Temporal Trends in In-Hospital Bleeding and Transfusion in a Contemporary Canadian ST Elevation Myocardial Infarction Patient Population

by

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ABSTRACT

Background:

Although ST-elevation myocardial infarction (STEMI) management has evolved substantially over the last decade, its impact on bleeding and transfusion rates are largely unknown in a 'real-world' Canadian population. Using a large Canadian population health database, we evaluated the temporal trends of in-hospital bleeding and transfusion rates in a contemporary Canadian STEMI population.

Methods:

Data from the Canadian Institute for Health Information (CIHI) included patients ≥20 years of age hospitalized for STEMI between April 2007 and March 2016 across all Canadian hospitals, except Quebec. Patients who underwent coronary artery bypass grafting (CABG) during hospitalization were excluded. International Classification of Diseases-10th Revision codes were used to determine STEMI episodes, identify in-hospital bleeding events, and comorbidities. The CIHI database also contained details on patients receiving transfusion during hospitalizations. Associations between bleeding or transfusion and in-hospital death or 30-day readmission with bleeding or transfusion were also reported.

Results:

Using 115,078 STEMI episodes, rates of in-hospital bleeding and transfusion declined between 2007 and 2016 from 4.0% to 2.8% (p<0.0001) and 4.7% to 3.8% (p<0.0001), respectively. However, variation in bleeding and transfusion rates were observed across Canadian provinces. Patients who experienced bleeding, or received a transfusion,

were older, female, and more commonly had diabetes, hypertension, or heart failure. Compared to patients who did not bleed or receive a transfusion, individuals who bled, or those who were transfused, or those who bled and were transfused, had increased median length of stay (7 days, 11 days, and 14 days, respectively [p<0.0001]). These groups also had higher in-hospital mortality (19.4%, 31.1%, and 30.7%, respectively [p<0.0001]).

Conclusion:

In summary, the proportion of Canadian STEMI patients experiencing in-hospital bleeding and transfusion have decreased over the past nine years. Further exploration is required to identify the practice patterns used to protect patients from bleeding events and excessive transfusions.

PREFACE

This thesis is an original work completed by myself, Dr. Debraj Das. It will ultimately be reformatted as a manuscript and submitted to a peer-reviewed journal for publication. The data for this project were obtained from the Canadian Institutes for Health Information (CIHI), which is a public database that provides information on Canada's health system and the health of Canadians (https://www.cihi.ca/en). The data acquisition was completed by Dr. Anamaria Savu and Dr. Padma Kaul. The data analysis, figure creation, and manuscript preparations were completed by myself with the support of Dr. Kevin R. Bainey, Dr. Robert C. Welsh, Dr. Anamaria Savu, and Dr. Padma Kaul. No part of this thesis has been previously published.

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This thesis would not have possible without the support of many people. I would first like to thank my current clinical and research mentors Dr. Kevin R. Bainey and Dr. Robert C. Welsh for their continued support throughout my cardiology residency. They are truly my role-models. I would also like to thank the biostatistician group at the Canadian VIGOUR Centre including Dr. Padma Kaul, Dr. Cindy Westerhout, and Dr. Anamaria Savu for their guidance in completing this project. I would also like to thank my original research mentors Dr. Paul W. Armstrong and Dr. Justin A. Ezekowitz for pushing me to open my horizons and consider a career as a clinician-scientist. Lastly, I would like to thank my family for their undying support.

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LIST OF ABBREVIATIONS

ACS – Acute Coronary Syndrome

CABG – Coronary Artery Bypass Grafting

CCI – Canadian Classification of Health Interventions

CHF – Congestive Heart Failure

CIHI – Canadian Institute for Health Information

FY – Fiscal Y

GRACE – Global Registry of Acute Coronary Events

GUSTO – Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndrome)

ICD – International Classification of Diseases and Related Health Problem

LOS – Length of Stay

OR – Odds Ratio

PCI – Percutaneous coronary intervention

STEMI – ST-segment elevation myocardial infarction

CHAPTER 1

INTRODUCTION

Several millions of patients worldwide suffer from an ST-elevation myocardial infarction (STEMI) annually[1]. The current standard of care is that each patient should receive dual antiplatelet therapy (DAPT), including aspirin and a P2Y12 inhibitor for a minimum of 12-months followed by aspirin indefinitely[2-4]. This therapy is particularly relevant in STEMI patients who are at the highest risk of a recurrent ACS and often receive drug-eluting stents as part of their revascularization strategy[5]. Patients, particularly over the age of 75, are the most likely to develop complications of STEMI including congestive heart failure (CHF), left ventricular (LV) dysfunction, cardiogenic shock, or ventricular arrhythmias[6].

Advancements in anti-thrombotic therapies for STEMI have improved patient outcomes over the past two decades[7-9]. Although rates of ischemic events have declined with the use of more potent pharmacotherapeutics, this has come at the cost of higher bleeding risk[8,10,11]. Analysis of data from the GRACE (Global Registry of Acute Coronary Events) registry has demonstrated a bleeding rate of 4.8% in STEMI patients and 4.0% in all patients with ACS[12]. With regards to transfusion rates, the GUSTO IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes) trial revealed that 8.6% of STEMI patients received a blood transfusion[13]. A meta-analysis of three large international trials found that 10% of all ACS patients received at least one in-hospital transfusion[14]. In these studies, patients who had a bleed or required a

transfusion had higher mortality, compared to those who did not experience either event[12-14]. However, these studies do not acknowledge contemporary practice patterns in the treatment of STEMI.

The ideal target for red blood cell transfusion in the setting of all ACS patients and particularly, STEMI patients, is still relatively uncertain. Meta-analysis data in patients suffering from any type of critical illness suggests a more restrictive strategy (hemoglobin level of <7 g/dL) significantly reduces cardiac events and total mortality[15]. In cardiac surgery literature, a restrictive strategy (hemoglobin level of <7.5 g/dL) was found to be noninferior compared to a liberal strategy (<9.5 g/dL) for the primary composite outcome of all cause death, myocardial infarction, stroke, or new onset renal failure[16]. The 2013 American College of Cardiology and American Heart Association guidelines suggest a threshold of <8 g/dL in STEMI patients without active ischemia[17]. However, other large organizations including the Canadian Cardiovascular Society, European Society of Cardiology and the American Association of Blood Banks, have no specific recommendations for transfusion thresholds in STEMI patients.

Accordingly, we examined temporal trends in bleeding and transfusion in Canadian patients hospitalized with a primary diagnosis of STEMI between April 2007 and March 2016. We also examined the associations between bleeding, transfusion and in-hospital mortality.

CHAPTER 2

METHODS

Hospital Discharge Abstract Database (DAD) data from the Canadian Institute for Health Information (CIHI) were used to identify all patients ≥20 years of age who were hospitalized at an acute-care hospital with a primary diagnosis of STEMI between April 1, 2007 and March 31, 2016. We assessed data for all provinces except Quebec due to unavailability. The following International Classification of Diseases version 10 (ICD-10) codes were used to identify hospitalizations with a primary diagnosis of STEMI (I21.0, I21.1, I21.2, I21.3) or unspecified ACS (I21.9). Only episodes that had an ICD-10 ECG code confirming the STEMI diagnosis (R94.30) in a secondary diagnosis field in any of the episode hospitalizations, were included in the analysis. The validity of these diagnostic codes for identifying ACS is variable and has been reported by Patel et al. to be 66.0% to 95.1% and a specificity of 80.2% to 100.0%[18]. We would estimate our specificity of the STEMI definition to be approximately 80%. Patients who underwent coronary artery bypass grafting (CABG) during hospitalization were excluded. Acknowledging, the common practice of inter-hospital transfer, concurrent hospitalizations occurring within 24 hours were considered as the same STEMI episode. We used previously defined ICD-10 codes to identify bleeding events, including gastrointestinal, intracranial, and respiratory sources (see Table 2 for full list of codes), if they occurred during any hospitalization of the STEMI episode[19].

Similarly, previously validated ICD-10 codes were used to identify the presence of comorbidities, such as diabetes, hypertension, congestive heart failure (CHF), cerebrovascular disease, renal disease, atrial fibrillation, and anemias or hemorrhagic conditions during the STEMI episode[20]. The Charlson Comorbidity Index was calculated to assess the overall comorbidity burden for each patient. Whether the patient has received transfusion or any other blood products, such as red blood cells, platelets, plasma or albumin, are routinely collected as part of the CIHI DAD. We did not have the sensitivity for the bleeding and transfusion events from the CIHI data. Canadian Classification of Health Interventions (CCI) codes were used to identify patients who underwent PCI. CCI codes for fibrinolytic therapy were available from fiscal year (FY) 2009/2010 onwards.

Patients were categorized into four groups, according to their bleeding/transfusion status: no bleed or transfusion, bleed without transfusion, transfusion without bleed, or bleed and transfusion. Chi-square tests for trends were used to examine whether the proportion of STEMI patients in the latter three groups changed over each FY. To examine differences in baseline characteristics, hospital length of stay (LOS), and outcomes across the four groups, ANOVA was used for continuous variables, and chi-square tests for categorical variables. Hospital LOS was calculated as the difference between the admission date of the first hospitalization and the discharge date of the last hospitalization during that STEMI admission. If a patient was admitted and discharged on the same day, the hospital length of stay was 1 day. Multivariate generalized

estimating equation modelling was used to assess the association between bleeding alone, transfusion alone, or the combination, on in-hospital mortality. The covariates included in the analysis were age, sex, Charlson index, and treatment (PCI and/or fibrinolysis). Age and sex were available for everyone however if Charlson indices, treatments, or bleed and transfusion data was unavailable from the data, they were assumed not exist.

CHAPTER 3

RESULTS

Between April 1, 2007 and March 31, 2016, there were a total of 167,525 hospitalizations for STEMI and 42,655 hospitalizations for unspecified ACS. After exclusions, 115,078 STEMI episodes of 112,162 patients were analyzed (Figure 1). The total number of STEMI episodes increased annually over the same period from 11,001 in FY 2007/08 to 13,588 in FY 2015/16. During this period, the trend of in-hospital bleeding and transfusion showed a decline from 4.0% to 2.8% (p<0.0001) and from 4.7% to 3.8%, (p<0.0001), respectively (Figure 2). In most STEMI episodes (73.8%), patients were treated with primary PCI. After FY 2009/10, when fibrinolytic data became available, the proportion of STEMI episodes treated with a pharmacoinvasive approach (use of both fibrinolytics and PCI) was 17.4%, fibrinolysis in isolation accounted for 5.4%, and PCI alone was used in 59.1% of cases. In 18.1% of episodes, the patient received no reperfusion or revascularization therapy (Table 1).

The largest proportion of STEMI episodes occurred in Ontario (48.1%, n=55,305) followed by British Columbia (15.5%, n=17,867) and Alberta (13.8%, n=15,920). Bleeding rates were highest in Prince Edward Island (4.3%, n=24/565) and lowest in British Columbia (3.0%, n=539/17867). Transfusion rates were highest in Ontario (4.9%, n=2699/55305) and Manitoba (4.9%, n=297/6083), and lowest in British Columbia (2.8%, n=508/17867) (Figure 3).

Patients who had an in-hospital bleed or who received a blood transfusion, were older and had more comorbidities, such as diabetes, hypertension, CHF, atrial fibrillation or

flutter, or renal disease compared to patients who had neither event (Table 1, $p<0.0001$). Bleeding and transfusion rates were higher in women (women vs. men; 3.6% vs. 3.1% and 6.7% vs. 3.3%, [$p<0.001$]). Patients who were transfused without a bleed (45.8%) or who had a bleed and were transfused (48.6%) had significantly higher rates of anemias or hemorrhagic conditions, compared to those that had a bleed and were not transfused (11.1%) or those who had no bleed or transfusion (1.9%) ($p<0.01$). Bleeding (OR=2.0, 95% CI 1.8-2.3, $p<0.0001$), transfusion (OR=4.2, 95% CI 3.8-4.7, $p<0.0001$) and both bleeding and transfusion (OR=3.6, 95% CI 3.1-4.3, $p<0.0001$) were significantly associated with in-hospital mortality after adjustment for patient age, sex, Charlson Comorbidity Index and treatment (PCI and/or fibrinolysis). For those patients that bled, were transfused, or experienced both, 30-day re-hospitalization for bleeding or transfusion were 4.9%, 7.1%, and 7.5%, respectively.

.Table 1. Patient characteristics and treatment by bleed and blood transfusion for 115,078 STEMI episodes

Variable	Without bleed or transfusion	Bleed without transfusion	Transfusion without bleed	Bleed and transfusion	Total
Total *n*	107675	2452	3641	1310	115078
Age, y , Mean (SD)	63.3 (13.6)	69.9 (13.1)	70.4 (13.1)	70.7 (12.9)	63.7 (13.7)
Age, y , Median (IQR)	62.0 (53.0, 73.0)	71.0 (60.0, 80.0)	72.0 (62.0, 81.0)	72.0 (62.0, 81.0)	62.0 (54.0, 74.0)
Male	77805 (72.3)	1753 (71.5)	1932 (53.1)	820 (62.6)	82310 (71.5)
Length of stay, day, Mean (SD)	5.3 (8.7)	11.8 (18.1)	18.9 (26.7)	25.2 (37.6)	6.1 (11.3)
Length of stay, day, Median (IQR)	4.0 (3.0, 6.0)	7.0 (4.0, 13.0)	11.0 (5.0, 21.0)	14.0 (7.0, 28.0)	4.0 (3.0, 6.0)

Anemias or hemorrhagic conditions	2084 (1.9)	273 (11.1)	1669 (45.8)	637 (48.6)	4663 (4.1)
Congestive heart failure	11122 (10.3)	595 (24.3)	1323 (36.3)	502 (38.3)	13542 (11.8)
Peripheral vascular disorders	1745 (1.6)	85 (3.5)	206 (5.7)	86 (6.6)	2122 (1.8)
Cerebrovascular disease (I60, I61, I62 are bleed codes)	1415 (1.3)	382 (15.6)	201 (5.5)	170 (13.0)	2168 (1.9)
Ischemic Stroke	591 (0.5)	46 (1.9)	107 (2.9)	51 (3.9)	795 (0.7)
TIA	181 (0.2)	2 (0.1)	18 (0.5)	10 (0.8)	211 (0.2)
Intracranial hemorrhage (all codes indicative of intracranial	0 (0.0)	322 (13.1)	0 (0.0)	91 (6.9)	413 (0.4)

hemorrhage are bleed codes)					
Dementia	1744 (1.6)	81 (3.3)	129 (3.5)	36 (2.7)	1990 (1.7)
Chronic obstructive pulmonary disease	4054 (3.8)	176 (7.2)	291 (8.0)	127 (9.7)	4648 (4.0)
Rheumatic disease	493 (0.5)	14 (0.6)	45 (1.2)	21 (1.6)	573 (0.5)
Peptic ulcer disease	108 (0.1)	150 (6.1)	45 (1.2)	225 (17.2)	528 (0.5)
Diabetes	24079 (22.4)	627 (25.6)	1397 (38.4)	452 (34.5)	26555 (23.1)
Paralysis	232 (0.2)	42 (1.7)	43 (1.2)	28 (2.1)	345 (0.3)
Renal disease	2524 (2.3)	154 (6.3)	422 (11.6)	147 (11.2)	3247 (2.8)
Liver disease	361 (0.3)	30 (1.2)	84 (2.3)	51 (3.9)	526 (0.5)
Cancer	1600 (1.5)	103 (4.2)	277 (7.6)	99 (7.6)	2079 (1.8)
Charlson score					
0	69013 (64.1)	908 (37.0)	1038 (28.5)	259 (19.8)	71218 (61.9)
1,2	29333 (27.2)	987 (40.3)	1339 (36.8)	534 (40.8)	32193 (28.0)
3,4	7978 (7.4)	422 (17.2)	922 (25.3)	375 (28.6)	9697 (8.4)

5+	1351 (1.3)	135 (5.5)	342 (9.4)	142 (10.8)	1970 (1.7)
Hypertension	48079 (44.7)	1245 (50.8)	1874 (51.5)	693 (52.9)	51891 (45.1)
Atrial fibrillation or flutter	7235 (6.7)	406 (16.6)	706 (19.4)	301 (23.0)	8648 (7.5)
Systemic embolism	116 (0.1)	11 (0.4)	31 (0.9)	13 (1.0)	171 (0.1)
Valvular disease	1795 (1.7)	83 (3.4)	231 (6.3)	85 (6.5)	2194 (1.9)
PCI	80339 (74.6)	1536 (62.6)	2232 (61.3)	777 (59.3)	84884 (73.8)
Fibrinolysis (after April 2009), n/N (%)	19798/86552 (22.9)	557/1850 (30.1)	454/2800 (16.2)	212/1031 (20.6)	21021/92233 (22.8)
PCI and fibrinolysis (after April 2009), n/N (%)	15282/86552 (17.7)	325/1850 (17.6)	303/2800 (10.8)	138/1031 (13.4)	16048/92233 (17.4)
PCI, only (after April 2009), n/N (%)	51666/86552 (59.7)	869/1850 (47.0)	1507/2800 (53.8)	510/1031 (49.5)	54552/92233 (59.1)
Fibrinolysis, only (after April 2009), n/N (%)	4516/86552 (5.2)	232/1850 (12.5)	151/2800 (5.4)	74/1031 (7.2)	4973/92233 (5.4)

Without PCI and without fibrinolysis (after April 2009), n/N (%)	15088/86552 (17.4)	424/1850 (22.9)	839/2800 (30.0)	309/1031 (30.0)	16660/92233 (18.1)
Discharged dead	7481 (6.9)	476 (19.4)	1131 (31.1)	402 (30.7)	9490 (8.2)
30-day re-hospitalization with bleeds or blood transfusion, post discharge, n/N (%)	1186/100194 (1.2)	97/1976 (4.9)	178/2510 (7.1)	68/908 (7.5)	1529/105588 (1.5)

Unless otherwise specified all values are n (%); All comparisons across the row were statistically significant at 0.0001 level; SD standard deviation; IQR interquartile range; TIA transient ischemic attack; PCI primary percutaneous coronary intervention

Table 2. International Classification of Disease-10th Revision Codes used to identify bleeding events

Code	ICD-10 CA description
H356	Retinal haemorrhage
H431	Vitreous haemorrhage
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I850	Oesophageal varices with bleeding
I9820	Oesophageal varices in diseases classified elsewhere with bleeding (code disabled in 2009)
I983	Oesophageal varices with bleeding in disease classified elsewhere
J942	Haemothorax
K2210	Ulcer of oesophagus, acute with haemorrhage
K2212	Ulcer of oesophagus, acute with both haemorrhage and perforation
K2214	Ulcer of oesophagus, chronic or unspecified with haemorrhage
K2216	Ulcer of oesophagus, chronic or unspecified with both haemorrhage and perforation
K226	Gastro-oesophageal laceration-haemorrhage syndrome
K250	Gastric ulcer, Acute with haemorrhage
K252	Gastric ulcer, Acute with both haemorrhage and perforation
K254	Gastric ulcer, Chronic or unspecified with haemorrhage
K256	Gastric ulcer, Chronic or unspecified with both haemorrhage and perforation
K260	Duodenal ulcer, Acute with haemorrhage
K262	Duodenal ulcer, Acute with both haemorrhage and perforation
K264	Duodenal ulcer, Chronic or unspecified with haemorrhage
K266	Duodenal ulcer, Chronic or unspecified with both haemorrhage and perforation
K270	Peptic ulcer, site unspecified, Acute with haemorrhage
K272	Peptic ulcer, site unspecified, Acute with both haemorrhage and perforation

K274	Peptic ulcer, site unspecified, Chronic or unspecified with haemorrhage
K276	Peptic ulcer, site unspecified, Chronic or unspecified with both haemorrhage and perforation
K280	Gastrojejunal ulcer, Acute with haemorrhage
K282	Gastrojejunal ulcer, Acute with both haemorrhage and perforation
K284	Gastrojejuna ulcer, Chronic or unspecified with haemorrhage
K286	Gastrojejuna ulcer, Chronic or unspecified with both haemorrhage and perforation
K290	Acute haemorrhagic gastritis
K3180	Angiodysplasia of stomach and duodenum with bleeding
K5520	Angiodysplsia of colon with bleeding
K625	Haemorrhage of anus and rectum
K6380	Angiodysplsia of small intestine, except duodenum with bleeding
K661	Haemoperitoneum
K920	Haematemesis
K921	Melaena
K922	Gastrointestinal haemorrhage, unspecified
M250	Haemarthrosis
N02	Recurrent and persistent haematuria
R04	Haemorrhage from respiratory passages
R31	Unspecified haematuria
R58	Haemorrhage, not elsewhere classified
S064	Epidural haemorrhage
S065	Traumatic subdural haemorrhage
S066	Traumatic subarachnoid haemorrhage

*ICD-10 code selection was guided by Danish registry study referenced below:

Sørensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009;374:1967-1974.

Figure 1. Flowchart of STEMI Episodes and Patients from the Canadian Institute of Health Information Database

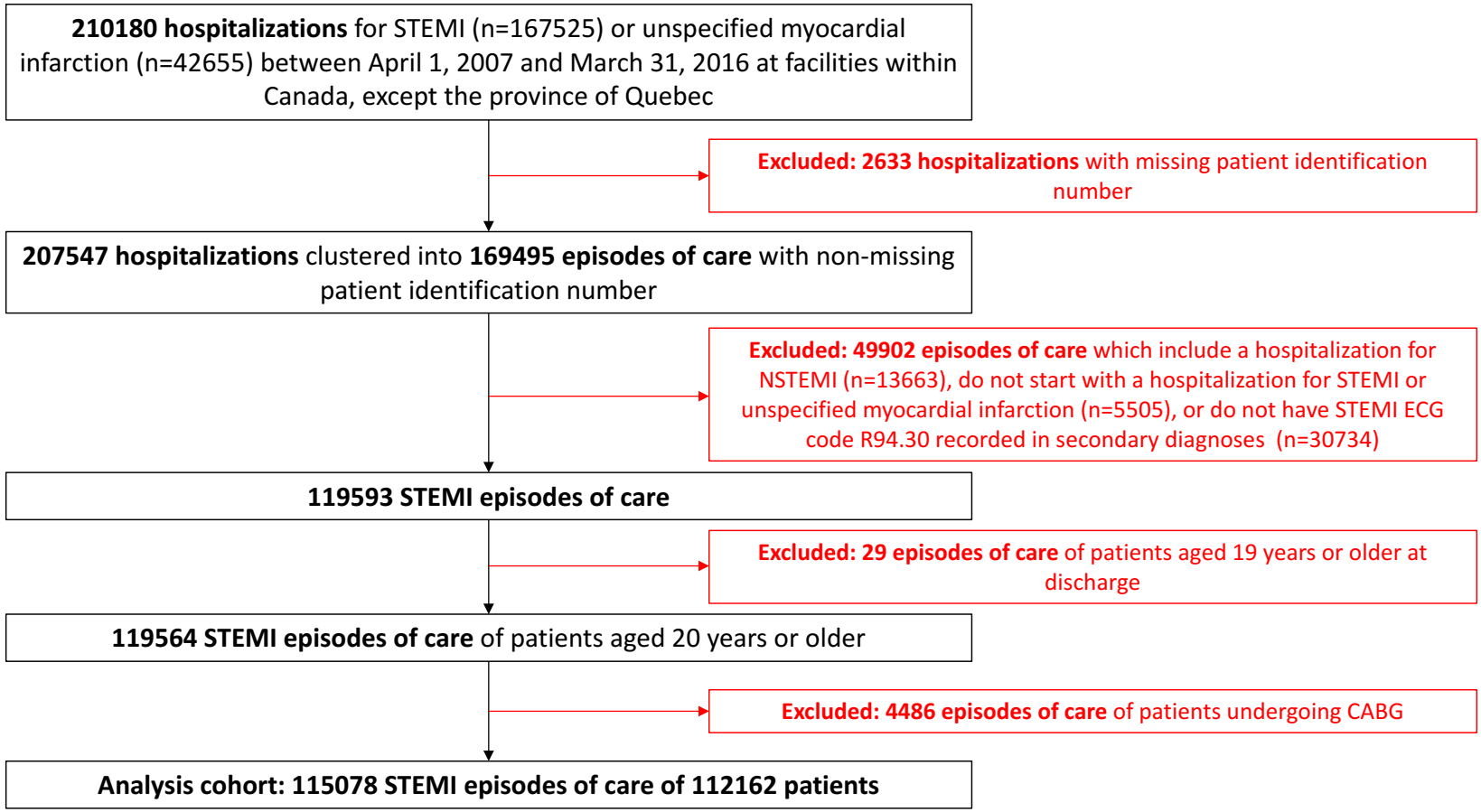


Figure 2. Trends of total bleed and total transfusion in STEMI episodes from April 2007 to March 2016. Total bleed includes patients who bled and who bled and received transfusion. Total transfusion includes patients who were transfused and who bled and received transfusion.

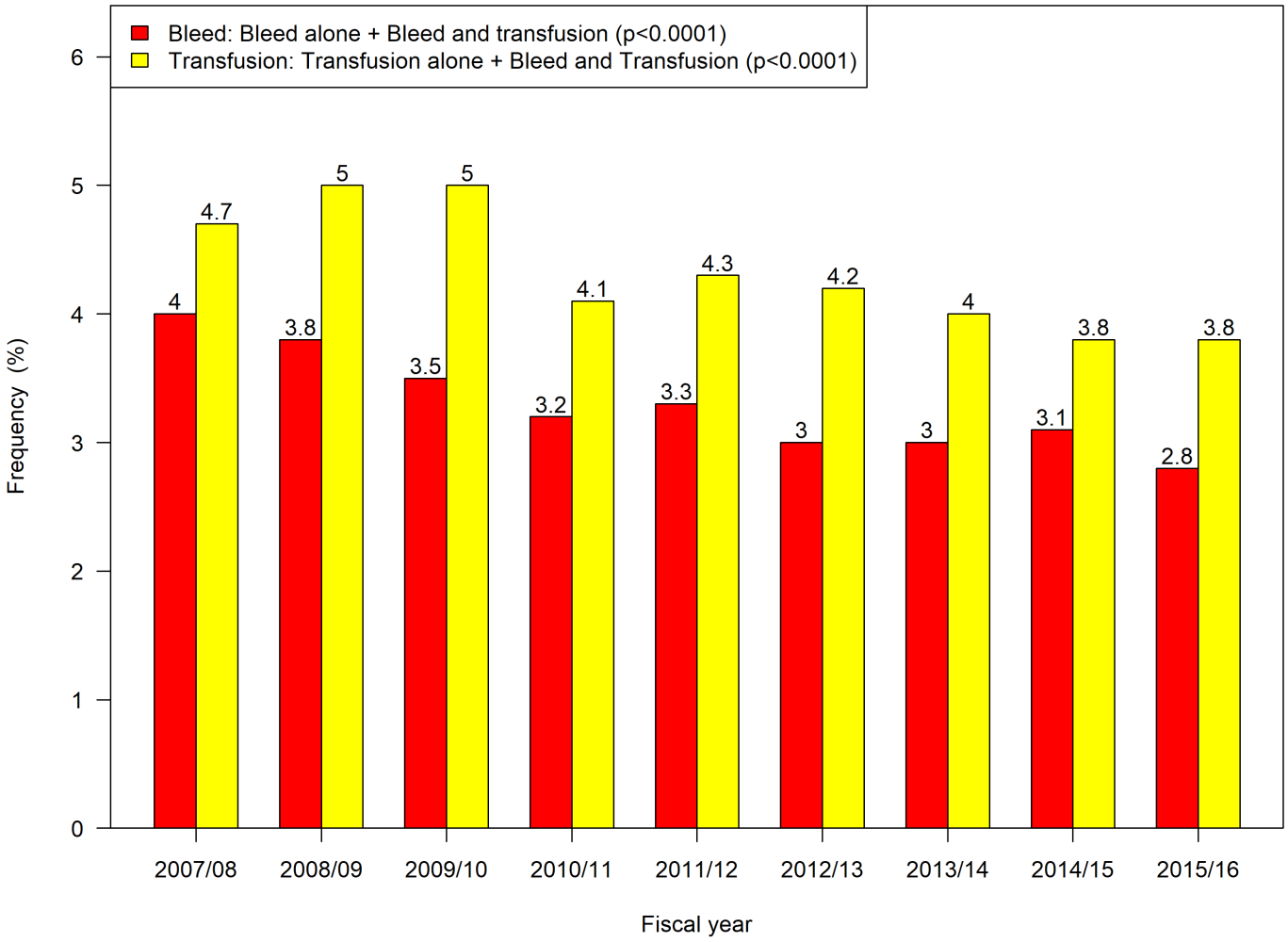


Figure 3. Trends of bleeding (top row) and blood transfusion (bottom row) in STEMI episodes from 2007 to 2016.

Graphs are separated by Maritimes (NFL, PEI, NS, NB), Central (ON), Prairies (MB, SK, AB) and West Coast (BC).

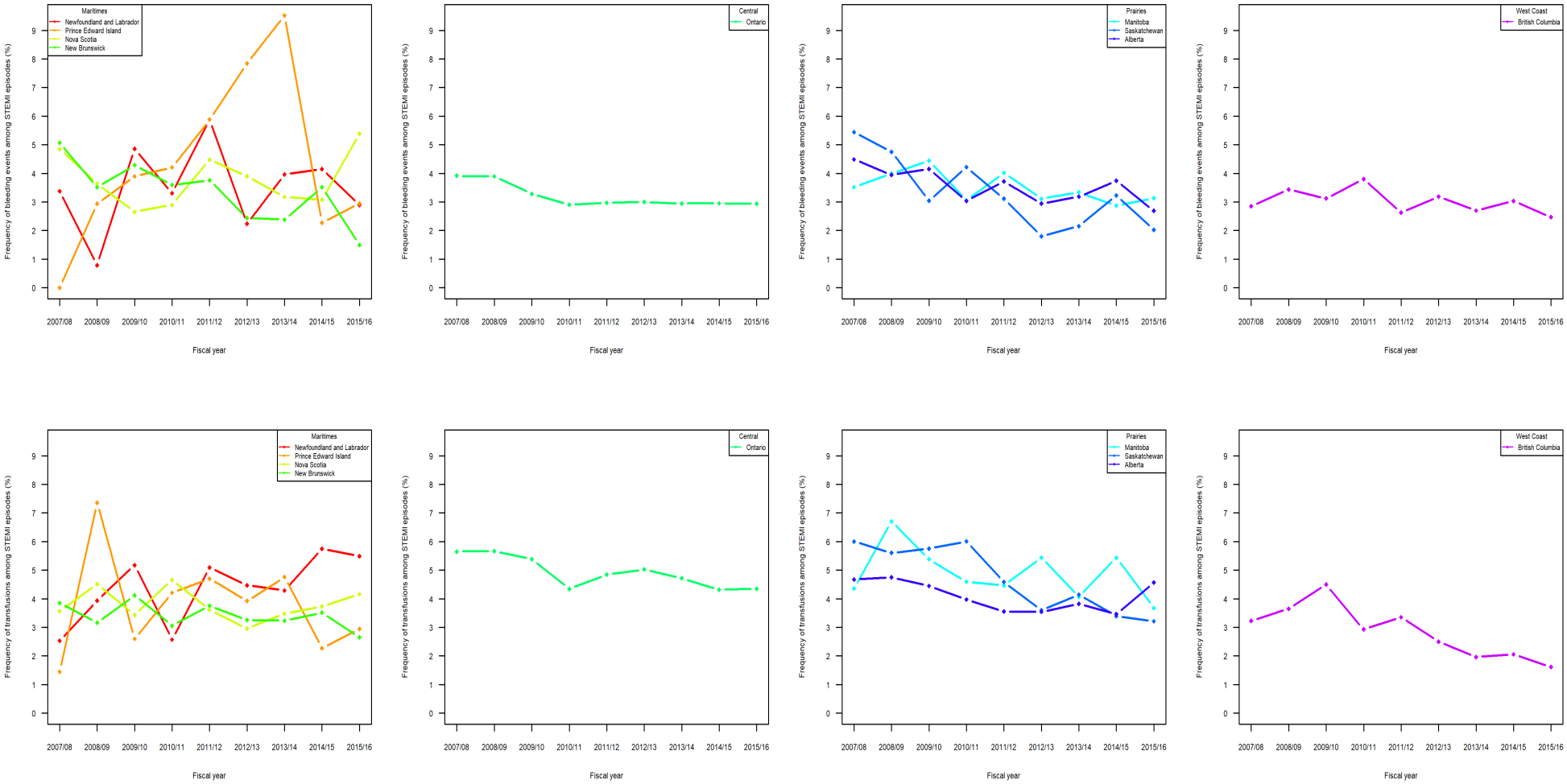
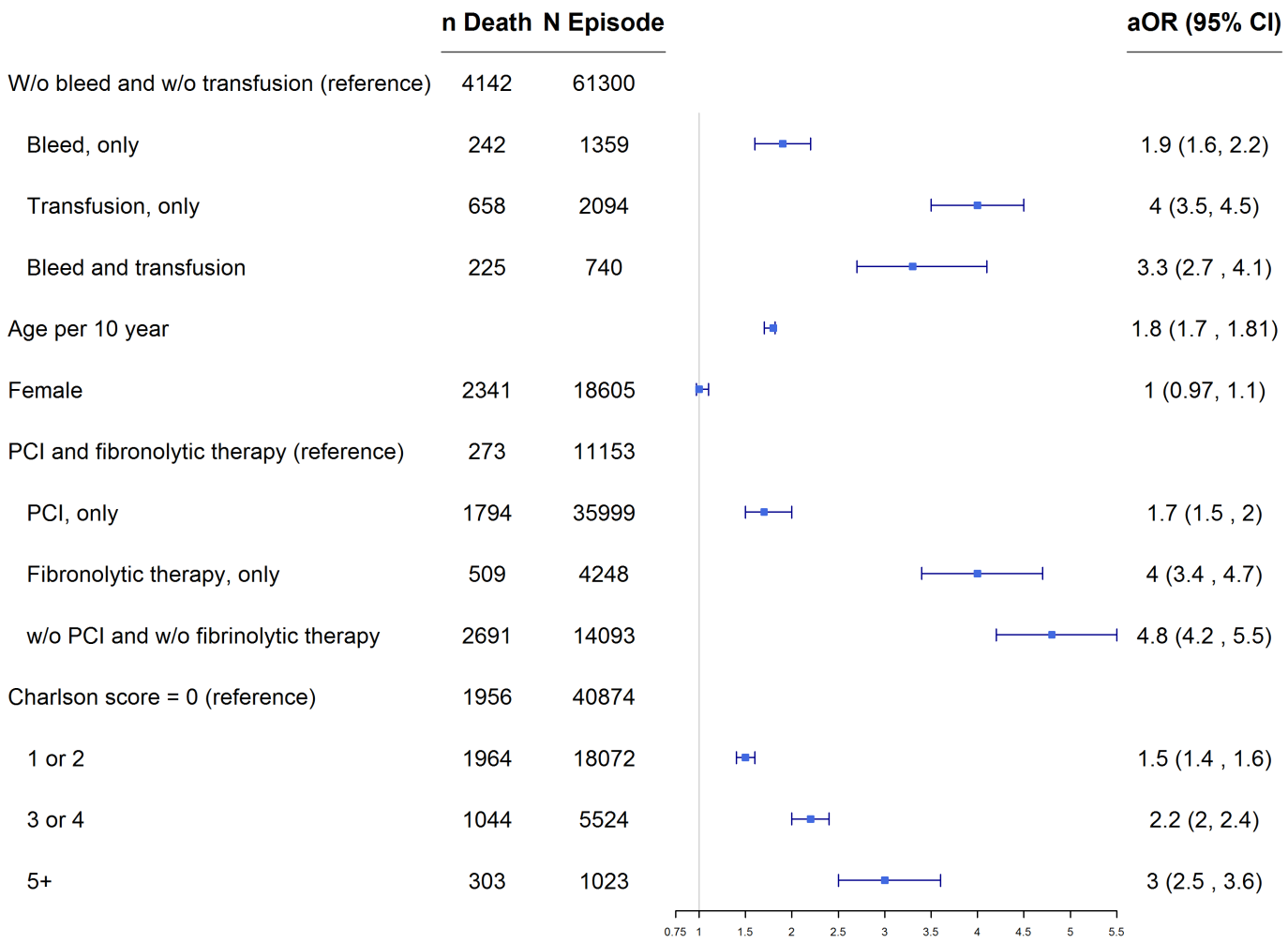


Figure 4. Forest Plot of Multivariate Analysis on In-Hospital Mortality from STEMI Episodes from 2007 to 2016



CHAPTER 4

DISCUSSION

Despite the use of more potent pharmacotherapy for the treatment of STEMI, we have found that in-hospital bleeding and transfusion rates have declined for Canadian STEMI patients. Although these data are reassuring, we found that patients who bled and/or were transfused had a higher likelihood of in-hospital death. The factors contributing to the decline in bleeding events over time are likely multi-factorial.

Bleeding complications related to PCI have been minimized with advances in procedural techniques, increased operator experience, and utilization of the radial approach for catheterization. The radial approach is known to have lower incidence of major bleeding and access site bleeding[21-23]. The most robust evidence supporting radial catheterization was published by Ferrante et al. in 2016, which included a meta-analysis of 24 trials including 22,843 patients[24]. All end points including, major bleeding, all-cause mortality, and major adverse cardiovascular events were lower in patients undergoing a radial approach. This benefit was consistent amongst all-comers with coronary artery disease including both stable and unstable patients. Experienced operators working at high volume centers are more likely to adopt a radial approach even in STEMI management[25-27]. For those patients that do undergo a transfemoral approach for PCI, closure devices may help mitigate access site bleeding although this is still controversial[28,29].

Although primary PCI has become standard of care in most centers due to its short- and long-term mortality benefit, fibrinolysis still plays an important role in contemporary STEMI management[30]. Interestingly, the association between fibrinolytics and increased major bleeding compared to primary PCI is still unclear with many studies showing no significant difference. Fibrinolytics are associated with higher rates of intracranial hemorrhage particularly in older patients and those individuals with multiple risk factors[31]. However, this is not consistently evident for all-comers receiving fibrinolytic therapy and especially in individuals who receive half-dose fibrinolysis and do not receive adjunct glycoprotein IIB/IIIA inhibitors[32]. Therefore, the contribution of fibrinolytics on overall bleeding and subsequent transfusion rates may be more limited than originally anticipated. This is particularly true with the use of more fibrin specific agents such as tenecteplase and is supported in ischemic stroke literature as well[33-35].

In our study, we observed both an increased length of stay, and higher in-hospital mortality rates were seen in patients who bled and/or received a transfusion. This finding agrees with the recent literature on the outcomes of STEMI patients who experience bleeding. A systematic review and meta-analysis by Kwok *et al*. indicated that major bleeding after PCI is independently associated with three times higher risk for mortality and major adverse cardiac events[36]. Rao *et a*l. report that even minor bleeds, often deemed ‘nuisance bleeds’, are substantial clinical events with real consequences[37]. Although speculative, even minor bleeds may prompt patients to discontinue secondary preventative medications which could lead to subsequent events.

From a transfusion perspective, data from Shishehbor *et al.* showed an associated short and long-term mortality amongst STEMI patients who were transfused[13]. Similar findings were discovered in the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial with transfusion after PCI for an acute myocardial infarction[38]. Furthermore a recent meta-analysis of five cohort studies including 21,770 patients confirmed that red blood cell transfusion was associated with in-hospital and long-term mortality, repeat emergency PCI, reinfarction, and heart failure[39]. In our study, transfused patients had worse outcomes after multi-variable modelling and almost half the patients who were transfused without a bleeding event had anemia. The mechanisms underlying transfusion related morbidity and mortality are still unclear. Laboratory models have indicated that increased viscosity and depleted nitric oxide levels result in poor oxygen delivery in addition to the pro-inflammatory properties of transfused blood[40-42]. The equipoise of transfusion in patients with STEMI is still unclear and the lack of consensus and guidelines result in each center establishing different thresholds for transfusion in asymptomatic patients[43]. As such, the ongoing multi-center Myocardial Ischemia and Transfusion (MINT) randomized trial (ClinicalTrials.gov Identifier: NCT02981407) (funded by the National Heart, Lung, & Blood Institute (NHLBI), National Institutes of Health) will help address the utility of transfusion in this setting.

Our study also confirms that provincial variation in in-hospital bleeding and blood transfusion does exist (Figure 3). Regional variability in STEMI management is well

documented in the Canadian landscape and may be contributory[44]. Even with most tertiary Canadian hospitals providing 24-hour primary PCI, this strategy is not universally available and regional transfer systems undoubtedly result in delays to door-to-balloon time and variability in anti-thrombotic management[45]. Variation in the uptake of radial coronary angiography may also be a contributing factor as centers with different expertise may rely heavily on femoral access. Although Canadian data on the rates of radial versus femoral approach is limited, this inconsistency is well-documented in the United States as well as worldwide[46,47].

Strengths and limitations exist for this study. We showed, using a large contemporary Canadian STEMI population, that bleeding and transfusion rates have declined over the past 9 years. Unfortunately, due to unavailability of data, the province of Quebec was not included in our analysis. A central limitation of our study is the use of the CIHI administrative data. Although it provides valuable data it has important limitations including the accuracy and completeness of coding of medical records. Notably, infarct categorization is likely a source of error with patients potentially being erroneously classified as a non-STEMI versus STEMI and vice versa, but this has been previously validated and appears to represent a minor issue[18]. The timeliness of the data is also a limitation that requires consideration as our anti-thrombotic regimens and door-to-balloon time in STEMI care have evolved since 2007 to 2019. We also did not have detailed clinical information, such as the site of bleeding, or hemoglobin levels, which would have contributed to the decision to transfuse a patient. Additional limitations include data for fibrinolytics being limited to fiscal 2009/10 onwards, lack of medication

data including specific P2Y12 inhibitors, and our inability to assess treatment differences at the provincial level. Lastly, our study is observational in nature and aimed at hypothesis-generation, with confounding variables still present.

Ultimately, it is reassuring to note that although the number of STEMI episodes have increased over time, the rates of in-hospital bleeding and transfusion have declined in Canada. However, incidence of bleeding and or transfusion identifies a patient population that is at a significantly higher risk of mortality. Further research is needed to examine the role of cardiac interventions and concomitant medications with bleeding and transfusion in a STEMI population.

CHAPTER 5

CONCLUSION

This large retrospective study has shown a statistically significant decline in both in-hospital bleeding and transfusion rates in a contemporary Canadian STEMI population between 2007 and 2016. Our study demonstrates the risk and impact of both in-hospital bleeding and transfusion and highlights the increase morbidity and mortality associated with both bleeding, transfusion, and the combination, compared to patients who have suffered neither of these events. Provincial variability in the Canadian STEMI landscape was also observed, which we believe is multi-factorial based on variation of clinical practice within regions.

Although it is reassuring that in-hospital bleeding, transfusion, and the combination have declined, the more complex management of STEMI patients occurs in secondary prevention, where the correct selection of antithrombotic therapy remains unclear. Clinicians must remain conscientious of these potent antithrombotic therapies at the time of discharge and in the outpatient setting. Balancing the risk of recurrent ischemia versus bleed risk, patient preferences, and drug cost and coverage all impact the long-term therapy decision. Guideline based therapy recommend DAPT for a minimum of 12-months, however the ATLAS ACS-2 trial has shown the benefit of adding low-dose rivaroxaban in an exclusive ACS population, which included 50% STEMI patients[48]. Similarly, at the 12-month mark clinicians now have a multitude of options, with no clear metric on deciding which patients will benefit from what strategy i.e. aspirin only, prolonged DAPT therapy, or dual-pathway. Both the DAPT and the PEGASUS-TIMI 54

(Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction) clinical trials have shown a benefit of prolonged DAPT in reducing the risk of cardiovascular death, myocardial infarction, or stroke[49,50]. Both studies demonstrated reduced ischemic events up to 30-months but at the cost of higher bleeding rates. Similarly, the dual-path way approach was tested in 27,395 patients in the COMPASS (Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease) trial, which showed a statistically significant benefit of low-dose rivaroxaban and aspirin on cardiovascular death, stroke, and nonfatal MI at a mean follow up of 23 months[51].

With the morbidity and mortality associated with bleeding and transfusion, moving forward it would be prudent to explore this relationship in a general ACS population, post-CABG, atrial fibrillation with ACS, and patients with peripheral vascular disease as well. A contemporary understanding of bleeding and transfusion rates in a complete vascular population will be essential in mitigating adverse outcomes.

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