	0.02 (0.47)	0.03 (0.52)
Hospital day, n	116,965	1,618	1,386	1,098	854	691
Hospital day, mean (SD)	7.72 (8.75)	0.12 (1.74)	0.10 (1.59)	0.09 (1.10)	0.09 (1.23)	0.08 (0.95)
Practitioner claims, n	169,118	4,301	3,013	2,557	2,112	1,818
Practitioner claims, mean (SD)	11.16 (8.73)	0.32 (1.80)	0.23 (1.62)	0.22 (1.60)	0.21 (1.81)	0.22 (1.74)
NSTEMI, N	20,922	18,360	17,438	14,707	12,180	9,986
Ambulatory care visit, n	20,745	811	545	412	240	214
Ambulatory care visit, mean (SD)	0.99 (2.40)	0.04 (0.74)	0.03 (0.47)	0.03 (0.48)	0.02 (0.32)	0.02 (0.28)
Hospital day, n	193,189	5,066	3,581	2,528	2,168	1,559
Hospital day, mean (SD)	9.23 (10.87)	0.28 (3.37)	0.21 (2.49)	0.17 (1.96)	0.18 (2.78)	0.16 (1.69)
Practitioner claims, n	177,569	7,954	5,643	4,263	3,482	2,653
Practitioner claims, mean (SD)	8.49 (8.43)	0.43 (2.83)	0.32 (2.29)	0.29 (2.09)	0.29 (2.03)	0.27 (2.02)
Undefined MI, N	5,134	3,475	3,252	2,836	2,488	2,182
Ambulatory care visit, n	4,477	278	223	70	84	28
Ambulatory care visit, mean (SD)	0.87 (2.24)	0.08 (1.19)	0.07 (1.27)	0.02 (0.24)	0.03 (0.54)	0.01 (0.14)
Hospital day, n	43,633	1,156	655	722	489	252
Hospital day, mean (SD)	8.50 (12.82)	0.33 (3.08)	0.20 (1.92)	0.25 (3.59)	0.20 (2.51)	0.12 (1.22)
Practitioner claims, n	32,409	1,287	1,119	916	782	588
Practitioner claims, mean (SD)	6.31 (7.69)	0.37 (2.01)	0.34 (2.55)	0.32 (2.10)	0.31 (2.27)	0.27 (2.28)

Table 5-3: Cardiac procedure in AMI patients by year from incidence in Alberta, Canada

Variable	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patient, N	41,210	35,462	34,028	29,150	24,579	20,456
Catheterization, n	36,588	589	459	441	343	303
Patient underwent catheterization, n (%)	28,858 (70.0)	460 (1.3)	349 (1.0)	347 (1.2)	258 (1.0)	224 (1.1)
PCI, n	24,646	335	241	237	211	181
Patient underwent PCI, n (%)	20,532 (49.8)	271 (0.8)	199 (0.6)	199 (0.7)	169 (0.7)	143 (0.7)
CABG, n	667	7	7	2	1	1
Patient underwent CABG, n (%)	667 (1.6)	7 (0.0)	7 (0.0)	2 (0.0)	1 (0.0)	1 (0.0)

Table 5-4: Care costs per AMI patient by year from incidence in $2016 values in Alberta, Canada

Variable, mean (SD)	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patient, N	41,210	35,462	34,028	29,150	24,579	20,456
All care costs						
Total	19,842 (9,042)	961 (2,714)	823 (2,306)	851 (2,247)	823 (3,106)	766 (2,185)
Ambulatory care	1,564 (3,043)	44 (566)	29 (368)	27 (342)	25 (354)	26 (333)
Hospitalization	16,094 (8,358)	331 (2,534)	249 (2,149)	247 (2,073)	209 (1,904)	217 (1,958)
Practitioner claims	1,582 (1,395)	50 (322)	38 (291)	37 (287)	37 (302)	36 (305)
Drug	603 (836)	536 (718)	508 (692)	540 (740)	553 (2,410)	486 (859)
Care costs by sex						
Male	20,329 (9,225)	942 (2,645)	810 (2,275)	837 (2,162)	823 (3,400)	768 (2,180)
Female	18,828 (8,613)	1,004 (2,863)	854 (2,375)	885 (2,433)	824 (2,237)	761 (2,199)
Care costs by age						
<50 years	20,504 (7,946)	843 (2,493)	719 (2,164)	810 (2,434)	814 (2,576)	856 (2,699)
50-59 years	20,853 (9,057)	840 (2,216)	728 (2,139)	782 (1,990)	793 (4,639)	727 (2,025)
60-69 years	20,690 (9,606)	991 (2,732)	839 (2,248)	876 (2,336)	827 (2,223)	745 (2,146)
70-79 years	20,251 (9,704)	1,046 (2,933)	912 (2,333)	929 (2,244)	914 (2,218)	852 (2,207)
≥80 years	17,118 (8,116)	1,105 (3,235)	954 (2,734)	879 (2,341)	752 (1,873)	616 (1,692)
Care costs by AMI type						
STEMI	21,060 (9,148)	864 (2,141)	757 (2,096)	778 (2,015)	732 (1,883)	715 (2,081)
NSTEMI	19,648 (8,792)	1,023 (2,848)	870 (2,408)	878 (2,310)	874 (3,954)	793 (2,258)
Undefined MI	17,039 (9,441)	1,015 (3,771)	845 (2,549)	1,010 (2,752)	939 (2,154)	834 (2,232)

Supplemental Table S5-1: Anatomical Therapeutic Chemical (ATC) code of AMI drugs

Drug group	ATC codes
Antihypertensive agents	C02
Diuretics	C03
Peripheral vasodilators	C04
Beta blockers	C07
Calcium channel blockers	C08
Agents acting on the renin-angiotensin system	C09
Lipid modifying agents	C10
Antithrombotic agents	B01

5.8. Figures

Figure 5-1: Patient selection flowchart

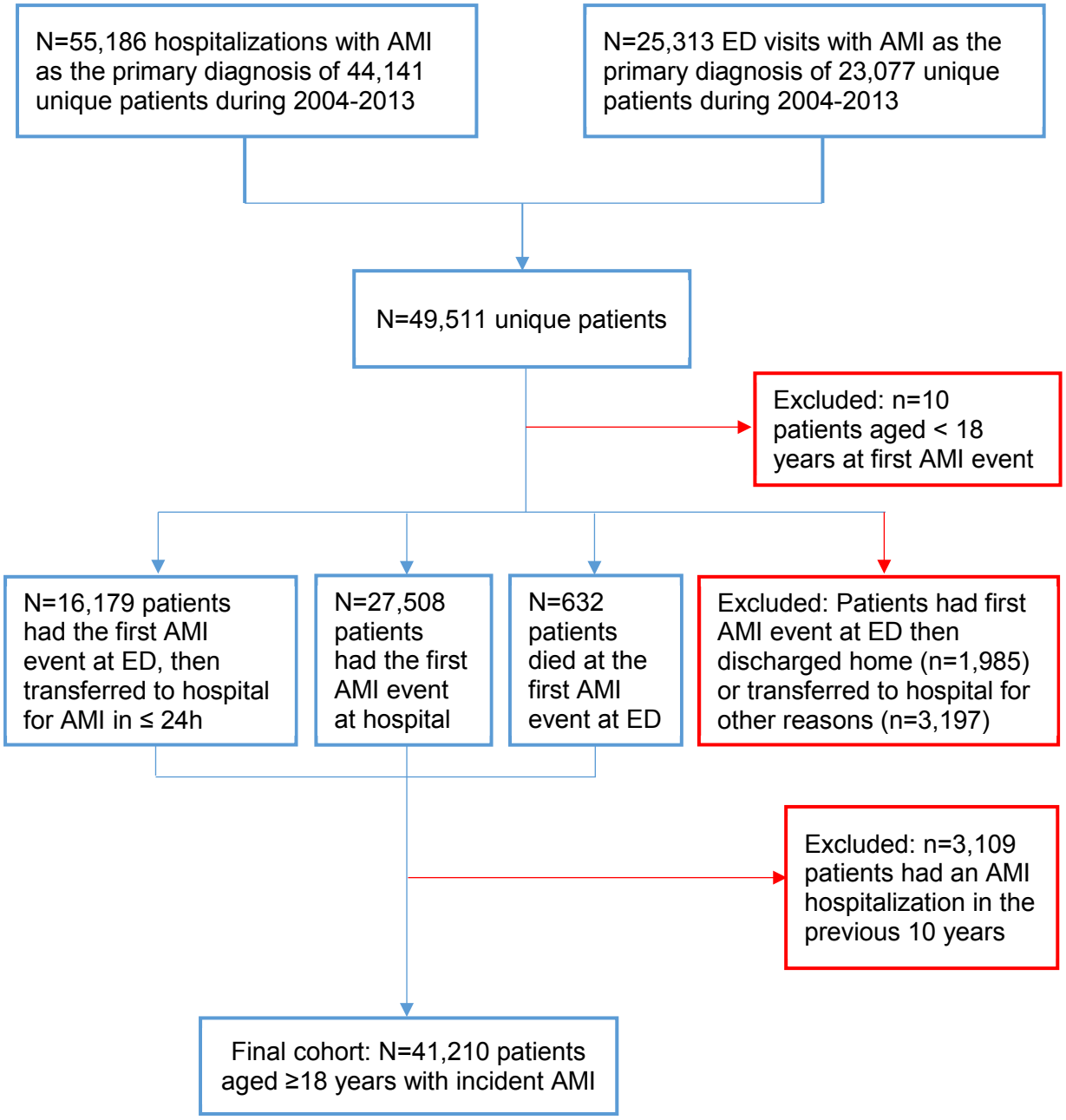


Figure 5-2: Distribution of costs per patient by year from incidence, 2008-2013, Alberta, Canada

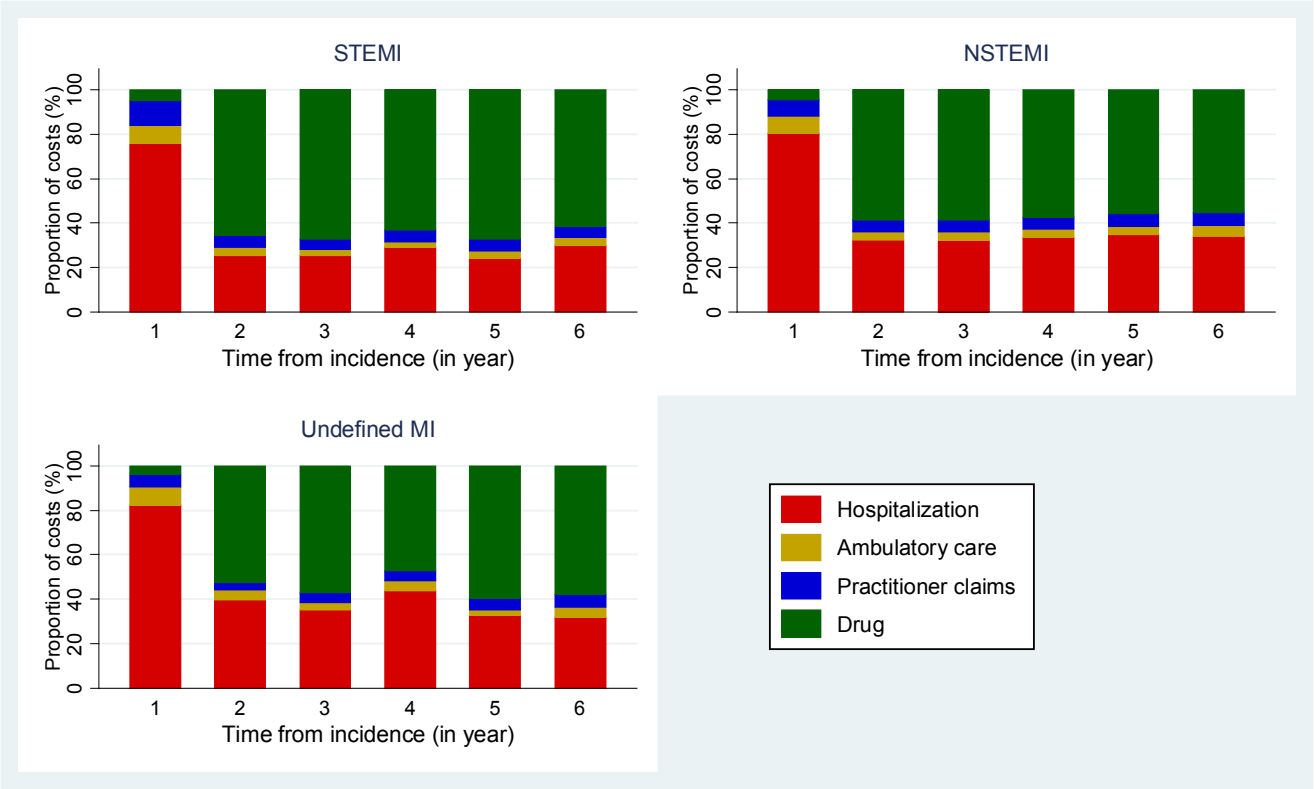
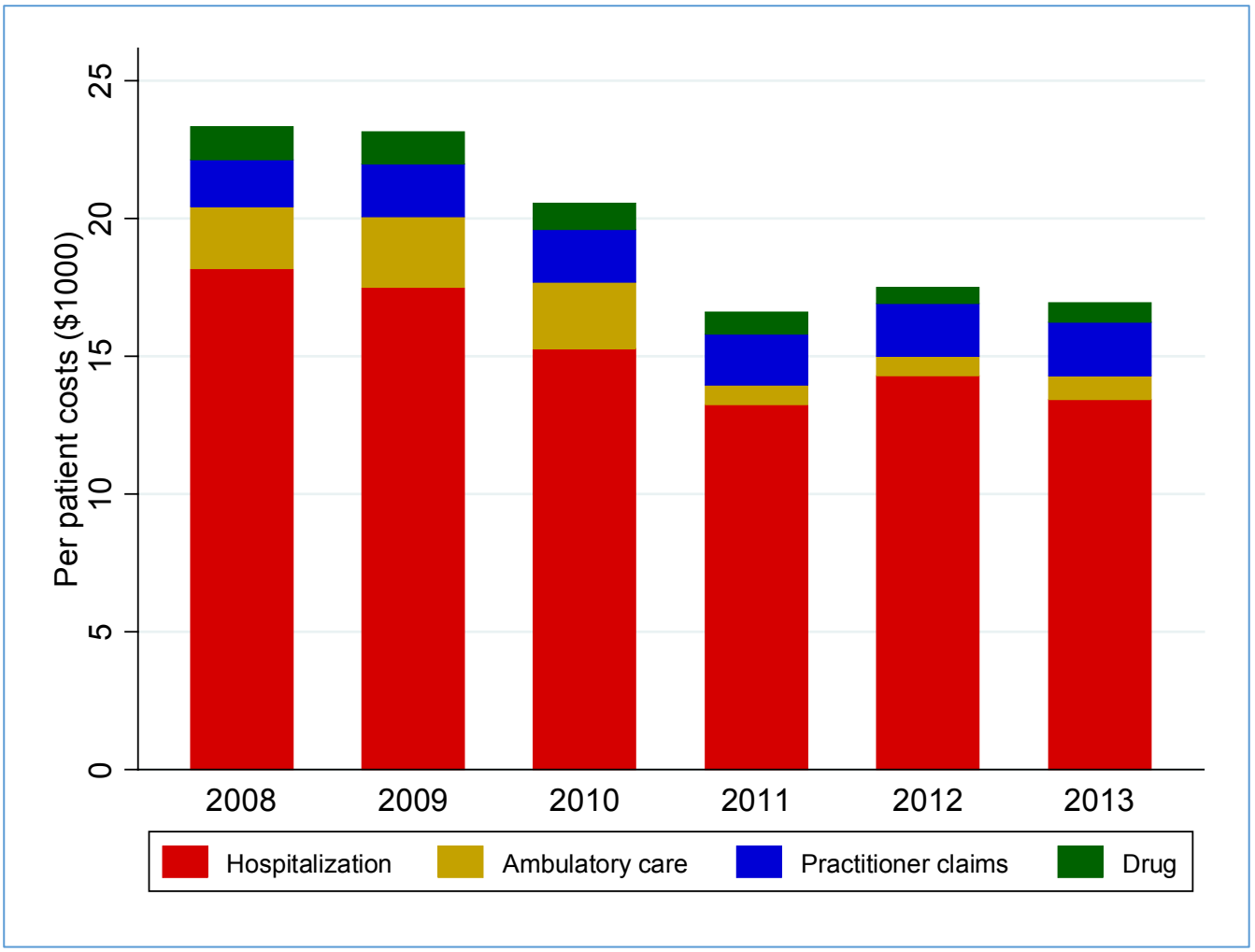


Figure 5-3: First year health care cost trend in Alberta, 2008-2013



Chapter 6 : DISCUSSION AND CONCLUSION

The overall objective of this thesis was to evaluate AMI care in Canada by inter-provincial comparison of health outcomes, resource use and costs to identify potential gaps for quality improvement. This thesis consists of 4 studies examining both health outcomes (chapters 2 & 3) and resource use and cost burden (chapters 4 & 5) of AMI care.

Despite a greater risk burden (in both higher age and comorbid conditions) in patients with AMI in recent years[26, 62, 63, 70], we observed a relatively stable trend in health outcomes over time. Specifically, in-hospital mortality among patients with STEMI presenting directly in PCI-capable hospitals (OR=1.03; p=0.091), 30-day in-hospital mortality after PCI (OR=1.01; p=0.399), and 30-day readmission after isolated-CABG (OR=0.99; p=0.116) remained unchanged; 30-day readmission after PCI (OR=1.06; p<0.001) increased slightly; and 30-day in-hospital mortality after isolated-CABG (OR=0.96; p=0.017) decreased modestly between 2004 and 2013. In fact, quality of AMI care in Canada (by means of case fatality rate) has remained close to top performers among OECD countries.[25, 93]

In addition, we observed a decreasing trend in the health care costs for AMI during the same period in the province of Alberta. The total annual costs of AMI decreased from $28.6 million in 2008 to $18.3 million in 2013 (p<0.001), while the costs per patient during the first year after incident AMI decreased from $23,327 in 2008 to $16,943 in 2013 (p<0.001). To a certain extent, the combination of stable health outcomes and decreased health care costs over time could indicate a success in AMI care in Canada.

There could be a number of potential areas for improvement in AMI care. First, there were large variations in both care practice and health outcomes across Canadian provinces. The rates of no reperfusion among patients with STEMI presenting directly to PCI-capable hospital ranged from 5.3% in New Brunswick to 49.8% in Manitoba. Accordingly, in-hospital mortality among this STEMI population varied from 4.6% in New Brunswick to 8.9% in British Columbia and Newfoundland and Labrador. Similarly, the rates of patients with AMI undergoing PCI varied from 26.9% in Newfoundland and Labrador to 53.3% in Saskatchewan and the rates of 30-day in-hospital mortality after PCI ranged from 1% in Prince Edward Island to 3.7% in Saskatchewan. The inter-provincial variations in all 5 health outcomes (in-hospital mortality, 30-day in-hospital mortality after PCI and after isolated-CABG, and 30-day readmission after PCI and after isolated-CABG) remained after risk adjustments.

The inter-provincial variations in care practice and health outcomes in Canada have also been reported earlier in the literature. For example, Schull et al.[51] reported a substantial variation in prehospital strategies (12-lead electrocardiogram, expedited ED transfer, prehospital bypass to a PCI-capable hospital, and prehospital fibrinolysis) for patients with STEMI both within and between 5 provinces including British Columbia, Alberta, Ontario, Quebec and Nova Scotia, which account for 89% of Canadian population in 2017.[97] Notably, prehospital fibrinolysis is only available in the province of Alberta despite the fact that prehospital lysis has been shown effective in reducing mortality.[17, 19, 101] Additionally, patients with STEMI who undergo prehospital lysis followed by transfer to an interventional center have better long-term outcomes than those who undergo primary PCI if the treatment could be provided within 2 hours of system onset.[102]

Similarly, based on AMI hospitalization data from 1997/98 and 1999/2000, Tu *et al.* found age-sex standardized in-hospital mortality rate varied from a low of 10.5% in Prince Edward Island to a high of 13.1% in Quebec.[45] In a more contemporary cohort of patients with AMI, we found that, although mortality outcomes have improved significantly, there continue to be large differences across Canadian provinces.

Even though variation in care practice may be inevitable in such diversified health care systems like in Canadian provinces, there is a need for a greater effort to strengthen provincial collaboration and coordination to improve the care practice and subsequently the quality of AMI care nationally. Patients with AMI should receive better and more equal care and associated health benefit regardless of their residence locations. Given the availability of international and national guidelines in AMI care, a better collaboration and coordination to improve care practice should be technically feasible.[13, 14, 21, 94, 103]

Development of a set of quality indicators in AMI care should be another area for improvement. The Canadian Institute for Health Information (CIHI) Cardiac Care Quality Indicators (CCQI) project provides a number of quality indicators regarding mortality and readmission after PCI, CABG and aortic valve replacement (AVR).[55, 60, 61] However, there is currently no specific quality indicator for AMI care. In chapter 3, we have shown that using the CCQI specifically for AMI care provides a great deal of data to better understand the performance of services. Given the importance of AMI care in determining overall population health[27, 93], we would recommend a separate set of quality indicators for AMI to be developed. In addition, a set of quality indicators for AMI care could assist the collaboration and coordination dialog we propose above. Our methods and findings in chapter 3, in conjunction

with the CCQI methodology[60, 61], could be used as the starting point for this development project.

In addition to the above mentioned results, this thesis provides a number of important findings. The superior in-hospital mortality of fibrinolysis followed by PCI in a systematic manner in chapter 2 (OR=0.92, p=0.440 for lysis and PCI ≤ 90 minutes; OR=0.42, p<0.001 for lysis and PCI > 90 minutes; compared to primary PCI ≤ 90 minutes) supports the use of fibrinolysis followed by PCI from a “real-world” perspective in the era of contemporary primary PCI. Even though primary PCI is the recommended reperfusion strategy for patients with STEMI if performed within 90 minutes of first medical contact[13, 14], we showed in chapter 2 that a substantial proportion of patients with STEMI could not undergo primary PCI in a recommended timely manner, especially for those who first present at non-PCI capable hospitals, due to geographical and resource limitations. This fact has also been reported previously.[104, 105] In this case, a pharmaco-invasive strategy where patients with STEMI are first stabilized by fibrinolysis and then are transferred to a PCI-capable center for catheterization and PCI is recommended.[20] This finding may be relevant to health policies concerning resource utilization for and operation of PCI-capable hospitals.

The stable outcomes observed in chapters 2 & 3 and the decrease of health care costs for AMI over time found in chapters 4 & 5 could have important policy implications in the era of exploding health care spending.[100] It suggests that a reduction of health care costs while maintaining quality of care could be feasible in a real-world practice. This finding is consistent with a large European study on AMI and stroke which concluded that hospitals with higher level of costs did not necessarily have a better quality of care.[106] In contrast, there are a

number of studies showing a negative association between health care spending and outcomes (i.e., higher spending is associated with reduced mortality and readmission),[107, 108] which could potentially lead to some reluctances and doubts when dealing with cost containments and improved efficiencies at the same time.

The trend of cost reduction may not be fully explained by using administrative health data. However, there may be several potential contributing factors. We observed a steady decrease in hospital length of stay (LOS) for patients with AMI from 7 days in 2004 to 5 days in 2013 ($p<0.001$). Further, Afana *et al.* reported an annual decrease of 0.3% in hospitalization costs for patients undergoing PCI from 2004 to 2009.[89] There may be other factors such as a shift in revascularization from CABG to less costly PCI for complex cases and advancements in adjuvant therapy, procedural techniques and stenting.[7] It was reported previously that differences in procedure and LOS could contribute 34% and 53% to the variation in total hospital costs, respectively [86]. This topic may warrant further research to better understand the root causes and to possibly replicate the cost-reduction practice to other jurisdictions.

In chapters 4 & 5, we found a common theme of the higher cost burden of NSTEMI. Even though STEMI is an acute condition requiring expedited diagnosis and intervention and is more costly to treat, it is NSTEMI to drive the cost burden of AMI. Between 2004 and 2013, the number of hospital admissions with NSTEMI was more than 50% greater than those with STEMI. In addition, a patient with NSTEMI spent longer time in hospital during the first year after incidence than a patient with STEMI did (9.23 vs. 7.72 days, $p<0.001$). In fact, the annual proportion of health care costs for patients with STEMI (34.2%) remained unchanged between 2004 and 2013 while the proportion of costs for patients with NSTEMI increased

significantly during this period (2004: 44.2%; 2013: 54.7%; p=0.006). Along with the increasing trend of NSTEMI patient proportion over time[90], the cost burden of NSTEMI could be even higher in the foreseeable future and this could have an impact on health care planning (i.e., funding allocation for human resources, care facilities and technologies for patients with AMI).

This thesis has several strengths. First, we used a large longitudinal population-based cohort of patients with AMI in all Canadian provinces except for Quebec (chapters 2 and 3). Second, this thesis is among the first to provide pan-Canadian data for AMI quality indicators. Third, we used patient-level data and focused on episode of care, which facilitated adequate risk adjustments. Finally, we provided a comprehensive assessment of health care costs for AMI which included hospital, ambulatory care, practitioner claims, and drug costs using both prevalence- and incidence-based approaches. However, there are several limitations. First, we used administrative health datasets. Although Canadian administrative data have been shown to be valid relative to chart abstraction, these data may be affected by data entry errors, omissions, and inconsistencies.[52, 53] Second, we used CIHI DAD and did not have access to data from the province of Quebec as the province submits hospitalization data in a separate format than the other provinces. Third, we used retrospective cohort study design, so categorization of patients into different revascularization groups may be subject to selection bias, i.e. some of the patients who were in the no-reperfusion group or in the lysis-only group may have been destined to receive PCI but did not survive long enough to do so. Finally, the resource use and cost burden were assessed in the province of Alberta only with Alberta specific cost norms. Therefore, interpretation of results in the whole Canadian context

should be taken with caution. Nonetheless, this thesis is among the first to provide comprehensive assessment of resource use and cost burden of AMI in Canada.

In conclusion, this thesis has several findings relevant to improvement of AMI care in Canada:

1. Despite of an increase in the use of contemporary primary PCI, health outcomes have remained stable over time in Canada, possibly reflecting an improvement when accounting for an increased risk burden of patients with AMI.
2. The cost burden of AMI have decreased over time, possibly suggesting a productivity improvement in AMI care. Additional research may be needed to better understand the trend and to replicate it to other jurisdictions. The combination of stable outcomes and decreased costs over time could indicate a success of AMI care in Canada.
3. Care practice and health outcomes have varied significantly across Canadian provinces. There should be a better pan-Canadian collaboration and coordination in AMI care to improve services provision nationally.
4. The methodology and findings of AMI quality indicators in this thesis could provide a starting point for a discussion on a set of care quality indicators specifically for AMI in Canada.
5. The use of fibrinolysis followed by PCI in a systematic manner in the era of contemporary primary PCI is supported from a “real-world” perspective.
6. Compared with other MI groups, NSTEMI is an important cost driver. This result may be relevant in resource allocation in AMI care in the future.

This thesis also suggests a number of potential research topics for the improvement of AMI care in Canada

1. Economic evaluation of prehospital STEMI program in Alberta: Although the prehospital STEMI program has been implementing for several years, there is no economic evaluation of this program. As discussed above, the prehospital program has shown effective in reducing mortality. An addition of an economic evaluation could provide a more comprehensive assessment of this program to inform decision making.
2. An assessment of resource use and cost burden of AMI in other provinces could be more informative to decision making in AMI care in Canada. It may also serve the discussion of a pan-Canadian collaboration and coordination in AMI care.
3. As Quebec accounts for 23% of Canadian population in 2017, inclusion of Quebec data would provide a better look at the AMI care in Canada.[97] The CIHI Hospital Morbidity Database could be used for this purpose as it combines both CIHI DAD and hospital data submitted by the ministère de la Santé et des Services sociaux du Québec.[109]
4. International comparison helps us learn from other health care systems. Currently, there lacks studies comparing AMI care between Canada and other countries with regard to both health outcomes, resource uses and costs. The European Health Care Outcomes, Performance and Efficiency (EuroHOPE, http://www.eurohope.info/) project has proved successful in evaluating both outcomes, uses of resources and costs of several conditions including AMI between European countries. Both Europe and

Canada could mutually benefit from a partnership to perform a transatlantic comparison in AMI care.

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