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Bridging Knowledge Gaps in the Management of Acute Coronary Syndromes

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Résumé

Contexte

L'occlusion d'une artère du cœur cause un syndrome coronarien aigu (SCA) soit avec une élévation du segment ST (IAMEST) ou sans élévation du segment ST (1). Le traitement des patients avec un IAMEST requiert soit une intervention coronarienne d'urgence (ICP primaire) ou une thérapie fibrinolytique (FL). La thérapie FL peut être administrée soit dans un contexte pré-hospitalier (PHL) ou à l'hôpital. Une prise en charge précoce des patients avec SCA peut être améliorée par un simple indice de risque.

Objectifs

Les objectifs de cette thèse étaient de : 1) comparer l'ICP primaire et la thérapie FL (2); décrire plusieurs systèmes internationaux de PHL; (3) développer et valider un indice de risque simplifié pour une stratification précoce des patients avec SCA.

Méthodes

Nous complétons des méta-analyses, de type hiérarchique Bayésiennes portant sur l'effet de la randomisation, d'études randomisées et observationnelles; complétons également un sondage sur des systèmes internationaux de PHL; développons et validons un nouvel indice de risque pour ACS (le C-ACS).

Résultats

Dans les études observationnelles, l'ICP primaire, comparée à la thérapie FL, est associée à une plus grande réduction de la mortalité à court-terme; mais ce sans bénéfices concluants à long terme. La FL pré-hospitalière peut être administrée par des professionnels

de la santé possédant diverses expertises. Le C-ACS a des bonnes propriétés discriminatoires et pourrait être utilisé dans la stratification des patients avec SCA.

Conclusion

Nous avons comblé plusieurs lacunes importantes au niveau de la connaissance actuelle. Cette thèse de doctorat contribuera à améliorer l'accès à des soins de qualité élevée pour les patients ayant un SCA.

Mots clés français

Infarctus du myocarde, Intervention coronarienne percutanée, Indice de risque, Thérapie fibrinolytique, Syndrome coronariens aigu, Méta-analyse, Thérapie de reperfusion, Service médicale pré-hospitalier.

Summary

Background

Acute occlusion of an artery of the heart results in acute coronary syndromes (ACS), either with ST-segment elevation (STEMI) or without ST-segment elevation (1). STEMI requires urgent treatment to restore coronary artery flow either by primary percutaneous coronary intervention (PCI) or fibrinolytic therapy (FL) (2). Although several randomized controlled trials (RCTs) demonstrate the superiority of primary PCI in reducing mortality compared to FL (2), the benefit of primary PCI over FL remains uncertain in unselected "real-life" patients (3,4).

FL can be administered either in the pre-hospital setting (i.e., pre-hospital FL (PHL)) or at the hospital. PHL is rarely available outside Europe (5,6). Insights into the organization of PHL systems of care may promote more widespread use of PHL.

Risk stratification of ACS patients should be prompt to ensure timely PCI for high-risk patients and to avoid unnecessary intervention in low-risk patients (7). Despite the availability of numerous ACS risk scores, there is still no simple risk score that can be easily applied in the initial management of ACS patients (8).

Objectives

The objectives of this doctoral dissertation were to address these current knowledge gaps in the optimal management of ACS. The objectives were to: 1) evaluate the efficacy, effectiveness, and safety of primary PCI and FL, (2) describe the infrastructure, processes and outcomes of several international PHL systems; and (3) develop and validate a novel clinical risk score for early risk stratification of ACS patients.

Methods

To address these objectives, I completed Bayesian hierarchical random-effects meta-analyses of published RCTs and observational studies which compare primary PCI and FL in patients with STEMI. I undertook a survey of the infrastructure, processes and outcomes of PHL in several European and North American pre-hospital emergency systems. Finally, I developed and validated an ACS risk score called the Canadian ACS (C-ACS).

Results

Primary PCI was superior to FL in reducing short-term mortality in RCTs and observational studies. However, the long-term survival benefit of primary PCI was noted only in RCTs, and not in the observational studies. PHL can be effectively delivered by health care professionals with variable levels of expertise. The new risk score, C-ACS, has good discriminant properties for short- and long-term mortality in patients with ACS.

Conclusions

The first manuscript of this dissertation has been recognized as one of the most valuable recent publications in STEMI management and has contributed to reorganization of STEMI care in Ontario. The other two manuscripts in this dissertation provide practical information and tools for health professionals caring for patients with ACS. In summary, this doctoral dissertation has and will continue to contribute to improve access to high quality care for patients with ACS.

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List of Abbreviations

ACS: Acute Coronary Syndromes

ACS-1: Acute Coronary Syndromes-1

ACS-2: Acute Coronary Syndromes-2

AMI: Acute Myocardial Infarction

AMI-QUEBEC: Acute Myocardial Infarction in Quebec

AMIS: Acute Myocardial infarction in Switzerland

APEX AMI: Assessment of Pexelizumab in Acute Myocardial Infarction Trial

CABG: Coronary Artery Bypass Surgery

CADILLAC: Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications

CCP: Cooperative Cardiovascular Project

CCU: Coronary Care Unit

CHF: Congestive Heart Failure

CI: Confidence Interval

CrI: Credible Intervals

CVA: Cerebro-Vascular Accident

CVD: Cardio-Vascular Disease

ECG: Electrocardiogram

EFFECT-1: Enhanced Feedback for Effective Cardiac Treatment-1

EMMACE: Evaluation of Methods and Management of Acute Coronary Events

EMS: Emergency Medical System

ER; Emergency Room

FL: Fibrinolytic Therapy

FRISC-II: Fast Revascularisation in Instability in Coronary Disease

GRACE: Global Registry of Acute Coronary Events

GRACE-CANADA: Global Registry of Acute Coronary Syndromes in Canada

GUSTO: Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries

HR: Heart rate

ICD: International Codification of Diagnoses

KAMIR: Korea Acute Myocardial Infarction Registry

MD: Medical Doctor

NA: Not Available

NNT: Number needed to treat

NSTEMI: Myocardial Infarction without ST-Segment Elevation

NSTE-ACS: Acute Coronary Syndromes without ST-segment elevation

OR: Odds Ratio

PAMI: Primary Angioplasty in Myocardial Infarction

PHL: Pre-Hospital administration of Fibrinolytic Therapy

PEPA: Proyecto de Estudio del Pronóstico de la Angina

PCI: Percutaneous Coronary Intervention

PHL: Pre-hospital Fibrinolytic Therapy

PURSUIT : Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy

PREDICT: Predicting Risk of Death in Cardiac Disease Tool

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

PRISM-PLUS: Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms trial

RUSH: Rush-Presbyterian-St. Luke's Medical Center Study

SBP: Systolic Blood Pressure

STEMI: Myocardial Infarction with ST-Segment Elevation

TIMI: Thrombolysis in Myocardial Infarction

List of Keywords

Myocardial Infarction, Percutaneous Coronary Intervention, Risk score, Fibrinolytic Therapy, Acute Coronary Syndromes, Meta-Analyses, Reperfusion Therapy, Pre-hospital Medical Service.

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Chapter 1.

Introduction

Cardiovascular diseases (CVD) are the leading causes of mortality worldwide (9) and the global CVD burden is enormous (9-10). As developing countries undergo epidemiologic transition from infectious to chronic diseases, the potential global burden of CVD mortality and morbidity is immense (11). One of the most common CVDs is acute coronary syndrome (ACS), which occurs secondary to acute total or partial occlusion of an artery that supplies blood to the heart (i.e., a coronary artery) by a blood clot (11). There are, among others, three critical issues related to ACS care that remain unresolved and are the focus of this dissertation. The following paragraphs describe each of these three issues.

Do the benefits of PCI over FL observed in RCTs extend to "real-'life" patients?

Acute myocardial infarction (AMI) with ST-segment elevation (STEMI) is a frequent and highly lethal type of ACS (2). STEMI occurs secondary to acute total occlusion of a coronary artery. Complete lack of blood flow will lead to irreversible cell death in the affected part of the heart. Management of STEMI requires urgent reperfusion therapy (RT) which restores blood flow in the occluded coronary artery (2).

RT can be provided either by the administration of FL medication which dissolves the blood clot, or by primary percutaneous coronary intervention (PCI) which involves the insertion of a catheter into the coronary artery to break up the blood clot (2). Twenty-six randomized clinical trials (RCT) (12-37) have reported survival benefit of primary PCI over FL in patients with STEMI. However, it remains unclear whether the survival benefit of primary PCI over FL can be replicated in "real-life" patients (3-4). Even though RCTs are generally considered the "gold standard" studies to evaluate the efficacy of interventions,

the benefits of complex interventions in "ideal" patients under "ideal" conditions may not be replicable in sicker, "real-life" patients in less than "ideal" conditions (38-39). The first knowledge gap addressed in this doctoral dissertation relates to whether or not the superiority of primary PCI over FL can be confirmed in unselected "real-life" patients.

Can PHL systems of care be implemented successfully outside Europe?

Pre-hospital administration of fibrinolytic therapy (PHL) improves survival compared to in-hospital administration of FL in patients with STEMI (40). However, due to the complexity of the pre-hospital emergency medical systems (EMS) required for PHL, this RT strategy is rarely available outside Europe (5-6). The second knowledge gap, addressed in this doctoral dissertation, relates to whether or not PHL can be administered by health care professionals with different expertises. Insights from successful PHL programs may allow more widespread implementation of PHL.

Can a new risk score discriminate high-risk ACS patients?

Despite the availability of several risk scores (40-64), there is no ideal risk score that can be used for rapid pre-hospital risk stratification of ACS patients (65). Prompt and accurate pre-hospital identification of high-risk ACS patients may guide early management of these patients including selection of the most appropriate hospital for them. The third knowledge gap, addressed in this doctoral dissertation, relates to whether a novel and simple risk score can be used for early risk stratification of ACS patients.

The objectives of the three manuscripts that comprise this dissertation are: (1) To compare the efficacy, effectiveness, and safety of primary PCI and FL for STEMI patients in RCTs and observational studies; (2) To describe the infrastructures, processes and outcomes of PHL in several international jurisdictions, and (3) To develop and validate a risk score for early pre-hospital risk stratification of ACS patients.

Structure of the thesis

The thesis is structured as follows: following an introduction in Chapter 1, the literature review in Chapter 2 is divided into four sections: 1) burden, pathophysiology and management of different types of ACS; 2) efficacy, effectiveness and safety of RT; 3) pre-hospital management of ACS and 4) risk stratification of patients with ACS. In Chapter 3, the objectives and research hypotheses of this doctoral dissertation are presented. In chapters 4-6, I describe the rationale, methodology and results of my work in three manuscripts, as followed:

- The first manuscript presented in Chapter 4 is entitled: "*Comparison of Primary Percutaneous Coronary Intervention and Fibrinolytic Therapy in ST-Segment Elevation Myocardial Infarction – Bayesian Hierarchical Meta-Analyses of Randomized Controlled Trials and Observational Studies."* This manuscript was presented at the American Heart Association Congress in 2007. It was published in Circulation in 2009 (66), (impact factor of the journal: 14.7 in year 2012).
- The second manuscript presented in Chapter 5 is entitled: "*The pre-hospital fibrinolysis experience in Europe and North America and implications for wider dissemination*". This manuscript was published in the Journal of the American College of Cardiology – Intervention in 2011 (67), (impact factor: 6.8 in year 2012).
- Finally, the third manuscript presented in Chapter 6 is entitled *"C-ACS: A New Risk Score for Early Prognostication in Acute Coronary Syndromes"*. This manuscript has been presented at the American Heart Association Congresses in 2007 and 2010 and is currently in press at the American Heart Journal (impact factor: 4.8 in 2012)

In Chapter 7, I discuss the results of the research undertaken in this doctoral dissertation including its limitations and strengths. I expand on the implications of the

findings in terms of cardiovascular care in Quebec and finally conclude on future research directions.

Chapter 2

Literature review

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death in every region of the world except sub-Saharan Africa (9-11). Within a few years, even in sub-Saharan Africa, CVDs mortality will exceed mortality related to infectious diseases (11). Although CVD has traditionally been thought of as a disease of affluent populations, urbanization and industrialization have resulted in the increased prevalences of several detrimental lifestyle habits (i.e., tobacco use, physical inactivity, sedentary behavior, and unhealthy nutrition) in developing countries. As developing countries undergo epidemiologic transition from infectious to chronic degenerative disease, the worldwide burden of CVD mortality will become enormous (11).

In the following literature review, I expand on the burden of CVD, the pathophysiology of CVD, the types of ischemic heart diseases, the management of acute myocardial infarction (AMI) and the importance of time delays to treatment. I also describe the infrastructure and functioning of several Canadian and international systems of AMI care, as well as the outcomes of patients with acute coronary syndromes (ACS) managed by these systems of care.

2.2 Pathophysiology of CVD

CVD comprises a wide range of cardiac, vascular (i.e., diseases of the vessels and cerebro-vascular diseases (i.e., diseases of the vessels that supply blood to the brain) (11). The most common cardiac diseases include ischemic heart diseases (i.e., diseases of the vessels that supply blood to the heart), congestive heart failure (i.e., weakness of the heart

muscle) and valvular heart diseases (i.e., diseases of the valves that separate the chambers of the heart) (11).

Ischemic heart disease is secondary to acute or chronic total or partial blockage of an artery supplying blood to the heart (i.e., a coronary artery) (11). Acute coronary syndromes (ACS) are conditions with acute blockage of the coronary artery. If the remaining blood supply is sufficient to maintain viability of the heart muscle, the acute blockage of the coronary artery results in unstable angina (68). If the blood supply is inadequate to maintain viability of the heart muscle, it results in acute myocardial infarction (AMI) (66). Acute total occlusion of the coronary artery results in ST-segment elevation AMI (STEMI) (1), while acute partial occlusion of the coronary artery induces an AMI without ST-segment elevation (NSTEMI) (68). STEMI is highly lethal and must be treated promptly (1-2). Since the management and prognosis of NSTEMI and unstable angina are similar, these syndromes are categorized together as ACS without ST-segment elevation (NSTE-ACS) (68).

Differentiation of STEMI and NSTEMI requires recognition of ST-segment elevation on the electrocardiogram (ECG) (68). An ECG is a test that evaluates the blood supply to the heart by positioning skin electrodes on the chest wall (69). The test is non-invasive, painless and requires approximately five minutes (69).

2.3 National and international burdens of CVD and AMI

CVDs are currently responsible for 30% of deaths worldwide (9). Every year, 80% of the 18 million CVDs deaths occur in low and middle-income countries (9). In developing countries, CVDs primarily affect middle-aged individuals and those older than 65 years. Combining years of potential lives lost secondary to premature death and years of productive life lost due to disability, the disability-adjusted-life years can reliably estimate

the socio-economic impact of CVDs. CVDs rank second to human immunodeficiency diseases, with a loss of 47 million disability-adjusted-life years worldwide on an annual basis (11).

Approximately 82 million American adults (i.e., 1 in 3 Americans) have one or more types of CVD (70). In 2007, CVDs were responsible for 8 million hospitalizations in the United States, and 450 000 hospitalizations in Canada (71). Every year, CVD-related deaths approximate 785 000 in the United States and 69 000 in Canada (71-72). Elimination of CVD would increase life-expectancy by 7 years in the United States, and 3 years in Canada (71-72).

Acute and chronic ischemic heart diseases are responsible for most of the CVD morbidity and mortality burdens (11). Ischemic heart diseases are responsible for more than 7 million deaths worldwide every year (11). There were 18 905 Canadian deaths due to ischemic heart diseases in 2002 (age and sex-standardized rates of 123/100 000 in males, and 64/100 000 in females) (71). These rates were lower than the American age and sex-standardized rates of ischemic heart diseases-related mortality, at 145 and 79 per 100 000 males and females, respectively (71-72). In 2006, ischemic heart diseases accounted for 160 323 Canadian hospitalizations (17% of all Canadian hospitalizations) and 13 836 deaths in Quebec (71-72). The age and sex-standardized rates of ischemic heart diseases-related hospitalization were 254/100 000 in Canada and 177/100 000 in Quebec (71-72).

AMI occurs when ischemic heart disease leads to partial death of the heart muscle (1, 65). Every year, there are 1.3 million AMIs in Europe (73). In the United States, AMI is responsible for 935 000 hospitalizations annually (70). In Quebec, the annual number of AMI hospitalizations approximated 15 000 (72). The age and sex-standardized AMI incidence in Canada is summarized in Table 1.

Table 1. Total population, percentage of population ≥65 years old, and incidence of acute myocardial infarction-related hospitalizations, by year and province, in Canada (71,72).

	Incidence of acute myocardial infarction per 100 000* Year			Total population, thousands (% ≥65 years old)
	2007	2008	2009	
Canada	219	217	209	34 108.8 (14)
Newfoundland and Labrador	351	347	329	509.7 (15)
Prince Edward Island	308	294	269	142.3 (15)
Nova Scotia	270	264	265	942.5 (16)
New Brunswick	278	269	255	751.8 (16)
Quebec	NA	221	214	7 907.4 (15)
Ontario	219	216	207	13 210.7 (14)
Manitoba	253	255	253	1 235.4 (14)
Saskatchewan	227	228	212	1 045.6 (15)
Alberta	221	205	200	3 720.9 (11)
British Columbia	169	169	164	4 531.0 (15)
Yukon	189	199	218	34.5 (8)
Northwest Territories	207	182	250	43.8 (5)
Nunnavut	256	112	192	33.2 (3)

*Adjusted for age, sex and co-morbidity

2.4 Management of STEMI

With complete occlusion of the coronary artery, death of the affected heart muscle will occur rapidly unless the coronary artery's blood flow can be promptly restored. It is of paramount importance to restore blood flow in the totally occluded coronary artery as promptly as possible (1, 76). Death may occur rapidly due to instability of the electrical system of the heart or secondary to acute heart failure. The amount of irreversibly damaged heart muscle increases exponentially with increasing time delays to treatment. Therefore, the sooner the coronary artery is opened, the lesser the damage to the heart (1-2,76). Restoration of blood flow during the first hour after coronary occlusion (i.e., often referred to as the "golden hour") can completely arrest the progression of the STEMI (1-2,77).

Reperfusion therapy (RT) is an intervention to restore blood flow in the affected coronary artery. Reperfusion can be accomplished either by administration of an intravenous medication (i.e., fibrinolytic therapy (FL)), or by inflation of a special catheter in the coronary artery (i.e., primary percutaneous coronary intervention (PCI)) (2). Delay to RT are detrimental because of it increases the risk of permanent heart damage and mortality (1-2,76).

2.4.1 Fibrinolytic therapy

Several types of FL medications are available. There are older medications such as streptokinase and urokinase, and newer medications including tissue plasminogen activator and tenecteplase. The newer medications have a success rate of more than 75% in restoring the coronary blood flow, compared to approximately 50% success rate with the older medications (2). The cost of FL ranges between 700 $ and 2 700 $ per dose for older type and newer type of FL, respectively (77). FL can be injected into a vein by a physician or specialized paramedical personnel (i.e., ambulance paramedics or nurses). FL can be administered in most emergency rooms or less commonly in the pre-hospital settings (PHL) (i.e., at the patient's home or in the ambulance).

2.4.2 Primary percutaneous coronary intervention

Percutaneous coronary intervention (PCI) is a procedure that involves insertion of a catheter into the coronary artery to break down the blood clot occluding the coronary flow (2). When the intervention is performed in the context of a STEMI without prior administration of FL, it is called "primary PCI" (2). Primary PCI is highly effective, with more than 90% success in restoring the coronary blood flow (2). The estimated cost of a primary PCI is approximately 5 000 $ (77).

2.4.3 Complications of RT

The main complications of RT include stroke, major bleeding and severe allergic reactions (2). Patients with STEMI may experience stroke due to bleeding in the brain or dislodging of a blood clot to the brain. Intracranial bleeding can be life-threatening or associated with permanent severe disability. Intracranial bleeding occurs in 1%-5% of patients who receive FL (80). Stroke is very rare (less than 1%) with primary PCI (81).

Major bleeding may occur following both types of RT (78). It can be secondary to the direct action of FL, or it can be caused by arterial damage related to primary PCI, or it can be due to concomitant medications (81). The cumulative incidence of major bleeding is highly variable, ranging from 0%-18%, depending on the definition of major bleeding (81). Serious allergic reactions occur in 1% of patients who receive older types of FL such as streptokinase and urokinase (2, 81). Although rare, these reactions are highly lethal. The newer FL agents such as tissue plasminogen activators, reteplase and tenecteplase, are not associated with allergic complications (2,81).

2.4.4 Efficacy and safety of RT

Summary of results of RCTs of RT

There are 26 RCTs that compare the efficacy of FL versus primary PCI (12-37). The majority of these RCTs have small sample sizes; only six included more than 400 patients (12,14-15,21,27,35-36). Since the time interval between publication of the first and last RCT on this subject (1993-2008) is long, there is marked heterogeneity across studies in the types of FL used as well as adjuvant therapies (81). There are also marked variations in the management of patients with STEMI including in-hospital or pre-hospital administration of FL, and primary PCI with or without inter-hospital transfer (81). The expertise of RT providers also varies across studies, with FL administered by less trained EMS personnel and primary PCI performed by less expert and experienced physicians in some RCTs (81).

Since their statistical powers are limited by their small sample sizes, the primary endpoints investigated in several RCTs are most frequently the composite of several endpoints. The most commonly used primary endpoint is a composite of all-cause mortality, reinfarction (i.e., recurrence of AMI) and stroke (12-37). However, these separate endpoints have very different clinical impacts, with reinfarction being the most benign complication compared to stroke or death (82). Furthermore, detection and ascertainment of reinfarction are highly inconsistent across studies. All-cause mortality is the most objective, reliable and valid endpoint and should have been considered separately from the other endpoints (82).

Potential bias in RCTs

Numerous potential biases may have compromised the internal validity of several RCTs. In this section, I summarize these potential biases. The main benefit of randomisation is to decrease potential confounding by ensuring equal probability for all patients of receiving either therapy, regardless of their characteristics (83). Prior knowledge of the assigned therapy may affect physician and/or patient decision to participate in the study. Therefore, it is crucial that neither the physicians nor the patients can predict the RT strategy assigned. Research personnel should not be able to alter the randomisation sequence.

Randomisation by sealed envelope is subject to manipulation by research personnel, if the allocated therapy can be visualized through the envelope (84-86). Randomisation remote from the research center should be the most reliable method since health care providers cannot tamper with the assignment. Sealed envelope randomization was used in eight (13,16,19-20,23-26) of 25 RCTs, so that randomization in these eight studies was subject to manipulation.

Randomization may not reduce all important differences in patient characteristics between intervention arms. RCTs with small sample sizes are particularly subject to this limitation (83,86-87). By chance, sicker or older patients may have been assigned to one intervention arm compared to the other arm. We observed a difference of 5 years in mean age and ≥10% difference in high-risk features between patients who received FL and patients who underwent primary PCI, in several RCTs. Of the 25 RCTs reviewed, there was no notable difference in patient characteristics in only seven studies (15,19,21,27,30,33,35-36).

Due to the natures of the interventions studied, none of the RCTs reviewed could be double-blinded. Therefore, both patients and health care providers were aware of the RT assigned, which may have affected the selection of adjuvant therapy. For example, patients randomly assigned to primary PCI would require transfer to tertiary teaching hospitals with PCI facility, in contrast to patients who received FL who would stay at smaller secondary hospitals. Patients who underwent primary PCI would be more likely to receive more evidence-based concomitant medications and interventions. The impacts of the RT might have been modulated by different concomitant therapies (81).

Knowledge of the type of RT received may induce information bias so that both care providers and/or patients are more likely to detect and/or report adverse outcomes related to the therapy received (81,88). Patients who received FL and their providers might be more likely to detect and report reinfarction and/or stroke symptoms since these complications are known to be more frequent with FL than with primary PCI. This could have induced a misclassification bias of the results against FL.

Misclassification bias might also occur if the endpoint adjudication committee is unblinded to the treatment assigned, and adjudicates the endpoints according to their RT

preference. The endpoint adjudicators were blinded to the therapy assigned in only 12 RCTs (12-15,17,20-23,26,31,37). Finally, loss to follow-up might induce selection bias when the sample of patients followed until the end of the study differs from the sample of patients originally enrolled. In general, follow-up was excellent in most RCTs, with complete follow-up in 12 studies (14,16,22-23,25-26,29,31,33,35-37,90). However, in one RCT (91) there was notable difference in follow-up between the two treatment arms, whereby more high-risk patients were lost to follow-up in the primary PCI arm compared to the high-risk patients who received FL (i.e., 58% versus 48%). Therefore, there was a potential bias favouring primary PCI in this study, since there might be more adverse events in the high-risk patients who were lost to follow-up in this treatment arm.

External validity of RCTs

The applicability of the results of RCTs to the "real-life" context is often assumed by the similarity between the patients enrolled and the interventions undertaken in these RCTs, with the patients and interventions performed in the "real-life" context. However, the patients enrolled in the RCT are generally younger, have fewer co-morbidity and less severe STEMI than "real-life" patients (92-93). In particular, all RCTs reviewed excluded patients at risk of renal failure due to the risk of kidney damage by radiology contrast agents (81). The patients at risk of bleeding were also excluded. Furthermore, the patients with cardiogenic shock (very severe STEMI) were either explicitly excluded or often not enrolled due to their inability to provide informed consent (81).

Delivery of RT within an "RCT context" is also generally different than delivery of RT within the "real-life" context. The process of obtaining informed consent can be lengthy and imposes additional delays to RT administration. Since the effectiveness of FL decreases more with longer time delays compared to primary PCI (76), any consent-related

delay might bias against FL. The median time delays to FL exceeded the recommended target of less than 30 minutes in several RCTs reviewed (81). On the other hand, primary PCI within the RCT context was generally performed expeditiously at excellent large-volume centers by expert personnel. The median time delays to primary PCI were generally within the target of ≤90 minutes (81). Timely primary PCI by expert personnel at expert centers may not always be possible outside the rigorously controlled conditions of RCTs. Therefore, the superiority of primary PCI over FL might not be able to be entirely replicated outside the "RCT" context.

Meta-analyses of RCT of RT

Due to the limited statistical power of most RCTs that compared primary PCI and FL, differences in all-cause mortality reduction between primary PCI and FL should be better evaluated by using meta-analyses. I identified 21 published systematic reviews of RCTs that compared primary PCI and FL (37, 92-112). Most meta-analyses showed that primary PCI was associated with a 5% mortality reduction compared to streptokinase (i.e., an older type of FL) (92). Primary PCI was associated with a reduction in mortality of 1% compared to in-hospital administration of tissue plasminogen activator (i.e., a newer type of FL) (92,96-97). On the other hand, there was no conclusive difference in mortality between primary PCI and pre-hospital administration of FL (97). Furthermore, the reduction in mortality of primary PCI was not consistently observed in the meta-analyses using more conservative random-effects models (94) and/or Bayesian methodology (100).

The majority of the meta-analyses reviewed showed short-term survival benefits of primary PCI and reductions in reinfarction and stroke of 1% compared to FL (92-93,95-96,98-99,101-112). The superiority in mortality reduction associated with primary PCI

compared to FL decreased with longer time delays to primary PCI (110). Primary PCI was associated with a 2% increase in major bleeds compared to FL (92).

All meta-analyses are potentially limited by publication bias, since authors and editors tend not to report research that does not show differences in the outcomes between intervention arms (113). Tests to detect this bias, such as funnel plots and trim and fill tests, are poorly sensitive and may not detect omission of major negative studies (110). All meta-analyses reviewed are subject to publication bias and might have over-estimated treatment effects.

The main limitation of several meta-analyses reviewed was the use of fixed- rather than random-effects models (37,92,96-98,101,106). In assuming similarity between the trials in terms of patients enrolled and in studies designs, fixed-effects models assume that the results are interchangeable across studies (113-114). Fixed-effects models are often employed following negative heterogeneity testing (113-114). However, the sensitivity of heterogeneity testing is poor, and therefore may miss major differences between trials (113-114). In these cases, the summary estimates tend to over-estimate the true difference between the interventions studied (114).

Random-effects meta-analyses assume that all trials are dissimilar and provide more conservative summary estimates than fixed-models (113-114). Summary estimates by random-effects meta-analyses are generally closer to the true differences in treatment effects than estimates from the fixed models (113-114). In addition to consideration of the differences between trials, Bayesian meta-analysis allows each individual study to borrow strength from the summary estimate (115-116). Hence, Bayesian models allow for better designed studies with smaller sample sizes to contribute more to the summary estimate than other types of random-effects models (115-116). Moreover, sub-optimally designed studies

with larger sample sizes have less impact on the summary estimate in Bayesian modeling (115-116). Consequently, the estimate of the difference in treatment effects is less likely to be biased by sub-optimal large studies in Bayesian meta-analyses (115-116).

There were only two meta-analyses that used random-effects Bayesian models. However, these meta-analyses were limited by lack of inclusion of recent studies that compared primary PCI with newer types of FL (100,110). Consequently, a new Bayesian meta-analysis including more recent RCTs is indicated, and is the rationale for the first manuscript of this doctoral dissertation (66).

Summary of results of observational studies

There are 31 observational studies that compared primary PCI and FL (3-4,117-145). The majority of studies showed that primary PCI was superior to in-hospital FL administration in reducing short and long-term mortality (117,119-120,124-126,129-130,134-136), in-hospital stroke (3,80,126-128,132,135-136,138-139) and reinfarction (120,126,136). However, the survival advantage of primary PCI was not consistently present in the four studies that compared primary PCI to pre-hospital administration of fibrinolytic therapy (PHL) (4,120,144-145). Primary PCI reduced mortality compared to PHL in one study (120), while a survival advantage with PHL was observed in another study (120), and no survival difference was observed between the two treatment arms in two other studies (144-145).

Potential biases of observational studies

Observational studies are often considered to be of inferior quality compared to RCTs, since they are more susceptible to bias and in particular to selection and confounding bias (39,146-149). Because treatment assignment is not controlled, there are frequently imbalances in the characteristics of patients enrolled that may bias treatments

effects (146-151). In the observational studies reviewed, a specific type of confounding bias, "confounding by indication" is of particular concern (151). This bias occurs when patients with cardiogenic shock (i.e., very severe STEMI) undergo primary PCI since it is the recommended RT in these patients (78). Inclusion of these patients in may bias against primary PCI since this might increase the mortality rate of primary PCI compared to FL.

Selection bias might impact observational studies in several ways (146-149). To avoid selection bias, all analyses should be performed using an intention-to-treat approach. Since primary PCI requires much longer time delays than FL, patients assigned to primary PCI might die while awaiting this intervention. Since administration of FL requires shorter time delays, patients receiving this treatment would be less likely to die before receiving FL. Exclusion of patients who die before receiving RT from the analyses, would induce selection bias in favour of primary PCI. Selection bias may also occur with sub-optimal follow-up when there was no consideration of events in patients lost to follow-up (146-149). Moreover, since observational studies might not have rigorously pre-defined their methodology for event detection and classification, these studies may also be subject to detection and misclassification bias (146-149).

Strengths of observational studies

Despite potential biases, well-designed observational studies may produce results as relevant as those of RCTs (39,150). High-quality cohort studies should involve concurrent rather than historical controls, clearly described inclusion criteria, definition of zero-time (i.e., time of study start) and adequate adjustment for differences in characteristics of patients between intervention arms (39,150). Furthermore, observational studies may address the limited external validity of many RCTs. Observational studies can provide unique "real-life" perspectives by including older and sicker patients who are frequently

excluded from RCTs (39). Effectiveness and safety of primary PCI undertaken in less than ideal conditions (i.e., low volume and less expert centers, lengthy time delays to RT) are best evaluated in observational studies (39,150). Observational studies with long follow-up periods are also more suitable than RCTs to assess the safety profile of RT in less selected patients with STEMI (39,150).

Rationale for a meta-analysis of observational studies

A systematic review of observational studies on RT has never been published. A Bayesian meta-analysis of observational studies may provide a better understanding of several aspects of RT that cannot be adequately evaluated in RCTs, including effectiveness and safety of RT in less selected patients with STEMI. This was the rationale for the Bayesian meta-analysis of observational studies in the first manuscript of this dissertation. (Manuscript 1).

2.4.5 Pre-hospital management of patients with STEMI

Although much less attention has been directed to pre-hospital emergency medical services (EMS) than to in-hospital management of a patient with STEMI, early EMS intervention can abort a STEMI and can improve patient outcomes (151-153). Prior to the introduction of primary PCI and PHL, traditional EMS management of patients with STEMI involved prompt transportation of these patients to the closest hospital only, regardless of whether or not this hospital had a PCI facility (154). During the past decade, several EMS innovations may have reduced time delays to RT such as 1) EMS diagnosis of STEMI (78,154-155), 2) EMS alert of ER personnel of the impending arrival of patients with STEMI (78-79,154-158) and 3) EMS administration of FL (PHL) (78-79, 151-153,157-158).

Diagnosis of STEMI is a two-step process: 1) electrocardiogram (ECG) acquisition and 2) ECG interpretation (1) (154). Although ECG acquisition skills can be learned rapidly, ECG interpretation is more complex. A false negative diagnosis of STEMI may delay RT, while a false positive diagnosis of STEMI may lead to inappropriately administered RT and may expose the patient to unnecessary life-threatening complications of RT (154).

EMS interpretation of ECG can be automated (i.e., generated electronically by a computer) or undertaken by EMS personnel or by a physician (154). Since most EMS systems do not have physician in the ambulances, interpretation of pre-hospital ECGs by a physician is only possible with transmission of these ECGs (154). However, ECG transmission may not be feasible due to lack of a wireless telephone system or lack of a physician assigned to this task (154). In these cases, automated and/or a paramedic's interpretation of the ECG may be used despite lower accuracy in ECG interpretation compared to physician's ECG interpretation (154).

EMS alert of ER personnel of the impending arrival of patients with STEMI can reduce time delays to RT (158). ER personnel can notify PCI personnel and/or prepare FL during the transportation of patient to the hospital. However, although alert of ER personnel by EMS appears to be straightforward, this step requires accurate EMS diagnosis of STEMI (154). Unnecessary and/or inappropriate notification of PCI personnel is costly and can divert ER care from other patients (154).

Compared to in-hospital administration of FL, PHL reduce times delays to FL (152-153), and therefore can improve survival of patients with STEMI (40). In rural areas, PHL may be the only RT strategy that can be available in a timely manner (79, 157). Despite the

complexity of PHL, the European Society of Cardiology has endorsed and implemented PHL, for over two decades, in Europe (152).

Care of patients with STEMI may be coordinated within a local network of EMS personnel and hospitals with or without a PCI facility (i.e., regionalized STEMI care) (79,155-157). Although the infrastructure and organization of STEMI care differs considerably between regions, regionalized STEMI care most frequently involves direct transportation of patients with STEMI by EMS to a hospital with PCI facility (PCI-hospital) rather than to the hospital closest to the patient (79,155-159). However, it remains unclear whether EMS transportation of patients with STEMI directly to a PCI-hospital is superior in reduction of mortality compared to transportation to the closest hospital. A meta-analysis of RCTs and observational studies reported an inconclusive difference in mortality between direct transportation of patients with STEMI to a PCI-hospital compared to transportation of these patients to the closest hospital (160).

Finally, it is essential to recognize the complexity of EMS organization. Pre-hospital STEMI care requires major investment that may divert resources from other critical areas. Large numbers of primary PCI-related ambulance transfers (i.e., direct transportation of patients with STEMI to a PCI-hospital bypassing the closest hospital, inter-hospital transfer for primary PCI, inter-hospital transfer back to the referring hospital) would reduce the number of ambulances available for other types of EMS care. Availability of ambulances is particularly critical in rural areas, where an ambulance cannot be occupied for prolonged periods to care for a single patient with STEMI. The quest for optimal pre-hospital STEMI management should be carefully planned to avoid jeopardizing STEMI patients by inappropriately delaying RT and depriving patients with other diseases of optimal EMS care.

2.4.6 Overview of national infrastructure and processes of care of patients with STEMI

In this section, we describe national and provincial pre- and in-hospital infrastructure currently available for managing patients with STEMI.

Pre-hospital care for patients with STEMI in Canada

EMS technicians (i.e., paramedics) are trained at different levels of expertise: advanced, intermediate and basic care (161). Paramedics trained in advanced care can manage patients without a physician's assistance. They can independently administer almost all medications, identify and manage patients with STEMI without requiring assistance by a physician (161). Paramedics trained in intermediate care can administer a limited number of medications and acquire ECG (161). They require assistance from a physician (generally by telephone) to manage patients with STEMI (161). Paramedics trained in basic care can only transport patients and perform basic cardiac resuscitation (161).

In manuscript 2 of this thesis, I describe variations in the infrastructure and processes of care as well as in the expertise of EMS personnel across several international settings. European EMS systems of care have the most expert personnel in the ambulances (i.e., physicians in France and Vienna, nurses in Sweden, paramedics trained in advanced cardiac care in the United Kingdom) (6,67). At the present time, most Canadian EMS systems have paramedics trained in advanced care, except in Quebec where most paramedics are only trained in intermediate care (161-162).

I summarize the key processes of EMS management of patients with STEMI in five Canadian provinces (85% of Canadian population) in Table 2. Less than half of Canadian paramedics can interpret ECG, and only a minority can transmit the pre-hospital ECG (162). Despite being the most populated provinces with the highest proportions of elderly,

EMS systems in Ontario and Quebec are the least developed, with fewer paramedics trained in ECG interpretation and transmission, PHL and re-direction of patients to PCI-hospitals (162). Alberta has the most organized EMS system of STEMI care, with the highest proportion of paramedics trained in PHL and in ECG acquisition, interpretation and transmission (162).

Overall, numerous obstacles limit optimal EMS management of patients with STEMI in Canada compared to European countries. In contrast to Europe, where PHL is successfully implemented in many countries (6,67,73), PHL is currently available in only two Canadian provinces (Alberta and Nova Scotia) (67). Considering its vast territory and its large rural population, Canada can potentially derive considerable benefit from more widespread implementation of PHL (67).

Table 2. Expertise of paramedics in STEMI care in selected Canadian provinces, (162-163).

	Province (year with available data)					
Expertise	Canada (2007)	Quebec (2011)	Ontario (2007)	Alberta (2007)	British Columbia (2007)	Nova Scotia (2007)
ECG acquisition, % of paramedics	47	100	55	80	10	80
ECG interpretation, % of paramedics	40	35	50	70	10	70
ECG transmission, % of paramedics	20	20	5	70	10	70
Expedited inter-hospital transfer to PCI-hospital, % of paramedics	45	NA	45	50	100	NA
Pre-hospital re-direct of patients with STEMI to PCI-hospital, % of paramedics	18	In urban areas only	10	50	100	NA
Pre-hospital fibrinolysis, % of paramedics	8	0	0	50	0	Pilot project

ECG: Electrocardiogram
NA: Not Available
PCI: Percutaneous Coronary Intervention
STEMI: ST-Segment Elevation Myocardial Infarction

Pre-hospital care of STEMI in Quebec

In Quebec, physicians are rarely present in ambulances (161). Management of patients in ambulances is generally under the responsibility of paramedics (161) with medical assistance available by phone only (161). In contrast to all other Canadian EMS, Quebec paramedics are only trained in intermediate care (161) and therefore can only perform basic management of STEMI patients (161). They cannot administer any drug intravenously (161).

Consequently, EMS STEMI management in Quebec has been limited to on-scene stabilization and transportation of patients to the assigned hospital (161). Compared to other jurisdictions, EMS interventions in Quebec are markedly limited in scope. For example, pre-hospital ECG is available in Quebec only since 2009 (164) compared to availability of this technique since 1990 in Sweden (67). The main obstacle to optimal EMS management of patients with STEMI in Quebec includes provision of care to a relatively small population distributed across a very large territory (165). Access to and transportation of patients in rural areas can be lengthy and problematic in Quebec, especially during the winter months (165)

In recent years, primary PCI has emerged as the preferred RT in Quebec (166). Quebec EMS redirects patients with STEMI more frequently to a PCI-hospital than to the closest hospital (166). Although re-direction of patients to a PCI-hospital (rather to the closest hospital) has been shown to be safe in Europe (27,28), ambulance transportation in Europe is generally within short distances and with expert medical escorts (i.e., physicians, intensive care nurses and/or advanced care paramedics) (66). The safety of transporting patients with STEMI by intermediate care paramedics to a PCI-hospital rather than to the closest hospital remains to be determined in Quebec.

Overview of structures of in-hospital STEMI care in Canada

The infrastructure for in-hospital STEMI care in Canada overall and five Canadian provinces are described in Table 3 (167). There are 1 449 PCI hospitals in the United States, with a ratio of one PCI-hospital per 215 359 Americans (168). In contrast, there are 40 Canadian PCI-hospitals, with a ratio of 1 PCI-hospital per 852 725 Canadians (169). Compared to other provinces, Quebec has the most PCI-hospitals per population (1 per 608 230) compared to 1 PCI-hospital per 943 571 in Ontario population, 1 per 1 240 333 in Alberta, 1 per 1 132 750 in British Columbia, and 1 per 942 500 in Nova Scotia (163,169).

Due to the smaller number of PCI-hospitals and more sparsely distributed population, only 64% of Canadians live within 60 minutes of a PCI-hospital, compared to 79% of Americans (168,169). Compared to other provinces, Ontario has the most optimal geographic distribution of PCI-hospitals. Seventy-three percents of the Ontario population live within a 60-minute access to a PCI-hospital compared to 69% of the Quebec population, 63% of Albertans, and 58% of British Columbians (169).

Table 3. In-hospital infrastructure for STEMI care in the United States and Canada (163,167-169)

	Canada	Quebec	Ontario	Alberta	British Columbia	Nova Scotia
Number of ER capable of RT	NA	111	NA	NA	NA	943
Number of PCI-hospitals	40	13	14	3	4	NA
Population per PCI-hospital	852 725	608 230	943 571	1 240 333	1 132 750	942 500
% of population ≤30 minutes of a 24/7 ER	NA	94.0	NA	NA	NA	NA
% of population ≤ 60 minutes of a PCI-hospital	64	69	73	63	58	36
% of population ≤ 120 minutes of a PCI-hospital	79	87	92	72	64	55

% of population ≤ 90 minutes of a PCI-hospital	72	80	83	68	63	42

ER: Emergency room
NA Not available
PCI-hospital: Hospital with facility for percutaneous coronary intervention
24/7: opened 24 hours on 7 days

2.5. Outcomes of patients with AMI

2.5.1 Mortality of patients with AMI

The 30-day mortality rates adjusted for age, sex and co-morbidity in some Canadian provinces are reported in Table 4 (171-172). Risk-standardized 30-day mortality is not available for Quebec due to co-morbidity coding different from other provinces (171-172). There is a 25% absolute decrease in AMI-related mortality in less than a decade (1998-2006) (171-172). This decline in AMI fatality in Canada is remarkable considering that the declines in fatality for two other important CVDs such as congestive heart failure and stroke, remain unchanged in Canada during the same decade (171-172).

Table 4. Thirty-day AMI-related mortality*, in Canada, (1998-2006) (171-172).

	Year								
	1998	1999	2000	2001	2002	2003	2004	2005	2006
Canada	12.6	12.1	11.8	11.4	11.3	11.1	10.3	10.0	9.4
Newfoundland and Labrador	NA							13.5	12.1
Prince Edward Island	12.7	12.3	12.0	13.0	14.6	14.3	14.2	12.8	11.3
Ontario	12.8	12.4	12.0	11.3	11.2	11.1	10.2	9.9	9.4
Manitoba	12.1	11.5	11.5	12.2	12.0	11.4	9.6	9.2	8.6
Saskatchewan	14.6	12.5	11.9	11.8	11.6	10.9	10.1	9.6	9.5
Alberta	10.4	9.9	9.6	10.2	9.4	9.3	8.2	8.4	7.8

*=AMI-related mortality adjusted for age, sex and co-morbidity
AMI: Acute Myocardial Infarction
NA: Not available

2.5.2 Re-hospitalization of patients with AMI

The 30-day AMI-related re-hospitalization can be a measure of the quality of care provided to patients with AMI since most of these patients should not require a re-hospitalization within 30 days (172). This outcome may reflect inadequate care, insufficient discharge planning and/or sub-optimal follow-up. Re-hospitalization rate should be adjusted for age and co-morbidity, since older patients with more co-morbidity are more likely to be re-hospitalized. The 30-day AMI-related re-hospitalization rates adjusted for co-morbidity, age and sex are summarized in Table 5.

The national 30-day rehospitalisation approximated 5% with the lowest rates observed in Alberta. There is a 35% decrease in 30-day re-hospitalization in Canada since 1998 (171-172). It is not possible to compare the 30-day AMI-related re-hospitalization rate in Quebec with other provinces due to different co-morbidity coding (171).

Table 5. Thirty-day AMI-related re-hospitalization adjusted for age, sex and co-morbidity in Canada, (1998-2006) (171-172).

Year	1998	1999	2000	2001	2002	2003	2004	2005	2006
Canada	7.3	6.7	4.5	6.9	7.1	6.2	5.6	5.1	4.7
Newfoundland and Labrador	NA					7.5	7.1	6.2	5.9
Prince Edward Island	10.7	10.8	6.5	8.3	11.4	9.6	8.5	6.4	5.9
Nova Scotia	8.6	8.6	5.1	9.0	8.7	7.8	7.0	6.2	5.5
New Brunswick	8.6	8.6	5.1	9.0	8.7	7.8	7.0	6.2	5.5
Quebec		6.3*		NA					
Ontario	7.5	6.9	4.7	7.2	7.2	6.1	5.4	4.9	4.6
Manitoba	NA						5.8	5.2	5.1
Saskatchewan	6.2	5.9	4.2	7.2	7.3	7.0	6.6	5.9	5.0

Alberta	5.6	5.3	3.5	4.9	4.8	4.4	4.2	4.0	3.7
British Columbia	7.3	6.6	4.0	6.4	7.4	6.2	5.6	5.3	NA

AMI: Acute Myocardial Infarction
NA: Not available
*: Age and sex-adjusted only

2.6 Outcomes of patients with STEMI

2.6.1 In-hospital mortality of patients with STEMI in several international registries

There is a remarkable international variation in the short-term mortality of patients with STEMI (Table 6). The rates varied from 4% in rural Illinois (176) to 10% (North Carolina) (179). It is not possible to compare these rates directly due to the inability to adjust for age and co-morbidity. There was no notable secular trend with the highest mortality (10%) reported for a fairly recent large cohort of patients with STEMI in North Carolina (RACE) (179). Mortality rate was 8.0% in the United States during 2003-2005 (139), and 8.5% in the United Kingdoms during 2009-2010 (151).

Table 6. Short-term mortality of patients with STEMI in several countries (during 1999-2010) (120,127-128,134, 139, 146,173-175,176-181).

Names of studies (country)	Year	N of patients (Mortality* stratified by RT, %)
Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA), (Sweden) (120)	1999-2004	16 043 FL (8.8) 7 084 primary PCI (3.5)
Global Registry of Acute Coronary Events (GRACE), (Global) (128)	1999-2000	3 419** (7.0)
Dryja et al., (Poland) (134)	2003	240 FL (7.9) 422 primary PCI (5.5)
Vienna STEMI registry, (Austria) (127)	2003	281 FL (8.2) 631 primary PCI (8.1)
EURO-HEART Survey of Acute Coronary Syndromes, (Europe) (174)	2000	4 431** (7.0)
EURO-HEART Survey of Acute Coronary Syndromes, (Europe) (175)	2004	3 004** (7.2)
COsti benefici delle strategie di RIperfusione nell'infarto miocardico acuto con ST sopralivellato, (Italy) (173)	2002-2004	812 (23.9)*** 902 (19.8)***
Global Registry of Acute Coronary Events	2005	992** (4.6)

(GRACE), (Global) (128)		
National Registry of Myocardial Infarction (NRMI-3/4) (United States) (139)	2003-2006	118 218** (8.0)
Minneapolis, (United States) (177)	2003-2006	NA for FL 1 345 primary PCI (4.9)
Mayo Clinic, (United States) (178)	2004-2006	131 FL (3.1) 258 Primary PCI without inter-hospital transfer: (6.6) 105 Primary PCI with inter-hospital transfer: (5.7)
French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI), (France) (146)	2005	466 FL (4.3) 564 primary PCI (5.0)
Reperfusion in Acute Myocardial Infarction in Carolina (RACE), (United States) (179)	2007	6 565** (10.1)
StatHeart Program, (United States) (176)	2005-2007	188** (3.7)
Croatian Primary PCI Network, (Croatia) (180)	2008	1 190** (4.4)
Myocardial Ischemia National Audit Program (MINAP), (England and Wales) (181)	2009-2010	31 430** (8.5)

FL: Fibrinolytic Therapy
NA : Not Available
PCI: Percutaneous Coronary Intervention
RT: Reperfusion Therapy
*: 30-day mortality or in-hospital mortality if 30-day mortality was not available
**: Type of reperfusion therapy was not specified
***: Includes patients who did not receive reperfusion therapy

2.6.2 In-hospital mortality of patients with STEMI in several Canadian registries

Data on in-hospital mortality of patients with STEMI in Canada are reported in Table 7. The in-hospital mortality varies markedly with rates ranging from 1.5% to 10.9%. In-hospital mortality approximates 6% in two large cohorts (168,182).

Table 7. Short-term mortality of patients with STEMI in Canada.

Registry	Year	Regions	Patients who received FL N (mortality*, %)	Patients who underwent primary PCI N (mortality*, %)

AMI-QUEBEC (182)	2003	Quebec	476 (5.6)	604 (7.9)
Matteau et al. (183)	2004-5	Montreal	NA	129.(10.9)
De Villiers et al. (160)	2005-6	Calgary	NA	358 (3.1)
Lemay et al. (119)	2005-6	Ottawa	NA	344 (4.7)
Quebec Heart and Lung Institute (184)	2004-5	Quebec city	NA	197 (1.5)
Lambert et al. (168)	2006-7	Quebec	392 (6.1)	1 440 (5.6)
Danault et al. (185)	2008	Sherbrooke	NA	370 (3.2)
GRACE, GRACE2, CANRACE (186)	1999-2008	Canada	1 308 (3.7)	716 (2.7)

AMI-QUEBEC: Acute Myocardial Infarction in Quebec
FL: Fibrinolytic Therapy
CANRACE: Canadian Registry of Acute Coronary Events
GRACE: the Global Registry of Acute Coronary Events GRACE2: Expanded GRACE
NA: Not available
PCI: Percutaneous Coronary Intervention
*: 30-day mortality or in-hospital mortality if 30-day mortality was not available

2.7 Management of patients with NSTE-ACS

Since the culprit coronary artery in patient with NSTE-ACS is only partially occluded, damage to the heart muscle of these patients is generally less extensive and the risks of mortality and heart failure are lower than those of patients with STEMI (187). The impact of delays to treatment on outcome of patients with NSTE-ACS is not as crucial as in patients with STEMI (187). Management of patients with NSTE-ACS frequently involves medications to thin the blood in the coronary artery (anti-platelets, blood thinners), medications to decrease the workload of the heart (anti-anginals), and non-urgent PCI (187).

2.7.1 Importance of risk stratification of patients with ACS

Patients with ACS have a very wide range of mortality risks that range from less than 5% to more than 80% (187-189). High-risk patients with ACS may derive survival benefit with potent medications and prompt coronary intervention (187-189). On the other hand, inappropriate use of aggressive medical and invasive interventions in low-risk

patients with ACS may only expose these patients to unwarranted adverse effects without benefit (187-189).

Rapid EMS risk stratification of patients with ACS may convey substantial benefit (158). Since early PCI is the treatment of choice for high-risk ACS, prompt identification of these patients is critical (158,164). Routine transfer of all ACS patients to PCI-hospitals would require large investments in EMS resources without benefitting the majority of these patients (192). Therefore, early pre-hospital risk stratification would benefit considerably patients with ACS in terms of directing them to the most appropriate hospitals (158).

Despite their abundance, risk scores are rarely applied in the management of patients with ACS (190). Health care providers often find data extraction and computation of risk scores inconvenient (190). There are frequent misperceptions that physician assessment alone is adequate for risk stratification of ACS patients (190). However, physician risk assessment is inferior to formal risk scores in predicting the risk of adverse events in patients with ACS (191).

I identify and summarize the characteristics and limitations of 25 ACS risk scores in Table 8. Most risk scores can only be applied in-hospital, once laboratory results become available. Eight of these risk scores can be applied at the time of the first EMS contact with the patients. Nevertheless, a few limitations hinder the use of these scores in early risk stratification, such as requirement for an ECG in three scores, requirement of a calculator or hand-held computer in four scores, and applicability in only selected patients in two scores.

Of all published risk scores, none has all desired attributes for early risk stratification of patients with ACS. In the third manuscript of this doctoral dissertation, I develop and validate a simple and accurate risk score that may be used for early risk stratification of patients with ACS.

Table 8. Characteristics of available scores for risk stratification of patients with acute coronary syndromes

Risk scores (alphabetical order)	Target populations	Indicators required	Tools required for computation	Time of application	Predicted survival	Limitations
AMIS (41)	All types of ACS	Age, Killip class, BP, pre-hospital cardiac arrest, history of heart failure, and cerebro-vascular disease	Hand-held computer	Can be applied at time of the first contact with the patient	1-year	• Requires history taking • Requires training for Killlip class
APEX AMI (42)	Patients with STEMI who undergo primary PCI	Age, BP, HR, laboratory values and ECG	Nomogram	Can be applied only after laboratory values become available	90-day	• Required laboratory results • Requires ECG
CADILLAC (43)	Patients with STEMI who undergo primary PCI	Age, laboratory values, Killip, angiogram	Can be calculated by hand	Can be applied only after coronary angiogram results become available	1-year	• Requires coronary angiogram • Requires training for Killip
CCP (44)	All types of ACS	Age, cardiac arrest and heart failure, BP, HR, ECG findings and laboratory values	Hand-held computer	Can be applied only at discharge	30-day	• Mainly used as risk adjustment between hospitals • Validated in patients ≥65 years old only
EMMACE (45)	All types of ACS	Age, BP and HR	Calculator	Can be applied at time of the first contact with the patient	30-day	• Requires calculator
FRISC-II (46)	NSTEMI	Age, male, diabetes, ECG and laboratory values	Can be calculated by hand	Can be applied only after laboratory results	1-year	• Delay required for laboratory results

				become available		
GRACE (47-48)	All types of ACS	Age, BP, HR history of heart failure, ECG and laboratory results	Hand-held computer	Can be applied only after laboratory values become available	6-month	• Requires history taking • Requires calculator
GUSTO (49)	STEMI	Age, HR, BP, Killip history of hypertension, cerebro-vascular disease, rrhythmia and ECG	Can be calculated by hand	Can be applied only at hospital admission	30-day	• Requires history taking • Requires training for Killlip class • Requires ECG • Can be applied only at hospital admission
KAMIR (50)	NSTEMI	TIMI risk index, Killip, ECG and laboratory values	Calculator	Can only be obtained in ER after laboratory results become available	1-year	• Delay required for laboratory results
Lloyd-Jones et al. (51)	NSTEMI	Age, prior MI, diabetes mellitus, heart failure, ECG , medication use, and laboratory values	Can be calculated by hand	Can be applied only at discharge	10-year	• Can only be used at hospital discharge
Mayo Risk score (52)	All types of ACS	Age, female sex, BP, Killip, laboratory values and ECG	Can be calculated by hand	Can be applied only after laboratory results become available	30-day	• Delay required for laboratory results • Requires training for Killip class
PAMI (53)	STEMI	Age, HR Killip and ECG	Can be calculated by hand	Time of first contact	6-month	• Can only be used in patients

				with the patient either pre-hospital or in the ER		with STEMI • Requires training for Killip class • Requires ECG
PEPA (54)	NSTE-ACS	Age, diabetes, Killip, ECG and laboratory values	Can be calculated by hand	Can be applied only after laboratory results become available	90-day	• Delay required laboratory results • Requires training for Killip class
Piombo et al. (55)	Unstable angina	Age, prior coronary artery bypass surgery, ECG and laboratory results	Can be calculated by hand	Can be applied only after laboratory results become available	In-hospital	• Requires ECG and laboratory results
PREDICT (56)	All types of ACS	Age, BP, HR, history of diabetes, stroke, myocardial infarction, CABG hypertension, ECG and laboratory values	Normogram	Can be applied only after laboratory results become available	6-year	• Requires ECG and laboratory results
PRISM-PLUS (57)	NSTE-ACS	Age, prior CABG, prior medication use and ECG	Can be calculated by hand	Can be applied at the time of first contact with patient	7-day	• Requires ECG and laboratory results
PURSUIT (58)	NSTEMI	Age, sex, BP, HR, presence of heart failure and ECG	Can be calculated by hand	Can be applied at the time of first contact with patient	30-day	• Requires training to recognize heart failure • Requires ECG
RUSH (59)	Patients with unstable angina	Age, history of myocardial infarction or diabetes,	Calculator	Can be applied only at hospital	In-hospital	• Requires history taking • Can be

		medications use		admission		applied only at hospital admission
Shock index (60)	Patients with STEMI who underwent PCI	BP and HR	Can be calculated by hand	Can be applied at the time of first contact with the patient	In-hospital	• No external validation available
TIMI-II (61)	STEMI	Age, sex, BP, diabetes mellitus, heart failure, and ECG	Can be calculated by hand	Can be applied at the time of first contact with the patient	6-week	• Requires ECG • Requires training to recognize heart failure
TIMI score (62)	Different risk models for STEMI and NSTEMI	History, ECG and laboratory results (for STEMI: weight is also required)	Can be calculated by hand	Can be applied only after laboratory results available	1-year	• Difficult to memorize • Requires ECG and laboratory results • Requires weight for patients with STEMI (not available generally in the pre-hospital setting)
TIMI Index (63)	All types of ACS	Age, BP and HR	Calculator	Can be applied at the time of first contact with the patient	10-year	• Requires calculator
ZWOLLE (64)	STEMI	Age, Killip, ECG and coronary angiogram	Can be calculated by hand	Can be applied only after coronary angiogram obtained	30-day	• Requires training for Killip class • Can only be used in patients with

						STEMI and only after coronary angiogram completed

AMI: Acute Myocardial Infarction
AMIS: Acute Myocardial infarction in Switzerland
APEX AMI: Assessment of Pexelizumab in Acute Myocardial Infarction Trial
CABG: Coronary Artery Bypass Surgery
CADILLAC: Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CCP: Cooperative Cardiovascular Project
EMMACE: Evaluation of Methods and Management of Acute Coronary Events
FRISC-II: Fast Revascularisation in Instability in Coronary Disease
GRACE: Global Registry of Acute Coronary Events
GUSTO: Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries
KAMIR: Korea Acute Myocardial Infarction Registry
NSTEMI: Myocardial Infarction without ST-Segment Elevation
PAMI: Primary Angioplasty in Myocardial Infarction
PEPA : Proyecto de Estudio del Pronóstico de la Angina
PURSUIT : Platelet glycoprotein Iib/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy
PREDICT: Predicting Risk of Death in Cardiac Disease Tool
PRISM-PLUS: Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms trial
RUSH: Rush-Presbyterian-St. Luke's Medical Center Study
STEMI: Myocardial Infarction with ST-Segment Elevation
TIMI: Thrombolysis in Myocardial Infarction

2. 8. Conclusion of the literature review

In summary, CVDs remain leading causes of mortality world-wide (9-10). AMIs are responsible for most of the CVDs burdens (9-10). In view of the aging population and increasing prevalence of diabetes mellitus and obesity (9-10), the global societal impact of AMI will become enormous. One type of AMI, STEMI, is highly lethal and should be diagnosed and treated promptly (1). There are marked variations internationally and nationally in the infrastructure for the management of patients with STEMI. The current EMS management of patients with STEMI in Quebec has many deficiencies (161-164).

There is a remarkable 25% decline in AMI case fatality in Canada during the last two decades. The Canadian in-hospital AMI mortality of 9% (172) is similar to the

mortality rates of AMI in many countries (139,174-181). Short-term STEMI-related mortality of 6% in Quebec (168, 182, 185) appears to be similar to the STEMI-related mortality in other jurisdictions.

Remarkable progress has been made in reducing mortality of patients with ACS in Canada and in other developed countries. Nevertheless, there remain major opportunities to improve ACS care, including more widespread pre-hospital implementation of ECG, PHL, and early EMS risk stratification (164). Since ACS constitute the bulk of CVDs (4), interventions to reduce mortality and morbidity of patients with ACS would substantially reduce the CVDs burdens.

Chapter 3.

Rationale and objectives of the thesis

The literature review identified three key gaps in the current scientific knowledge:

1. There remains uncertainty in terms of whether the superiority in mortality reduction with primary percutaneous coronary intervention (PCI) compared to fibrinolytic therapy (FL) observed in selected patients with myocardial infarction and ST-elevation (STEMI) in randomized controlled trials (RCTs), can be replicated in "real-life" patients within "real-life" contexts. "Real-life" patients with STEMI are generally older and with more co-morbidity than patients enrolled in RCTs (38,193). Primary PCI is complex, time and labor-intensive, and available at only a minority of hospitals in the "real-life" context (168,169,199). Additionally, adverse effects of reperfusion therapy (RT) may not be adequately characterized by RCTs due to the highly selected patient population (38,193-197). Moreover, since the follow-up of most RCTs are often limited in duration (i.e., ≤1 year) (81), it remains unclear whether the reduction in mortality with primary PCI compared to FL persists with longer follow-up (81). Finally, the survival benefit of primary PCI might have been over-estimated due to many methodological flaws of several previous meta-analyses and RCTs (198). Due to all the above reasons, additional information from observational studies may improve the inference based on only RCTs (199-201).

- Time delay to RT is the main modulator of survival benefits of both primary PCI and FL (2). Both RT strategies become less effective after prolonged delays (2). Furthermore, patients with STEMI are at the highest risk of dying during the earliest hours (76). Therefore, it is crucial that delays to RT be minimized as much as possible. Considering the inclement climate and vast geography in Canada, timely provision of RT can be problematic for a large number of patients with STEMI (67,169).

Since prehospital fibrinolysis (PHL) can be initiated at time of the first contact between the paramedics and patients with STEMI, it can be a remarkable time-saving RT strategy. PHL has been implemented successfully in several European jurisdictions (6,73). Due to lack of physicians and nurses in North America (6), it remains unclear whether PHL can be adapted to the Canadian context (203-204). Detailed appraisal of the infrastructure, processes and outcomes of effective PHL programs may assist stakeholders to initiate PHL programs in Canada.

Optimal management of patients with acute coronary syndromes (ACS) requires early and accurate risk stratification of these patients (189-190). Physician assessment is subjective, potentially biased and less precise than formal ACS risk scores (191). However, due to their complexity, currently available risk scores are infrequently used (190). Physicians tend to rely on their clinical judgement only and often under-estimate the mortality risk of patients with ACS (191). Consequently, high-risk patients with ACS may not be able to receive promptly life-saving interventions. A straightforward risk score which can be easily memorized, calculated by hand and requires only simple clinical variables, would be of great use for early risk stratification of patients with ACS.

In this dissertation, I will address these three knowledge gaps by:

- Performing Bayesian meta-analyses of RCTs and observational studies to compare short and long-term mortality reductions of primary PCI and Fl. Bayesian meta-analysis accounts for heterogeneity between studies and allows smaller studies to borrow strength from the overall estimate (115-116). For this reason, large studies with biases would have less impact on the summary estimate with Bayesian meta-analysis, than with conventional random- and fixed-effect models. Additionally, meta-analysis of observational studies

will provide in-depth evaluation of the safety and effectiveness of primary PCI and FL in "real-life" patients within "real-life" context. (Manuscript 1) (66).

- Surveying of several international and national PHL programs to provide an understanding of the pre-hospital infrastructure required for PHL implementation in Canada. (Manuscript 2) (67).
- Developing a simple risk score that can accurately predict short and long-term mortality in patients with ACS (Manuscript 3) (205). Availability of a simple risk score will allow for early risk stratification and tailored management of patients with ACS.

Chapter 4.

Manuscript 1

4.1 Preamble

Although primary percutaneous coronary intervention (PCI) is more effective than fibrinolytic therapy (FL) in restoring flow in the occluded coronary artery of patients with acute myocardial infarction and ST-elevation (STEMI) (2), accessibility to primary PCI is limited with only a fraction of hospitals able to deliver this reperfusion therapy (RT) in a timely manner (166,168-169). Prolonged delays to primary PCI may attenuate the survival benefit (2,76,78).

The safety and efficacy of primary PCI and FL have been evaluated in 25 randomized controlled trials (RCTs) (12-37). Considering the relatively small sample size and limited power of most RCTs, survival benefits of the two reperfusion strategies can only be reliably evaluated in meta-analyses (198). Of the 21 published meta-analyses of RCTs that compared primary PCI and FL (37,92-112), only four (94, 103,100,110) used random-effects models. All other meta-analyses used fixed-effects models since heterogeneity testing suggested lack of variation between trials (37,92-93,95-99,101-109). However, heterogeneity testing are poorly sensitive and may fail to detect significant differences between RCTs (112,114-115). Fixed-effects models may over-estimate the difference in efficacy between treatment arms, if they do not take the heterogeneity between RCTs into account (112,114-115).

In considering inter-RCT variation, random-effects models commonly provide more conservative estimates of the difference in efficacy between treatment arms (113-115). In addition to conventional random-effects models, Bayesian hierarchical random-effects models allow individual studies to borrow strength from the global estimate (115-116).

Consequently, small well-designed studies can contribute more to the global estimate (115-116) and studies with large sample sizes but with sub-optimal designs have less impact on the global estimate (115-116).

Furthermore, there is no prior systematic review of observational studies. Although RCTs are generally considered the gold standard for evaluation of efficacy, observational studies provide invaluable information about the effectiveness and safety of RT administration in "real-life" patients in "real-life" context (39,195-197). In the first manuscript of this thesis, I systematically reviewed all published observational studies that compared primary PCI to FL (66). This systematic review of effectiveness and safety of RT in "real-life" patients in "real-life" context contributes unique insights into the external validity of previous RCTs.

4.2 Methods

4.2.1 Literature search

I searched the following databases (with no language restrictions) using the following keywords: "angioplasty", "fibrinolysis", "thrombolysis", "FL", "acute myocardial infarction", "percutaneous coronary intervention", "reperfusion therapy", "coronary stent" as keywords to identify RCTs and observational studies that compare primary PCI and FL in STEMI: BIOSIS, Cinahl, Embase, Pubmed, Web of Science, Cochrane Library, health technology assessment agencies and Current Contents. In addition, I hand-searched the reference lists of published articles to ensure retrieval of all pertinent studies on STEMI.

4.2.2 Inclusion of studies

I included only studies that used full-dose commercially approved FL such as streptokinase, urokinase, and fibrin-specific agents such as tissue plasminogen activators,

tenecteplase, and reteplase. In addition, the selected studies had to report mortality for both treatment arms (primary PCI and FL) separately. Finally, all observational studies retained had to meet the quality requirements suggested by Concato et al. (39) such as inclusion of concurrent rather than historical controls, and these studies should also have clearly defined inclusion criteria.

4.2.2 Exclusion of studies

I excluded studies in which the investigators used experimental FL agents (i.e., not commercially approved) or intra-coronary administration of FL (non-conventional method of administration). In addition, I excluded studies presented or published as abstracts or as conference proceedings.

4.2.3 Definition of endpoints

The endpoints of interest were short and long-term all-cause mortality, reinfarction and stroke. All-cause mortality was selected as the primary endpoint since it is the most objective and reliable endpoint (82). I elected not to use cardiovascular mortality since this endpoint depends on subjective classification of mortality causes and may be more prone to ascertainment bias. All endpoints were analyzed as distinct events rather than as a composite endpoint comprising multiple events. The approach of combining endpoints is suboptimal due to equal weights attributed to endpoints with unequal clinical relevance (i.e. death would have an equal weight to more benign endpoint such as re-hospitalization) (82).

4.2.4 Data abstraction

Two independent observers (i.e., I and SP (i.e., the second author of this manuscript) completed data abstraction and disagreements were resolved by consensus.

4.2.5 Evaluation of study quality

I assessed the qualities of the RCTs and observational studies retained in conformity with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (206). I completed detailed qualitative assessment of the internal and external validity and potential biases for each study. I elected not to complete a quantitative evaluation of study quality by scales since inappropriate scoring of study quality may result in erroneous adjustment of the overall treatment effect (207).

4.2.6 Statistical methods

Methodology of meta-analysis

Meta-analysis can be undertaken using either a frequentist (114) or Bayesian approach (115-116). In a frequentist meta-analysis, the summary statistic is calculated as a weighted average of the treatment results pooled across studies (114). The weights reflect the amount of information from each study (114).

Frequentist meta-analysis can be undertaken either with a fixed-effects model or with a random-effects model (113). In a fixed-effects model, the weight of each study is determined by the precision of the study (115). It is assumed that the true treatment effect is the same across studies and that variation among studies is entirely due to chance. In a random-effects model, the effect sizes are assumed to differ between studies. The effects sizes effects are normally distributed with mean and variance (τ^2) in random-effects models (115). The weight of each study is determined as W_i=1/(SE of the treatment effect)^2+ τ^2 (115). In general, the random-effects models provide more conservative estimates of the treatment effects with wider confidence intervals than the fixed-effects models (113-115). The W_i (1/SE of the treatment effect)^2+ τ^2) varies less across studies in the random-effects models than the W_i (1/(SE of the treatment effect)^2 of the fixed-effects

models. Consequently, smaller studies are given more weight in a random-effects model than in a fixed-effects model (113-115).

The application of a fixed-effects model is only valid in the absence of excess variation in the results across studies (113-115). Statistical tests of homogeneity (also called tests of heterogeneity) are generally used to evaluate homogeneity of results across studies (113). However, these tests often have poor sensitivity for significant inter-study variation, especially in meta-analyses of a small number of studies (112). Therefore, the potential false-negativity of the test of homogeneity (or heterogeneity) and the incorrect application of a fixed-effects model should always be considered (112). By contrast, if there is statistical evidence of heterogeneity, the inter-study variation is beyond random variation and cannot be ignored (112-115). In this circumstance, random-effects models should be used to pool findings from previous studies (113-115).

Bayesian meta-analysis is based on the Bayesian theorem that allows for integration of prior beliefs (115). Bayesian statisticians specify a prior probability distribution, based on a prior belief, such as expert opinion of the treatment effect (115-116). The summary estimate also called the posterior probability distribution results from incorporation of the prior probability distribution into the pooled data (115-116). Thus, Bayesian methodology allows for incorporation of different sources of evidences such as expert opinions in addition to the studies included in the models (115-116). Non-informative priors can be used to analyze data without consideration of prior beliefs, (i.e. the pooled estimates derived mainly from the findings of previous studies, and without consideration of expert opinion) (115-116).

Bayesian modeling can be either random or fixed-effects (115-116). Similar to the frequentist approach, Bayesian hierarchical random-effects meta-analysis takes the intra

and inter-studies variation into account (115-116). In addition, Bayesian meta-analysis allows for each study to borrow strength from the overall estimate (115-116). In other words, a study with markedly different results from the other studies would have less impact on the overall estimate, in a Bayesian model compared to other types of meta-analyses (116).

All statistical meta-analyses methods have their own advantages and disadvantages (112-115). Since it is unlikely that the effect of primary PCI and FL is similar across studies, a fixed-effects model is not appropriate. Bayesian random-effects modeling is a more suitable approach since it takes the inter-trial variation into account (115-116).

I completed separate meta-analyses for each endpoint, for RCTs and observational studies separately. In these models, the probability of an event within each group in each trial was assumed to follow a binomial distribution (116). The models allowed for the probability of an event to vary both between treatment arms within each study, and between studies (116). The logarithms of the odds ratios (ORs) were assumed to have a normal distribution (116). The means of the normal distribution of the logarithm of the odds ratios across studies represented the average effect across studies, and the variances represented the variability between studies (116).

I selected non-informative prior distributions for all parameters of interest, so that the results would primarily reflected the findings from included studies, without considering prior knowledge or subjective beliefs (116). Sensitivity analyses varying the prior distributions did not change posterior inferences substantially. Consequently, the estimates of odds ratios and 95% credible intervals were not substantially affected by the choice of a prior distribution.

I computed inferences by using a Gibbs sampler algorithm (WinBUGS software version 1.4.2, MRC Biostatistics Unit, Cambridge, UK). The final summary statistics were based on 120,000 iterations. The forest plots were completed with R 2.4.1 software (www.**r**-p**r**oject.o**r**g/). The numbers needed to treat was 1/absolute risk difference for each outcome of interest.

Evaluation of publication bias

Publication bias is the "*tendency of authors and editors to publish studies with positive results" (*89*).* Publication bias can also occur from "size bias" when studies with larger sample sizes are preferentially published relative to smaller studies (89). Since the quality of the study design does not necessarily relate to the sample size of the study, a meta-analysis may be flawed by lack of inclusion of small un-biased studies and/or inclusion of large and biased studies (112-115). Another type of publication bias is "suppression bias" which occurs when studies are prevented from being published if the results may be harmful to the sponsor's financial interest (208). "Language bias" may results from the lack of inclusion of studies published in languages other than English (208).

I tested for publication bias by constructing funnel plots for RCTs and observational studies separately. Funnel plots are plots of the treatment effects on the horizontal axis against a measure of the studies sizes on the vertical axis (114,208). The results of small studies are generally less precise and are more scattered around the overall estimate (114,208). The results of larger studies are more precise and concentrate around the overall estimate (114,208). This gives the appearance of an inverted funnel (114,208). In the event of non-publication of small negative studies, the funnel plot will be asymmetrical

because of lack of small studies on one side of the funnel plot (114,208). Funnel plots are performed with MIX *(*www.**mix**-for-meta-analysis.info). (Appendix 1).

Contributions of Co-Authors

Dr Huynh and Perron completed the literature search, read the abstracts, selected the studies to be included in the meta-analyses, read all selected manuscripts in whole, completed data abstraction and cross-validated the abstracted data.

Dr Huynh completed all data analyses including random-effects Bayesian modeling, forest plots and funnel plots under the supervision of Dr Lawrence Joseph.

Dr Lawrence Joseph supervised the statistical analyses, reviewed and provided statistical inputs into the draft and final manuscript.

Drs O'Loughlin, Labrecque, Tu and Theroux reviewed and provided inputs into the study design, results and manuscript.

Comparison of Primary Percutaneous Coronary Intervention and Fibrinolytic Therapy in ST-Segment Elevation Myocardial Infarction – Bayesian Hierarchical Meta-Analyses of Randomized Controlled Trials and Observational Studies.

Running title: Meta-analyses of primary PCI and fibrinolysis

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Structured abstract

Background: Published meta-analyses comparing primary percutaneous coronary intervention with fibrinolytic therapy in patients with ST-segment elevation myocardial infarction include only randomized controlled trials. We aim to obviate the limited applicability of randomized controlled studies to real-world settings by undertaking meta-analyses of both randomized controlled trials (RCT) and observational studies.

Methods and Results: We included all RCTs and observational studies, without language restriction, published up to 1 May 2008. We completed separate Bayesian hierarchical random-effect meta-analyses for 23 randomized controlled studies (8,140 patients) and 32 observational studies (185,900 patients).

Primary percutaneous coronary intervention (PCI) was associated with reductions in short-term (≤6-week) mortality of 34% (Odds Ratio (OR): 0.66; 95% Credible Interval (CrI): 0.51-0.82) in randomized trials, and 23% lower mortality (OR: 0.77, 95% CrI: 0.62-0.95) in observational studies. Primary PCI was associated with reductions in stroke of 63% in RCTs and 61% in observational studies. At long-term follow-up (≥1 year), primary PCI was associated with a 24% reduction in mortality (OR: 0.76, 95% CrI: 0.58-0.95) and a 51% reduction in reinfarction (OR: 0.49, 95% CrI: 0.32-0.66) in RCTs. However there was no conclusive benefit of primary PCI at long-term in the observational studies

Conclusions: Compared to fibrinolytic therapy, primary percutaneous coronary intervention was associated with short-term reductions in mortality, reinfarction and stroke in ST-segment elevation myocardial infarction. Primary PCI was associated with long-term reductions in mortality and reinfarction in RCTs, but there was no conclusive evidence for a long-term benefit in mortality and reinfarction in observational studies.

Condensed abstract

We conducted separate hierarchical Bayesian random-effects meta-analyses of all randomized controlled trials and observational studies that compared primary percutaneous coronary intervention with fibrinolytic therapy (published up to 1 May 2008). Primary percutaneous coronary intervention was associated with reductions in short-term mortality, reinfarction and stroke in both types of studies. The benefits in mortality and reinfarction reductions associated with primary PCI remained at long-term follow-up in the randomized controlled studies. There was no conclusive long-term benefit associated with primary percutaneous coronary intervention in the observational studies.

Abreviations

AMI: Acute Myocardial Infarction

CrI: Credible Intervals

OR: Odds Ratio

NNT: Numbers Needed to Treat

PCI: Percutaneous Coronary Intervention

Q1:Q3: First quartile, third quartile

RCT: Randomized Controlled Trial

STEMI: ST Segment Elevation Myocardial Infarction

Introduction

Several randomized controlled trials (RCTs) (1-23) show that primary PCI is associated with reductions in mortality, reinfarction and stroke compared to fibrinolytic therapy. However many aspects of reperfusion therapy might not be optimally assessed in RCTs. First, the benefit of primary PCI may not be replicable under sub-optimal conditions such as at low-volume and less expert PCI centers (24), outside regular working hours, or after lengthy inter-hospital transfer. Second, use of rescue or elective PCI was limited (less than 20%) in several RCTs (1, 8, 11-12,14, 16-17,20-22), while rescue or elective PCI is generally performed as indicated in the real-world. Furthermore, patients with ST-segment elevation myocardial infarction (STEMI) enrolled in RCTs are generally younger with fewer co-morbid conditions than patients in the "real-world" (25). Therefore extrapolation of the safety and effectiveness of primary PCI and fibrinolytic therapy observed in RCTs to the "real-world" STEMI population might not be entirely appropriate. Previous meta-analyses included only RCTs. We aim to obviate the limitations of these analyses by examining results from observational studies, in addition to those of RCTs. We also include recently published data from several RCTs that were not considered in previous meta-analyses.

Methods

Search strategy

We retrieved RCTs and observational studies that compared primary PCI and fibrinolytic therapy in STEMI from the following databases: BIOSIS, Cinahl, Embase, Pubmed, Web of Science, Cochrane Library, health technology assessment agencies and Current Contents (up to 1 May 2008) (no language restriction), using the following

keywords: “angioplasty”, “fibrinolysis”, “thrombolysis”, “fibrinolytic therapy”, “acute myocardial infarction”, “percutaneous coronary intervention”, “reperfusion therapy”, “coronary stent”, “ treatment” and “management”. In addition, we hand-searched the references of published articles to ensure identification of all published STEMI trials.

Inclusion criteria

Only studies that used full-dose commercially approved fibrinolytic therapy such as streptokinase, urokinase, and fibrin-specific agents such as tissue plasminogen activators, tenecteplase, and reteplase were retained for analysis. We retained only studies that reported results for both treatment arms (primary PCI and fibrinolytic therapy). Finally, the observational studies retained had to fulfill the quality requirements suggested by Concato et al. (26) including: inclusion of concurrent rather than historical controls, clearly defined inclusion criteria and time of entry into the study.

Exclusion criteria

We excluded studies that used facilitated PCI, experimental fibrinolytic agents (other than the agents listed above), or intra-coronary administration of fibrinolytic therapy as well as studies that enrolled mainly patients with contra-indications to either fibrinolytic therapy or primary PCI. For studies that compared primary PCI, facilitated PCI and fibrinolytic therapy (2,16,22), we excluded patients who underwent facilitated PCI from the analysis. We also excluded studies presented or published only as abstracts or conference proceedings, because detailed appraisal of the methodology and potential biases was not possible.

Endpoints

All endpoints were analyzed as distinct events rather than as a composite endpoint comprising multiple events. The latter approach can be suboptimal because of equal

contributions to the composite endpoint by endpoints with unequal clinical relevance (27). Intra-cranial bleeding was compiled as stroke and therefore excluded from major bleeding. Major bleeding included all hemorrhagic complications that were severe or life-threatening or required transfusion. Short-term endpoints included all events up to 6 weeks after the index STEMI. Long-term endpoints included all events that occurred at least one year after the STEMI.

Study quality

We critically appraised the quality of the RCTs and observational studies in conformity with the CONSORT and the MOOSE guidelines (28-29). We elected not to use scales to evaluate the quality of each study since this approach is controversial with potentially inappropriate adjustment of the treatment effects and marked variation in treatment effects depending on the scale used (30).

Data extraction

Two reviewers (TH and SP) independently selected studies for inclusion, extracted data, and evaluated the quality of each study. Disagreements were resolved by consensus between the two reviewers.

Statement of Responsibility

The first author (TH) had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

- **Statistical methods**

We completed separate meta-analyses for each endpoint, for RCTs and observational studies separately. Since it was unlikely that the effect of primary PCI and

fibrinolytic therapy would be similar across studies due to differences in study design and patient characteristics, a fixed-effect model was not appropriate. Therefore we used a Bayesian hierarchical random-effects model to take inter-trial variation in treatment effects into account (31).

In our models, the total number of events within each group in each trial was modeled as a binomial random variable. The models allowed for the probability of an event to vary both between treatment arms within each study, and between studies. The logarithms of the odds ratios were assumed to have a normal distribution. The mean of the normal distribution of the logarithm of the odds ratios across studies represented the average effect across studies, and the variance represented the variability between studies.

Bayesian analysis allows integrating new information into existing knowledge. Substantive prior knowledge can be included into Bayesian analysis through the choice of a prior distribution. Since we wanted our results (i.e., the posterior distributions) to primarily reflect data from previous studies, we selected non-informative prior distributions for all parameters of interest. These included normal densities (mean: 0 and tau=0.00001 (variance of 10^5) for the logarithm of the odds ratios, and sigma (sigma= uniform on the interval (0,2)). Sensitivity analyses varying the prior distributions for sigma and a gamma prior distribution (0.001,0.001) did not change posterior inferences substantially. Therefore, our estimates of odds ratios and 95% credible intervals were not greatly affected by our choice of a prior.

Inferences were calculated using a Gibbs sampler algorithm as implemented through WinBUGS software (version 1.4.2, MRC Biostatistics Unit, Cambridge, UK). To ensure convergence of the Gibbs sampler algorithm, three Markov Monte-Carlo

chains were run and convergence was assessed after 60,000 iterations. The final summary statistics were based on 120,000 iterations, 100,000 of them for burn-in. The forest plots were completed with R 2.4.1 software (www.r-project.org/). We examined for potential publication bias with funnel plots, fail-safe N and trim and fill (www.meta-analysis.com). Sensitivity analyses were performed with non-Bayesian statistical methods, random-effect restricted maximum likelihood method (SAS 8.0) and random effects model (DerSimonian and Laird) (NCSS-2007). The results were essentially similar to those obtained by Bayesian hierarchical meta-analyses.

Results

Figure 1 describes the selection of studies into the analysis. Twenty-three RCTs (1-23) and 32 observational studies (24, 31-62) were retained. The mean age of patients enrolled ranged from 57 to 80 years in the RCTs and from 57 to 91 years in the observational studies. Two RCTs (2,4) and 7 observational studies reported pre-hospital administration of fibrinolytic therapy (23,35,39,49,61-62). Fibrin-specific agents were used primarily in 16 RCTs (1-4,6-12,14-15,19-20, 22) and 11 observational studies (24,33,35,37,41,43-44,48,53,57,61). (Appendix Tables 1 and 2)

Primary PCI was associated with an approximate 34% short-term reduction in mortality (OR: 0.66; 95% CrI: 0.51-0.82) in RCTs (Figure 2), and an approximate 23% lower mortality in observational studies (OR: 0.77, 95% CrI: 0.62-0.95) (Figure 3). There was no conclusive difference in mortality in the meta-analysis of observational studies that used pre-hospital fibrinolytic therapy (23,35,39,49,61-62). Estimate of the difference in mortality between primary PCI and pre-hospital fibrinolytic therapy could not be done with certainty since there were only two RCTs that used pre-hospital fibrinolysis (2,4).

In RCTs, primary PCI was associated with a 24% reduction in long-term mortality (OR: 0.76, 95% CrI: 0.58-0.95) (Figure 4). However, in observational studies, there was no conclusive difference between the two reperfusion strategies in long-term mortality (OR: 0.88, 95% CrI: 0.68-1.18) (Figure 5). Reductions in short-term reinfarction of 65% and 53% were observed in RCTs and observational studies, respectively (Table 1). An approximate 51% reduction associated with primary PCI in long-term reinfarction was noted in RCTs, while there was no conclusive difference in reinfarction between treatments in the observational studies (Table 1). Primary PCI was associated with a 60% reduction in stroke in both RCTs and observational studies (Table 1). Although inconclusive due to the limited number of studies available, the risk estimates were consistent with a possible increase in major bleeding associated with primary PCI (Table 1).

Absolute risk reductions in short-term mortality with primary PCI were approximately 2.2% (95% CrI: 1.3%-3.2%) in RCTs, and 1.1% (95% CrI: 0.4%-1.5%) in observational studies (Table 2). Absolute risk reductions in short-term reinfarction were approximately 4.5% in RCTs, and 2.9% in observational studies. Absolute reductions in stroke were approximately 1.2% in RCTs, and 0.6% in observational studies. At long-term follow-up, primary PCI was associated with absolute reductions in long-term mortality of 3.5% (95% CrI: 0.7-6.4) and in reinfarction of 3.4% (95% CrI: 1.6-5.9) in RCTs, without conclusive evidence for reductions in long-term mortality and reinfarction in observational studies.

The numbers needed to treat (NNT) to prevent one short-term death with primary PCI was 45 in RCTs and 91 in observational studies (Table 2). The NNT was 29 in RCTs to prevent one long-term death. More specifically, for 100 patients treated with primary

PCI, in conditions similar to those in the RCTs, there would be two deaths and five reinfarctions prevented at short-term; three deaths and five reinfarctions prevented in the long-term. For 100 patients treated with primary PCI, in conditions similar to those in observational studies, one death and three reinfarctions would be prevented in the short-term, with no conclusive long-term benefit. For stroke reduction, approximately one event would be prevented in 100 patients treated with primary PCI in conditions similar to those in the RCTs, while only one stroke would be prevented in approximately 200 patients treated with primary PCI in conditions similar to those in the observational studies.

Discussion

Our meta-analyses improve on previous systematic reviews by including short-term results from three recent RCTs (2, 19-21) and inclusion of observational studies (28,32-62). Our study incorporates events at 1-year and includes long-term results from five RCTs that were not considered in earlier reviews (data at 1-year from Dobrycski and PRAGUE-1 (21,63), at 2-year from the PAMI-1 (64) at 3-year from DANAMI-2 (65), at 5-year from PRAGUE-2 (66) and at 8-year from the Zwolle Study (67). Given the marked heterogeneity in study designs and patient populations across studies, our random-effects hierarchical Bayesian meta-analyses are more appropriate models (37) than the fixed-effects models.

Several biases may affect the internal validity of RCTs, including lack of central randomization and a blinded adjudication committee, both of which may affect the integrity of randomization and objective ascertainment of endpoints. Only 10 RCTs specified use of central randomization (1, 3-5,10,16-17,20,22,23). Outcome adjudication by a blinded committee was mentioned in only 10 RCTs (1-2,4-6,9-12,15).

Observational studies are susceptible to many biases including among others, selection and confounding biases. Observational studies that exclude patients who did not undergo a planned primary PCI may be subject to selection bias. Only three observational studies included all patients assigned to primary PCI regardless of whether or not they underwent successful PCI (24,38-39).

Confounding bias may occur in observational studies when patient characteristics affect the treatment received and the outcomes. Patients who received fibrinolytic therapy were older than patients who received primary PCI in three observational studies (34-35,40). There were more patients with anterior STEMI, heart failure or cardiogenic shock in the primary PCI group in six studies (34,39-41,45,48), and in patients who received fibrinolytic therapy in two studies (33,35). Primary PCI patients received more optimal medical therapy and coronary intervention, and in addition were more likely to be treated at high-volume hospitals than patients who received fibrinolytic therapy (35,41,44,48).

The internal validity of both RCTs and observational studies may be affected by differential loss to follow-up in the treatment groups. With the exception of one study (64) that reported high attrition (16%), long-term follow-up was almost complete in most RCTs. Five observational studies reported at least 95% long-term follow-up (33-34,39,45,62). Our risk estimates remained virtually unchanged when restricted to studies with optimal follow-up.

The applicability of results from RCTs to "real-world" setting is generally limited. Several RCTs excluded elderly patients (7,13-14,21,22), patients with renal disease (3-4,10,12), those in cardiogenic shock (1,4,7,9,14,19,22), patients with Killip class 2

(8,18,20,23) and patients with left bundle branch block (1,6,8,18,21) so that their results may not be applicable to these high-risk patient groups.

The long-term attenuation of the early reductions in mortality and reinfarction associated with primary PCI may be due to optimal long-term medical therapy that may have delayed the long-term progression of coronary artery disease equally in both treatment arms. The reduced magnitudes of risk reductions associated with primary PCI in observational studies compared to those in RCTs might reflect "real-world" practice. Greater use of in-hospital PCI (≥30%) following fibrinolytic therapy in observational studies (24,35,41,43-44,55,62) may partially explain the smaller reductions in short-term mortality and reinfarction associated with primary PCI. In the "real-world", primary PCI may also be less successful when performed in less than optimal conditions. In observational studies, the lack of conclusive long-term benefits with primary PCI may be explained by optimal medical therapy and/or the judicious use of coronary interventions in patients who received fibrinolytic therapy.

Limitations

These meta-analyses have several limitations that warrant mention. First, the comparison of primary PCI with pre-hospital fibrinolysis could not be ascertained with certainty due to the small number of studies that used this reperfusion strategy. The efficacy and safety of pre-hospital fibrinolysis compared to primary PCI may be better evaluated in future large studies. Second, the greater use of thienopyridines in primary PCI than in the fibrinolytic therapy arm might have partially confounded the results. The mortality difference between primary PCI and fibrinolytic therapy may be attenuated with more systematic administration of thienopyridines following fibrinolytic therapy. On the other hand, recent technological advances in primary PCI may further increase the

mortality and reinfarction benefits associated with primary PCI. Third, the validity of our meta-analysis of long-term mortality in observational studies was potentially limited by the lack of long-term data from the large observational studies NRMI-3/4 (56). Nonetheless, it would be unlikely that long-term data from NRMI-3/4 would modify our results since there was no short-term mortality difference between the two treatment arms in this study. Fourth, our estimate of long-term mortality may have been influenced by the large observational RIKS-HIA study (35). However, sensitivity analyses excluding the study RIKS-HIA showed essentially similar results with no conclusive difference in long-term mortality between the two treatment arms. Finally, reports with positive findings are more likely to be reported, published and cited (68). However, the lack of asymmetry in the funnel plots suggests that we did not miss major negative studies.

Conclusions

Compared to fibrinolytic therapy in STEMI, primary PCI was associated with short-term reductions in mortality, reinfarction and stroke in both RCTs and observational studies and with long-term reductions in reinfarction and mortality in RCTs. There was no conclusive difference in long-term mortality and reinfarction between primary PCI and fibrinolytic therapy in the observational studies reviewed. The potential benefit of pre-hospital fibrinolysis compared to primary PCI cannot be reliably ascertained from this review.

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Conflict of Interest Disclosures

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Figure 1a. QUOROM flow diagram of randomized controlled studies

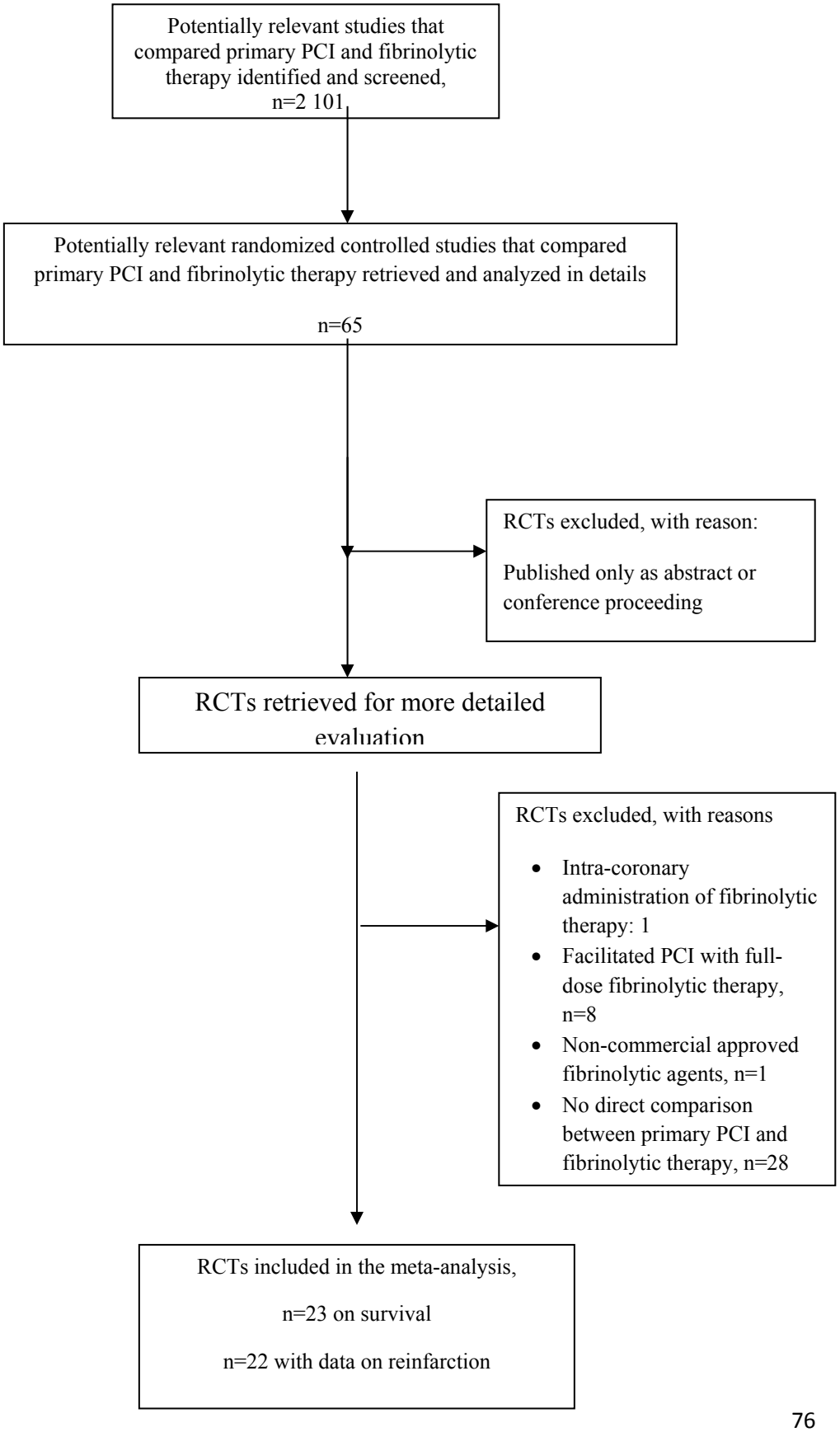
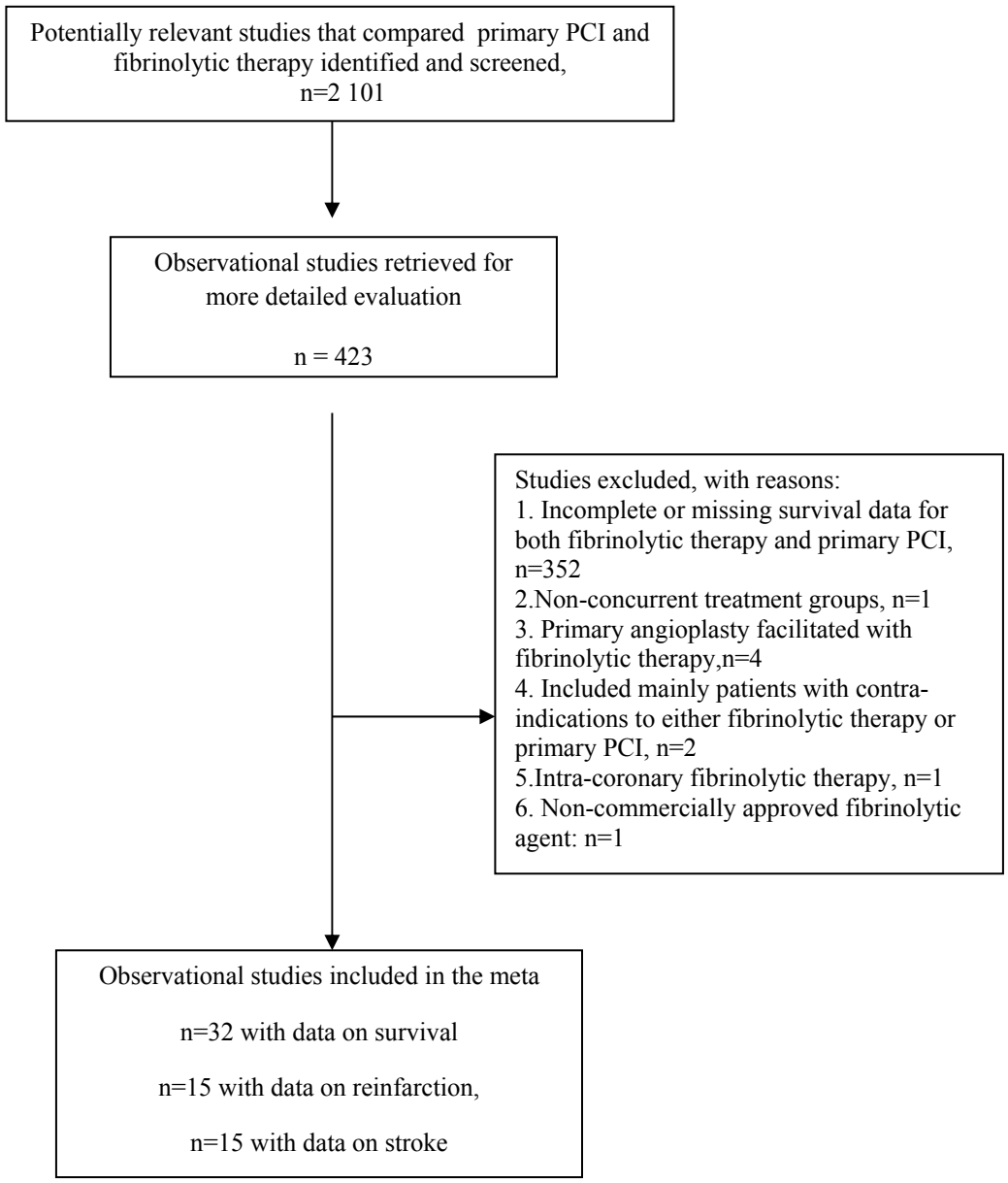


Figure 1b. QUOROM flow diagram of observational studies



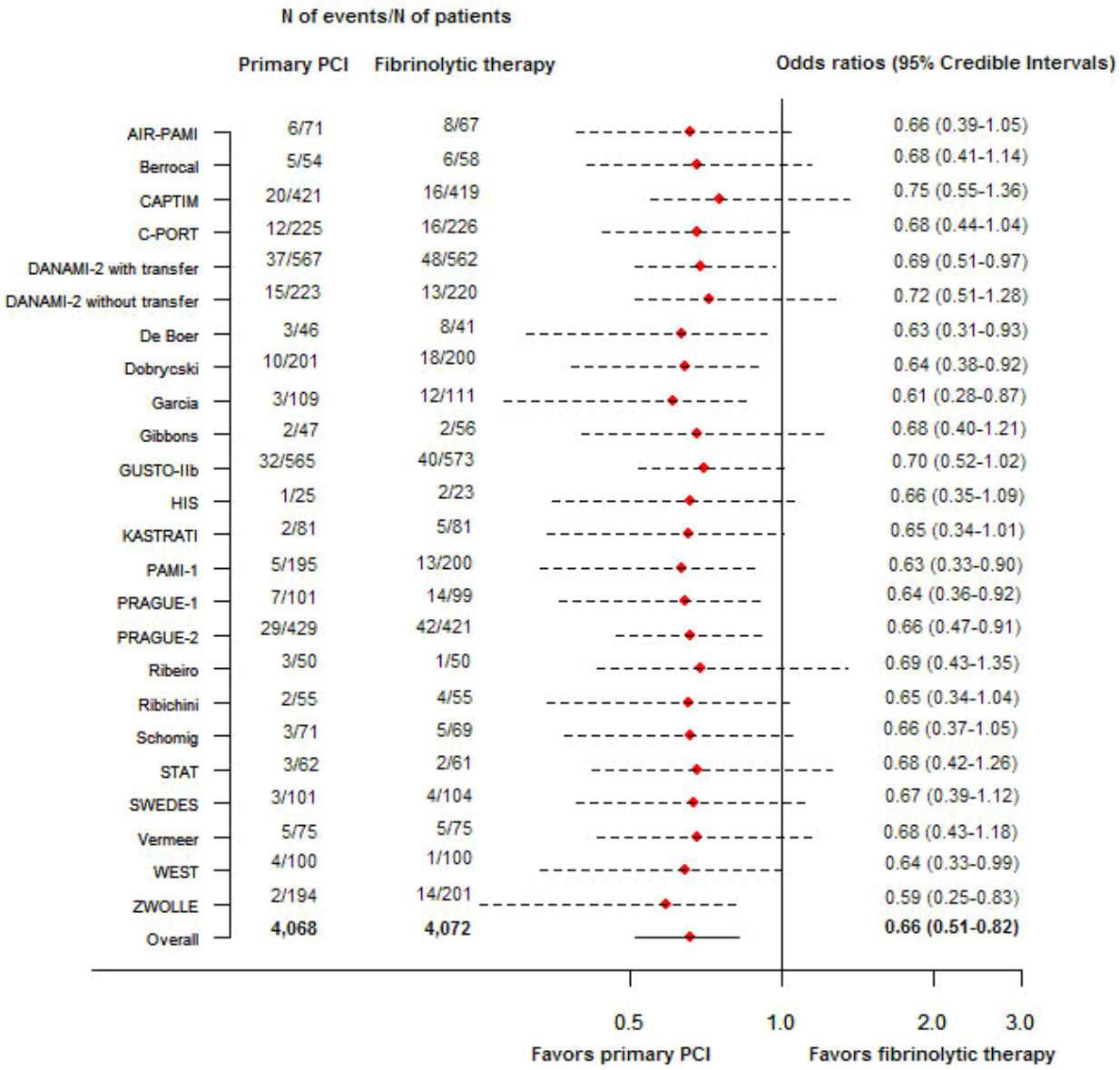


Figure 2. Forest plot of all-cause short-term mortality in randomized controlled studies

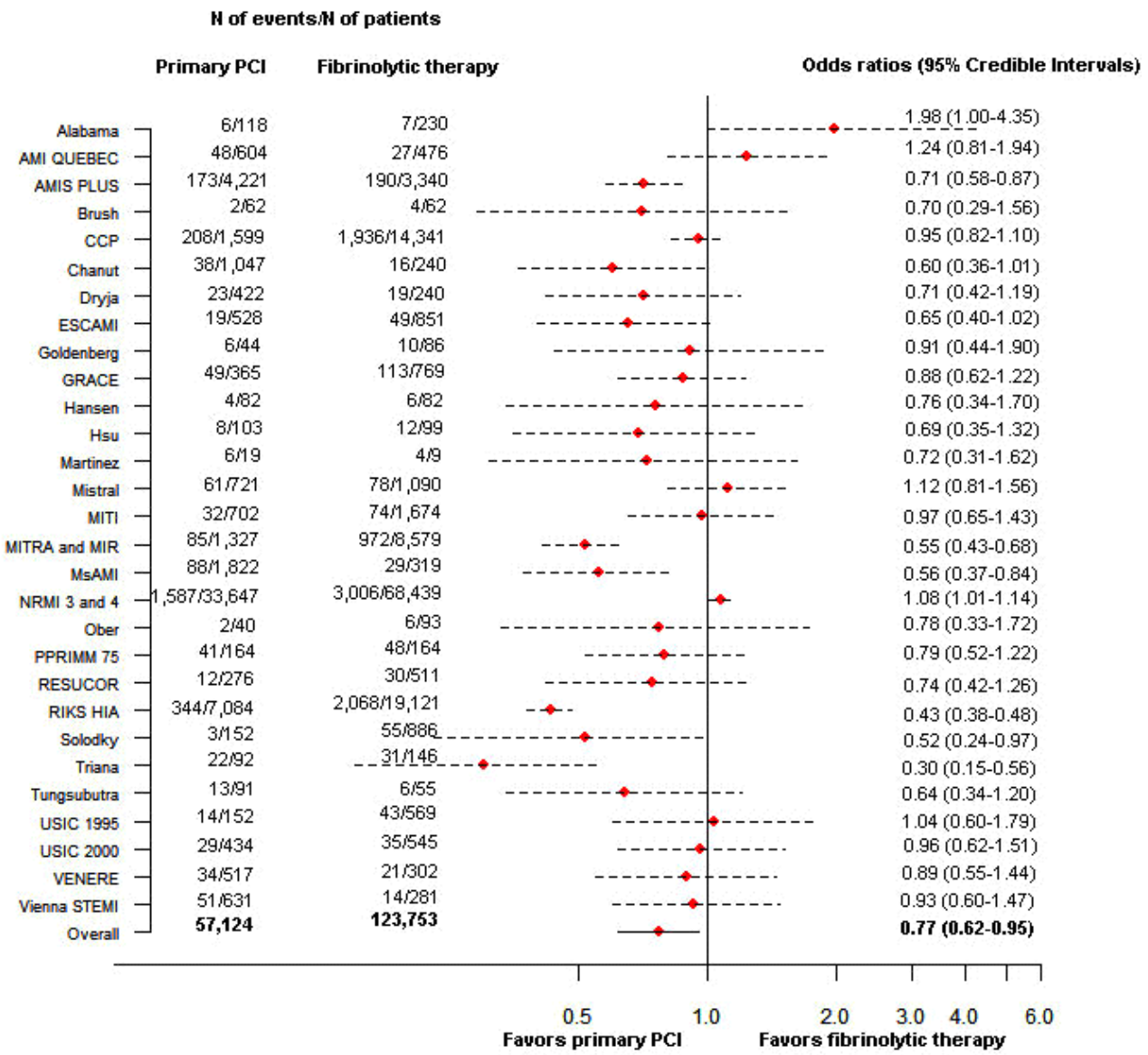


Figure 3. Bayesian forest plot of all-cause short-term mortality in observational studies

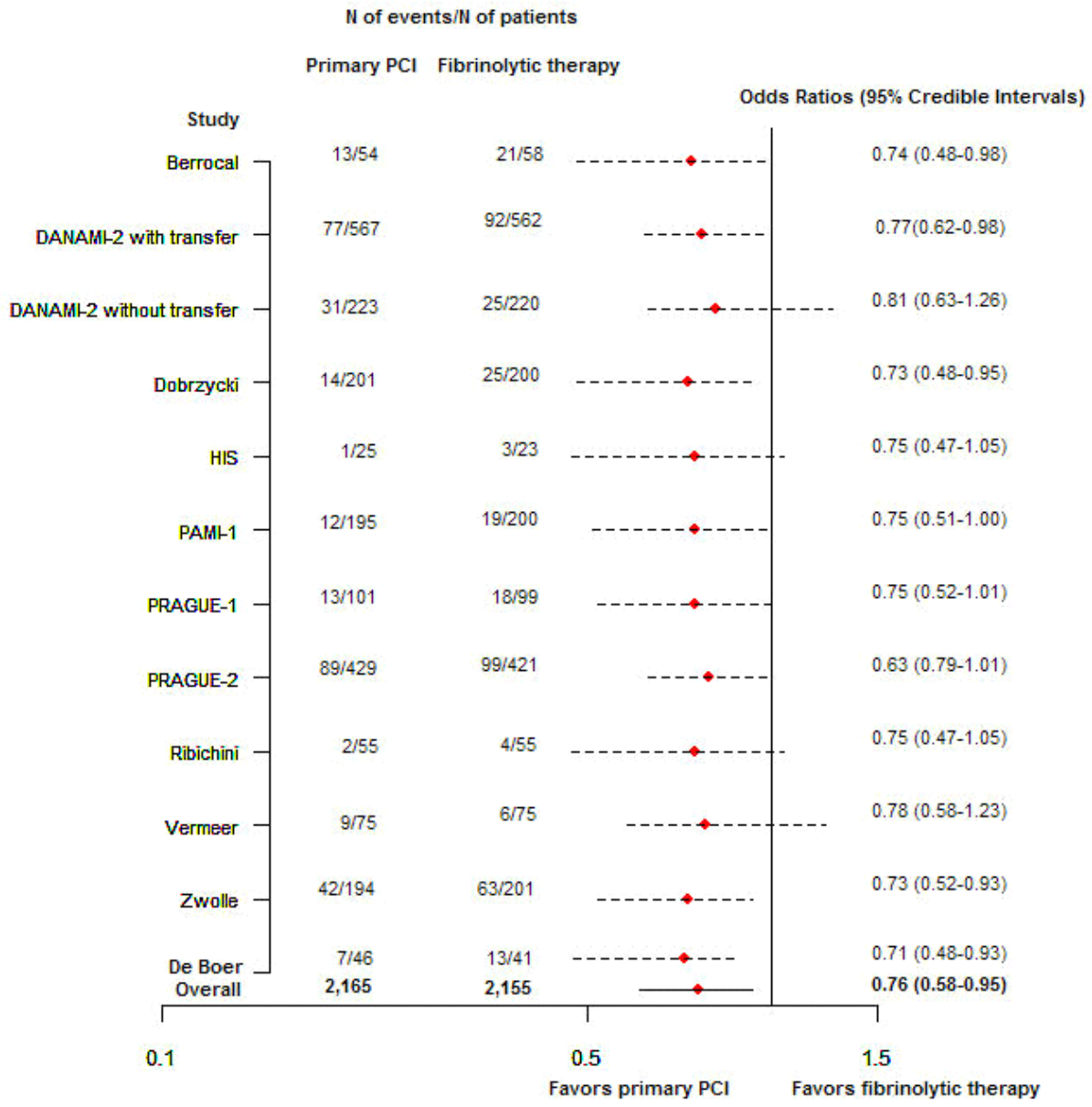


Figure 4. Bayesian forest plot of all-cause long-term mortality of randomized controlled studies

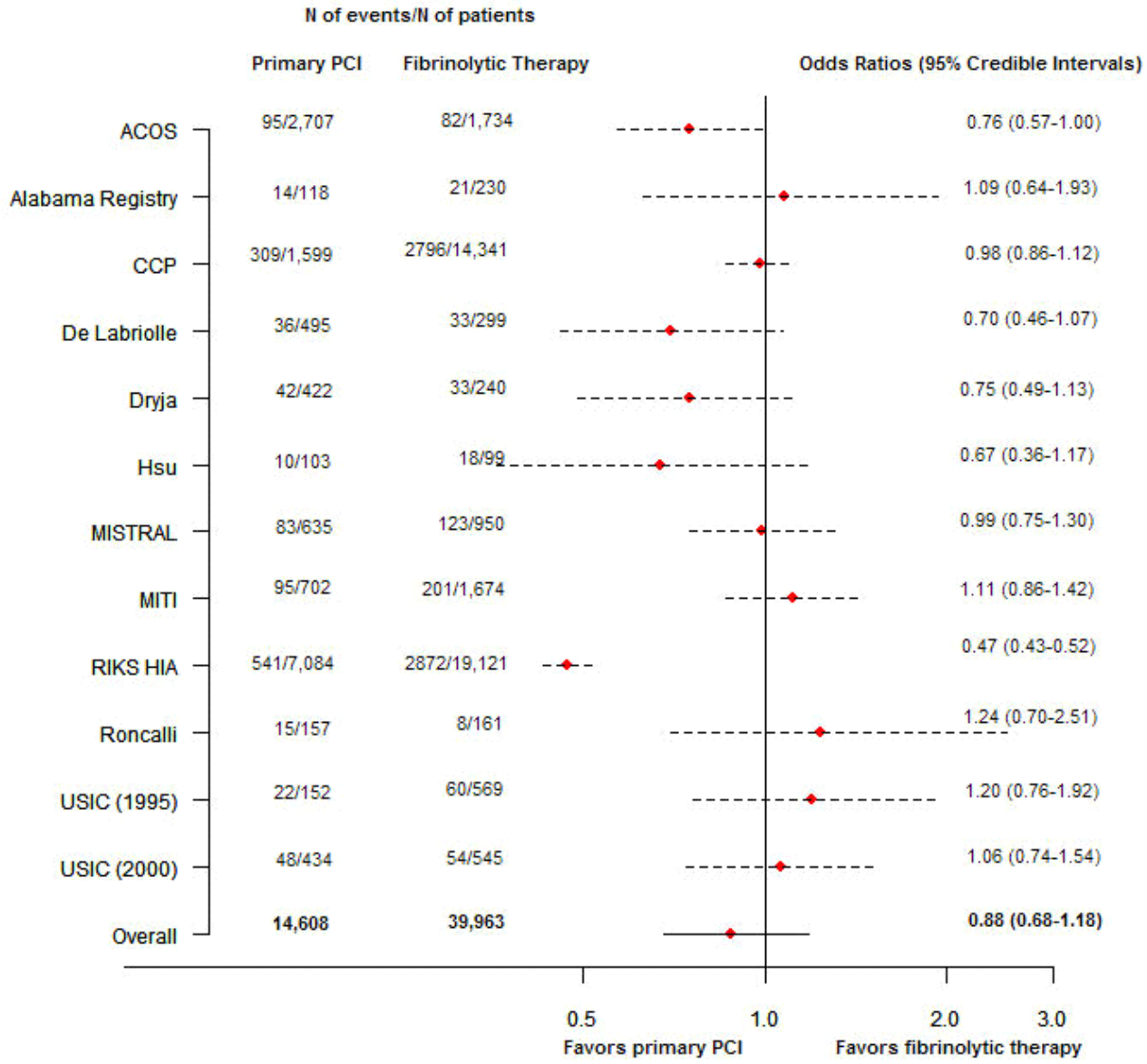


Figure 5. Bayesian forest plot of all-cause long-term mortality in observational studies

Table 1. Meta-analyses of major adverse outcomes

Randomized controlled trials

Outcome	N of studies	N of patients	Odds ratios (95% credible intervals)
Short-term mortality	23	8 140	0.66 (0.51-0.82)
Long-term mortality	11	4 320	0.76 (0.58-0.95)
Short-term reinfarction	22	7 937	0.35 (0.24-0.51)
Long-term reinfarction	9	4 121	0.49 (0.32-0.66)
Stroke	21	7 932	0.37 (0.21-0.60)
Major bleeding	15	4 624	1.40 (0.88-2.00)

Observational studies

Outcome	N of studies	N of patients	Odds ratios (95% credible intervals)
Short-term mortality	29	180 877	0.77 (0.62-0.95)
Long-term mortality	12	54 571	0.88 (0.60-1.18)
Short-term reinfarction	15	45 087	0.47 (0.32-0.67)
Long-term reinfarction	4	32 181	0.58 (0.29-1.21)
Stroke	15	35 158	0.39 (0.29-0.61)
Major bleeding	10	19 459	1.30 (0.37-4.42)

Table 2. Absolute risk reductions and numbers needed to treat

Outcome	% of events in the fibrinolytic therapy group		Absolute risk reductions,% (95% Credible Intervals)		Numbers needed to treat with primary PCI to prevent one event	
	RCT	Observational studies	RCT	Observational studies	RCT	Observational studies
Short-term mortality	7.1	7.3	2.2 (1.3-3.2)	1.1 (0.4-1.5)	45 (31-77)	91 (67-250)
Short-term reinfarction	6.7	9.4	4.5 (3.6-5.4)	2.9 (1.3-4.8)	22 (19-28)	35 (21-77)
Long-term mortality	16.7	11.7	3.5 (0.7-6.4)	1.1 (3.0 reduction to 2.4 increase)	29 (16-143)	NA
Long-term reinfarction	9.4	5.8	3.4 (1.6-5.9)	2.4 (4.0 reduction to 5.7 increase)	29 (17-63)	NA
Stroke	1.9	0.8	1.2 (0.8-1.5)	0.6 (0.5-0.7)	83 (67-125)	166 (143-200)

RCT: Randomized Controlled Trial
PCI: Percutaneous Coronary Intervention
NA: Not applicable since there was no conclusive benefit with primary PCI

Chapter 5

Manuscript 2

5.1. Preamble

The survival benefit of reperfusion therapy (RT) declines rapidly with prolonged time delays to restoration of flow in the occluded coronary artery (76). Early RT administration, within the first hour of symptom onset of myocardial infarction with ST-segment elevation (STEMI), provides the greatest reductions in mortality and permanent heart damage (2,76). Of the two available RT strategies, fibrinolytic therapy (FL) is more likely to be administered within the first hour of STEMI symptoms than primary percutaneous coronary intervention (PCI) (208).

The greatest reduction in delays to FL can be achieved with pre-hospital administration of fibrinolytic therapy (PHL) (208). Although PHL has been widely implemented in Europe for more than a decade (6,73), it is available in two Canadian provinces only (Alberta and Nova-Scotia) (67). Increased access to PHL can potentially save a large number of lives (208).

The limited availability of PHL in Canada is due to several obstacles including lack of trained paramedics, absence of pre-hospital ECG (162) and the high costs of drug acquisition (81). Insights from existing emergency medical systems (EMS) that have already successfully delivered PHL may assist in the implementation of this RT in Quebec (67). The survey described in the second manuscript of this dissertation is the first to describe the infrastructure of several existing PHL programs as well as the mortality and major adverse outcomes of patients managed by each PHL program (67). I also described the EMS organization required for rapid transportation of patients for primary PCI (67). The pre-hospital perspective, as described in the second manuscript, is complementary to

the evaluation of in-hospital RT described in the first manuscript (66). Findings from these two manuscripts may assist health care professionals in their selection and optimization of RT for patients with STEMI.

5.2. Methods

5.2.1. Selection of PHL programs

To identify pre-hospital systems of care that have delivered PHL, I retrieved RCTs and observational studies which evaluated PHL from the following databases: BIOSIS, Cinahl, Embase, Pubmed, Web of Science, Cochrane Library, health technology assessment agencies and Current Contents (up to 1 May 2008) with no language restriction, using the following keywords: "fibrinolysis", "thrombolysis", "fibrinolytic therapy", "acute myocardial infarction", "pre-hospital fibrinolytic therapy" and "reperfusion therapy". In addition, I hand-searched the references of all articles retrieved to assure identification of all PHL programs. Finally, I contacted several cardiology experts in STEMI management to inquire about existing PHL programs in Europe and North America.

I obtained 100% response from the leading investigators of the seven PHL programs contacted including those in England/Wales, France, Vienna and Sweden (Europe), Edmonton and Nova-Scotia (Canada) and Houston (United States).

5.2.2. Affiliated PHL research programs and national registries

All PHL programs contacted have affiliated research projects. These include the Myocardial Ischemia National Audit Project (MINAP) in England/Wales (209), the French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI) in France (145), the Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) in Sweden (120), the Vienna-STEMI Registry in Vienna (127), the Alliance

for Myocardial Infarction Care Optimization (AMICO) in Houston (5), the Vital Heart Response in Edmonton (210) and the Cardiovascular Health Nova Scotia Program in Nova Scotia (211).

5.2.3. Data collection

Population and geography data

I obtained data on the territory and population served by the PHL programs surveyed from the official website of United Nations Statistics (212-213). For jurisdictions other than countries, I extracted population and geography data for 2008, from websites describing national statistics (i.e., for England and Wales (Office for National Statistics of England) (214), for Nova Scotia and Edmonton (Statistics Canada) (215), for Vienna (City of Vienna Information Center) (216), and for Houston (the United States Census Bureau) (217). Data on the number of hospitals, the proportion of hospitals with PCI facilities (PCI-hospital), and the annual incidence of STEMI within each jurisdiction were provided by the leading investigators of each PHL program surveyed (67).

Survey on pre-hospital resources

In August 2008, I emailed a self-administered questionnaire (Appendix 2) to the lead investigators of participating PHL programs. The questionnaire collected data on pre-hospital services available, as well as information on the infrastructure of the PHL program and how the program worked (i.e., its processes). Questionnaires were completed by all lead investigators in April 2009 (Appendix 2). I re-contacted respondents in June 2010 to inquire about recent modifications to the PHL programs.

Outcome data

Investigators were asked to report aggregate outcome data since the initiation of the PHL program, and also for the most recent years 2005-08. I could not obtain individual patient data from the PHL programs surveyed due to confidentiality issues.

Contributions of Co-Authors

Dr Huynh completed the literature search, designed the survey, contacted the investigators of the pre-hospital services, compiled the responses from the survey, drafted the manuscript, and completed the final manuscript for publication

Drs Birkhead, Huber, Stenestrand, Welsh and Danchin provided information on infrastructure, processes and outcomes of prehospital fibrinolysis administered by their pre-hospital services, reviewed and provided input into the draft and final manuscript.

Dre O'Loughlin participated in the study design, reviewed and provided input into the draft and final manuscript.

Drs Denktas, Travers and Sookram provided information on infrastructure, processes of prehospital fibrinolysis of their prehospital services, reviewed and provided input into the draft and final manuscript.

Dr Schull assisted Dre Huynh in designing the survey and provided input into the draft and final manuscript.

Dr Weston, Jernberg, Theroux, Timmis and Smalling reviewed and provided input into the draft and final manuscript

The pre-hospital fibrinolysis experience in Europe and North America and implications for wider dissemination

Brief Title: Pre-hospital Fibrinolysis – International Perspectives

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Key words: acute myocardial infarction, fibrinolysis, percutaeous coronary intervention, electrocardiogram

Word count: 4,506 including abstracts, references and tables and excluding acknowledgement

Abbreviations

AMI: Acute Myocardial Infarction

AMICO: Alliance for Myocardial Infarction Care Optimization

ECG: Electrocardiogram

FAST-MI: French Registry on Acute ST-Elevation Myocardial Infarction

FL: Fibrinolytic therapy

MINAP: Myocardial Ischemia National Audit Project

OCDE: Organisation for Economic Co-operation and Development

PCI: Percutaneous Coronary Intervention

PHL: Pre-Hospital Fibrinolysis

RCT: Randomized Controlled Trial

RIKS-HIA: Register of Information and Knowledge about Swedish Heart Intensive Care Admissions

STEMI: St-Segment Elevation Myocardial Infarction

The pre-hospital fibrinolysis experience in Europe and North America and implications for wider dissemination

Structured Abstract

Objectives

The objective of this manuscript was to describe the infrastructure and processes of selected European and North American PHL programs. A secondary objective is to report outcome data from the PHL programs surveyed.

Background

Despite its benefit in reducing mortality in patients with ST-segment elevation myocardial infarction (STEMI), pre-hospital fibrinolysis (PHL) remains under-used in North America. Examination of existing programs may provide insights to help address barriers to the implementation of PHL.

Methods The leading investigators of PHL research projects/national registries were invited to respond to a survey on the organization and outcomes of their affiliated PHL programs.

Results

PHL was successfully deployed in a wide range of geographical territories (Europe: France, Sweden, Vienna, England and Wales; North America: Houston, Edmonton and Nova Scotia) and was delivered by health care professionals of varying expertises. In-hospital major adverse outcomes were rare, with mortality ranging from 3% to 6%, reinfarction from 2% to 5% and stroke less than 2%.

Conclusion

Combining formal protocols for PHL for some patients with direct transportation of others to a PCI-hospital for primary PCI would allow for tailored reperfusion therapy for

patients with STEMI. Insights from a variety of international settings may promote widespread use of PHL and increase timely coronary reperfusion worldwide.

Condensed Abstract

Pre-hospital fibrinolysis had been successfully deployed in a wide range of geographical territories (Europe: France, Sweden, Vienna, England and Wales; North America: Houston, Edmonton and Nova Scotia) and delivered by health care professionals of varying expertises. In-hospital major adverse outcomes were rare with mortality ranging from 3%-6%, reinfarction from 2%-5% and stroke <2%. Combining formal protocols for PHL for some patients with direct transportation of others to a PCI-hospital for primary PCI would allow for tailored reperfusion therapy for patients with STEMI. Insights from a variety of international settings may promote widespread use of PHL and increase timely coronary reperfusion worldwide.

Background

Timely reperfusion through the administration of fibrinolytic therapy (FL) or primary percutaneous intervention (PCI) is critical in the management of acute myocardial infarction with ST-segment elevation (STEMI) (1,2). Compared to in-hospital administration, pre-hospital administration of FL (PHL) allows for earlier treatment and better survival (3). While primary PCI is the preferred reperfusion therapy, PHL may be superior to primary PCI in reducing mortality in patients with STEMI who present early (i.e., less than 2 hours after onset of symptoms) (4-5). For rural populations, PHL may be the only reperfusion strategy that can be provided in a timely manner (6).

PHL requires a complex pre-hospital system of care to enable prompt and accurate recognition of STEMI and skilled management of life-threatening complications of PHL such as arrhythmia, major bleeding and stroke (6). In spite of this complexity, PHL has

been endorsed by the European Society of Cardiology (8-10) and well established in Europe for over two decades (8-10). In contrast, PHL is available in very few American and Canadian regions (11) despite the larger territories and high proportion of rural populations in these countries compared to Europe (11-13).

Insights into the infrastructure and processes that support PHL care in Europe and North America may assist other jurisdictions to implement PHL systems of care. Based on the longer European experience, patients who received PHL in these regions are more likely to have more favorable survival and fewer major complications compared to patients treated by less experienced PHL programs. Therefore, European PHL survival data may serve as an optimal benchmark for other PHL programs. The primary objective of this manuscript was to describe the infrastructure and processes of care in selected European and North American PHL programs. The secondary objective was to report outcome data from the PHL programs surveyed.

Methods

Selection of PHL programs

We contacted cardiology experts in STEMI treatment to inquire about available PHL programs in Europe and North America. We obtained 100% response from the leading investigators of the seven PHL programs contacted: England/Wales, France, Vienna and Sweden from Europe, Edmonton and Nova-Scotia from Canada and Houston (Texas) from the United States.

Affiliated PHL research programs/national registries

All participating PHL programs had affiliated research projects which included the Myocardial Ischemia National Audit Project (MINAP) in England/Wales (14), the French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI) in France (15), the

Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) in Sweden, the Vienna-STEMI Registry in Vienna, the Alliance for Myocardial Infarction Care Optimization (AMICO) in Houston, the Vital Heart Response in Edmonton and the Cardiovascular Health Nova Scotia Program in Nova Scotia.

Data collection

PHL may have different impacts on STEMI morbidity and mortality depending on the rural urban mix of the population served, and access to hospitals that can deliver alternate reperfusion therapy such as primary PCI. Most recent data relevant to each PHL program included in this study on the territory and population served were extracted from the official website of United Nation Statistics (available only for the year 2008) (16). We defined "rural" as all "non-urban" regions with a population of less than 1000 persons, and a population density less than 400 persons per km^2 (Organisation for Economic Co-operation and Development's (OCDE) definition (17). For jurisdictions other than countries, we extracted population and geography data in 2008 from the national statistical websites (i.e., for England and Wales (Office for National Statistics of England (18), for Nova Scotia and Edmonton (Statistics Canada) (19), for Vienna (City of Vienna Information Center) (20), and Houston (United States Census Bureau) (21)). The lead investigators of the PHL programs provided data on the number of hospitals, the proportion of hospitals with PCI facilities (PCI-hospital), and the annual incidence of STEMI within their jurisdictions.

In August 2008, we mailed a self-administered questionnaire (Appendix 2) to the lead investigators of the seven participating PHL programs. The questionnaire collected data on pre-hospital services available, as well as information on the infrastructure of the PHL program and how the program worked (i.e., its processes). Questionnaires were

completed in April 2009. We re-contacted respondents in June 2010 to inquire about recent modifications to the PHL programs.

. The investigators were also asked to report aggregate data since the initiation of the PHL program and also for the years 2005-08. Outcomes data in these recent three years would be more clinically relevant than outcome data in the past decade since there were numerous recent innovations in the treatment of STEMI. Due to confidentiality issues, we could not obtain individual patient data from the PHL programs surveyed.

Results

There was marked variation in the proportion of the population living in rural areas, and the mean population density in the areas surveyed (Table 1). The mean population density varied from 16 persons/km^2 in Nova Scotia to 4,189 persons/km^2 in Vienna. The proportion of the population living in rural areas varied from 5% in Vienna to 45% in Nova Scotia. Access to a PCI-hospital was limited in Nova Scotia, with only one PCI-hospital in this Canadian province (ratio of 900,000 persons/PCI-hospital, compared to 175,000 persons/PCI hospital in Houston, United States).

In Vienna and France, 95% and 100% respectively of ambulances were staffed by physicians (Table 3). All the other PHL programs surveyed had paramedics and nurses (Sweden) able to provide advanced cardiac life support (i.e., advanced care paramedics (ACP)). The PHL programs in London, Vienna, Houston, Edmonton, Sweden and Halifax had integrated regional networks to facilitate direct transfer of patients for primary PCI.(Table 4). In Vienna and Sweden, all STEMI patients were transported directly to a PCI-hospital for primary PCI, except for patients who lived in very remote rural areas in Sweden. In England/Wales, at the time of this survey, there was no formal transportation arrangement for primary PCI outside London. In the greater London area, all STEMI

patients were transported directly for primary PCI. In Nova Scotia, direct transfer for primary PCI was only possible for patients with STEMI living in Halifax.

Except for England/Wales where paramedics could independently initiate PHL, PHL could only be administered after transmission of pre-hospital ECG and authorization from responsible physicians in the other PHL programs (Table 4). In Houston, Nova-Scotia and Edmonton, PHL was administered by paramedics; in Sweden by ambulance nurses; and in France and Vienna, PHL was administered by physicians in the ambulances.

Tables 5 and 6 describe the characteristics and outcomes of patients who received PHL. Reinfarction was uncommon with cumulative incidences that ranged from 2.4% (France) to 5.8% (England/Wales). Less than 2% of PHL patients (≤0.6% in most programs) experienced in-hospital stroke. The French PHL program had the lowest mortality at 2.7% in-hospital and 4.5% at 1-year while Sweden had the highest in-hospital mortality at 6.5% and 10.7% at 1-year.

Discussion

Although the efficacy and safety of PHL has been demonstrated in several randomized clinical trials (RCT)s (2-5), the generalizability of these results is limited by differences in characteristics of patients and systems of care in the "real-life" context. "Real-life" patients are often older and sicker with more co-morbidity than patients enrolled in RCTs (22). Because of their generally larger samples sizes and longer follow-up durations than RCTs (23-24), data from cohort studies such as those reported in this manuscript, may offer invaluable insights into the "real-life" effectiveness of PHL.

There are several barriers to PHL implementation in North America (25). First, the cost of a PHL program may be prohibitive for many pre-hospital agencies (25). Furthermore, emergency physicians may be reluctant to authorize PHL for patients whom

they have not yet evaluated, for fear of litigation. There may also be misperception that PHL is not necessary considering that 79% of Americans and 59% of Canadians live within an hour of a PCI-hospital (13,26) and therefore should be able to undergo primary PCI in a timely manner. However, the above estimates were based on geographic distance without consideration of bad weather and traffic congestion. Despite the large number of PCI-hospitals and shorter distance to PCI-hospitals in Europe, PHL remains a valuable reperfusion strategy endorsed by the European Society of Cardiology (8-10).

Pre-hospital ECG is an essential prerequisite for PHL, which is endorsed by the American Heart Association and American College of Cardiology (2). However, only a minority of North American pre-hospital medical services can perform ECGs in ambulances (11,12). Transmission problems might also prevent implementation of pre-hospital ECG in many regions. Among the PHL programs surveyed, ECG interpretation in ambulances can either be automated (i.e., interpreted by a computer) or undertaken by paramedics or by nurses. Although ECG transmission could be helpful for patients with unclear diagnoses, well-trained paramedics and nurses could diagnose and treat most STEMI successfully without ECG transmission.

The outcomes reported in this manuscript provide critical insights into the effectiveness and safety of PHL within several different contexts and time spans. These results were similar to the outcomes reported by other American PHL programs (27). Denktas et al. reported similarly low incidences of major adverse outcomes (mortality of 3.8%, stroke of 1.8% and reinfarction of 0.8%). The higher in-hospital and one-year mortality in patients who received PHL in Sweden, relative to PHL in other jurisdictions may be partially explained by a 5-year difference in mean age. Overall, the relatively low incidences of major adverse outcomes following PHL suggest that this reperfusion strategy

can be administered safely and effectively by health care professionals of diverse trainings and expertises.

PHL should not be viewed as an alternate option, but rather as a complementary reperfusion strategy to primary PCI for patients with STEMI. An ideal PHL program would incorporate formal protocols that identify patients who would benefit from direct transport for primary PCI where appropriate, and those who would benefit from early FL. It would need to assess *who* the patient is (i.e. patient characteristics), *where* the patient is (i.e. distance from a PCI hospital), *what* is available for treatment, and *how soon* the patient presents after onset of symptoms. In this way, tailored reperfusion therapy could be provided for each STEMI patient depending on their characteristics and circumstances.

In addition to facilitating transfer, integrated regional networks of PCI-hospitals can be invaluable for continuing cardiac care following PHL. After PHL, patients can be transferred to PCI-hospitals and then triaged for selective non-urgent PCI for patients with successful coronary flow restoration with PHL or rescue PCI for patients who did not have successful PHL. By expediting coronary reperfusion, PHL can prevent undue time delays with the associated increased risks of mortality and irreversible myocardial damage. In addition, PHL may reduce the economic burden of STEMI by decreasing the need for urgent PCI outside regular working hours.

Limitations

First**,** comparison of morbidity and mortality data across PHL programs could not be undertaken due to the lack of individual patient data. Second, our description of infrastructures and processes of selected PHL programs relied on self-administered questionnaires completed by different administrators. Although we did query some inconsistencies and cross-check some data with other sources of information (28) and other

experts in reperfusion therapy, we did not systematically validate all responses provided by the investigators. Third, our survey did not incorporate economic and quality assurance aspects (i.e., paying process of the fibrinolytic drugs, training and monitoring of outcomes, etc). Finally, the outcome data were drawn from observational studies and therefore subject to all the biases inherent to this type of study such as selection, confounding and information bias. In spite of these limitations, we believe that the outcome data on PHL as reported in this manuscript, provide valuable information and may serve as a benchmark for other programs of reperfusion therapy.

Conclusion

PHL has been successfully deployed in a wide range of geographical contexts with varying population densities, access to PCI-hospitals and annual incidence of STEMI. PHL systems comprise a variety of processes that can be adapted to local contexts. PHL can be safely delivered by health care professionals with different levels of training and expertise in a wide variety of settings. Even in areas with rapid access to primary PCI, PHL remains a valuable reperfusion strategy for patients with expected prolonged time delays from first medical contact to coronary flow restoration by primary PCI.

Combining PHL with formal protocols for direct transportation of patients to a PCI-hospital for primary PCI would allow tailored reperfusion therapy for patients with STEMI. Insights from a variety of international settings may promote widespread use of PHL and increase timely coronary reperfusion worldwide.

Table 1. Characteristics of countries, provinces and cities with pre-hospital fibrinolysis programs in 2010

	Country			Province	City		
	England/ Wales	Sweden	France	Nova-Scotia Canada	Housto Texas United States*	Edmonton (Canada)	Vienna Austria
Total population (million) served by the PHL program	54.5	9.0	61.0	0.9	2.1	1.2	1.7
Area (km^2) served by PHL program	151 174	441 370	551 500	55 491	1 499	9 532	414
Population density (mean no. persons/km^2)	360	21	112	16	1 400	126	4,589
Rural population (% of total population)	20	15	17	45	NA	15	5
No. STEMI/year	27 000	6 000	35 000	NA	211	780	1 200
No. STEMI/100, 000 population	50	66	55	NA	10	65	70
No. hospitals that provide STEMI care	224	74	223	8	30	5	6
No. hospitals with PCI facility (% of hospitals that provide STEMI care)	98 (44)	29 (39)	127 (57)	1 (12.5)	22 (73)	2 (40)	6 (100)
Population per hospital with PCI facility	556 122	310 344	480 315	900 000	175 000	600 000	316 666

PCI: Percutaneous Coronary Intervention
STEMI: acute myocardial infarction with ST-segment elevation
NA= Not available

Table 2. Interpretation and transmission of pre-hospital ECG in 2010

	Country			Province	City		
	England and Wales	Sweden	France	Nova-Scotia Canada	Houston Texas United States	Edmonto nCanada	Vienna Austria
Year pre-hospital ECG became available	2000	1990	1990	2006	2005	2002	2000
% of ambulance personnel trained to interpret ECG	100	100	100	100	100	32	100
Electronic transmission of ECG, % of pre-hospital ECG	Not routinely done	100	0	100	100	100	Pilot
Failed electronic transmission of pre-hospital ECG	NA	≤1%	NA	10	20	2	NA

ECG: Electrocardiogram
NA: Not applicable
STEMI: ST-Segment Elevation Myocardial Infarction

Table 3. Expertise of the professionals responsible for pre-hospital management of patients with STEMI in 2010

	Country			Province	City		
	England and Wales	Sweden	France	Nova-Scotia Canada	Houston Texas United States	Edmonton Alberta Canada	Vienna Austria
MD in the ambulances, % of ambulances	0	0	100	0	0	0	95
% of ambulances with advanced care paramedics	100	100	100	51	100	100	5
Responsible for telephonic guidance for STEMI management	ER MD or CCU nurses	ER or CCU MD	NA	ER MD	ER MD	ER MD and cardiologist	ER MD and cardiologist

Advanced care paramedics: paramedics who can provide advanced cardiac life support without supervision
CCU: Coronary Care Unit
ER: Emergency room affiliated with the surveyed pre-hospital services
MD: Medical Doctor
NA: Not applicable
PCI: Percutaneous Coronary Intervention

Table 4. Pre-hospital care of patients with ST-Segment Elevation Myocardial Infarction in 2010

	Country			Province	City		
	England and Wales	Sweden	France	Nova Scotia Canada	Houston, Texas, United States	Edmonton, Canada	Vienna, Austria
Routine transfer of patients for primary PCI, % of STEMI patients	100 for London, no routine transfer for primary PCI outside London	87	NA	Only in Halifax	85	60	100*
Authorize PHL	Paramedics	ER MD	MD in the ambulances	MD affiliated with the pre-hospital services	ER MD	MD affiliated with the pre-hospital services	MD in the ambulances
Routine angiography after PHL, % of patients who received PHL	75	50	85	100% in Halifax only	100	90	90

MD: Medical Doctor
ER = Emergency room
FL= Fibrinolytic Therapy
NA = Not Available
PHL= Pre-hospital Fibrinolysis
TNK = Tenecteplase

Table 5. Characteristics of patients who received pre-hospital fibrinolytic therapy

	England and Wales 2003-8	France 2000	France 2005	Edmonton 2000-2002	Vienna 2003-8	Vienna 2005-8	Sweden 1995-2008	Sweden 2005-8
No. of patients	12 888	180	331	119	350	191	6,643	883
Mean age, years (SD)	62.1 (12)	59.4 (13)	60.5 (13)	61.3 (NA)	58 (12)	57 (12)	66.4 (11)	66.7 (11)
Female, %	21.8	16.0	20.5	24.4	26.6	28.6	28.0	27.0
Mean systolic blood pressure, mmHg (SD)	133 (25)	127 (23)	130 (25)	120	129 (27)	132 (27)	135.5 (27.6)	135.9 (27.6).
Prior myocardial infarction, %	11	10	9	17.1	12	12	17	13
Prior PCI, %	13	7	7	NA	5	5	5	6
Prior CABG, %	2	2	2	NA	1	0.5	3	2
Prior CVA, %	2	1	1	NA	NA	NA	4	5

PCI: Percutaneous Coronary Intervention
CABG: Coronary Artery Bypass Surgery
CVA: Cerebro-Vascular Accident
NA: Not Available

Table 6. Major adverse events in patients who received pre-hospital fibrinolytic therapy

Jurisdiction	England Wales 2003-8	France 2000	France 2005	Edmonton 2000-2002	Vienna 2003-8	Vienna 2005-8	Sweden 1995-2008	Sweden 2005-8
Major bleed, %	0.9*	NA	1.2	10.9	3.7	3.1	2.4	3.5
Reinfarction, %	5.2†	2.8	2.4	5.0	5.4	5.2	2.9	1.5
Stroke, %	0.5#				1.4			
		1.1	0.6	1.7		1.6	0.6	0.8
In-hospital mortality, %	3.3§	3.3	2.7	3.4	6.5	4.7	6.5	5.7
One-year mortality, %	6.9‖	5.6	4.5	NA	NA	NA	10.9	10.4

*= Data available for 11 170 patients
†= Reinfarction was ascertained only since 2005
= Data available for 11 310 patients
§= Data available for 5 941 patients (2007-8)
‖= Data available for 5 721 patients (2007-8)
NA = Not available

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Chapter 6

Manuscript 3

6.1 Preamble

The extensive reviews of pre- and in-hospital reperfusion therapies (RT) in the first two manuscripts of this dissertation (66-67) will contribute to improved management of patients with acute myocardial infarction and ST-segment elevation (STEMI). Although highly lethal, STEMI constitutes only a minority of the burdens of mortality and morbidity of acute coronary syndromes (ACS) (187). The majority of patients with ACS have ACS without ST-segment elevation (NSTE-ACS) (187). This condition occurs with sub-total occlusion of a coronary artery (187). Patients with NSTE-ACS often have poorer long-term survival than that of patients with STEMI due to more co-morbidity and less optimal use of evidence-based medical therapy (218).

Management of patients with ACS varies substantially from basic medication such as aspirin for low-risk patients, to urgent percutaneous coronary intervention (PCI) for high-risk patients (7,189). Inappropriate administration of potent medications or invasive intervention in low-risk patients is costly and exposes these patients to unnecessary side effects (7,189). Conversely, high-risk patients with ACS might not receive life-saving procedures or medication if they are not identified as high-risk in a timely manner (7,187-190). Therefore, early and accurate stratification of patients with ACS according to risk is the cornerstone of the optimal management of these patients (7,187-190).

There are numerous prognostic tools available to assess ACS risk during hospitalization (219). However, there are no appropriate tools to assess risk during the pre-hospital period. To be widely applicable in the pre-hospital context and to avoid undue delays in providing optimal care to ACS patients, the ideal ACS risk score should be

simple, easy to memorize and "calculable" by health care providers without advanced medical training (i.e., primary care paramedics, ambulance technicians). Its computation should not require a calculator or hand-held personal computer and it should not require lengthy questioning or examination of patients. In addition, the ideal risk score should be accurate for risk stratification in all types of ACS. The availability of pre-hospital recording and interpretation of electrocardiograms is highly variable and even non-existent in several Canadian jurisdictions (162). Therefore, a pre-hospital risk score should not require an electrocardiogram and should have similar prognostic value in all types of ACS patients.

The last manuscript of this thesis describes the development and validation of a risk score, the Canadian Acute Coronary Syndromes (C-ACS) index (204). The prognostic value of the C-ACS index is examined in six large datasets of patients with ACS (204). Its simplicity renders this risk score useful for pre-hospital management of patients with ACS.

6.2. Methods

6.2.1 Inclusion of datasets and patients with ACS

The risk score was developed and validated using datasets of observational studies since risk score based on RCTs might have lower predictive value in "real-life" patients with ACS (220). I identified observational studies of patients with ACS in the "Pubmed" database using the following keywords: "acute coronary syndromes", "myocardial infarction", and "unstable angina". To enable completion of the analysis within a reasonable time frame, I initially retained only observational studies of ACS patients in Canada. I contacted the principal investigators of each study to solicit their collaboration either by providing their dataset, or by undertaking the required analyses with their datasets. Subsequently, the FAST-MI principal investigator manifested interest in the risk score and volunteered to participate in this project (145).

Description of included datasets

I had direct access to the AMI-QUEBEC (Acute Myocardial Infarction in Quebec) (182) and the CANADA ACS-1 (Acute Coronary Syndromes-1) datasets (7). Direct access to the other datasets (i.e., CANADA ACS-2 (Acute Coronary Syndromes-2) (8), GRACE-CANADA (Global Registry of Acute Coronary Syndromes in Canada) (186), the EFFECT-1 (221) and the FAST-MI (FAST-MI French registry of Acute ST-elevation and non–ST-elevation Myocardial Infarction) (145) was not possible due to local institutional regulations. The biostatisticians affiliated with these research groups completed the analyses of these datasets.

Inclusion of patients with ACS - All datasets retained included only adult patients (i.e., ≥18 years old) who survived long enough for presentation at the hospital. We did not include patients who died at home or during ambulance transportation. We also excluded patients without a final diagnosis of an ACS condition (i.e., unstable angina, STEMI, non-STEMI).

6.2.2 Definitions of endpoints and ascertainment of survival status

Definitions of endpoints

The primary endpoints of interest were short- and long-term all-cause mortality. I selected all-cause mortality as the primary endpoint since this is the most objective and reliable endpoint (82). Its ascertainment does not depend on subjective classification of cause of death, which may be prone to ascertainment bias (82). Short-term mortality was defined as all-cause mortality that occurred up to 30 days after the index ACS event. Long-term mortality was defined as all-cause mortality that occurred at least 30 days after the index ACS event.

Determination of survival status

Local data abstractors determined the in-hospital survival status of patients in the studies included in this analysis. One-year survival was ascertained by contacting patients enrolled in the CANADA ACS-1-2 study (telephone contact with patients and/or families), and through linkage with health care databases in the EFFECT-1 (221), and FAST-MI (145). Five-year survival was ascertained through linkage with provincial and institutional health care administrative databases for the AMI-QUEBEC study (182). Data on one-year survival were not available for the GRACE-CANADA study (186).

6.2.3. Development of the risk score

Selection of components for the risk score

Since the purpose of this project was to develop a risk score that can be applied in a pre-hospital context, I retained only those clinical variables that are generally available at the time of the first medical contact. I excluded variables requiring electrocardiographic (ECG) data. Variables retained for consideration in the risk score were age, female gender, history of diabetes mellitus, prior myocardial infarction, prior coronary intervention, prior stroke, systolic blood pressure (SBP), heart rate (HR) and Killip class (i.e., a class of severity of myocardial infarction categorized by the presence or absence of heart failure. Killip class is an ordinal scale with values ranging from 1-4, with 1 indicating absence of heart failure and 4 indicating severe heart failure).

Since I had full access to the data, I used the AMI-QUEBEC (182) and the CANADA ACS-1 (7) datasets to develop the risk score. I completed univariate logistic regression analyses to assess the association between each indicator with in-hospital mortality. I entered indicators with p-values ≤ 0.10 univariately into a multivariate logistic regression model, and used backward selection to identify variables with independent associations

with in-hospital mortality. Indicators retained in the final model included age, systolic blood pressure (SBP), heart rate (HR) and Killip class at initial presentation.

To ensure simplicity, I transformed the indicators in the risk score into categorical variables. I tested alternate combinations of categorical variables (≥65 years, ≥70 years, ≥75 years), SBP (<100 mmHg, <120 mmHg), HR (≥100/minute, ≥120/minute), and (Killip ≥1, ≥2, ≥3). For each combination, I calculated the area under the receiver operating characteristic curve. A receiver operating curve is the plot of sensitivity versus 1-specificity (i.e., a plot of proportion of true positives versus false positives for all values of the risk score).

The area under this curve, also called the c-statistic or the c-index, is the probability that a patient who dies has a risk score value greater than that of a patient who survives (222-225). C-statistics have values ranging from 0.5 (no discrimination) to 1 (perfect discrimination) (222-223). The final cut-off values were selected based on the combination of indicators and cut-offs with the highest c-statistic. The final risk score is a composite of four categorical variables: age ≥75, SBP <100 mm Hg, HR >100/minute, and Killip class >1. It is continuous with values ranging from 0 to 4, with each indicator assigned a score of 0 or 1 depending on its presence or absence.

Potential collinearity of the components of the risk score

In a correlation matrix, there was no statistically significant correlation between the indicators retained in the C-ACS, suggesting absence of significant collinearity in the model.

Discriminant and calibration functions

I evaluated the discriminant function (i.e., ability of the risk score to correctly classify subjects with and without risk) using a receiver operating curve (222). C-statistics of

approximately 0.75 or greater are considered to have superior discrimination value (222-223).

The calibration function of a risk score is the estimated predictive value of the risk score (223-225). An assessment of calibration refers to the direct comparison of the observed and predicted mortality (223-225). I evaluated calibration using the Hosmer-Lemeshow goodness of-fit test. This test compares the observed and predicted proportions within each decile of estimated risk (223). A p-value ≥0.10 indicates no statistically significant difference between observed and expected values (i.e., a good fit of the model) (223).

Sensitivity analyses

In patient with impaired heart function, the heart generally compensates by increasing its rate to maintain adequate blood flow. Tachycardia (HR >100 per minute) is frequently the result of depressed heart function. However, injury to the electrical system of the heart of AMI patients may induce very slow HR (HR <50 per minute) or very fast HR (HR>150 per minute) (1). These patients may have HR <50 per minute or >150 per minute, regardless of heart function. The proposed risk score may be less accurate in predicting mortality in these patients.

Analyses of receiver operating curve and goodness-of-fit tests were undertaken initially including all patients. I then undertook sensitivity analyses excluding patients with an initial HR <50 per minute and >150 per minute in all datasets.

Subgroup analyses

I determined the c-stastistics of the C-ACS in several subgroups of patients in the AMI-QUEBEC dataset for both short- and long-term mortalities in Appendix 5. The index has good discriminant properties in all of the subgroups studied (i.e. ≥0.70) except in

patients ≥65 years old where its c-statistics are 0.69 for both short- and long-term mortalities. These results suggested that the C-ACS should have good predictive values in identifying the majority of patients at increased risk for short- and long-term death.

Missing data

I first evaluated discriminant function and model fit in a dataset including only patients with complete data on age, Killip class, blood pressure and heart rate. I then reran the analyses imputing values for missing indicators using three different methods (means, estimates of maximum likelihood and regression).

Contribution of Co-Authors

Dre Huynh completed the literature search, contacted the principal investigators of the observational studies of ACS, validated the risk score, drafted the manuscript, and completed the final manuscript for publication.

Dr Kouz had the original idea of the novel risk score, participated in the selection of the components of the risk score, and provided input into the initial draft and final manuscript.

Dr Andrew and Raymond Yan participated in the selection of the components of the risk score, assisted in the analysis of the CANADA-ACS 1 and 2, and provided input into the initial draft and final manuscript.

Dr Danchin analyzed the FAST-MI data provided input into the initial draft and final manuscripts.

Dre O'Loughlin participated in the study design, reviewed all draft versions and final manuscript.

Ms Chong analyzed data of the EFFECT-1 study and provided input into the final manuscript.

Drs Schampaert, R Yan, Rinfret, Tardif, Eisenberg, Afilalo, Dery, Mansour, Lauzon, Nguyen and Ko reviewed and provided input into the final manuscript.

Dr Tu is the principal investigator of the EFFECT-1 study, reviewed and provided input into the final manuscript.

Dr Goodman is the principal investigator of the CANADA ACS 1 and 2, CANADA-GRACE, participated in the study design, reviewed and provided input into the final manuscript.

C-ACS: A New Risk Score for Early Prognostication in Acute Coronary Syndromes

***Running title**:* C-ACS: A new risk score

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Abreviations

ACS: Acute coronary syndromes

AODE: Averaged One- Dependence Estimators

AMI-QUEBEC: Acute Myocardial Infarction in Quebec

CI: Confidence Interval

C-ACS: Canada Acute Coronary Syndrome Risk Score

EFFECT: Enhanced Feedback for Effective Cardiac Treatment

FAST-MI French registry of Acute ST-elevation and non–ST-elevation Myocardial Infarction

EMMACE: Evaluation of the Methods and Management of Acute Coronary Events

CANADA-GRACE: Global Registry of Acute Coronary Events (Canadian subgroup)

HR: Heart Rate

NA: Non-Applicable

NSTE-ACS: Non- ST-Segment Elevation Acute Coronary Syndromes

PAMI: Primary Angioplasty in Myocardial Infarction

PCI: Percutaneous Coronary Intervention

ROC: Receiver Operating Curve

SBP: Systolic Blood Pressure

STEMI: ST-Segment Elevation Myocardial Infarction

TIMI: Thrombolysis in Myocardial Infarction

C--ACS: A New Risk Score for Early Prognostication in Acute Coronary Syndromes

Abstract

Background: There are several prognostic risk scores for acute coronary syndromes (ACS), but none are appropriate for use at the time of first medical contact with ACS patients. The objective of this study was to develop a simple risk score that can be used for pre-hospital risk stratification of ACS patients.

Methods: We developed the risk score using data from the AMI-QUEBEC and Canada ACS-1 registries, and then validated it in four large datasets of ACS patients (the Canada ACS-2, Canada -GRACE, EFFECT-1 and FAST-MI registries). The "C-ACS risk score" ranged from 0-4, with 1 point each assigned for the presence of age ≥75 years, Killip >1, systolic blood pressure <100 mmHg and heart rate <100 beats/minute. The primary endpoints used to validate the score were short- (in-hospital or 30-day) and long-term (1 or 5-year) all-cause mortality.

Results: The C-ACS had good predictive validity for short and long-term mortality of patients with STEMI and NSTE-ACS. The negative predictive value of a C-ACS score ≥1 is excellent (i.e. a C-ACS score of 0 correctly identifies ≥98% short-term survivors and ≥91% long-term survivors).

Conclusion: The C-ACS risk score permits early identification of high risk ACS patients. Since the score is simple, and easy to memorize and calculate, it can be rapidly applied by health care professionals without advanced medical training.

Condensed Abstract

We developed a risk score for early risk prognostication of patients with acute coronary syndromes. The C-ACS risk score is an ordinal scale with 1 point assigned to each of age ≥75 years, Killip >1, systolic blood pressure <100 mmHg and heart rate <100 beats per minute. The C-ACS risk score has good predictive validity with c-statistic values ≥0.75 for short- and long-term mortality in six large cohorts of patients with acute coronary syndromes. Since this risk score is simple and easy to memorize and calculate, it can be used by health care professionals without advanced medical training.

C-ACS: A New Risk Score for Early Prognostication in Acute Coronary Syndromes

Background

Patients with acute coronary syndromes (ACS) have marked variation in mortality risk (1-2). High-risk patients derive survival benefit with administration of potent medications and prompt coronary revascularization (1-2). However, inappropriate use of these treatments in low-risk patients exposes them unnecessarily to possible adverse side effects (1-2).

Several ACS prognostic risk scores exist, but none is appropriate for early risk stratification at the time of the first medical contact between the health care provider and the patient, before the results of electrocardiogram (ECG) or cardiac biomarkers are available. To be easily applicable at the time of first medical contact, an ACS risk score must be simple and easy to memorize and calculate by health care providers without advanced medical training. The objective of this study was to develop and validate a simple, accurate risk score that can be used for early risk stratification of ACS patients at the time of the first medical contact.

Methods

Inclusion of datasets of ACS patients

We used the AMI-QUEBEC (Acute Myocardial Infarction in Quebec) (3) and the Canada ACS-1 registries (4) to develop the risk score. We validated the risk score in four datasets of ACS patients (i.e., the Canada ACS- 2 registry (5), Canada GRACE (Global Registry of Acute Coronary Events (Canadian subgroup) (6), EFFECT-1 (Enhanced Feedback for Effective Cardiac Treatment), (7) and the FAST-MI (French registry of Acute ST-elevation and non–ST-elevation Myocardial Infarction) (8). All six datasets included

adult patients only (i.e., >18 years old) who survived long enough for hospital admission. Patients who died at home or during ambulance transportation were excluded.

The AMI-QUEBEC Study was a retrospective chart review of all patients with STEMI admitted to 17 Quebec hospitals in 2003 (3). The EFFECT-1 study randomly sampled AMI patients in the Ontario hospital administrative database (7). The Canada-GRACE study enrolled ten consecutive patients with ACS monthly during a 6-month period at participating hospitals (8). Enrolment of patients was consecutive in all other studies. Four studies (i.e., the Canada ACS-1 and-2, Canada-GRACE, and FAST-MI) collected data prospectively (4-6, 8). Written informed patient consent was required in three studies (i.e., the Canada ACS-1 and -2 and FAST-MI) (4-5, 8). For patients with more than one ACS admission during the study period, only the first ACS admission was retained for analysis in all studies.

Definitions of endpoints

Endpoints - The primary endpoints were short and long-term all-cause mortality. Short-term mortality was defined as all-cause death that occurred during hospitalization for the index ACS event (AMI-QUEBEC, Canada ACS-1, ACS-2, Canada-GRACE and EFFECT-1) (3-7) or 30-day mortality (FAST-MI) (8). Long-term mortality was defined as all-cause mortality at one year (ACS-1 and 2, EFFECT-1) (4-5, 7), (FAST-MI) (8) and 5-year following the index ACS event (AMI-QUEBEC) (3).

Determination of survival status - In-hospital survival status was determined in chart reviews. Long-term survival was ascertained in telephone contacts with patients and/or their families in the Canada ACS-1 and 2 registries (4-5), or through linkage with the provincial health care databases in the EFFECT-1 (7) and the AMI-QUEBEC studies. In the FAST-MI study, survival data were obtained by contacting patients, families and

attending physicians; missing survival data were collected through linkage with administrative datasets (8). Data on one-year survival were not available in the Canada-GRACE study.

Development of risk score

Selection of variables

We retained only clinical variables as possible components of the risk score which can be easily obtained in the pre-hospital setting or emergency room. Categorical indicators considered for inclusion in the score included: female sex, history of diabetes mellitus, prior myocardial infarction, prior coronary intervention (i.e., coronary artery bypass surgery or percutaneous coronary intervention (PCI)) and prior stroke. Continuous indicators included age, initial systolic blood pressure (SBP), and initial heart rate (HR). Initial Killip class was considered as ordinal.

Statistical analyses

We used the AMI-QUEBEC and the CANADA-ACS-1 datasets to develop the risk score. Univariate logistic regression models were used to assess the association between each indicator and in-hospital mortality. We then entered indicators with p-values ≤ 0.10 into a multivariate logistic regression model with stepwise selection to identify indicators that were independently associated with in-hospital mortality. We tested the fit of the final model with the Hosmer-Lemeshow Goodness of Fit test.

A risk score with categorical rather than continuous variables would be more easily remembered and applied by clinicians. Therefore, we tested alternate combinations of categorical variables ($\geq$65 years, $\geq$70 years, $\geq$75 years), SBP (<100 mmHg, <120 mmHg), HR ($\geq$100/minute, $\geq$120/minute), and (Killip $\geq$1, $\geq$2, $\geq$3). For each combination, we calculated the c-statistic (i.e., area under the receiver operating characteristic (ROC) curve).

C-statistic values of ≥0.75 are generally considered to have good discriminant properties (9). The final risk score was an ordinal scale ranging from 0-4, with 1 point assigned for age ≥75 years, Killip >1, SBP <100 mmHg and HR >100 beats/minute. We named it the C-ACS risk score (C for Canada, and ACS for Acute Coronary Syndrome).

We compared the predictive value of the C-ACS risk score with other existing risk scores including GRACE (10), EMMACE (Evaluation of the Methods and Management of Acute Coronary Events) (11), TIMI risk score (Thrombolysis in Myocardial Infarction) (12), TIMI risk index (13), PAMI (Primary Angioplasty in Myocardial Infarction) (14) in the AMI-QUEBEC and CANADA ACS-1(15). We computed the predictive values of the C-ACS risk score for patients with STEMI and ACS without ST-segment elevation (NSTE-ACS) in the other datasets (Canada ACS-2, Canada-GRACE, EFFECT-1 and FAST-MI). We examined the positive and negative predictive values of each of the four values of the C-ACS risk score in all six datasets.

Data from EFFECT-1 were analyzed using SAS version 9.1. Data from all other studies were analyzed using SPSS version 18. Comparison of c-statistics across risk scores was undertaken with MEDCALC version 12.1.1.

Results

Characteristics of the registries are summarized in Table 1. Missing data prevented computation of the C-ACS risk score in only a minority of patients (4.1% in AMI-QUEBEC, 8.0% in ACS-1, 4.2% in ACS-2, 8.2% in CANADA-GRACE 1.6% in EFFECT-1 and 0.8% in FAST-MI).

We described selected characteristics and mortality in patients in each registry in Table 2. There were a total of 33,162 patients (30% female). Most had ACS without ST-segment elevation (NSTE-ACS). Patients enrolled in the Canada ACS-1 and-2 and

Canada-GRACE registries had the lowest mortality (<4% during hospitalization; <9% at 1-year). The EFFECT-1 patients had the highest mortality (10% in-hospital; and 17% at 1-year for STEMI and 22% for NSTE-ACS).

Tables 3 and 4 compare the c-statistic of the C-ACS risk score to that of other risk scores in the AMI-QUEBEC and CANADA ACS-1 cohorts. In the AMI-QUEBEC study, which included only STEMI patients, the C-ACS c-statistic for long-term mortality was comparable to those of more complex risk scores (GRACE, EMMACE, PAMI, TIMI risk score and TTIMI risk index). In the CANADA ACS-1 cohort, which enrolled STEMI and NSTE-ACS patients, the c-statistic of the C-ACS risk score was adequate (≥ 0.73) but slightly inferior to other risk scores in predicting short- and long-term mortality. Table 5 reports the c-statistic of the C-ACS risk score in both types of ACS (with and without ST-segment elevation) in all six datasets (Table 5). The c-statistic of the C-ACS risk score was fair with values ≥0.72 in all registries.

We examined the positive and negative predictive values of each of the four values of the C-ACS risk score in the six datasets. The negative predictive value (NPV) of a C-ACS score ≥1 was excellent at ≥98% for in-hospital mortality and ≥91% for long-term mortality (a C-ACS score of 0 correctly identified ≥98% of in-hospital survivors and ≥91% of long-term survivors).

Discussion

Clinical relevance of a risk score for early risk stratification of ACS patients

The relevance of creating another risk score when there are already several risk scores available for ACS prognostication may be questioned (10-14, 17-28). Most existing risk scores require clinical and biological data that only become available after hospitalization and testing. Only the TIMI risk index (13), AODE (Averaged One- Dependence

Estimators) (17) and EMMACE (11) can be applied at the time of the first medical contact. However, these risk scores require computation by calculators or hand-held computers. Furthermore, the TIMI risk index has not been validated in patients with heart rates ≥150 or <50 per minute (13). In contrast to the TIMI risk index and the EMMACE risk score, the C-ACS risk score does not require ECG, blood sampling or a calculator. C-ACS can be easily memorized and calculated and it is applicable in all types of ACS patients. Since ECG acquisition and/or interpretation is difficult or impossible in many North-American pre-hospital settings (29), the lack of requirement for ECG makes the C-ACS risk more easily applicable than other risk scores in North America.

High-risk NSTE-ACS patients who require urgent PCI may benefit from direct transfer to hospitals with on-site PCI facilities. However, routine re-direction of NSTE-ACS patients to hospitals with on-site PCI facilities would divert limited resources (i.e., mobilization of ambulances for prolonged periods of time) without benefit to most NSTE-ACS patients. The excellent negative predictive value (≥0.95) and good sensitivity (≥0.82) of a C-ACS score ≥1, suggests that a C-ACS score of 0 is useful in the early identification of low-risk NSTE-ACS patients who do not need urgent PCI and can be managed conservatively initially. In-hospital management of these low-risk patients may be undertaken later after applying more complex risk scores. Patients with a C-ACS score ≥3 should be managed more aggressively with rapid transport to a hospital with a PCI facility, since these patients have a high mortality risk.

Validity of the C-ACS risk score

Risk scores can be validated either internally or externally. External validation is preferred since internal validation is prone to over-optimism (30-31). The external validation of the C-ACS risk score in several large populations with STEMI and NSTE-

ACS), across different time periods (EFFECT- 1 was conducted in 1999, and the other studies were conducted during 2003-2005), different geographical locations and systems of care (i.e., several Canadian provinces, and France) and diverse therapeutic strategies (i.e., more frequent invasive interventions in the AMI-QUEBEC and FAST-MI patients versus more conservative management in EFFECT-1, Canada ACS-2, and Canada GRACE patients) supports its predictive value and applicability to ACS patients in diverse contexts. Furthermore, the good predictive value of the C-ACS risk score in the various registries suggests that it may be more valid in real-life patients, in contrast to other risk scores that were validated in randomized clinical trials (32).

Potential uptake of the C-ACS risk score

Despite their superiority to physician assessment (32-33), ACS risk scores remain under-used in clinical practice (34-35). This may in part contribute to the "treatment paradox" whereby high-risk ACS patients are often undertreated compared to lower-risk patients (36-37). The reluctance of physicians to apply a formal risk score in the management of ACS patients might be due to the complexity of available risk scores, the requirement for a calculator or computer, as well as limited availability of data for several clinical variables (34-35). The C-ACS score may promote more optimal early management of ACS patients because it is a simple ordinal scale with indicators that can be easily obtained at the first medical contact.

Limitations

Study limitations include use of a categorical rather than a continuous scoring system, which may decrease the precision of the C-ACS score. However, a categorical system is preferable in emergency situations due to its simplicity. Second, we did not assess the accuracy and reliability of the indicators that comprise the C-ACS risk score. In particular,

the Killip classification is subjective and its accuracy might vary depending on the expertise of the observer. Nevertheless Killip class ≥1 requires only simple indicators such as the presence of pulmonary rales and normal blood pressure. These simple indicators can be evaluated by most health care professionals without advanced medical training. Third, due to its ordinal scale with only four possible values, we could not assess the calibration of the C-ACS score. However, in agreement with Lee et al. (33) we believe that the discriminant function of a risk score should be given priority over its calibration. Depending on the case-mix of patients, all risk scores need to be re-calibrated for each population of interest. Finally, the risk score was developed and validated in patients who survived to presentation at the hospital. The applicability and accuracy of the C-ACS risk score for patients who die prior to hospital presentation remain to be determined.

Conclusion

The new C-ACS risk score has good predictive validity for short- and long-term mortality in several ACS populations. It permits rapid identification of high risk ACS patients, before biological markers can be obtained. Since this risk score is simple and easy to memorize and calculate, it can be rapidly applied by health care professionals without advanced medical training. Prompt early stratification of ACS patients will facilitate management tailored to individual patient risk profiles. C-ACS risk score could have a large impact on early ACS care.

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Table 1. Characteristics of the datasets used to develop or validate the C-ACS risk score

	AMI-QUEBEC	Canada ACS-1	Canada ACS-2	Canada-GRACE	EFFECT-1	FAST-MI
Sample size	1 554	4 627	1 956	10 195	11 159	3 670
Sampling method	Consecutive	First 10 consecutive patients monthly	First 10 consecutive patients monthly	First 10 consecutive patients monthly	Random selection	Consecutive patients hospitalized during one month
Enrolment period	2003	1999-2001	2002-3	2004-2006	1999-2001	October 2005
Data collection	Retrospective	Prospective	Prospective	Prospective	Retrospective	Prospective
Number of hospitals (Location)	17 (Quebec Canada)	51 (Canada)	51 (Canada)	55 (Canada)	103 (Ontario Canada)	223 (France)
Type of ACS	STEMI	STEMI NSTE-ACS	NSTE-ACS	STEMI NSTE-ACS	STEMI NSTE-ACS	STEMI NSTE-ACS
Patient consent required	No	Yes	Yes	Yes at some hospitals	No	Yes
Survival data available	In-hospital Five-year	In-hospital One-year	In-hospital One-year	In-hospital Six-month	In-hospital One-year	In-hospital One -year

ACS: Acute Coronary Syndromes
AMI-QUEBEC: Acute myocardial infarction in Quebec
EFFECT-1: Enhanced Feedback for Effective Cardiac Treatment
Canada-GRACE: Global registry of Acute Coronary Events (Canadian subgroup)
NSTE-ACS: Acute Coronary Syndromes without ST-segment elevation
STEMI: ST-segment Elevation Myocardial Infarction
FAST-MI: French registry of Acute ST-elevation and non–ST-elevation Myocardial Infarction

Table 2. Clinical characteristics and mortality of patients enrolled in ACS datasets used to develop or validate the C-ACS risk score.

	AMI-QUEBEC	Canada ACS-1	CanadaACS-2	Canada-GRACE	EFFECT-1	FAST-MI
Age, mean (SD)	62 (14)	65 (12)	66 (13)	67 (13)	67 (14)	67 (14)
Age 75 years, %	19.3	25.3	27.5	31.2	34.9	34.6
Female, %	27.9	31.4	32.9	34.1	35.7	31.5
STEMI, %	100	36.8	0	27.5	49.3	51.0
Diabetes mellitus, %	14.5	25.1	27.2	27.2	25.5	35.9
Prior PCI, %	12.2	14.1	21.5	17.3	3.2	14.1
Prior CABG, %	3.9	12.5	14.5	12.3	6.5	5.7
Killip >1, %	17.5	17.3	16.0	16.2	26.6	24.0
Initial SBP, mean, (SD)	138(32)	148 (29)	149 (30)	145 (29)	146 (33)	140 (29)
Initial HR, mean, (SD)	77(21)	76 (21)	79 (20.4)	82 (22)	84 (25)	80 (20)
Initial SBP <100 mmHg, %	10.8	3.0	2.8	4.8	6.3	6.0
Initial HR >100/min, %	14.5	11.2	12.5	15.9	21.0	13.3
Short-term mortality (%)						
STEMI	6.2	3.9	NA	3.4	9.9	7.7 at 30-day
NSTE-ACS	NA	1.6	1.8	2.6	9.7	5.6 at 30-day
Long-term mortality (%)						
STEMI	11.8 at 5-year	11.9	NA	NA	17.1	11.9
NSTE-ACS	NA	8.3	6.9	NA	21.8	16.0

ACS: Acute Coronary Syndromes
AMI: Acute Myocardial Infarction,
AMI-QUEBEC: Acute myocardial infarction in Quebec
CABG: Coronary Artery Bypass Surgery
Canada- GRACE: Global registry of Acute Coronary Events (Canadian subgroup),
EFFECT-1: Enhanced Feedback for Effective Cardiac Treatment
FAST-MI: French registry of Acute ST-elevation and non–ST-elevation Myocardial Infarction
HR: Heart Rate
NA: Not available,
NSTE-ACS: Acute Coronary Syndromes without ST- segment elevation,
PCI: Percutaneous Coronary Intervention
SBP: Systolic Blood Pressure
SD: Standard deviation
STEMI: ST-segment Elevation Myocardial Infarction.

Table 3. Comparison of the c-statistic for short-term mortality of the C-ACS risk scores and other available ACS risk scores in the development datasets

Risk Score	AMI-QUEBEC		CANADA ACS-1	
	C-statistic (95% CI)	p-values*	C-statistic (95% CI)	p-values*
C-ACS	0.73 (0.72-0.75)	Not Applicable	0.75 (0.74 to 0.77)	Not Applicable
EMMACE	0.76 (0.75-0.77)	0.03	0.81(0.80 to 0.82)	0.009
GRACE	0.78 (0.77-0.79)	<0.001	0.82(0.81 to 0.83)	0.006
PAMI	0.77 (0.76- 0.79)	<0.001	0.77 (0.76-0.78)	0.20
TIMI Index	0.77 (0.76-0.78)	0.04	0.80 (0.79 to 0.81)	0.04
TIMI Risk Score	0.77 (0.75-0.79)	0.80	NA	NA

***:** Comparison of the c-statistic of the risk score with the C-ACS by DeLong et al.'s method
ACS: Acute Coronary Syndromes
C-ACS: Canada Acute Myocardial Infarction
CI: Confidence Intervals
EMMACE: Evaluation of the Methods and Management of Acute Coronary Events
GRACE: Global Registry of Acute Coronary Events
TIMI: Thrombolysis in Myocardial Infarction
PAMI: Primary Angioplasty in Myocardial Infarction

Table 5. C-statistics of the C-ACS score for prediction of mortality of patients with ACS in several datasets

Short-term mortality

	In-hospital AMI-QUEBEC (95% CI)	In-hospital Canada-ACS-1 (95% CI)	In-hospital Canada-ACS-2 (95% CI)	In-hospital Canada-GRACE (95% CI)	In-hospital EFFECT-1 (95% CI)	Thirty-day FAST-MI (95% CI)
STEMI	0.78 (0.74-0.83)	0.74 (0.68-0.81)	NA	0.78 (0.85-0.82)	0.79 (0.78-0.81)	0.76 (0.72-0.80)
NSTE-ACS	NA	0.75 (0.68-0.82)	0.74 (0.69-0.80)	0.79 (0.76-0.82)	0.79 (0.77-0.80)	0.73 (0.68-0.78)

Long-term mortality

	Five-year AMI-QUEBEC (95% CI)	One-year Canada ACS-1 (95% CI)	One-year Canada ACS-2 (95% CI)	One-year Canada-GRACE (95% CI)	One-year EFFECT-1 (95% CI)	One-year FAST-MI (95% CI)
STEMI	0.76 (0.72-0.81)	0.72 (0.68-0.76)	NA	NA	0.79 (0.77-0.80)	0.78 (0.74-0.81)
NSTE-ACS	NA	0.74 (0.71-0.78)	0.74 (0.71-0.77)	NA	0.77 (0.76-0.79)	0.73 (0.70-0.76)

ACS: Acute Coronary Syndromes
AMI-QUEBEC: Acute myocardial infarction in Quebec
Canada-GRACE : Global registry of Acute Coronary Events (Subgroup of enrolled patients from Canada)
CI: Confidence Intervals
EFFECT-1: Enhanced Feedback for Effective Cardiac Treatment
NA: Not Applicable
NSTE-ACS: Non-ST-segment elevation Acute Coronary Syndromes
STEMI: ST-Segment Elevation Myocardial Infarct

Chapter 7

Discussion

In this chapter, I re-state the rationale for this thesis and summarize the results of each manuscript. The strengths and limitations of each manuscript, as well as the contribution of this work to the literature of acute coronary syndromes (ACS) are delineated. Finally, I discuss future research directions and the impact of the findings of this doctoral dissertation on the organization of health care in Quebec.

7.1 Rationale for the three manuscripts in this doctoral dissertation

ACS causes a large number of cardiovascular (CVD) deaths worldwide and generates enormous direct and indirect healthcare costs (10-11). Myocardial infarction with ST-segment elevation (STEMI) accounts for a large proportion of the ACS burden (10-11). Several recent innovations, such as primary percutaneous coronary intervention (PCI) and pre-hospital administration of fibrinolytic therapy (FL), improve survival in patients with STEMI in randomized controlled trials (RCT)s. However, numerous questions remain about the feasibility, effectiveness, and safety of these treatments in less selected "real-life" patients, outside the rigorously controlled context of RCTs (38,194-198). Systematic reviews including recent RCTs using pre-hospital administration of FL (i.e., PHL) and associated interventions/medications (stents, novel medications) may provide a more accurate and contemporary comparison of primary PCI and FL. Furthermore, inclusion of data from observational studies would provide additional insight into safety and effectiveness of these two RT strategies in "real-life" patients.

Despite its proven superiority in mortality reduction compared to in-hospital administration of FL, PHL remains under-used outside Europe. Understanding of the infrastructure and processes required for safe and effective PHL may assist policy-makers

in implementation of this RT strategy in North America. Outcome data of patients who received PHL by experienced emergency medical system (EMS) personnel can serve as benchmark for other EMS providers.

Optimal ACS management includes accurate and early risk stratification of ACS patients (7,187-190). However, despite superior discriminant validity compared to subjective physician evaluation, currently available risk scores remain infrequently used in the prognostication of ACS patients (191-192). Suboptimal use of these risk score is likely due to the requirement for clinical data which may not be easily available, as well as for complex calculation. Considering the widespread increased use of early PCI in patients with ACS (73,176-186), an accurate and user-friendly risk score may be of great utility in pre-hospital risk stratification of patients with ACS, so that these patients can be transported to the most appropriate hospital.

7.2 Summary of the results of this doctoral dissertation

Overall, the three manuscripts in this thesis shed insight into critical knowledge gaps in the management of patients with ACS. Although the efficacy and safety of primary PCI have been well demonstrated in several RCTs and meta-analyses of RCTs, its benefit in terms of reduction in mortality and morbidity in "real-life" patients with STEMI remain unclear (81). Our meta-analysis of observational studies supports the superiority of primary PCI in reducing short-term (<6-weeks) mortality and stroke compared to FL in "real-life" patients with STEMI (66). However, there was no conclusive evidence for a difference in long-term mortality and re-infarction between primary PCI and FL in the observational studies reviewed (66). In the second manuscript, I showed that PHL can be safely administered in diverse international systems of care by health care providers with different levels of expertise (67). Finally, I developed a simple risk score that can be easily

used by health care providers at the time of the first contact with ACS patients (204). The validation of the C-ACS risk score in several large datasets of patients with different types of ACS and within diverse systems of care suggests excellent internal and external validity of this risk score (204).

7.3 Limitations

In this section, I discuss the limitations specific to each manuscript.

7.3.1 Bayesian meta-analyses comparing primary PCI versus FL in RCTs and observational studies

The main limitation of these meta-analyses is the potential for publication bias inherent in all meta-analyses. It is well known that researchers and editors tend not to publish studies with negative results (i.e. when there is no detectable difference between the two treatment arms) (89). Nevertheless, the lack of asymmetry in our funnel plots suggests that there was no omission of major negative studies (112). Another limitation of these meta-analyses is the inability to compare primary PCI with PHL, since PHL was administered in only three RCTs (12,13,15). Third, exclusion of studies not published as full manuscripts (i.e., presented as conference proceedings or in abstracts) might have affected the estimate of treatment effect. However this exclusion was justified by the need for detailed quality evaluation for bias detection.

7.3.2 International perspectives on pre-hospital FL

Limitations of this manuscript include the lack of individual patient data, which prevented direct comparison of outcomes between the PHL programs surveyed (67). Furthermore, the results of this manuscript are based primarily on self-administered questionnaires completed by the administrators of participating PHL programs (67). Although I queried inconsistencies in the data, and cross-checked the results with other

sources of information (73) such as with experts in RT, I did not systematically validate all responses provided by the administrators. Lastly, the outcome data in this paper were drawn from observational studies and are therefore subject to all biases inherent in this type of study including selection, confounding and information bias (146-149).

7.3.3 C-ACS: A new risk score for early ACS prognostication

Use of a categorical rather than a continuous scoring system likely decreased the precision of the C-ACS score. However, a categorical system is preferable in emergency situations due to its simplicity. Second, although I could have included more covariates in the model to improve its accuracy, I limited the model to four variables to maintain its simplicity. Third, the validity and reliability of the clinical measurements used in the C-ACS risk score were not ascertained. Nevertheless, all required clinical measurements are easy to obtain and can be rapidly obtained by most health care professionals without advanced medical training. Fourth, the C-ACS risk score is developed and validated in studies that included only patients who survived to presentation at the hospital (7-8,145,182, 186.221). The prognostic value of this risk score might differ if patients who died before reaching the hospital were included. Finally, it remained possible that the increased mortality of patients with high C-ACS scores might be also due to different in-hospital management compared to patients with lower C-ACS scores.

7.4 Study strengths

7.4.1 *Bayesian meta-analyses comparing primary PCI versus FL in RCTs and observational studies*

Our meta-analyses improved on previous systematic reviews by including short-term results from four recent RCTs (2, 19-21). I also incorporated events at 1 year, as well as longer-term results from five RCTs that were not considered in earlier reviews

(i.e., data at 1-year from Dobrycski and PRAGUE-1 (32,90), at 2-years from the PAMI-1 (91) at 3-years from DANAMI-2 (225), at 5-years from PRAGUE-2 (226) and at 8-years from the Zwolle Study (227). Given the marked heterogeneity across RCTs in study design and patient populations, the random-effects hierarchical Bayesian approach is more appropriate (113-115) than the fixed-effects models used in previous meta-analyses (37,92,96-98,101,106). Bayesian meta-analysis allows studies with small sample sizes to contribute more to the overall estimate. Consequently, larger studies (with flaws in study design) would have less impact on the global estimate than with other non-Bayesian random-effects models (116).

This study is the first systematic review that incorporates results from observational studies that compare the effectiveness of primary PCI and FL. Incorporation of evidence from observational studies enhances the external validity of previous meta-analyses (199-201). The inclusion of several international cohorts of "real-life" STEMI patients provides additional global perspectives on reperfusion strategies. Finally, the estimates of the numbers needed to treat to save one event in RCTs and observational studies provide additional insight to clinicians and policy-makers in terms of selecting the most appropriate RT.

7.4.2 *International perspectives on PHL*

Our survey represents the first collaboration between several North American and European pre-hospital ACS systems of care (67). In addition to detailed multinational descriptions of the infrastructures and processes for managing patients with STEMI, I also reported the outcomes of PHL administered by a variety of health care providers, within diverse pre-hospital EMS programs (67). This study provides unique international perspectives on the feasibility, effectiveness and safety of PHL. Since PHL expedites

administration of FL, and decreases the time delay to coronary reperfusion, more widespread implementation of PHL may reduce myocardial (heart) damage as well as mortality related to STEMI globally.

7.4.3 C-ACS: A new risk score for early ACS prognostication

The validation of the C-ACS risk score in several large datasets of patients with STEMI and NSTE-ACS), across different time periods (EFFECT- 1 was conducted in 1999, and the other studies were conducted in 2003-2005), geographic locations and systems of care (several Canadian provinces and France) and diverse therapeutic strategies (more frequent invasive interventions in the AMI-QUEBEC and FAST-MI patients (145,182) versus more conservative management of the EFFECT-1 (221), Canada ACS 1 and 2 (7-8), and Canada GRACE patients (186)) supports its discriminant value and external generalizability to ACS patients within diverse contexts. Furthermore, the good discriminant validity of the C-ACS risk score in several large datasets suggests that this risk score may be applicable in real-life patients, in contrast to other risk scores that were validated primarily in RCTs (220). Since it is a simple ordinal scale that incorporates indicators that can be easily obtained at the first medical contact, the C-ACS score may promote more optimal early management of ACS patients.

7.5 Impacts of the publications from this doctoral dissertation

In this section, I list the main citations and impacts that have emanated to date from the manuscripts in this doctoral dissertation. The first manuscript was selected as one of "*the most important manuscripts, as selected by the editors, published in Circulation and the Circulation subspecialty journals, most read manuscripts published on the topic of cardiovascular interventions in 2009 and 2010"* (230). This manuscript is highlighted as one of *"the most important manuscripts, as selected by the editors, that have been*

published in the Circulation portfolio. The studies included in this article represent the most noteworthy research in the area of ST-elevation myocardial infarction. (231). The manuscript is mentioned as one of the *"major scientific work in the field of Interventional Cardiology in 2009*" by the editors of the Journal of American College of Cardiology (232). This manuscript is also cited by the European Society of Cardiology Textbook of Intensive and Acute Cardiac Care (232). Recently, the Ontario Medical Advisory cited this manuscript several times in their recommendations on re-organization of care for patients with STEMI in Ontario for the year 2010 (111).

The second manuscript "*The pre-hospital fibrinolysis experience in Europe and North America and implications for wider dissemination" was* published in JACC Cardiovascular Intervention in 2011. Following its publication, I was contacted by Dr Young (i.e., the Health Canada Officer responsible for care in the First Nations) for advice concerning the feasibility of implementing PHL in Northern Quebec (234).

The last manuscript '*C-ACS: A New Risk Score for Early Prognostication in Acute Coronary Syndromes"* is currently in press by the American Heart Journal.

7.6 Future research

Future research which raises awareness of the importance of timely treatment will stimulate interest and efforts to deliver the best care to all patients with ACS. Continuous monitoring of treatment delays in prospective registries will enable recognition of the types of patients at risk of treatment delays, and systems of care with sub-optimal performance. Solutions to delays to RT requires close collaboration between hospitals with and without PCI-facilities and pre-hospital systems of care. Participation in ACS research will facilitate and strengthen multi-institutional cooperation.

Because of its vast geography, sparsely-populated territories, and inclement winter weather, many patients with ACS experience excessive delays to RT in Canada (229). It is critical that EMS health providers strive to improve the care of ACS patients in Canada. Since primary PCI within acceptable delays is not possible for all Canadians, it is essential that alternate RT strategies such as PHL be implemented, especially for the many Canadians living in remote rural areas (202). Future research should focus on the feasibility, effectiveness and safety of PHL in rural regions in Canada.

Pre-hospital innovations should aim for treatment tailored to the mortality risk of individual patients with ACS. The C-ACS score may be useful for rapid risk stratification of patients with ACS, to enable the most appropriate treatment for each individual ACS patient. However, the applicability and prognostic value of the C-ACS needs to be validated prospectively in the pre-hospital setting.

Chapter 8

Conclusions

The findings of this doctoral dissertation make substantial contributions to current knowledge in ACS management. Incorporation of long-term mortality data from recent RCTs into the meta-analyses described in the first manuscript supports the survival benefit of primary PCI observed in the rigorously controlled conditions of RCTs. The lack of conclusive difference in long-term mortality between primary PCI and FL in observational studies, suggests attenuation in the survival benefit of primary PCI in "real-life" STEMI patients within "real-life" contexts. This finding corroborates current international STEMI recommendations that FL is an acceptable alternative to primary PCI when primary PCI cannot be provided within optimal time delays (79).

Although PHL improves survival compared to in-hospital administration of FL, its safety and effectiveness have not been well characterized in "real-life" STEMI patients outside the RCT context. The pre-hospital infrastructure required for PHL has not been adequately studied, so that the comprehensive description of several existing pre-hospital systems of care that provide PHL in the second manuscript may assist policy-makers to implement PHL and reduce STEMI-related mortality.

Finally, in view of the trend towards early use of PCI in patients with ACS, it is imperative that health care providers have access to a simple method to risk stratify patients with ACS at the time of initial contact. Early ACS management can then be appropriately tailored to the patient's mortality risk to maximize the benefits and minimize the risks of invasive coronary intervention. The proposed ACS risk score, the C-ACS has the required simplicity for use in the early management of patients with ACS. Its benefit in the pre-

hospital management of ACS patients will need to be demonstrated prospectively in future studies.

Overall, the three manuscripts in this thesis (66,67,204) address major knowledge gaps in ACS care and the findings provide critical and practical knowledge and tools for health care providers. This doctoral dissertation will contribute to making timely and high-quality ACS care more accessible.

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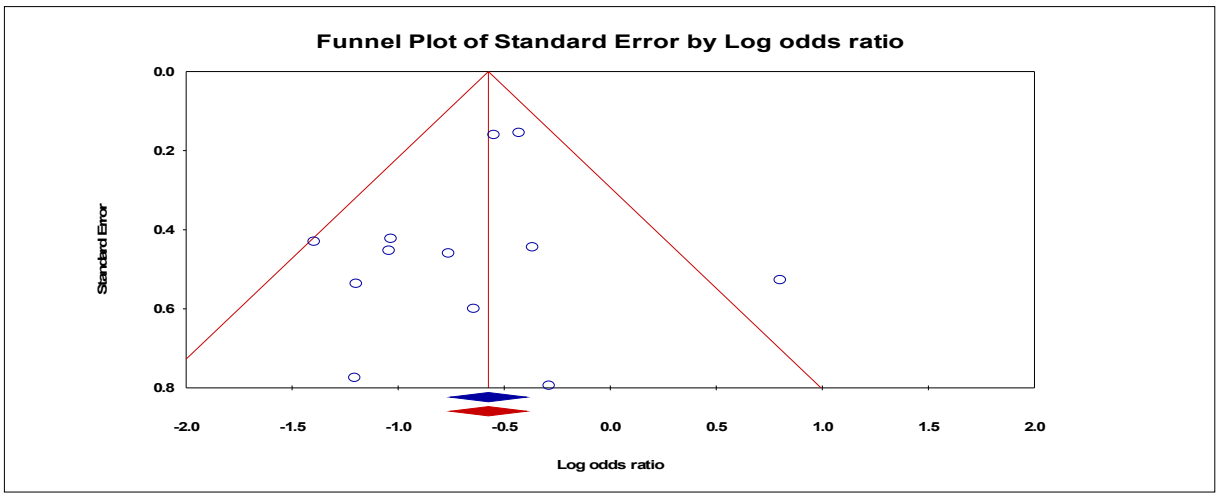
Appendix 1. Funnel Plot of short-term mortality

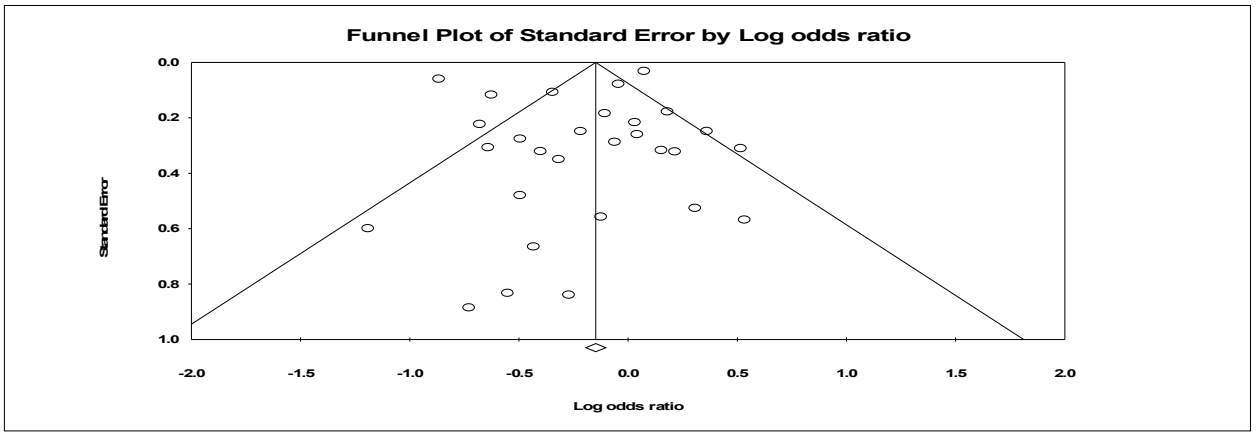
Randomized controlled studies



The fail-safe N is 51. This means that we would need to locate and include 51 'null' studies in order for the combined 2-tailed p-value to exceed 0.050.

Under the random effects model the point estimate and 95% confidence interval for the combined studies is 0.71061 (0.59005, 0.85580). Using Trim and Fill these values are unchanged (blue and red diamonds for original estimate and estimate with Trim and Fill, respectively).

Observational Studies



The fail-safe N is 212. This means that we would need to locate and include 212 'null' studies in order for the combined 2-tailed p-value to exceed 0.050.

Under the random effects model the point estimate and 95% confidence interval for the combined studies is 0.82688 (0.68204, 1.00248). Using Trim and Fill these values are unchanged.

APPENDIX 2. SURVEY ON INTERNATIONAL INFRASTRUCTURE AND PROCESS OF PRE-HOSPITAL FIBRINOLYSIS.

Name of respondent	
Jurisdiction (city/country)	
Date	

Question	Answers
1.1 Populations with access to pre-hospital fibrinolytic therapy	
1.2 Names of cities covered by this survey	
1.3 Number of hospitals involved	
1.4 % of hospitals with cardiac cath labs facilities	
1.5 % of rural territories covered (rural defined as <2,500 population/US census)	

SECTION 2. EXPERTISE OF PRE-HOSPITAL PERSONNLE

Definitions

ACP: An advanced care paramedic (ambulance technician) with advanced cardiac life support training

PCP: Emergency Medical [paramedic (ambulance technician) without advanced cardiac life support training

Question	Answers
2.1 Approximate % of pre-hospital transports by ACPs	
2.2 Approximate % of pre-hospital transports by PCPs	
2.3 Approximate % of pre-hospital transports with physicians	
2.4 Approximate % of pre-hospital transports with nurses	
2.5 Other medical or paramedical personnel in the ambulances	

SECTION 4. PRE-HOSPITAL 12 LEAD ELECTROCARDIOGRAM (ECG) CAPABILITY

Question	Answers
3.1 Indicate the estimated proportion of all **ambulances** equipped with cardiac monitors with 12 lead ECG capability (0-100%)	_____%
3.2 Indicate the estimated proportion of all **paramedics** able to acquire 12-lead ECG (0-100%)	_____%
3.3 Indicate the year when 12 lead ECG capability began to be routinely used.	Year: _____
3.4 Indicate whether the cardiac monitors routinely generate **automated interpretations** of the 12 lead ECGs.	☐ Yes ☐ No
3.5 Indicate whether the cardiac monitors with 12 lead capability include software decision tools for reperfusion or fibrinolysis. (e.g., Thrombolysis Prediction Instrument [TPI] index)	☐ Yes ☐ No

**Fibrinolysis/Reperfusion Therapy includes intravenous thrombolysis (eg TNK, tPA, streptokinase) and Percutaneous Coronary Intervention (PCI)*

SECTION 4: PRE-HOSPITAL 12 LEAD ECG INTERPRETATION

Question	
4.1 Approximately what proportion of all paramedics have training for a) direct interpretation of ECG tracings; b) interpretation of automated ECG messages?	a) Direct interpretation of ECG tracings: 0-100% _____ b) Interpretation of automated ECG messages: 0-100% _____
4.2 Indicate the year when this training of paramedics began. *Select N/A if not applicable.*	a) Direct interpretation of ECG tracings: Year: _____ or ☐ N/A b) Interpretation of automated ECG messages: Year:_____ or ☐ N/A

SECTION 5. PRE-HOSPITAL 12 LEAD ECG TRANSMISSION AND ED NOTIFICATION

Definitions

STEMI: STEMI refers to an ST segment elevation acute myocardial infarction that is suspected based on a 12 lead ECG

ED: Emergency Department

Question	Answers
5.1 Do the paramedics that acquire 12 lead ECGs routinely **transmit** them (e.g., by modem, cell phone, radio, etc.) to the receiving hospital prior to their arrival if they suspect an acute STEMI?	☐ Yes ☐ No
5.2 Indicate the year when transmission of 12 lead ECGs from ambulance to hospital began.	Year: _____
5.3 Approximate proportions of failures of transmission of pre-hospital ECG (0-100%)	_____
5.4 At the ED, who is the responsible person assigned to review the transmitted ECG	☐ Emergency physician ☐ Cardiologist on call ☐ Interventional cardiologist ☐ Nurse ☐ Other personnel, please specify _____

SECTION 6. PRE-HOSPITAL AMI BYPASS PROTOCOLS

Definitions

Pre-hospital re-direct agreements: *Pre-hospital re-direct agreements refer to the formal protocols allowing paramedics to routinely bypass the closest ED(s) and directly transfer a suspected or confirmed STEMI patient to a hospital with a cardiac catheterization facilities for primary PCI.*

Question	Answers
6.1 Do the operators have formal written medical **re-direct agreements** allowing paramedics to bypass the closest ED(s) and transport a patient directly to hospitals with cardiac catheterization facilities if the Paramedics suspect an acute STEMI?	☐ Yes ☐ No
6.2 Indicate the year when these agreements came into effect.	Year: _____
6.3 When an acute STEMI is suspected by a **Paramedic**, estimated proportions of patients who were re-directed to hospital with PCI capability (0-100%)	_____

SECTION7. PRE-HOSPITAL FIBRINOLYSIS

Question	Answers
7.1 Is the pre-hospital fibrinolysis a routine part of the pre-hospital management of acute STEMIs?	☐ Yes ☐ No
7.2 Is there a fibrinolysis checklist or similar decision tool employed as routine practice by **Paramedics**?	☐ Yes ☐ No
7.3 Is there any age exclusion of patients from pre-hospital fibrinolytic therapy	☐ Yes ☐ No
7.4 If yes, please provide the age cut-off	_____
7.5 Who decides to initiate pre-hospital fibrinolysis	☐ Paramedics ☐ Physician in the ambulances ☐ Emergency physician at the hospital ☐ Cardiologist at the hospital
7.6 Medications routinely administered at the time of pre-hospital fibrinolysis, please check all that apply	☐ Aspirin ☐ Thienopyridines ☐ Anticoagulant, type LWMH _____

	or UFH_____ ☐ Beta-blockers ☐ Others, please specify _____
7.7 Types of fibrinolytic agents, and approximate % used	☐ tenecteplase, % used _____ ☐ tissue plasminogen activator, % used _____ ☐ reteplase,. % used _____ ☐ streptokinase, % used _____ ☐ Others, please specify _____ % used _____
7.8 After **successful** pre-hospital fibrinolysis (defined as complete or partial resolution of chest pain, ST elevation <90 minutes from administration of fibrinolytic therapy, are the patients **routinely or selectively** sent to hospitals with cardiac cath labs (0-100%)?	☐ Routine ☐ Selective, if selective, please indicate approximate % of patients sent to hospitals with cardiac cath labs (0-100%) _____
7.9 After **successful** pre-hospital fibrinolysis, are the patients **routinely** or **selectively** sent for <24 hour coronary angiogram	☐ Routine ☐ Selective, if selective, please indicate approximate % who undergo <24-hour coronary angiogram (0-100%)_____
7.10 After **successful** pre-hospital fibrinolysis, approximate median delay between pre-hospital fibrinololytic therapy and same-day	_____

coronary angiogram	
7.11 After **successful** pre-hospital fibrinolysis, are patients **routinely or selectively** sent for in-hospital coronary angiogram	☐ Routine ☐ Selective, if selective, please indicate approximate % of patients who undergo in-hospital coronary angiogram (0-100%)_____
7.12 After **unsuccessfu**l pre-hospital fibrinolysis (defined as lack of ST resolution and symptoms at 90 minute after pre-hospital FL) are the patients **routinely or selectively** sent for urgent/rescue coronary angiogram	☐ Routine ☐ Selective, if selective, please indicate approximate % of patients who undergo in-hospital coronary angiogram (0-100%)_____

SECTION 8. OUTCOMES OF STEMI PATIENTS

Question	Answers
8.1 Is there **systematic** collection of **in-hospital** outcomes of STEMI patients	☐ Pre-hospital fibrinolytic therapy ☐ Primary PCI ☐ No reperfusion therapy
8.2 If not **systematic** collection of **in-hospital** outcomes of STEMI patients, please estimate % of patients with available in-hospital outcomes data	_____ Pre-hospital fibrinolytic therapy _____ Primary PCI _____No reperfusion therapy
8.3 Is there **systematic** collection of **1-year** outcomes of STEMI patients	☐ Pre-hospital fibrinolytic therapy ☐ Primary PCI ☐ No reperfusion therapy
8.4 If not **systematic** collection of in-hospital outcomes of STEMI patients, please estimate % of patients with available **1-year** outcomes data	_____ Pre-hospital fibrinolytic therapy _____ Primary PCI _____No reperfusion therapy

Appendix 3. Predictors of in-hospital mortality in the AMI-QUEBEC dataset

Univariate models

Predictors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-values	OR (95% CI)	p-values
Age	1.06 (1.04-1.07)	<0.001	1.63 (1.34-1.97)	<0.001
Female gender	1.85 (1.21-2.80)	0.004	0.96 (0.59-1.57)	0.28
Diabetes mellitus	1.40 (0.82-2.38)	0.221		
Prior AMI	1.78 (1.14-2.78)	0.011	1.15 (0.69-1.90)	0.60
Prior PCI	1.36 (0.83-2.23)	0.219		
Prior CABG	1.31 (0.56-3.08)	0.539		
Prior stroke	2.02 (1.05-3.88)	0.034	1.01(1.00-1.02)	0.96
Aspirin use	1.91 (1.34-2.72)	<0.001	1.30 (0.87-1.94)	0.20
Initial SBP (mmHg)	0.988 (0.982-0.995)	<0.001	1.10 (0.90-1.22)	0.02
Initial HR per minute	1.02 (1.01-1.03)	<0.001	1.22 (1.10-1.34)	<0.003
Killip class, for every class increase	2.32 (1.94-2.78)	<0.001	1.91 (1.54-2.38)	<0.001

Multivariate model with age, BP, HR and Killip as categorical variables

Age ≥75 years*	3.53 (2.25-5.54)	<0.001
SBP <100 mmHg	2.23 (1.30-2.81)	0.003
HR >100 per minute	1.80 (1.08-2.99)	0.02
Killip class >1	3.22 (2.01-5.16)	<0.001

AMI: Acute Myocardial Infarction,

CABG: Coronary Artery Bypass Graft Surgery,

CI: Confidence Intervals,

HR: Heart Rate

OR: Odds Ratios,

PCI: Percutaneous Coronary Intervention,

SBP: Systolic Blood Pressure

Appendix 4. Distribution of the C-AMI risk score in the different datasets

C-ACS	AMI-QUEBEC %	Canada ACS-1 %	Canada ACS-2 %	Canada-GRACE %	EFFECT-1 %	FAST-MI %
STEMI						
0	66.4	57.5	NA	54.0	49.0	53.9
1	20.3	27.9	NA	28.6	29.8	30.5
2	9.0	11.7	NA	12.5	13.7	12.1
3 and 4	4.4	3.0	NA	4.9	5.6	3.5
NSTE-ACS						
0	NA	58.7	56.5	52.3	38.5	40.4
1	NA	29.6	30.1	32.3	30.1	34.0
2	NA	9.8	11.4	12.0	20.3	20.4
3 and 4	NA	1.9	2.0	3.4	9.7	5.2

ACS: Acute Coronary Syndromes

AMI: Acute Myocardial Infarction

AMI-QUEBEC: Acute myocardial infarction in Quebec

EFFECT-1: Enhanced Feedback for Effective Cardiac Treatment

GRACE (Canada): Global registry of Acute Coronary Events (Canadian subgroup)

NA: Non-applicable

STEMI: ST-segment Elevation Myocardial Infarction

FAST-MI: French registry of Acute ST-elevation and non–ST-elevation Myocardial Infarction

Appendix 5. Subgroup analyses of the C-AMI score in the AMI-QUEBEC study

Subgroups of patients	In-Hospital Mortality C-statistics OR (95% CI)	Five-Year Mortality C-statistics OR (95% CI)
≥65 years old	0.69 (0.62-0.76)	0.69 (0.63-0.85)
Diabetics	0.75 (0.65-0.86)	0.81 (0.74-0.89)
Females	0.72 (0.63-0.80)	0.75 (0.62-0.81)
Males	0.78 (0.71-0.85)	0.74 (0.68-0.81)
Heart rate 50-150 per minute	0.76 (0.71-0.82)	0.77 (0.73-0.81)

C-AMI: Canada Acute Myocardial Infarction

OR: Odds Ratios

CI: Confidence Intervals