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ECONOMIC ANALYSIS OF PREHOSPITAL STRATEGIES FOR STEMI

ECONOMIC ANALYSIS OF DIFFERENT CORONARY SYNDROME TREATMENT STRATEGIES IN A PREHOSPITAL SETTING

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ABSTRACT

BACKGROUND

For ST-segment elevation myocardial infarction (STEMI) patients received by emergency medical services (EMS), prehospital identification with 12-lead electrocardiogram/cardiography (ECG) and advanced notification of the receiving centre may increase access to primary reperfusion and reduce mortality, compared to standard cardiac monitoring. The lifetime benefits and costs of upgrading to a 12-lead ECG system are uncertain.

OBJECTIVES

To determine the cost-effectiveness of prehospital identification with 12-lead ECG and advanced notification vs. no prehospital identification and no advanced notification.

METHODS

A probabilistic Markov model was designed from a government payer perspective. Outcomes were lifetime incremental quality-adjusted life-years (QALYs) and healthcare costs. Type of primary reperfusion, 30-day and one-year mortality came from a cohort study conducted in Ontario. Reinfarction, stroke and revascularization rates were derived from the literature. Inpatient costs and professional fees came from the Ontario government; follow-up costs from published literature. The analysis was stratified by eligibility to bypass to a percutaneous coronary intervention (PCI) centre.

RESULTS

In bypass eligible settings, prehospital identification and advanced notification led to an average 0.23 additional QALYs and $1,501 additional costs over no prehospital identification and no advanced notification. In bypass ineligible settings, it led to an average 0.15 fewer QALYs and $130 additional costs. It was a cost-effective strategy 87% and 40% of the time in bypass eligible and ineligible settings, respectively, at a willingness-to-pay of $50,000/QALY.

CONCLUSIONS

In bypass eligible settings, prehospital identification with 12-lead ECG and advanced notification is a cost-effective intervention. In bypass ineligible settings, there is no evidence of cost-effectiveness.

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ABBREVIATIONS

AMI acute myocardial infarction

AHA/ACC American Heart Association/American College of Cardiology

ARR absolute risk reduction

ARTS Arterial Revascularization Therapies Study

ASA aspirin

CAD coronary artery disease

CADTH Canadian Agency for Drugs and Technologies in Health

CAPTIM Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction

CABG coronary artery bypass graft

CAD coronary artery disease

CCC Clinical Classification Categories

CCI Canadian Classification of Health Interventions

CCN Cardiac Care Network

CCS Canadian Cardiovascular Society

CCU coronary care unit

DOM dominated

DANAMI-2 Danish Acute Myocardial Infarction 2 trial

DET deterministic

DR discount rate

DTB door-to-balloon

DTN door-to-needle

ECG electrocardiogram/cardiography

ED emergency department

EDS Evidence Development and Standards team

EFFECT Enhanced Feedback for Effective Cardiac Treatment

EMS emergency medical services

EP emergency physician

FB fibrinolysis

FMCTB first medical contact-to-balloon

GRADE Grading of Recommendations Assessment, Development and Evaluation

HUI Health Utilities Index

ICD-9 International Classification of Diseases, Ninth Revision

ICD-9-CM International Classification of Diseases, Ninth Revision-Clinical Modification

ICD-10-CA International Classification of Diseases and Related Health Problems, 10th Revision, Canadian enhanced version

ICER incremental cost-effectiveness ratio

ICU intensive care unit

ISIS-2 Second International Study of Infarct Survival-2 trial

LBBB left bundle branch block

LY life year

MAS Medical Advisory Secretariat

MI myocardial infarction

MOHLTC Ministry of Health and Long-Term Care

NA not applicable/available

NIAP National Infarct Angioplasty Project

NMB net monetary benefit

NOS not otherwise specified

NSTEMI non-ST-segment elevation myocardial infarction

OCCI Ontario Case Costing Initiative

OHTAC Ontario Health Technology Assessment Committee

PCI percutaneous coronary intervention

PREDICT Prehospital Evaluation and Economic Analysis of Different Coronary Syndrome Treatment Strategies

QALY quality-adjusted life-year

RCCC Regional Cardiac Care Centre

SD standard deviation

SK streptokinase

SO symptom onset

STEMI ST-segment elevation myocardial infarction

TIMI Thrombolysis in Myocardial Infarction

WTP willingness-to-pay

Y.O. year old

1 INTRODUCTION

1.1 OVERVIEW

Death due to acute myocardial infarction (AMI) is the leading cause of death in Ontario[1,2]. Over the last twenty years, a wealth of evidence has established that early recognition and early reperfusion reduce myocardial necrosis and mortality[3–11]. While many randomized trials have focused on determining the efficacy of in-hospital interventions such as percutaneous coronary intervention (PCI) or fibrinolysis[4,12], there has been less attention paid to prehospital strategies.

Prehospital identification of AMI; advanced notification of the receiving emergency department (ED); and bypass to a Regional Cardiac Care Centre (RCCC)* with PCI capability (in Ontario, also equivalent to a PCI-centre) have been implemented in many communities[13]. However, implementation of these strategies across urban and rural communities is variable in Ontario[14]. Some emergency medical services (EMS) in the province have primary care paramedics with prehospital identification of AMI not within the scope of their practice. Other EMS services do not have ambulances outfitted with the equipment necessary to identify an AMI. In these jurisdictions, AMI is identified after the patient arrives at the hospital. As well, some jurisdictions may not be in close proximity to a PCI centre, limiting the treatment possibility to only fibrinolysis[15].

Prehospital services — or emergency medical services — are funded by a global budget that is managed by the municipalities but is financed 50/50 between the provincial government and the municipalities. The provincial government considers all services that are the standard of care in its calculation for its share for each municipal budget. Because prehospital identification of AMI; advanced notification of the receiving ED; and bypass to a PCI hospital are not considered the standards of care by the Ministry of Health and Long-Term Care (MOHLTC), the burden of financing these prehospital strategies falls solely on the municipality. Smaller communities may not have the means to upgrade their paramedics' training and vehicle equipment to support such prehospital strategies.

While the economic impact of in-hospital interventions such as PCI and fibrinolysis have been studied, less attention has been paid to the economic impact of prehospital strategies. The incremental costs of supporting prehospital identification of AMI; advanced notification of the receiving ED; and bypass to an interventional hospital may be

* A RCCC offers cardiac catheterization and many centres also offer angioplasty, cardiac surgery and heart rhythm services. It should be noted that all PCI centres are also RCCCs; a RCCC with PCI capability is also thus referred to as a PCI centre in this document.

considerable; however, there may also be considerable long-term cost savings.

Differences in the standard of care for prehospital management of STEMI across communities in Ontario may be due, in part, to limited evidence. This thesis aims to examine the cost-effectiveness of 12-lead and 3-lead ECG. The identification and implementation of an optimal prehospital management strategy may help to provide consistent and optimal care for all STEMI patients in Ontario.

1.2 BURDEN OF AMI AND STEMI

AMI is an event where the blood supply to the heart, or myocardium, is interrupted, resulting in death of heart tissue. The two types of AMI are STEMI and non-ST-segment elevation myocardial infarction (NSTEMI). A STEMI produces an elevation in the electrical tracing of the heart that can be detected by health care professionals with the use of a 12-lead electrocardiogram/cardiography (ECG); a NSTEMI does not present any recognizable electric tracings and therefore identification is confirmed with a blood test. AMIs are caused by a rupture of thickened, scarred and fatty tissue — or atherosclerotic plaque — of one of the coronary arteries. The ruptured plaque, in addition to the body's immune response, produce a blockage in the coronary artery[16]. The blockage deprives the heart of blood and oxygen and results in cell death. Time is an important prognostic factor. The longer the blockage, the more extensive the cell death[17–19].

The median age of AMI patients in Ontario is 69 years[2]. Men constitute 65% of AMI patients[2]. Between the ages of 35 and 84 years, women have higher in-hospital mortality rates compared to men; women also have higher one-year readmission rates for AMI, congestive heart failure and angina following initial AMI, compared to men[2]. Many patients who present with AMI also have at least one modifiable cardiac risk factor; 33% are current smokers, 44% have hypertension, 31% have hyperlipidemia and 26% have diabetes[20].

Death due to AMI is the leading cause of all death (both sexes, all age groups) in Ontario, representing 10.1% of all deaths[1,2]. The 30-day mortality rate of AMI has been steadily dropping over two decades since the 1980s[1]; during 1997–2000, it was 12% and the one-year mortality rate was 20%[20].

While the 30-day mortality rates are decreasing, the aggregate burden still remains considerable. The number of AMI-deaths is projected to steadily increase due to population growth and aging. It will have doubled in the twenty years leading up to 2018[1].

AMI patients spend a median six days in the hospital[20]. About 8.4% of AMI patients are re-admitted due to another AMI and a further 8.5% are re-admitted for congestive heart failure within one year[21]. The burden of AMI also extends to survivors of AMI. Survivors of AMI live on with heart disease. Living with heart disease is associated with a lower health-related quality of life compared to those living without any heart disease[1]. Some post-AMI survivors may suffer from prob-

lems walking or may live with pain; being not happy or not interested in life; a restriction of activities requiring varying levels of assistance with activities for daily living; or a restriction in employment participation. Women living with heart disease following an AMI have reported greater functional restrictions and activity restrictions compared to men living with heart disease following an AMI[1].

The economic burden of AMI in Ontario has not been well documented. However, cardiovascular disease — including AMI, other coronary heart diseases and other cardiovascular diseases — was estimated to cost $5.5 billion in direct and indirect costs per year; this represents 2% of the provincial gross domestic product[22]. Cardiovascular disease also represents 20% of all acute care hospital costs, 15% of all home care costs, 10% of all medical services costs and 17% of drug expenditures in the province[22].

1.3 CURRENT TREATMENT OPTIONS FOR STEMI

The goal of treatment for AMI, and thus STEMI, is prompt reperfusion. Reperfusion is a restoration of blood flow to the areas deprived of blood. Longer delays to reperfusion lead to greater cell death and higher risk of mortality and morbidity[23]. There are two primary reperfusion options for AMI: fibrinolysis/thrombolysis and PCI. In addition, patients who receive fibrinolysis may also receive early revascularization with PCI. Finally, some patients may not receive any primary reperfusion treatment.

Fibrinolysis is a pharmacological therapy which uses a drug to dissolve the occluding thrombus. Widespread use in STEMI patients began in the 1980s with streptokinase[24,25]. Then, accelerated alteplase became the standard after it was shown to be superior to streptokinase in the early–mid 1990s[26,27]. Today, tenecteplase is the standard for AMI because it is the easiest fibrinolytic to administer and its efficacy profile is equivalent to accelerated alteplase while its safety profile is slightly superior[28,29].

Patients who are given a fibrinolytic agent as well as aspirin have a 42% reduced odds of mortality at five weeks compared to patients who receive neither[25]. The Canadian Cardiovascular Society (CCS) recommends a goal time from first medical contact-to-start of reperfusion therapy of 30 minutes for fibrinolysis[30]. The first medical contact has typically been defined as arrival in the hospital but some now promote that it should begin with first contact with prehospital care providers where they can recognize and begin management of a STEMI[31,32]. In fact, the first medical contact is defined by the CCS as the time when the prehospital care provider(s) arrive on scene.

Another treatment option is PCI. PCI is a non-surgical technique that uses a catheter — a long and fine tubular surgical instrument that is inserted through a peripheral blood vessel — to perform any number of catheter-based techniques. The most common primary intervention for STEMI is angioplasty. Angioplasty uses a balloon to physically widen the narrowed blood vessel; sometimes, a coronary artery stent

is inserted to hold the artery open. PCI is a procedure which requires a special facility called a catheterization laboratory (cath lab) as well as specially trained interventional cardiologists to perform the procedure. The CCS recommends a first medical contact-to-start of PCI therapy (balloon inflation) goal of 90 minutes[30]. As with their recommendations regarding fibrinolysis, in practice this time delay is applied to a door-to-balloon measure — the time from entry through hospital door to balloon inflation.

Patients who receive fibrinolysis may also go on to receive early revascularization with PCI — early PCI — following fibrinolysis. Early PCI within 24 hours following initial hospitalization has been shown to reduce 30-day reinfarction and reischemia while not increasing the risk of stroke compared to a standard protocol of revascularization only when there is failed reperfusion — rescue PCI[33–35]. However, no differences in 30-day mortality have been shown.

Finally, although timely fibrinolysis and PCI are the recommended primary reperfusion treatment strategies for patients with STEMI, some patients may not receive any primary reperfusion treatment. A population based observational study revealed that 41% of STEMI patients in Ontario from 1999–2001 do not receive fibrinolysis or PCI[20]. This population has generally not been well reported on. However, a review of the burden of STEMI patients who do not receive any reperfusion found that Ontario is not alone in its experience with a large prevalence of this population[36]. Age >75, symptom onset >12 hours, spontaneous reperfusion, female sex and presence of comorbidities have been associated with no reperfusion; however, these factors alone do not explain the large prevalence of no reperfusion observed in many different jurisdictions[36]. STEMI patients who do not receive any primary reperfusion strategy will generally receive at least aspirin, which has been shown to reduce mortality, reinfarction and stroke over no aspirin[25].

1.4 TIME-TO-TREATMENT ON PATIENT OUTCOMES

The ischemic time is defined as the length of time a part of the heart is deprived of blood flow and oxygen. Longer ischemic times are associated with higher risks of death[17–19,23,37]. Therefore, it is important that the time-to-treatment is minimized. The time-to-treatment includes the time from symptom onset, through to first medical contact, arrival at the hospital and start of reperfusion therapy. However, a number of different time points have been used as performance measures. The most frequently used performance measures denote the hospital delay; door-to-balloon time refers to the time from hospital arrival to balloon inflation for PCI while door-to-needle time refers to the time from hospital admission to needle insertion for fibrinolysis.

The importance of time was confirmed in the seminal Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico trial (published in 1986) where it was found that very early thrombolytic

therapy confirmed a 50% reduction in mortality in STEMI patients treated with streptokinase within one hour of the onset of symptoms[24]. These findings were later elaborated on by the Thrombolysis in Myocardial Infarction (TIMI)-2 trial[37] which showed that each hour of delay led to an increase in absolute mortality of 1%. This laid the foundation for the later establishment of the "golden hour", which indicated the time period where the clinical benefits were greatest[38].

1.5 BENEFITS AND LIMITATIONS OF PCI

The body of evidence suggesting that PCI offered a benefit over fibrinolysis did not accumulate until the late 1990s. PCI has since shown to be associated with a higher likelihood of infarct artery patency; TIMI grade 3 flow; as well as lower rates of emergency repeat revascularization procedures[39]. A number of meta-analyses of RCTs have also shown PCI to reduce short-term mortality, long-term mortality, reinfarction, and stroke in the majority of patients[4,12,39,40].

Although PCI may offer reduced mortality and morbidity compared to fibrinolysis in the majority of patients with STEMI, there is a smaller benefit when it is performed at low-volume PCI centres[41]. In addition, PCI may not be feasible due to limited access. Efforts in Ontario to increase access to timely PCI are discussed further in Section 1.6.

PCI may be delayed during any or all of the following: notification of the catheterization laboratory team; assembly of the cath lab team; and long-distance transport for patients bypassed from other regions. If these delays are significant, the mortality benefit of PCI over fibrinolysis may be negated. Therefore, the outcomes of the two reperfusion methods may be similar.

A number of meta-regressions have shown that as the expected delay of PCI over fibrinolysis increases, the treatment benefit over fibrinolysis reduces; in general, the treatment benefit of PCI over fibrinolysis is thought to be negated when the treatment delay is somewhere between 60 and 120 minutes[4,6,9,10]. The time delay where the relative PCI benefit is negated depends on the ischemic time and the risk profile of the patient. Pinto et al. found that the relative PCI benefit was negated after 40–58 minutes in patients under 65 years of age with symptom onset <2 hours[10] while results from the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial suggest that, overall, PCI and fibrinolysis result in similar 30-day mortality for patients with a symptom onset <2 hours[42].

In this context of limited access to PCI and its comparable performance to fibrinolysis where the symptom onset delay is relatively short, fibrinolysis occupies an important role in the timely reperfusion of STEMI patients. In fact, the Cardiac Care Network (CCN) of Ontario (www.ccn.on.ca), a major proponent of increasing access to urgent PCI, highlight the necessity of fibrinolysis. This is discussed further in Section 1.7.

In recognition that early reperfusion is associated with better outcomes, the CCS and the American Heart Association/American College of Cardiology (AHA/ACC) have recommended a goal time of <90 minutes from first medical contact-to-reperfusion for PCI and <30 minutes from first medical contact-to-reperfusion for fibrinolysis[30,43].

1.6 ACCESS TO PCI IN ONTARIO

In 2004, the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study group published a report of 5 PCI centres and 39 non-PCI centres in Ontario that had collected data on STEMI patients from 1999–2001[20]. According to EFFECT, only 59% of all STEMI patients received either fibrinolysis or PCI. Of these patients, 99% received fibrinolysis while 3% received PCI within 24 hours of admission[20,44]. PCI within 24 hours of admission was either primary PCI or PCI following fibrinolysis. No centre reported a PCI use of greater than 40% and this included all PCI within 24 hours. Overall, PCI use was low.

Beginning in 2004, Ontario implemented a province-wide regional system of care for STEMI patients[14]. The goal of the system was to increase access to urgent PCI. Although PCI had been shown to be superior to fibrinolysis when implemented within the targeted time, PCI was only offered to a minority of STEMI patients. A regional model was designed to increase access to PCI by triaging and transferring patients to a RCCC with PCI capability — synonymous to a PCI centre, in Ontario.

The capability to triage to a PCI centre from both non-PCI centres and directly from the field was implemented in three steps. The first step was the restructuring of existing PCI-centres to operate on a 24 hour, 7 day a week basis by 2005/06. Each PCI-centre was required to maintain a minimum of two cardiac cath labs on-site, establish standardized protocols and algorithms for single-call direct activation/notification of the cath lab and direct patient transfer to the cath lab.

The second step was to implement inter-hospital transfer from a non-PCI centre to a PCI-centre[14]. STEMI patients presenting at non-PCI centres were eligible for inter-hospital transfer by EMS if they could be transported to a PCI-centre for PCI with a maximum door-to-balloon of 90 minutes. This 90 minute window was divided into 30 minutes for door-in-door-out at the non-PCI referring centre, 30 minutes for transportation by EMS and 30 minutes for door-to-balloon at the receiving PCI centre so that patients within 30 minutes of a PCI-centre would be eligible.

The third step required the use of prehospital 12-lead ECG to identify STEMI in the field. The third step implemented the capability to transfer directly from the field and notify the receiving centre in advance of arrival[14]. This was the last step in the development of the regional system because many of the supporting infrastructures for inter-hospital transfer such as centralized coordination, emergent transfer protocols and target times were similar. In order to identify

STEMIs, EMS required equipment upgrades and paramedic training. Also required were protocols for the EMS authorizing bypass of nearest emergency departments for direct transport to a PCI-centre, direct communication and activation of the PCI-centre cath lab and direct admission to the cath lab upon admission from EMS. STEMI patients identified in the field were eligible for direct transport to the nearest regional cath lab for PCI, perhaps even bypassing the nearest ED, provided that transport to the PCI-centre would not exceed 60 minutes.

The capability for direct transfer — the third and final step in Ontario's regional system to increase access to PCI — provides the greatest potential reduction in ischemic times. Direct field transfers only need to drive to the PCI-centre. Time is not spent in the ED of a non-PCI centre, arranging for transport and/or completing a second transport. In order to save time, prehospital identification and advanced notification of the receiving centre is required for direct routing of STEMI patients to centres with PCI capacity.

Ontario has eighteen RCCCs; fourteen are also PCI centres, either full service (PCI and cardiac surgery) or stand-alone PCI centres. As of 2010, the CCN reported that all eleven PCI centres with full service programs in Ontario had regional 24/7 operations, regional transport/inter-hospital transfer capability, and EMS triage capability; of the three stand-alone PCI centres, only one provided 24/7 operations, regional transport/inter-hospital transfer capability and EMS triage capability[45]. Although the CCN is committed to increasing access to timely PCI, Patel et al concluded that, in 2006, almost 30% of Ontarians lived beyond timely access to a PCI-centre[15]. However, timely access was defined by transport distance and, therefore, it represented the best-case scenario. As previously stated, actual use of PCI was very low before the CCN began regionalizing care. Although it is expected that access to PCI has increased over the years, there has been no published information to confirm this or characterize the magnitude of improvement.

1.7 THE ROLE OF FIBRINOLYSIS

Direct transfer from the field to a PCI centre cannot be implemented in all jurisdictions as some 30% of the Ontario population are beyond timely access to PCI[15]. STEMI patients residing in these areas rely on fibrinolysis for timely reperfusion.

The CCN recognized the important role of fibrinolysis in two of their recommendations, even though much of their policy was aimed at increasing access to urgent PCI. First, fibrinolysis was recommended in patients who present to a hospital within 12 hours of symptom onset and who cannot receive primary PCI within 90 minutes of hospital admission, or for whom PCI is contraindicated[14]. Second, careful consideration for fibrinolysis was recommended in all patients who arrive to a hospital within 2 hours of symptom onset[14] as there is a particular benefit derived from very early reperfusion in this group[3,24,37,38].

Prehospital identification and advanced notification of the receiving centre may still improve patient outcomes in settings beyond timely access to PCI. Earlier activation of STEMI thrombolysis protocols at the receiving centre can theoretically help reduce hospital delays. Therefore, in both jurisdictions within and beyond a 60 minute transport to a PCI-centre, prehospital identification and advanced activation may be a critical capability for the reduction in ischemic time and, by association, mortality and morbidity.

1.8 PREHOSPITAL 12-LEAD ECG FOR THE IDENTIFICATION OF STEMI

Prehospital identification is not possible without a 12-lead electrocardiogram (ECG). A 12-lead ECG measures the electrical activity of the heart over time using 10 electrodes, or leads, that are attached across the thorax, on the arms and on the legs to produce 12 different electrical tracings. A 12-lead ECG is necessary to identify a STEMI. However, some EMS in the province are not able to provide 12-lead ECG and therefore only have basic monitoring capability with a 3-lead ECG. The 3-lead ECG cannot identify a STEMI. As EMS vehicles have traditionally carried only 3-lead ECGs and, thus, EMS were traditionally not involved in the immediate identification of a STEMI. Operation and interpretation of the 12-lead ECG also requires special training. In Ontario, primary care paramedics and advanced care paramedics require continuing education in order to interpret 12-lead ECGs. Interpretation can be completed by paramedic with additional education, computer interpretation or by a physician via telemetry. Telemetry allows remote data transmission of a 12-lead ECG from the EMS to the cardiologist for interpretation.

Prehospital 12-lead ECG has been shown to be accurate in identifying STEMIs[46] and associated with faster reperfusion times[47,48] and reduced mortality[48] for STEMI patients receiving fibrinolysis. It may also reduce door-to-balloon time[49] and mortality[50] for STEMI patients receiving PCI.

Although prehospital 12-lead ECG may reduce time to treatment and mortality, upgrading to a system utilizing 12-lead ECG may be costly. In addition to the cost of the 12-lead ECG unit, training will need to be given to EMS personnel so that they are able to identify and/or interpret a 12-lead ECG reading. As well, EMS personnel may require additional training in advanced life support for extended ambulance transport. Downstream resource use costs will likely include the hospitalization costs of PCI and fibrinolysis as prehospital identification and advanced notification of the receiving centre is likely to increase access to either primary reperfusion method. Infrastructure costs are also likely; a centralized, systematic and continuous monitoring of care pathways and patient outcomes is necessary for performance and progress over time. However, there may also be further costs or, even, further savings. Savings may include decreased utilization of health care resources following prehospital 12-lead ECG if it in-

creases access to primary PCI as patients treated with PCI have shown to have lower revascularization rates compared to those treated with fibrinolysis[51]. Increased access to primary PCI would similarly result in savings from decreased hospitalizations due to reductions in reinfarction and stroke as evidence has shown PCI to reduce both reinfarction and stroke over fibrinolysis[39,40,51,52].

The Ontario Health Technology Assessment Committee (OHTAC) initially estimated the prehospital-specific budget impact of the PCI regional network recommended by the CCN. First-year and one-time EMS-related expenditures were estimated to be $224 million while the annual base budget was estimated at $99 million[53]. However, the total capital costs still required today are significantly less as many communities have already implemented EMS 12-lead ECG programs on their own accord.

In summary, for STEMI patients, longer ischemic times are associated with excess mortality[4,6,9,10,17–19,23,37]. Therefore, the goal of treatment is the rapid reperfusion of blood to these ischemic areas[23,30]. Of the two widely used primary treatments, primary PCI is superior to fibrinolysis[12]; however, PCI is also associated with increased delays to treatment[4,6,9,10]. Therefore, primary PCI is recommended in patients who can receive it within 90 minutes of first medical contact[30]. To facilitate wider access to primary PCI, Ontario embarked on a regional network of PCI-centres and non-PCI centres[14]. Critical to the success of this network and critical to reducing treatment delays may be the ability to identify a STEMI in the field by EMS using 12-lead ECG and notify the receiving centre. Previous systematic reviews have suggested a reduction in treatment delay and mortality in systems that use prehospital 12-lead ECG[47–50]. However, there is little evidence of the joint health and cost consequences following prehospital identification with 12-lead ECG vs. no prehospital identification.

1.9 THESIS OBJECTIVES

The purpose of this thesis is to estimate the economic impact following different prehospital management strategies of STEMI patients in Ontario. The objectives of this thesis include:

1. Review the published literature comparing the short-term mortality, first medical contact-to-reperfusion time and door-to-reperfusion time of prehospital identification with 12-lead ECG and advanced notification compared to no prehospital identification and no advanced notification in STEMI patients received by EMS.

2. Review the published literature comparing the economic efficiency of prehospital identification with 12-lead ECG and advanced notification to no prehospital identification and no advanced notification in STEMI patients who are received by EMS.

3. Determine the cost-effectiveness of prehospital identification with 12-lead ECG and advanced notification at the receiving centre compared to a strategy of no prehospital identification and no

advanced notification in chest pain patients received by EMS with confirmed STEMI in bypass eligible and bypass ineligible patients. Bypass eligibility was defined as a transport distance from pick-up to the nearest RCCC with PCI capability (PCI-centre) less than 60km.

2

LITERATURE REVIEW

This chapter provides a review of the literature on the effectiveness and cost-effectiveness of prehospital 12-lead ECG and advanced notification compared to no prehospital identification and no notification.

2.1 EFFECTIVENESS OF PREHOSPITAL IDENTIFICATION WITH 12-LEAD ECG AND ADVANCED NOTIFICATION

The effectiveness of prehospital identification with 12-lead ECG and advanced notification must first be demonstrated before any economic evaluation is performed. Economic evaluations presume effectiveness of the health technology of interest; decision makers are not interested in the efficient provision of services that are less effective compared to standard practice[54].

In patients who receive fibrinolysis, previous reviews have found a reduction in mortality and door-to-needle time with prehospital identification with 12-lead ECG[47,48]. However, the mortality estimate originated from just one included study and the door-to-needle time showed heterogeneity, perhaps due to large differences in baseline times which themselves may be due to the differences in study settings. While the use of prehospital identification with 12-lead ECG and advanced notification may benefit patients who receive fibrinolysis, it may also benefit patients by increasing access to timely PCI[55]. Previous literature reviews have found that prehospital identification with 12-lead ECG and advanced notification was associated with a reduction in door-to-balloon times[49,50]. However, the door-to-balloon time excludes important prehospital time. A more relevant performance measure for the system may be first medical contact-to-reperfusion time; for patients treated with PCI, this would be a first medical contact-to-balloon time.

A review of prehospital triage also found a statistically significant mortality reduction associated with prehospital identification with 12-lead ECG and advanced notification[50]. Although a statistically significant mortality reduction was found, the precision around the point estimate was very low. In addition, the review included studies investigating prehospital combination fibrinolysis with facilitated PCI[50] — half-dose fibrinolysis followed by immediate transfer for PCI. However, in Ontario, prehospital fibrinolysis is not used and facilitated PCI is not common. Previous reviews[47–50] included few studies yet there remain many additional published studies[55–76].

The objective of the current review was to evaluate the short-term mortality, first medical contact-to-reperfusion time, door-to-balloon time and door-to-needle time following prehospital identification with 12-lead ECG and advanced notification compared to no prehospital identification and no advanced notification in STEMI patients received

by EMS. The analysis was stratified by the type of primary reperfusion treatment received: PCI or fibrinolysis.

2.1.1 *Methods*

2.1.1.1 *Literature search*

A literature search was undertaken for the purposes of locating clinical studies assessing prehospital identification with 12-lead ECG and advanced notification. A search strategy was constructed using controlled vocabulary and keywords focusing on the concepts of "electrocardiogram", "advanced notification", "emergency medical services" and "myocardial infarction". The search strategy was limited to English language publications and studies of humans. Separate strategies were adapted depending on the database searched. The search strategies are presented in the Appendix A.1.1. The following bibliographic databases were searched: EMBASE via OVID (1988 to 2012 week 31); PUBMED (1988 to 2012 week 31); and Cochrane Central Register for Controlled Trials via WILEY (no date restrictions). The search was also restricted to studies published after 1988 in PUBMED and EMBASE. It was in 1988 that the landmark Second International Study of Infarct Survival-2 trial (ISIS-2) showed the benefits of streptokinase, aspirin and combination streptokinase with aspirin in patients with AMI[25].

2.1.1.2 *Inclusion criteria*

Studies were included if they met the following inclusion criteria:

- comparative observational or randomized study design,
- patients with STEMI treated with primary PCI or fibrinolysis,
- "intervention" group included prehospital identification with 12-lead ECG and advanced notification,
- "control" group included basic cardiac monitoring (3-lead ECG),
- outcomes included short-term mortality (in-hospital or 30-day), door-to-balloon/needle time or first medical contact-to-balloon/needle time.

2.1.1.3 *Exclusion criteria*

Studies were excluded for the following reasons:

- "control" group included no prehospital identification, advanced notification or activation protocols, or transportation to a destination other than the local ED,
- either cohort group made use of prehospital fibrinolysis, where the patient was eligible,

- either cohort group included walk-ins (eg. walk-ins are patients who transport themselves to the ED and thus are not transported via EMS),
- a study of less than 30 participants.

2.1.1.4 *Outcomes*

Outcomes of interest included:

- Short-term mortality (mortality within 30 days),
- Mean first medical contact-to-balloon delay (in minutes) defined as EMS contact or, if unavailable, 911 call or EMS ECG reading,
- Mean first medical contact-to-needle delay (in minutes) defined as EMS contact or, if unavailable, 911 call or EMS ECG reading,
- Mean door-to-balloon time (in minutes) defined as the time from first hospital admission to balloon inflation.
- Mean door-to-needle time (in minutes) defined as the time from hospital admission to needle insertion.

2.1.1.5 *Selection process*

Titles and abstracts were assessed for full-text retrieval using a predetermined screening form (Appendix A.1.2) that mirrored the inclusion and exclusion criteria. The full texts of all included abstracts were screened for final inclusion using the same screening criteria.

2.1.1.6 *Data abstraction*

The following study characteristics were abstracted:

- study design,
- country of origin,
- jurisdiction size,
- protocol for ECG interpretation,
- protocol for advanced notification and/or activation,
- presence of bypass eligibility,
- protocol for EMS transport destination,
- presence of inter-hospital transfer,
- patient inclusion and exclusion criteria.

2.1.1.7 *Quality assessment*

Study quality was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[77]. GRADE is a system of rating the quality of medical evidence. Evidence can be high quality (further research is very unlikely to change the confidence in the estimate), moderate quality (further research is likely to have an important impact on the confidence in the estimate and may change the estimate), low quality (further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate) and very low quality (any estimate of effect is very uncertain)[77].

Observational studies begin with a low quality rating; randomized studies begin with a high quality rating[77]. The quality of evidence can be upgraded or downgraded due to study limitations, inconsistency of results, indirectness of evidence, imprecision and/or reporting bias. GRADE gives an overall quality rating and individual quality ratings for each outcome. The overall quality is an assessment of "critical" outcomes. For this review, mortality within 30-days was considered "critical" while the first medical contact-to-balloon and door-to-balloon were considered "important".

2.1.1.8 *Data analysis*

For outcomes with non-significant chi-squared values for heterogeneity, pooled estimates were completed. All estimates were pooled using Review Manager 5.1.6 (Cochrane Collaboration). For short-term mortality (categorical), random-effects Mantel-Haenszel risk ratios were planned. For time differences (continuous), random effects inverse variance mean differences.

Where the mean and standard deviation were not reported, they were estimated using a previously proposed method by Hozo et al.[78]. Using simulation methods, they identified formulas that best estimate the mean when the sample size is less than or equal to 25 and greater than 25. For sample sizes greater than 25, the mean is best estimated by the median.

Formulas were also identified that best estimated the variance when the sample size was less than or equal to 25, 26-70 and greater than 70. For sample sizes greater than 70, the variance was best estimated by the range divided by 6. For sample sizes 25-70, the variance was best estimated by the range divided by 4.

2.1.1.9 *Sensitivity analyses*

Subgroup analyses were conducted for jurisdiction type. In regional jurisdiction areas, bypass of a non-PCI hospital is possible. This may be associated with greater reductions in door-to-balloon and system delays compared to local jurisdiction areas where all patients are presenting locally to the PCI centre. Subgroup analyses were also conducted for the protocols of advanced notification and activation; it was thought that different pathways to eventual cath lab/ED acti-

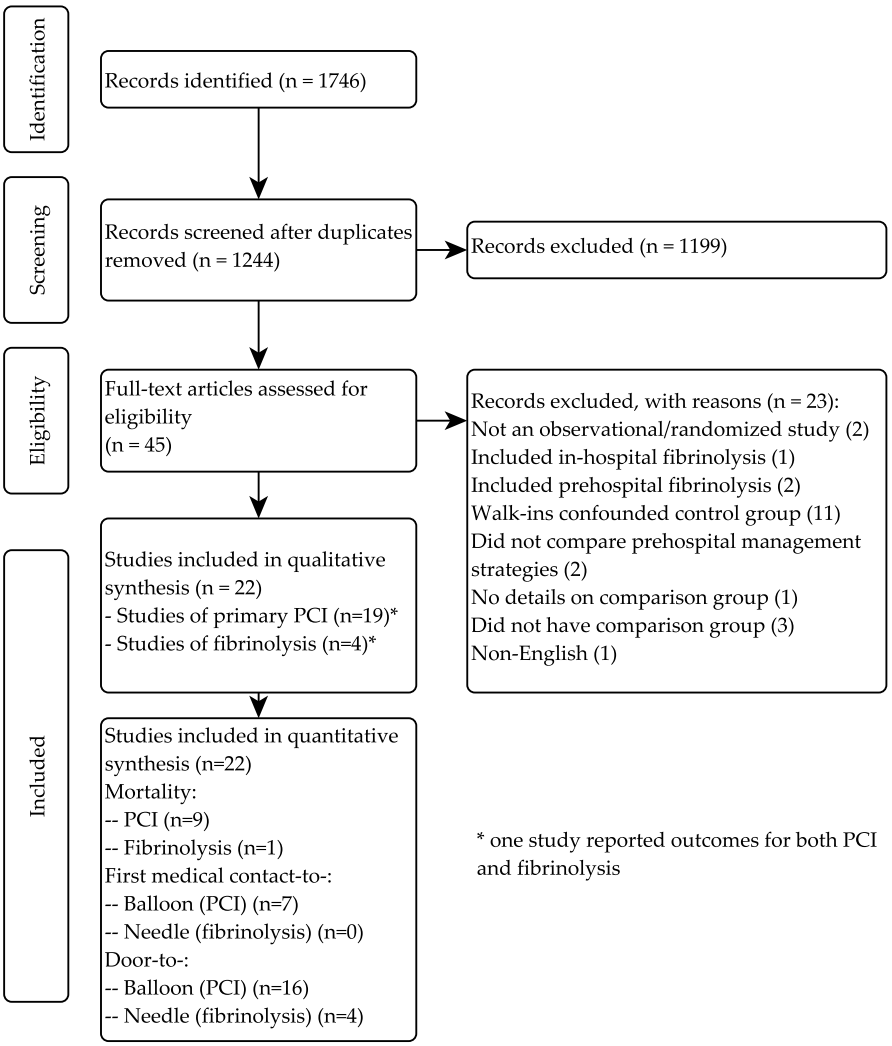


Figure 1: Flow diagram of study inclusion

vation may contribute to differences in outcomes. Jurisdictions that allowed for direct activation by the EMS may have had different outcomes compared to jurisdictions that required emergency physician consultation and/or cardiologist consultation.

2.1.2 *Literature search results*

A flow diagram of the literature search results is presented in Figure 1. After duplicates were removed, the initial search returned 1,244 unique citations. The full texts of 45 articles were screened[55–76,79–101]; 22 studies were included for final review[55–76] and 23 studies were excluded[79–101]. Reasons for exclusion included: not an observational or randomized study[79,80]; included patients who received in-hospital fibrinolysis[81]; used prehospital fibrinolysis[82,83]; confounded by walk-ins[84–94]; did not evaluate prehospital management strategies[95,96]; did not include any details on its comparison group[97]; did not have a comparison group[98–100] and not published in English[101].

It should be noted that one study reported outcomes for both patients who received primary PCI and fibrinolysis[55]. Therefore, while

there were 22 studies included for review, there were 19 studies of primary PCI and 4 studies of fibrinolysis (Figure 1).

2.1.2.1 *Post-hoc modifications*

Some trials only reported the inter-quartiles. In these cases, the minimum and maximum were estimated by extending the inter-quartiles by half the interquartile range.

In one included study, the sample sizes for the cohorts had to be inferred[55]. Canto et al. evaluated patients who received fibrinolysis, PCI or no medical intervention[55]. The sample sizes were inferred from the proportion of patients who received prehospital ECG, stratified by primary intervention received. This was different than the reported total number of patients who received PCI for the door-to-balloon time (n=5,103 vs. n=4,932) and the total number of patients who received fibrinolysis for the door-to-needle time (n=26,406 vs. n=26,559). Therefore, the sample size was scaled down using the same proportion of prehospital ECG to no prehospital ECG reported in the study until the sample sizes matched the reported totals. A much smaller sample size was reported for the in-hospital mortality estimate for patients who received PCI (n=2,895) and fibrinolysis (n=17,028) and therefore the sample sizes were also scaled down to match this number. While this practice had an effect on precision of the point estimate, it did not affect the point estimates themselves as they were reported directly.

In another study, the sample size for the historical controls was not given. Melville et al.[75] reported on 11 people in the intervention arm over a time period of three months. The time period for the historical controls was three years. It was assumed the rate of STEMI who were fibrinolyzed was comparable. Therefore, the sample size was estimated to be 132 participants.

2.1.2.2 *Characteristics of studies where patients received PCI*

STUDY SETTING Study characteristics of included studies are presented in Table 1. Nineteen studies included 15,803 participants. However, in one registry study, there were 4,931 participants with door-to-balloon times but only 2,894 participants with mortality outcomes. Only two studies were conducted in Canadian settings[59,66]. Ten of the studies were from the US[55–57,60,61,67,69,71,72]; two studies were from Denmark[68,70]; two from the Netherlands[62,64]; two from Australia[58,63]; and one from Italy[65].

Included study designs were varied: three registry studies[55,61,65]; four prospective observational studies with concurrent controls[56,58,62,63]; four prospective observational studies with historical controls[67,68,70,71]; five before-after cohort studies[57,59,60,64,66]; and three retrospective studies with concurrent controls[69,72,73]. About half of the studies assessed a regional system to some degree: six studies included the regional catchment of multiple PCI-centres[61,62,65,68,70,98]; four studies included the regional catchment of a single PCI-centre[58,59,63,66]; eight studies assessed the local catchment of a single PCI-centre[56,57,60,64,67,69,71,73]; and

Table 1: Characteristics of included studies in patients who received PCI (n=19)

STUDY	TYPE OF STUDY/SETTING	INTERVENTION GROUP	CONTROL GROUP	OTHER INCL/EXCLUSION	OUTCOMES
Canto, 1997[55] n=4,932 US	Registry study; Regional jurisdict'n of multiple PCI centres	Diagnosis: source unclear; Advanced notificat'n: protocol unclear; Bypass eligibility unclear; EMS transport protocol unclear,	Unclear. Likely EMS direct to local ED (PCI or non-PCI centre); Inter-hospital transfer excluded.	Incl: STEMI transported by EMS Excl: Inter-hospital transfer	In-hospital mortality, DTB, DTN
Diercks, 2009[61] n=7,098 US	Registry study; Regional jurisdict'n of multiple PCI centres	Diagnosis: source unclear; Advanced notificat'n: protocol unclear; Bypass eligibility unclear; EMS transport protocol unclear,	Unclear, likely EMS direct to local ED (PCI or non-PCI centre); Inter-hospital transfer likely eligible but not protocol driven.	Incl: STEMI transported by EMS to an ACTION hospital. Excl: pts not evaluated first in ED or cath lab, pts transferred to non-ACTION hospital	In-hospital mortality, DTB
Martinoni, 2011[65] n=1,529 Italy	Registry study; Regional jurisdict'ns of multiple-PCI centres	Diagnosis: cardiologist via telemetry, Advanced notificat'n: cath lab by cardiologist; Bypass eligible; EMS direct to cath lab.	EMS direct to ED of PCI centre	Incl: STEMI/LBBB, SO<12hrs, received by EMS, treated w/PCI. Excl: centres with >10 PCI in STEMI/year.	30-day mortality, FMCTB
van't Hof, 2006[62] n=454 Netherlands	Pros. study with concurrent controls (post-hoc trial analysis); Regional jurisdict'n of multiple PCI centres	Diagnosis: software; Advanced notificat'n: cath lab by EMS; Bypass eligible; EMS direct to cath lab.	EMS direct to local ED of non-PCI centre; Inter-hospital transfer to PCI centre	Incl: SO<6hrs, STEMI, received by EMS, treated w/PCI. Excl: age >80yrs, women $\geqslant$ 50yrs, prev thrombolysis, prev warfarin/acenocoumarol, contraindication to glycoprotein 2a/3b	30-day death
Carstensen, 2007[58] n=301 Australia	Prospective observat'l study with concurrent controls; Regional jurisdict'n of single PCI centre	Diagnosis: EP via telemetry; Advanced notificat'n: cath lab by EP; Bypass eligible; EMS direct to cath lab.	EMS direct to local ED (PCI/non-PCI centre), Inter-hospital transfer to PCI centre eligible	Incl: STEMI, SO<24hrs, received by EMS, treated w/PCI. Excl: cardiac arrest.	In-hospital mortality, DTB

STUDY	TYPE OF STUDY/SETTING	INTERVENTION GROUP	CONTROL GROUP	OTHER INCL/EXCLUSION	OUTCOMES
Brown, 2008 n=48 US	Prospective observat'l study with concurrent controls; Local jurisdict'n of single PCI centre	Diagnosis: paramedic and software; Advanced notificat'n: cath lab, source unclear; Bypass not applicable; EMS transport protocol unclear.	EMS direct to ED of PCI centre	Iincl: STEMI received by EMS, treated w/PCI. Excl: none stated.	In-hospital mortality, DTB
Hutchison 2009[63] n=229 Australia	Prospective observat'l study with concurrent controls; Regional jurisdict'n of single PCI centre	Diagnosis: paramedic and EP via telemetry; Advanced notfication: ED by EMS, cath lab by EP; Bypass eligible; EMS direct to cath lab.	EMS direct to local ED (PCI/non-PCI centre), Inter-hospital transfer to PCI centre eligible	Incl: STEMI/LBBB received by EMS, treated w/PCI. Excl: none stated.	DTB
Wall, 2000[71] n=77 US	Prospective study with historical controls; Local jurisdict'n of single PCI centre	Diagnosis: EP via telemetry; Advanced notificat'n: ED by EMS, cath lab by EP; Bypass not applicable; EMS direct to ED.	EMS direct to ED of PCI centre	Incl: STEMI patients received by EMS, treated w/PCI. Excl: None stated.	DTB
Terkelsen, 2005[70] n=76 Denmark	Prospective observat'l study with historical controls; Regional jurisdict'n of multiple PCI centres	Diagnosis: MD via telemetry or MD in ambulance; Advanced notificat'n: cath lab by EMS; Bypass eligible; EMS direct to cath lab.	EMS direct to local ED of non-PCI centre; Inter-hospital transfer to PCI centre.	Incl: STEMI pts received by EMS, treated w/PCI. Excl: SO>12hrs, PCI physician did not confirm STEMI, unconscious on arrival	In-hospital mortality, FMCTB, DTB
Sejersten, 2008[68] n=235 Denmark	Prospective observat'l study with historical controls; Regional jurisdict'n of multiple PCI centres	Diagnosis: cardiologist via telemetry; Advanced notificat'n: cath lab by cardiologist; Bypass eligible; EMS direct to cath lab.	EMS direct to local ED of non-PCI centre; Inter-hospital transfer to PCI centre	Incl: STEMI, SO<12hrs, received by EMS, treated w/PCI. Excl: none stated.	FMCTB, DTB

STUDY	TYPE OF STUDY/SETTING	INTERVENTION GROUP	CONTROL GROUP	OTHER INCL/EXCLUSION	OUTCOMES
Nestler, 2011[67] n=88 US	Prospective observat'l study with historical controls; Local jurisdict'n of single PCI centre	Diagnosis: paramedic; Advanced notificat'n: cath lab by EMS; Bypass not applicable; EMS direct to cath lab.	EMS direct to ED of PCI centre	Incl: STEMI received by EMS, treated w/PCI. Excl: none stated.	FMCTB, DTB
LeMay, 2006[66] n=121 Canada	Before-after cohort study; Regional jurisdict'n of single PCI centre;	Diagnosis: paramedic; Advanced notificat'n: cardiology team by EMS; Bypass eligible, EMS direct to cath lab.	EMS direct to local ED (PCI/non-PCI centre); Inter-hospital transfer to PCI centre eligible; 12-lead ECG possible but no Advanced notificat'n.	Incl: STEMI, SO<12hrs, received by EMS, treated w/PCI. Excl: SO>12hrs, absent vital signs, severe hemodynamic instability, LBBB.	In-hospital mortality, DTB
van de Loo, 2006[64] n=137 Netherlands	Before-after cohort study; Local jurisdict'n of a single PCI centre	Diagnosis: paramedic; Advanced notificat'n: ICU and PCI team by EMS but not protocol driven; Bypass not applicable; EMS direct to cath lab.	EMS direct to ED of PCI centre	Incl: STEMI/LBBB/cardiac arrest/STEMI+cardiogenic shock; received by EMS and treated w/PCI. Excl: none stated.	In-hospital mortality, FMCTB, DTB
Dhruva, 2007[60] n=49 US	Before-after cohort study; Local jurisdict'n of single PCI centre	Diagnosis: software, paramedic and cardiologist via telemetry; Advanced notificat'n: cardiologist by EMS, cath lab by cardiologist; Bypass not applicable; EMS direct to cath lab.	EMS to ED of PCI centre	Incl: STEMI received by EMS, treated w/PCI. Excl: none stated.	In-hospital mortality, DTB
Camp-Rogers, 2011[57] n=53 US	Before-after cohort study; Local jurisdict'n of single PCI centre	Diagnosis: software and EP; Advanced notificat'n: ED by EMS, cath lab by EP; Bypass not applicable; EMS direct to cath lab.	EMS direct to ED of PCI centre; Inter-hospital transfer excluded.	Incl: STEMI received by EMS, treated w/PCI. Excl: inter-hospital transfer, significant treatment delay (undefined).	FMCTB, DTB

STUDY	TYPE OF STUDY/SETTING	INTERVENTION GROUP	CONTROL GROUP	OTHER INCL/EXCLUSION	OUTCOMES
Cheskes, 2011[59] n=175 Canada	Before-after cohort study; Regional jurisdict'n of single PCI centre	Diagnosis: software and paramedic; Advanced notificat'n: cath lab by EMS; Bypass eligible; EMS direct to cath lab.	Prehospital ECG, EMS direct to local ED (PCI/non-PCI centre); Inter-hospital transfer eligible	Incl: STEMI/LBBB, received by EMS, treated w/PCI. Excl: morbid obesity (>200kg).	FMCTB
Swor, 2006[69] n=100 US	Retrospective study with concurrent controls; Local jurisdict'n of single PCI centre	Diagnosis by software; Advanced notificat'n: AMI team by EP via paramedic radio report; Bypass not applicable; EMS direct to ED.	EMS direct to ED of PCI centre	Incl: STEMI received by EMS, treated w/PCI. Excl: inter-hospital transfer.	DTB
Strauss, 2007[73] n=35 US	Retrospective study with concurrent controls; Local jurisdiction of a single PCI centre	Diagnosis: paramedic; Advanced notificat'n: cath lab and ED by EMS; Bypass not applicable; EMS direct to ED and then to cath lab	EMS direct to ED of PCI centre	Incl: STEMI, SO<12hrs, received by EMS, treated with PCI	DTB
Yongquist, 2008[72] n=56 US	Retrospective study with concurrent controls; jurisdict'n size unclear; single PCI centre; US	Diagnosis: software during weekday, EP after ED arrival during night/weekend; Advanced notificat'n: cath lab by EMS during weekday, ED activation during night/weekend; Bypass eligibility unclear; EMS direct to cath lab during weekday, direct to ED during night/weekend	EMS direct to ED of PCI centre	Incl: STEMI received by EMS, treated w/PCI. Excl: none stated.	DTB, mortality (follow up unclear)

acute myocardial infarction (AMI); door-to-balloon (DTB); door-to-needle (DTN); emergency department (ED); emergency medical services (EMS); emergency physician (EP); first medical contact-to-balloon (FMCTB); intensive care unit (ICU); left bundle branch block (LBBB); percutaneous coronary intervention (PCI); symptom onset (SO); ST-segment elevation myocardial infarction (STEMI)

for one study the catchment area was unclear but it involved a single PCI-centre[72].

TREATMENT PROTOCOLS Most of the included studies relied on additional interpretation of ECG in addition to built-in software interpretation. ECG interpretation and STEMI identification was performed by paramedics in six studies[56,59,64,66,67,73]; software only in two studies[62,69]; cardiologist via telemetry in two studies[65,68]; emergency physician via telemetry in three studies[57,58,71]; paramedic and emergency physician, via telemetry, in one study[63]; paramedic and cardiologist, via telemetry, in one study[60]; and ambulance physician, general practitioner or emergency physician, via telemetry, in one study[70]. In one study, software only was used during the weekday while on nights/weekends the emergency physician made the diagnosis after ED arrival[72]. Finally, in three studies the protocol was not clear[55,56,61].

Protocols for advanced notification also varied. The cath lab was activated by EMS in seven studies[59,62,64,66,67,70,73]; by a cardiologist in three studies[60,65,68]; and by an emergency physician in four studies[57,58,63,71]. In one study, the emergency physician activated the cath lab based solely on paramedic [and software] interpretation via radio communication[69]. In another study, the EMS activated the cath lab directly during weekdays while the emergency physician activated it after ED arrival on nights/weekends[72]. Finally, in three studies the protocol was not clear[55,56,61].

Most studies with regional catchments had a protocol for bypassing the nearest local hospital for a regional PCI centre[58,59,62,63,65,66,68,70]; however, inter-hospital transfer from a non-PCI centre to a PCI centre was explicitly excluded in four studies[55,57,69,98]. In two studies with regional catchments, the protocol was not clear[61,72]. All studies of local catchments did not assess bypass patients[56,57,60,64,67,69,71,73].

The EMS transported patients directly to the cath lab in twelve studies[57–60,62–68,70] and to the ED in three studies[69,71,73]. In another study, EMS transported patients directly to the cath lab during weekdays and to the ED on nights/weekends[72]. Finally, in three studies the protocol was unclear[55,56,61].

Generally, eligibility criteria was appropriately developed and applied in all studies. All studies included STEMI patients received by EMS who were later treated with PCI. Symptom onset duration was restricted to 6 hours in one study[62]; 12 hours in five studies[55,66,68,70,73]; and 24 hours in one study[58] while it was not restricted in the remaining studies.

CHARACTERISTICS OF OUTCOMES The median and interquartile range was reported in thirteen studies[55,58,59,61–63,65–68,70,71,73] while five studies reported the mean and standard deviation[56,57,60,64,72]. In one study, only medians were reported along with the entire population's standard deviation[69].

It was not clear whether the door-to-balloon time included the first hospital door for inter-hospital transfers in three studies[61,63,66]; how-

ever, it likely did not include the first hospital door. This omission would favour the no prehospital cohort group.

2.1.2.3 *Characteristics of studies where patients received fibrinolysis*

STUDY SETTING Study characteristics of included studies are presented in Table 2. Four studies included 17,313 participants; however, in one registry study[55], there were 26,558 participants with door-to-needle times but only 15,982 participants with mortality outcomes. Three studies were from the US[55,74,75] and one was from the UK[76].

Included study designs were varied: one registry study[55]; two prospective observational studies with historical controls[74,75]; and one before-after cohort study[76]. All studies assessed a local jurisdiction but some assessed multiple jurisdictions: two studies assessed single centres[75,76]; one study assessed multiple centres[55]; and it was not clear in one study[74].

TREATMENT PROTOCOLS ECG interpretation and STEMI identification protocols were performed by paramedics in one study[76]; paramedic and emergency physician via telemetry in one study[74]; ED nurse via telemetry in one study[75]; and in one study it was not clear[55].

Fibrinolysis was administered in the coronary care unit (CCU) in two studies[75,76]; advanced notification of the CCU was performed by the EMS in one study[75] and in the other it was not clear[76]. Fibrinolysis was administered in the ED in one study[74]; advanced notification of the ED or emergency physician was made by the EMS. Finally, the site of administration and any associated advanced notification protocols were not clear in one study[55].

The EMS transported patients directly to the ED in one study[74] and to the CCU in two studies[75,76]. In one study, transport protocols were not clear[55].

Generally, eligibility criteria was appropriately developed and applied in all studies. All studies included chest pain patients but reported on those with AMI. Fibrinolysis was limited to eligibility criteria; however, eligibility criteria was not explicitly reported.

CHARACTERISTICS OF OUTCOMES The median and interquartile range of the door-to-needle was reported in one study[55] while three studies reported the mean and standard deviation[74–76]. No studies reported the first medical contact-to-needle time and only one study reported mortality[55].

2.1.3 *Data synthesis*

2.1.3.1 *Quantitative results*

SHORT-TERM MORTALITY In patients who received PCI, mortality within 30 days was reported in nine of nineteen studies[55,56,58,61,62,65,66,70,72] that included 3,114 participants in the prehospital identification and advanced notification group compared to 9,612 in the comparison

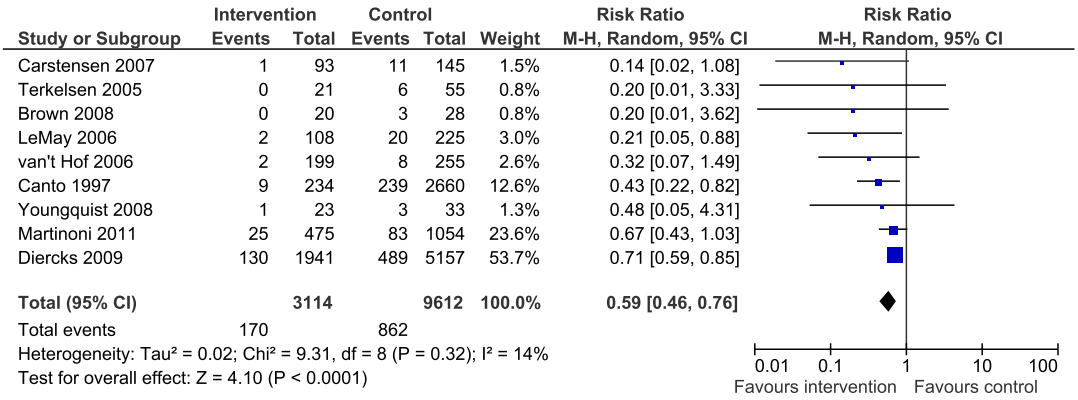


Figure 2: Mortality within 30 days in patients treated with primary PCI. Prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control).

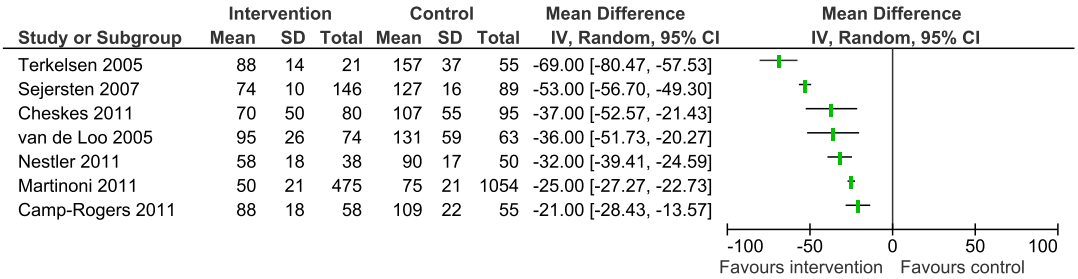


Figure 3: The mean and mean difference in first medical contact-to-balloon time for prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control). Negative numbers indicate a reduction in delay (favours intervention).

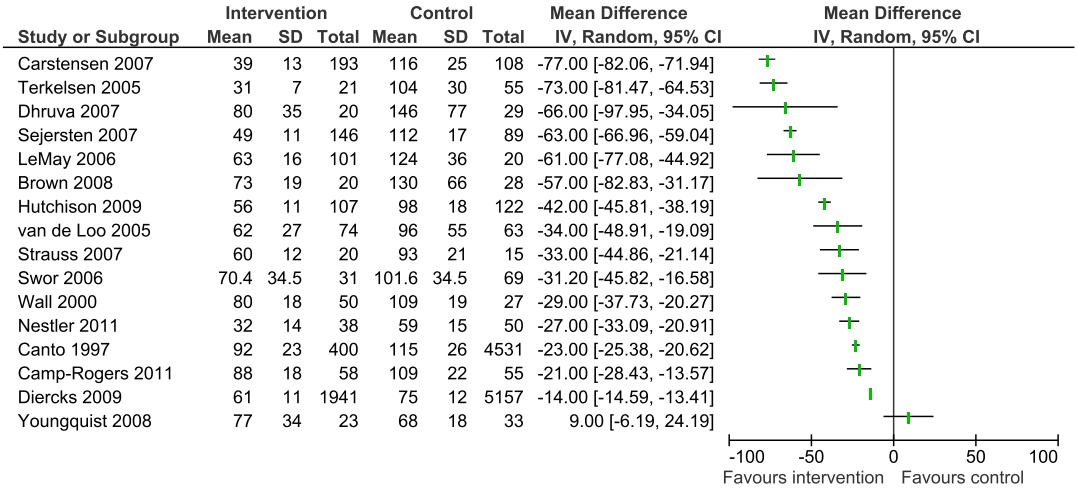


Figure 4: The mean and mean difference in door-to-balloon time for prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control). Negative numbers indicate a reduction in delay (favours intervention).

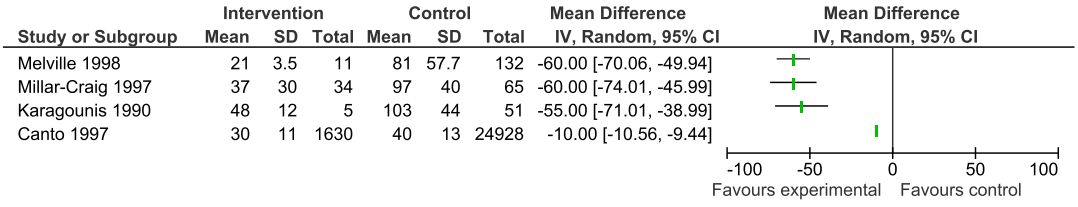


Figure 5: The standardized mean difference in door-to-needle time for prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control). Negative numbers indicate a reduction in delay (favours intervention).

Table 2: Characteristics of included studies where patients received fibrinolysis (n=4)

STUDY	TYPE OF STUDY/SETTING	INTERVENTION GROUP	CONTROL GROUP	OTHER INCL/EXCLUSION	OUTCOMES
Canto, 1997[55] n=17,026 US	Registry study; Regional jurisdict'n of multiple centres	Diagnosis: source unclear; Adv. Notificat'n: protocol unclear; Bypass eligibility unclear; EMS transport protocol unclear,	Unclear. Likely EMS direct to local ED (PCI or non-PCI centre); Inter-hospital transfer excluded.	Incl: STEMI transported by EMS Excl: Inter-hospital transfer	In-hospital mortality, DTB, DTN
Karagounis, 1990[74] n=56 US	Prospective observat'l study with historial controls; Jurisdict'n size not clear;	Diagnosis: paramedic & EP via telemetry; Adv. Notificat'n: EP/ED by EMS; Bypass not applicable; EMS direct to ED.	EMS direct to ED	Incl: chest pain with AMI; Excl: none stated.	DTN
Melville, 1998[75] n=143 UK	Prospective observat'l study with historical controls; Local jurisdict'n of single centre	Diagnosis: ED nurse via telemetry; Adv. Notificat'n: ED nurse by EMS, no mention of CCU activation; Bypass not applicable; EMS direct to CCU of same hospital.	EMS direct to ED	Incl: chest pain with STEMI; Excl: none stated.	DTN
Millar-Craig, 1997[76] n=99 US	Before-after cohort study; Local jurisdict'n of single centre	Diagnosis: paramedic; Adv. Notificat'n: CCU via EMS; Bypass not applicable EMS direct to CCU	EMS direct to ED	Incl: chest pain with AMI; Excl: none stated.	DTN

acute myocardial infarction (AMI); door-to-balloon (DTB); door-to-needle (DTN); emergency department (ED); emergency medical services (EMS); emergency physician (EP); symptom onset (SO); ST-segment elevation myocardial infarction (STEMI)

group. Prehospital identification with 12-lead ECG and advanced notification led to a 41% relative risk reduction in mortality over no prehospital identification (9 studies; n=12,726; RR 0.59; 95%CI=0.46–0.76; p<0.0001) (Figure 6). Heterogeneity was found to be low (χ^2=9.31; df=8; p=0.32; I^2=14%) (Figure 6). The three registry studies[55,61,65] accounted for 90% of the weight; they also reported the smallest effect sizes (Figure 6). The remaining 10% was shared by six studies that reported two or less events in the prehospital identification and advanced notification cohort and one study where the sample sizes had to be imputed. The reduction in short-term mortality following prehospital identification with 12-lead ECG is robust to their exclusion in the analysis (3 studies; n=11,431; RR 0.67; 95%CI=0.56–0.81; p<0.0001; I^2=6%).

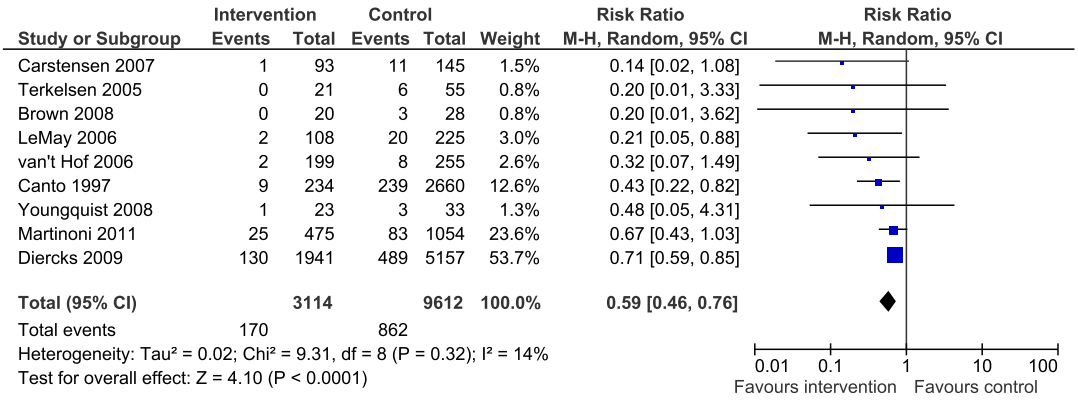


Figure 6: Mortality within 30 days in patients treated with primary PCI. Prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control).

In patients who received fibrinolysis, mortality within 30 days was reported in just one of four studies[55] and it was reported for in-hospital mortality. The study included 1,044 participants in the prehospital identification group and 15,982 participants in the comparison group. Prehospital identification with 12-lead ECG and advanced notification led to a 29% reduction in in-hospital mortality (RR 0.71; 95%CI=0.54–0.93; p=0.01).

FIRST MEDICAL CONTACT-TO-BALLOON TIME First medical contact-to-balloon time was reported in seven of nineteen studies[57,59,64,65,67,68,70] that included 892 participants in the prehospital identification and advanced notification group compared to 1,461 in the comparison group. Very large heterogeneity precluded any pooled quantitative analysis of first medical contact-to-balloon times (χ^2=208.17; df=6; p<0.00001; I^2=97%). Although heterogeneity was very large, all studies reported significant reductions in the mean first medical contact-to-balloon time with prehospital identification with 12-lead ECG and advanced notification compared to no prehospital identification and no advanced notification (Figure 7). The smallest mean reduction was 21 minutes while the largest mean reduction was 69 minutes (Figure 7).

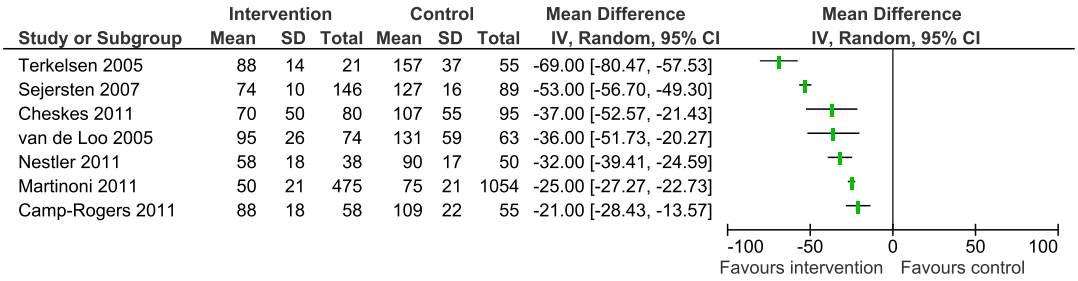


Figure 7: The mean and mean difference (minutes) in first medical contact-to-balloon time for prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control). Negative numbers indicate a reduction in delay (favours intervention).

DOOR-TO-BALLOON TIME Door-to-balloon times were reported in sixteen of nineteen studies[55–58,60,61,63,64,66–73] that included 3,243 participants in the prehospital identification and advanced notification group compared to 10,451 in the comparison group. Very large heterogeneity precluded any pooled quantitative analysis of door-to-balloon times (χ^2=1,607.59; df=15; p<0.00001; I^2=99%). Prehospital identification with 12-lead ECG and advanced notification was associated with significant reductions in mean door-to-balloon in all studies except one (Figure 8); a 9 minute mean increase was reported for this study[72]. The largest mean reduction was 77 minutes.

DOOR-TO-NEEDLE TIME Door-to-needle times were reported in four of four studies[55,74–76] that included 1,680 participants in the prehospital identification group compared to 25,176 participants in the comparison group. Prehospital identification with 12-lead ECG and advanced notification was associated with a mean reduction in door-to-needle time in all studies (Figure 9). However, heterogeneity was found to be very high (χ^2=173.18; df=3; p<0.00001; I^2=98%) (Figure 9). Heterogeneity could be entirely explained by the registry study with very high precision resulting from a sample size of 26,558[55]. This registry reported a much smaller mean reduction (−10 minutes; 95%CI= −10.56 to −9.44 minutes).

2.1.3.2 *Sensitivity results*

JURISDICTION TYPE No subgroup differences were detected when first medical contact-to-balloon time was grouped by jurisdiction type (χ^2=2.35; df=1; p=0.12; I^2=57.5%) (Figure 10a). The heterogeneity was very large for the regional jurisdiction subgroup (4 studies; n=2,015; χ^2=197.37; df=3; p<0.00001; I^2=98%) while it was modestly reduced for the local jurisdiction subgroup (3 studies; n=338; χ^2=5.47; df=2; p<0.06; I^2=63%) (Figure 10a). In the local jurisdiction subgroup, first medical contact-to-balloon was reduced by a mean 28.44 minutes (95%CI=−37.41 to −19.47 minutes) following prehospital identification with 12-lead ECG and advanced notification compared to no prehospital identification and no advanced notification.

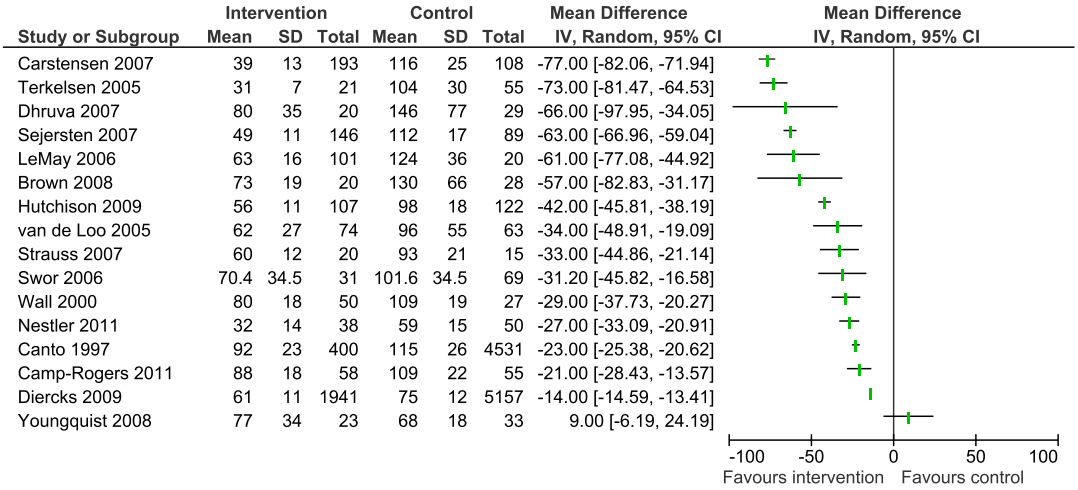


Figure 8: The mean and mean difference in door-to-balloon time (minutes) for prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control). Negative numbers indicate a reduction in delay (favours intervention).

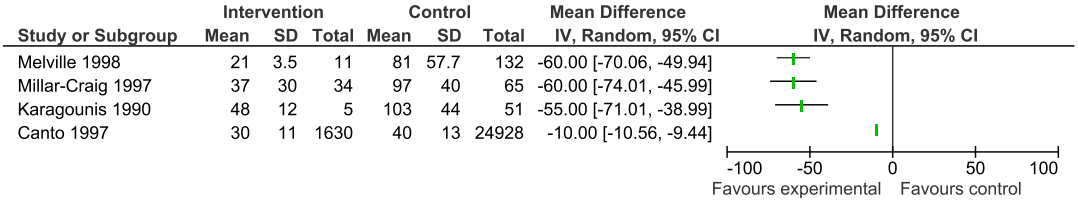
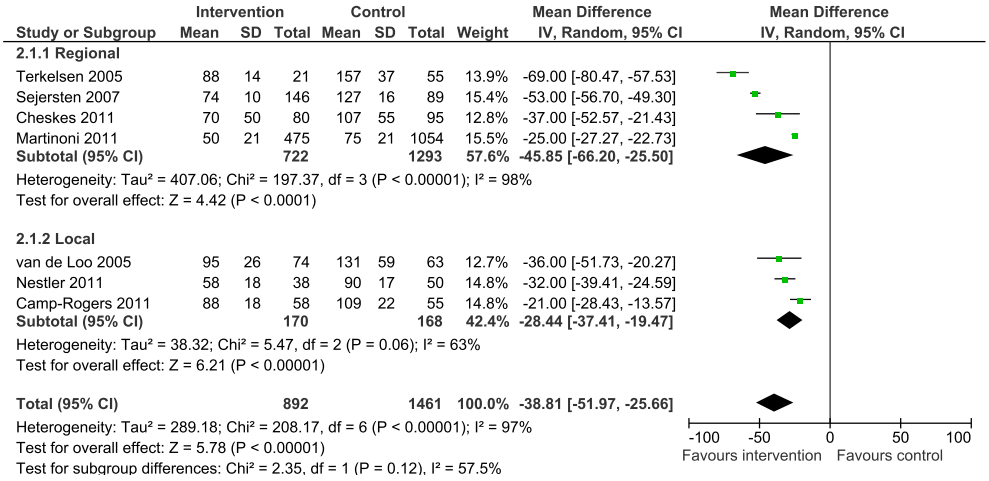


Figure 9: The mean difference in door-to-needle time (minutes) for prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control). Negative numbers indicate a reduction in delay (favours intervention).

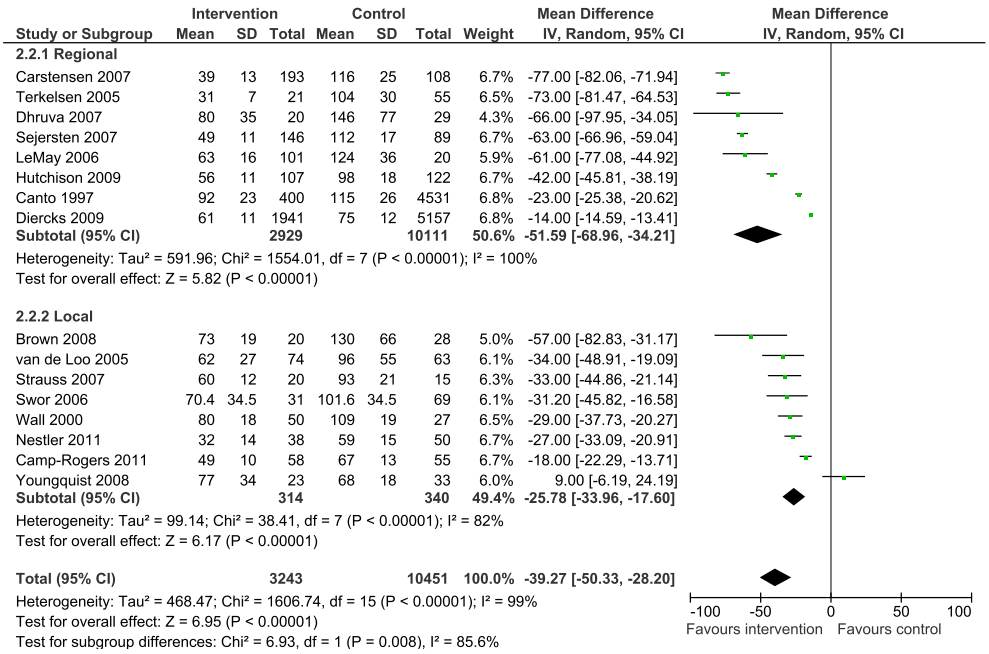
Subgroup differences were also detected when door-to-balloon time was grouped by jurisdiction type (χ^2=6.93; df=1; p<0.008; I^2=85.6%) (Figure 10b). However, heterogeneity was very large for the regional jurisdiction subgroup (8 studies; n=13,040; χ^2=1,554.01; df=7; p<0.00001; I^2=100%) and the local jurisdiction subgroup (8 studies; n=654; χ^2=38.41; df=7; p<0.00001; I^2=82%) (Figure 10b).

CATH LAB ACTIVATION PROTOCOL No subgroup differences were detected when first medical contact-to-balloon time was grouped by cath lab activation protocol (χ^2=5.23; df=2; p=0.07; I^2=61.7%) (Figure 11a). The heterogeneity remained very large in studies that employed cath lab activation by cardiologist (3 studies; n=1,939; χ^2=160.02; df=2; p<0.00001; I^2=99%) or EMS (3 studies; n=301; χ^2=28.85; df=2; p<0.00001; I^2=93%); there was only one study that employed cath lab activation by emergency physician (Figure 11a)

Subgroup differences were detected when door-to-balloon time was grouped by cath lab activation protocol (χ^2=71.21; df=3; p<0.00001; I^2=95.8%) (Figure 11b). There was no heterogeneity in studies that employed cath lab activation by cardiologist (2 studies; n=284; χ^2=0.003; df=1; p=0.86; I^2=0%); prehospital identification with 12-lead ECG and advanced notification led to a mean 63.05 minute reduction in door-

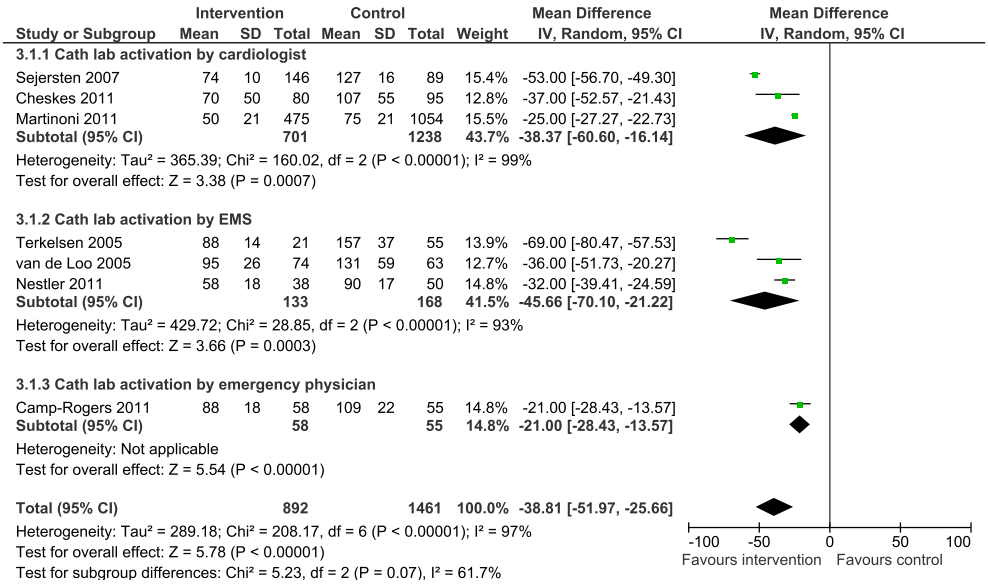


(a) First medical contact-to-balloon time

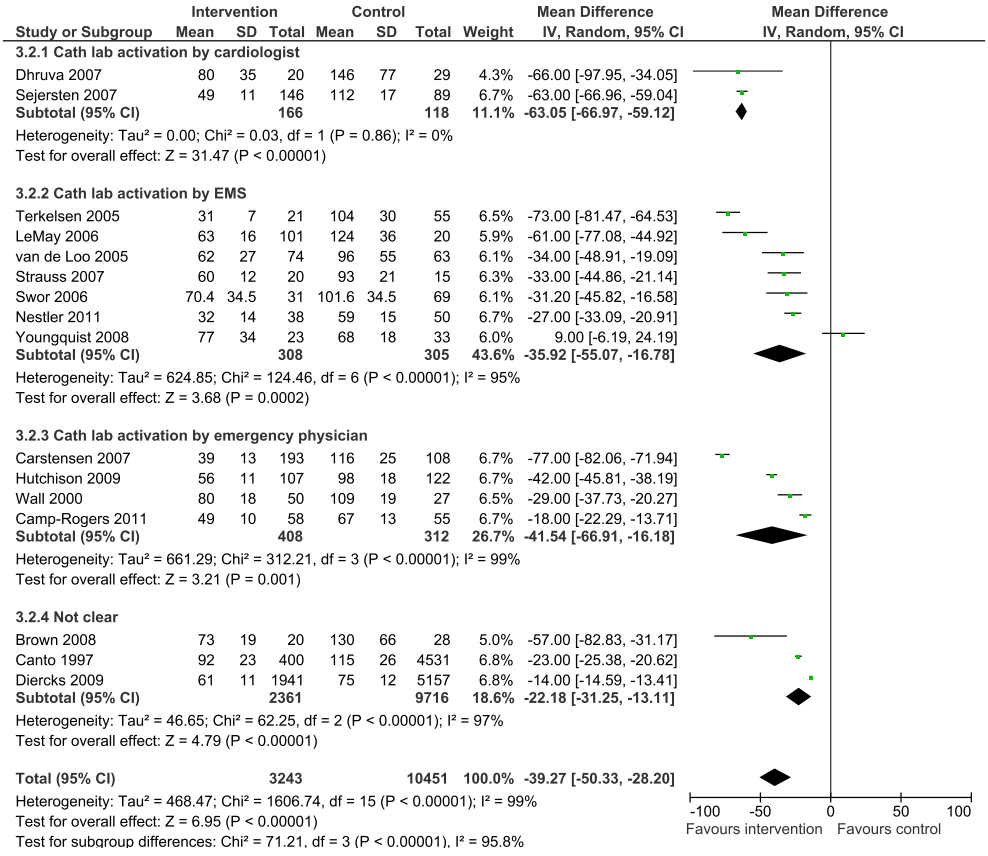


(b) Door-to-balloon time

Figure 10: Mean difference in first medical contact-to-balloon time (minutes) by regional or local jurisdiction type for prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control). Jurisdiction type was either regional or local. Negative numbers indicate a reduction in delay (favours intervention).



(a) First medical contact-to-balloon time



(b) Door-to-balloon time

Figure 11: Mean differences in first medical contact-to-balloon and door-to-balloon time (minutes) by cath lab activation protocol for prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control). Cath lab activation was grouped by EMS activation, emergency physician activation and cardiologist activation. Negative numbers indicate a reduction in delay (favours intervention).

to-balloon time (95%CI=−66.97 to −59.21 minutes; p<0.00001). However, there was very large heterogeneity in studies that employed cath lab activation by EMS (7 studies; n=613 χ^2=124.46; df=6; p<0.00001; I^2=95%); emergency physician activation protocols (4 studies; n=720; χ^2=321.21; df=3; p<0.00001; I^2=99%); or where it was not clear (3 studies; n=13,659; χ^2=62.25; df=2; p<0.00001; I^2=97%) (Figure 11b).

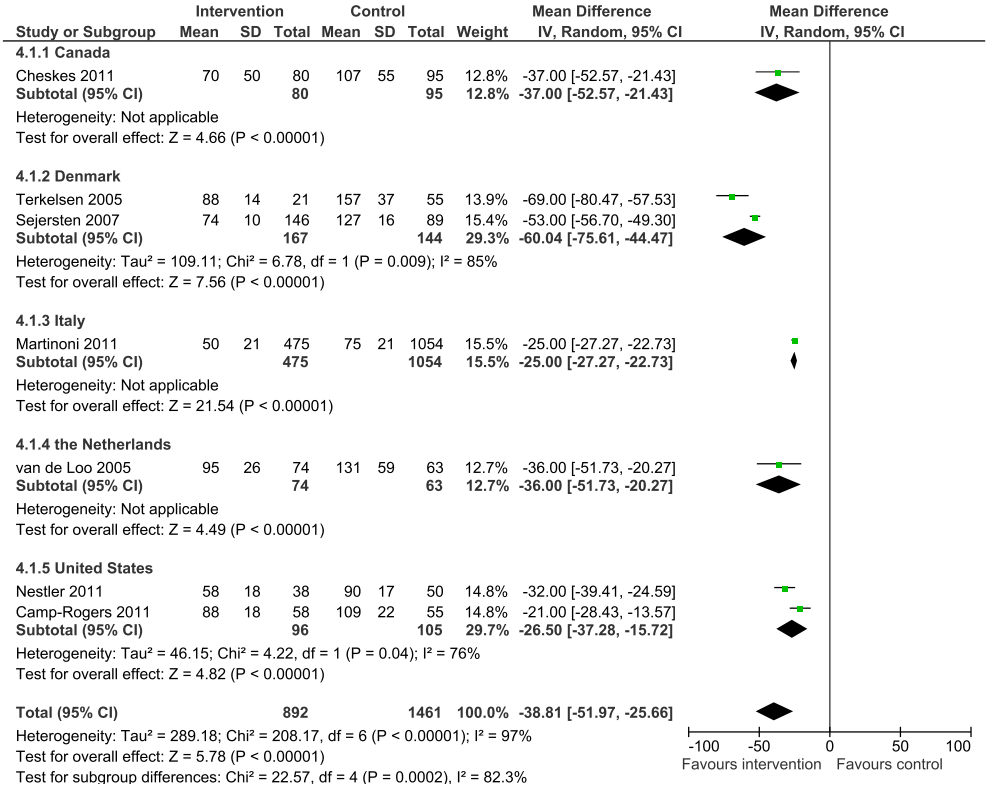
COUNTRY Subgroup differences were detected when first medical contact-to-balloon time was grouped by country (χ^2=22.57; df=4; p<0.0002; I^2=82.3%) (Figure 12a). However, there was only one study for Canada, Italy and the Netherlands, respectively. As well, very large heterogeneity persisted within the country groups of Denmark (2 studies; n=311; χ^2=6.78; df=1; p<0.009; I^2=85%) and the United States (2 studies; n=201; χ^2=4.22; df=1; p=0.04; I^2=76%) (Figure 12a).

Subgroup differences were also detected when door-to-balloon was grouped by country (χ^2=69.66; df=4; p<0.00001; I^2=94.3%) (Figure 12b). However, very large heterogeneity generally persisted within the country groups of Australia (2 studies; n=530; χ^2=117.23; df=1; p=0.0007; I^2=99%); Denmark (2 studies; n=4.39; χ^2=4.39; df=1; p=0.04; I^2=77%); and the United States (9 studies; n=12,495; χ^2=119.08; df=8; p<0.00001; I^2=93%) (Figure 12b). The studies from the Netherlands showed no heterogeneity (2 studies; n=237; χ^2=0.07; df=1; p<0.79; I^2=0%); the pooled estimate favoured a mean reduction of 32.57 minutes (95%CI= −43.01 to −22.13 minutes; p<0.00001) with prehospital identification with 12-lead ECG and advanced notification (Figure 12b). There was only one study from Canada.

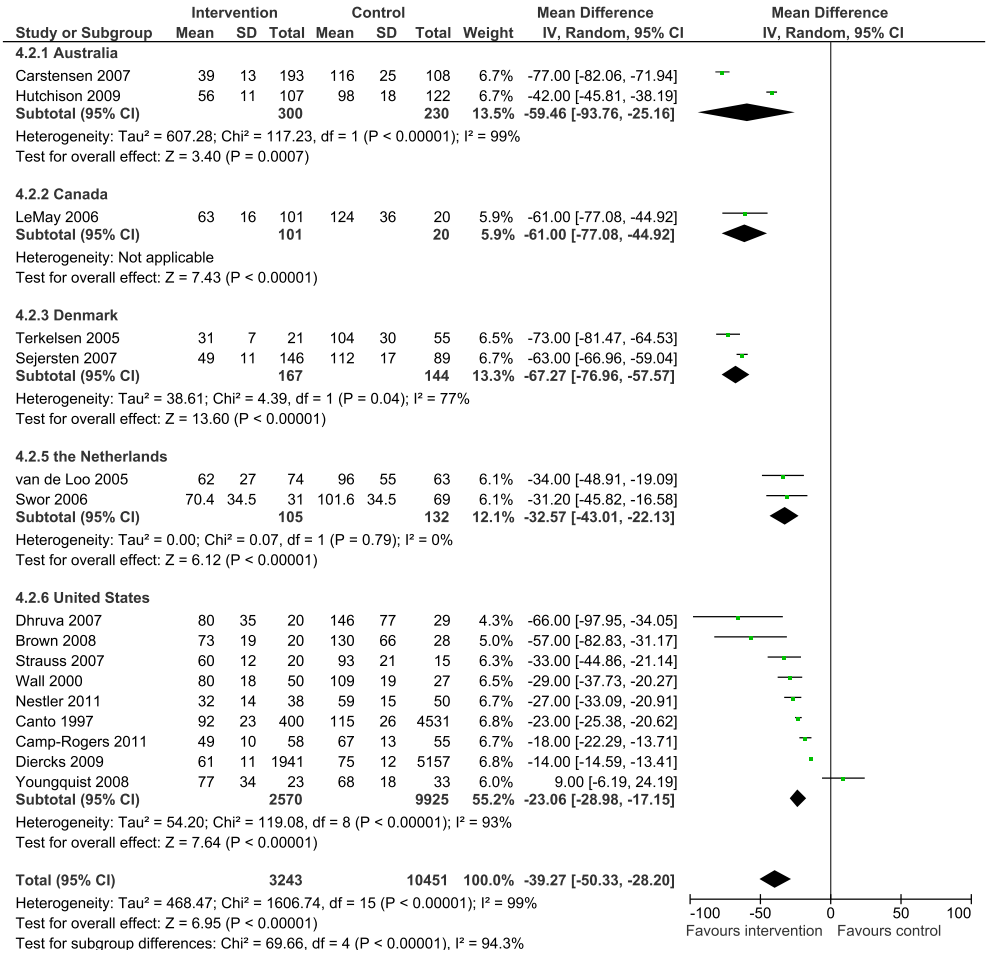
2.1.3.3 *Quality of included studies*

The GRADE evidence profile is presented in Table 3. The methodology of the available evidence was of observational design. The quality of such methodology is low in the absence of additional factors that lower or increase its overall quality. No serious risk of bias; inconsistency; indirectness; imprecision or publication bias was detected that would affect the overall magnitude, direction, or precision of results.

The quality of evidence was upgraded to moderate for first medical contact-to-balloon time and door-to-balloon time and door-to-needle time as there was evidence of a large effect (Table 3). There were a number of reasons why it was not upgraded to high quality. For the outcomes of first medical contact-to-balloon time and door-to-balloon time, pooled results showed heterogeneity and/or inconsistency in addition to a number of studies not having reported the mean and standard deviation. For the door-to-needle time, small sample sizes in addition to a number of studies not having reported the mean and standard deviation limited a high quality rating. Finally, the quality of evidence for the critical outcome of mortality within 30 days was low.



(a) First medical contact-to-balloon time



(b) Door-to-balloon time

Figure 12: Mean differences in first medical contact-to-balloon and door-to-balloon time (minutes) by country for prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control). Negative numbers indicate a reduction in delay (favours intervention).

Table 3: GRADE summary of findings

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prehospital identification	Risk difference with Prehospital identification with 12-lead ECG (95% CI)
Short-term mortality in patients who receive PCI	12726 (8 studies)	⊕⊕⊖⊖ LOW[1,2]	RR 0.59 (0.46 to 0.76)	Study population	
				9 per 100	4 fewer per 100 (from 2 fewer to 5 fewer)
				Moderate	
				9 per 100	4 fewer per 100 (from 2 fewer to 5 fewer)
Short-term mortality in patients who receive fibrinolysis	17026 (1 study)	⊕⊕⊖⊖ LOW[1,3]	RR 0.71 (0.54 to 0.93)	Study population	
				70 per 1000	20 fewer per 1000 (from 5 fewer to 32 fewer)
				Moderate	
					-
First medical contact-to-balloon time[4]	2353 (7 studies)	⊕⊕⊕⊖ MODERATE[4,5,6,7] due to large effect	Not estimable[4]	See comment	See comment
Door-to-balloon time[4]	13694 (16 studies)	⊕⊕⊕⊖ MODERATE[4,8,9] due to large effect	Not estimable[4]	See comment	See comment
Door-to-needle time	26856 (4 studies)	⊕⊕⊕⊖ MODERATE[1,10,11,12] due to large effect	Not estimable	See comment	See comment

[1] One large study used data from a voluntary registry.
[2] All small studies reported relative risk much less than the pooled estimate. However, the results are robust to their exclusion.
[3] Only one study included.
[4] Heterogeneity precluded pooling results.
[5] Five of seven studies reported median and interquartile range.
[6] All studies showed a statistically significant mean reduction with the intervention group compared to the control group.
[7] The mean reduction ranged from 21 minutes to 69 minutes.
[8] One study (n=56) found a statistically non-significant mean increase with the intervention group over the control group. Thirteen studies (n=8672) found a statistically significant reduction with the intervention group over the control group.
[9] Ten of sixteen studies reported mean and interquartile range.
[10] One study reported median and interquartile range.
[11] One study had only 5 participants in the intervention group.
[12] Studies show a large mean reduction, in general.

2.1.4 *Discussion*

The review found only observational studies. It found low quality evidence showing a strong association between prehospital identification with 12-lead ECG and advanced notification with a reduction in short-term mortality; moderate quality evidence of a reduction in first medical contact-to-balloon times; and moderate quality evidence of a reduction in door-to-balloon times compared to no prehospital identification in patients with STEMI who receive PCI.

In patients who received PCI, there was low quality evidence for a 41% reduction in short-term mortality following prehospital identifi-

cation with 12-lead ECG and advanced notification relative to no prehospital identification and no advanced notification due to methodological bias inherent in observational study design. Three large registry studies provided consistent estimates of a reduction in short-term mortality following prehospital identification with 12-lead ECG and advanced notification. One study was a voluntary registry[55]. The remaining two registry studies were of large hospital networks serving a diversity of geographical settings, including urban and rural areas, much like the geographical landscape in Ontario[61,65].

There was also low quality evidence for a 29% reduction in in-hospital mortality following prehospital identification with 12-lead ECG and advanced notification relative to no prehospital identification and no advanced notification in patients who received fibrinolysis. Only one registry was identified and it was a voluntary registry[55].

There was moderate quality of evidence for reductions in first medical contact-to-balloon and door-to-balloon times because of very large effect sizes. Despite high levels of heterogeneity for door-to-balloon and first medical contact-to-balloon times, very large and statistically significant reductions were found in nearly all studies. As well, on the absolute scale, the smallest of reductions in first medical contact-to-balloon were considerable (21 minutes); the biggest reductions were very large (69 minutes). For door-to-balloon, they were as large as 77 minutes, although one study found an increase of 9 minutes.

While there are factors which affect the magnitude of benefit, at a minimum, prehospital identification with 12-lead ECG and advanced notification is associated with a very large reduction in first medical contact-to-balloon and door-to-balloon times relative to no prehospital identification and no advanced notification. However, there was one smaller study that, conversely, found a non-significant increase of 9 minutes[72]. The reason for this observation may be because the night-time/weekend protocol was identical for both prehospital identification and no prehospital identification groups; identification and catheterization lab activation was initiated only after the patient was received in the ED.

There was moderate quality of evidence for reductions in door-to-needle time. One study included only five patients in its prehospital identification and advanced notification group[74]. The three small studies[74–76] showed much greater reductions in door-to-needle times compared to the one large registry study[55]. However, the three small studies had considerably longer baseline times, ranging from 81–103 minutes in the control group in contrast to 40 minutes in the registry study. The potential for door-to-needle reduction is likely less for the registry study. This was also reflected by a considerably smaller mean reduction in door-to-needle time (10 vs. 55–60 minutes).

Both shorter first medical contact-to-balloon, door-to-balloon times and door-to-needle times have been previously shown to be associated with mortality reductions[3,5,31,32,102,103]. It is likely that the reduction in short-term mortality following prehospital identification with 12-lead ECG and advanced notification observed in this analysis was the result of reductions in ischemic time through reductions in first

medical contact-to-balloon, door-to-balloon times and door-to-needle times. However, this analysis could not be stratified by cut-off points for any of the time outcomes; thus, inferences of associations between the first medical contact-to-balloon, door-to-balloon or door-to-needle with mortality are not based on formal statistical testing.

This review found variation in the jurisdiction type and in the protocols for ECG interpretation; advanced notification and cath lab activation; bypass eligibility; and transport destination in studies of patients who received PCI. This likely contributed to the very large statistical heterogeneity detected in the outcomes of door-to-balloon and first medical contact-to-balloon time. Subgrouping by any one of these factors did not explain heterogeneity.

Because a regional jurisdiction allows for bypass of a non-PCI centre, the potential time savings are greater compared to a local jurisdiction where patients are not transferred in from other hospitals or other areas. The door-to-balloon time reduction was found to be different based on jurisdiction type but there were no differences in first medical contact-to-balloon time reduction when studies were grouped by jurisdiction type. Very large imprecision and inconsistency can be observed in the regional subgroups of both the outcomes of door-to-balloon and first medical contact-to-balloon time. These limitations prohibit any definite conclusions about the jurisdiction type on reductions in treatment delay, although results suggest that there may be a greater reduction associated with a regional jurisdiction type.

Subgroup differences were detected when first medical contact-to-balloon and door-to-balloon times were grouped by country. Although pooled estimates are shown, direct interpretation is problematic given that, generally, very large heterogeneity was detected in all the subgroups. Two studies from the Netherlands displayed zero statistical heterogeneity but it is questionable whether this is really due to factors that can be summarized by a grouping level such as a country when all of the other groups displayed extremely large imprecision and inconsistency. Therefore, although there may be differences related to the country setting, no definite conclusions can be made about the relative effect of different countries on target times. Even so, it remains clear that prehospital identification with 12-lead ECG and advanced notification reduced both first medical contact-to-balloon and door-to-balloon times in all the included studies.

Advanced activation of the cath lab has been shown to reduce treatment delay[104,105] and a lot of attention has been given to emergency physician/ED activation[106–109]. This review found no differences in the magnitude of reduction when studies were grouped by cath lab activation via EMS, emergency physician or cardiologist. However, very large imprecision and inconsistency remained within the subgroups and therefore this result should not be interpreted as hypothesis-testing. Even so, it remains clear that both first medical contact-to-balloon and door-to-balloon times were reduced following prehospital identification with 12-lead ECG and advanced notification in all the included studies, regardless of cath lab activation protocol.

There are several concerns regarding the reporting of time delays. Most studies reported a door-to-balloon time or door-to-needle time in studies of patients with PCI and fibrinolysis, respectively, but not a first medical contact-to-balloon or -needle time. However, door times may not be the optimal outcome for the system. It neglects any transport time and may be a biased outcome when there is capability for bypass of a non-PCI centre in the case of patients who are eligible for PCI. In recognition that the EMS plays an important role in the continuum of STEMI patient care, the first medical contact-to-balloon may be the best measure of system performance[30–32].

In three regional studies of patients that received PCI that employed inter-hospital transfer from a non-PCI centre, it was not clear that the "door" in door-to-balloon was the non-PCI centre door. Using the door of the PCI centre would exclude inter-hospital transfer time as well as hospital delay at the non-PCI centre. However, the lack of clarity did not have an effect on the conclusions as there was still a large reduction found despite this potential bias, which would favour the no prehospital identification cohorts.

There are several previous reviews comparing prehospital identification with 12-lead ECG and advanced notification to no prehospital identification and no advanced notification[47–50]. Some of their included studies employed prehospital fibrinolysis or had small sample sizes less than 30 and, thus, were not included in this review; however, all other included studies met the inclusion criteria for this review.

Results from this review are similar. Bradley et al. conducted a qualitative review of four studies. They also concluded that prehospital ECGs were associated with a reduction in door-to-balloon time and the reduction was greatest when the cath lab was activated prior to hospital arrival[49].

Brooks et al. later followed with a systematic review and meta-analysis to determine whether prehospital triage and direct transportation of STEMI patients from the scene to an interventional centre for primary PCI resulted in lower 30-day all-cause mortality[50]. Included in their analysis were five studies. As well, studies were grouped according to whether or not the control group received prehospital fibrinolysis. In studies where the control group received prehospital fibrinolysis, no reduction in mortality was detected with prehospital triage and direct transportation to an interventional centre. In studies where no prehospital fibrinolysis was performed, prehospital triage and direct transportation to an interventional centre was associated with a 76% relative risk reduction (RR 0.24; 95%CI=0.07–0.87; p=0.03; I^2=0%). However, one study had zero events while the other study had just two events in the intervention group. Therefore, results displayed very large confidence intervals.

As most of the studies in the present review also employed a protocol of direct triage to an interventional centre, results can be compared with the Brooks et al. review. This review included two of the five studies and excluded the remaining three[110–112] because they employed prehospital fibrinolysis. This review confirms a mortality ben-

efit associated with prehospital identification with 12-lead ECG; it also characterizes the magnitude with a higher degree of precision.

Brainard et al. also conducted a systematic review of prehospital 12-lead ECG in patients who received fibrinolysis[47]. They included four studies and found a mean difference of 24.7 minutes with prehospital 12-lead ECG. However, no estimate of heterogeneity was given. This review included one of the included studies and excluded the remaining three studies because of small sample sizes[113,114] and because no full-text was published[115]. The two studies with small sample sizes otherwise fit the inclusion criteria. Their inclusion does not change the overall conclusion; the characteristics of these studies along with their data synthesis with the four studies already included are provided in Section A.1.3.

Morrison et al. followed with a more detailed systematic review of prehospital 12-lead ECG on AMI times and mortality in patients who were treated with fibrinolysis. They included five studies[48]. Prehospital 12-led ECG was found to be associated with a weighted mean reduction in door-to-needle time of 36.1 minutes. However, the pooled estimate showed significant heterogeneity at the 1% level. All included studies in the Morrison et al. review did show a reduction in door-to-needle time. Prehospital 12-lead ECG was also attributed with a non-significant absolute risk reduction in mortality of 7.2%. The present review included two of the studies and excluded the remaining three because of small sample sizes[113,114] and because no full-text was published[116]. The two studies with small sample sizes otherwise fit the inclusion criteria. Their inclusion does not change the overall conclusion; the characteristics of these studies along with their data synthesis with the four studies already included are provided in Section A.1.3. This review also found a reduction, albeit on a much smaller scale; about a 2.0% absolute risk reduction. The reduction was also found to be statistically significant.

Decision makers are interested in the expected outcome and thus all future studies should report mean times where times are reported. Jurisdictions should consider using first medical contact-to-reperfusion time as a more important performance measure compared to door-to-balloon time or door-to-needle time. Door-to-balloon time should be measured from the first hospital encountered so that more system-relevant time is captured. Finally, future research should include a detailed description of relevant prehospital and hospital protocols, including: ECG interpretation; advanced notification and activation, bypass eligibility, interhospital transfer eligibility; and transport destination eligibility.

2.1.5 *Conclusions*

In conclusion, prehospital identification with 12-lead ECG and advanced notification was found to be associated with a reduction in short-term mortality, first medical contact-to-balloon time, door-to-balloon time and door-to-needle time compared to no prehospital

identification and no advanced notification in STEMI patients received by EMS who were treated with PCI and fibrinolysis. As well, reductions in first medical contact-to-balloon and door-to-balloon time were not well explained by differences in jurisdiction type, cath lab activation protocol or country, respectively.

2.2 COST-EFFECTIVENESS OF PREHOSPITAL IDENTIFICATION WITH 12-LEAD ECG AND ADVANCED NOTIFICATION

Prehospital 12-lead ECG and advanced notification is associated with reductions in reperfusion times and short-term mortality both for STEMI patients who receive fibrinolysis or PCI among those received by EMS[55–76,113,114].

While there are benefits of prehospital identification with 12-lead ECG and advanced notification, there may also be many costs. Fixed capital costs may include the 12-lead ECG machine, EMS training for 12-lead ECG interpretation and/or performance monitoring infrastructure (1.8). There may also be differences in downstream health care resource use due to increased access to primary reperfusion, changes in the use of early PCI or revascularization and differences in the rates of reinfarction or stroke (Section 1.8).

The objective of this review was to examine the literature on the cost-effectiveness of prehospital identification with 12-lead ECG and advanced notification to no prehospital identification and no advanced notification in STEMI patients who are received by EMS.

2.2.1 *Methods*

2.2.1.1 *Literature search*

A literature search was undertaken for the purposes of locating full economic evaluations assessing prehospital identification with 12-lead ECG and advanced notification in patients with STEMI. A search strategy was constructed using controlled vocabulary and keywords focusing on the concepts of "electrocardiogram", "advanced notification", "emergency medical services" and "myocardial infarction". The following bibliographic databases were searched: EMBASE via OVID (1988 to 2012 week 31); PUBMED (1988 to 2012 week 31); the National Health Service Economic Evaluation Database via the Centre for Reviews and Dissemination (inception to 2012 week 31); and the National Health Service Health Technology Database via the Centre for Reviews and Dissemination (inception to 2012 week 31). For the EMBASE and PUBMED databases, an economic filter adapted from the Canadian Agency for Drugs and Technologies in Health (CADTH)[117] was applied and the search was limited to English language articles published after 1988.

2.2.1.2 *Inclusion criteria*

Studies were included if they met the following inclusion criteria:

- study was a full economic evaluation[54] (eg. cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis),
- relevant patient population were patients with STEMI,
- "intervention" group included prehospital identification with 12-lead ECG and advanced notification,
- "control" group included basic cardiac monitoring (3-lead ECG).

2.2.1.3 *Exclusion criteria*

Studies were excluded for the following reasons:

- "control" group included no prehospital identification, advanced notification or activation protocols, or transportation to a destination other than the local ED,
- either cohort group made use of prehospital fibrinolysis, where the patient was eligible,
- either cohort group included walk-ins; walk-ins are patients who transport themselves to the ED and thus are not transported via EMS.

No restrictions were made with respect to study model design aspects, such as the perspective, time horizon, discount rate or type of sensitivity analysis.

2.2.1.4 *Outcomes*

Outcomes of interest included the incremental cost effectiveness ratio, net monetary benefit, the incremental health care costs, and the incremental health benefit. No restriction was made on the type of effectiveness outcome.

2.2.1.5 *Study selection*

Screening was completed using a two-step process. Stage one was title and abstract screening and stage two was full-text review. Titles and abstracts were assessed by the author for full-text retrieval using a predetermined screening form (Appendix A.2.2) that mirrored the inclusion and exclusion criteria. The full texts of all included abstracts were screened for final inclusion using the same screening form. Details of prehospital management strategy were not expected to always be clearly reported so studies with an unclear inclusion status were included and this was to be noted in the discussion of results.

2.2.1.6 *Data abstraction*

A number of data items were planned for abstraction from the full text to facilitate a comparison of study settings, methodology and results. This was based on the Canadian Agency for Drugs and Technologies in Health guidelines for economic evaluation[118] and the

summary items used in the Centre for Reviews and Dissemination database[119]. The following data items were abstracted:

- study question,
- type of evaluation,
- target population,
- comparators,
- perspective,
- time horizon,
- effectiveness data sources,
- cost data sources,
- discount rate,
- type of sensitivity analysis,
- effectiveness results,
- cost results,
- cost-effectiveness results,
- conclusion.

2.2.1.7 *Quality assessment*

Methods for rating the study quality have been relatively well developed for randomized clinical trials[77,120]. However, methods for rating the study quality of economic evaluations have been less well researched. When the study quality of economic evaluations are ever assessed, a checklist developed by Drummond et al.[54] is most often used. The checklist is more of a qualitative summary of key items; it does not provide an overall assessment or score.

2.2.1.8 *Data analysis*

Pooled estimates were not planned as large differences in geographic settings and protocols were expected. A qualitative summary was planned to summarize the results of each included study alongside its methodology and potential implications for a Canadian setting.

2.2.2 *Literature search results*

The flow of study inclusion is presented in Figure 1. The search produced 236 citations of which 3 were included for full-text review[121–123]. None of the studies were included for final review because they were not a study of prehospital strategies[121] or the full-text not available[122,123]. Full-text was not available because authors did not respond for one citation[122]. For the other, authors indicated the full-text has not been submitted for publication[123].

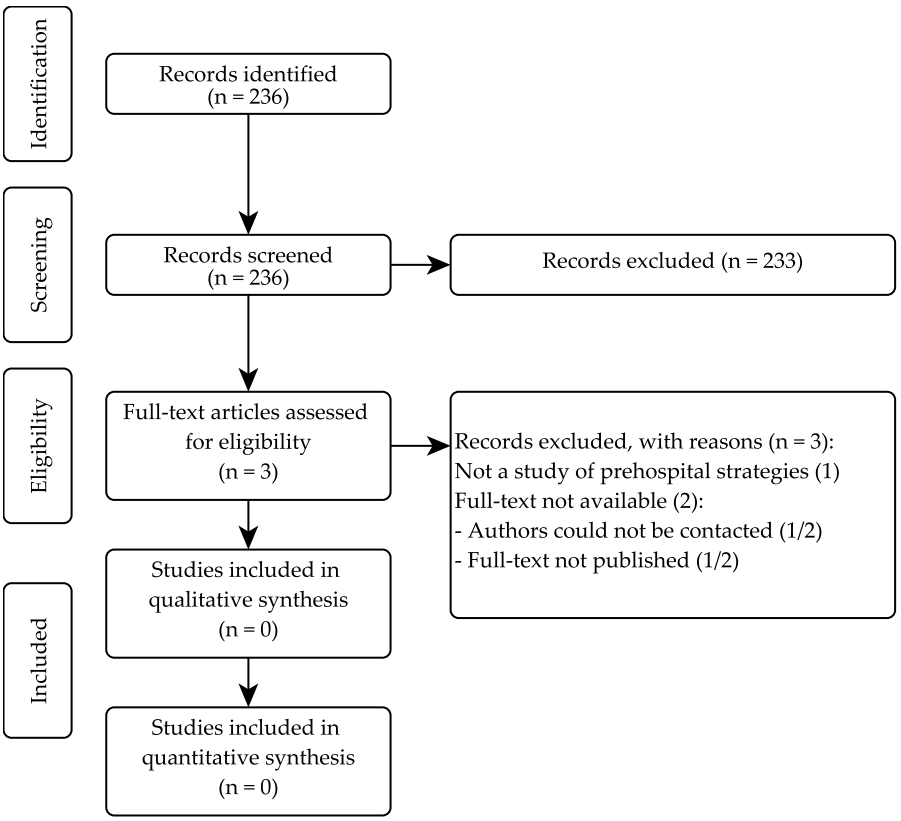


Figure 13: Flow diagram of study inclusion

2.2.3 *Conclusion*

A search of the literature returned no studies comparing the cost-effectiveness of prehospital identification of STEMI with 12-lead ECG to a strategy of no identification in STEMI patients received by EMS.

2.3 SUMMARY OF LITERATURE REVIEWS

There is low-quality evidence in the literature of the effectiveness of prehospital identification with 12-lead ECG and advanced notification in reducing short-term mortality, first medical contact-to-balloon time, door-to-balloon time and door-to-needle time compared to no prehospital identification and no advanced notification in STEMI patients. However, there is no evidence in the literature of the cost-effectiveness of prehospital identification with 12-lead ECG and advanced notification.

3

ECONOMIC EVALUATION

3.1 INTRODUCTION

Due to the scarcity of healthcare resources, policy makers are faced with difficult allocation decisions[54,124]. Economic evaluation of different programs or alternatives can be useful for the efficient allocation of health resources. An economic evaluation seeks to identify and make explicit one set of criteria for the selection of the optimal program or alternative[54]. Thus, an economic evaluation can be defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences"[54].

An economic evaluation considers the inputs and outputs of different programs or alternatives. The inputs are the costs of the program or alternative; the outputs are the consequences (benefits and harms) following the program or alternative.

There are four types of economic evaluations: cost-minimization, cost-effectiveness, cost-utility and cost-benefit analysis. The first, the cost-minimization analysis, compares only the costs of different alternatives or programs. It assumes the consequences of the alternatives are equivalent. This is generally an unreasonable assumption as data do not typically support inferences of equivalency[54]. The assumption becomes more untenable once an economic evaluation attempts to model second order uncertainty[125] — the uncertainty in the parameter estimates.

Cost-effectiveness analyses compare the incremental costs and incremental effects. It requires an effect measure that is common to both alternatives or programs. Naturally, the explicit analysis of effects and costs mean that equivalency is not assumed, unlike cost-minimization.

Cost-utility analyses compare the incremental costs and incremental utilities. Instead of an effect measure, a broader measure of benefit of the alternatives or programs is used; utility. Utilities, unlike effectiveness measures, can be used for a broad set of interventions whose primary effectiveness measures are varied[54,126,127]. Therefore, utilities facilitate comparisons of different programs. In addition, most interventions affect a number of outcomes, including: life years, disability, pain, and side-effects, to name a few. Utilities capture mortality and morbidity[54,126,127]. Finally, different effect outcomes may not all be valued equally by the patient; utilities also address this issue as well.

For cost-utility analyses, pre-scored multi-attribute health status classification systems such as the EQ-5D or the Health Utilities Index (HUI) are used to determine the utilities for each health state. Here, the utility depends on a number of attributes. The EQ-5D uses five attributes: mobility, self-care, usual activity, pain/discomfort and anxiety/depression[128]. The EQ-5D-5L has five levels: no problem,

slight problems, moderate problem, severe problems and extreme problems[129] whereas the more common, but older, EQ-5D-3L (previously referred to as the EQ-5D) has three levels. Therefore, there are 3,127 health states after "unconscious" and "dead" are also added for the EQ-5D-5L and 245 health states for the EQ-5D-3L. The utility is measured for all of these health states using standard gamble or time trade-off and the results are then used to determine a scoring function that describes the utility decrements for each level in each dimension[130,131]. For the EQ-5D-5L, the utility typically ranges from 0 to 1 for any health state; 0 indicates death and 1 indicates full health; however, there are instances where health states are considered worse than death and therefore have a negative utility[132,133].

The HUI is also a generic, multi-attribute utility scoring system[134–136]. The HUI measures health status and health-related quality of life to generate utility scores. There are two HUI instruments that are independent of each other: the HUI2 and HUI3. In general, the HUI3 is used as the measure for primary analyses. The HUI3 includes eight domains: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain[136]. Each domain has five to six levels of ability/disability. The utility typically ranges from 0 to 1. However, the HUI allows for health states with a utility worse than death; the lowest possible score for the HUI3 is -0.36[134]. The utility is derived in the same way as the EQ-5D-5L.

The final type of economic evaluation is the cost-benefit analysis. While cost-effectiveness or cost-utility analyses require a decision maker's criterion of value (such as the willingness-to-pay (WTP) threshold), cost-benefit analyses do not[54]. Cost-benefit analyses are grounded in welfare economic theory[137]; as such, the relevant perspective is the individual. The outcome is the net social benefit which is the net of the benefit and the costs, both in monetary terms. One of the central tenets of this theory is "Pareto" improvement[54]. There are two types of Pareto improvements. An actual Pareto improvement is when one or more individuals are better off with the program while no one is worse off. A potential Pareto improvement is when the gainers could compensate the losers and still remain better off. The Pareto improvements are used to assign monetary values to health outcomes. This is done using one of three general approaches: human capital[138], revealed preferences[139] and contingent valuation[140]. A full discussion of these methods is beyond the scope of this introduction.

There exist many different model types employed in economic evaluations, including: decision tree, Markov and microsimulation models, to name a few. A decision tree maps mutually exclusive sequences of events in pathways or "branches" along with their associated health benefits and costs[54,141]. The expected costs and outcomes are the summation of the pathway values weighted by the pathway probabilities.

The structure of the decision tree is easily interpreted when the number of pathways is small. This is typical for models with a short-term time horizon with relatively few health states. However, the decision tree can become quite "bushy" as the number of branches in-

creases[54,126]. Decision models with longer time horizons, such as a lifetime time horizon, may require a couple of added features over decision trees. One may be the need to model the continuing risk of any number of complications. As well, they must allow for a competing risk of death[54,126]. These features can add considerably to the number of branches in a decision tree.

A Markov model is a commonly used method to handle the multiplicity of possible pathways as well as a competing risk of death over long time horizons[126]. Generally, a Markov model simulates an entire cohort. In the model, disease states represent the possible consequences while transitions between the disease states replace the pathway probabilities of a decision tree. The model is run over discrete time periods, or cycles. With each cycle, a cost and effect accrues for each state. The sums of these costs and effects, weighted by the time the cohort spends in each state, are the expected costs and effects.

There are two general categories of costs to consider in an economic evaluation: direct and indirect costs. Direct costs are the resources consumed (costs) that are attributed to the comparator(s) of interest[54]. These costs would include operating expenses and out-of-pocket expenses. Indirect costs typically indicate the time consumed or freed by the comparator(s) of interest[54]. Indirect costs generally focus on productivity losses.

The costs that are used in an economic evaluation depend on three things. First, the perspective of the analysis. The perspective determines the relevant costs to be included. For example, a societal perspective may warrant inclusion of indirect costs; however, these costs may not be as relevant for a healthcare payer perspective. Second, the comparison in the analysis. If the comparison is restricted to the programs or treatments immediately under study, common costs may be excluded. Third, the magnitude of costs. Costs, typically of small magnitude, that are unlikely to change results are not worth considering. Alternatively, a more narrow consideration of costs may be better because it does not unnecessarily complicate the analysis. This would not affect the incremental differences.

3.2 METHODS

3.2.1 *The PREDICT Study*

Some of the data used in the model was derived from a subset of the PREDICT study. This section provides some brief background on the study.

In 2004, the CCN of Ontario recommended that primary PCI become the dominant strategy for the reperfusion of STEMI in Ontario[14]. In response, the Medical Advisory Secretariat (MAS) (part of the MOHLTC but now the Evidence Development and Standards team (EDS) of Health Quality Ontario) conducted a review of primary angioplasty and concluded that it was unrealistic to deliver primary PCI to all patients with STEMI in Ontario. MAS and the OHTAC instead recom-

mended that Ontario aim to optimize the delivery of both fibrinolysis and PCI[53,142]. Recommendations were also made to the MOHLTC to consider optimizing prehospital strategies such as including prehospital ECGs and examine a long-term plan for prehospital care[53].

To identify the optimal prehospital management strategy of STEMI patients, the MOHLTC funded a cohort study. Its purpose was to estimate the health and cost consequences following the use of prehospital identification of STEMI with 12-lead ECG and advanced notification of the receiving centre[143]. PREDICT was a prospective observational study carried out from 2008 to 2012. A full description on rationale, development and implementation of the PREDICT study has been previously published. In summary, the study was set in regions of Ontario with a population of 3,043,853 served by 14 EMS under the medical control of 4 regional base hospital programs[143]. The geographic region represented rural, suburban, and metropolitan areas covering 25% of the population in Ontario. PREDICT enrolled all chest pain patients received by EMS; however, the target population were those chest pain patients who were identified as STEMI patients. STEMI patients received prehospital 12-lead ECG with advanced notification of the receiving centre or they received no prehospital 12-lead ECG and no advanced notification of the receiving centre. These two cohorts were also further stratified by the eligibility to bypass the nearest receiving centre for a PCI centre. Bypass eligibility was based on a maximum transport distance of 60km from the patient's pick-up location to the PCI centre.

The economic model developed here took the form of a cost-utility analysis. A cost-utility analysis can help capture the quality of life following myocardial infarction as well as associated complications. Aligned with the preliminary PREDICT database, the mean age of a chest pain patient was 63.8 years old.

The two prehospital managements strategies were stratified by eligibility to bypass, based on a maximum transport distance of <60km from the patient's pick-up location to the PCI centre. Therefore, for patients who were eligible for bypass, the two comparison strategies were: prehospital 12-lead ECG with advanced notification of the receiving centre; and no prehospital identification with no advanced notification. Similarly, for patients who were not eligible for bypass, the two comparison strategies were: prehospital 12-lead ECG with advanced notification of the receiving centre; and no prehospital identification with no advanced notification.

Incremental health outcome measures included incremental life years (LYs) and QALYs; incremental economic outcome measures included only the healthcare resource cost in 2012 Canadian dollars.

The analysis took the perspective of a third-party healthcare payer, namely the Ontario MOHLTC. The MOHLTC is the principal payer of medical costs in the province of Ontario; it pays directly for all inpatient costs, physician fees, prescription drugs for seniors, some allied health and 50% of EMS costs.

The analysis took a lifetime time horizon. A 3% discount rate was used in the base case for both cost and health consequences.

3.2.2 *Model structure*

The relevant health states for this model were determined after reviewing the literature on STEMI and in consultation with an emergency medicine physician. The relevant health states were: post-myocardial infarction (MI), reinfarction, stroke, revascularization, post-reinfarction, post-stroke and death. Revascularization was any PCI received beyond the acute phase (post-30 days).

The model structure was divided into a short-term one-year decision tree followed by a lifetime Markov model. The structure of the model was the same for each prehospital management strategy (12-lead ECG and 3-lead ECG).

SHORT-TERM MODEL The decision tree begins with a STEMI and one of the four prehospital management strategies. The short-term is divided into two cycles: 1-30 days and 31-365 days. During both periods, patients are at risk of the following events: death, reinfarction, stroke and revascularization. The pathways for each of these events are represented by branches in Figure 14. Patients remain in the post-MI state if they do not have an event during the previous period. Similarly, patients with a stroke or reinfarction remain in the post-stroke and post-MI states, respectively, if they survive the previous period. Patients with a revascularization return to post-MI. Only patients in post-MI can suffer a reinfarction or revascularization. Death, however, is possible from all health states in the one-year and lifetime models. Post-event states are used to reflect different health and costs outcomes.

Stroke is only modeled for the first 30 days because emboli resulting from the coronary thrombus are not expected to be different beyond the acute period among the treatments[51]. Similarly, revascularization is attributed to the first year as evidence from long-term follow-up has shown revascularizations are mainly performed within the first 6 months following STEMI[51].

LONG-TERM MODEL Following the first year, patients who are alive enter the long-term Markov model in one of the following health states: post-MI, post-reinfarction, or post-stroke. The long term model is run in yearly cycles beginning on day 366 following the initial STEMI. Figure 15 presents a diagram of the Markov model. Health states are indicated by rectangles and possible transition pathways are indicated by directional arrows. Dotted circular arrows indicate that returning to the same health state was possible. The hatched bordered rectangles indicate post-event states. Similar to the decision tree, only patients who are in post-MI can suffer a reinfarction. Death, however, is possible from all health states. It should also be noted that stroke is not modeled beyond the first 30 days following initial STEMI

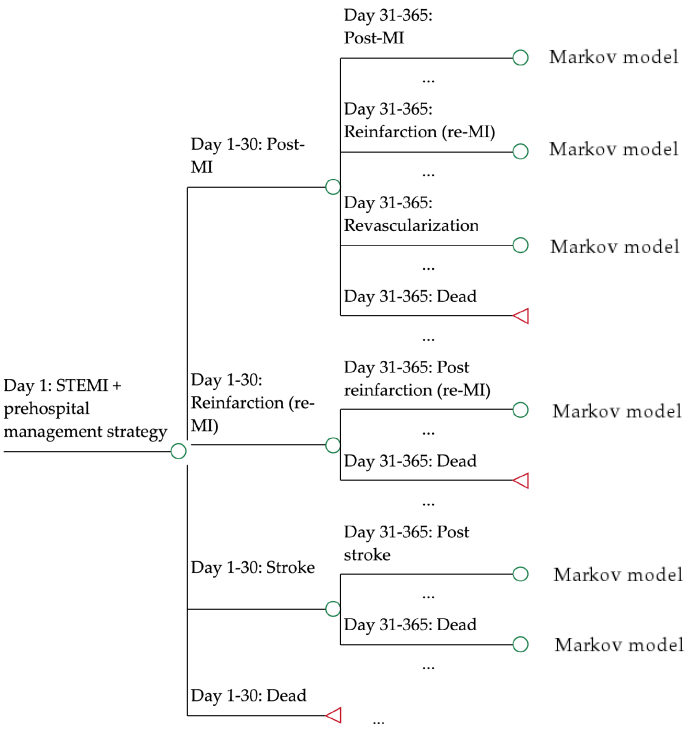


Figure 14: Short-term decision tree model. The model is divided into two time periods: day 1-30 and day 31-365. Each branch of the tree is a health state. Chance nodes, represented by circles, indicate possible transitions to other health states. Death is a terminal node, indicated by a triangle.

for reasons previously discussed; thus, patients who suffer a stroke begin the long-term model in post-stroke.

POST-EVENT STATES Health consequences, cost consequences and the probabilities of subsequent events may change with time. To model differences in one or more of these, post-event states are used. These are also known as "tunnel states". A separate post-event state is used for each cycle. Each post-event state is associated with different probabilities, QALYs and/or costs.

Although the post-event state is visually represented by a single state (Figure 14,15), there are separate states for each of the years following the index year. For example, a patient who suffers a reinfarction and survives for three years transitions through reinfarction, post-reinfarction second year and post-reinfarction third year before transitioning to death. Post-event states are not modeled past the fifth year following the index event as it is assumed that the average yearly probabilities and outcomes have stabilized. There is one exception: the age-related baseline post-STEMI mortality risk following the initial STEMI.

3.2.3 *Model parameters*

Death at 30 days, death at one year and the probability of primary reperfusion were taken from a subset of the PREDICT study. The probabilities of reinfarction, stroke, revascularization following each type

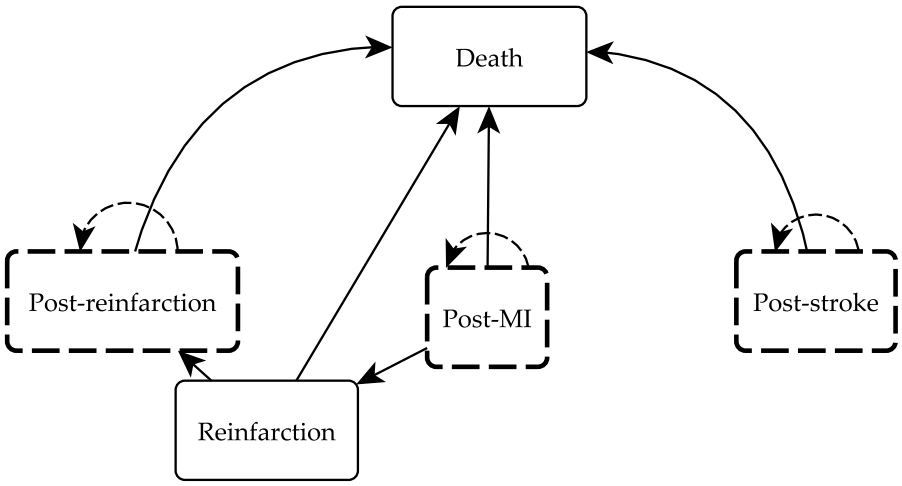


Figure 15: Long-term Markov model. Rectangles represent health states; dotted rectangles represent post-event states. Directional arrows represent possible transitions; dotted circular arrows indicate remaining in the same health state was possible. Death is an absorbing state.

of reperfusion treatment as well as survival post- reinfarction, stroke and revascularization were modeled using the literature. Utilities and costs were also obtained from the literature. Relevant literature was identified through a literature review.

3.2.3.1 *Mortality*

A subset of the PREDICT dataset provided the mortality estimates for the model at 30-days and one-year.

The initial estimated relative risk of mortality at 30 days in the 12-lead cohort compared to the 3-lead cohort with eligibility to bypass was 0.54 (standard deviation (SD): 1.54, p=0.19). Similarly, at one year, the relative risk was 0.59 (SD: 1.81, p=0.14). In the bypass ineligible stratum, the 12-lead cohort had a relative risk of 1.39 (SD: 4.00, p=0.73) and at one year the relative risk was 1.00 (SD: 2.71, p=1.00) (Table 4).

MORTALITY FOLLOWING THE FIRST YEAR The short-term incremental mortality reduction following aspirin, fibrinolysis* or PCI have been shown to be sustained in the long-term[51,52,144]. However, while they are sustained, no additional incremental benefits have been seen in the long-term beyond the first year[51,52,144]. Therefore, this model used the same hazard functions obtained from the literature for mortality beyond the first year in all cohorts.

Caro et al. derived age-specific functions that modeled the hazard of death following an AMI and stroke, respectively, over the long-term[145]. From the Saskatchewan Administrative Database, they included 15,590 patients with an index diagnosis of myocardial infarction and 18,704 patients with an index diagnosis of stroke in 1990–1995 and followed them until 2000. Although AMI and stroke care has changed since the time period used in the Caro et al. study, these

* Long-term follow-up studies have evaluated streptokinase

improvements are not expected to have led to significant incremental differences in the risk of mortality following different reperfusion treatments beyond the first year.

Mortality following reinfarction was modeled using the same hazard curves as post-AMI; however, they were adjusted for history of previous AMI with the appropriate beta coefficients provided by Caro et al[145]. Similarly, mortality following stroke was also adjusted for previous history of AMI.

The absolute mortality probabilities following index STEMI, subsequent stroke or subsequent reinfarction for a selection of years are presented in Table 4.

3.2.3.2 *Primary reperfusion*

The type of primary reperfusion treatment received — either no reperfusion treatment (aspirin only), fibrinolysis with early PCI, fibrinolysis only (without early PCI; generally a policy of rescue PCI†), or primary PCI — following each prehospital management strategy determined its distribution across the initial health states. In reality, the likelihood of receiving these treatments are based, primarily, on eligibility and access. To reflect the Ontario landscape, the likelihood of receiving no treatment, fibrinolysis or primary PCI following the different prehospital management strategies was derived from a subset of the PREDICT study. Any differences in eligibility and access across the four cohorts would result in differences in the proportion of treatments received. This would lead to a different distribution across the health states which would also lead to differences in outcomes.

The probabilities of receiving no reperfusion treatment, fibrinolysis only, fibrinolysis with early PCI and primary PCI, obtained from a subset of the PREDICT study. In the 12-lead bypass eligible arm, 34% received no treatment, 18% received primary fibrinolysis and 48% received primary PCI compared to 63%, 13% and 24% in the 3-lead bypass eligible arm, respectively. In the 12-lead bypass ineligible arm, 52% received no treatment, 39% received primary fibrinolysis and 9% received primary PCI compared to 73%, 20% and 7% in the 3-lead bypass ineligible arm, respectively.

The ratio of receiving no reperfusion treatment, fibrinolysis only, fibrinolysis with early PCI and primary PCI, obtained from a subset of the PREDICT study. In the 12-lead bypass eligible arm, the ratio of 1.9:1:2.7 for receiving no treatment, primary fibrinolysis and primary PCI, respectively. In comparison, the ratio for the treatments outlined above was 4.9:1:1.9 in the 3-lead bypass eligible arm.

In the 12-lead bypass ineligible arm, 5.8:1:4.3 received no treatment, primary fibrinolysis and primary PCI compared to 10.4:2.8:1 in the 3-lead bypass ineligible arm, respectively.

† Rescue PCI is a standard protocol of revascularization only when there is failed reperfusion[33–35]. This was contrasted with early PCI in Section 1.3.

Table 4: Clinical & utility parameters. The variable name, distribution, parameters and reference are shown.

VARIABLE	DIST	PARAMETERS					REF
		μ	α	β	RR	SD	
30-DAY DEATH							
12- vs. 3-lead, bypass	Normal				0.54	1.54	PREDICT
12- vs. 3-lead, no bypass	Normal				1.39	4.00	PREDICT
ONE-YEAR DEATH							
12- vs. 3-lead, bypass	Normal				0.59	1.81	PREDICT
12- vs. 3-lead, no bypass	Normal				1.00	2.71	PREDICT
DEATH FOLLOWING INITIAL STEMI*							
All treatments, Y2	Beta	0.02					145
All treatments, Y3	Beta	0.03					145
All treatments, Y4	Beta	0.03					145
All treatments, Y5*	Beta	0.04					145
DEATH FOLLOWING REINFARCTION*							
All treatments, Y1	Beta	0.06					145
All treatments, Y2	Beta	0.03					145
All treatments, Y3	Beta	0.03					145
All treatments, Y4	Beta	0.04					145
All treatments, Y5†	Beta	0.05					145
REINFARCTION							
FB/ASA alone, Y1	Beta	0.06	83	1287		0.01	51,52
FB/ASA alone, Y2	Beta	0.03	32	1338		0.01	51,52
FB/ASA alone, Y3	Beta	0.03	96	685		0.01	51,52
FB/ASA alone, Y4	Beta	0.01	10	771		0.01	51,52
FB/ASA alone, Y5†	Beta	0.01	10	771		0.01	51,52
FB + early PCI vs. FB	Normal				0.65	0.20	33
PCI vs. FB	Normal				0.60	0.13	51,52
STROKE							
FB/ASA alone, 30-day	Beta	0.02	16	765		0.01	146
FB + early PCI vs. FB	Normal				0.59	0.38	33,40
PCI vs. FB	Normal				0.37	0.27	40
REVASCULARIZATION							
FB/ASA alone, Y1	Beta	0.34	266	515		0.02	51
FB + early PCI vs. FB	Normal				1.00	0.00	‡
PCI vs. FB	Normal				0.47	0.10	51
UTILITIES							
Post-MI	Beta	0.63	870	513		0.01	147
Reinfarction	Beta	0.61	298	195		0.02	147
Stroke	Beta	0.52	361	329		0.02	147
Revascularization	Beta	0.61§					148

aspirin (ASA); fibrinolysis (FB); percutaneous coronary intervention (PCI)

* Scale and shape parameters were not probabilistic; refer to source[145] for more details
† Only shown up to year 5
‡ Assumed to be equivalent to FB
§ The utility of post-MI minus 0.018, the utility decrement of revascularization with PCI from no revascularization[148] carried out for six months

3.2.3.3 *Risk of reinfarction, stroke and revascularization following fibrinolysis only (without early PCI)*

The follow-up studies of Danish Acute Myocardial Infarction 2 trial (DANAMI-2)[146] are some of the longest follow-up studies of randomized controlled trials comparing PCI (with stenting) to fibrinolysis (alteplase)[51,52]. DANAMI-2 randomized 790 patients to primary PCI and 782 patients to fibrinolysis. Enrolment began in 1997 and terminated in 2001. The median length of follow-up was 7.8 years with a loss to follow-up of only 0.5%[52].

REINFARCTION The cumulative risk of reinfarction increased from 12.3% to 18.5% at three and eight years following treatment with fibrinolysis of initial STEMI[51,52]. When this was converted to yearly probabilities, the average baseline risk of reinfarction ranged from 6.1% in the first year to 1.3% in the eighth year (Table 4).

STROKE The 30-day baseline risk of stroke following fibrinolysis was 2% in DANAMI-2[146]. This is what was used in the model (Table 4).

REVASCULARIZATION At three years following fibrinolysis, 34% of patients received revascularization with PCI[51]. This is what was used in the model (Table 4).

3.2.3.4 *Relative risk following early PCI to fibrinolysis only (without early PCI)*

Evidence from RCTs is limited to short-term time horizons[33–35]. The most recent and comprehensive meta-analysis compared early PCI to the standard practice of rescue PCI within 24 hours of hospital admission[33].

REINFARCTION Early PCI was associated with a 36% odds reduction of reinfarction at 6-12 months (6 trials; n=2,757; OR 0.64; 95%CI=0.40–0.98; I^2=21%) compared to rescue PCI[33]. The statistical analysis was repeated in Review Manager 5.1 to obtain a relative risk estimate of 0.65 (95%CI=0.43–0.96), also using a random-effects Mantel-Haenszel model (Table 4).

STROKE Early PCI trended toward a non-significant 37% odds reduction of stroke at 30-days (7 trials; n=2,961; OR 0.63; 95%CI=0.31–1.26; p=0.21; I^2=0%)[33]. This analysis was also repeated in Review Manager 5.1 to obtain a relative risk estimate (RR 0.59; 95%CI=0.28–1.22) (Table 4).

REVASCULARIZATION Early PCI was not associated with any difference in revascularization at 30 days compared to rescue PCI (OR 0.49; 95%CI=0.14–1.74; p=0.27; I^2=91%). It was associated with a statistically significant reduction at 6-12 months (OR 0.38; 95%CI=0.18–0.83; p=0.02; I^2=82%). However, both estimates showed very large heterogeneity and inconsistency which made the pooled estimates

subject to a very high risk of bias. Therefore, the relative estimate was assumed to be 1.00 (Table 4).

3.2.3.5 *Risk of reinfarction, stroke and revascularization following no reperfusion treatment (aspirin only)*

Some patients do not receive any primary reperfusion strategy following a STEMI. However, these patients would generally receive at least aspirin, just like all other patients with STEMI.

This economic analysis evaluated all STEMI patients received by EMS. It was important to determine the outcomes of patients who receive aspirin alone. Section A.3 describes the calculation of how the outcomes of reinfarction, stroke and revascularization following aspirin alone compare to fibrinolysis in addition to aspirin.

When aspirin alone was compared to fibrinolysis in addition to aspirin (Section A.3), no differences were detected, precision was very low yet sample size was relatively large, and the wide confidence intervals were balanced about the line of no difference. Therefore, for this economic analysis, the probabilities of reinfarction and stroke following aspirin were assumed to be equivalent following combination fibrinolysis and aspirin. The probability of revascularization was also assumed to be equivalent in the absence of evidence. These probabilities were described previously in Section 3.2.3.4; a list of these probabilities can be found in Table 4.

3.2.3.6 *Risk of reinfarction, stroke and revascularization following primary PCI*

REINFARCTION DANAMI-2 found that primary PCI reduced the risk of reinfarction over fibrinolysis[146]. In addition, the risk was lower not only in the short-term but also in subsequent years[51,52]; the Kaplan-Meier curves show a divergence over the eight years of follow-up. At the end of eight years following STEMI, primary PCI was associated with a statistically significant 40% relative risk reduction in reinfarction over fibrinolysis (HR 0.60; 95%CI=0.46–0.77, p<0.001)[52] (Table 4).

STROKE Because long-term follow-up of stroke was not relevant, the relative risk could be taken from a meta-analysis of randomized controlled trials evaluating the short-term. Hyunh et al. performed a Bayesian meta-analysis with non-informative priors of 23 randomized controlled trials comparing primary PCI to fibrinolysis[40]. PCI was associated with a 63% odds reduction in stroke compared to fibrinolysis in the short-term (⩽6 weeks after the index STEMI) (21 trials; n=7,932; OR 0.37; 95%CI=0.21–0.60). Here, the odds ratio was used as the risk ratio because there was not enough information to determine the risk ratio (Table 4). Odds ratios have been shown to estimate the risk ratio for rare outcomes such as stroke.

REVASCULARIZATION Results from DANAMI-2 were used to generate Mantel-Haenszel risk ratios in Review Manager 5.1. At three years following index STEMI, primary PCI was associated with a 53%

reduction in revascularization with PCI[51] (RR 0.47; 95%CI=0.39–0.57; p=0.00001). As the majority of these procedures occured within the first six months, this estimate was used for the first year only (Table 4).

3.2.3.7 *Utilities*

In this economic model, the utilities for myocardial infarction, stroke and revascularization were derived from published literature. Sullivan et al. published a catalogue of EQ-5D scores using community-based UK-preference weights and EQ-5D questionnaire responses from the Medical Expenditure Panel Survey[147]. Included in their study were 79,522 individuals. Coefficients for utility decrements were determined using censored least absolute deviation regression for different International Classification of Diseases, Ninth Revision (ICD-9) and Clinical Classification Categories (CCC) codes — the CCC is a diagnosis and procedure categorization scheme and is based on International Classification of Diseases, Ninth Revision-Clinical Modification (ICD-9-CM)[149]. The utility decrements were then used to determine the actual utility.

The utility values for the CCC codes of AMI (CCC 100), coronary atherosclerosis (CCC 101) and acute cerebrovascular disease (CCC 109) were used for the utilities for STEMI, post-MI and stroke, respectively. The utility for STEMI was used for the first year following STEMI or reinfarction; thereafter, the utility of post-MI was used.

Although there is evidence that utilities improve over time[150], there is no single source of high-quality evidence following both AMI and stroke patients over time. Therefore, the utilities following post-MI and stroke were assumed to remain constant over time.

The utility of revascularization with PCI was also determined from the literature. A utility decrement was applied to the utility of STEMI or reinfarction using a previously published method[148]. Bowen et al. used EQ-5D utility values from the Arterial Revascularization Therapies Study (ARTS)[151] to estimate the QALYs over six months post-PCI revascularization and over the same time period without any revascularization. To estimate this, they used measurements of utility at baseline and six months and assumed the change in utility was constant over time to integrate the QALYs. There was a utility decrement of 0.018 between those who did not have a revascularization and those who had a revascularization with PCI (0.430 vs. 0.412). In this model, this decrement was carried out for the first six months; thereafter, the utility was assumed to be equivalent again to post-MI. The utility parameters are summarized in Table 4.

3.2.3.8 *EMS costs*

Important costs were determined through discussions with several directors of EMS in Ontario. The principal costs were determined to be the equipment used for 12-lead ECG and paramedic training.

The 12-lead ECG is read using a defibrillator; the capability to read and display a 12-lead ECG is generally a software capability. Therefore,

if existing equipment is not currently 12-lead capable, a software upgrade is possible. Alternatively, instead of a software upgrade, the equipment can be replaced with one that has the software included. An equipment upgrade costs around $3,000 while a new machine costs about $25,000.

For the base case analysis, it was assumed that all equipment were upgraded and not newly purchased. The defibrillators are replaced every five years on average. Because the equipment upgrade is primarily for the use of prehospital 12-lead ECG, the additional costs were attributed to those patients who would benefit most from that technology: STEMI patients. The average number of STEMI patients seen per five years was projected and divided from the total costs of equipment upgrades. The average number of STEMI patients seen per year was determined using Thunder Bay as a model. The Superior North EMS serves the entire Thunder Bay region. The EMS consists of 17 EMS stations in the region around Thunder Bay. They operate 8 ambulances in the city with 12-lead ECG. Thunder Bay itself is served by a single PCI centre. Superior North EMS was chosen because it recently switched from standard 3-lead ECG to 12-lead ECG.

Paramedic training generally includes a half-day course. The associated costs included wages. The average wage of a primary care paramedic was taken from the Ontario Paramedic Association. The additional costs were attributed to those patients who would make use of that training: STEMI patients. From Thunder Bay, the average number of STEMI patients seen per year per paramedic was determined and divided from the total cost of training per paramedic. Thundery Bay has 18 advanced care paramedics and 62 primary care paramedics.

The total per-patient cost for equipment upgrades was estimated to be $207 while the per-patient cost for paramedic training was $67.55. The total incremental EMS costs per patient for those who received 12-lead ECG was therefore estimated to be $274.55.

Table 5: Summary of EMS unit and total costs per-patient used in the model. Costs in 2012 Canadian dollars.

	COST ($)
ECG equipment upgrade, 12-lead capable (per-patient)	207.00
Paramedic 12-lead training (per-patient)	67.55
Total EMS costs (per-patient)	274.55

3.2.3.9 *Hospitalization costs*

Hospitalization costs were estimated from the Ontario Case Costing Initiative (OCCI) by restricting the diagnosis and intervention. The diagnoses were restricted by using the Canadian Coding Standards (CCS) for the International Classification of Diseases and Related Health Problems, 10th Revision, Canadian enhanced version (ICD-10-CA). The ICD-10-CA was developed by Canadian Institute for Health In-

formation for morbidity classification in Canada. The interventions were restricted by using the Canadian Classification of Health Interventions (CCI). A list of relevant CCS and CCI codes are presented in Table 13 and Table 14 (**??**). There are six codes for AMI (I21.0-9); one code for STEMI (R94.30); one code for ECG (2HZ24JAXJ); one code for fibrinolysis (1ZZ35HA1C); and sixteen codes for PCI (1IJ50.**).

The total mean cost of a hospital visit for emergency fibrinolysis for STEMI included the ambulatory care costs — represented by the cost of a 50mg vial of tenecteplase — and inpatient costs once the patient was admitted. The cost of tenecteplase was obtained from one of the Hamilton area hospitals. The total mean cost for patients who received only ASA was simply the inpatient costs of patients who received fibrinolysis.

Early PCI during the initial hospital stay was also possible. However, the OCCI is limited in its ability to apply multiple restrictions at the case level. Simply adding the OCCI estimate for PCI to the estimate for fibrinolysis would double-count a considerable portion of the resource use and cost. Therefore, for patients who received primary fibrinolysis and revascularization during their initial hospital stay, the sum of the mean cost of revascularization and the mean cost of the thrombolytic drug was used as the total mean cost. For patients who received primary PCI and received revascularization during their initial hospital stay, the sum of the mean cost of primary PCI and half the mean cost of the revascularization was used as the total mean cost. After discharge, patients may have been readmitted for a planned revascularization procedure. For these patients, the diagnosis was restricted to atherosclerotic cardiovascular disease (CCS=I25.10) as they no longer had an acute myocardial infarction.

The costs of hospitalization according to the intervention received are provided in Table 6. The mean total ambulatory care costs were estimated to be $2,700 (SD=$1,353) while the mean total inpatient costs were estimated to be $5,552 (n=239; SD=$4,916) for an overall mean total of $8,252 (SD=$5,099). The mean total inpatient costs of patients who received ASA alone were $5,552 (SD=$1,353), the same as those who received fibrinolysis. The mean total cost of primary PCI for STEMI was estimated to be $11,216 (n=4,030; SD=$15,509), considerably higher than fibrinolysis.

Revascularization with PCI was estimated to cost a mean total of $8,238 (n=3,644; SD=$7,081), much lower compared to primary PCI.

3.2.3.10 *Physician Fees*

Physician fees were based on the Ontario Physician Schedule of Benefits and include both inpatient and outpatient related fees. A list of physician fees is provided in Table 15 (**??**). All episodes of care, categorized by the primary intervention received, were subject to fees for consultation, diagnostic test, treatment and follow-up. The expected fees for each episode of care were determined in consultation with expert opinion.

Table 6: Hospitalization costs by treatment. All costs are in 2012 Canadian dollars, taken from the Ontario Case Costing Initiative, except where noted.

TREATMENT	DIAGNOSES	N	LOS (DAYS)		COST ($)	
			MEAN	STD	MEAN	STD
ASA only	AMI, STEMI	NA	3.3	3.4	5,552	4,916
Fibrinolysis	STEMI	NA	NA	NA	2,700	NA
Tenecteplase*	STEMI	NA	NA	NA	1,353	2,700
Fibrinolysis inpatient care	AMI	239	3.3	3.4	5,552	4,916
Primary PCI	AMI, STEMI	4030	4.0	7.4	11,216	15,509
Revascularizat'n: PCI	CAD	3644	1.9	2.8	8,238	7,081

acute myocardial infarction (AMI); aspirin (ASA); coronary artery disease (CAD); not applicable/available (NA)

* Cost was taken from a Hamilton area hospital.

CONSULTATION General consultation services for patients who received aspirin alone or fibrinolysis included the emergency physician consult of $97.60 (fee code H055). For patients who received PCI, a cardiologist consult of $157.00 (fee code A605) and an anaesthesiologist consult of $106.80 (fee code A015) were billed as well as emergency consultation premiums of $36.40 for travel and $59 per-patient for both the cardiologist and anaesthesiologist. Revascularization procedures excluded emergency consultation premiums. In addition, the consultation fees for revascularization during the initial hospital stay were the same as revascularization at any other time.

DIAGNOSTIC SERVICES There were no unique diagnostic services performed for patients who received aspirin alone or fibrinolysis. Services for diagnostic testing were only included for patients who receive PCI. For patients who received PCI, $118.70 was billed for an angiogram (fee code G297).

TREATMENT There were no particular procedure fees for patients who received aspirin alone. Procedure fees for patients who received fibrinolysis were only $6.15 for the intravenous administration of a drug (fee code G379). This was the only procedure administered which was expected to be different to patients who received PCI.

The basic procedure fee for PCI was $471.60 (fee code Z434); however, also added to this were stent and anaesthesiology fees. The average number of stents was estimated to be 1.48 using data from a previous registry study of drug eluting stent use in Ontario[152]; however, this figure was rounded down to be conservative. Thus, $78.95 was billed for stenting (fee code G298). Anaesthesiologists have a unit fee of $15.01 which is applied to basic units and time units. Basic units are set for each procedure while time units depend on the operative time; the methodology can be found in the Ontario Schedule of Benefits. An operative time of one hour was used for PCI. The corresponding anaesthesiologist procedure fee was $150.10. These fees were no different for procedures with PCI.

FOLLOW-UP Follow-up outpatient physician services were considered to be the same following aspirin alone, fibrinolysis or PCI. Follow-up was assumed to include a general practitioner consult of $77.20 (fee code A005) and a cardiologist assessment of $79.85 (fee code C603).

The total and component physician fees according to the intervention received are provided in Table 7. Fees for aspirin alone and fibrinolysis were nearly the same ($260.80) while for primary PCI, it was considerably higher ($1,287.80), mainly because the difference in treatment fees. Physician fees were lower for the brief care given at the non-PCI centre prior to transfer. Fees for revascularization with PCI were less than primary PCI ($1,054.45).

Table 7: Summary of total physician fees by treatment. All estimates are in 2012 Canadian dollars.

DESCRIPTION	CONSULT	TESTS	TREATMENT	FOLLOW-UP	TOTAL
Aspirin alone	97.60	0.00	0.00	157.05	254.65
Fibrinolysis	97.60	0.00	6.15	157.05	260.80
Primary PCI	311.40	118.70	700.65	157.05	1,287.80
Revascularizat'n via PCI	157.00	118.70	621.70	157.05	1,054.45

3.2.3.11 *Follow-up costs*

For each health state, the average annual cost of healthcare resource use for each year following discharge into the community was obtained from a costing study comparing diabetic and non-diabetic patients in Ontario. Goeree et al. compared the healthcare resource cost — as identified by the Canadian Institutes for Health Information's Discharge Abstracts Database and the Same Day Surgery Database — of diabetic patients in the Ontario Diabetic Database to matched controls from linked healthcare administrative data[153]. This model made use of the non-diabetic control cohort. The resources costs for the first, second, third, fourth and fifth years since index event were reported for myocardial infarction (n=5,409), stroke (n=22,619) and angina (n=522,146). These costs were used for STEMI/reinfarction and stroke, respectively.

The average total annual costs following STEMI, reinfarction and stroke are shown in Table 8. Average total annual costs decreased as time since index event increased. For a STEMI or a reinfarction, the costs decreased from $10,579 in the first year to $2,280 in the fifth year. For a stroke, the costs decreased from $20,351 in the first year to $3,618 in the fifth year. Costs following stroke were higher for every year compared to STEMI or reinfarction.

The aforementioned EMS costs, hospitalization costs and physician fees were parameterized for use in the model. These parameters are summarized in Table 9. Not all parameters were probabilized. There

Table 8: Yearly cost of complication by year following index event in 2012 Canadian dollars.

		COST BY YEAR SINCE EVENT, $				
COMPLICATION	N	1	2	3	4	5
STEMI/reinfarction	5,409	10,579	3,484	2,963	2,467	2,280
Stroke	22,619	20,351	4,624	4,270	3,759	3,618

is no uncertainty in the physician fees as these are set by the MOHLTC. Total acute costs are the sum of hospitalization costs and physician fees; they are shown for illustrative purposes.

3.2.4 *Analysis*

The probabilistic economic model was designed in Microsoft Excel 2010. Monte Carlo simulation method was used to compute the results. Monte Carlo simulation relies on random sampling of the model parameters. All parameters were sampled from a probability distribution. Transition probabilities and utility estimates were sampled from beta distributions, cost estimates from gamma distributions and relative risk ratio estimates from normal distributions. A total of 2,000 simulations were completed; it was found that results did not differ with 2,000 or 10,000 simulations.

Where the average incremental QALYs and costs were both higher or lower, an incremental cost-effectiveness ratio (ICER) was calculated.

3.2.5 *Sensitivity*

The role of probabilistic modeling is to describe the impact of uncertainty in the input parameters on the outcomes of interest[126]. Parameter uncertainty was inherently built into this model as it was designed as a probabilistic model. As previously described, the Monte Carlo simulation randomly samples each input parameter from its probability distribution. The joint uncertainty of QALYs and costs across all simulations can be described in a plot; the cost-effectiveness plane.

The collective uncertainty of all the parameters serves to generate uncertainty at the decision making level. To characterize the decision uncertainty, a net monetary benefit (NMB) approach was used. The NMB is the net valuation of all benefits and costs; valuation of the benefits is dependent on the WTP. The WTP is the threshold dollar figure amount a decision maker is willing to pay for an incremental unit of benefit; here, the WTP is a dollar per QALY [gained]. The distribution of NMB across all the Monte Carlo simulations for a given WTP can be used to rank the treatments by the probability of having the largest NMB.

Some parameters were fixed. These parameters can only be tested through deterministic sensitivity analyses. Such analyses were con-

Table 9: Cost parameters. The variable name, distribution, parameters and reference are shown. Units in 2012 Canadian dollars.

VARIABLE	DIST	PARAMETERS				REF
		μ	α	β	SD	
FOLLOW-UP						
Stroke, Y1	Gamma	20,351	25	814	4,070	153
Stroke, Y2	Gamma	4,624	25	185	925	153
Stroke, Y3	Gamma	4,270	25	171	854	153
Stroke, Y4	Gamma	3,759	25	150	752	153
Stroke, Y5	Gamma	3,618	25	145	724	153
MI, Y1	Gamma	10,579	25	423	2,116	153
MI, Y2	Gamma	3,484	25	139	697	153
MI, Y3	Gamma	2,963	25	119	593	153
MI, Y4	Gamma	2,467	25	99	493	153
MI, Y5	Gamma	2,280	25	91	456	153
EMS COSTS						
EMS 12-lead cost	DET	275				*
HOSPITALIZATION COSTS						
No treatment	Gamma	5,552	1	4,353	4,916	154
Fibrinolysis, inpatient	Gamma	5,552	1	4,353	4,916	154
Tenecteplase	Gamma	2,700	182	15	200	154
Primary PCI	Gamma	11,216	1	21,445	15,509	154
Revascularization	Gamma	8,238	1	6,086	7,081	154
PHYSICIAN FEES						
No treatment	DET†	255				155
Fibrinolysis	DET†	261				155
Fibrinolysis + early PCI	DET†	1,344				155
Primary PCI	DET†	1,288				155
Revascularization	DET†	1,054				155
TOTAL ACUTE COSTS						
No treatment	‡	5,807				
Fibrinolysis	‡	8,252				
Fibrinolysis + early PCI	‡	15,260				
Primary PCI	‡	12,504				
Revascularization	‡	9,292				

aspirin (ASA); deterministic (DET); fibrinolysis (FB); percutaneous coronary intervention (PCI)

* Estimated through discussions with several directors of EMS in Ontario

† Fixed cost with no uncertainty

‡ Imputed cost; sum of inpatient costs and physician fees. Shown are the mean costs.

ducted for an average age of 70, an average age of 55, a discount rate of 5% and a discount rate of 0%.

The entire analysis was also repeated for a patient population with symptom onset to ambulance greater than 30 minutes and less than 6 hours.

3.3 RESULTS

3.3.1 *Bypass eligible*

The 12-lead cohort had a mean 0.38 incremental gain in LYs, 0.23 incremental gain in QALYs and cost $1,501 more compared to the 3-lead cohort (Table 10). The associated ICER was $6,423 per QALY.

Table 10: Expected results of effects, costs and incremental effects and costs of prehospital identification with 12-lead ECG and advanced notification (12-lead) vs. no prehospital identification and no advanced notification (3-lead) in both bypass eligible and bypass ineligible for direct transfer to a PCI centre.

	BYPASS ELIGIBLE		BYPASS INELIGIBLE	
	12-LEAD	3-LEAD	12-LEAD	3-LEAD
ABSOLUTE				
LYs	8.98	8.60	8.37	8.52
QALYs	5.54	5.31	5.17	5.26
Cost	$53,670	$52,169	$52,770	$52,640
INCREMENTAL				
ΔLYs	0.38		−0.15	
ΔQALYs	0.23		−0.10	
ΔCost	$1,501		$130	
ICER(per QALY)	$6,423		DOM	

dominated (DOM); life year (LY); not applicable/available (NA); quality-adjusted life-year (QALY)

Incremental results from the probabilistic model show simulations in all four quadrants of the cost-effectiveness plane; however, most appear to be in the northeast and southeast quadrants (Figure 16). Most of the simulations show an incremental benefit in QALYs as most are found in the eastern quadrants. However, there is more uncertainty about the costs. Although more simulations show incremental costs, there is a considerable proportion that show incremental cost savings.

Decision uncertainty is summarized in the cost-effectiveness acceptability curve (Figure 17). Prehospital 12-lead ECG with advanced notification has a 36% probability of being cost-effective at a WTP of zero. This increases rapidly to a probability of 80% at a WTP of $25,000/QALY and then decelerates until there is an 87% probability at $50,000/QALY. Beyond $50,000/QALY, the probability increases marginally to an asymptote just short of 90%.

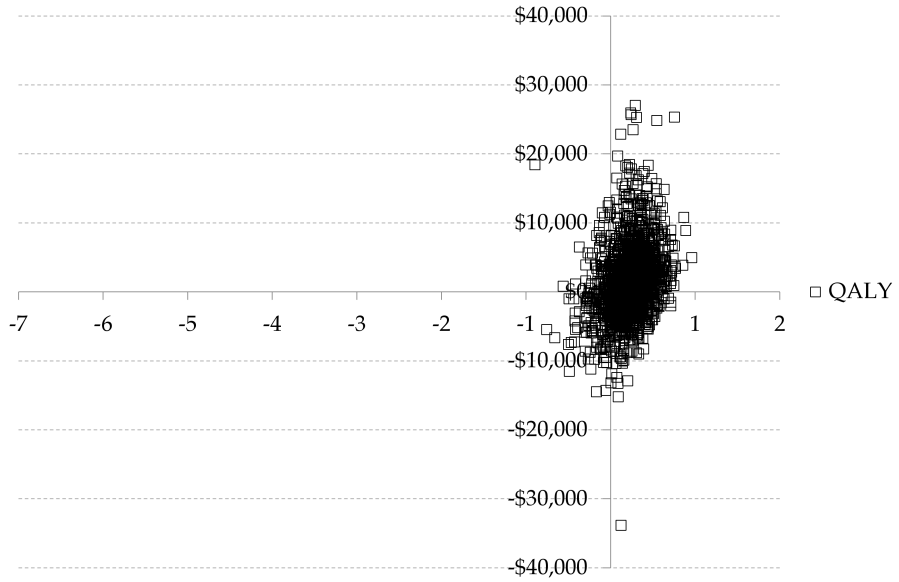


Figure 16: Cost-effectiveness plane for the bypass eligible stratum. Incremental effects and costs as well as the probability of being cost-effective for prehospital identification with 12-lead ECG and advanced notification (12-lead cohort) vs. no prehospital identification and no advanced notification.

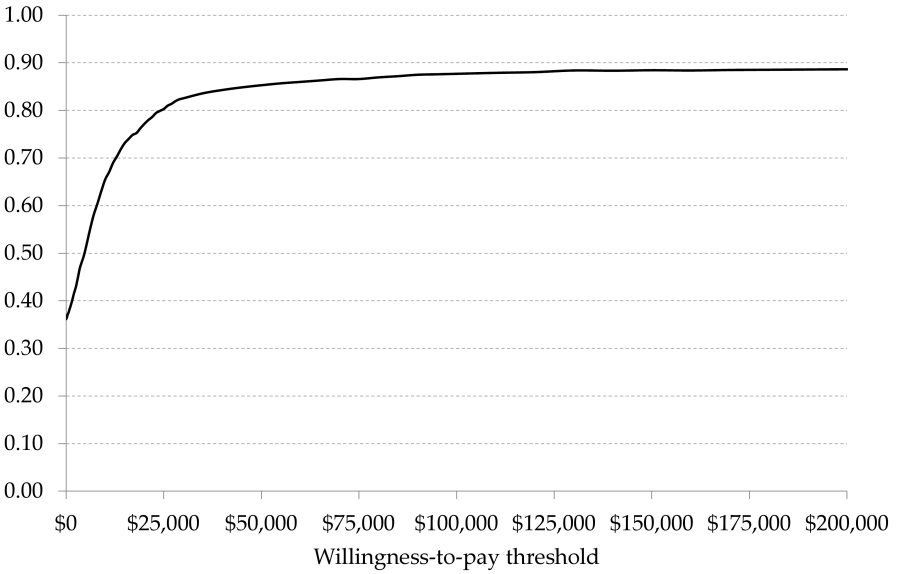


Figure 17: Cost-effectiveness plane for the bypass eligible stratum. Incremental effects and costs for prehospital identification with 12-lead ECG and advanced notification (12-lead cohort) vs. no prehospital identification and no advanced notification.

3.3.2 *Bypass ineligible*

Contrary to the bypass eligible group, the 12-lead cohort had 0.15 fewer LYs, 0.10 fewer QALYs and cost $150 more compared to the 3-lead cohort (Table 10). Being less effective and more costly, prehospital identification with 12-lead ECG and advanced notification was therefore dominated by no prehospital identification and no advanced notification.

Incremental results from the probabilistic model show simulations in all four quadrants of the cost-effectiveness plane; however, most appear to be less effective in the southwest and northwest quadrants (Figure 18). More simulations show fewer incremental QALYs but there is still a considerable proportion that show an incremental benefit. Compared to the QALYs, the costs are highly variable; however, the simulations appear balanced about the x-axis.

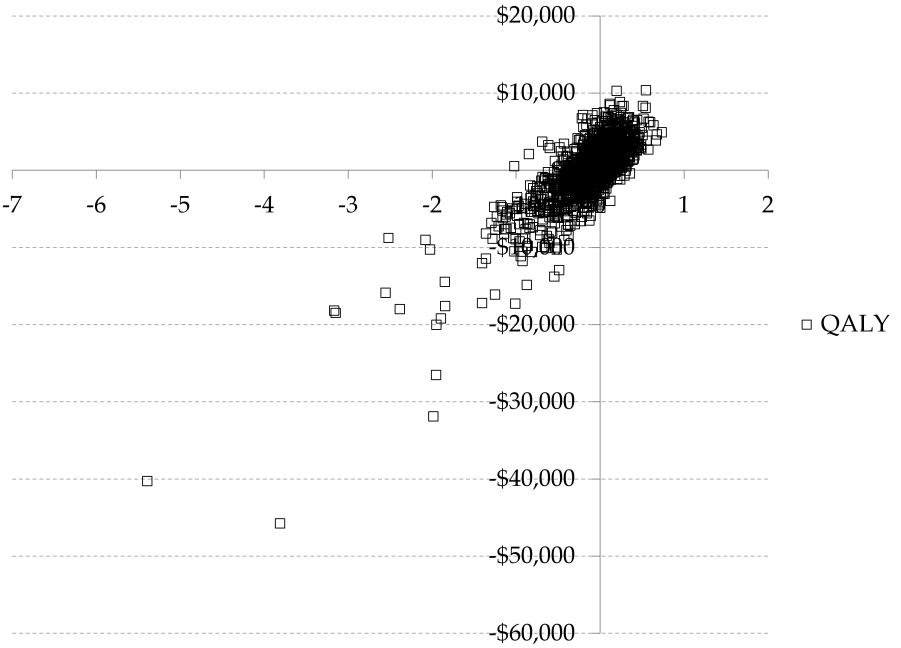


Figure 18: Cost-effectiveness plane for the bypass ineligible stratum. Incremental effects and costs for prehospital identification with 12-lead ECG and advanced notification (12-lead cohort) vs. no prehospital identification and no advanced notification.

Decision uncertainty is summarized in the cost-effectiveness acceptability curve (Figure 19). Prehospital 12-lead ECG with advanced notification has a 40% probability of being cost-effective at a WTP of zero. This drops to a low of 28% at a WTP of $7,000/QALY. It steadily rises to 40% at a WTP of $50,000/QALY. Beyond a WTP of $55,000, the probability rises marginally to an asymptote of 43%.

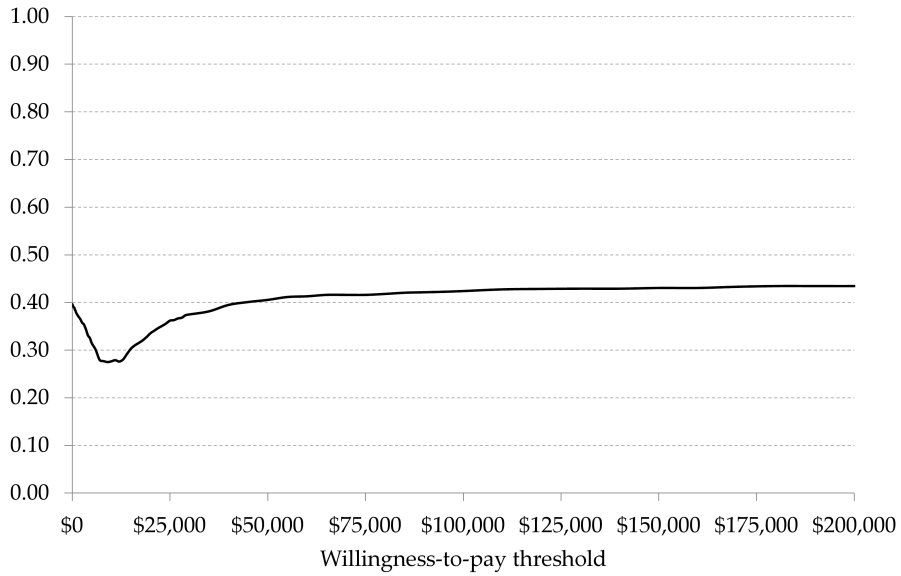


Figure 19: Cost-effectiveness acceptability curve for the bypass ineligible stratum. The probability of being cost-effective for prehospital identification with 12-lead ECG and advanced notification (12-lead cohort) vs. no prehospital identification and no advanced notification. The acceptability curve decreases as the WTP increases up to $7,000/QALY because more of the simulations in the southwest quadrant are included before those in the northeast quadrant are included and the balance of costs and effects favours a net monetary loss.

3.3.3 *Sensitivity*

The probabilistic model was run again for the following different base cases: an average age of 70, an average age of 55, a discount rate of 5% and a discount rate of 0%.

3.3.3.1 *Bypass eligible*

Average incremental LYs and QALYs for the 12-lead cohort increased for the 55 year old and 0% discount rate base cases while they decreased for the 70 year old and 5% discount rate base cases (Table 11). Average incremental costs for the 12-lead cohort increased for the 70 year old and 5% discount rate base cases and decreased for the 55 year old and 0% discount rate base cases, although it still remained a higher cost (Table 11).

Table 11: Deterministic sensitivity analyses for a 70 y.o., 55 y.o., 5% discount rate, 0% discount rate and restricted symptom onset to ambulance between 30 mins and 6 hours

	BYPASS ELIGIBLE						BYPASS INELIGIBLE					
	12-LEAD VS. 3-LEAD						12-LEAD VS. 3-LEAD					
	BASE	70 Y.O.	55 Y.O.	5% DR	0% DR	30MIN<SO <6HR	BASE	70 Y.O.	55 Y.O.	5% DR	0% DR	30MIN<SO <6HR
ΔLYs	0.38	0.33	0.45	0.33	0.49	0.89	−0.15	−0.16	−0.23	−0.12	−0.22	−0.39
ΔQALYs	0.23	0.20	0.28	0.20	0.30	0.55	−0.10	−0.10	−0.14	−0.08	−0.14	−0.24
ΔCost	$1,501	$1,692	$1,177	$1,781	$1,185	$4,410	$130	$154	−$223	$372	−$332	−$664
ICER	$6,423	$8,289	$4,218	$8,732	$3,937	$8,041	DOM	DOM	$1,593	DOM	$2,371	$2,767

dominated (DOM); discount rate (DR); symptom onset (SO); year old (Y.O.)

Any differences in average incremental QALYs and costs had little effect on the decision outcome. All of the cost-effectiveness acceptability curves show similar decision outcomes across the range of WTP (Figure 20).

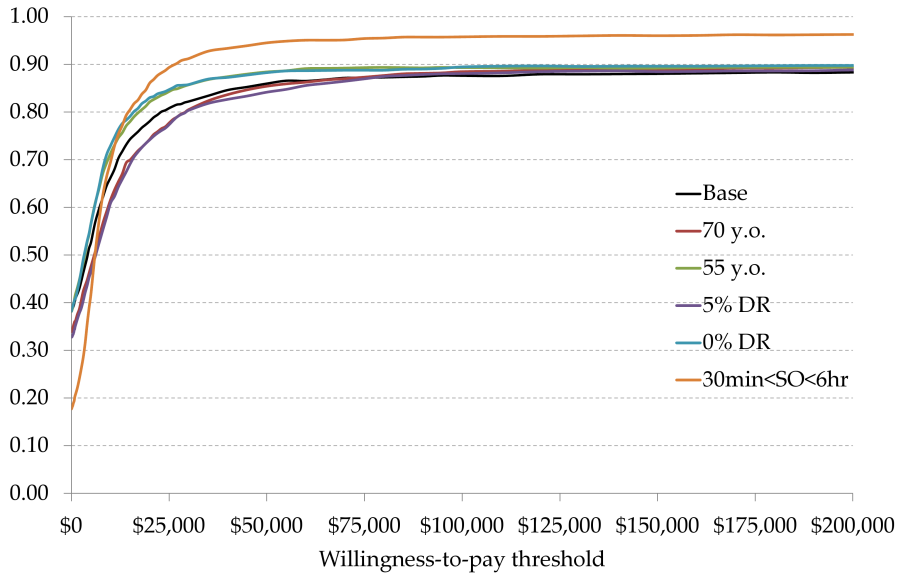


Figure 20: Probabilities of cost-effectiveness as a function of WTP for prehospital identification with 12-lead ECG and advanced notification (12-lead cohort) for a base case with average age of 70, an average age of 55, a discount rate of 5%, a discount rate of 0%, and symptom onset between 30 minutes and 6 hours, compared to no prehospital identification and no advanced notification (3-lead cohort), for the bypass eligible stratum.

3.3.3.2 *Bypass ineligible*

Average incremental LYs and QALYs for the 12-lead cohort remained the same or increased to a larger reduction for the 70 year old, 55 year old and 0% discount rate base cases while they decreased in magnitude for the 5% discount rate base case. The slight mean incremental cost increased for the 70 year old and 5% discount rate base cases while the difference became a cost savings for the 55 year old and 0% discount rate base cases (Table 11).

On average prehospital identification with 12-lead ECG and advanced notification was dominated by no prehospital identification and no advanced notification for the 70 year old and 5% discount rate base cases; it showed less average effectiveness at greater average cost.

Again, any differences in average incremental QALYs and costs had little effect on the decision outcome. All of the cost-effectiveness acceptability curves show similar decision outcomes across the range of WTP (Figure 21).

3.3.3.3 *Symptom onset between 30 minutes and 6 hours*

The analysis was repeated again for patients with symptom onset to ambulance between 30 minutes and 6 hours.

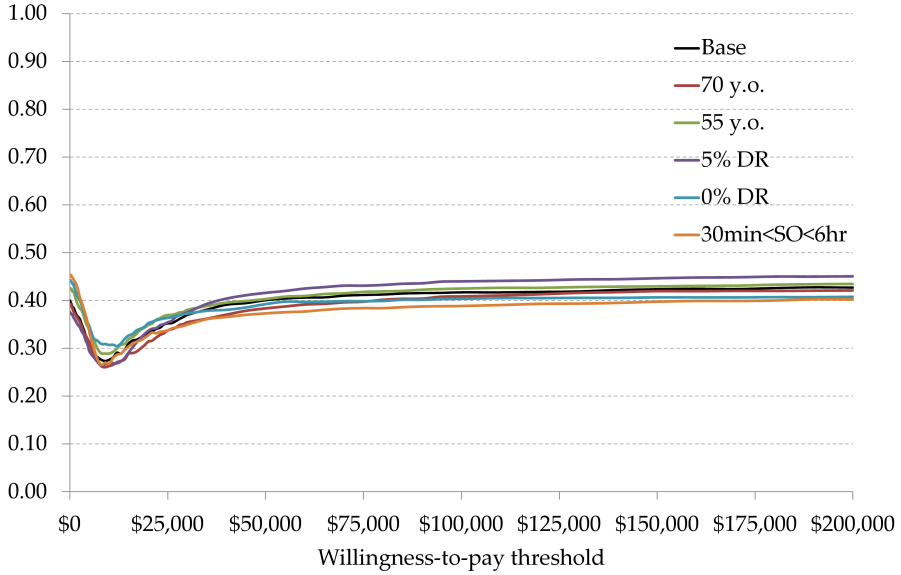


Figure 21: Probabilities of cost-effectiveness as a function of WTP for prehospital identification with 12-lead ECG and advanced notification (12-lead cohort) for a base case with average age of 70, an average age of 55, a discount rate of 5%, a discount rate of 0%, and symptom onset between 30 minutes and 6 hours, compared to no prehospital identification and no advanced notification (3-lead cohort), for the bypass ineligible stratum.

The distribution of simulations for the 12-lead bypass cohort right-shifted in the cost-effectiveness plane (**??** Figure 23). This led to higher average incremental LYs and QALY along with the higher costs associated with extending life expectancy (Table 11). At all WTP, save very low WTP below $10,000/QALY, the probability of cost-effectiveness was higher than the base case analysis (Figure 20). At $50,000/QALY, prehospital identification with 12-lead ECG and advanced notification was 95% likely to be cost-effective.

For the bypass ineligible cohort, the distribution of simulations spread more into the southwest quadrant, though the magnitude of shift was not as dramatic as the bypass eligible cohort (**??** Figure 24). The incremental loss in LYs and QALYs increased (Table 11). This led to a lower probability of cost-effectiveness at nearly all WTP (Figure 21). When viewing the cost-effectiveness acceptability curve (Figure 21), the probability is higher at very low WTP because of the lower costs associated with reducing life expectancy.

4

DISCUSSION

Increased likelihood of receiving primary PCI in the 12-lead bypass eligible cohort resulted in greater LYs and QALYs from averting events such as death, reinfarction, and stroke; however, this was not enough to offset the higher inpatient costs along with the extension of life. When considering the costs and QALYs together, prehospital identification with 12-lead ECG and advanced notification was shown to be a cost-effective management strategy at common WTP.

The cost-effectiveness acceptability curve for the bypass eligible stratum begins at 38% because 38% of the simulations show cost savings. It reaches an asymptote just shy of 90% because 90% of the simulations show greater incremental QALYs.

Unlike PCI, fibrinolysis is not associated with decreased stroke, reinfarction or revascularization against a background of aspirin, as previously mentioned (Chapter 3).

The reduction in life expectancy in 12-lead vs. 3-lead bypass ineligible cohort nearly offset the additional costs of tenecteplase as the average lifetime incremental costs were negligible. When considering the costs and QALYs together, there was no evidence that prehospital identification with 12-lead ECG and advanced notification was cost-effective at common WTP. In fact, the cost-effectiveness acceptability curve showed there was a very low probability of cost-effectiveness at low WTP.

The acceptability curve for the bypass ineligible stratum decreases as the WTP increases up to $7,000/QALY because more of the simulations in the southwest quadrant are included before those in the northeast quadrant are included and the balance of costs and effects favours a net monetary loss. Beyond a WTP or $7,000/QALY, the reverse happens. The acceptability curve begins at 40% because 40% of the simulations show cost savings. It reaches an asymptote at 43% because 43% of the simulations show greater incremental QALYs.

This evaluation was conducted to ascertain the cost-effectiveness of prehospital identification with 12-lead ECG and advanced notification compared to no prehospital identification and no advanced notification, stratified by eligibility to bypass to a PCI centre. In doing so, a contemporary portrait was obtained of the natural history of STEMI patients in Ontario who received different prehospital management strategies.

The body of evidence showing the effectiveness of prehospital identification and advanced notification in reducing reperfusion delay and mortality has accumulated over time[55–76,113,114]. Although the gap in adoption has been previously described for widely recommended strategies (such as paramedic training in the acquisition and interpretation of 12-lead ECGs and EMS transport bypass protocols)[156],

it is unclear how these recommended strategies translated into actual use among those EMS that have adopted them.

In the early 2000s, global registry databases, including a Canadian one[157], found that around 30% of STEMI patients did not receive reperfusion[158–160].

Previously, prehospital studies of STEMI patients have generally restricted their analyses to patients that received primary reperfusion, either fibrinolysis or PCI[55–76,113,114]. Few have reported on STEMI patients that do not receive primary reperfusion. Future studies should explore this gap to ascertain differences bypass eligible and bypass ineligible sites in how the 12-lead ECG is being used and how decisions lead to primary reperfusion.

Prehospital identification and advanced notification of STEMI is a health systems intervention; as such, it is generally not possible to compare against a concurrent control using the same EMS service or receiving hospital. Single-center studies have therefore generally used historical controls. The use of historical controls reduces the heterogeneity between service providers seen in multi-centre studies. However, the risk of bias would increase if the quality of STEMI care has changed over the studied time period. In Ontario, the quality of STEMI patients has changed appreciably in the past 5 years.

This economic evaluation used mortality estimates and treatment proportions for the four cohorts from an observational cohort study. The disadvantages of this data source are common to all observational studies. One of these disadvantages is that causal inferences of prehospital management strategy and mortality may be biased due to confounding variables. PREDICT stratified the cohorts based on one confounder – eligibility to bypass to a PCI centre.

Mortality estimates used in this model showed considerable uncertainty.

While there are multiple imputation methods for missing data[161], a better solution to the fragile and imprecise mortality estimates may be to model them with a surrogate outcome using published equations. The association between longer ischemic times with excess mortality has been fairly well documented[4,6,9,10,17–19,23,37]. It may be possible to use the door-to-balloon/needle time to predict 30-day mortality for each patient. However, the limitation in this approach is that these models were built using data from randomized trials in different settings. Due to a more restrictive inclusion, these models have limited validity for patients with longer symptom onset or door-to-balloon/needle delay that are more common in the "real-world". In addition, the randomized trials were all generally conducted at high-volume PCI centres. Although these are limitations, they may be outweighed by the advantages.

The Canadian guidelines for STEMI care have recommended that all patients who can achieve a first medical contact-to-balloon time less than 90 minutes receive primary PCI[30], which, in practice, is generally applied to a door-to-balloon time instead. In addition, the recom-

mended time is the same for patients who present to a non-PCI hospital or to a PCI hospital. However, the American and European guidelines recommend that for patients who present to a non-PCI centre, the [first] door-to-balloon time should not exceed 120 minutes[162,163]. Aligning the Canadian guidelines would increase access to primary PCI, though it is unclear by how much.

As previously mentioned in the introduction, the MOHLTC provides a maximum 50% of required land ambulance service funding while the municipalities are responsible for the balance of funding as well as the service provision. What is "required" is determined by the MOHLTC. Of relevance to land ambulance service, the Ministry has set standards for: ambulance service patient care and transportation[164]; basic and advanced life support patient care[165,166]; land ambulance certification[167]; land ambulance and emergency response vehicles[168]; and ambulance equipment[169].

Standards for equipment such as the ECG are defined in the ambulance equipment standards[169]. The ambulance equipment standards have not been revised since 2000. In their current state, there is no requirement for the on-board defibrillator to be able to produce 12-lead ECG readings. What is required, is a "three lead" ECG cable. In addition, there is no mention of the requirements for the software that accompanies the defibrillator.

Uncertainty in the cost-effectiveness in bypass ineligible settings may be reduced by enrolling more patients or by modeling final outcomes using a surrogate such as time to reperfusion delay.

A randomized trial conducted in Canada[170] as well as previous meta-analyses[33–35] have shown the benefit of early PCI, yet its use among patients who received fibrinolysis was very low in this study.

Several studies have shown that primary PCI is cost-effective when compared to fibrinolysis in patients with STEMI[171–175]. However, there are no known economic evaluations of prehospital management strategies for STEMI. The closest study to an economic analysis of prehospital management strategies for STEMI is an economic analysis of STEMI patients treated at hospitals in the National Infarct Angioplasty Project (NIAP) — a project aimed to expand primary angioplasty — to hospitals not in the NIAP, conducted by Wailoo et al[176]. The study was a "real-world" study using a UK observational database incorporated into a decision analytic model. The NIAP was found to increase baseline access to primary reperfusion more than the 12-lead cohort. Wailoo et al. found the NIAP hospitals had a mean 0.18 additional QALYs and a mean £900 (C$1,422) additional costs. This economic analysis also found that increasing access to primary PCI through prehospital identification and advanced notification was cost-effective.

5

CONCLUSIONS

This thesis saw the development of an economic model of the different prehospital management strategies. The results of the model show that prehospital identification with 12-lead ECG and advanced notification is a cost-effective management strategy compared to no prehospital identification and no advanced notification where patients are eligible for bypass to a PCI centre. However, where patients were not eligible for bypass, it was uncertain whether prehospital identification and advanced notification was cost-effective. Uncertainty may be reduced by modeling mortality with a surrogate outcome such as time to reperfusion delay.

This thesis has shown that the cost-effectiveness of prehospital identification with 12-lead ECG and advanced notification may depend on access to primary PCI.

I

APPENDICES

A

LITERATURE REVIEW

A.1 LITERATURE REVIEW OF EFFECTIVENESS OF PREHOSPITAL IDENTIFICATION WITH 12-LEAD ECG

A.1.1 *Search strategies*

EMBASE via OVID (1988 to 2012 week 31)

	SEARCHES	RESULTS
1	exp Electrocardiography/	71473
2	(electrocardiograph* or electrocardiogram* or ECG or EKG or cardioscope*).ti,ab.	84051
3	((ED or department or lab* or prehospital) adj3 (notif* or activat*)).ti,ab.	2001
4	exp emergency health service/	48799
5	exp rescue personnel/	4526
6	(EMS or ambulance* or emergency medical service* or emergency service* or emergency technician* or emergency medical service or emergency medical technicians or rescue personnel or emergency health service or medical emergency service or emergency medical technician* or paramedic).ti,ab.	19913
7	(pre-hospital or prehospital).ti,ab.	9618
8	exp heart infarction/	185126
9	(myocardial infarct* or AMI or (acute* adj MI) or ST segment elevation or ST elevation or STEMI or heart attack or heart infarct*).ti,ab.	143367
10	or/1-3	125385
11	or/4-7	67141
12	or/8-9	215478
13	and/10-12	1272
14	(review or editorial or letter or note).pt.	3267357
15	13 not 14	1066
16	limit 15 to (human and english language and yr="1988 -Current")	723
15	13 not 14	709

PUBMED (1998 to 2012 week 31)

	SEARCHES	RESULTS
#19	Search #17 not #18	896
#18	Search (review[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR case reports[pt] OR guideline[pt]) AND ("1988/01/01"[Date - Publication] : "3000"[Date - Publication])	3499282
#17	Search #15 OR #16	1216
#16	Search #14 AND (publisher[sb] OR in process[sb] OR pubmednotmedline[sb])	24
#15	Search (#14 AND Humans[Filter]) AND English[Filter]	1192
#14	Search #11 AND #12 AND #13	1451
#13	Search #9 OR #10	147251
#12	Search #5 OR #6 OR #7 OR #8	97104
#11	Search #2 OR #3 OR #4	201043
#10	Search myocardial infarct*[tiab] OR AMI[tiab] OR acute* MI[tiab] OR ST segment elevation[tiab] OR ST elevation[tiab] OR STEMI[tiab] OR heart attack[tiab] OR heart infarct*[tiab]	31120
#9	Search Myocardial Infarction[mh]	136300
#8	Search pre-hospital OR prehospital[tiab]	8286
#7	Search EMS OR ambulance*[tiab] OR emergency medical service*[tiab] OR emergency service*[tiab] OR emergency technician*[tiab] OR emergency medical service[tiab] OR emergency medical technicians[tiab] OR rescue personnel[tiab] OR emergency health service[tiab] OR medical emergency service* OR emergency medical technician*[tiab] OR paramedic[tiab]	22141
#6	Search Emergency Medical Technicians[mh]	4523
#5	Search Emergency Medical Services[mh]	84126
#4	Search ED notif*[tiab] OR ED activat*[tiab] OR department notif*[tiab] OR lab* notif*[tiab] OR lab activat*[tiab] OR prehospital notif*[tiab] OR prehospital activat*[tiab]	82
#3	Search electrocardiograph*[tiab] OR electrocardiogram*[tiab] OR ECG[tiab] OR EKG[tiab] OR cardioscope*[tiab]	94613
#2	Search Electrocardiography[mh]	167708

Cochrane Register of Controlled Trials via WILEY (no date restriction)

	SEARCHES	RESULTS
#1	MeSH descriptor Electrocardiography explode all trees	7179
#2	(electrocardiograph* OR electrocardiogram* OR ECG OR EKG OR cardioscope*):ti,ab,kw	11718
#3	((ED OR department OR lab* or prehospital) NEAR/3 (notif* OR activat*)):ti,ab,kw	27
#4	MeSH descriptor Emergency Medical Services explode all trees	2405
#5	MeSH descriptor Emergency Medical Technicians explode all trees	104
#6	(EMS OR ambulance* OR emergency medical service* OR emergency service* OR emergency technician* OR emergency medical service OR emergency medical technicians OR rescue personnel OR emergency health service OR medical emergency service OR emergency medical technician* OR paramedic):ti,ab,kw	3656
#7	(pre-hospital OR prehospital):ti,ab,kw	584
#8	MeSH descriptor Myocardial Infarction explode all trees	7892
#9	(myocardial infarct* OR AMI OR (acute* NEXT MI) OR ST segment elevation OR ST elevation OR STEMI OR heart infarct*):ti,ab,kw	14191
#10	(#1 OR #2 OR #3)	11807
#11	(#4 OR #5 OR #6 OR #7)	4115
#12	(#8 OR #9)	14255
#13	(#10 AND #11 AND #12)	127

A.1.2 *Screening form*

Is the study a primary observational or randomized study?
[YES] Include.
[NO] Exclude.
[UNCLEAR] Include.

Is the relevant population STEMI?
[YES] Include.
[NO] Exclude.
[UNCLEAR] Include.

Does the intervention group include prehospital identification with 12-lead electrocardiogram with advanced notification?
[YES] Include.
[NO] Exclude.
[UNCLEAR] Include.

Does the control group include prehospital identification, prehospital notification or activation of catheterization laboratory or ED, bypass of a non-PCI centre or direct transportation to the catheterization laboratory for PCI?
[YES] Exclude.
[NO] Include.
[UNCLEAR] Include.

Does either prehospital strategy include the explicit use of prehospital fibrinolysis?
[YES] Exclude.
[NO] Include.
[UNCLEAR] Include.

Does the control group or intervention group include walk-ins?
[YES] Exclude.
[NO] Include.
[UNCLEAR] Include.

Does the study have 29 or less participants?
[YES] Exclude.
[NO] Include.
[UNCLEAR] Include.

Include only those studies which were coded as "include" for all questions. Exclude all others.

A.1.3 *Inclusion of two studies of fibrinolysis with sample sizes <30*

The characteristics of the two studies[113,114] are presented in Table 12. One study was a small randomized control trial conducted for a local jurisdiction of multiple centres. The diagnosis was made by the emergency physician via telemtry. Advanced notification of the emergency physician/ED was made by the EMS who transported the patient directly to the ED. The other was a prospective observational study with historical controls conducted for a local jurisdiction of a single centre. Diagnosis was made by the paramedic and emergency physician upon ED arrival. EMS transported patients directly to the ED.

The door-to-needle times for the four studies included in the original analysis along with the two studies with sample sizes <30 are summarized in Figure 22. There were 1,705 participants in the prehospital identification group compared to 25,199 in the comparison group. Very large heterogeneity precluded any pooling of results (χ^2=177.94; df=5; p<0.00001; I^2=97%).

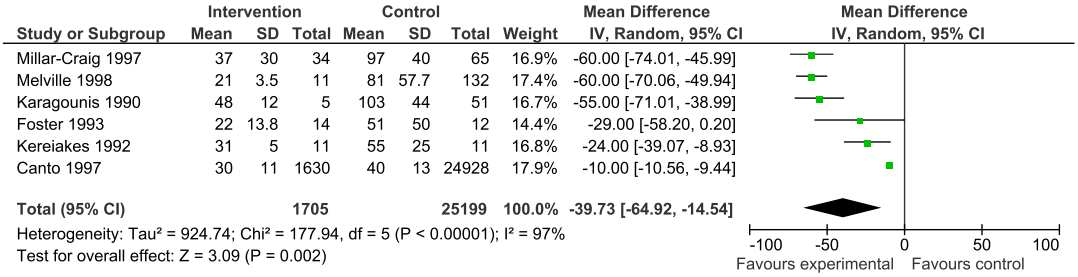


Figure 22: The mean difference in door-to-needle time (minutes) for prehospital identification and advanced notification (intervention) vs. no identification, no advanced notification (control) with additional included studies. Negative numbers indicate a reduction in delay (favours intervention).

Table 12: Characteristics of included studies with sample size <30 where patients received fibrinolysis (n=2)

STUDY	TYPE OF STUDY/SETTING	INTERVENTION GROUP	CONTROL GROUP	OTHER INCL/EXCLUSION	OUTCOMES
Kereiakes, 1992[114] n=22 US	Randomized controlled trial; Local jurisdict'n of multiple centres	Diagnosis: EP via telemetry; Adv. Notificat'n: EP/ED via EMS; Bypass not applicable; EMS direct to ED.	EMS direct to ED	Incl: chest pain with AMI; Excl: none stated.	DTN
Foster, 1994[113] n=26 US	Prospective observat'l study with historical controls; Local jurisdict'n of single centre	Diagnosis: paramedic & EP upon ED arrival; Adv. Notificat'n: ED by EMS; Bypass not applicable EMS direct to ED	EMS direct to ED	Incl: chest pain with AMI, treated with fibrinolysis; Excl: advanced malignancy; "do not resuscitate" documentation; <21 years of age; patients unaable to give a history because unreliable history, full cardiac arrest	DTN

acute myocardial infarction (AMI); door-to-needle (DTN); emergency department (ED); emergency medical services (EMS); emergency physician (EP)

A.2 LITERATURE REVIEW OF COST-EFFECTIVENESS OF PREHOSPITAL IDENTIFICATION WITH 12-LEAD ECG

A.2.1 *Search strategies*

EMBASE via OVID (no date restriction)

	SEARCHES	RESULTS
1	exp Electrocardiography/	71473
2	(electrocardiograph* or electrocardiogram* or ECG or EKG or cardioscope*).ti,ab.	84051
3	((ED or department or lab* or prehospital) adj3 (notif* or activat*)).ti,ab.	2001
4	exp emergency health service/	48799
5	exp rescue personnel/	4526
6	(EMS or ambulance* or emergency medical service* or emergency service* or emergency technician* or emergency medical service or emergency medical technicians or rescue personnel or emergency health service or medical emergency service or emergency medical technician* or paramedic).ti,ab.	19913
7	(pre-hospital or prehospital).ti,ab.	9618
8	exp heart infarction/	185126
9	(myocardial infarct* or AMI or (acute* adj MI) or ST segment elevation or ST elevation or STEMI or heart attack or heart infarct*).ti,ab.	143367
10	or/1-3	125385
11	or/4-7	67141
12	or/8-9	215478
13	and/10-12	1272
14	exp Economics/	173930
15	"Quality of Life"/ or "Value of Life"/ or Quality-Adjusted Life Years/	279851
16	exp Models, Economic/ or Markov Chains/ or Monte Carlo Method/ or Decision Trees/	149500
17	(economic$ or cost? or costing? or costly or costed or price? or pricing?).tw.	441944
18	(pharmacoeconomic? or (pharmaco adj economic?) or budget$ or expenditure$).tw.	55821
19	(value adj1 (money or monetary)).tw.	337
20	(fee or fees or "quality of life" or qol$ or hrqol$).tw.	180093
21	("quality adjusted life year$" or qaly$ or cba or cea or cua or utilit$ or markov$ or monte carlo).tw.	174825
22	(decision adj2 (tree$ or analys$ or model$)).tw.	11940
23	((clinical or critical or patient) adj (path? or pathway?)).tw.	4307
24	(managed adj2 (care or network?)).tw.	18879
25	exp Health Economics/ or exp Health Care Cost/ or exp Quality of Life/	661332
26	or/14-25	1371714
27	and/13,26	185
28	(review or editorial or letter or note).pt.	3267357
29	27 not 28	139
30	limit 29 to (english language and yr="1988 -Current")	118

PUBMED

	SEARCHES	RESULTS
#32	Search #30 not #31	80
#31	Search (review[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR case reports[pt] OR guideline[pt]) AND ("1988/01/01"[Date - Publication] : "3000"[Date - Publication])	3499282
#30	Search #28 OR #29	116
#29	Search #27 AND (publisher[sb] OR in process[sb] OR pubmednotmedline[sb])	1
#28	Search #27 AND English[Filter]	116
#27	Search #14 AND #26	126
#26	Search #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	941817
#25	Search managed care[tw] OR managed network[tw]	28341
#24	Search clinical path*[tw] OR critical path*[tw] OR patient path*[tw]	15779
#23	Search decision tree$[tw] OR decision analys$[tw] OR decision model$[tw]	3700
#22	Search quality adjusted life year$[tw] OR qaly$[tw] OR cba[tw] OR cea[tw] OR cua[tw] OR utilit$[tw] OR markov$[tw] OR monte carlo[tw]	83958
#21	Search fee[tw] OR fees[tw] OR quality of life[tw] OR qol$[tw] OR hrqol$[tw]	188682
#20	Search value for money[tw] OR monetary[tw]	4544
#19	Search pharmacoeconomic?[tw] OR pharmaco economic?[] or economic? pharmaco[tw] OR budget$[tw] OR expenditure$[tw]	38263
#18	Search economic$[tw] OR cost?[tw] OR costing?[tw] OR costly[tw] OR costed[tw] OR price?[tw] OR pricing?[tw]	405573
#17	Search Models, Economic[mh] OR Markov Chains[mh] OR Monte Carlo Method[mh] OR Decision Trees[mh]	38960
#16	Search Quality of Life[mh] OR Value of Life[mh] OR Quality-Adjusted Life Years[mh]	108211
#15	Search Economics[mh]	455136
#14	Search #11 AND #12 AND #13	1451
#13	Search #9 OR #10	147251
#12	Search #5 OR #6 OR #7 OR #8	97104
#11	Search #2 OR #3 OR #4	201043
#10	Search myocardial infarct*[tiab] OR AMI[tiab] OR acute* MI[tiab] OR ST segment elevation[tiab] OR ST elevation[tiab] OR STEMI[tiab] OR heart attack[tiab] OR heart infarct*[tiab]	31120
#9	Search Myocardial Infarction[mh]	136300
#8	Search pre-hospital OR prehospital[tiab]	8286
#7	Search EMS OR ambulance*[tiab] OR emergency medical service*[tiab] OR emergency service*[tiab] OR emergency technician*[tiab] OR emergency medical service[tiab] OR emergency medical technicians[tiab] OR rescue personnel[tiab] OR emergency health service[tiab] OR medical emergency service* OR emergency medical technician*[tiab] OR paramedic[tiab]	22141
#6	Search Emergency Medical Technicians[mh]	4523
#5	Search Emergency Medical Services[mh]	84126
#4	Search ED notif*[tiab] OR ED activat*[tiab] OR department notif*[tiab] OR lab* notif*[tiab] OR lab activat*[tiab] OR prehospital notif*[tiab] OR prehospital activat*[tiab]	82
#3	Search electrocardiograph*[tiab] OR electrocardiogram*[tiab] OR ECG[tiab] OR EKG[tiab] OR cardioscope*[tiab]	94613
#2	Search Electrocardiography[mh]	167708

National Health Service Centre for Reviews and Dissemination (no date restriction)

	SEARCHES	RESULTS
1	MeSH DESCRIPTOR Electrocardiography EXPLODE ALL TREES	224
2	electrocardiograph* OR electrocardiogram* OR ECG OR EKG OR cardioscope*	527
3	ED notif* OR ED activat* OR department notif* OR lab* notif* OR lab activat* OR prehospital notif* OR prehospital activat*	1
4	MeSH DESCRIPTOR Emergency Medical Services EXPLODE ALL TREES	525
5	MeSH DESCRIPTOR Emergency Medical Technicians EXPLODE ALL TREES	15
6	EMS OR ambulance* OR emergency medical service* OR emergency service* OR emergency technician* OR emergency medical service OR emergency medical technicians OR rescue personnel OR emergency health service OR medical emergency service OR emergency medical technician* OR paramedic	580
7	Prehospital or pre-hospital	108
8	MeSH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES	718
9	myocardial infarct* OR AMI OR acute MI OR ST segment elevation OR ST elevation OR STEMI OR heart infarct*	2051
10	#1 OR #2 OR #3	533
11	#4 OR #5 OR #6 OR #7	705
12	#8 OR #9	2057
13	#10 AND #11 AND #12	38

A.2.2 *Screening form*

Is the study a cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis or costing study?
[YES] Include.
[NO] Exclude.
[UNCLEAR] Include.

Is the relevant population STEMI?
[YES] Include.
[NO] Exclude.
[UNCLEAR] Include.

Does the intervention group include prehospital identification with 12-lead electrocardiogram with advanced notification?
[YES] Include.
[NO] Exclude.
[UNCLEAR] Include.

Does the control group include prehospital identification, prehospital notification or activation of catheterization laboratory or ED, bypass of a non-PCI centre or direct transportation to the catheterization laboratory for PCI?
[YES] Exclude.
[NO] Include.
[UNCLEAR] Include.

Does either prehospital strategy include the explicit use of prehospital fibrinolysis?
[YES] Exclude.
[NO] Include.
[UNCLEAR] Include.

Does the control group or intervention group include walk-ins?
[YES] Exclude.
[NO] Include.
[UNCLEAR] Include.

Include only those studies which were coded as "include" for all questions. Exclude all others.

A.3 RISK OF REINFARCTION, STROKE AND REVASCULARIZATION FOLLOWING NO REPERFUSION TREATMENT (ASPIRIN ONLY)

A.3.1 *Methods*

The incremental effect of fibrinolysis and aspirin versus aspirin alone can be determined with a closer look at ISIS-2[25]. ISIS-2 was a randomized factorial trial that randomized streptokinase to placebo, and as-

pirin to placebo in 17,187 participants. Of all the patients in the streptokinase cohort, 50% received aspirin; of all patients in the aspirin cohort, 50% received streptokinase. Because the treatment effects are independent and additive[25], the absolute risk reduction (ARR) in the cohort with combination streptokinase and aspirin over the cohort with neither treatment was the sum of the ARRs from streptokinase alone and aspirin alone, respectively (Equation 1). Similarly, the ARR of the streptokinase cohort over the cohort with neither treatment was the ARR of streptokinase alone over neither treatment plus 50% of the ARR of aspirin alone over neither treatment (Equation 2). And likewise, the ARR of the aspirin cohort over neither treatment cohort was the ARR of the aspirin alone over neither treatment plus 50% of the ARR of streptokinase alone over neither treatment (Equation 3). This can also be extended to the placebo groups (Equation 4,5). Using simple algebra, one can derive the ARRs of streptokinase alone and aspirin alone, respectively.

The algebra is summarized by the following equations:

$$\mathrm{ARR}_{\text{ISIS-2 SK+ASA cohort}} = \mathrm{ARR}_{\text{SK alone}} + \mathrm{ARR}_{\text{ASA alone}} \tag{1}$$

$$\mathrm{ARR}_{\text{ISIS-2 SK cohort}} = \mathrm{ARR}_{\text{SK alone}} + \frac{1}{2}\mathrm{ARR}_{\text{ASA alone}} \tag{2}$$

$$\mathrm{ARR}_{\text{ISIS-2 ASA cohort}} = \mathrm{ARR}_{\text{ASA alone}} + \frac{1}{2}\mathrm{ARR}_{\text{SK alone}} \tag{3}$$

$$\mathrm{ARR}_{\text{ISIS-2 no SK cohort}} = \frac{1}{2}\mathrm{ARR}_{\text{ASA alone}} \tag{4}$$

$$\mathrm{ARR}_{\text{ISIS-2 no ASA cohort}} = \frac{1}{2}\mathrm{ARR}_{\text{SK alone}} \tag{5}$$

where SK is streptokinase and ASA is aspirin. Note, all ARRs are compared to treatment with neither aspirin nor streptokinase. These equations apply to mortality, reinfarction and stroke.

With the ARRs, the absolute risk following aspirin alone can be determined. Then, the risk ratio of combination fibrinolysis plus aspirin versus aspirin alone can be computed. Using this method, the risk ratio between of any outcome for any two of the four cohorts in ISIS-2 can be determined.

The aforementioned method was used to derive the relative effects on reinfarction and stroke, respectively, of aspirin compared to combination fibrinolysis plus aspirin from ISIS-2[25]. Mantel-Haenszel risk ratios were computed in Review Manager 5.1 (Cochrane Collaboration). At the time of ISIS-2 in 1988, PCI was not yet a widespread practice and so revascularization was not captured.

A.3.2 *Results*

No differences were found in 35-day reinfarction (n=8,590; RR 0.96; 95%CI=0.71–1.31; p=0.82) or stroke (n=8,590; RR 1.09; 95%CI= 0.62–1.91; p=0.77) when combination streptokinase and aspirin were compared to aspirin alone. All estimates showed wide confidence intervals relatively balanced about the line of no difference.

A.3.3 *Conclusion*

No differences were detected, precision was very low yet sample size was relatively large, and the wide confidence intervals were balanced about the line of no difference. Therefore, for this economic analysis, the probabilities of reinfarction and stroke following aspirin were assumed to be equivalent following combination fibrinolysis and aspirin. The probability of revascularization was also assumed to be equivalent in the absence of evidence.

A.4 CLASSIFICATION CODES AND FEE CODES

Table 13: Canadian Classification of Health Interventions (CCI) codes used in the Ontario Case Costing Initiative databases.

INTERVENTION	CCI CODE	DESCRIPTION
Fibrinolysis	1ZZ35HA1C	Pharmacotherapy, total body, percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal], using thrombolytic agent.
ECG	2HZ24JAXJ	Electrophysiological measurement, heart, using recording electrodes [or ECG NOS]. External application. Excludes: that done as part of sleep studies, that done for cardiac stress test.
CABG	1IJ76DAXXQ	Bypass, coronary arteries, using combined sources of tissue [e.g. graft/pedicled flap], endoscopic approach.
	1IJ76LAXXA	Bypass, coronary arteries, using autograft [e.g. saphenous], open approach (sternotomy).
	1IJ76LAXXG	Bypass, coronary arteries, using pedicled flap [e.g. internal mammary, thoracic], open approach [sternotomy].
	1IJ76LAXXN	Bypass, coronary arteries, using synthetic tissue (graft), open approach [sternotomy].
	1IJ76LAXXQ	Bypass, coronary arteries, using combined sources of tissue [e.g. graft/pedicled flap], open approach.
	1IJ76WKXXA	Bypass, coronary arteries, using autograft [e.g. saphenous], minimal (beating heartkeyhole) incisional technique [e.g. MIDCAB].
	1IJ76WKXXG	Bypass, coronary arteries, using pedicled flap [e.g. internal mammary, thoracic], minimal (beating heartkeyhole) incisional technique [e.g. MIDCAB].
	1IJ76WKXXQ	Bypass, coronary arteries, using combined sources of tissue [e.g. graft/pedicled flap], minimal (beating heartkeyhole) incisional technique [e.g. MIDCAB].
	1IJ76BQXXA	Bypass, coronary arteries, using autograft [e.g. saphenous], endoscopic approach with robotic telemanipulation of tools
	1IJ76DAXXA	Bypass, coronary arteries, using autograft [e.g. saphenous], endoscopic approach.
PCI	1IJ50GQOD	Dilation, coronary arteries, without stent insertion, using ultrasound (and balloon) dilator, percutaneous transluminal approach [e.g. with angioplasty alone]
	1IJ50GQBD	Dilation, coronary arteries, without stent insertion, using ultrasound (and balloon) dilator with (endovascular) stent, percutaneous transluminal approach [e.g. with angioplasty alone]
	1IJ50GQBF	Dilation, coronary arteries, without stent insertion, using laser (and balloon) dilator, percutaneous transluminal approach [e.g. with angioplasty alone]
	1IJ50GUBD	Dilation, coronary arteries, without stent insertion, using balloon or cutting balloon dilator, percutaneous transluminal approach [e.g. with angioplasty alone]
	1IJ50GUOD	Dilation, coronary arteries, without stent insertion, using ultrasound (and balloon) dilator, percutaneous transluminal approach [e.g. with angioplasty alone]
	1IJ50GTBD	Dilation, coronary arteries, without stent insertion, using balloon or cutting balloon dilator, percutaneous transluminal approach with atherectomy [e.g. rotational, directional, extraction catheter, laser]
	1IJ50GTBF	Dilation, coronary arteries, without stent insertion, using laser (and balloon) dilator, percutaneous transluminal approach with atherectomy [e.g. rotational, directional, extraction catheter, laser]

INTERVENTION	CCI CODE	DESCRIPTION
	1IJ50GQOE	Dilation, coronary arteries, with (endovascular) stent insertion, using ultrasound (and balloon) dilator with (endovascular) stent, percutaneous transluminal approach [e.g. with angioplasty alone]
	1IJ50GQNR	Dilation, coronary arteries, with (endovascular) stent insertion, using (endovascular) stent only, percutaneous transluminal approach [e.g. with angioplasty alone]
	1IJ50GQOA	Dilation, coronary arteries, with (endovascular) stent insertion, using balloon or cutting balloon dilator with (endovascular) stent, percutaneous transluminal approach [e.g. with angioplasty alone]
	1IJ50GQOB	Dilation, coronary arteries, with (endovascular) stent insertion, using laser (and balloon) dilator with (endovascular) stent, percutaneous transluminal approach [e.g. with angioplasty alone]
	1IJ50GTOA	Dilation, coronary arteries, with (endovascular) stent insertion, using balloon or cutting balloon dilator with (endovascular) stent, percutaneous transluminal approach with atherectomy [e.g. rotational, directional, extraction catheter, laser]
	1IJ50GUOA	Dilation, coronary arteries, with (endovascular) stent insertion, using balloon or cutting balloon dilator with (endovascular) stent, percutaneous transluminal approach with thrombectomy
	1IJ50GUOB	Dilation, coronary arteries, with (endovascular) stent insertion, using laser (and balloon) dilator with (endovascular) stent, percutaneous transluminal approach with thrombectomy
	1IJ50GTOE	Dilation, coronary arteries, with (endovascular) stent insertion, using ultrasound (and balloon) dilator with (endovascular) stent, percutaneous transluminal approach with atherectomy [e.g. rotational, directional, extraction catheter, laser]
	1IJ50GUOE	Dilation, coronary arteries, with (endovascular) stent insertion, using ultrasound (and balloon) dilator with (endovascular) stent, percutaneous transluminal approach with thrombectomy

coronary artery bypass graft (CABG); electrocardiogram/cardiography (ECG); not otherwise specified (NOS); percutaneous coronary intervention (PCI)

Table 14: Canadian Coding Standards for International Classification of Diseases-10.

DIAGNOSIS	CODE	DESCRIPTION
AMI	I210	Acute transmural myocardial infarction of anterior wall
	I211	Acute transmural myocardial infarction of inferior wall
	I212	Acute transmural myocardial infarction of other sites
	I213	Acute transmural myocardial infarction of unspecified site
	I214	Acute subendocardial myocardial infarction
	I219	Acute myocardial infarction, unspecified
STEMI	R9430	Electrocardiogram suggestive of ST segment elevation myocardial infarction [STEMI]
CAD	I2510	Atherosclerotic heart disease of native coronary artery

acute myocardial infarction (AMI); ST-segment elevation myocardial infarction (STEMI); coronary artery disease (CAD)

Table 15: Summary of fee codes from the Ontario Schedule of Benefits for Physician Services.

SERVICE	CODE	FEE ($)
Consult, general practitioner	A005	77.2
Consult, cardiologist	A605	157
Consult, anaesthesiologist	A015	106.8
Consult, emergency physician	H055	97.6
Assessment, cardiologist	C603	79.85
Assessment, vascular surgeon	A173	44.4
Emergency consult premium, patient	C990–C997	59
Emergency consult premium, travel	C960–964	36.4
Angiography	G297	118.7
Bypass graft angiography	G509	80.4
PCI	Z434	471.6
Stenting premium	G298	78.95
Fibrinolysis	G379	6.15
Assistant unit fee	-	12.04
Anaesthesiologist unit fee	-	15.01

A.4.1 *Cost-effectiveness planes*

For bypass eligible patients, the simulations are mostly in the northeast quadrant; the 12-lead cohort shows higher incremental QALYs and costs compared to the 3-lead cohort (Figure 23. For bypass ineligible patients, the simulations are mostly in southwest quadrant, although they also occupy both northern quadrants as well (Figure 24). The 12-lead cohort generally shows fewer QALYs and variable costs compared to the 3-lead cohort.

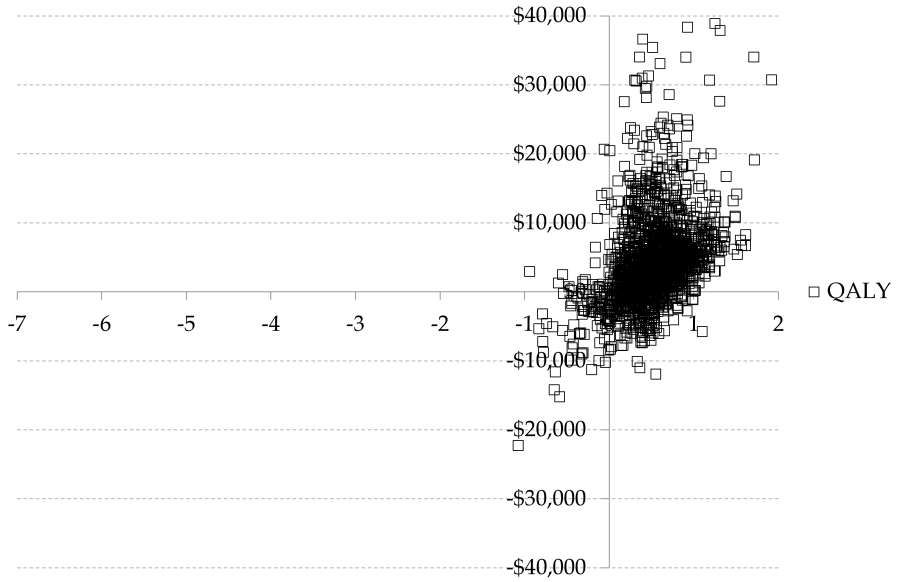


Figure 23: Cost-effectiveness planes restricted for patients with symptom onset between 30 minutes and 6 hours for the bypass eligible stratum. Incremental effects and costs following prehospital identification with 12-lead ECG and advanced notification (12-lead cohort) with eligibility for bypass, compared to no identification and no advanced notification (3-lead cohort).

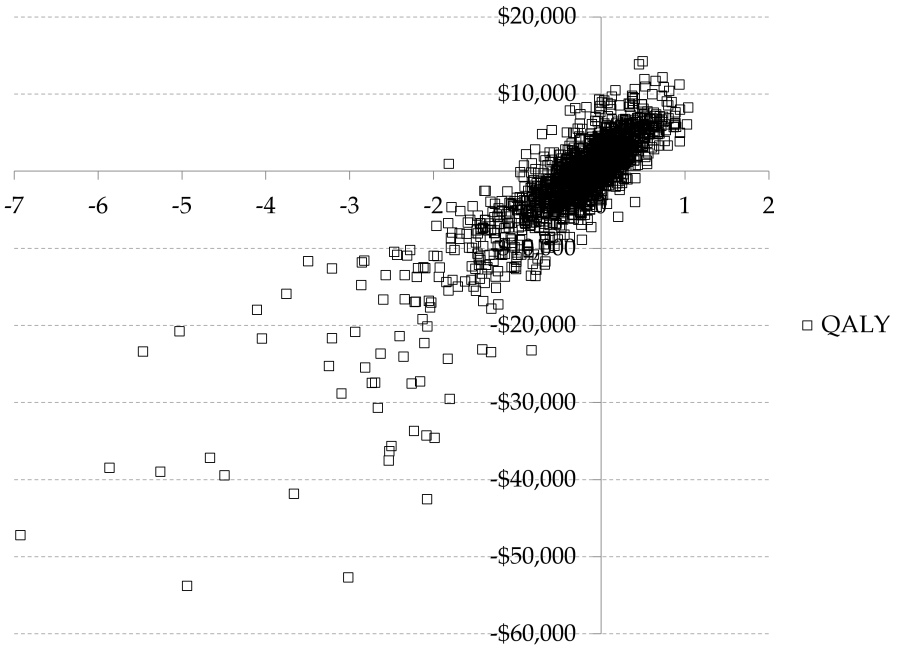


Figure 24: Cost-effectiveness planes restricted for patients with symptom onset between 30 minutes and 6 hours for the bypass ineligible stratum. Incremental effects and costs following prehospital identification with 12-lead ECG and advanced notification (12-lead cohort) with eligibility for bypass, compared to no identification and no advanced notification (3-lead cohort).

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