The prehospital electrocardiogram in suspected acute coronary syndrome

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ABSTRACT

Acute coronary syndrome (unstable angina and myocardial infarction) is associated most often with a narrowed coronary artery, leading to inadequate blood perfusion (ischemia) of cardiac muscle. Timely diagnosis and treatment is important. For acute myocardial infarction with an elevated ST-segment (STEMI) on an electrocardiogram (ECG), rapid reperfusion therapy is critical for survival. Prehospital ECG strategies are being implemented across Quebec to reduce STEMI treatment delay, but ambulance personnel in this province are not permitted to interpret ECGs. The objectives of this thesis were (1) to examine the diagnostic performance of computerized prehospital ECG interpretation; (2) to estimate the additional time spent "on scene" to acquire prehospital ECGs; and (3) to examine the similarities and differences in information provided by pairs of prehospital and initial in-hospital ECGs. The thesis used data on 1560 patients served by the *Urgences-santé* ambulance operator in 2005-2006 in metropolitan Montreal-Laval. Using a Bayesian latent class model, the statistical analysis was unique in the literature in considering data from three tests simultaneously (ECG reading by computer and by cardiologists, and hospital diagnosis) and assuming all were imperfect. Sensitivity and specificity of the computer for detection of true ST-segment elevation on the prehospital ECG were estimated as 78.8% (95% credible interval: 68.6-87.3%) and 98.9% (98.2-99.4%), respectively. Sensitivity and specificity for detection of true STEMI were estimated as 69.2% (59.1-78.2%) and 98.9% (98.1-99.4%), respectively; estimated prevalence of STEMI was 9.0% (7.0-11.4%). Positive and negative predictive values for STEMI were estimated as 85% (76-91%) and 97% (96-98%), respectively. In multivariate regression analysis, younger age was the only patient factor associated with

higher sensitivity. Broadening the "ECG positive" criteria to increase the computer's sensitivity correspondingly decreased specificity. Average on-scene time was 4.9 minutes longer (95% confidence interval: 4.4-5.5) for prehospital ECG patients compared to a historic sample without ECGs. The prehospital ECG demonstrated substantial "added value" regarding signs of ischemia and arrhythmias not observed on the in-hospital ECG. These results are relevant and timely for health care decision-makers and emergency medical services in Quebec, and have implications for the optimal use of prehospital electrocardiographic information.

RESUME

Le syndrome coronarien aigu (angor instable et infarctus du myocarde) est le plus souvent associé à un rétrécissement d'une artère coronaire, entraînant une irrigation sanguine insuffisante (ischémie) du muscle cardiaque. Il importe de le diagnostiquer et de le traiter promptement. Dans les cas d'infarctus aigu du myocarde avec élévation du segment ST (IAMEST) à l'électrocardiogramme (ECG), l'administration rapide d'un traitement de reperfusion est essentielle à la survie. Des stratégies d'ECG préhospitaliers sont implantées à travers le Québec afin de réduire le délai de traitement de l'IAMEST, mais, dans cette province, les techniciens ambulanciers ne sont pas autorisés à interpréter les ECG. Les objectifs de cette thèse étaient (1) d'examiner la validité diagnostique de l'interprétation informatisée de l'ECG préhospitalier; (2) d'estimer le délai additionnel passé « sur place » par le personnel ambulancier pour réaliser les ECG préhospitaliers; et (3) d'examiner les similarités et les différences observées dans l'information fournie par des paires d'ECG préhospitalier et intrahospitalier initial. À ces fins, nous avons utilisé les données sur 1560 patients ayant eu recours aux services de l'entreprise d'ambulances Urgences-santé au cours de la période 2005-2006 dans la région métropolitaine de Montréal et de Laval. Grâce à un modèle bayésien de classe latente, nous avons procédé à une analyse statistique inédite dans la littérature en incorporant trois tests simultanément (interprétation des ECG informatisée et par des cardiologues, et diagnostic hospitalier) et en assumant que ceux-ci n'étaient pas parfaitement justes. La sensibilité et la spécificité de l'ordinateur pour la détection d'une « vrai » élévation du segment ST sur l'ECG préhospitalier ont été estimées à 78,8 % (intervalle de crédibilité à 95 % : 68,6-87,3 %) et 98,9 % (98,2-99,4 %), respectivement. La sensibilité et la spécificité pour la détection

d'un « vrai » IAMEST ont été estimées à 69,2 % (59,1-78,2 %) et 98,9 % (98,1-99,4 %), respectivement; la prévalence estimée de l'IAMEST était de 9,0 % (7,0-11,4 %). Les valeurs prédictives positive et négative pour l'IAMEST ont été estimées à 85 % (76-91 %) et 97 % (96-98 %), respectivement. Dans l'analyse de régression multivariée, l'âge était le seul facteur lié au patient pour lequel nous avons observé une association significative avec la sensibilité; la relation était inversément proportionnelle. Le fait d'inclure d'autres interprétations informatisées de l'ECG évoquant la possibilité d'un infarctus, pour accroître la sensibilité de l'ordinateur, a entraîné une diminution proportionnelle de la spécificité. Le délai moyen « sur place » était plus long de 4,9 minutes (intervalle de confiance à 95 % : 4,4-5,5) dans le groupe de patients qui ont eu un ECG préhospitalier par rapport à un échantillon historique qui n'avait pas eu d'ECG préhospitalier. L'ECG préhospitalier présentait une « valeur ajoutée » substantielle en ce qui a trait aux signes d'ischémie et aux arythmies non observés sur le premier ECG intrahospitalier. Ces résultats sont pertinents pour les décideurs en matière de soins de santé et les services préhospitaliers d'urgence au Québec, et ont une incidence sur l'utilisation optimale des renseignements électrocardiographiques préhospitaliers.

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CHAPTER 1: INTRODUCTION

Acute coronary syndrome is characterized by an imbalance between the oxygen supply and demand of cardiac muscle. This condition is most often associated with ischemia – that is, inadequate blood perfusion – as a result of sudden partial or complete blockage in coronary arteries. Acute coronary syndrome accounts for 20% of all deaths in Canada (CCORT, 2006). The conditions classified under acute coronary syndrome are unstable angina, for which the ischemia is not severe enough to result in tissue damage, and acute myocardial infarction. The latter is further categorized into Non ST-segment Elevation Myocardial Infarction (NSTEMI) and ST-segment Elevation Myocardial Infarction (STEMI), which is the most severe condition, on the basis of electrical signals captured on an electrocardiogram. Between 4,000 and 5,000 cases of STEMI are thought to arise in Quebec each year (RQCT, 2005). The most recent data available from the *Institut national de santé publique du Québec* indicate that 16,200 hospitalized persons had a primary diagnosis of acute myocardial infarction in Quebec in 2007-08.[1]

A study of 2,401 STEMI patients admitted to 80 hospitals in Quebec in the 6-month period of Oct 1, 2006 to March 31, 2007 showed that 61% arrived by ambulance (AETMIS, 2008a). For individuals suspected to be experiencing an acute cardiac event such as myocardial infarction, the use of ambulance services provides an opportunity for prehospital personnel to gather critical clinical information prior to hospital arrival. Using data from ambulance services in metropolitan Montreal-Laval, Quebec, this thesis

[1] The *Institut national de santé publique du Québec* (INSPQ) is responsible for providing annual rates of hospitalization for acute myocardial infarction, based on the Med-Echo administrative database. A code for an ECG reading of ST-segment elevation was introduced in April, 2007, but a count of final diagnoses of STEMI is not available.

examines various aspects of the prehospital electrocardiogram. While the focus of the thesis is on the detection of STEMI, the use of prehospital electrocardiographic information as an indicator for other forms of myocardial ischemia is also addressed.

This introductory chapter has five parts. Section 1.1 provides clinical background on acute coronary syndrome, STEMI and the electrocardiogram. The electrocardiographic features related to myocardial ischemia are summarized in this part. Section 1.2 presents an overview of prehospital electrocardiogram programs. Section 1.3 introduces the Quebec context of the research. Section 1.4 begins with a brief summary of the scientific literature in the areas studied by the thesis[2], in order to demonstrate the rationale for the overall research objectives which are presented at the end of this part. Section 1.5 provides an overview of the types of data analyzed and the relevance of the research for health services in Quebec.

1.1 CLINICAL BACKGROUND

The acute coronary syndrome conditions represent a physiological continuum, with varying levels of ischemia resulting from imbalance between the metabolic demands of the myocardium and the supply of oxygenated blood. The most common mechanism of acute coronary syndrome involves an unstable plaque rupturing in a coronary artery, leading to aggregration of platelets and formation of a blood clot (thrombus) which can completely or partially block the vessel (Antman et al., 2004; Braunwald et al., 2002). NSTEMI is thought to be due to a partial or intermittent blockage, whereas obstruction is complete and prolonged in STEMI (Anderson et al., 2007; Bassand et al., 2007).

[2] This literature review is presented in more detail in Chapter 2.

Continuation of ischemia beyond a few minutes causes myocardial injury, but no tissue death will occur if blood flow is rapidly restored. In acute myocardial infarction, some permanent damage to the tissue (necrosis) occurs, rendering the cells non-functional and resulting in leakage of enzymes into the bloodstream. Thus, a rise and fall in the levels of these cardiac markers in the blood over a period of time can signal the presence of an infarction.

Since STEMI is associated with a sudden, complete obstruction in one or more coronary arteries, rapid restoration of blood flow through reperfusion therapy is crucial for patient survival (Antman et al., 2004; Armstrong et al., 2004). Thrombolytic medications and percutaneous coronary intervention (PCI) dissolve or disrupt the blockage by pharmacological or mechanical means, respectively. Thus, "time-to-reperfusion" is an important prognostic and quality of care indicator in clinical management of STEMI. Although NSTEMI and unstable angina are in principle less grave conditions, their detection and their immediate treatment with certain agents are also important (Turnipseed et al., 2010; Antman et al., 2004).

In general, a patient diagnosed with acute coronary syndrome in an emergency department should be hospitalized for therapy, bed rest, oxygen if necessary and cardiac rhythm monitoring (Gibler et al., 2005; Braunwald et al., 2002). In addition, ischemic and infarction processes are dynamic and patients with unstable angina, for example, may develop STEMI (Antman et al., 2005). Thus, the rapid identification of acute coronary syndrome, leading to appropriate and timely treatment, improves patient outcomes and

reduces use of hospital resources (related, for example, to unnecessary diagnostic investigations and longer length of stay). Earlier decisions about the need to admit these patients might also reduce overcrowding in hospital emergency rooms, assuming in-patient beds are available.

Chest pain is a common indicator of acute coronary syndrome, particularly when accompanied by left arm pain, nausea, sweating, and difficulty breathing, although it can be associated with a variety of health problems (Achar et al., 2005). Chest pain is one of the most frequent symptoms reported by people calling for an ambulance (Feldman et al., 2006). Non-chest pain presentations of acute coronary syndrome exist, particularly among women, the elderly and diabetic patients. These symptoms include a feeling of weakness or dizziness, gastrointestinal symptoms, palpitations, and abdominal and back pain (Harris, 2006; Gupta et al., 2002).

The electrocardiogram (ECG) is the principal tool used to diagnose STEMI among patients with suspected cardiac ischemia (Antman et al., 2004). The ECG is thus essential to determine eligibility for reperfusion treatments (Hahn and Chandler, 2006; Johnston et al., 2006). It can also be used to detect non-ST segment elevation injury patterns (Turnipseed et al., 2010). To obtain electrocardiographic information, recording electrodes at the end of cables are applied on the patient's skin in standardized areas on the limbs and chest. "Twelve-lead" ECG data takes the form of a tracing that displays the recording of 12 different electrical signals, made at approximately the same time.[3]

[3] In the rest of this section, the sources of the material are Mirvis and Goldberger (2008) and Aehlert (2006), unless otherwise indicated.

Electrical activity within the heart is due to the flow of charged particles across membranes of cells that are responsible for stimulating cardiac muscle to contract. A wave of depolarization (causing a positive charge inside cells) and then repolarization (restoring a negative charge) travels in the heart, normally starting at the atria at the top and moving through the ventricles below. Since measurement is made at the level of the skin, the ECG does not directly measure all of the heart's electrical activity but the net result of individual currents in the mass of atrial and ventricular cells. The position of the electrodes allows different areas ("territories") of the heart to be monitored.

The ECG machine records the voltage between pairs of electrodes and the magnitude of the current determines how far a pen moves vertically on ECG paper (as time passes on the horizontal axis), creating a tracing. Movement in a positive or negative direction from the baseline creates waveforms (named as P, Q, R, S, T and U waves). The ST segment is the portion between the end of the QRS wave complex and the beginning of the T wave, and represents the early phase of repolarization of the ventricles. Ischemia affects myocardial cells involved in contraction and in conducting electrical impulses. The resulting delays in depolarization and repolarization can be detected on an ECG. Not all ST-segment elevation is caused by myocardial infarction. The ST segment can also be raised due to diseases such as pericarditis, among other causes, or as a normal variant.

ST-segment depression can indicate NSTEMI or unstable angina (Anderson et al., 2007). This indicator is distinct from "reciprocal" ST-segment depression in the leads opposite to those displaying ST-segment elevation in STEMI. T wave abnormalities (e.g.

inversions) can be associated with ischemia and could have diagnostic value when combined with other features. During an infarction, T waves may first become very tall (within the first few minutes), and later can begin to invert, with these inversions persisting for months or years afterwards. Most patients with STEMI go on to develop pathologic (wide or deep) Q waves, which often remain indefinitely after the infarction event as an indicator of non-conductive tissue; these do not develop among most patients with NSTEMI.

A left bundle branch block (LBBB) is an abnormality in the electrical conduction within the left ventricle of the heart and can also be identified on an ECG. Because LBBB itself produces ST segment changes, it can complicate the identification of STEMI. An acute LBBB may be secondary to an infarction. LBBB can also be a chronic condition associated with other heart disease. Rapid reperfusion treatment is recommended in current clinical practice guidelines for patients showing signs of a presumed new LBBB on an ECG (Antman et al., 2004; 2008). When a pacemaker is operating (delivering current to depolarize the heart, from an implanted or external unit), an LBBB pattern is generally seen on an ECG due to a delay in the depolarization of the left ventricle.

Finally, arrhythmia refers to an abnormal heart beat (in general, too fast, too slow or irregular). The primary tool used for their detection is the electrocardiogram (Mirvis and Goldberger, 2008). There are four major categories of arrhythmias: premature beats, supraventricular tachycardias (fast heart rate, including atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia), ventricular arrhythmias (including

ventricular tachycardia and ventricular fibrillation), and bradyarrhythmia (slow heart rate).[4] Some forms of arrhythmia are benign; others can lead to serious complications (e.g. atrial fibrillation and flutter). Arrhythmias most often occur in the absence of ischemia, but can occur during an acute coronary event, and some are life-threatening (particularly ventricular arrhythmias). Certain arrhythmias require in-hospital treatment (at least initially) and rhythm monitoring (Fuster et al., 2006; Blomström-Lundqvist et al., 2003).

1.2 PREHOSPITAL ECG PROGRAMS

Given appropriate training, a 12-lead ECG can be performed by ambulance personnel in the prehospital setting. The electrocardiographic tracing must then be interpreted in order to detect signs of ischemia and infarction. In the prehospital setting, this interpretation can be carried out by on-site or remotely-located physicians (who receive the data through a communication device), by appropriately-trained ambulance personnel, or by computer. Computer ECG interpretation software has been available since the 1980s and has undergone developments to improve its diagnostic test performance over the years.

The rationale behind prehospital ECG programs is that notifying a hospital in advance that an ambulance is on its way with a possible STEMI patient can decrease "time-to-reperfusion". Time can be saved by accelerating in-hospital processes such as preparing personnel and equipment and contacting on-call cardiologists. The ambulance can also be given priority in the emergency department arrival area. Prehospital ECGs are usually performed stationary since the movement of an ambulance can decrease the quality of the

[4] http://www.nhlbi.nih.gov/health/dci/Diseases/arr/arr_types.html, accessed January 30, 2010.

signal. The extra time spent to acquire the ECG data before transporting the patient is thought to be minimal – estimated as 1.2 minutes in a meta-analysis (Morrison et al., 2006) and 5 to 6 minutes in a review (Ting et al., 2008) – compared to the potential time saved before reperfusion treatment (thrombolysis) by advance notification, estimated in two meta-analyses as about 25-35 minutes (Morrison et al., 2006; Brainard et al., 2005). Decreased "time-to-reperfusion" reduces in-hospital mortality from STEMI (McNamara et al., 2006). Even a 10-minute reduction in treatment delay is associated with lower mortality at 6 months (Nallamothu et al., 2007). For every 30 minutes saved before PCI, it is estimated that 1-year mortality decreases by 7.5% (De Luca et al., 2004).

Prehospital ECGs can also be used to activate the preparation of a specialized in-hospital facility used for diagnostic angiography and PCI (a cardiac catheterization laboratory) prior to the patient's arrival. When the patient then arrives at the hospital, he/she can be "fast-tracked" in the emergency department, or may even be taken directly to a coronary care unit or the catheterization laboratory, "bypassing" the emergency room. In a "diversion" model, prehospital ECGs are used to preferentially transport ambulance patients to centres with cardiac catheterization laboratories, even if other hospitals (without PCI facilities) are closer. Some programs combine features of more than one of the models described above. Finally, prehospital ECGs can be used to determine need for administration of thrombolytic medication by ambulance paramedics, but this more technically advanced model will not be discussed in this thesis.

Recent North American clinical guidelines and position statements by organizations such as the American Heart Association, the American College of Cardiology, the National Association of EMS Physicians, the American Ambulance Association, and the Canadian Cardiovascular Society Working Group recommend the performance of prehospital ECGs by ambulance services (Ting et al., 2008; NAEMSP, 2008; Jacobs et al., 2007; Garvey et al., 2006; Armstrong et al., 2004; Antman et al., 2004). Three of these sources specify that prehospital ECGs be acquired by advanced life support paramedics (NAEMSP, 2008; Garvey et al., 2006; Antman et al., 2004). Only Antman et al. (2004) provide the level of evidence associated with their systematic literature review: their recommendation is based on conflicting results from non-randomized studies, but the weight of the evidence favours efficacy.

In Appendix A, I present a review of the effectiveness of various program models implementing prehospital ECGs (as outlined above), in terms of time savings prior to reperfusion treatment, based on the published scientific literature since 2003[5]. Appendix A shows that the time savings can reach about 30-60 minutes for emergency department bypass (i.e., direct access to cardiac catheterization laboratories) or early activation of the laboratory. A similar range in time savings can be obtained in diversion programs (when compared to patients arriving directly at a centre with PCI facilities); savings can reach 60 minutes or more in comparison with transferred patients[6]. My review confirms that the

[5] As described in Appendix A, the literature search spanned the period January 2004 to July 2009.
[6] Transferred patients arrived first at emergency departments of hospitals without specialized facilities and were then transported by ambulance to centres with cardiac catheterization laboratories.

focus in the recent (English-language) published literature has been prehospital ECG programs that involve advanced life support paramedics[7].

1.3 QUEBEC CONTEXT OF THE THESIS

Urgences-santé, the ambulance service for the cities of Montreal and Laval, was the first such organization in Quebec (among more than 85 ambulance operators in the province) to launch a prehospital ECG program, in 2003. The corporation equipped 50 ambulances (out of a total fleet size of 165) and trained approximately 200 technicians, from one of its three operational centres, in 12-lead ECG acquisition. *Urgences-santé* serves a population of about 2.24 million, the largest catchment population in the province, over an area of 744 square km (*Urgences-santé,* 2006). The organization is the second largest ambulance operator in Canada and the fifth largest in North America *(Corporation Urgences-santé*, 2007; Williams, 2007). As elsewhere in Quebec, *Urgences-santé* employs ambulance technicians trained in basic life support[8], although a very small number of advanced life support paramedics currently also work for the organization. (Other provinces in Canada such as Ontario and Alberta have greater numbers of advanced life support paramedics.)

Quebec data from 80 hospitals in a 6-month period in 2006-07 (AETMIS, 2008a) indicate that STEMI treatment delays were generally long when compared to recommendations

[7] However, it can sometimes be difficult to determine the level of training of ambulance personnel in the literature: the term "paramedic", while usually referring to those with advanced life support training, can be used in a more general sense to indicate an emergency medical services provider working out-of-hospital.
[8] Quebec's basic life support ambulance personnel can administer certain medications and oxygen and perform semi-automated defibrillation, but cannot initiate intravenous access or endotracheal intubation (AETMIS, 2005).

from North American clinical practice guidelines (Antman et al., 2007; 2004). Median delay between hospital triage and thrombolytic treatment, or "door-to-needle" time, was 32 minutes (10^{th} – 90^{th} percentile: 13-84 minutes). Thus, less than half of the 388 patients treated with thrombolysis (47%) met the recommended maximum of 30 minutes for this delay. For the 514 patients who presented at a hospital with PCI facilities, median delay before PCI balloon inflation, or "door-to-balloon" time, was 82 minutes (46-161). The recommended door-to-balloon time of 90 minutes or less was met by 59% of these patients. Finally, a large proportion of STEMI patients (945/2401; 39%) were transferred from the initial receiving hospital to a site with PCI capability. This process was associated with particularly long delays: median door-to-balloon time (from first hospital arrival) was 123 minutes (78-214), with only 19% meeting the recommended delay of 90 minutes or less. These patients spent a long period at the first hospital before departure by ambulance for the PCI facility. Fifty percent of transferred patients did not leave the emergency department until at least 55 minutes later (10^{th} – 90^{th} percentile: 26-134 minutes), whereas the recommended maximum is 30 minutes. Similar results were generally found in an earlier study of 17 Quebec hospitals, based on 2003 data (Huynh et al., 2006).

As of March 2008, the Quebec health ministry officially committed to developing prehospital ECG capability throughout the provincial land ambulance system. Given the current context of basic life support ambulance services in the province, the implementation of prehospital ECG programs raises various health services issues. One of these concerns how correctly patients with and without STEMI can be identified. Basic

life support ambulance technicians are not currently permitted by Quebec law to interpret electrocardiographic data. At the time of writing this thesis, *Urgences-santé* uses the computer software's generated ECG interpretation in an advanced hospital notification program. Warnings of a possible STEMI by the computer (giving an ***Acute MI*** signal) are relayed by ambulance personnel to receiving hospitals. It is thus important to consider how well this computer software performs.

1.4 SCIENTIFIC BACKGROUND AND RESEARCH OBJECTIVES

In previous studies of the diagnostic performance of computerized prehospital ECG interpretation, specificity was found to be high; that is, there was a high probability that the software would not give the ***Acute MI*** signal in the absence of STEMI. However, sensitivity was in general poor, with the computer often not providing this signal when STEMI was present. In the largest prior study, advanced life support paramedics used a much older version of the computer software currently employed by *Urgences-santé*, and the criteria for performing a prehospital ECG were much more restrictive (and thus the prevalence of STEMI was substantial). Although patient eligibility criteria for an applied prehospital ECG program may need to be limited for practical reasons, the possibility of bias in estimates of diagnostic test performance is reduced when a broad spectrum of patients with and without the disease of interest are investigated (Ransohoff and Feinstien, 1978).[9] Thus, the evaluation of diagnostic tests is best performed when the persons with the disease (i.e. STEMI) show variety in terms of pathological factors (e.g. extent of infarction), clinical characteristics (e.g. time since symptom onset, age, sex), and co-morbid conditions (e.g. other disorders associated with

[9] This phenomenon has been termed "spectrum bias" (Nicoll and Detmer, 1997).

electrocardiographic abnormalities that could be mistaken for infarction). Likewise, among the persons without the disease there should ideally be features present that could be confused with STEMI (e.g. with respect to symptomatic and electrocardiographic presentation).

Previous studies in this area have considered the reference diagnoses to be without error (i.e., as perfect, "gold" standards). In fact, both physician detection of ST-segment elevation and hospital diagnosis of STEMI are imperfect (Larson et al., 2007; Schull et al., 2006; Christenson et al., 2004; Erling et al., 2004; Pope et al., 2000). One aim of this thesis was thus to incorporate imperfect "reference" tests in the analysis of diagnostic performance, among less highly selected patients. In addition, to my knowledge, no recent study exists in the published scientific literature that has directly tested ways to improve sensitivity (and at what cost to specificity) by examining the computer interpretations generated when cases of STEMI were missed (the most recent program revision I identified, by Elko et al., was published in 1992).

Another issue in the basic life support context concerns how much time, on average, is required to perform the prehospital ECG. The length of this delay can be considered an indicator of safety, since longer time "on-scene" prolongs the "out-of-hospital" period, increasing the risk of adverse events such as serious arrhythmia and cardiac arrest. Basic life support ambulance personnel may be especially concerned about spending additional time on-scene with a chest pain patient, as traditional training focuses on minimizing delay in this situation. I identified only one small previous study of on-scene time

involving solely basic life support personnel in the published literature, from suburban and rural United States. As prehospital ECG capability is expanded across the province, it is important to measure the extent of this delay associated with a program in Quebec.

Finally, the prehospital ECG provides an earlier diagnostic test, compared to an ECG performed in hospital, for patients suspected to be experiencing an acute coronary event. The prehospital ECG data are recorded closer in time to the onset of symptoms, or even during symptoms that may have been alleviated by the time the patient arrives at a hospital (spontaneously or as a result of prehospital medication[10]). This information can be combined with the initial in-hospital ECG in a serial manner for interpretation by hospital physicians. Patient management may be affected when there are differences in ECG abnormalities between two tracings, ongoing abnormalities, or absence of abnormalities at both times. It is recognized that in-hospital serial ECGs are useful for diagnosis and surveillance of ischemia (Garvey et al., 2006). Thus, the incremental ("added") value of a prehospital ECG is important when viewed as part of a serially-performed measure.

There is interesting but limited research on additional information provided by prehospital ECGs when compared valuable to initial in-hospital ECGs. With the exception of one small study, the potential added value of this information does not appear to have been examined among patients for whom the criteria for performing prehospital ECGs are broad (thus, with a lower prevalence of acute coronary syndrome), nor for data acquired by basic life support providers. To my knowledge, no previous

[10] e.g. aspirin, which inhibits the action of platelets, and nitroglycerin, which relaxes blood vessels

published study has investigated comparative ECG information on both possible ischemia and arrhythmias.

This thesis thus has the following overall objectives:

Regarding diagnostic performance,

- estimate the diagnostic test performance of the computerized interpretation of prehospital ECGs performed in the basic life support setting with regards to the diagnosis of STEMI (with and without assuming perfect reference standards)

Regarding safety,

- estimate the average time for prehospital ECG acquisition by basic life support personnel

Regarding added value,

- examine similarities and differences between prehospital and initial in-hospital ECGs with respect to abnormalities indicative of ischemia and with respect to arrhythmias

1.5 OVERVIEW OF THESIS DATA AND STUDY RELEVANCE

The research in this thesis is based on quantitative analyses of data collected by *Urgences-santé* as part of standard prehospital care in 2005-06 in the metropolitan region of Montreal and Laval. I amassed these data retrospectively, starting in 2007, for this thesis. Prior to 2007, emergency physicians on the research team[11] had collected tracings and overseen entry of the computerized interpretations in a database. The patient samples

[11] As of 2007, the "research team" involved me, three emergency physicians (two of these working for *Urgences-santé*), two cardiologists and a data technician. Two of the emergency physicians were also members of my thesis supervisory committee.

comprise clinically stable adults with symptoms suspected to be cardiac in origin (predominantly chest pain), for whom *Urgences-santé* ambulance personnel performed a prehospital ECG between January 1, 2005 and December 31, 2006. Since not all consecutive ECGs from that period were available in 2007, this constitutes a convenience sample.

The analysis of diagnostic performance uses the prehospital ECG computerized interpretations generated in 2005-06 and blinded readings of the same tracings carried out retrospectively by cardiologists for this project in 2007. The analysis of added value uses readings of both the prehospital ECGs and the matching initial in-hospital ECGs carried out retrospectively by cardiologists for this project in 2008-09. Diagnostic information from the hospital charts of each transported person is also employed in this thesis, as are standard ambulance data collected in the course of service.

This thesis was conducted within the broad conceptual framework of health technology assessment (HTA), based on my experience with the *Agence d'évaluation des technologies et des modes d'intervention en santé* (the Quebec Agency for Health Services and Technology Assessment). HTA aims to examine the benefits and risks, and the organizational, economic, social and ethical issues related to the use of a health technology, broadly defined. Thus, a health technology can include a medical device, diagnostic test, procedure, care process or program. HTA is intended to inform health care decision-makers in government, hospitals, and professional organizations, among others. Some of the material presented in Appendix A stems from an HTA report on

management of STEMI in the acute care phase for which I conducted a literature review on prehospital ECG programs (AETMIS, 2008b).

In examining benefits and risks of obtaining prehospital electrocardiographic data, this thesis is relevant and timely for health care decision-makers in Quebec. These stakeholders include leaders in government, ambulance organizations, emergency departments and cardiology services, as the province increases its investment in programs carried out, at present, by basic life support care providers. The results of studying diagnostic performance, in particular, have potential immediate impact on how prehospital ECG interpretation is carried out and used by *Urgences-santé* and other ambulance operators in Quebec. The thesis addresses issues relevant for longer-term considerations on how to optimize the collection and use of this type of prehospital clinical information.

CHAPTER 2: LITERATURE REVIEW, HYPOTHESES AND OBJECTIVES

2.1 DIAGNOSTIC PERFORMANCE OF THE COMPUTERIZED ECG INTERPRETATION

Diagnostic test performance is important to assess if implementing an ECG-based prehospital "triage" tool to identify patients at high risk for STEMI. High sensitivity – a high proportion of test positives among those with STEMI – would allow the identification of most STEMI patients. This would minimize the number of test "false negative" patients missing the opportunity for quicker evaluation on hospital arrival, for example. High specificity – a high proportion of test negatives among those without STEMI – would minimize the number of test "false positive" patients referred for reperfusion treatment and unnecessary activation of specialized facilities, for instance.

Prehospital ECG programs in Quebec must use alternatives to paramedic ECG interpretation since ambulance personnel are not legally permitted to carry this out, as mentioned in Chapter 1. Although some current programs in Quebec and elsewhere in Canada involve electronic transmission of tracings to a physician for interpretation (Schull et al., 2009), this process has important technological and organizational implications. A trial implementation of transmission by *Urgences-santé* was halted in Montreal-Laval in 2003-04 due to technical problems, and the organization opted for computer software ECG interpretation instead. Although computerized ECG interpretation is widely available, the diagnostic test performance of the latest software does not appear to have been studied in the prehospital basic life support context.

The largest published study of computerized prehospital ECG interpretation included 1189 chest pain patients under the age of 75 years. Kudenchuk et al. (1991) found that computerized interpretation had a low sensitivity of 52% and a high specificity of 98%, compared to hospital discharge diagnosis of STEMI. Consensus interpretation of the prehospital ECGs by clinicians, in contrast, showed a sensitivity of 66% and a specificity of 95%. Because this study was part of a larger trial of prehospital reperfusion therapy, these patients met strict selection criteria, including chest pain for less than 6 hours[12]. One third of the patients (33%; n=391) received a hospital diagnosis of STEMI.

In analyses stratified by patient factors, computer sensitivity compared to hospital diagnosis was estimated by Kudenchuk and colleagues as slightly higher (i.e., 56%) for those younger than 65 years, for those without cardiac history, or for patients with an infarction in the anterior region. Sensitivity was 59% for patients with symptom onset less than 30 minutes before the prehospital ECG. The sensitivity estimate was 74% when ST-segment elevation was accompanied by other "QRS" or "ST" changes, and was 87% for those with an inferior infarction.

Kudenchuk et al. assumed the hospital diagnosis was a perfect reference standard in their analysis. In reality, this reference is not without error. In addition to missed diagnoses of STEMI and acute coronary syndrome in the hospital setting (Schull et al., 2006; Christenson et al., 2004; Pope et al., 2000), physician interpretation of ST-segment elevation has been associated with inter-observer disagreement (Erling et al., 2004;

[12] The other criteria were: no insulin-dependent diabetes, renal insufficiency nor contra-indications for reperfusion (thrombolytic) medication, such as a bleeding condition, previous stroke, recent major surgery, trauma or gastrointestinal bleeding, cancer or terminal illness, or severe hypertension.

Massel, 2003) and a 9.2% false positive rate in a prehospital ECG program involving advance catheterization laboratory activation (Larson et al., 2007).

In two other published studies that jointly considered other ECG characteristics (e.g. T wave inversion), and that changed the threshold magnitude to define ST-segment elevations or depressions in certain leads, computer sensitivity was estimated as 64% when compared to discharge diagnosis (Elko et al., 1992) and 76% versus cardiologist reading (Eskola et al., 2005), while maintaining an estimated specificity of at least 98%. Again, the reference diagnoses were assumed to be without error. All three studies reviewed here used the GE Marquette 12 SL ECG Analysis Program™, which has been refined since its introduction in 1980 (GE Medical Systems, 2000). *Urgences-santé* uses version 14 of this program, while Kudenchuk et al. (1991) used versions 4-6.

2.2 SAFETY

It appears that little research has been published on the time spent by basic life support ambulance personnel on ECG acquisition. Morrison et al. (2006) estimated in a meta-analysis that prehospital ECG programs (with advance hospital notification) increased mean on-scene time by 1.19 minutes (95% confidence interval: -0.84 – 3.21), based on three studies totalling 519 patients. About 60% of the total control sample was concurrent; the rest was historical. Among the other studies of prehospital ECG programs reviewed in Appendix A[13], a few provide this kind of safety data, reporting mean increases compared to historical controls of 1.2 minutes (Brown et al., 2008) for total

[13] These studies were published between January 2004 and July 2009.

transport time[14], and, for on-scene time, 1.84 minutes (Drew et al., 2004) and 7 minutes (Sejersten et al., 2008; Clemmensen et al., 2005).[15] All of these data appear to have been generated by advanced life support paramedics[16] or ambulance physicians (the latter reported by Sejersten and colleagues, based on a prior pilot study). A recent study of prehospital ECG abnormalities by Turnipseed et al. (2010) estimated a 3-minute average increase in on-scene time, compared to historical controls, but involved at least one advanced life support paramedic in each ambulance team. Caudle et al. (2009) showed an increase of 2 minutes in median on-scene time (in a "before-after" study), but these data combined runs by advanced and basic life support ambulance crews.

In the course of my literature search on prehospital ECG programs, I found one study that provided on-scene time data solely from the basic life support setting. In a mixed rural and suburban population, volunteer ambulance personnel acquired ECGs on 77 patients in an 18-month period (in 1996-97; Provo and Frascone, 2004). Mean on-scene time was 5.0 minutes longer (95% CI: 3.6-6.4) for the 77 prehospital ECG patients (presenting on odd-numbered days) than for 100 concurrent controls (for the study, no ECGs were performed on even-numbered days). Compared to 205 historical controls, mean on-scene time was 4.3 minutes longer (95% CI: 3.0, 5.5). (Interestingly, ECGs were not acquired for 43% of eligible patients, due to technician concern about delaying transport,

[14] This was defined as the time between initial contact with emergency medical services (presumably the "911" call or equivalent) to ambulance arrival at hospital.
[15] According to Brooks et al. (2009), two other references included in Appendix A provide on-scene time data, but it was not possible to find these data in the source study in one case (Le May et al., 2006); the groups being compared both appeared to contain some prehospital ECG acquisition in the other study (Terkelsen et al., 2005). The reported increases in median times were 2 and 7 minutes, respectively. The former study involved advanced life support paramedics.
[16] As previously noted, it was necessary in some cases to assume that the term "paramedic" referred to ambulance personnel with advanced life support training.

discomfort with the procedure or dealing with female patients, or reluctance to undress patients in cold weather.)

2.3 ADDED VALUE

There is a growing body of literature which addresses the added value of ECGs acquired prior to hospital arrival, by examining information provided by prehospital and initial in-hospital tracings. Table 1 presents design characteristics and results of six published studies[17], ordered from the most recent to the least. For this table, I used the frequencies of the abnormalities and other information provided by the study authors to summarize the detection of features on both ECGs, the prehospital ECG only, and the in-hospital ECG only, wherever possible.[18] The denominator for these frequencies thus was the total count of an observed abnormality.

There were dissimilarities between the previous studies with respect to patient selection criteria and prevalence of diagnosed acute coronary syndrome and acute myocardial infarction in the samples. Delay between the two ECGs also likely varied, but was only reported in two investigations (Kudenchuk et al., 1998; Adams et al., 1993). The study by Herlitz et al. (2002) had the broadest criteria for prehospital ECG acquisition, including a wide spectrum of symptoms besides chest pain.

[17] A seventh study, by Arntz and colleagues (2004), appears to be described in an abstract only. ECG interpretation category changed from prehospital to initial in-hospital ECG for 17.4% of 224 patients diagnosed with acute coronary syndrome. However, a large proportion of patients (2/3) received prehospital thrombolytic therapy. There was not enough information provided by the abstract to judge the impact of the intervention on the validity of the results.

[18] It was not always possible to determine cross-tabulations of the abnormalities across ECGs.

Table 1. Summary of studies comparing abnormalities on prehospital and initial in-hospital ECGs

Study	No. of patients	On both ECGs (total count[1]): proportion of total count	On prehospital ECG only: proportion of total count	On in-hospital ECG only: proportion of total count	Patient selection criteria[2]	Prevalence of ACS / AMI (%)
Drew et al., 2006	433	n/a	4.4% greater frequency of arrhythmias[3]	n/a	broad	40 / 14
Drew et al., 2004	23	STE (3): 100% ischemia[4] (7): 29%	STE: 0% ischemia: 71%	STE: 0% ischemia: 0%	broad	100 / 26
Herlitz et al., 2002	163	ischemia[5] (94): 79%	ischemia: 13%	ischemia: 9%	very broad	30 / 14
Kudenchuk et al., 1998	2665	STE (678): 52% STD (821): 56% T inv (1474): 67% Q (691): 49% LBBB (71): 65%	STE[6]: 22% STD: 23% T inv: 18% Q: 13% LBBB: 20%	STE[6]: 26% STD: 21% T inv: 15% Q: 38% LBBB: 15%	narrow	47 / 30
Adams et al., 1993	137	STE/BBB (75): 64% ischemia[7] (75): 53%	STE/BBB: 20% ischemia: 23%	STE/BBB: 16% ischemia: 24%	narrow	ns / 68 (STEMI)
Aufderheide et al., 1990	151	STE (15): 93% n/a	STE: 7% 3.3% greater detection of ischemia[8] among angina patients[9]	STE: 0% n/a	broad	56 / 16 (STEMI)

ACS: acute coronary syndrome; AMI: acute myocardial infarction; STE: ST-segment elevation; STD: ST-segment depression; T inv: T wave inversion; LBBB: left bundle branch block; BBB: bundle branch block; n/a: not available based on information provided in article

1. For each type of abnormality in this column, the total count in brackets is the number of abnormalities observed on each single ECG added to the number of abnormalities observed on both ECGs, the latter counted just once. For example, in the study by Drew et al. (2004), there were 2 ischemic features observed on both ECGs and 5 observed only on the prehospital ECG, for a total of 7 observed abnormalities.

2. narrow: patients potentially eligible for prehospital thrombolysis (for Adams et al. [1993], this was determined by general practitioners); broad: presence of chest pain "or anginal equivalent" (for Drew et al. [2006], p. S158); very broad: presence of chest pain, shortness of breath, "a feeling of arrhythmia", loss of consciousness, muscular or epigastric pain, "tiredness", or "a bad general condition" (Herlitz et al. [2002]; p. 196)

3. Frequency of arrhythmias on the prehospital ECG was 33.3% (n=144) compared to 28.9% (n=125) on the in-hospital ECG. The arrhythmias noted were sinus tachycardia, sinus bradycardia, atrial fibrillation or flutter, "supraventricular tachycardia of unknown mechanism", sustained ventricular tachycardia, complete heart block, and "sinus arrest with junctional or ventricular escape rhythm" (p. S159).

4. ST-segment depression and/or T wave inversion

5. ST-segment elevation or depression, T wave inversion, or Q waves

6. including conclusive ST-segment elevation (≥ 1 mm) on this ECG and borderline elevation (< 1 mm) on the other ECG, or borderline ST-segment elevation on this ECG and no elevation on the other ECG

7. ST-segment elevation that was not anterior alone ("anterior, lateral, or anterolateral"), inferior alone, nor "anterior and inferior", or ST-segment depression without ST-segment elevation, T wave inversion, Q waves, or "other abnormality" (no other information provided) (p. 410)

8. ST-segment depression, T wave inversion, or other abnormalities suggestive of ischemia (according to cardiologists)

9. Two patients out of 61 with a hospital diagnosis of angina pectoris showed ischemia on the prehospital ECG but not on the in-hospital tracing.

Two studies found that ST-segment elevation was more often present on the prehospital ECG alone than only on the initial in-hospital ECG (Adams et al., 1993; Aufderheide et al., 1990). This finding contrasts with results from Kudenchuk et al. (1998). Although narrow patient selection criteria were used by both Kudenchuk and colleagues and Adams et al., these studies differed in terms of delay between ECGs, with a mean of 24 minutes (standard deviation: 11 minutes) and a median of 125 minutes, respectively.

Both Drew et al. (2004) and Herlitz et al. (2002) found signs of possible ischemia (other than ST-segment elevation) more often on the prehospital ECG alone, than on the in-hospital ECG alone. The difference in frequency was particularly marked for Drew and colleagues in their small sample of patients all later diagnosed with acute coronary syndrome. Kudenchuk et al. (1998) also observed this phenomenon for ST-segment depression, T wave inversions, and LBBB, as did Aufderheide and colleagues (1990) for indicators of ischemia among patients with angina[19]. In the one investigation of arrhythmias, more tachycardias and atrial fibrillation/flutter were observed on the prehospital ECG than on the in-hospital tracing (Drew et al., 2006). In terms of diagnostic utility, the two studies that examined ECG data according to interpretation categories[20] found that group assignment differed depending on which ECG was used for 16% (Herlitz et al., 2002) and 26% (Adams et al., 1993) of all patients.

Previous studies thus provide varying frequencies of additional information arising from prehospital ECGs. The present thesis sought to quantify this informational value in the

[19] presumably including stable and unstable angina
[20] i.e., ischemic/pathologic, not ischemic/normal; STEMI or BBB/non-specific change/normal, respectively

context of broad ECG eligibility criteria, and using a method that more closely imitated clinical practice, as will be described further in section 3.10.

2.4 RESEARCH HYPOTHESES

Based on the literature reviewed above, the *a priori* hypotheses for this thesis are as follows:

1) Sensitivity of the computerized interpretation of prehospital ECGs (compared to cardiologist reading and to hospital diagnosis) will be modest, whereas specificity will be high.

2) Patient factors will be associated with estimates of test performance of the computerized interpretation.

3) The inclusion of other ECG interpretations indicative of ischemia, injury or infarct by the computer will improve its sensitivity at a non-negligible "cost" of loss in specificity.

4) Acquisition of prehospital ECGs will be associated with an increase in on-scene time of about 5 minutes.

5) For patients with ST-segment elevation on the initial in-hospital ECG, a substantial proportion of the prehospital ECGs will also show ST-segment elevation. A small proportion of patients will show ST-segment elevation on the prehospital ECG only.

6) A small proportion of patients will show arrhythmias or signs of ischemia other than ST-segment elevation (in particular ST-segment depression) on the prehospital ECG, but not on the initial in-hospital ECG.

2.5 RESEARCH OBJECTIVES

The objectives of this thesis are as follows:

1) To estimate the diagnostic test performance of computerized prehospital ECG interpretation compared to reading by cardiologists, and compared to hospital diagnosis, with and without assuming perfect references.

2) To examine the influence of patient age, sex, cardiac history, location of the infarction and time from symptom onset to acquisition of the prehospital ECG on the diagnostic test characteristics of the computerized interpretation.

3) For cases where STEMI was deemed to be likely by the cardiologists, but not indicated by the computer (i.e., "false negatives" assuming a perfect reference), to examine which computer interpretations were given and how test performance could be affected by broadening the computer's definition of the outcome.

4) To estimate the additional time spent by ambulance technicians at the patient encounter site ("on-scene time") for patients with prehospital ECGs, when compared to patients without prehospital ECGs.

5) Using pairs of prehospital and initial in-hospital ECGs read by cardiologists, to measure how often ST-segment elevation was observed on both ECGs, the initial in-hospital ECG alone, and the prehospital ECG alone.

6) Using pairs of prehospital and initial in-hospital ECGs read by cardiologists, to measure how often ST-segment depression, T wave inversion, abnormal Q waves, LBBB, and certain types of arrhythmias were observed on both ECGs, the initial in-hospital ECG only, and the prehospital ECG only.

CHAPTER 3: METHODS

The material in this chapter is presented according to the order of the research objectives. Thus, the chapter begins with the methods used to study the diagnostic performance of the computerized interpretation of the prehospital ECGs. The methodologies for the safety analysis (on-scene time) and then the added value (paired ECG) research follow. The statistical analysis section (3.12) addresses all three main topics.

3.1 ACQUISITION OF ECGS AND COMPUTERIZED INTERPRETATIONS

Prehospital ECGs that had been acquired by basic life support ambulance personnel as part of standard care in metropolitan Montreal-Laval, Quebec over the period January 1, 2005 to December 31, 2006 were collected for this research. An attempt was made to obtain all consecutive tracings; however, due to a number of tracings being misplaced, a sample of available ECGs was used. Standard 12-lead ECGs were acquired with Zoll M Series® monitor-defibrillators using the GE-Marquette 12SL ECG Analysis Program™ version 14. The following text presents the methods of the *Urgences-santé* prehospital ECG program, whereas subsequent sections describe the research methods employed for the thesis.

The indications for ECG acquisition in 2005-06 included chest pain of suspected cardiac origin, of at least 20 minutes in duration, and either age 35 years or older (with or without a history of prior cardiac disease), or age 18 years or older with cardiac disease history. A combined standard protocol was used to determine eligibility for ECG acquisition and oral administration of nitroglycerin and/or aspirin in this time period. The prehospital

medication program, which started about one year prior to the prehospital ECG initiative, is relevant for the analysis of on-scene time which will be described in section 3.8.

Ambulance personnel were instructed to carry out the ECG before administration of any medications (if possible) and to inquire about the duration of symptoms, and the quality, history, and severity of any chest pain. They were trained to consider chest pain as a feeling of pressure or of being squeezed, crushed, punched, or in a vice in the anterior thoracic (retrosternal) region. Patients could alternatively have a sensation of suffocation or indigestion, non-continuous pain for more than 12 hours, or typical angina pain with a history of atherosclerotic or cardiac disease. Hemodynamically unstable persons – defined as those with a heart rate of less than 50 or more than 150 beats per minute, a systolic blood pressure under 100 mmHg, a non-alert level of consciousness, or oxygen saturation of 91% or less in room air – were not eligible for prehospital ECGs. Patients in cardiac arrest were also not eligible.

When the prehospital ECG program was initially launched, 212 ambulance technicians received four hours of training in May 2003. These personnel received re-briefings with instructors in 2005 and were updated as needed. A quality assurance process verified whether the acquisition and non-acquisition of ECGs adhered to protocol, using filed tracings and information recorded on ambulance forms by the technicians as part of standard practice. The ECGs were performed at the patient encounter site unless they needed to be done in the stationary ambulance for safety or privacy. Two copies of the

tracings were printed: one was to be left in the patient's hospital chart if transported and the other was to be returned to *Urgences-santé* quality assurance with completed forms.

The ambulance technicians read the printed copy of the computer's ECG interpretation. They were instructed to notify the receiving hospital of a possible acute myocardial infarction (i.e., STEMI, denoted by an ***Acute MI*** code) by cellular phone while en route. It should be noted that all patients attended to by ambulance personnel are to be transported to hospital unless the patient refuses and signs a "refusal of transport" form.

3.2 PREHOSPITAL ECG READINGS BY CARDIOLOGISTS 1, 2 AND 3

Two Royal College Board-certified cardiologists, blinded to the computerized diagnoses and patient information, retrospectively and independently reviewed paper versions of each tracing using a standardized data entry form. To avoid confusion, I refer to these as cardiologists 1 and 2. The form was developed by an emergency physician on the research team, in consultation with the other members, and pilot tested by one of the cardiologists. The cardiologists were told the patients were adults presenting to ambulance services with chest pain. They noted the presence or absence of pathological Q waves, pathological ST-segment elevation, early repolarization ST-segment elevation (benign), ST-segment depression, pericarditis, a pacemaker, left bundle branch block, left ventricular hypertrophy, atrial fibrillation, other arrhythmias, and other ECG abnormalities.

The diagnostic result for the cardiologists was the presence or absence of acute ST-segment elevation that would have warranted immediate consideration for reperfusion therapy. This result was chosen to reflect the reality of the diagnostic process and associated decision-making that could be required by a physician receiving a prehospital ECG. The cardiologists made this judgement independently of any consideration about the type of reperfusion indicated. The definition of an ST-segment elevation for this result was at least 0.1 mV in at least 2 contiguous[21] chest leads or at least 2 adjacent limb leads, consistent with clinical practice guidelines from the American College of Cardiology and American Heart Association (Antman et al., 2004; Braunwald et al., 2002), and as used by the ECG readers in the study by Kudenchuk et al. (1991).[22] The ST-segment elevation had to be otherwise not diagnostic of early repolarization ST-segment elevation, left bundle branch block, left ventricular hypertrophy, or pericarditis (American College of Emergency Physicians, 2000). For cases of infarction suspected to be in the posterior territory, the leads could display "reciprocal" ECG changes; that is, an ST-segment elevation could be observed as ST-segment depression in contiguous chest leads, possibly accompanied by large R waves in chest leads V1 and V2 (that is, reflected Q waves from the back of the heart).

Disagreement between the two cardiologists regarding the principal diagnostic result was resolved by consensus, when possible. A total of 82 ECGs were discussed: 79 for which

[21] Anatomically contiguous leads "monitor" the same territory of the heart. ECG abnormalities indicative of myocardial infarction are seen only in the leads directly reflecting the specific territory of the infarct (Aehlert, 2006).

[22] It should be noted that two definitions of an ST-segment elevation are used in medicine, and each is supported by several consensus documents. The alternate definition is also used in this thesis; see section 3.10.

only one reader thought an acute ST-segment elevation was present and three where one reader observed acute ST-segment elevation and the other considered the tracing illegible. When consensus could not be reached (for 17 ECGs), a third cardiologist (cardiologist 3) interpreted the ECGs, blinded to the other readings, and the majority (2/3) decision was used. In the 55 cases where the ECG tracing was considered illegible, the cardiologists documented the reason(s).

3.3 COMPUTERIZED PREHOSPITAL ECG INTERPRETATIONS

According to Kudenchuk et al. (1991), the ECG interpretation computer software defines an ST-segment elevation as an elevation of at least "0.1 mV for frontal plane [limb] and lateral chest leads and 0.2 mV for anterior chest leads" (p. 1487).[23] This definition was reconfirmed for version 14 of the program by my personal communication with the company in March, 2007. When analyzing ST-segment elevation, the algorithm also considers the degree of the elevation, the ST:T ratio, and reciprocal ST-segment depression in 'mirror image' leads (GE Medical Systems, 2000). The computer summary diagnosis of ***Acute MI*** indicates the presence of ST segment elevation, with or without ST-segment depression, T wave inversion, or Q waves.

3.4 ACQUISITION AND EXTRACTION OF HOSPITAL CHART DATA

For each transported patient, a copy of relevant portions of the hospital chart was requested from the medical archivist department of the centre where the patient was

[23] Since this means that, in theory, the software used a more restrictive definition than cardiologists 1 and 2, the positive cases identified by the clinicians were checked with regards to the heights of the ST-segment elevations and the associated types of leads. If the cardiologists had used the computer's definition, the same cases would have been identified by them as result positive.

initially received (see Table 2). For feasibility and logistic reasons, copies of subsequent charts for patients who were later transferred to another hospital were not requested. The goal of this work was to assign a hospital diagnosis with respect to the symptoms for which each patient sought emergency medical services, if transported to hospital by ambulance.

Three bilingual senior medical archivists, whom I specifically employed and trained for this study, extracted data from these copies at *Urgences-santé.* They used a French-language computerized Access database and were not aware of the computer and cardiologists' prehospital ECG interpretations. I developed the database content in consultation with three emergency physicians, cardiologists 1 and 2 and one of the medical archivists. I also consulted with experts in studies of acute myocardial infarction at the Institute for Clinical Evaluative Sciences in Toronto, Ontario.

One archivist and an *Urgences-santé* data research technician carried out the computer programming for the database. I developed a detailed guide to data extraction in French in consultation with all three archivists. This was used for training and on-going support and information. Each archivist completed 20 hours of practical training with the database. The language of most of the charts was French, and the archivists were selected for their aptitude in working in both English and French.

Table 2 describes the sources of information requested from the hospital charts and the types of patient data extracted.

Table 2. Hospital chart data used in this thesis

SOURCE OF INFORMATION	DATA EXTRACTED
Triage sheet	Triage time Medical history Previous PCI or CABG
Physician and nurse notes during ED stay (including specialist consultations)	Medical history Previous PCI or CABG Physician final diagnostic impression First destination on leaving ED (home, catheterization laboratory, admitted, left hospital before diagnostic work-up completed) Administration of a thrombolytic agent Mention of ST-segment elevation or LBBB
Initial in-hospital ECG	Time of ECG
Biochemistry reports during ED stay	Cardiac enzyme results* in first 24 hours after triage First creatinine result (see end of section 3.6)
Discharge summary sheet (for admitted patients)	Length of stay Discharge diagnoses Comorbid chronic conditions Any use of angiography, PCI or CABG
Hospital admission form (for admitted patients)	Length of stay (if not specified on summary sheet)
Death certificate (if applicable)	Time and cause(s) of death

Abbreviations: PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; ED: emergency department; LBBB: left bundle branch block

*all available results in 24 hours, which could vary by hospital; tests for total creatine kinase and creatine kinase-MB were still used at most sites along with those for troponin-T and/or troponin-I, which are newer and more specific to myocardial damage

The major areas of the charts that provided information were: (1) the physician notes and the diagnostic tests related to suspected acute coronary syndrome (i.e., ECG, cardiac enzyme blood tests) carried out while in the emergency department, and especially in the first 24 hours after arrival (triage); (2) the information sheet completed by the triage nurse on patient arrival; (3) the discharge summary sheet completed by a physician for all admitted patients; and (4) the death certificate for patients who died in the hospital but were never admitted. Some data could arise from more than one source. For example, prior medical history was generally collected at triage and by the first emergency physician to examine the patient, and could also be documented by a consulting specialist.

The information that was particularly critical for the analysis included diagnostic data (i.e. discharge diagnosis, final diagnostic impression and/or results of cardiac enzyme testing and ECGs, cause of death), the administration of thrombolytic agents in the emergency department or transfer to a catheterization laboratory (especially whether the latter was within 4 hours of hospital arrival), and the patient's prior medical history. A copy of the initial in-hospital ECG was used to assist with diagnostic outcome coding, when needed, and was necessary for the analysis of the paired ECGs (objectives 5 and 6).

For admitted patients, the discharge summary sheet was the principal source of diagnostic information. For patients discharged home from the emergency room or transferred to another facility (and never admitted at the first receiving hospital), I used the emergency department notes where a physician summarized final diagnostic impressions. For

patients who died without ever being admitted as in-patients, I used the death certificate in the hospital chart. Deaths during the hospital stay for admitted patients were also noted for descriptive purposes.

The database program was pilot tested for two days by the medical archivists prior to its finalization. During data extraction, any handwriting in the charts that was very difficult to decipher was read by more than one archivist, and then me, or, if necessary, by one of the emergency physicians on the research team. As part of the training, I verified data by performing two independent extractions of a random 5% of 100 charts after each archivist completed 100 and then 200 charts. An error rate was calculated using a denominator of 34 variables in the database. The overall error rate was 3.92% (40 errors / 34 variables x 30 charts). Fifteen percent of these errors affected medical history and 12.5% concerned diagnostic information, the two most important variables in the database for the analysis, yielding overall error rates of 0.49 and 0.59%, respectively. The largest group of errors (17.5%) involved data regarding the departure from the emergency department (e.g. time of departure). The errors were discussed with the archivists and corrected.

In addition, certain data extracted during the first two weeks of each archivist's work and from a further random sample of charts were verified against the chart copies. These data included medical history, the final diagnostic impressions in the emergency department (ED), the first destination on leaving the ED (e.g. hospital admission, discharge, catheterization laboratory) and discharge diagnoses for admitted patients. These data were verified by me or a study archivist for a minimum of 35% of charts per archivist.

3.5 CODING OF HOSPITAL DIAGNOSES

I assigned hospital diagnoses following predefined criteria, determined in consultation with clinician members of the research team. As previously noted, the source of diagnostic information varied depending on the type of patient, i.e. whether admitted at the initial hospital, discharged home without being admitted, transferred to another hospital, deceased at the initial hospital without being admitted, or left the emergency department without being discharged by a physician (often, prior to complete diagnostic work-up).

For admitted patients (or those who died during their stay as in-patients), the diagnoses on the hospital discharge summary sheet were supplemented by other chart information if necessary (i.e., initial in-hospital ECG, cardiac enzyme tests in first 24 hours after triage). In Quebec in the time period of the prehospital ECG sample (2005-6), the principal discharge diagnosis listed on the hospital summary sheet did not necessarily reflect the condition for which emergency consultation was originally sought. Thus, if acute myocardial infarction (AMI) (or STEMI or NSTEMI) was listed as the principal diagnosis or as a secondary diagnosis on the summary sheet, this diagnosis was assigned if there was evidence of an increase in cardiac enzymes within 24 hours of arrival in the emergency department (or ST-segment elevation, in the case of STEMI, if this diagnosis was made without enzyme test results). The time at triage was used as the hospital arrival time. This approach was employed in order to exclude infarctions that arose during the hospital stay. For each centre, the hospital-specific cut-off was used to define an increase in cardiac enzymes.

For non-admitted patients discharged from the emergency room and for patients who were transferred to another hospital and did not return to be admitted at the initial centre, the final diagnostic impression listed by a physician in the chart was used to assign an "emergency department" diagnosis. This information was supplemented by cardiac enzyme results in the first 24 hours after hospital arrival and the initial in-hospital ECG, if necessary. For patients who died and were never admitted, the death certificate was used to extract the cause(s) of death and code a diagnosis. This source was also supplemented by cardiac enzyme results and the initial in-hospital ECG, if necessary. Finally, the emergency department notes and results of any available diagnostic tests were consulted for patients who left the hospital without being officially discharged. For most of these cases there was not enough information to assign a diagnosis.

Hospital diagnoses were categorized as "STEMI", "NSTEMI", "unstable angina", "NSTEMI or unstable angina" (when it was not possible to clearly differentiate between these), "Other cardiac diagnosis" (including stable angina, congestive heart failure, arrhythmia, and pericarditis), "Other non-cardiac diagnosis" (including gastrointestinal, pulmonary, neurological, psychiatric, obstetrical or gynaecological disorder, intoxication, and atypical and non-organic chest pain), "Undefined diagnosis, not ACS" (in the absence of acute coronary syndrome, but when it was not possible to designate as other cardiac or non-cardiac), or "Missing" (chart not available, information missing from chart, patient left hospital before full diagnostic work-up was complete). If a discharge summary for an admitted patient was missing from the chart, the final diagnostic

impression in the emergency room was used. Each patient was assigned to one diagnostic category.

These categories appear to be sufficiently similar for comparison to those used by Kudenchuk et al. (1991), the largest previous published study of computerized ECG interpretation: the 1991 study used "AMI", "unstable angina", "stable coronary artery disease" (i.e., stable angina), and "no evidence of acute coronary ischemia" (p. 1487). Although Kudenchuk et al. used an "AMI" category, which in current clinical practice includes STEMI and NSTEMI, the diagnostic outcome that they studied was in fact AMI associated with ST-segment elevation and thus STEMI. For the analysis of diagnostic test performance, I dichotomized hospital diagnoses as STEMI or not STEMI (all other categories combined).

Another challenge in using hospital summary sheets to assign discharge diagnoses was that in Quebec at the time period of the study sample, some hospitals did not differentiate between STEMI and NSTEMI on these sheets. The more general term "AMI" was often used. Older terms such as "non-Q wave AMI" or "subendocardial infarction", both usually indicative of NSTEMI, were sometimes employed. I used methods also implemented for a province-wide field evaluation of STEMI management in 80 hospitals which was developed and performed for AETMIS at the same time as this thesis project, and for which I served as a consultant researcher and advisor (AETMIS, 2008a).

Thus, a diagnosis of STEMI was assigned to admitted (or deceased non-admitted) patients if (1) STEMI was specifically indicated on the discharge summary sheet (or death certificate), or (2) AMI was indicated on the summary sheet (or death certificate) and presence of ST-segment elevation was noted by an emergency physician or by a consulting cardiologist in the ED notes, or (3) AMI was indicated on the summary sheet (or death certificate) and a thrombolytic agent was administered (since this treatment is only indicated for STEMI), or (4) AMI was indicated on the summary sheet (or death certificate), the patient was sent directly to a catheterization laboratory for percutaneous coronary intervention (PCI) within 4 hours of the hospital triage time, **and** (since PCI can also be performed in cases of NSTEMI) the presence of ST-segment elevation was either mentioned in the chart or retrospectively observed using a printed copy of the initial in-hospital ECG by two independent cardiologists. These cardiologists (who I refer to as cardiologists 4 and 5, and who did similar work in the AETMIS study) were blinded to the computerized interpretation of the prehospital and in-hospital ECGs, the interpretation of the prehospital ECG by cardiologists 1, 2 and 3, and patient information (except for the indication of symptoms suggestive of acute coronary syndrome). Appendix B summarizes the analytic roles of each of the five cardiologists involved in this thesis.

The review of the in-hospital ECGs by cardiologists 4 and 5 was performed separately from their other readings, of paired ECGs, completed for the research described in section 3.10 (i.e., objectives 5 and 6). They were asked to indicate whether ST-segment elevation was definitely present, possibly present, or not present for each reviewed ECG. For STEMI to be assigned, both had to specify “definitely” or “possibly” present, or one had

to indicate “definitely” and the other had to indicate “possibly”. The cut-off of 4 hours for direct transfer to a catheterization laboratory was chosen to indicate STEMI as a result of a pilot study for the AETMIS field evaluation which indicated that, of patients sent within 4 hours, 85% had STEMI (15% had NSTEMI). A longer cut-off would increase the proportion of patients without STEMI.

For patients who were transferred from the emergency room of the receiving centre to another hospital, a diagnosis of STEMI was assigned if the patient was transferred directly to a catheterization laboratory within 4 hours of triage and either (1) STEMI was specifically indicated in the emergency department physician notes or (2) ST-segment elevation was “definitely present” on the initial in-hospital ECG according to at least one of cardiologists 4 and 5 (or “possibly present” by both, as described above). Patients discharged home from the emergency department were considered to be free from STEMI (see statistical analysis section for more details about this assumption). For patients who left the emergency department without being officially discharged, a diagnosis of STEMI was assigned if (1) STEMI was specifically indicated in the physician notes or (2) ST-segment elevation was definitely/possibly present on the initial in-hospital ECG according to at least one of/both cardiologists 4 and 5 (as above).

A diagnosis of NSTEMI was assigned to admitted (or deceased non-admitted) patients if (1) NSTEMI was specifically indicated on the discharge summary sheet (or death certificate), or (2) AMI was indicated on the summary sheet (or death certificate) and there was no evidence of a thrombolytic agent having been administered, nor the patient

having been sent for PCI within 4 hours of the triage time, nor any evidence of an ST-segment elevation being documented in the ED notes. In the case of (2), the initial in-hospital ECG was also retrospectively read by cardiologists 4 and 5 (as above) to confirm the absence of ST-segment elevation. For this reading, both cardiologists had to concur that an ST-segment elevation was absent.

For transferred patients, a diagnosis of NSTEMI was assigned if (1) NSTEMI was specified in the emergency department physician notes (regardless of whether the transfer was to a catheterization laboratory or not) or (2) AMI was indicated in the notes but the patient's transfer was not an urgent transfer to a catheterization laboratory. As for admitted patients, cardiologists 4 and 5 also had to concur that an ST-segment elevation was absent on the initial in-hospital ECG in the case of (2). Patients discharged home from the emergency department were considered to be free from NSTEMI (see statistical analysis section for more details). For patients who left the emergency department without being officially discharged, a diagnosis of NSTEMI was assigned if (1) NSTEMI was specifically indicated in the physician notes, or (2) AMI was indicated in the physician notes, there was no evidence of an ST-segment elevation being documented in the notes and cardiologists 4 and 5 concurred that an ST-segment elevation was absent on the initial in-hospital ECG.

The designation of angina as "unstable" or "stable" was more complicated when the term "angina" was used on its own in the hospital charts. If "angina" was indicated and the patient was admitted or transferred to another hospital, a diagnosis of unstable angina was

assigned. Conversely, persons diagnosed with “angina” or “atypical angina” who were discharged home were considered to have had stable angina.

Most kinds of arrhythmia were considered as “Other cardiac” diagnoses (e.g. atrial or ventricular fibrillation, atrial flutter, “flutter”, second or third degree atrio-ventricular block, sinus bradycardia, unexplained bradycardia, paroxysmal supraventricular tachycardia, and “tachyarrhythmia”), except for sinus tachycardia, “tachycardia” (without other specifics), and “tachycardia of unknown origin”, which were considered “Other non-cardiac” diagnoses. Palpitations as a final diagnostic impression or diagnosis on a discharge summary sheet were considered “Other non-cardiac”.

3.6 CODING OF OTHER HOSPITAL DATA

Cardiac history was extracted from the hospital chart using the triage sheet, supplemented by physician and nursing notes in the emergency department and any historical information (clearly indicated as such) on the discharge summary sheet, if the patient was admitted. Following consultation with clinician members of the research team, I defined cardiac history (that is, evidence of prior ischemic heart disease) as any angina, myocardial infarction, acute coronary syndrome (not otherwise specified as unstable angina or AMI), coronary artery disease or malady, coronary atherosclerosis, heart ischemia, prior PCI, prior coronary artery bypass graft surgery (CABG), cardiac insufficiency, congestive heart failure, acute pulmonary oedema or cardiac arrest, prior to the encounter resulting in the prehospital ECG. Previous “heart disease, unknown kind” and a prior “cardiac problem” were considered too imprecise to include in this definition.

These categories appear to be sufficiently similar for comparison to those used by Kudenchuk et al. (1991), who defined cardiac history as previous myocardial infarction, angina or congestive heart failure (p. 1488). Congestive heart failure, acute pulmonary oedema, and cardiac insufficiency were considered to be synonymous.

The primary territory of the infarction (as predominantly anterior, inferior, or other), for patients identified with STEMI was assigned in two ways, depending on the source of the information. The territory categories were similar to those employed by Kudenchuk et al. (1991). I assigned infarct territory according to the hospitals for a patient with a hospital diagnosis of STEMI using the discharge summary (if specified there) or in the emergency department physician notes (with preference given to hospital cardiologist notes, in the latter case).

Infarct territory according to the cardiologists, for patients considered to have ST-segment elevation consistent with STEMI, was based on information about the leads on the prehospital ECG which displayed the ST-segment elevation. Table 3 shows the correspondence between the lead specifications and territory, which was adapted from Kudenchuk et al. (1991) in consultation with experts in the research team (i.e., cardiologist 3 and an emergency physician).

Table 3. Infarction territory based on cardiologist interpretation of the prehospital ECG (adapted from Kudenchuk et al., 1991)

Leads for ST-segment elevation	Infarct territory	Code for analysis
any 2 contiguous leads of V1 to V4	anterior	anterior
any 2 contiguous leads of V1 to V6 and at least one of I and aVL	antero-lateral	anterior
any 2 contiguous leads of II, III, aVF	inferior	inferior
any 2 contiguous leads of II, III, aVF and at least one of V5 and V6	infero-lateral	inferior
at least 2 contiguous leads of V5 and V6 or I and aVL	lateral	other
ST-segment depression in any 2 contiguous leads of V1 to V3	posterior	other

Using Table 3, I assigned the infarction territory using the lead specifications of the two cardiologists; my coding was verified by an emergency physician on the research team. In cases where consensus on the leads was not reached between cardiologists 1 and 2, cardiologist 3 was asked to assign the territory and the majority decision was used (thus, the same method as was used to assign presence or absence of STEMI).

The following data were also extracted from the hospital charts: creatinine level in first test after triage (as an indicator of renal dysfunction)[24], time of initial in-hospital ECG, and length of hospital stay (either as an inpatient or in the emergency department).

3.7 AMBULANCE DATA

Urgences-santé maintains computerized databases of service information for every emergency call received and each patient encounter. These data include the timing of different events (such as the time at arrival at the patient's site and the time at departure for hospital) and information collected by the technicians on ambulance forms, stored in databases linked through a patient identification number.

I assigned the symptomatic nature of each prehospital patient using information on principal complaints found in check boxes on the computerized versions of the ambulance forms and text written by the technician(s) about the patient's symptoms. The presenting complaint was classified in a hierarchical manner according to six predefined categories: (1) chest pain, (2) shortness of breath, (3) weakness / dizziness / fainting /

[24] In a few cases where an emergency physician assisted with my coding of the hospital diagnosis, high initial creatinine (associated with renal dysfunction) made cardiac ischemia less likely as the origin of elevated creatine kinase and troponin results.

altered consciousness / numbness in left arm, (4) palpitations / tachycardia (fast heart beat), (5) abdominal pain, and (6) other. These categories were chosen while considering literature on the prevalence of typical and atypical presentations in STEMI/AMI by Hahn and Chandler (2006), Harris (2006), AHA (2005), and Goldman and Kirtane (2003), and were adapted from those by Gupta et al. (2002).

Chest pain included pain in the retrosternal region (in the centre of the chest, behind the sternum), the left arm, the jaw or the neck, and epigastric pain (above the umbilicus). When multiple complaints were present including chest pain, the patient was classified in the chest pain category. A similar method was used for each category, such that patients classified in the shortness of breath group, for example, could have other symptoms but did not report chest pain. Those classified as abdominal pain could have other symptoms but did not report chest pain, shortness of breath, weakness / dizziness / fainting / altered consciousness / numbness in left arm, or palpitations / tachycardia.

Falls were included only if preceded by cardiac symptoms or weakness. "Other" included back pain, headache, gastrointestinal symptoms (nausea, vomiting), more generalized musculoskeletal pain, anxiety, symptoms of panic attack, generalized oedema, convulsions, sweating, intoxication (by alcohol or street drugs), and the absence of symptoms in the first five categories. A small number of patients with prehospital ECGs were excluded, who had experienced chest pain following a trauma: a motor vehicle or work-related accident (including electrocution and exposure to noxious gas), or a fall not preceded by cardiac symptoms or weakness.

I examined the test performance of the computerized prehospital ECG interpretation using all eligible patients in the study sample, regardless of age and membership in the symptomatic nature categories 1 through 6. These analyses were then run again using only patients in category 1 (chest pain with or without other symptoms), in order to restrict to a more homogeneous sample and to facilitate comparison with results by Kudenchuk et al. (1991).

I calculated delay from symptom onset to pehospital ECG using the time of symptom onset according to the technicians on the computerized versions of the ambulance forms (based on interview of the patient, his/her companion(s), or witnesses), subtracted from the time stamp of the ECG (automatically recorded by the machine). Delay data were considered missing when a specific time of symptom onset was not provided. The only exception to this was a multivariate regression analysis of factors affecting the computer's diagnostic sensitivity, for which estimates of the delay were generated if possible, using less specific information, in order to gain sample size. In addition to analyzing the delay data in continuous form, categories adapted from Kudenchuk et al. (1991) were used when studying the impact of delay on the computer's test performance in strata: (1) 0-29 minutes; (2) 30-59 minutes; (3) 60-119 minutes; and (4) 120 minutes or more.

I calculated on-scene time, spent by ambulance personnel at the patient encounter site, by subtracting, for transported patients, the time of ambulance departure for the hospital

from the time of ambulance arrival at the patient's address[25]. These two time points are automatically recorded when the technician presses a button on the ambulance computer, and are later entered in an administrative database at *Urgences-santé*. Although ambulance personnel can also write the time of arrival at the patient's side and the time of departure for hospital on forms, these are likely to be less reliable and more subjective than the computerized time data, according to prehospital experts at *Urgences-santé*. The time required to get to the patient's side once ambulance personnel arrived at the address (due to elevators, stairs, locked doors, crowds, snow and ice, etc.) was assumed to not be systematically different between the groups of patients with and without prehospital ECGs.

The time data could be missing or errors introduced if the procedure for recording the times in the ambulance computer was not correctly followed. For example, if the time stamp button was not pressed on arrival at a patient's destination but was pressed on return to the ambulance, the time of "arrival" may be very close in time (or equal) to the next time stamp, normally pressed when departing for the hospital. This will result in an artificially short on-scene time. Likewise, if the time stamp button was not pressed on departure for hospital but much later, the time of "departure" may be very close in time to the subsequent time stamp, normally pressed when arriving at the hospital. The latter situation will result in an artificially long on-scene time.

[25] Technically, then, the on-scene time definition used in this thesis includes the delay due to "patient access" and "vehicle access" (with the patient on a stretcher) as well as time "on-scene", if the last is considered to be spent by the side of the patient.

Based on consultation with emergency physicians affiliated with *Urgences-santé* on the research team, if the total on-scene time was less than 5 or greater than 90 minutes, the data were assumed to be in error and the patient was excluded from the analysis. It was also possible for one or both time points to be missing from the administrative database[26]; in this case, patients were excluded from the analysis.

3.8 SELECTION OF PATIENTS FOR ON-SCENE TIME (OBJECTIVE 4)

For the analysis of on-scene time, comparison patients were chosen from a historical period prior to that of the prehospital ECG sample, taking advantage of a phase during which no ECG training was yet available at *Urgences-santé*. The two groups being compared were attended to by ambulance technicians from the same operational centre[27], allowing for the possibility of overlap in personnel (although turnover of ambulance staff can be high). This approach also allowed for a greater possibility of overlap in the geographic region served during the calls, than if concurrent comparison patients had been chosen (who would necessarily have been served by different personnel from another operational sector).

All patients selected for the on-scene time analysis had to have received at least one dose of aspirin or nitroglycerin from *Urgences-santé* personnel (most often given at the patient encounter site, at least initially in the case of nitroglycerin). Thus, both groups were suspected of having a cardiac problem and eligible (in theory for the comparison patients)

[26] For logistical reasons, I did not attempt to search for this information in other sources.
[27] A specific group of ambulance technicians and vehicles are assigned to and operate out of each centre. Each operational centre has a defined geographical area that it predominantly serves, but all ambulances can also 'migrate' to other regions, as needed, to maintain coverage and vehicle flow.

for a prehospital ECG, since the criteria for these prehospital medications and an ECG were the same (as mentioned in section 2.3.1). The historical comparison patients were attended to in the time period May 1, 2002 – April 30, 2003, after the medications program had officially started (in April 2002), but before the first training session on performing prehospital ECGs (in May 2003).

3.9 STUDY SAMPLE FOR ADDED VALUE ANALYSIS (OBJECTIVES 5 & 6)

In order to be considered for the added value (paired ECG) analysis, all patients had to be transported to hospital and alive on arrival so that there was the opportunity for diagnostic work-up and in-hospital ECG acquisition. As previously mentioned, each hospital was asked to provide a copy of the first ECG acquired after patient arrival.

The pairs of ECGs used in this analysis were generated in two settings (prehospital and in-hospital) without synchronization of machine times. Recognizing this limitation, it was nonetheless relevant to estimate the length of time which elapsed between these serial measures, for data validation and descriptive purposes. I calculated the delay between the ECGs by subtracting the time of the earlier, prehospital ECG (printed on the tracing) from the time stamp printed on the initial in-hospital ECG[28].

In cases where the archivists suspected that the in-hospital ECG provided was not the initial ECG, based on the delay since hospital triage and the physician and nursing notes (which indicated an earlier in-hospital ECG), the patient was excluded from the paired sample. The patient was also excluded from the analysis if there was a delay of more than

[28] The data entry of all ECG time stamps was checked for accuracy.

6 hours between the prehospital ECG and the in-hospital ECG provided[29]. This cut-off was used firstly since these in-hospital ECGs were unlikely to be the initial ones in the context of suspected acute coronary syndrome.[30] Secondly, even if the correct ECG was provided, the goal of the analysis was to examine added value in the acute medical context. Even in the less urgent case (i.e., relative to STEMI) of suspected acute coronary syndrome without ST-segment elevation, recent American guidelines recommend repeated ECGs at 15- to 30-minute intervals (Anderson et al., 2007). European guidelines recommend a first ECG within 10 minutes of first medical contact (which some of the hospital clinicians may have considered the prehospital ECG) and the next within a maximum of 6 hours in the absence of recurrent symptoms (Bassand et al., 2007).

3.10 PAIRED ECG READINGS BY CARDIOLOGISTS 4 AND 5 (OBJECTIVES 5 & 6)

Two Royal College Board-certified cardiologists who work in university hospital settings retrospectively and independently reviewed paper versions of the prehospital and first in-hospital ECGs using a standardized data entry form (in either paper or electronic format). They were blinded to patient information regarding name, age, and sex. The form was independently pilot tested by both cardiologists using eight pairs of tracings. The cardiologists were told the patients were adults presenting with symptoms suggestive of acute coronary syndrome.

The cardiologists were given the matching ECGs for each patient, with the prehospital tracing marked as A and the first in-hospital tracing marked as B. This was done in order

[29] This strategy assumed the machine time stamps were correct.
[30] Also, none of these long delays were attributable to lengthy transport time.

to more closely imitate the reality of clinical practice – where a physician in an emergency department would have access to both ECGs and would know which tracing was which – and for feasibility reasons (since the prehospital ECG printout is distinct). The time stamp on each ECG was hidden from the cardiologists, as well as the computerized interpretation of each tracing, so that readings were based solely on the electrocardiographic information. For tracing B, the names of the hospital, ECG technician and physician were not necessarily hidden.

Each pair of ECGs was inspected for predefined, electrocardiographically significant differences. Significant differences between the two ECGs were defined as presence versus absence of ST-segment elevation, "pseudo-STEMI" (i.e., ST-segment elevation not thought to be due to infarction), LBBB/pacemaker, certain arrhythmias, or other ECG abnormalities indicative of ischemia (i.e., ST-segment depression, T wave inversion, pathologic Q waves). Pacemaker rhythms were included since their ECG pattern can mask or mimic signs of ischemia. An ECG showing only a functioning pacemaker was considered in the same manner as one displaying LBBB. When there were significant differences between the ECGs, the presence or absence of the predefined features were noted on the form for each ECG. If there were no significant differences between the two ECGs, the presence of the similar features were recorded. If either ECG was illegible, the frequency of this occurrence was tallied and the pair of tracings was not interpreted.

The definitions of all the ECG features of interest were available as reminders on the paper and electronic versions of the form, and were discussed with the readers prior to the

pilot test session. These definitions were as follows. ST-segment elevation referred to presence of an elevation of at least 2 mm (0.2 mV) in precordial leads V2-V3 and/or at least 1 mm (0.1 mV) in two or more other contiguous leads, and absence of signs of LBBB, a pacemaker, pericarditis, left ventricular hypertrophy, and benign early repolarization ST-segment elevation. This definition of ST-segment elevation is consistent with that by the American College of Cardiology and the European Society of Cardiology (Alpert et al., 2000) and a recent joint international task force (Thygesen et al., 2007) (and, in theory, more restrictive than that used by cardiologists 1, 2 and 3 for the computer diagnostic performance analysis). Differences in the presence versus absence of "borderline" ST-segment elevation, associated with a maximum elevation of less than 1 mm, were also recorded.

Pseudo-STEMI referred to presence of ST-segment elevation thought to be indicative of pericarditis, left ventricular hypertrophy, or benign early repolarization. LBBB referred to a QRS duration > 120 ms in the presence of normal sinus or supraventricular rhythm; a QS or RS complex in lead V1; broad or notched R waves in leads V5 and V6, or an RS pattern; and R peak time ≥ 0.006 seconds without Q waves in lead I, V5 or V6 (Braunwald, 1997). The presence of pacing spikes initiating a widened QRS interval indicated a functioning pacemaker. The arrhythmias that were noted were atrial fibrillation or flutter, paroxysmal supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, second or third degree atrioventricular heart block, or bradyarrhythmia (Dubin, 2000)[31].

[31] Other forms of arrhythmia, such as premature beats, were considered too non-specific for the purposes of this analysis, since they are more benign in general.

ST-segment depression referred to presence of a downward ST deflection of at least 0.5 mm (0.05 mV) in two or more contiguous leads (including reciprocal changes). T wave inversion referred to presence of negative T waves of at least 1 mm (0.1 mV). Abnormal Q waves referred to presence of Q waves of at least 0.03 seconds in width and at least 1 mm (0.1 mV) in depth in two or more contiguous leads. These definitions are consistent with a task force document on clinical data standards in acute coronary syndrome (Cannon et al., 2001).

More than one reader was used to compare the ECGs. Given the large number of abnormalities studied and in order to reflect the reality of unique interpretative style, the results were analyzed according to each cardiologist, without attempting consensus. The clinical reality of an emergency department is also such that "consensus" readings on all of the features of interest would be the exception rather than the norm.

3.11 ECG DATA VERIFICATION AND CLEANING

For the analysis of diagnostic performance, the ECG interpretation data generated by cardiologists 1, 2 and 3 and by the computer were entered in computerized databases. The computer data were entered in an Excel spreadsheet by a clerk at *Urgences-santé*, and all data were checked against the original computerized printout of the tracing by me or by the *Urgences-santé* data research technician. The cardiologists used photocopies of the tracings for their readings, without patient identifiers or the computerized interpretation displayed. One cardiologist directly entered ECG interpretations in an Access database; these data were verified for internal consistency using cross-tabulations. For practical

reasons the other cardiologist entered ECG interpretations on the printed form version of the Access database and the data were then entered in the database by a second clerk; in this case, all data were checked by me against the original forms. The original prehospital ECG tracings were used by me and the *Urgences-santé* data technician to verify the identification numbers for each patient, and thus to link to information in the administrative databases and to a hospital chart number for transported patients. In cases where more than one prehospital ECG was performed for the same patient during the same encounter, the first tracing was used for my analysis.

For the added value (paired ECG) analysis, the ECG interpretation data generated by the cardiologists 4 and 5 were entered in computerized databases. One cardiologist directly entered data in an Access database; these were verified for internal consistency using cross-tabulations. For practical reasons the other cardiologist entered data on a paper version and these were then entered in an Access database by me; all such data were double-checked by me against the original forms.

The cardiologists involved in this part of the thesis were distinct from those who read the prehospital ECGs for the analysis of the computer's diagnostic performance for STEMI. As noted in Section 3.5, the cardiologists involved in the paired analysis reviewed a number of initial in-hospital ECGs to confirm some of my coding for the hospital diagnoses. This review was performed as a separate exercise with distinct copies of the tracings, asking for confirmation of the presence or absence of ST-segment elevation only, and was not done in the same time period as the reading of the paired ECGs.

3.12 STATISTICAL ANALYSIS

3.12.1 Diagnostic test characteristics, assuming perfect references (objective 1)

I first estimated the diagnostic test characteristics for the computer code of "***Acute MI***" (which implies STEMI) using simple 2 x 2 tables and assuming perfect reference tests (either the consensus cardiologist interpretation or hospital diagnosis). All 2 x 2 table analyses in this thesis, as well as descriptive statistics, were carried out using SPSS Statistics software version 17.0. The Meta-DiSc software version 1.4 was used to generate 95% confidence intervals for the diagnostic performance estimates when using 2 x 2 tables. The first analysis (versus the cardiologists' interpretation) was also run with and without cases of posterior STEMI to look for any impact on the estimates. This was done since confirmation of a STEMI in this heart territory usually requires an ECG using 15 leads, rather than the standard 12 used for the prehospital ECGs in this project[32].

The comparison with clinician reading of the same prehospital ECG examines what I will call the computer software's "field" diagnostic test performance (i.e., considering only the information available in the prehospital, or field, setting). The comparison with the hospital diagnosis examines what I will call the computer software's "absolute" test performance. Here, the estimates indicate how well the computerized interpretation of the prehospital ECG agrees with a more complete diagnosis (based on more tests and duration of observation) that is likely to be closer to the underlying true status. In addition to considering the "field" and the "absolute" performance of the computer software (depending on which reference was used), this thesis also generated different estimates

[32] Electrical activity from the posterior surface of the heart is not directly measured on a standard 12-lead ECG (Aehlert, 2006).

depending on whether each reference was assumed to be "perfect" (this section) or "imperfect" (section 3.12.3). In the results, the following terms will be used to distinguish the four types of estimates: "field – perfect reference", "field – imperfect reference", "absolute – perfect reference", and "absolute – imperfect reference".

3.12.2 Agreement between cardiologists 1 and 2 (objective 1)

The level of agreement for the dichotomous diagnostic result of "acute ST segment elevation that warrants immediate consideration for reperfusion therapy" based on the retrospective interpretation of the prehospital ECGs by cardiologists 1 and 2 was measured by calculating the Kappa statistic. The results of the initial readings were used (i.e., prior to the consensus discussion of discordant interpretations). This analysis was carried out using SPSS Statistics software. I calculated the approximate 95% confidence interval using the general equation: Kappa estimate ± 1.96 × (standard error of estimate).

3.12.3 Diagnostic test characteristics, imperfect references (objective 1)

Analysis perspective. In the next set of analyses, I used Bayesian latent class models to examine the diagnostic test characteristics for the computer code of "***Acute MI***" without assuming the reference tests were perfect. Briefly, the Bayesian perspective allows for the incorporation of explicit prior information about a parameter of interest (concerning imperfect diagnostic performance, in this case, according to expert opinion or literature review, for example) which is considered in the analysis along with the likelihood of the observed data. This method generates posterior estimates for the parameter, now that a prior opinion has been updated with study data. Credible intervals

for the posterior estimate – analogous to confidence intervals in an analysis from a frequentist perspective – have the practical advantage, not available with frequentist methods, of allowing direct statements to be made about the probability of an estimate being in a specific interval. A brief overview of the Bayesian approach and latent class models is presented in Appendix C.

Prior probability distributions. Prior probability distributions were used to incorporate information, available before the analysis, about the likely range in sensitivity and specificity of the reference tests. For hospital diagnoses, I searched for published literature on the prevalence of missed diagnoses of STEMI among patients discharged from emergency departments to inform my estimate of sensitivity. I looked at the prevalence of ST-segment elevation among patients without acute coronary syndrome in Kudenchuk et al. (1998) as an indication of specificity. These approaches yielded estimates of 95-99% for the sensitivity (Schull et al., 2006; Pope et al., 2000) and 97-99% for the specificity of the hospital STEMI diagnosis. For the cardiologist parameters, I found estimates in the literature with regards to the detection of ST-segment elevation (suspected STEMI): 80-95% for sensitivity and 90-99% for specificity (Youngquist et al., 2007; Feldman et al., 2005; Sejersten et al., 2002; Kudenchuk et al., 1998).

The above literature information was simply used to inform starting points for the prior probability distributions, and was combined with expert clinical opinion, for two reasons. Firstly, the extent of the applicability of the published estimates to hospitals and cardiologists in Montreal and Laval, and to the somewhat heterogeneous nature of the

presenting symptoms in the present study, is uncertain. Secondly, these literature-derived intervals are relatively narrow, especially with respect to hospital diagnoses. Such strong prior information does not reflect the actual level of certainty of my expectations, and may differ considerably from the observed data. Wider priors give more weight to the observations. Prior to the analysis, I asked cardiologists 3, 4 and 5 on the research team for their clinical opinion on best and worst diagnostic performance in general, based partly on their experience in Quebec hospitals. I then considered both sources in choosing values for the lower and upper limits of the parameters, giving more weight to the expert opinions where these diverged from the literature estimates.

This prior information was expressed in the form of a beta distribution with an associated mean and standard deviation (this distribution is described further in Appendix C). The estimated ranges were considered to be equal-tailed 95% probability intervals. The beta prior densities for each parameter were designated by using the centre of the range as the mean and defining the standard deviation as one quarter of the total range (Joseph et al., 1995). The α and β parameters for the beta prior densities were calculated from the means and standard deviations using the formulae in Appendix C. Table 4 displays the values that were used in the analysis. In all the latent class model analyses, I used low information uniform densities[33] for the computer's test performance, whereby all values of sensitivity and specificity within a feasible range are *a priori* equally likely.

[33] A beta (1,1) density is equivalent to a uniform density on the interval [0, 1].

Table 4. Prior probability distributions and prevalence values used in latent class models

Parameter	**Latent variable (true state)**	**Range (%)**	**Mean (sd)**	**α, β**
Hospital sensitivity	STEMI	85-97	91 (3.0)	81.90, 8.10
		Wider range used for sensitivity analysis:		
		65-99	82 (8.5)	15.93, 3.50
Hospital specificity	STEMI	85-95	90 (2.5)	128.70, 14.30
		Wider range used for sensitivity analysis:		
		70-99	84.5 (7.25)	20.21, 3.71
Cardiologist sensitivity	ST-segment elevation (suspected STEMI)	85-95	90 (2.5)	128.70, 14.30
		Wider range used for sensitivity analysis:		
		80-98	89 (4.5)	42.14, 5.21
Cardiologist specificity	ST-segment elevation (suspected STEMI)	80-92	86 (3.0)	114.19, 18.59
		Wider range used for sensitivity analysis:		
		80-99	89.5 (4.75)	36.38, 4.27
Prevalence of STEMI		0.5-20	10.25 (5.125)	3.49, 30.54

sd=standard deviation

Since the hospital diagnoses were assigned by me using the available chart information, there is the possibility of misclassification, particularly among transferred patients (for whom only information from the first hospital was available) and non-admitted patients with maladies that were considered by the hospital physician(s) to be cardiovascular in origin. Considering the hospital diagnoses to be an imperfect reference in the analysis also decreases the impact of misclassification errors made in the course of this research.

Sensitivity analysis. I performed sensitivity analysis for the effect of the prior probability distributions by running supplemental models containing wider intervals, and also using low information prior distributions for some of the parameters. Table 4 also presents the range in values used for the sensitivity analysis of the priors (see "wider range used for sensitivity analysis"). The ensemble of analyses was used to draw overall conclusions about test performance.

Underlying prevalence of STEMI. The Bayesian approach to analysis of diagnostic test performance also required a prior density over the prevalence of the disease of interest. Based on a literature review, Youngquist et al. (2007) provide two possible intervals for the underlying STEMI prevalence in the population of patients eligible for prehospital ECGs. The higher of these is applicable to chest pain patients with more typical presentation and varies from 5 to 20%. The lower estimated interval is intended to represent a more heterogeneous population of patients with atypical presentations and varies from 0.5 to 5%. I combined these estimates conservatively, to obtain an interval of

0.5 to 20%. Table 4 also shows the prevalence values used in the analysis[34], calculated in the same manner as the prior probability distributions.

I did not alter the STEMI prevalence values in the prior sensitivity analysis. Given the ECG eligibility criteria for the study subjects and assuming the sample was reasonably representative, I was reasonably confident that the true prevalence lay within the interval used.

Two-test models. I used the "BayesLatentClassModels" software version 1.3 to run analyses of the computer's and the cardiologists' prehospital ECG interpretations, and of the computer's interpretations and the hospitals' diagnoses, in "2-test" models. Since all tests were now considered imperfect, this produced estimates of the sensitivity and specificity of each test, as well as the underlying prevalence of disease. These models, which implemented one latent variable related to the "true disease status" (unknown), assumed no significant correlation between the two tests. However, since the interpretations by the computer and the "consensus cardiologist" are based on the same prehospital electrocardiographic data, there is likely to be some conditional dependence between their results (even though the cardiologists were blinded to the computerized readings), just as correlation is expected between the cardiologist readers.[35] Thus, conditional on the patient's underlying true status (STEMI absent or present, which is unknown), the probability that the cardiologists provided an interpretation of ST-segment

[34] An additional numeric step was required to convert the α and β to the type of parameters required by the BayesLatentClassModel program; see Appendix C for details.
[35] There is also likely to be a certain level of correlation between the computer's interpretations and the hospital diagnoses, since the hospital physicians (in 2005-06) would have had access to the computerized ECG readings as long as the prehospital tracing was present in the patient's chart.

elevation, given a computer result of ***Acute MI***, is likely to be different than the probability that the clinicians would not have given a reading of ST-segment elevation, given no ***Acute MI*** computer result.

Three-test model. I developed a model implementing two latent variables to allow for conditional dependence between the computer and the cardiologists' interpretations (Dendukuri et al., 2009), and which considered the three tests simultaneously. A diagram of the 3-test model is presented in Appendix D. The latent variable related to the prehospital ECG status allowed for correlation between the data from the computer and the cardiologists, within a second latent variable related to the true disease status. As before, the "BayesLatentClassModels" software version 1.3 was used for the analyses.

The positive and negative "absolute" predictive values (and their 95% credible intervals) for the computer's prehospital ECG interpretation (with respect to STEMI) were calculated using the "PredictiveValues" software version 1.3.1. This method allows for imperfect test performance and a disease prevalence that is not exactly known. The 95% credible intervals from the posterior distributions provided the inputs[36] for the computer's sensitivity and specificity and the prevalence of STEMI.

3.11.4 Impact of patient factors on computer test performance (objective 2)

Stratified analysis. To examine the possible association of patient factors with the diagnostic performance of the computerized ECG interpretation, I performed stratified

[36] For each parameter, the midpoint of the 95% credible interval was assigned as the mean and one-quarter of the total interval width was assigned as the standard deviation.

analysis in two ways: using simple 2 x 2 tables for the comparison of the computer with the cardiologists as a perfect reference (regarding "field – perfect reference" performance), and using the 3-test Bayesian latent class model to generate both field and absolute estimates and allow all reference tests to be imperfect.

The factors of interest were patient age and sex, principal infarct territory, cardiac history, and delay between symptom onset and the prehospital ECG (as examined by Kudenchuk et al., 1991). The stratified method required the age and delay variables to be categorical in format (unlike in the regression analyses presented in the next section, where they remained continuous). I used the categories implemented by Kudenchuk et al. (1991) except that the categories containing the greater ages and longest delays were not truncated to less than 75 years and less than 6 hours, respectively. SPSS Statistics and Meta-DiSc software were used.

In the 2 x 2 table analysis, I used the infarct territory as designated by the cardiologists (coded as described in section 2.3.6). For the analysis of infarct territory with the stratified 3-test method, patients were considered "test positive" for the cardiologists, and for the hospitals, only when meeting the designation of interest for each stratum (i.e. inferior or anterior territory[37]), and according to two different sources. The cardiologists' interpretations of the prehospital ECGs were used for the cardiologists' designations of

[37] Otherwise, when positive for the other territory of infarct, the test data were considered missing for that analysis (rather than negative, which implied no infarct). As examples for the inferior territory analysis, a "+ + +" patient had a computer interpretation of ***AMI*** and an inferior infarct was present according to both the cardiologists and hospitals. A "+ - +" patient did not have STEMI according to the cardiologists (the middle test), was computer-positive and the hospital diagnosis was inferior STEMI. If the cardiologists' interpretation was anterior infarct in this example, data for this test were missing (and thus the patient was not included in the analysis of inferior territory). A "- - -" patient did not have STEMI according to all three tests. (See Appendix F for raw data.)

territory. The hospitals' designations used the territory information on the discharge summary (if specified there) or in the emergency department physician notes (with preference given to cardiologist notes, in the latter case).

Multivariate logistic regression. The objective of the regression analysis, which used a hierarchical Bayesian latent class approach, was to examine the independent effect (if any) of the factors examined in the previous section on the computer software's absolute sensitivity, without assuming a perfect reference standard. A multivariate regression model was used so that the variables could be considered simultaneously and without any categorization. More details about this method are provided in Appendix C.

I provided the data and analytic objectives to a statistician who developed a custom-built software program, written in WinBUGS. The analysis incorporated the diagnostic information from all three tests (computer, cardiologists, hospitals) with one latent variable for the "true disease status". Instead of using a second latent variable in the model (as in the previously described 3-test model), a correlation term was introduced in the analysis to allow for conditional dependence between the interpretations by the computer and the cardiologists. The computer's sensitivity was considered as a binary dependent variable and a logistic regression model was used. Because of potential problems with statistical collinearity in this regression framework (since the infarct designations by the cardiologists and hospitals were very similar), only one source was used to indicate infarct territory. The cardiologists' designations were chosen because

these were based on the same ECG data (acquired at the same point in time) as those read by the computer.

Due to the large amount of missing delay data (for 42% of patients), the regression model was first run without this factor. Detailed descriptive statistics were then carried out using this variable, graphically plotting delay data versus the computer sensitivity estimate generated for each subject in the regression model. For those for whom a specific time of symptom onset was not provided but enough information was available to make an estimate, either the estimated delay was used (if a single value) or delay data were imputed using an estimated range of values. This process was carried out to determine whether it was worthwhile to include the delay variable in the regression model despite the large amounts of missing data.

3.12.5 Examination of "false-negative" computer results (objective 3)

Based on the published literature I hypothesized that, compared to assessment by cardiologists as a perfect reference, the computerized prehospital ECG interpretation would have lower field sensitivity. Maximizing the computer's "field – perfect reference" sensitivity is important because a health care system might want to respond in each case where a clinician initially suspected STEMI based on an ECG (regardless of the patient's final true disease status). Also, the identification of "false negatives" for the analysis described below requires a reference to be considered as the"truth". In order for the cardiologists' readings to be considered a generalizable reference here it was necessary to assume that the cardiologists read the prehospital ECGs for this study in a similar manner

as they would have in an emergency room setting, and were generally representative of clinicians that would manage similar patients.

The purpose of this analysis was to examine the interpretations given by the computer software when the consensus cardiologist reading was "positive", but the computer did not indicate ***Acute MI*** (i.e. field "false negatives"), and subsequently to explore whether the computer's field sensitivity could be improved, and at what cost to specificity, if other interpretations were also considered as "positive" signals.

The computer's interpretations for each "false negative" patient were examined in detail. I specifically looked for interpretations related to other ECG abnormalities possibly indicative of ischemia, including mention of infarct, ST-segment elevation possibly or probably associated with pericarditis or early repolarization (which can mimic signs of ischemia), ST-segment abnormalities associated with subendocardial[38] injury or ischemia, and abnormal T waves associated with ischemia. If any of these types of interpretations was provided for at least two of the false negative patients I recalculated sensitivity and specificity by recoding the patients as "computer positive", and compared these estimates to the original values. To compare impact on diagnostic test performance, I plotted the revised sensitivity versus [1 –specificity], which is equivalent to the cumulative percentages of true positives versus false positives, as the computer interpretations considered "positive" were increasingly broadened. This approach allowed graphical examination of the trade-off between identification of true and false positives.

[38] The subendocardium of the ventricles is particularly susceptible to ischemia because of its high oxygen demand and distance from the heart's surface where the coronary arteries originate (Aehlert, 2006).

3.12.6 On-scene time (objective 4)

Mean on-scene time (in minutes, to two decimal points) was compared between the patients with prehospital ECGs and the comparison patients without prehospital ECGs. Multivariate linear regression analysis with on-scene time as the dependent variable was then used to adjust for potential imbalance between the two groups in certain factors that might be associated with on-scene time: patient age, patient sex, season (winter or not), and number of prehospital medications (aspirin or nitroglycerin) received. "Winter" season, when temperatures are low and precipitation takes the form of snow or freezing rain, was defined as the period December 1 to March 31. For these analyses I used SPSS Statistics software.

3.12.7 Comparison of prehospital and initial in-hospital ECGs (objectives 5 & 6)

Using the interpretations by cardiologists 4 and 5, the frequency of each abnormality of interest on both ECGs, the prehospital ECG alone and the initial in-hospital alone was determined for each reader separately, using SPSS Statistics software. The abnormalities were ST-segment elevation and depression, T wave inversion, abnormal Q waves, LBBB/pacemaker, and arrhythmias. Since only clinical significance of the findings was considered, no statistical testing was performed.

3.13 MISSING ECG INFORMATION

For the prehospital ECGs read by cardiologists 1 and 2, the consensus interpretation was considered to be missing whenever one or both cardiologists found the tracing to be illegible due to a technical problem. These patients were excluded from the analysis in 2

x 2 tables; the results are thus generalizable only to cardiologist-readable ECGs. Likewise, in the paired ECG analysis, data were considered missing for each reader (cardiologist 4 or 5) whenever the reader considered one or both tracings to be illegible.

3.14 ETHICS APPROVAL

This research was approved by the ethics review board of the *Institut de Cardiologie de Montréal* (the Montreal Cardiology Institute). The research compliance letters are reproduced in Appendix E.

CHAPTER 4: RESULTS

4.1 EXCLUSIONS AND SAMPLE CHARACTERISTICS

From the sample of 1560 available prehospital ECGs in the 2-year study period, 1500 tracings were eligible for analysis of the computer's diagnostic performance. Sixty tracings (3.8%) were excluded for the following reasons: duplicates of the same tracing (n=6), a three-lead ECG (n=1), additional ECGs performed for the same patient encounter (n=20), patient aged under 18 years (n=1), ECG performed after a trauma (n=14), and computerized interpretation missing (n=18).

For the analysis of the computer's performance compared to the cardiologists' readings, an additional 55 patients were excluded since their prehospital ECGs were not initially interpreted by at least one of the two clinicians[39] (thus, a total exclusion rate of 7.4% [115/1560]). The lack of interpretation was due to technical problems or illegibility, with some ECGs affected by multiple issues: 39 (71%) were missing signals from certain leads, 9 (16%) had wandering baselines (affecting recognition and measurement of elevations and depressions), 5 (9%) had other artefacts (that can resemble arrhythmia and can be caused by loose electrodes), and 7 (13%) were of poor quality (e.g. the original printouts were too light; a signal was not clearly discernible).

Table 5 displays characteristics for the 1445 patients who were included in the analysis when the computer software interpretations were compared with the consensus cardiologist results.

[39] As described in the methods section, the main clinician readers in this part were cardiologists 1 and 2; cardiologist 3 read a small number of tracings (17) for which consensus between cardiologists 1 and 2 could not be reached.

Table 5. Characteristics of 1445 patients for whom the computerized interpretation was compared with the consensus cardiologist result

% male (n)	53.1 (768)
Age (years)	
Mean, standard deviation	66.5, 15.6
Minimum, median, maximum	18.0, 70.0 100.0
Symptomatic nature of presentation as recorded by ambulance technician, % (n)	
Chest pain	84.7 (1224)
Weakness / dizziness / fainting	8.3 (120)
Shortness of breath	3.0 (44)
Palpitations / tachycardia	1.0 (15)
Abdominal pain	0.9 (13)
Other	2.0 (29)
Delay from symptom onset time to prehospital ECG	
10^{th} percentile, median, 90^{th} percentile, in minutes	27.0, 88.0, 339.7
Missing a symptom onset time, % (n)	43.2 (625)
Patient transported to hospital, % (n)	1401 (97.0)

As shown in Table 5, the majority of patients – about 85% of the sample – presented to the ambulance technicians with a complaint of chest pain (with or without other accompanying symptoms). The next most frequent complaint, for patients not reporting any chest pain, was a feeling of weakness, dizziness or fainting. Just over half of the patients were male and mean age was about 67 years.

The delay from symptom onset to the time when the prehospital ECG was recorded varied greatly, but was skewed towards shorter values: the delay was 88 minutes or less for 50% of persons with data. About nine percent had delays of more than 6 hours (not shown in Table 5). A large proportion of the sample was missing delay information. For 24.6% of patients the data provided for symptom onset referred to a delay, a period or an event (e.g. "about an hour ago", "in the last 2-3 hours", "in the night", "during dinner"), so that I could not subtract a distinct onset time from the time stamp on the tracing[40]. For the remaining 18.6% of the sample, there was no mention of a symptom onset time on the ambulance forms.

Returning to the sample of 1500 patients eligible for investigation, 1454 (96.9%) of these were transported by *Urgences-santé* to 21 different hospitals[41]. None of the patients died (or had a cardiac arrest) in the prehospital setting. Hospital chart information (from the initial receiving centre) was requested for 1343 (92.5%) of the transported patients. For the other 111 patients (7.4%), the chart could not be requested due to limited availability

[40] Also, for patients who provided a specific delay, such as "20 minutes ago", the time interval between this response being provided and the prehospital ECG being performed (i.e., the tracing's time stamp) was unknown; thus, delay data were considered missing in this case (as described in the methods, section 3.7).
[41] The non-transported patients refused to be taken to hospital.

of archival personnel by the time verification of patient identity was completed (the duration of the verification process was not related to seriousness of the patient's condition). Of the 1343 files requested, 1334 (99.3%) were obtained, for an overall rate of success of 91.8% (1334/1454) among all transported patients. Eight charts were not available from the archive departments and one chart was requested from the wrong hospital. Table 6 presents and compares the characteristics of the transported patients according to the status of the chart.

As shown in Table 6, a somewhat greater proportion of the patients for whom hospital chart information was obtained presented to the ambulance technicians with chest pain. A slightly larger number of patients among those without chart information had shortness of breath. This latter group also had a greater proportion of female patients. None of these differences were greater than 10% in magnitude. There was a tendency towards shorter delays between symptom onset and the prehospital ECG in the group with chart information. The rest of the characteristics studied were more similar in the two groups. Table 6 also shows that the patients analyzed for the computer's test performance compared to the hospital diagnosis were very similar, with respect to the factors in the table, to those studied in comparison with the consensus cardiologist reading (Table 5).

Table 7a presents the outcome of each patient's evaluation at the initial receiving hospital and the hospital diagnosis for the 1334 patients with chart data. The 1294 patients with a known diagnosis were included in the analysis when the computer software interpretations were compared to the hospital results.

Table 6. Characteristics of patients transported to hospital according to chart status

	Chart obtained (N=1334)	**Chart not obtained or not requested (N=120)**
% male (n)	53.4 (712)	45.8 (55)
Age (years)		
Mean, standard deviation	66.8, 15.3	69.2, 16.0
Minimum, median, maximum	18.0, 70.0, 95.0	20.0, 73.0, 100.0
Symptomatic nature of presentation, % (n)		
Chest pain	86.1 (1149)	79.2 (95)
Weakness / dizziness / fainting	7.8 (104)	8.3 (10)
Shortness of breath	2.6 (35)	8.3 (10)
Palpitations / tachycardia	0.8 (11)	0.8 (1)
Abdominal pain	0.9 (12)	0.8 (1)
Other	1.7 (23)	2.5 (3)
% transported to a hospital with catheterization facilities (n)	76.4 (1019)	71.7 (86)
Delay from symptom onset time to prehospital ECG (minutes)		
10^{th} percentile, median, 90^{th} percentile	26.0, 84.0, 335.4	30.8, 117.0, 505.0
Missing a symptom onset time, % (n)	42.0 (561)	47.5 (57)
0-59 minutes, % (n)	37.6 (291)	34.9 (22)
1 hour – 1 hour 59 minutes, % (n)	23.2 (179)	15.9 (10)
2 hours – 5 hours 59 minutes, % (n)	30.5 (236)	38.1 (24)
6 hours or more, % (n)	8.7 (67)	11.1 (7)

Table 7a. Characteristics of 1334 patients for whom a hospital chart was obtained

	%	n
Admitted to inpatient ward at initial receiving hospital[1]	33.7	450
Transferred to a second hospital[2]	8.0	106
Discharged home from emergency department[3]	56.3	751
Died prior to hospital admission	0.6	8
Left hospital before diagnostic work-up completed (n=14) or without official discharge (n=5)[4]	1.4	19
Hospital diagnosis		
STEMI	6.4	86
NSTEMI	9.1	121
STEMI or NSTEMI[5]	0.1	1
Unstable angina	6.7	89
NSTEMI or unstable angina[6]	0.4	5
Other cardiac diagnosis	22.0	293
Other non-cardiac diagnosis	51.5	687
Undefined diagnosis (but definitely not acute coronary syndrome)[7]	0.9	12
Missing	3.0	40
Cardiac history present	58.6	782

[1] for eight patients, discharge summary missing
[2] for one patient, final emergency department notes missing
[3] for 12 patients, final emergency department notes missing
[4] no hospital diagnosis for the 19 patients in this category
[5] patient died before admission; it was not possible to confirm STEMI or NSTEMI based on the available 3-lead ECGs
[6] it was not possible to determine which diagnosis was present based on the available information
[7] there was sufficient information to rule out acute coronary syndrome but not to establish a definitive diagnosis

One hundred and fifty initial in-hospital ECGs were read by cardiologists 4 and 5[42] to confirm the type of acute myocardial infarction (i.e. STEMI or NSTEMI) or the type of acute coronary syndrome (acute myocardial infarction or unstable angina), since these were not clearly specified in the chart information obtained. For 21 of these patients assigned to the STEMI category, both cardiologists stated ST-segment elevation was "definitely present"; for 5 others, one cardiologist considered the elevation "definitely present" and the other said it was "possibly present". For one patient who died before admission, it was not possible to determine whether the diagnosis was STEMI or NSTEMI[43]. In all cases where NSTEMI was assigned as the diagnosis, cardiologists 4 and 5 agreed that ST-segment elevation was "definitely not present".

As shown in Table 7a, about one-third of the patient sample were admitted to an inpatient ward at the initial receiving hospital; a further 8% were transferred to another hospital. Just over half of the sample was discharged from the emergency department (i.e. without an inpatient ward admission). Just over 6% of the sample received a diagnosis of STEMI. There was a clear diagnosis of acute myocardial infarction for 15.6% (208/1334), and 22.6% were diagnosed with an acute coronary syndrome (302/1334). Another one-fifth of patients had a cardiac diagnosis other than acute coronary syndrome. The most common diagnosis overall was non-cardiac, for about half of the patients. More than half of patients had a cardiac history[44].

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[42] Cardiologists 4 and 5 were not involved in the prehospital ECG interpretations for this part of the thesis.
[43] The patient was assigned a hospital diagnosis of NSTEMI, and the effect of assigning STEMI instead was checked for the analysis of computer test performance where the reference (hospital) diagnosis was assumed to be perfect (section 4.2.1).
[44] As described in the methods section, cardiac history was defined as any previous history of angina, myocardial infarction, acute coronary syndrome (not otherwise specified as unstable angina or acute myocardial infarction), coronary artery disease or malady, coronary atherosclerosis, heart ischemia, PCI,

Table 7b displays the hospital diagnosis and proportion with a cardiac history according to the outcome of the patient's evaluation at the initial receiving hospital. STEMI was diagnosed most often, as expected, among admitted patients and those that died before admission at the initial receiving hospital. (The same pattern was seen for NSTEMI). Four patients diagnosed with STEMI were transferred to another hospital (i.e., were never admitted at the first hospital). Similar proportions of admitted and transferred patients had other cardiac diagnoses. The majority of discharged patients had a non-cardiac diagnosis. Finally, the proportion of patients with a cardiac history was greatest among transferred and admitted patients. Over half the discharged patients also had a cardiac history. Twenty-six admitted patients died during their hospital stay (5.9%; not shown in Table 7b).

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coronary artery bypass graft surgery, cardiac insufficiency, congestive heart failure, acute pulmonary oedema or cardiac arrest.

Table 7b. Hospital diagnosis by type of patient

Hospital diagnosis	Admitted		Transferred (ED* diagnosis used)		Discharged from ED*		Died before admission		Left hospital without diagnosis	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
STEMI	78	(17.3)	4	(3.8)	0	(0.0)	4	(50.0)	0	(0.0)
NSTEMI	113	(25.1)	5	(4.7)	2	(0.3)	1	(12.5)	0	(0.0)
STEMI or NSTEMI	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Unstable angina (UA)	59	(13.1)	30	(28.3)	0	(0.0)	0	(0.0)	0	(0.0)
NSTEMI or UA	2	(0.4)	2	(1.9)	1	(0.1)	0	(0.0)	0	(0.0)
Other cardiac	77	(17.1)	17	(16.0)	199	(26.5)	0	(0.0)	0	(0.0)
Other non-cardiac	113	(25.1)	45	(42.4)	527	(70.2)	2	(25.0)	0	(0.0)
Undefined (not ACS**)	0	(0.0)	2	(1.9)	10	(1.3)	0	(0.0)	0	(0.0)
Unknown	8	(1.8)	1	(0.9)	12	(1.6)	0	(0.0)	19	(100)
Total	450		106		751		8		19	
Cardiac history present	289	(64.2)	81	(76.4)	399	(53.1)	5	(62.5)	8	(42.1)

*ED=emergency department; **ACS=acute coronary syndrome

Table 8 presents the characteristics for the 86 patients who received a hospital diagnosis of STEMI. The STEMI patients were predominantly male, with a mean age of about 64 years. Almost all had presented with chest pain, and for 50% of the patients the delay from symptom onset to the prehospital ECG was shorter than that seen for the overall samples (Tables 5 and 6), at 61 minutes or less. About 40% had a history of cardiac disease. Ninety percent of patients were initially transported to a hospital capable of performing percutaneous coronary intervention. The infarcts were assigned primarily to the inferior region for almost half of the patients.

Two-thirds of the STEMI patients were taken to the catheterization laboratory for percutaneous coronary intervention (PCI) within 4 hours of hospital arrival. Another 11.6% also received PCI as their initial treatment, but with greater delays or after an unknown delay. Less than 5% received thrombolytic agents as their initial reperfusion treatment.[45] Five patients (5.8%) did not receive reperfusion therapy at the first receiving hospital (where they were admitted), but were sent within 6 hours of arrival for treatment at a hospital with PCI facilities (and then returned). Two patients with a diagnosis of "aborted" STEMI received PCI, after 6 days in one case and after an unknown delay for the other[46]. A total of 6.9% of the patients died either before admission or during their hospital stay due to acute myocardial infarction (n=5) or cardiogenic shock after acute myocardial infarction (n=1). One of these deaths occurred 7 days after admission; the others were all within 12 hours of hospital arrival.

[45] A similar result was observed for Montreal in a field evaluation of STEMI care: in a 6-month period in 2006-07, 3.2% of STEMI patients (18/547) were initially treated with thrombolysis (AETMIS, 2008a).
[46] The latter patient was noted in the chart to have had a "spontaneous" abortion of STEMI (i.e., without intervention).

Table 8. Characteristics of 86 patients with a hospital diagnosis of STEMI

% male (n)	72.1 (62)
Age (years)	
Mean, standard deviation	63.6, 14.5
Minimum, median, maximum	40.0, 62.5, 89.0
Symptomatic nature of presentation as recorded by ambulance technician, % (n)	
Chest pain	98.8 (85)
Abdominal pain	1.2 (1)
% with cardiac history	39.5 (34)
% transported to a hospital with PCI facilities	90.7 (78)
Delay from symptom onset time to prehospital ECG	
10^{th} percentile, median, 90^{th} percentile, in minutes	20.8, 61.0, 192.6
Missing a symptom onset time, % (n)	33.7 (29)
Of those with data,	
0-59 minutes, % (n)	43.9 (25)
1 hour – 1 hour 59 minutes, % (n)	22.8 (13)
2 hours – 5 hours 59 minutes, % (n)	29.8 (17)
6 hours or more, % (n)	3.5 (2)
Predominant territory of infarct (according to hospital[1])	
Inferior	45.4 (39)
Anterior	36.0 (31)
Other	10.5 (9)
Not specified in chart information received	8.1 (7)
Initial reperfusion treatment	
To lab for PCI within 4 hours of ED* arrival	68.6 (59)
To lab for PCI more than 4 hours after ED arrival	4.6 (4)
PCI after an unknown delay[2]	7.0 (6)
Thrombolysis	4.6 (4)
Sent to a second hospital for PCI	5.8 (5)
Aborted STEMI	2.3 (2)
Not specified in chart information received	7.0 (6)
% deaths	
Before admission	4.6 (4)
After admission	2.3 (2)
Vital status unknown (transferred without returning)	4.6 (4)
% elevated cardiac enzymes within 24 hours of ED arrival	80.2 (69)
% non-elevated cardiac enzymes	16.3 (14)
% no enzyme testing results	3.5 (3)

*ED: emergency department

[1] as specified on the discharge summary or in the ED notes (the latter if not admitted or not specified on the discharge summary)

[2] three of these six patients received PCI within 24 hours of hospital arrival

Regarding the cardiac enzyme status of the 86 patients with a final diagnosis of STEMI, 69 (80%) had documentation of an elevation within 24 hours of hospital arrival. One of these 69 patients had a "borderline" elevation and documented ST-segment elevation on a hospital ECG. Among the 14 patients with non-elevated enzyme results, all had documented ST-segment elevation on an ECG in the hospital chart except for one patient, for whom cardiologists 4 and 5 agreed that ST-segment elevation was "definitely present" on the initial in-hospital ECG. For thirteen of the patients with non-elevated enzyme results it appeared that only one set of enzyme tests were performed and most left the emergency room relatively rapidly: nine were sent to a cardiac catheterization facility (at the same hospital or transferred) within 60 minutes of hospital arrival[47]. For the eight patients with symptom onset data and non-elevated enzyme results who rapidly left the emergency room, the median delay between symptom onset and the prehospital ECG was 53.5 minutes. In comparison, the median delay for the 49 patients with onset data and elevated enzyme results was 77.0 minutes.

For three patients with a final diagnosis of STEMI, there were no biochemistry laboratory results in the chart information received. Two of these had ST-segment elevation specified in their charts. The last of these three patients died before admission of an acute myocardial infarction caused by stent thrombosis, and one of cardiologists 4 and 5 considered ST-segment elevation to be "possibly present" on the initial in-hospital ECG. The chart information for this patient was reviewed by an emergency physician on the research team who agreed that STEMI was the most appropriate diagnosis.

[47] The one patient with two negative enzyme results left the emergency room within 10 minutes for the catheterization laboratory.

4.2 TEST PERFORMANCE OF COMPUTER (OBJECTIVE 1)

4.2.1 Analysis assuming perfect reference tests

The computerized interpretations of the prehospital ECGs were first compared to reference tests considered to be perfect "gold standards" (although their sensitivity and specificity are not 100% in reality). The two references were the consensus cardiologist readings of the same ECGs, and the hospital diagnosis. As outlined in the methods chapter, the first of these contrasts examined "field" performance while the second considered "absolute" detection of STEMI. A "field – perfect reference" analysis is of interest if one considers that any positive result of possible STEMI by clinicians based on ECG data acquired in the field (e.g. if transmitted electronically by ambulance personnel) would have required a response (such as a hospital alert). This scenario assumes that the ECG readers were reasonably representative of cardiologists in general and would have interpreted the data similarly at the time. Using perfect references for the first set of analyses also allowed comparison with previous studies.

Table 9 shows that the computerized interpretation had an estimated sensitivity of about 57%, and a specificity of about 99%, when assuming the cardiologists' reading was a perfect reference test. The specificity estimate indicates that there was a very high probability that a patient without ST-segment elevation, according to the cardiologists, had a negative computerized interpretation (and a very low probability of testing positive). However, the computer would have missed a substantial proportion of patients (43%) suspected by the cardiologists to have STEMI.

Table 9. Test performance of computer, assuming perfect reference tests

Computer versus	Sensitivity: proportion, % (95% confidence interval)	Specificity: proportion, % (95% confidence interval)	Total N
Cardiologists (all patients)	70 / 124, 56.5 (47.3 – 65.3)	1303 / 1321, 98.6 (97.9 – 99.2)	1445
Cardiologists (chest pain only)	68 / 117, 58.1 (48.6 – 67.2)	1092 / 1107, 98.6 (97.8 – 99.2)	1224
Cardiologists (no posterior infarct)	69 / 121, 57.0 (47.7 – 66.0)	1303 / 1321, 98.6 (97.9 – 99.2)	1442
Hospitals (all patients)	60 / 86, 69.8 (58.9 – 79.2)	1187 / 1208, 98.3 (97.4 – 98.9)	1294
Hospitals (chest pain only)	59 / 85, 69.4 (58.5 – 79.0)	1009 / 1028, 98.2 (97.1 – 98.9)	1113

See Appendix F for raw data

These test performance estimates remained very similar when only chest pain patients were included (85% of the sample), or when the three patients thought by the cardiologists to have a posterior infarct[48] were excluded. The confidence intervals for the point estimates of the computer's sensitivity were fairly wide, with a range of close to 20% (i.e. from 47 to 65%). The confidence intervals for specificity showed higher precision, as expected given the large denominator of "negative" results.[49]

The kappa coefficient for the initial level of agreement between the two cardiologists for presence or absence of the outcome was 0.665 (95% confidence interval: 0.594 – 0.736), based on 1445 tracings. This result indicates good agreement (Byrt, 1996) but also demonstrates variability in interpretation, further suggesting that the cardiologists' reading is not truly a perfect reference test.

A few points should be made here about the relative accuracy of the two reference tests used in this thesis. Compared to the cardiologists' prehospital ECG reading, a hospital diagnosis (for the same presenting event) has potential, overall, to be closer to the "true" STEMI status of each patient, since it is based on a longer period of observation and more complete information, as mentioned in the methods. Such information includes the

[48] Posterior infarcts were included for the rest of the analyses for objective 1.

[49] Likelihood ratios can also be used to express these results. The positive likelihood ratio for the computer compared to the cardiologists, for example, was estimated as 41.4 (95% confidence interval: 25.5 – 67.2; not shown in Table 9). This parameter divides the sensitivity by (1 – specificity) and thus is the ratio of the probability of testing "positive" among patients with the disease (true positive rate) to the probability of that result in patients without the disease (false positive rate). Here, for every patient without STEMI that tested "computer positive", 41 patients with STEMI also tested computer positive. The negative likelihood ratio, which divides (1 – sensitivity) by the specificity, compares the false negative and true negative rates. Compared to the cardiologists, the computer had a negative likelihood ratio of 0.44 (95% confidence interval: 0.36 – 0.54; not shown in Table 9). This implies that for every 10 patients with STEMI that tested "computer negative", 4.4 patients without STEMI also tested computer negative. Since these ratios are a function of the sensitivity and specificity estimates they do not add much information and thus will not be reported elsewhere in this thesis.

physical status of the patient (including appearance and the evolution of pain and other symptoms), the patient's medical history, results of cardiac enzyme testing and serial ECGs[50], and even diagnostic angiogram findings from the catheterization laboratory. This may mean that the hospital physicians, having more information, had better ability to detect STEMI when present and to rule out STEMI when absent. Although it is possible that clinicians in general may tend to "over-identify" ST-segment elevation on an ECG (as seen by Kudenchuk et al., 1991[51]) in an effort not to miss a true case of STEMI, this may have led to more false positives for the ECG readers on the research team (who had more limited, cross-sectional information) rather than for the hospital diagnoses.

It should thus be kept in mind that several factors are at play once hospital diagnosis is used as a reference in the analysis, including differences in the type of information being used and differences in the clinical status of the patient over time. Also, ECGs of poor legibility according to the cardiologists were not excluded when the computer was compared to the hospitals alone. The cardiologists' interpretations were based on the consensus readings by the same two clinicians involved in this study (except in a few cases where input from a third cardiologist was required). The hospital diagnoses arose from 21 individual health care centres with an unknown number of different emergency physicians and cardiologists involved in the diagnostic process.

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[50] A patient's electrocardiographic status is, in general, dynamic over time, and a proportion of STEMI patients showing ST-segment elevation on a prehospital ECG may not do so on a later ECG due to a phenomenon known as "spontaneous reperfusion" (i.e., in the absence of treatment). Also, it is possible that a patient who is having an ST-segment elevated acute myocardial infarction by the time s/he is in hospital may not show ST-segment elevation at the time of the prehospital ECG. (These issues will be explored further in the "paired ECG" analysis). Thus, as far as ECG data are concerned, some discordance between prehospital and in-hospital data is to be expected (and is thus acceptable for a prehospital ECG program).

[51] The false positive rate of the clinician readers in this study was 5%, as opposed to 2% for the computer.

Table 9 shows that, when compared to the hospital rather than the consensus cardiologist as a perfect reference, the point estimate for the absolute sensitivity of the computer was more than 10 percentage points higher, at about 70%[52]. This implies that some patients suspected to have STEMI by the cardiologists (but not given the ***Acute MI*** code by the computer) did not have a hospital diagnosis of STEMI, and were thus considered "truly negative" here. This result also suggests that the software's sensitivity has greatly improved since the 1991 study by Kudenchuk and colleagues. The absolute specificity estimate when compared to the hospital reference was 98%.

Since the predictive ability of a test with respect to disease status is of interest to clinicians (and other health decision-makers) I calculated the positive and negative predictive values of the computerized interpretation compared to the hospital diagnosis. These values should be interpreted with much caution, however, as they are functions of both the accuracy of the test and the prevalence of the disease. The study sample may not entirely reflect the true prevalence of STEMI in Montreal-Laval, if patients missing from the sample tend to have STEMI (or tend to not have STEMI). Further, other settings may differ in prevalence for a wide variety of reasons. Assuming the prevalence in the sample was reasonably representative for the sake of these calculations (considering the hospital diagnosis as a perfect reference test), the probability of a STEMI diagnosis when the computer result was ***Acute MI*** (positive predictive value) was 74.1%[53]. This implies a considerable false positive rate, of about 26%, such that actions based on a

[52] For this analysis, the one patient diagnosed with acute myocardial infarction of uncertain type was considered to have a hospital diagnosis of NSTEMI (as mentioned previously). When this patient was recoded as having STEMI instead, the sensitivity point estimate decreased slightly to 69.0% (from 69.8%, for all patients in Table 10).

[53] The data for this calculation are found in the first 2x2 table under section 2 of Appendix F.

positive computer signal might be unnecessary 1 in every 4 times. The probability of STEMI being absent when the computer result was not ***Acute MI*** (negative predictive value) was 97.9%. Predictive values will be considered further in section 4.2.3, employing an estimate of the prevalence of STEMI.

I also examined the absolute test performance (i.e., with respect to hospital diagnosis) for the group of 55 tracings that were considered illegible by the cardiologists. For the 47 patients with a hospital diagnosis in this group, computer sensitivity was estimated as 66.7% and specificity as 95.5%, assuming a perfect reference. These values should be interpreted with particular caution due to the small numbers of "true positives", but they indicate that the false positive rate may be higher for the computer when the legibility of the tracing (judged by a clinician reader) is poor. In addition, neither clinicians' readings nor hospital diagnoses are actually without error. The Bayesian latent class analysis models in the next two sections allow estimation of all the parameters of interest without assuming any single test to be perfect.

4.2.2 Bayesian 2-test analysis (imperfect tests)

In the second stage of the analysis, I used Bayes latent class models to incorporate prior information about the likely sensitivity and specificity of the cardiologists' interpretations and hospital diagnoses (as described in the methods section, and displayed in the second column of Table 10). I also incorporated prior information about the underlying true prevalence of STEMI in the sample (i.e., 0.5-20%). I used uniform beta densities for the computer's test performance. The analysis produced estimates of sensitivity and

specificity for both "tests" (i.e., the computer and the cardiologist, or the computer and the hospital). A fifth parameter, the underlying prevalence of disease, was also estimated. Table 10 shows that the computer's field sensitivity was estimated to be 81% (using the median of the posterior distribution as the best estimate) in the model containing the computer and the cardiologists' test results. The credible interval for the computer's sensitivity shows there is a 95% probability of its value being between 65% and 98%, given the data collected and the prior distributions used. The difference between the point estimate of 81% and that from the non-Bayesian analysis (57%) demonstrates the impact of considering prior expectations about the imperfect test performance of the cardiologists and about the underlying prevalence of disease.

Field specificity of the computer remained very similar to that in the non-Bayesian analysis, at over 99%. The absolute sensitivity and specificity of the cardiologists' interpretations were estimated to be 89% and 96%, respectively. The point estimate for the underlying prevalence of STEMI was 8.8%. The results were similar when the sample was restricted to chest pain patients, with the only notable differences being a slightly higher field sensitivity for the computer (83.5% point estimate) and an estimated prevalence of STEMI of 9.9%.

Table 10. Test performance of computer, 2-test latent class models

Model containing computer and	Priors	Posterior estimates				
	Sensitivity, specificity intervals (%) respectively	Sensitivity of computer: median % (95% credible interval)	Specificity of computer: median % (95% credible interval)	Sensitivity of cardiologists / hospitals*: median % (95% credible interval)	Specificity of cardiologists / hospitals*: median % (95% credible interval)	Prevalence of STEMI: median % (95% credible interval)
Cardiologists (all)	85-95 80-92	81.0 (65.3-97.9)	99.4 (98.6-99.9)	88.8 (82.5-93.6)	96.2 (94.7-97.4)	8.8 (7.0-10.9)
Cardiologists (chest pain)	85-95 80-92	83.5 (66.6-97.4)	99.6 (98.7-1.0)	89.0 (83.2-93.7)	95.7 (94.1-97.2)	9.9 (7.8-12.2)
Hospitals (all)	85-97 85-95	89.8 (75.1-99.4)	99.2 (98.1-99.9)	87.7 (78.2-94.9)	97.5 (96.5-98.4)	8.3 (6.6-10.3)
Hospitals (chest pain)	85-97 85-95	89.0 (73.9-99.0)	99.2 (97.9-1.0)	87.6 (78.4-95.2)	97.2 (95.9-98.2)	9.5 (7.6-11.8)

*depending on which second test was used

All models converged well.

See Appendix F for raw data

Table 10 also shows that when the hospital reference was assumed to be imperfect using the prior distributions as specified, the absolute sensitivity point estimate increased from about 70% in the non-Bayesian analysis to nearly 90%. The point estimate for absolute specificity remained very high. Results were consistent when only chest pain patients were included.

I performed a sensitivity analysis to examine the impact of the choice of prior densities on the 2-test Bayesian results[54]. This analysis showed that the estimates of the sensitivity of the computer depended to a large extent on the prior densities used for the second test[55]. Specificity estimates, on the other hand, were essentially not affected. When the prior intervals for the cardiologists were widened to 80-98% for sensitivity and 80-99% for specificity, the field sensitivity estimate for the computer decreased by over 20 percentage points (compared to Table 10, first row), to 59.8% (95% credible interval: 49.4-71.1%). The computer's field sensitivity was similarly lower – estimated to be 58.4% (95% credible interval: 49.1-69.2%) – when I specified a uniform prior for the cardiologists' specificity (maintaining the cardiologists' sensitivity interval at 85-95%). When I specified a uniform prior for the cardiologists' sensitivity (maintaining the cardiologists' specificity interval at 80-92%), there was less impact on the results, with a computer field sensitivity estimate of 77.7% (95% credible interval: 61.3-94.9%).

I also modified the prior densities for the hospital parameters to examine the impact on this 2-test model. When I widened the priors for hospital sensitivity and specificity to 65-

[54] without restricting to chest pain patients
[55] The prior density for the underlying prevalence of disease was kept at 0.5-20% for all of the sensitivity analyses.

99% and 70-99%, respectively, the estimated absolute sensitivity for the computer was 71.6% (95% credible interval: 59.4-86.3%), a decrease of about 18 percentage points compared to Table 9 (third row). Again, absolute specificity was essentially unaffected. As above, the computer's absolute sensitivity decreased a similar extent, to 70.9% (95% credible interval: 60.4-81.8%), when a uniform prior was used for the hospitals' specificity (maintaining the hospitals' sensitivity at 85-97%). A uniform prior for the hospital sensitivity (maintaining the hospitals' specificity at 85-95%), had minimal impact on the computer absolute sensitivity estimate, which remained at 88.1% (95% credible interval: 71.2-99.2%). The results for the computer test sensitivity thus depended greatly in these 2-test models on the extent of possible false positives (as indicated by the prior specificity intervals) for the cardiologist (or hospital) data.

The models described in this section assume that the results of the two tests are not correlated. As discussed in the methods section, this assumption may not be valid particularly for the prehospital ECG interpretations. The last stage of the analysis was based on a model of conditional dependence between the computer and cardiologist.

4.2.3 Bayesian 3-test analysis (imperfect tests)

The 3-test model incorporated the distribution of the patients according to computerized interpretation, cardiologists' reading and hospital diagnosis, thus considering all available data simultaneously. As described in the methods and shown in Appendix D, the structure of this model allows for correlation between the data from the computer and cardiologists (the latent variable related to the true prehospital ECG status), within a

second latent variable related to the true disease status. The model estimated diagnostic performance for each test with respect to the true prehospital ECG status and the true disease status separately (seven parameters in all). The latent variable structure allowed for both field and absolute diagnostic performance of the computer to be examined in the one model, with all tests considered imperfect. The patient sample for the 3-test model was restricted, by necessity, to those for whom the cardiologists considered the prehospital ECG to be legible and for whom a hospital diagnosis was available[56].

Table 11 shows that the sensitivity estimate for the computer was higher with respect to the true prehospital ECG status (field performance) than the true disease status (absolute performance), which is clinically intuitive. A similar pattern was seen for the sensitivity estimate for the cardiologists. The two specificity estimates for the computer were essentially equivalent. The field sensitivity of the computerized interpretation with respect to prehospital ST-segment elevation was estimated by this model to be 79%, with a 95% credible interval of 69 to 87%. Field specificity was estimated as 99%, with a very narrow credible interval. The absolute sensitivity of the computerized interpretation with respect to STEMI was estimated to be 69%, with a 95% credible interval of 59 to 78%. Absolute specificity was again estimated as 99%, with a similarly narrow credible interval.

[56] assuming no multiple imputation for missing data

Table 11. Test performance of computer, 3-test latent class model

Test or condition	Priors for each test or disease Total N=1258		Posterior estimate of test sensitivity: mean % (95% credible interval)	Posterior estimate of test specificity: mean % (95% credible interval)
Computer	Sensitivity: uniform prior	Specificity: uniform prior	For phECG*: 78.8 (68.6 – 87.3)	For phECG: 98.9 (98.2 – 99.4)
			For STEMI**: 69.2 (59.1 – 78.2)	For STEMI: 98.9 (98.1 – 99.4)
Cardiolo- gists	Sensitivity: 85-95%	Specificity: 80-92%	For phECG: 92.1 (87.7 – 95.3)	For phECG: 96.1 (95.0 – 97.1)
			For STEMI: 81.3 (73.7 – 87.3)	For STEMI: 96.1 (94.8 – 97.0)
Hospitals	Sensitivity: 85-97%	Specificity: 85-95%	For phECG: 90.0 (83.5 – 94.7)	For phECG: 97.3 (96.3 – 98.1)
			For STEMI: 90.8 (84.4 – 95.5)	For STEMI: 98.4 (97.6 – 99.0)
STEMI	Lower limit: 0.5%	Higher limit: 20%	Prevalence: 9.0 95% credible interval: 7.0 – 11.4	

*true prehospital ECG status (latent variable 1 in Appendix D)
**true disease status (latent variable 2 in Appendix D)

All models converged well. See Appendix F for raw data

The prevalence estimates in this 3-test model are provided for four groups[57] since there are two binary latent variables in the model structure. The estimate for the underlying prevalence of STEMI, combining the two STEMI-positive groups, was 9% with a credible interval of 7-11.4%. The results showed very low prevalence (less than 0.1%[58] with a 95% credible interval of 0.0-0.5%) for the group with a positive prehospital ECG and no STEMI. Estimates for all parameters were the same as in Table 11 when the sample was restricted to chest pain patients, except for a slightly higher estimated prevalence of STEMI (10.5%; 95% credible interval: 8.1-13.3%).

Using the 3-test model results, I estimated the positive predictive value of the computer with respect to STEMI to be 85.0% (95% credible interval: 76.3-91.4%), assuming the true point prevalence of the disease is 9.2%. This implies that for every 100 patients with a computer-positive interpretation, actions based on this result would most likely be unnecessary for 15. The negative predictive value of the computer was estimated to be 97.0% (95.6-98.0%). Thus, since the disease prevalence was assumed to be fairly low, a negative computer result was still most likely to be associated with absence of STEMI.

The sensitivity analysis performed for this 3-test model (with conditional dependence) showed that the results were not as dependent on the choice of prior densities as the 2-test models. Table 12 shows the impact on the computer test performance estimates as the prior intervals for the sensitivity and specificity of the cardiologists and the hospitals were changed.

[57] prehospital ECG+/STEMI+; prehospital ECG-/STEMI-; prehospital ECG+/STEMI-; prehospital ECG-/STEMI+

[58] The point estimate for prevalence was 0.000 implying a value too small to quantify but less than 0.001.

Table 12. Summary of sensitivity analysis, 3-test latent class model

Change to prior sensitivities and specificities	Computer test performance			
	Field sensitivity, % **(95% credible interval)** **Change from Table 11**	**Field specificity, %** **(95% credible interval)** **Change from Table 11**	**Absolute sensitivity, %** **(95% credible interval)** **Change from Table 11**	**Absolute specificity, %** **(95% credible interval)** **Change from Table 11**
Widened priors for cardiologists and hospitals[1]	76.2 (65.2-85.5) ↓2.6	98.9 (98.2-99.4) 0.0	64.7 (54.4-74.5) ↓4.5	98.9 (98.1-99.4) 0.0
Uniform priors for cardiologists	77.7 (67.1-86.4) ↓1.1	98.9 (98.2-99.4) 0.0	68.2 (57.9-77.7) ↓1.0	98.8 (98.0-99.3) ↓0.1
Uniform priors for hospitals	77.3 (66.9-85.8) ↓1.5	99.0 (98.2-99.5) ↑0.1	64.8 (55.0-74.1) ↓4.4	98.9 (98.2-99.5) 0.0

[1]Priors changed to 80-98% and 80-99% for cardiologist sensitivity and specificity, respectively, and 65-99% and 70-99% for hospital sensitivity and specificity, respectively (as in the sensitivity analysis for the 2-test models)

In all three analyses, the computer specificity estimates stayed essentially the same, when compared to the "base" model in Table 11. The sensitivities of the computer changed by less than 5%, the differences being most pronounced (decreases of about 4.5%) for the absolute sensitivity estimates when prior intervals for both the cardiologists and the hospitals were widened, and when uniform priors for the hospital parameters were used.[59] The hospital parameters thus appeared to have the most influence. Indeed, the 3-test results appear to be very driven by the hospital information, since the "base" estimates for the computer's absolute diagnostic performance (Table 11) were very similar to those generated by the 2 x 2 analysis using the hospital reference (Table 9). The point estimates for STEMI prevalence in the sensitivity analysis varied very little, from 9.1% to 9.6% (not shown in Table 12); the "base" prevalence in Table 11 was 9.0%. The 3-test model, therefore, appears to be more robust than the Bayesian 2-test analyses in statistical terms.

4.3 FACTORS AFFECTING COMPUTER TEST PERFORMANCE (OBJECTIVE 2)

4.3.1 Stratified analysis

As described in the methods, patient factors affecting the test performance of the computer were examined using stratified analysis in two ways. The results of the analysis with a perfect cardiologist reference are summarized in Table 3. This analysis explored the impact of the factors on field performance assuming all clinician-positive signals were of interest.

[59] The prior density for the underlying prevalence of disease was again kept at 0.5-20% for all sensitivity analyses.

Table 13. Stratified analysis of computer test performance, cardiologists as perfect reference

Group of patients	Sensitivity, % (proportion)	95% confidence interval for % sensitivity	Specificity, % (proportion)	95% confidence interval for % specificity
All (Table 9)	56.5 (70/124)	47.3-65.3	98.6 (1303/1321)	97.9-99.2
Females	53.8 (21/39)	37.2-69.9	98.7 (630/638)	97.5-99.5
Males	57.6 (49/85)	46.4-68.3	98.5 (673/683)	97.3-99.3
65 years and over	49.3 (33/67)	36.8-61.8	98.6 (781/792)	97.5-99.3
64 years and under	64.9 (37/57)	51.1-77.1	98.7 (522/529)	97.3-99.5
Anterior infarct*	46.9 (30/64)	34.3-59.8	98.6 (1303/1321)	97.9-99.2
Inferior infarct*	72.3 (34/47)	57.4-84.4	98.6 (1303/1321)	97.9-99.2
Cardiac history	36.8 (21/57)	24.4-50.7	98.6 (684/694)	97.4-99.3
No cardiac history	72.7 (40/55)	59.0-83.9	98.8 (474/480)	97.3-99.5
Delay from symptoms to prehospital ECG				
0-29 minutes	61.5 (8/13)	31.6-86.1	100.0 (94/94)	96.2-100.0
30-59 minutes	39.1 (9/23)	19.7-61.5	98.3 (175/178)	95.2-99.7
60-119 minutes	66.7 (14/21)	43.0-85.4	97.5 (158/162)	93.8-99.3
120 minutes or more	55.2 (16/29)	35.7-73.6	98.0 (294/300)	95.7-99.3

*according to the cardiologists, based on the leads displaying ST-segment elevation (as described in the methods chapter)

See Appendix F for raw data

Table 13 shows that there was variability in the computer sensitivity point estimates for each factor, but the extent of the differences was largest with respect to age, infarct territory (according to the cardiologists) and cardiac history. As in the study by Kudenchuk et al. (1991), for which hospital diagnosis was used as the reference and all patients were under the age of 75 years[60], the computer's sensitivity was higher for patients younger than 64 years, for those without a cardiac history, and for inferior infarcts. The improvement in computer sensitivity for inferior, as opposed to anterior, infarcts (i.e., higher by 25%) was similar in magnitude to that observed by Kudenchuk and colleagues in 1991 (i.e., 31%). Unlike in the 1991 study (where sensitivity was 11-16% higher for the 0-29 minute group compared to the others), there was no clear trend with the categorical version of the delay variable. Specificity point estimates for the computer remained between 98% and 100% for all groups.

Table 14 presents the results of the stratified analysis using the 3-test Bayes latent class model. In this case the absolute test performance of the computer for diagnosis of STEMI was examined, allowing for imperfect tests and correlation between the computer and the cardiologists' interpretations of the prehospital ECG, and considering all data simultaneously. Using this model, most of the same patterns with respect to variability of the computer's sensitivity were seen as in Table 13, although the point estimates were generally higher. The differences between the sensitivity estimates in different strata in Table 14 were largest for sex and cardiac history: these were about 13% higher both for

[60] Also, all patients in the study by Kudenchuk et al. (1991) had chest pain within 6 hours of paramedic arrival. For the 1445 patients in this thesis, about 85% had chest pain, with 91% of those with data having a symptom onset within 6 hours of the prehospital ECG recording. Almost 40% of the 1445 patients were aged 75 years or older.

Table 14. Stratified analysis of computer test performance, 3-test latent class models

Group of patients	Sensitivity for true disease status, %	95% confidence interval for % sensitivity	Specificity for true disease status, %	95% confidence interval for % specificity
All (Table 11)	69.2	59.1 – 78.2	98.9	98.1 – 99.4
Females	57.2	40.8 – 72.8	98.8	97.6 – 99.5
Males	69.9	57.9 – 80.3	98.9	97.8 – 99.6
65 years and over	62.2	48.1 – 75.3	98.6	97.5 – 99.4
64 years and under	68.6	55.3 – 80.1	99.2	97.9 – 99.8
Anterior infarct*	67.0	51.2 – 80.3	98.9	98.1 – 99.4
Inferior infarct*	70.3	56.5 – 81.8	98.9	98.2 – 99.4
Cardiac history	57.6	42.1 – 72.2	98.5	97.5 – 99.3
No cardiac history	70.8	58.9 – 81.2	99.2	98.0 – 99.8
Delay from symptoms to prehospital ECG				
0-29 minutes	56.1	32.1 – 75.7	99.1	96.1 – 99.9
30-59 minutes	45.6	25.0 – 66.1	98.3	95.4 – 99.6
60-119 minutes	71.6	54.5 – 84.9	97.9	94.0 – 99.6
120 minutes or more	60.3	42.3 – 76.7	97.5	95.2 – 99.0

* according to the cardiologists and to the hospitals, depending on the test

All models converged well.

See Appendix F for raw data

males (compared to females) and for those without a cardiac history (compared to those with such history). The sensitivity estimates for the two age categories were closer in value using the 3-test model but were still higher for patients younger than 64 years. The delay groups showed a similar pattern of variability for sensitivity as in Table 13. The computer specificity results in Tables 13 and 14 were essentially equivalent.

The main difference between the stratified analyses performed with respect to the cardiologists only (as a perfect reference; Table 13) and with respect to both the cardiologists and the hospitals (without perfect references; Table 14) concerned infarct territory. The inferior territory was associated with a much higher computer sensitivity point estimate (for ST-segment elevation) in the former 2 x 2 table analysis. The computer sensitivity point estimates for STEMI diagnosis using the 3-test model differed for anterior and inferior territory by only 3.3%. Thus, when considering the diagnostic information from the hospitals, and using the Bayesian latent class model method to examine association with "true disease status", infarct territory had much less impact on the computer's sensitivity. Indeed, when I examined 2 x 2 tables for the comparison of the computer with the hospitals (assuming a perfect reference test like Kudenchuk et al., 1991), the point estimates for computer sensitivity for anterior versus inferior territory were 76.7% and 78.4%, respectively. This similarity of estimates was not observed by Kudenchuk and colleagues. It should be noted that the statistical power of the current analysis for sensitivity was lower than in the previous study due to the rarer underlying prevalence of STEMI.

4.3.2 Bayesian hierarchical regression analysis

In the multivariate regression model containing age, sex, cardiac history and infarct territory, the only variable with good evidence for an independent association with the computer's absolute sensitivity for identification of STEMI was age. As in the analysis in the previous section, this model incorporated data from all three tests. The adjusted odds ratio for a 10-year difference in age was estimated to be 7.88, which means that an affected patient 10 years younger was nearly 8 times more likely to be identified by the computer software as having a positive (***Acute MI***) interpretation. For a 5-year difference in age the adjusted odds ratio was 2.81. Although it is almost 100% certain that there is some relation between patient age and the computer's absolute sensitivity (since the 95% credible intervals did not include the null odds ratio value of 1), these intervals were very wide: 1.03 to 297 per 10-year change and 1.02 to 17.2 per 5-year difference. The wide intervals in this model are mostly due to the small number of patients with a positive diagnosis, leading to a small sample size for estimating effects of any variable on the sensitivity. The adjusted odds ratio estimates for all other variables in the model included 1, but were again wide and thus inconclusive as to any effects.

These results differ from those by Kudenchuk et al. (1991) who found that both younger age and absence of a cardiac history were independently associated with the computer's sensitivity. However, their multivariate logistic regression model assumed the hospital diagnosis was a perfect reference, leading to confidence intervals that were almost certainly too narrow and possibly biased estimates, and they did not include infarct territory as an independent variable.

Descriptive statistics with the delay variable showed no effect of this factor on the computer's sensitivity. High and low sensitivity values occurred in equal frequencies across the range of delay, despite how this variable was scaled in scatter plots. Thus, the delay variable was not included in the multivariate regression model.

4.4 IMPROVING COMPUTER TEST PERFORMANCE (OBJECTIVE 3)

On examination of the 54 computer "false negatives", compared to the consensus cardiologist readings of the prehospital ECGs, several interpretations emerged with potential to increase the computer's "field – perfect reference" sensitivity. The six most frequent groups of interpretations (given for two or more patients) are presented in Table 15, in order of decreasing clinical severity and specificity. In comparison with the original "field – perfect reference" sensitivity and specificity of the computer software (56.5 and 98.6%, respectively, using only ***Acute MI*** as a positive interpretation), Table 15 shows the revised diagnostic performance estimates (compared to consensus cardiologist interpretation as a perfect gold standard) when each group of interpretations was progressively added to the definition of "computer positive".

Table 15 shows that, as more interpretations were considered positive, nearly the same gains in sensitivity were obtained as losses in specificity. Implementing the first category, such that possibly acute or "age undetermined" infarcts were included as a positive interpretation, increased field sensitivity substantially (by about 15%) with a concomitant decrease in specificity of about 16%. The rest of the sensitivity gains were smaller in magnitude, since fewer patients were recoded. If every mention of an infarct by the

Table 15. Frequent computer interpretations among "false negative" patients and impact on test performance, cardiologists as a perfect reference test

Computer interpretation (numbered according to infarct and ST elevation levels in Figure 1)	n patients recoded as computer + among reference +	Cumulative revised computer field sensitivity, % (change from 56.5)	Cumulative revised computer field specificity, % (change from 98.6)
1. Infarct, possibly acute [or] 1b. Infarct, age undetermined*	19†	71.8 (↑15.3)	82.4 (↓16.2)
2. Possible infarct, age undetermined	4	75.0 (↑18.5)	79.4 (↓19.2)
3. Cannot rule out infarct, age undetermined	6	79.8 (↑23.3)	75.0 (↓23.6)
1. ST elevation, consider injury or acute infarct [or] ST elevation, consider early repolarization, pericarditis or injury [or] ST elevation, probably due to early repolarization	4	83.1 (↑26.6)	74.9 (↓23.7)
2. Marked ST abnormality, possible subendocardial injury [or] ST depression, consider subendo-cardial injury or digitalis effect	2	84.7 (↑28.2)	72.5 (↓26.1)
3. ST abnormality and T wave abnormality, consider ischemia [or] ST abnormality and T wave abnormality, consider ischemia or digitalis effect	6	89.5 (↑33.0)	64.3 (↓34.3)

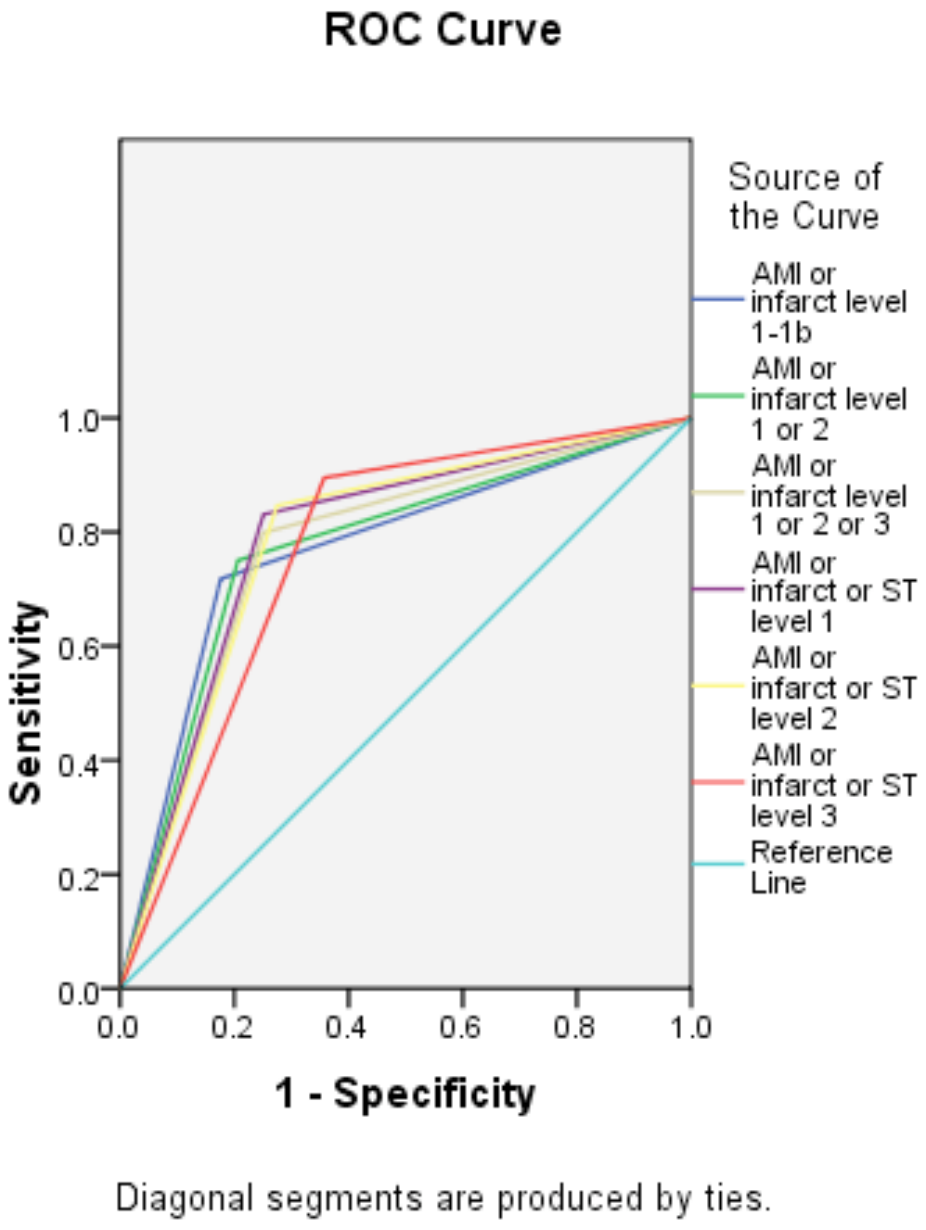
*thus, the software was not able to determine if the infarct was recent
†Only one tracing was interpreted as "infarct, possibly acute"; 18 were "infarct, age undetermined".

See Appendix F for raw data

computer software were to be considered suspect (i.e. considering the first three categories in Table 14 as a positive interpretation in addition to ***Acute MI***), the field sensitivity would be almost 80%, halving the percentage of false negative results (from about 43 to 20%). However, the "trade-off" would be a field specificity of 75%, or a 25% probability that a patient not considered to have ST-segment elevation by the clinicians would test positive according to the computer software (rather than 1.4% for ***Acute MI***). Using all six categories in Table 15 would yield a "field – perfect reference" sensitivity of close to 90%, but a low specificity of about 64%.

Figure 1 demonstrates, using a receiver-operator characteristics curve, the effects of expanding the computerized interpretations considered to be positive on the percentage of true positives (on the vertical axis) and false positives (on the horizontal axis). The six "sources of the curve" (in the legend to the right of the figure) represent the combinations of the six groups of interpretations displayed in the rows in Table 15, and "AMI" refers to the ***Acute MI*** signal.

Figure 1. True positives versus false positives for different combinations of computer interpretations



The applicability of these "field – perfect reference" test performance results depends on the generalizability of the consensus cardiologist interpretations. From a given decision-maker's perspective, it may be useful also to know how the absolute performance results for the computer compare when the hospital diagnosis is considered instead as the perfect reference standard. This may particularly be the case with respect to specificity, if clinicians tend to "overcall" STEMI in the field setting. The data for this comparison are provided in Appendix F.

The revised specificities in the analysis using a perfect hospital reference were very similar to those in Table 15, differing for each category by less than 2%. The revised sensitivities were higher than those in Table 15 by about 2 to 6.5%. If only possibly acute and "age undetermined" infarcts were considered (in addition to ***Acute MI***), sensitivity and specificity compared to hospital diagnosis would be 77.9% and 81.8%, respectively. If every mention of an infarct by the computer software were to be considered suspect, the corresponding revised sensitivity and specificity values would be 82.6% and 73.6%, respectively. The broadest definition (using all six groups of interpretations) was associated with a sensitivity of 91.9% and a specificity of 63.2%. As an additional, final step in the analysis, the broadest computer coding was also run with the 3-test latent class model. Absolute sensitivity and specificity for the outcome of STEMI were 88.6% and 63.9%, respectively. Thus, regardless of the reference group chosen, or whether perfect or imperfect reference tests were considered, such broadening of the computer software's "high risk for infarction" signal yielded a large proportion of false positives.

4.5 SAFETY: TIME SPENT "ON-SCENE" (OBJECTIVE 4)

4.5.1 Descriptive data

To be included in the safety analysis, the patients for whom a prehospital ECG was performed and the historical comparison patients had to have received at least one dose of aspirin or nitroglycerin from *Urgences-santé* ambulance technicians (operating out of the same administrative centre), as described in the methods chapter. All patients also had to have been transported to hospital, in order to calculate an "on-scene time", defined as the time interval between ambulance arrival at the patient's destination and departure with the patient for hospital.

From the sample of 1561 patients with a prehospital ECG in 2005-06, 76 (4.9%) were excluded from the safety analysis for the following reasons: duplicate patient (with more than one copy of the same tracing or more than one ECG performed, n=26), 3-lead ECG performed (n=1), ECG performed during transport (n=1), patient aged under 18 years (n=1), and patient not transported to hospital (n=47). Of the 1485 patients who remained, 1042 (70.2%) received prehospital aspirin and/or nitroglycerin.

From the sample of 1793 patients without a prehospital ECG but who received aspirin and/or nitroglycerin in 2002-03, 15 (0.8%) were excluded from the safety analysis for the following reasons: patient aged under 18 years (n=4) and patient not transported to hospital (n=11). A further 130 patients were excluded because they were missing age or sex information in the *Urgences-santé* databases used to select the sample[61]. Thus, exclusions from the comparison group amounted to 8.1% of the original number of

[61] For logistical reasons, I did not attempt to search for this information in other sources.

patients. By design, all 1648 patients who remained received prehospital aspirin and/or nitroglycerin.

Of the 1042 prehospital ECG patients who received aspirin or nitroglycerin, 52 (5.0%) were missing information required to calculate an on-scene time. For the 1648 comparison patients, 213 (12.9%) were missing such data. As mentioned in the methods (section 3.7), I also excluded patients from the analysis for whom the calculated on-scene time was less than 5 minutes or greater than 90 minutes (as presumed errors). Five patients from the prehospital ECG group and eleven comparison patients were thus excluded[62]. The final numbers of patients in this analysis were 985 and 1424 with and without a prehospital ECG, respectively.

Table 16 presents characteristics of the two groups of patients included in the safety analysis. This table serves to examine potential confounders which may be associated with both the duration of on-scene time and membership in one of the groups. For example, receiving more than one prehospital medication could lengthen on-scene time, as could older patient age and female sex. The latter two factors may be associated with longer clinical examination and questioning by ambulance personnel and more time required to position the ECG electrodes. Attending to a patient in winter may increase the time required to get to the patient's side from the ambulance (and back to the vehicle), or for a patient to prepare for departure to hospital.

[62] Four ECG patients had on-scene times between 1.43 and 2.68 minutes and one had an on-scene time of 125.55 minutes. The eleven excluded comparison patients had on-scene times between 1.70 and 4.53 minutes.

Table 16. Characteristics of patients included in safety analysis

	Prehospital ECG patients (2005-6) N=985	**Historical comparison patients (2002-3) N=1424**
% male (n)	51.7 (509)	45.6 (649)
Patient age (years)		
Mean, standard deviation	67.4, 14.6	66.8, 14.8
Minimum, median, maximum	29.0, 70.0, 95.0	18.0, 69.0, 99.0
Transported during winter*, % (n)	33.8 (333)	31.0 (441)
Prehospital medication(s) received, % (n)		
Nitroglycerin only	12.4 (122)	5.5 (78)
Aspirin only	8.6 (85)	1.3 (19)
Both aspirin and nitroglycerin	79.0 (778)	93.2 (1327)

*defined as the months of December through end of March

Table 16 shows that there was a somewhat greater proportion of males in the prehospital ECG group. A greater proportion of the comparison patients had received two prehospital medications. About one-third of each group was attended to during winter months. The age statistics for the two groups were very similar[63].

4.5.2 Comparison of on-scene time

The results of the comparison of the mean on-scene time for the two groups are presented in Table 17. On-scene time varied from about 5 to 75 minutes, with a mean of about 25 minutes for the prehospital ECG patients and about 20 minutes for the historical comparison patients. Adjusting for the effects of potential confounding factors, membership in the prehospital ECG group was associated with just under 5 additional minutes of on-scene time.

The next independent variable with the most impact on on-scene time was sex, with female patients being associated with about 2 additional minutes (95% confidence interval: 1.47, 2.54) of on-scene time. Attending to a patient in winter was associated with about 1 additional minute (95% confidence interval: 0.42, 1.54). Number of medications and age had negligible independent impact on on-scene time.

[63] Only eight comparison patients were under the minimum age (29 years) of the prehospital patients.

Table 17. Comparison of on-scene time*

	Time in minutes	
	Prehospital ECG patients n1=985	**Historical comparison patients n2=1424**
Mean, standard deviation (sd) 10th percentile, median, 90th percentile Minimum, maximum	25.22, 7.09 17.41, 24.70, 33.43 5.30, 75.48	20.42, 6.45 12.80, 19.95, 28.53 5.55, 61.57
Unadjusted difference in means (95% confidence interval[1])	4.80 (4.24, 5.36)	
Adjusted[2] difference in means (95% confidence interval[3])	4.94 (4.39, 5.48)	

*exceptionally, since the time data were expressed to 1/100th of a second, the values in Table 17 are presented to two decimal places

[1]computed as: difference in means ± $1.96 \times \sqrt{(sd1^2/n1 + sd2^2/n2)}$

[2]adjusted for season (winter or not winter), number of prehospital medications received (1 or 2), patient sex and age

[3]computed as: adjusted beta coefficient for group variable ± 1.96(standard error of beta coefficient)

4.6 ADDED VALUE: ANALYSIS OF PAIRED ECGS (OBJECTIVES 5 & 6)

From the sample of 1560 available prehospital ECGs in the 2-year study period, 1472 tracings were eligible for the paired ECG analysis. Eighty-eight prehospital tracings (5.6%) were excluded for the following reasons: duplicates of the same tracing (n=6), a three-lead ECG (n=1), additional ECGs performed for the same patient encounter (n=20), patient aged under 18 years (n=1), ECG performed after a trauma (n=14), and patient not transported to hospital (46). A total of 1352 of the 1472 charts (91.8%) were requested from the initial receiving hospitals; 120 were not requested for feasibility reasons (as was the case for the non-requested charts in section 4.1, on computer test performance).

Of the 1352 files requested, 1349 (99.8%) were obtained, for an overall rate of success of 91.6% (1349/1472) among all eligible patients. There were 106 further exclusions, however, to form the sample of paired ECGs for interpretation by the readers (cardiologists 4 and 5). For 43 patients, no in-hospital ECG was available (either not provided by the archive department or not performed). For four patients the initial in-hospital tracing was not a 12-lead ECG (i.e. they were rhythm strips or 3-lead ECGs). The chart information for one patient was misplaced at the *Urgences-santé* administrative centre before the in-hospital ECG could be copied. Finally, for 58 patients (4.4% of the 1302 with in-hospital 12-lead ECGs) it was likely that the in-hospital tracing provided was not the initial ECG (or the first in-hospital ECG was acquired more than 6 hours after the prehospital tracing).

The total number of paired ECGs in the analysis sample was thus 1243. As shown in Table 18, just over half of this sample was male and the mean age was about 67 years. The vast majority of patients presented with chest pain. For patients with symptom onset data (59% of the sample), the median delay from onset to the prehospital ECG time stamp was 84 minutes. The median delay between the prehospital and the initial in-hospital ECG was 45 minutes (for 1233 patients). Twenty-three percent of the sample received a hospital diagnosis of acute coronary syndrome. Approximately 16% of patients were diagnosed with acute myocardial infarction. Less than half the patients with infarction had a hospital diagnosis of STEMI, for an overall prevalence in the paired ECG sample of 6.6%.

A small number of ECG pairs could not be compared due to problems with legibility. Reader A found 22 prehospital ECGs and 2 in-hospital ECGs illegible (2.0% of the total pairs), while these figures for reader B were 10 and 1, respectively (0.95% of the total pairs). Thus, results were generated for 1219 pairs for reader A and 1232 pairs for reader B.

Table 18. Characteristics of paired ECG sample (N=1243)

% male (n)	53.1 (660)
Patient age (years)	
Mean, standard deviation	66.8, 15.4
Minimum, median, maximum	19.0, 70.0, 95.0
Symptomatic nature of presentation as recorded by ambulance technician, % (n)	
Chest pain	87.1 (1083)
Weakness / dizziness / fainting	7.6 (95)
Shortness of breath	2.3 (29)
Palpitations / tachycardia	0.9 (11)
Abdominal pain	0.7 (9)
Other	1.3 (16)
Delay from symptom onset time to prehospital ECG	
10^{th} percentile, median, 90^{th} percentile, in minutes	26.0, 84.0, 340.0
Missing a symptom onset time, % (n)	41.4 (514)
Delay from prehospital ECG to initial in-hospital ECG (n=1233*)	
10^{th} percentile, median, 90^{th} percentile, in minutes	29.0, 45.0, 78.0
Hospital diagnosis, % (n)	
STEMI	6.6 (82)
STEMI or NSTEMI	15.9† (198)
STEMI or NSTEMI or unstable angina	23.0 (286)
Other cardiac diagnosis	22.6 (281)
Non-cardiac diagnosis	50.8 (632)
Undefined diagnosis (but definitely not acute coronary syndrome)	0.8 (10)
Missing	2.7 (34)

*For four patients, an ECG time was unreadable. Six additional delays were excluded from this descriptive analysis because the lack of synchronization of the two machines generated either negative values or a delay of less than 5 minutes. (These figures were not due to daylight savings time adjustments). Because of this synchronization issue, analysis with the inter-ECG delay was limited to that presented in Table 18.
†This percentage could be as high as 16.3%, since there were five patients for whom it was not possible to determine whether the hospital diagnosis was NSTEMI or unstable angina.

Table 19 presents, according to reader, the frequencies of the ECG abnormalities on both tracings, the prehospital ECGs only, and the initial in-hospital ECGs only (as in Table 1). More than one type of abnormality could be present on the same ECG (or pairs of ECGs). While there were differences in the overall frequencies of the abnormalities observed by the two readers (particularly for ST-segment depression, T wave inversion, and abnormal Q waves), similar patterns emerged with respect to the added value of the prehospital ECG information.

For the majority of patients with an ST-segment elevation compatible with acute ischemia, this feature was evident on both ECGs. An acute ST-segment elevation was observed only on the prehospital ECG approximately 5 and 15% of the time, depending on the reader. A comparable frequency of 7% was observed by Aufderheide and colleagues (1990). Across the two clinicians, the prehospital ECG detected every acute ST-segment elevation observed on the initial in-hospital tracing except for one. This finding can also be considered "added value" of the prehospital tracings since the same information could have been provided sooner if, for example, the ECGs were transmitted from the field to a receiving hospital. The prehospital ECGs also detected the vast majority (over 90%) of the total LBBB/pacemaker abnormalities observed.

Table 19. Abnormalities on one or both ECGs, according to reader A or B

Abnormalities	Reader	Both ECGs	Pre-hospital ECG only		Initial in-hospital ECG only	Total frequency of abnormality
		n (% of total frequency)	n (% of total frequency)	% of legible tracings *	n (% of total frequency)	
ST-segment elevation considered acute	A	58 (95.1)	3† (4.9)	0.25	0 (0.0)	61
	B	73 (83.9)	13‡ (14.9)	1.1	1 (1.2)	87
ST-segment depression	A	83 (80.6)	17 (16.5)	1.4	3 (2.9)	103
	B	124 (67.4)	54 (29.4)	4.4	6 (3.2)	184
T wave inversion	A	48 (85.7)	4 (7.15)	0.33	4 (7.15)	56
	B	151 (76.6)	26 (13.2)	2.1	20 (10.2)	197
Abnormal Q waves	A	45 (95.7)	1 (2.15)	0.08	1 (2.15)	47
	B	90 (90.0)	1 (1.0)	0.08	9 (9.0)	100
Any of the above	A	213 (87.3)	23 (9.4)	1.9	8 (3.3)	244
	B	343 (75.6)	78 (17.1)	6.3	33 (7.3)	454
LBBB/ pacemaker	A	79 (91.9)	3 (3.5)	0.25	4 (4.6)	86
	B	84 (91.3)	5 (5.4)	0.41	3 (3.3)	92
Arrhythmias	A	88 (80.7)	19 (17.4)	1.6	2 (1.8)	109
	B	91¶ (78.4)	21 (18.1)	1.7	4 (3.4)	116

*the proportions present among all legible tracings: 1219 and 1232, respectively, for readers A and B
†for one patient, conclusive elevation on prehospital ECG and borderline elevation (<1.0 mm) on in-hospital ECG
‡either conclusive elevation on prehospital ECG and borderline elevation (<1.0 mm) on in-hospital ECG (n=3 patients), or borderline elevation on prehospital ECG and no elevation on in-hospital ECG (n=1)
¶for two patients, the type of arrhythmia present on both ECGs differed: it was supra-ventricular tachycardia on the prehospital ECG and atrial fibrillation on the in-hospital ECG

Note: categories are not mutually exclusive

Among patients with ST-segment depression, this abnormality was observed only on the prehospital ECG about 17 to 29% of the time, depending on the reader (as opposed to 3% of the time on the in-hospital tracing alone). ST-segment depression was thus considerably less likely to be sustained than ST-segment elevation, and the prehospital ECG information provided substantial added value in this regard. Information on such "transient" ST-segment depression would, in general, make a diagnosis of acute coronary syndrome and hospital admission more likely.

When presence of T wave inversion differed between the pairs of ECGs, it was observed slightly more often on the prehospital ECG alone by reader B. Reader A, by contrast, found the same (low) frequency of T wave inversion on single prehospital or in-hospital ECGs. Both readers commented, however, that the prehospital ECG would demonstrate added value even if a T wave inversion was only present on the initial in-hospital ECG, since such serial information would indicate that the abnormality observed in hospital was new. Reader B also observed a higher frequency of abnormal Q waves on only the later, initial in-hospital ECG than on the prehospital tracing alone.

Table 19 shows that very similar overall frequencies of arrhythmia were observed by readers A and B. Additional arrhythmias were more likely to be seen on the prehospital ECG: about eighteen percent of the time when arrhythmias were observed, they were detected only on the earlier tracing. Of patients with prehospital arrhythmias alone, 62-74% had atrial fibrillation or flutter, depending on the reader, and the others had supraventricular tachycardia (21-38%) or ventricular tachycardia (5% [n=1]; reader A).

Drew et al. (2006) similarly found tachycardias to be more frequent on the earlier ECG. The prehospital information would thus serve to clarify diagnosis and management of these arrhythmias.

Finally, the frequencies of any possible signs of ischemia combined (i.e., ST-segment elevation or depression, T wave inversion or abnormal Q waves) are also presented in Table 19. Using the total count of ischemic indicators on at least one ECG as the denominator (i.e., 244 or 454), about 9 to 17% were observed only on the prehospital ECG, compared to 3 to 7% on the later ECG (thus, a difference between ECGs of about 6 to 10%). Using the total number of legible paired tracings as the denominator (i.e., 1219 or 1232), the prevalence of abnormalities compatible with ischemia on the prehospital ECG alone was between 2 and 6%. The previous study by Herlitz and colleagues, which was the most similar to the present work in terms of patient selection criteria and hospital diagnoses[64], yielded comparable results, with a frequency difference between ECGs of 4% and a prehospital ECG-specific prevalence of 7.4%.

[64] approximately 30% for acute coronary syndrome and 14% for acute myocardial infarction

CHAPTER 5: DISCUSSION AND CONCLUSIONS

5.1 DIAGNOSTIC PERFORMANCE OF COMPUTERIZED INTERPRETATION

This thesis used several analytical approaches to estimate the diagnostic performance of the computerized ECG interpretation. In all cases, specificity of the computerized interpretation was very high and showed little variation. The point estimates for sensitivity were more varied. Unlike previous studies, a Bayesian method was employed to estimate sensitivity and specificity, allowing all tests to be considered imperfect and incorporating prior expectations about the diagnostic performance of the clinicians (for prehospital ECG interpretation) and the hospitals (for detection of STEMI)[65]. For feasibility reasons, the clinician reference used was the consensus interpretation by cardiologists, rather than by emergency physicians. The latter group, however, is in general more often involved in the initial reading of ECGs, including prehospital tracings, in acute hospital care.

The 3-test latent class model considered all data simultaneously, for cardiologist-readable tracings and ambulance-transported patients who mostly presented with chest pain and who had sufficient chart information to retrospectively assign a hospital diagnosis. The model also allowed for conditional dependence between the prehospital ECG readings by the computer software and the cardiologists. The sensitivity analyses showed that the results of the 3-test model were relatively robust when the prior probabilities for the diagnostic performance of the non-computer tests were varied.

[65] In a previous study using Bayesian analysis, Youngquist et al. (2007) incorporated imperfect test performance for "human" readers to estimate positive predictive value of computerized prehospital ECG interpretation.

Two types of estimates about the computer software's diagnostic validity were generated: "field" and "absolute" test performance. Which of these results are of most interest is a matter of perspective. Field performance – the ability to detect ST-segment elevation indicative of STEMI – is important for prehospital emergency services. Such services need to have an idea of the accuracy of the computer software in the field, generating signals to which they must respond: that is, they will assume the ST-segment elevation is due to STEMI, despite the fact that the actual diagnosis may end up being different. (This applies to a system without prehospital thrombolysis, since reperfusion treatment in the field requires more certainty about the presence of STEMI). Absolute performance – the ability to detect true STEMI – is important from the perspective of the hospital, where decisions about clinical management (e.g. further diagnostic testing, reperfusion treatment) are made.

For specificity of the computerized interpretation, the field and absolute point estimates from the 3-test model were equivalent (98.9%), with narrow and essentially equal 95% credible intervals (about 98.1 to 99.4%). Regardless of the perspective, the computer software's sensitivity was more modest, with a field point estimate of 78.8%, and an absolute point estimate of 69.2%. Since the 95% credible intervals for these sensitivities overlapped, there may actually be less difference between the true parameter values (on the other hand, there could also be more). Taken together, the sensitivity estimates indicate, however, that the computer software likely misses at least 1 in 5 patients that are truly "positive".

The ideal in a prehospital ECG strategy would be to identify all cases of possible STEMI even at the expense of misidentifying some unaffected persons (still assuming a system without prehospital thrombolysis). Subsequent diagnostic performance analysis in this thesis examined possibilities for increasing the computer software's sensitivity. The multivariate logistic regression demonstrated that, of the patient factors studied (age, sex, cardiac history, infarct location, and delay since symptom onset), only younger age was associated with higher sensitivity. Thus, it was not possible to propose a set of clinical factors that might be used to identify a subgroup of patients for whom the computer software's sensitivity for STEMI would be expected to be substantially higher. Further research could examine whether other factors related to symptomatic presentation (e.g. location, quality and severity of pain; accompanying symptoms) are associated with greater computer sensitivity, keeping physiological differences related to sex in mind.

The analysis of "field false negatives" showed that the gains in sensitivity if other computer interpretations were considered suspect (such as any mention of an infarct, other than ***Acute MI***, or ST-segment abnormality) came at a large cost to specificity. Gains of 15-33% in sensitivity were associated with corresponding decreases in specificity of 16-34%. No matter how the data were analyzed (with respect to choice or accuracy of the "reference" tests), the effect of capturing more STEMI diagnoses for early catheterization laboratory activation, for example, would be to bring more patients without STEMI to this facility. Thus, a decision about the use of additional computerized interpretations is a matter of balancing benefits and risks.

From the patient's perspective, the increased computer software sensitivity (of close to 90%, using the broadest definition and the 3-test model) would clearly have an important impact on outcomes for those with STEMI. However, if patients were directed to a catheterization laboratory solely on the basis of the prehospital ECG, the accompanying decreased specificity would engender risks for unaffected persons. Diagnostic coronary angiography, the initial step prior to PCI, is an invasive procedure. Also, the use of a given laboratory for an individual without STEMI renders that facility unavailable for a STEMI patient for a period of time.

From the perspective of the hospital and the health care system, "risks" of false positives include, depending on the program model, how many unnecessary advance emergency department notifications can be handled, the costs of unnecessary coronary angiography if a laboratory is activated, and the long-term effects of false alerts on personnel response and morale. Time of day may be important to consider as well: more false alerts may be tolerated by personnel for early laboratory activation, for instance, during fully-staffed, regular working hours than off-hours. Another factor to be considered is the use of coronary angiography and PCI for acute coronary syndrome patients without STEMI, since some false positive, "unaffected" patients may still have significant coronary artery disease. Both "conservative" and "early invasive" clinical management strategies exist for such patients (Anderson et al., 2007). If the latter approach is favoured, the fast-tracking of NSTEMI and unstable angina patients to a catheterization laboratory may not be considered a "false positive" action. Among the 21 patients with positive computer

interpretations but without a hospital diagnosis of STEMI (assuming, for the sake of this argument, the diagnosis was correct), 8 (38%) had NSTEMI or unstable angina.

One strategy for maximizing detection of STEMI, but minimizing computer-generated false alarms that elicit a system response, may be to invest in the technology and infrastructure to transmit prehospital ECGs with any mention of an infarct (other than ***Acute MI***) or mention of ST abnormality for reading by a physician. This clinician could be a hospital-based emergency physician or on-call cardiologist, or an on-call emergency medical services physician (working for the ambulance service). The physician could be responsible for decision-making regarding the appropriate response, such as activation of catheterization laboratory personnel. Using the legal framework of "delegated acts", the physician could instruct the basic life support ambulance personnel to carry out a hospital alert if necessary, in an advance hospital notification model.

The above discussion focuses on the intrinsic sensitivity and specificity of the computerized prehospital ECG interpretation. From a health care decision-maker's perspective, it is the predictive value of the computer that provides practical information about the impact of its diagnostic validity. Predicting the probability of disease for a given test result requires knowledge of the disease prevalence. The sample used in this thesis did not contain some of the patients who had a prehospital ECG performed in 2005-06. It was generated in a "real world" setting early in the implementation of a program, missing some patients eligible for a prehospital ECG, perhaps containing some

not eligible, and including heterogeneous clinical presentations. The underlying, true prevalence of STEMI is therefore unknown.

The 3-test model generated an estimate of the prevalence of STEMI based on the observed data and the prior expected prevalence, which was set to vary between 0.5 and 20% based on published scientific literature. Using the model-estimated prevalence of 9.2%[66], the absolute positive and negative predictive values of the computer software were 85 and 97%, respectively. Thus, provided the disease prevalence in a given setting is indeed about 9%, the current computer software accurately predicts absence of STEMI 97% of the time, missing 3 in 100 patients requiring reperfusion. Actions based on a computer-positive result would be appropriate 85% of the time; the software incorrectly predicts the presence of STEMI 15 times for every 100 patients. In this scenario, it is appropriate to fast-track computer-positive patients for possible reperfusion treatment, but there will be an estimated 15% "false alarm" rate.

Positive predictive values need to be interpreted with much caution, since they are highly dependent on the actual disease prevalence (in addition to sensitivity and specificity). In a Bayesian analysis, Youngquist et al. (2007) showed that a STEMI prevalence of 5-20% was associated with an estimated positive predictive value of 83% for computerized interpretation of prehospital ECGs. This figure decreased markedly to 43% if the prevalence was only 0.5-5%. Using the thesis results as another example, halving the

[66] The mid-point of the 95% credible interval for the posterior estimate (i.e., 7.0-11.4%) was used as the mean prevalence to generate the predictive values.

prevalence to 4.6% (all other figures remaining the same[67]) is associated with a positive predictive value of 72.6% (95% credible interval: 56.1-84.7%), or a point estimate of more than 25% false alarms.

In Montreal-Laval, catheterization laboratory personnel are not on-site outside of regular working hours, except at one institution. Emergency department and cardiac catheterization laboratory personnel would need to consider what approximate frequency of unnecessary responses they would be willing to accept in a prehospital ECG program based on computerized interpretation.[68] Since the credible interval for positive predictive value spanned 76 to 91%, there is a 95% probability, based on this thesis analysis, that false alarms could be made 9 to 24% of the time. Indeed, the error rate may be considerably higher, if broad ECG eligibility criteria are used and STEMI prevalence is quite a bit less than 9.2%.

The restriction of prehospital ECG eligibility criteria would also tend to decrease false alarms by increasing the prevalence of STEMI and the positive predictive value of the computerized interpretation, as suggested by Youngquist et al. (2007). A stricter definition of eligibility, at least among males, would involve restriction to more typical, and more recent, presentations of chest pain (such as those used by Kudenchuk et al., 1991). Among females, however, such restrictions may actually decrease prevalence of

[67] assuming relative constancy of the sensitivity and specificities estimates when prevalence was changed, and maintaining a standard deviation of 1.1%.

[68] For example, a recent study of a prehospital ECG program found that there was either no need for PCI (according to a physician) or no acute occlusion in coronary arteries (by PCI) for 25.7% of 529 consecutive patients with an "acute infarction" computerized interpretation who were diverted to designated PCI facilities (Swan et al., 2009). Three different ECG machines were used, including the Zoll M Series. The indications for a prehospital ECG were chest pain, shortness of breath, loss of consciousness or dizziness.

STEMI, because of the elevated numbers of women with atypical STEMI presentations. One particular challenge in the basic life support setting is minimizing the complexity of decision-making regarding prehospital ECG eligibility. Youngquist et al. (2007) suggest that it would be useful for ambulance personnel to have a non-ECG-based tool to predict the likelihood of STEMI, and thus to gauge the benefit of acquiring an ECG, but this does not appear to currently exist.

Despite the modest sensitivity estimates for the computer software, its negative predictive value was calculated to be high using the model-estimated prevalence of STEMI. Since disease prevalence lower than 9% is more likely than a higher frequency, decision-makers can be reassured that, based on the Bayesian analysis in this thesis, there is a high probability that a patient with a negative computer result does not have STEMI. If the prehospital ECG eligibility criteria were to be restricted such that the prevalence increased, however, the probability of STEMI patients among computer-negative persons would rise. A doubling of the prevalence, for example, would be associated with an increase in the proportion of missed cases (from 3 to 6.6%, keeping sensitivity and specificity constant). In this scenario, it would be even more important to have clinicians read transmitted ECGs that do not indicate ***Acute MI*** but mention a possible infarct or a ST abnormality.

Computerized prehospital ECG interpretation could be used in a diversion model with or without prior transmission of tracings to clinicians. Patients with a computer signal of ***Acute AMI*** could be rapidly transported to the closest facility with cardiac

catheterization facilities. To save the most time, the catheterization laboratory could be activated while the ambulance is en route, unless there is a concern about the number of false alarms, in which case expedited assessment in the emergency department is an option. Patients with the broader computerized interpretations of an infarct or ST abnormality could also be directly transported to a PCI facility, where further diagnostic testing (ECGs, enzymes, etc.) could be carried out, without activation of the catheterization laboratory prior to hospital arrival.

A diversion system would likely be favoured in regions with good access to PCI facilities, such as in Montreal-Laval where, at the time of submitting this thesis, seven institutions have such resources. Thrombolysis is rarely used in this area; inter-hospital transfer for primary PCI is common and is associated with lengthy delays before treatment (AETMIS, 2008a; Huynh et al., 2006). Based on the published evidence reviewed in Appendix A and given the particular context (including absence of investment in prehospital thrombolysis[69]), prehospital diversion in this metropolitan region has the potential to greatly improve treatment delay overall. A diversion strategy would have to consider various factors that could affect safety and treatment delay, such as the clinical stability of the patient, expected availability of a catheterization laboratory (especially during the day when scheduled procedures are taking place) and transport issues (e.g. traffic congestion and road conditions).

[69] Particularly in rural regions of Quebec with long transport times to hospital, prehospital thrombolysis offers the potential for greatly reduced treatment delays for eligible patients. This approach would, however, require a long-term commitment to training of ambulance personnel, with medical oversight by physicians (who would need to verify the prehospital ECG) in order to delegate the act of administering treatment. Although a full discussion of this strategy is beyond the scope of the thesis, prehospital thrombolysis could be advantageous in urban settings as well when delays to PCI are anticipated (due to poor transport conditions or occupied laboratories), in accordance with current clinical guidelines.

Allocating the decision-making regarding catheterization laboratory activation to the hospital setting (whether involving prehospital ECG transmission or expedited emergency department assessment) is likely to reduce false alarms but not eliminate them. Youngquist et al. (2008) compared cardiac catheterization laboratory activations made on the basis of computer-interpreted prehospital ECGs (using GE-Marquette 12SL software) on weekdays, with activations by emergency department physicians on weekends made after hospital arrival of patients (but with advance emergency department notification). Activations were considered "false positive" if there was no "culprit lesion or significant coronary artery disease on cardiac catheterization" (Youngquist et al., 2008, p. 785), or the patient had non-elevated cardiac enzymes accompanied by ST-segment elevation attributable to causes other than STEMI. For this single, small academic institution in the first year of a prehospital ECG program, false positives were found for 39% (9/23) of computer activations and 9% (3/33) of physician activations.

Similarly, Larson et al. (2007) found false laboratory activation rates of 9.5 to 14%, depending on the clinical definition, for emergency department physicians (with or without cardiologist consultation) at community hospitals. These results were based on 1345 patients transferred to a single institution for PCI. In a system undergoing widespread implementation of prehospital ECG programs for the first time, however, false positive activations by hospital physicians may be more acceptable than those generated by computerized interpretation.

Finally, the proportion of "poor quality" prehospital tracings according to the cardiologists in the diagnostic performance analysis was 3.5%. Comparable estimates have been reported in the scientific literature (Turnipseed et al., 2010). Based on my analysis with these tracings, however, there was indication that false positives on the part of the computer among patients without a STEMI diagnosis were more frequent when the quality of the ECG was poor. Indeed, Swan et al. (2009) recently found that missing lead recordings and poor baselines on prehospital ECGs were associated with 2.5 and 1.7 greater odds, respectively, of a false positive computer interpretation.[70] Some of the problems in the thesis sample, such as artefact, may have been caused by patient movement or tremor, while others such as missing leads or wandering baselines could have been related to skin preparation, electrode placement and integrity of the equipment. Distortion due to movement of the ambulance did not appear to be a likely contributor: based on a comparison of the time stamps of the tracings and the ambulance computers' arrival and departure times[71], only one or two of the ECGs may have been performed in a moving vehicle. This specificity result highlights the significance of thorough ambulance personnel training to ensure good quality tracings. It is important that the prehospital ECG is acquired correctly the first time: since a positive computer signal is still more likely a true positive, spending time to redo the ECG may not be advisable.

5.2 SAFETY

As indicators of safety, no patients in the prehospital ECG sample died in the prehospital setting or had a cardiac arrest. The additional time spent to acquire the prehospital ECG

[70] 95% confidence intervals for the odds ratios were 1.3-5 for missing leads and 0.73-4 for poor baselines.
[71] keeping in mind that the two clocks were not necessarily synchronized

(in 2005-06) among patients who were also given aspirin, nitroglycerin or both was estimated as 4.9 minutes (95% confidence interval: 4.4-5.5 minutes). This estimate is consistent with literature values, particularly the one previous study identified that was performed in the basic life support context.

The analysis of on-scene time was limited by the use of a comparison with historical controls (from 2002-03), a methodology that was also used by all previous studies I identified in the published literature except one (i.e., Provo and Frascone, 2004). The length of time spent on-scene in general, for activities other than ECG acquisition, may have improved over the years. Thus, if concurrent controls had been used instead, and had a faster average on-scene time (relative to the historical controls), the amount of time attributed to the prehospital ECG in 2005-06 would have been longer. On the other hand, since the thesis data were recorded several years ago, near the start of a prehospital ECG program, the current delay associated with ECGs acquired by ambulance personnel may have reduced.

The multivariate analysis of on-scene time adjusted for several potential confounding variables such as the number of prehospital medications given, patient age and sex, and whether the call was during winter. Electrocardiogram acquisition could also relate to the level of experience of the ambulance technicians. The prehospital ECG personnel may have had more experience particularly because of the potential overlap of technicians in the two groups (operating out of the same centre). It was not feasible to obtain data on personnel experience level, and thus this remains a limitation of the multivariate analysis.

Another improvement on the design of this study would have been to compare the same pool of ambulance technicians, perhaps acquiring prehospital ECGs only on odd days (an allocation method used by Provo and Frascone, 2004).

The estimated additional time spent on-scene may not be entirely due to the acquisition of the prehospital ECG. There could have been other different procedures between the two comparison groups (other than administration of nitroglycerin and aspirin), or longer time spent on history taking or acquiring vital signs. Carrying out a hospital alert would not be expected to increase delay in the prehospital ECG group since this procedure is meant to be done during transport to hospital. Since the delay to get to the patient's side was included in the "on-scene" definition, the analysis assumed this access time was not systematically different between the two groups.

Within the limitations outlined above, the approximately 5-minute estimate for prehospital ECG acquisition is particularly useful for health care decision-makers in Quebec, since it is specific to the basic life support context. As examined in Appendix A, prehospital ECG programs are associated with time savings of considerably more than 5 minutes in the published literature for most models (except for advance hospital notification alone and door-to-balloon time). Thus, it is likely that the "cost" of additional delay on-scene is worth the time benefit of prehospital ECG programs, if these strategies are appropriately implemented. A number of factors are necessary for the effective and safe delivery of a prehospital ECG program, including the following (Frendl et al., 2009; AETMIS, 2008b; Ting et al., 2008; de Villiers et al., 2007; Moyer et al., 2007; Bradley et

al., 2006a; Garvey et al., 2006; Vaught et al., 2006; Bradley et al., 2005; Antman et al., 2004):

- specialized training and ongoing use of skills for ambulance personnel;
- purchase of high quality ECG equipment and other devices, depending on transmission procedures (cell phone, modem), as well as technical support and backup systems for communication problems;
- acceptance and support of the program by all stakeholders in several different settings, including emergency medical services providers and dispatchers, hospital clinicians, cardiology communities (such as the *Réseau québecois de cardiologie tertiaire*), medical associations, worker unions, and governmental bodies;
- integration of prehospital and hospital services through efficient communication of ECG data to emergency departments, cardiac catheterization laboratories, or coronary care units (by verbal or electronic means) and use of structured protocols;
- clear allocation of professional roles and responsibilities; and
- monitoring systems for quality control.

5.3 ADDED VALUE

In the sample of cardiologist-readable paired ECGs, the prehospital ECG provided important gains in information about transient abnormalities not detectable on the initial in-hospital ECG. This was particularly the case for ST-segment depression and arrhythmias, where 17-29% of these abnormalities were only observed on the prehospital ECG. Five to 15% of ST-segment elevations were found only on the prehospital ECG. It

is also significant that the prehospital ECG detected every ST-segment elevation observed on the initial in-hospital tracing and considered acute by the two clinicians except one. For STEMI, then, the prehospital ECG is not only valuable for earlier management but may also identify patients who spontaneously reperfuse. For ST-segment depression and arrhythmias, the prehospital ECG may increase diagnostic yield when normalization occurs before hospital arrival. Since arrhythmia detection is also possible on a simpler, 3-lead ECG (or even an automated external defibrillator device, which is standard ambulance equipment), the detection of ST-segment depression is particularly pertinent to the added value of the prehospital 12-lead ECG.

The involvement of more than one cardiologist reader in the ECG interpretation is a strength of this analysis since each will have his/her own training, experience and clinical management style. The data were presented separately in order to capture this variability. The approach of comparing the pairs of ECGs in this thesis differs from the previous published studies in which the two tracings were generally read separately[72]. This raises the possibility of measurement bias by which, for example, a reader could examine the prehospital ECG more attentively in order to increase the chances of finding an 'added' value. The risk of bias was considered to be sufficiently minor, for two senior cardiologists with no vested interest in prehospital ECG programs, to be worth the gains in clinical validity and generalizability.

The study design had several limitations with respect to arrhythmias. The type of arrhythmia was not recorded when it was the same on both ECGs. Also, since the

[72] Three prior studies did not specify the reading methods (Drew et al., 2006, 2004; Herlitz et al., 2002).

prehospital ECG eligibility criteria were naturally targeted to detection of acute myocardial infarction, these were not very specific to identification of arrhythmias (which are more related to palpitations or a feeling of weakness, for example, than chest pain). Thus, the arrhythmia figures may not reflect true prevalence of these electrocardiographic features.

The added value analysis considered presence versus absence of most features of interest, including "borderline" ST-segment elevation. Other features that differ between serial ECGs could be important for clinical management. These changes might include differences in size (such as the depth of T-wave inversions) or shape (such as the "stiffness" of a ST-segment).

Among their conclusions, Kudenchuk et al. (1998) advance the hypothesis that prehospital tracings may improve interpretation of serial ECGs even among less experienced readers, by providing an opportunity to observe abnormalities that may be more complex to interpret on an individual basis. The added value of the ambulance ECG for the detection of transient abnormalities could be promoted during the implementation phase of prehospital ECG programs, to increase acceptance by hospital clinicians. The additional information has the potential to clarify diagnosis and thus reduce the time required for management decisions to be made in the emergency department, which could lead to improved patient outcomes and reduced hospital costs.

5.4 GENERAL STRENGTHS AND LIMITATIONS

Unlike many recent studies involving prehospital ECG programs in the published scientific literature, this thesis addressed issues particularly pertinent to basic life support ambulance personnel in Quebec. The computerized ECG interpretations and on-scene time data arose from a "real world" setting, in an early phase of program implementation but not in the context of a prospective research study. The potential impact of "being studied" on ambulance personnel performance (i.e., the Hawthorne effect) may thus be lessened in this context. The samples of patients examined in this thesis were substantial, at 1200 or more for each of the three areas of study. To my knowledge, these sample sizes are larger than those in previous published studies of patients meeting broad ECG eligibility criteria. The statistical methodology employed in the diagnostic performance part of the thesis allowed for both imperfect test performance on the part of the cardiologist readers and the hospital diagnoses, and misclassification of the latter during data coding.

This thesis does not examine a strict consecutive series of patients: study membership was determined by the availability, in 2007, of a prehospital ECG acquired in 2005-06. Tracings may have been lost on scene, at the hospital, at the end of an ambulance team's shift, in transit to the administrative centre, and during or after quality assurance procedures by *Urgences-santé*. It was assumed for this thesis that these were mostly random losses, and that the diagnostic performance of the computerized ECG interpretation, the on-scene time, and the relative distribution of paired ECG

abnormalities, did not systematically differ for patients not included in the sample, when compared to those included, such that a selection bias would be created.

The study sample is also likely to miss a proportion of patients eligible for prehospital ECGs but for whom no ECG was performed by the ambulance technicians, for a variety of possible reasons. It could be, as suggested by a previous study by Provo and Frascone (2004) and local anecdotal information, that prehospital ECGs are less likely to be performed on large-breasted women, women in general, hirsute persons or the very aged. If these features are associated with a different level of test performance – such as lower sensitivity or specificity associated with incorrect placement of electrodes or poor electrode contact – it is possible to make Bayesian statistical adjustment by assigning a prior probability distribution to a factor that is used to weight the likelihood of data for such groups. However, it was decided for the purposes of the thesis that this would not be worthwhile since informative prior estimates for such differential sensitivities or specificities were not readily available. For example, although Kudenchuk et al. (1991) found indication of somewhat lower sensitivity for the computerized interpretation associated with greater patient age, their sample did not include the particularly aged, over 75 years. These patient features could also affect the estimate of additional on-scene time, since it may take longer to acquire an ECG.

Some quality assurance data from the prehospital ECG program in 2005-06 are available, and are based on retrieval of the specialized ambulance form on interventions (i.e., medications, ECGs) and the tracings at the administrative centre. The following quality

assurance results should be interpreted as general trends since there were tracings in the thesis sample that were not part of the assurance process (i.e., 29% of the thesis ECGs).

Based on 3054 evaluations in the 2-year period, an ECG should have been acquired but was not about 25% of the time: the rate of non-adherence to the protocol was 18%, and in 6.4% of cases the ECG machine was not available or not functioning. Fifteen percent of the time, the patient was not eligible for an ECG and none were performed. For 18% of patients, the tracing was missing, and an additional 6.5% were verified by quality assurance but no ECG was present in the thesis sample. This implies that about 25% of acquired prehospital ECGs from the early stage of the program are likely missing from the present analysis, as well as ECGs from another 25% of eligible patients.

Given the retrospective nature of this study, the tracings were read by cardiologists and the hospital diagnoses were assigned (using portions of charts) a few years after the ECGs were acquired. The validity of the diagnostic classifications thus partly depends on the data extraction by the archivists and (my) non-physician coding. However, systematic methods were used, the archivists were very experienced and well-trained, and physicians were consulted for coding questions when necessary.

Certain data may be more likely to have problems with validity, such as symptom onset times which relied on patient recall and transcription onto (and extraction from) ambulance forms. Better recall of clinical onset by patients (or witnesses) was likely when symptoms were more severe and/or there was a shorter delay before contacting

emergency medical services. This particular variable was also often missing, limiting the generalizability of the analysis of the relationship between delay since symptom onset and diagnostic sensitivity of the computer. If errors of recall went systematically in a certain direction, and this had a differential association with test results, overall validity may have been affected as well. For example, if among the truly very recent onset patients the delay was systematically overestimated, a real association of shorter delay with higher sensitivity may have been missed. Likewise, such a relationship would be missed if those with truly later onset, associated with a lower sensitivity, tended to underestimate delay since symptom onset.

Finally, in my search of the published scientific literature on prehospital ECG programs and diagnostic performance of prehospital ECGs, I excluded articles (based on title) that examined prehospital thrombolysis. As a result, I may have missed articles that could have provided background information relevant to my study objectives.

5.5 CONCLUDING REMARKS

Prehospital ECG programs have the potential to greatly reduce treatment delay for STEMI patients. The prehospital ECGs studied were acquired in an early stage of program implementation and in the basic life support ambulance setting. The five main conclusions of this thesis are listed below.

- Computerized interpretation of prehospital ECGs showed modest sensitivity and high specificity (for the ***Acute MI*** signal). This was the case when the outcome of interest was the detection of ST-segment elevation on the prehospital ECG (i.e., suspected STEMI) or the detection of underlying STEMI.
- Of the patient factors studied, only younger patient age was a significant predictor of higher sensitivity. Broadening the "outcome positive" criteria to increase the computer's sensitivity correspondingly decreased specificity.
- Using a model-estimated disease prevalence of 9.2%, the probability of STEMI being absent when the computer tested positive was 15%; the probability of STEMI being present when the computer tested negative was 3%. These predictive values would change if the true (unknown) prevalence were different, or if ECG eligibility criteria were modified.
- Prehospital ECGs were associated with an acceptably small increase in average on-scene time (about 5 minutes), compared to the potential for reducing treatment delays in the literature. No patients in the prehospital ECG sample died or had a cardiac arrest prior to hospital arrival.
- Prehospital ECGs provided substantial added value for the identification of transient signs of ischemia and arrhythmia, not observed on the initial in-hospital ECG.

My initial involvement with prehospital ECG programs was a result of work in health technology assessment. Considering the results of the quantitative analyses, the literature review of effectiveness (Appendix A), and the local context of clinical practice and health

care resources, I conclude this thesis with five policy recommendations for health services:

- Ensure high-quality training of all ambulance personnel in the acquisition of prehospital ECGs; choose workable eligibility criteria so that enough ECGs are performed to ensure technician competence without over-burdening personnel and leading to excessive false alarms.
- Use prehospital ECGs to send ambulances to the closest PCI hospital when ***Acute MI*** is signalled, activating the cardiac catheterization laboratory and initiating appropriate medical therapy while en route. This recommendation is applicable to the Montreal-Laval region where ample cardiac catheterization resources exist and inter-hospital transfer prior to first reperfusion treatment is currently frequent.
- Transport the patient to the closest PCI hospital when any other mention of an infarct or ST abnormality (other than ***Acute MI***) is present in the computerized prehospital ECG interpretation, but do not activate the catheterization laboratory before hospital assessment of the patient, or transmission of the prehospital ECG for reading by a physician.
- Ensure receiving hospital physicians are aware of a patient's prehospital ECG.
- Fully engage all stakeholders in the development of a prehospital ECG strategy and monitor implementation, including actual rate of affected patients being missed by the computer and unaffected patients being falsely identified.

The clinical information provided by the prehospital electrocardiogram is important for diagnosis and management of STEMI patients, as well as those with other forms of acute coronary ischemia and arrhythmias. The implementation of the policy recommendations stemming from this thesis has the potential to improve health services, decrease mortality, and reduce health care costs for ambulance users in Quebec.

APPENDIX A: LITERATURE REVIEW ON EFFECTIVENESS OF PREHOSPITAL ECG PROGRAMS

Objectives

The primary objective of this review was to summarize, in quantitative terms, the time saved before reperfusion treatment associated with prehospital ECG programs in the published English scientific literature, according to the type of study and the type of program. The secondary objectives were to determine the level of training of ambulance personnel in the reviewed studies (if possible, based on information provided in the articles), and to summarize any data provided on time spent to perform prehospital ECGs for the purposes of the literature review in Chapter 2.

Literature searching, article selection and data extraction methods

The search for literature was carried out in two phases. In phase 1, the scientific literature published in English between January 2004 and June 2007 was searched using the Pubmed, Cochrane Library, Web of Science and EMBASE bibliographic databases. The search strategy was adapted from those used by Morrison et al. (2006) and Brainard et al. (2005) (see Figure A1). In phase 2, the automated monthly Pubmed update system was used to search for articles published in English between January 2007 and July 2009, using the same Pubmed search strategy as in phase 1. In both phases, reference lists of retrieved articles were also searched.

Figure A1. Key words and databases used for literature searching in phase 1

Pubmed (same key words used for phase 2)
(electrocardiography[mh:noexp] OR electrocardiogra* OR ECG OR EKG OR cardioscop* OR (electrode* AND (cardiac OR coronary OR myocard*) AND (prehospital* OR domicil* OR "pre-hospital" OR paramedic* OR "in-field" OR "out-of-hospital" OR "in field" OR "out of hospital" OR emergency medical technician[mh] OR EMT OR EMTs OR ambulances[mh] OR (emergency AND technician*) OR ambulance* OR transportation of patients[mh] OR Emergency Medical Service Communication Systems[mh] OR communication OR transport* OR transmission OR telemedic* OR telecardio* OR "tele-cardiology" OR telephon*)
OR
(prehospital OR domiciliary OR pre-hospital OR in-field OR emergency medical services OR emergency medical technician OR ambulance OR transportation of patients) AND (electrocardiography OR "electrocardiography" OR electrocardiogram OR ECG OR EKG OR electrodes) AND
(myocardial infarction OR angina pectoris OR chest pain OR ST segment OR myocardial ischemia OR cardiac ischemia OR coronary disease OR coronary care nursing)
AND NOT
("non ST-elevation" OR "non ST elevation")

Cochrane Library
(electrocardiogra* OR ECG OR EKG OR cardioscop*)
AND
(emergenc* OR ambulance* OR transport* OR prehospital* OR pre hospital* OR out-of-hospital* OR paramedic* OR para medic* OR domiciliary OR in field OR myocardial infarction OR heart infarction OR heart attack* OR cardiology OR ST segment OR ST elevation)

Web of Science and EMBASE
Ti=(emergenc* OR ambulance* OR transport* OR prehospital* OR pre-hospital* OR out-of-hospital* OR paramedic* OR domiciliary) AND TS=(electrocardiogra* OR ECG OR EKG OR cardioscop*)
OR
TS=(emergenc* OR ambulance* OR transport* OR prehospital* OR pre-hospital* OR out-of-hospital* OR paramedic* OR domiciliary) AND Ti=(electrocardiogra* OR ECG OR EKG OR cardioscop*)
OR
(prehospital? OR domicil? OR "pre-hospital" OR paramedic? OR "in-field" OR "out-of-hospital" OR "in field" OR "out of hospital" OR "emergency medical technician" OR EMT OR EMTs OR (emergency AND technician?) OR ambulance? OR ambulat? OR emergenc? OR communication OR transport? OR transmission OR telemedic? OR telecardio? OR "tele-cardiology" OR telephon?)/de,ti) AND (electrocardiograph? OR electrocardiogra? OR ECG OR EKG OR cardioscop? OR electrocardiography!/de)

Studies were excluded for the following reasons:

- data were provided only for physician-staffed ambulances
- based on the title of the publication, the study was an evaluation of a prehospital thrombolysis program
- no comparative effectiveness data were provided
- delays were not provided in terms of minutes
- the study was a pilot test of an investigation already included in the analysis
- only an abstract was available

The first two exclusions were made in order to increase the relevance to the prehospital care system in Quebec.

For reasons of feasibility, the literature search and review methods were not technically "systematic" (as outlined in standard texts such as the Centre for Reviews and Dissemination guidance, 2009). That is, I was the sole reviewer, restrictions to certain bibliographic databases were made and the total numbers of references collected and excluded were not tallied. In reviewing the articles, study quality was not examined in depth; however, the study design was used as a general indicator of the strength of the evidence. The literature selection methods, however, were systematically applied, as were the methods of data extraction.

"Door-to-needle" and "door-to-balloon" times are standard performance indicators in acute care management of STEMI, referring to the delay between hospital arrival and administration of thrombolytic medication ("needle") or balloon inflation in a coronary

artery during PCI. I thus sought to extract time savings data with regards to these indicators; if this was not possible, I chose the closest available time period.

The results are summarized in Tables A1a-c, ordered according study design (starting with the strongest) and then by study year (starting with the most recent, or alphabetically if same year). A "controlled" design involved only concurrent control subjects, a "before/after" design included only historical control patients, and a "mixed" design employed both types of controls. The tables also group the studies with respect to the type of action carried out on the basis of the prehospital ECG information (e.g. notifying the hospital that a possible STEMI patient will arrive; bypassing the emergency department to be taken directly to a coronary care unit or catheterization laboratory).

In summarizing the results of Tables A1-c, I considered the comparisons with ambulance control patients (rather than self-transported individuals) to be the most valid data. Self-transport, as opposed to use of an ambulance, has been found to be associated with longer treatment delays in general (So et al., 2006; Swor et al., 1994). For each group of studies, I report the estimates of time savings associated with the highest level of evidence in the text that follows.

Results: advance hospital notification

This model was associated with savings of about 30 minutes for door-to-needle time, based on two meta-analyses, which used the same studies except for one for their

calculations (Morrison et al., 2006; Brainard et al., 2005)[73]. Door-to-balloon times were minimally reduced (by 5-14 minutes when compared to other ambulance patients) in controlled analyses, including an observational study (Swor et al., 2006), a survey of hospitals (Bradley et al., 2006b) and an analysis of registry data (Diercks et al., 2009). In a comparison of patients transferred for primary PCI, Terkelsen et al. (2005) found a 41-minute reduction in the median time from ambulance call to balloon, due to faster transport time to local hospitals and more rapid turnaround at the initial receiving centre. (Median delay from the door of the PCI hospital to balloon in this study was actually slightly longer, by 3 minutes, for the group containing 65 patients with prehospital ECGs.)

Results: emergency department bypass

This model was associated with savings of 25 minutes for median door-to-needle and median door-to-balloon time, based on a controlled study (Bang et al., 2007). This investigation had the largest sample size of ambulance-transported patients of all studies reviewed.

Results: early activation of catheterization laboratory

This model was associated with variable time savings, even when restricting the analysis to comparisons with concurrent controls. Three studies found reductions of about 30 minutes in mean or median delay (Swor et al., 2006; Strauss et al., 2007; Adams et al., 2006); the program investigated by Adams et al. (2006) also involved emergency

[73] In the analyses of door-to-needle time, one study in Morrison et al. (2006) and three studies in Brainard et al. (2005) were randomized.

department bypass. Afolabi et al. (2007) and Bradley et al. (2006b) observed reductions of about 15 minutes, while time savings of nearly 60 minutes were found by Brown et al. (2008).

Results: prehospital diversion to a PCI hospital

This last group can be divided into studies comparing diverted patients to those who were admitted directly to the same PCI centre, and to those who were transferred from a local hospital. For the first comparison, the "door" is at the same hospital. Compared to concurrent directly admitted patients, this model was associated with savings of 25-27 minutes before balloon inflation or open artery (Sivagangabalan et al., 2009; Gross et al., 2007). Zanini et al. (2008) likewise found a reduction of 24 minutes, using the starting point of "first medical contact" which likely refers to the advanced life support ambulance for the prehospital ECG patients. The emergency department was bypassed by the prehospital ECG patients in the investigation by Zanini and colleagues (2008). All three of these studies involved at least some self-transported patients in the comparison sample.

Compared to concurrent transferred patients, this model was associated with savings of about 60 minutes or more from door to balloon or open artery (Sivagangabalan et al., 2009; Le May et al., 2008; Zanini et al., 2008; Carstensen et al., 2007; Gross et al., 2007). Only the study by Carstensen and colleagues (2007) did not contain any self-transported controls. Finally, the study by Sejersten et al. (2008) deserves mention since it was the only one reviewed with delay data available for ambulances staffed solely by basic life

support personnel. Compared to historical transferred controls, median door-to-balloon time was reduced by 72 minutes for these 45 patients (Sejersten et al., 2008).

I did not extract data on mortality associated with prehospital ECG programs. During the writing of the thesis a systematic review of mortality associated with diversion programs was published (Brooks et al., 2009). In a subgroup analysis, the data on in-hospital deaths from Le May et al. (2006) and Terkelsen et al. (2005) were pooled. Prehospital diversion was associated with decreased in-hospital mortality when compared to transport to the closest local hospital (followed by inter-hospital transfer in the study by Terkelsen and colleagues), with a relative risk of 0.24 (95% confidence interval: 0.07-0.87). An association with pooled short-term mortality (in-hospital and at 30 days) was not seen when diversion was compared to prehospital thrombolysis (two studies). The latter finding is expected given the impact of decreased ischemic time on mortality.

Table A1a. Summary of effectiveness data (ordered by strength of design, and recency)

Design*	Study	n pre-hospital ECG patients	n comparison patients**	Time variable	Reduction in minutes (per comparison)
Group 1: Advance hospital notification					
meta-analysis (3 studies)	Morrison et al., 2006	84	97	mean DTN	36.1
meta-analysis (4 studies)	Brainard et al., 2005	54	45	mean or median DTN	24.7
controlled (registry)	Diercks et al., 2009	72 1501	167 3563	median DTN median DTB	10 14
controlled	Eckstein et al., 2009	ns	ns self-transport	median DTB	13
controlled (survey)	Bradley et al., 2006b	144 sites	143 sites	median DTB	6.8
controlled (registry)	Curtis et al., 2006	1599 1696	33771 19581 (both include self-transport)	mean DTN mean DTB	10.1 16.3
controlled	Swor et al., 2006	62	69	mean DTB	5.3
controlled	Terkelsen et al., 2005	85‡	55	median EMS call-to-balloon	41
Group 2: Emergency department bypass					
controlled	McLean et al., 2008	247	31 self-transport	median DTN	12
controlled	**Bang et al., 2007**	**261 (BLS: 3% of 237)**	**235 (BLS: 72% of 187)**	**median DTN median DTB**	**25 25**
before/after *in regular hours*	Dhurva et al., 2007	12	14	mean door-to-open vessel	65

DTN=door to needle; DTB=door to balloon; ns=not specified; EMS=emergency medical services (i.e. ambulance); BLS=basic life support; *see definitions in text; **comparison patients were transported by ambulance unless otherwise noted; ‡delay data provided for 85 but only 65 had a prehospital ECG

Information in bold means at least some basic life support personnel were involved

Table A1b. Summary of effectiveness data (ordered by strength of design, and recency)

Study	Design*	n pre-hospital ECG patients	n comparison patients**	Time variable	Reduction in minutes (per comparison)
Group 3: Early activation of catheterization lab (+ ED bypass where noted with a †)					
control-led	Afolabi et al., 2007	100	18 hospital alert 5 no alert 44 self-transport	mean DTB	15 17 52
control-led	Bradley et al., 2006b	33 sites	61 sites, hospital alert	mean DTB	15.4
control-led	Swor et al., 2006	31	62 hospital alert‡ 69 no alert	mean DTB	25.9 31.2
mixed	Brown et al., 2008	20	28 concurrent 30 historical	mean DTB	57 68
mixed	Dorsch et al., 2008	172†	405 (190 historical)	median DTB	14
mixed	Strauss et al., 2007	20	15 concurrent 15 historical	median DTB	34 54
mixed	Adams et al., 2006	24†	19 no transmission° 101 self-transport 48 historical	median door-to-open vessel	28 46 51
before/ after	**Caudle et al., 2009**	**39† (12 BLS)**	**42 (13 BLS)**	**median DTB**	**25**
before/ after	Kordish et al., 2008	76	47	mean DTB	38
before/ after *in off-hours*	Dhurva et al., 2007	8	15	mean door-to-open vessel	59
before/ after	Vaught et al., 2006	ns (2003) 92 (1995-97)	ns (1993) ns (1993)	median DTB	0 17
before/ after	Sekulic et al., 2005	6	ns	mean DTB	44
RCT pilot + before/ after	Drew et al., 2004	2	1 concurrent ns historical	mean DTB	92-101 49-58

DTB=door to balloon; ED=emergency department; ns=not specified; RCT=randomized controlled trial
*see definitions in text; **comparison patients were transported by ambulance unless otherwise noted;
‡these comparison patients also had prehospital ECGs; °prehospital ECG transmission failed

Information in bold means at least some basic life support personnel were involved

Table A1c. Summary of effectiveness data (ordered by strength of design, and recency)

Study	**Design***	**n pre-hospital ECG patients**	**n comparison patients****	**Time variable**	**Reduction in minutes** (per comparison)
Group 4: Prehospital diversion to PCI hospital with alert during transport (+ ED bypass where noted with a †)					
control-led	Sivaganga-balan et al., 2009	163	202 direct admission to PCI hospital (54 self-transport) 259 transferred (101 self-transport)	median DTB	27 68
control-led	Le May et al., 2008	135	209 transferred with lab activation (105 self-transport)	median DTB	54
control-led	Zanini et al., 2008	136†	~176 self-transport, direct admission to PCI hospital ~87 self-transport, transferred	mean first medical contact-to-balloon	24 68
control-led	Carstensen et al., 2007	108	193 transferred	median DTB	77
control-led	Gross et al., 2007	73	32 self-transport, direct admission to PCI hospital 95 self-transport, transferred (4 sites)	mean door to open vessel	25 46-84
control-led	Terkelsen et al., 2005	21‡	85 hospital alert, then transferred^{o} 55 transferred, no alert	median EMS call-to-balloon	40 81
before/ after	**Sejersten et al., 2008**	**45† (all BLS)** 101	**89 transferred** 89 transferred	**median DTB**	**72** 55
before/ after	Clemmensen et al., 2005	113	223 transferred	mean door-to-start of PCI	53

DTB=door to balloon; ED=emergency department; EMS=emergency medical services

*see definitions in text; **comparison patients were transported by ambulance unless otherwise noted; ‡only 10/21 had a prehospital ECG; ^{o}65 of these comparison patients had a prehospital ECG

Information in bold means at least some basic life support personnel were involved

APPENDIX B: ANALYTIC ROLES OF CARDIOLOGISTS IN THIS THESIS

Cardiologist	**Analytic roles**
1	Interpretation of prehospital ECGs for diagnostic performance objectives Consensus discussion of discordant ECG interpretations with cardiologist 2
2	Interpretation of prehospital ECGs for diagnostic performance objectives Consensus discussion of discordant ECG interpretations with cardiologist 1
3	Interpretation of prehospital ECGs for diagnostic performance objectives, in cases where cardiologists 1 and 2 could not reach consensus (regarding presence/absence of ST-segment elevation or infarction territory)
4	Verification of presence/absence of ST-segment elevation on initial in-hospital ECG for patients with a hospital diagnosis of acute myocardial infarction (not specified as STEMI or NSTEMI) Interpretation of paired ECGs for added value objectives
5	Verification of presence/absence of ST-segment elevation on initial in-hospital ECG for patients with a hospital diagnosis of acute myocardial infarction (not specified as STEMI or NSTEMI) Interpretation of paired ECGs for added value objectives

APPENDIX C: BAYESIAN METHODS USED IN THIS THESIS

Estimation of diagnostic test performance in the absence of a gold standard

When a standard 2 x 2 table is used to summarize the results of applying two diagnostic tests to a given sample of subjects, one of these tests is often assumed to be perfect. Thus the sensitivity and specificity of this "reference" test are assumed to be 100%, and no statistical estimation of their values is carried out. In reality, these test properties are rarely 100% and their true value is usually unknown. When this is not taken into account, point estimates of test performance parameters and their confidence intervals will likely be biased.

With a Bayesian approach to analyzing diagnostic test performance, there is no need to assume the existence of a perfect reference standard. The numbers of true positive and true negative subjects, for the disease of interest, are considered as unknown or "latent" data. Prior information about the diagnostic performance of one or more of the tests is combined through Bayes Theorem with the likelihood function for the observed data, to form a posterior distribution over all unknown parameters of interest. This process then generates estimates of the performance parameters for each test, and of the underlying prevalence of the disease in the population from which the study sample was derived.

To generate samples from the target joint posterior density, a Gibbs sampler algorithm is employed. These random samples are then used to generate summaries of the posterior estimates (e.g. median values and 95% credible intervals), replacing the need for exact analytic calculations.

The prior information about the parameters (i.e. test sensitivity, test specificity, prevalence of the disease) is expressed statistically in the form of a beta distribution with an associated α and β. Using this kind of distribution simplifies calculations, matches the range of the test parameters (i.e., the distribution takes values between 0 and 1 when its density is positive), and is flexible in shape (allowing for a variety of choices of α and β). For each parameter, the mean (μ) and the standard deviation (σ) of the beta distribution can be assigned using the prior information and then used to define the α and β using the following equations:

$$\alpha = \frac{\mu(\sigma^2 + \mu^2 - \mu)}{\sigma^2} \qquad \text{and} \qquad \beta = \frac{(\mu - 1)(\sigma^2 + \mu^2 - \mu)}{\sigma^2}$$

Latent class structures and conditional dependence between diagnostic tests

The Bayesian model used in this thesis when the results of two diagnostic tests were compared incorporated one latent variable. This variable represents the unknown true disease status and is binary, with two classes: one for the true disease status being positive (i.e. those with STEMI; Class 1) and one for the true disease status being negative (i.e. those without STEMI; Class 2). In order to run the BayesLatentClassModels software program, the prior information regarding the underlying prevalence of the disease has to be provided in the form of "Dirichlet parameters". The Dirichlet parameter for Class 1 is equivalent to the β parameter of a beta density, while that for Class 2 is equivalent to the α parameter of this density.

The "one latent variable" model assumes conditional independence between the two diagnostic tests. A "two latent variable, 3 test" model was also used in this thesis in order

to incorporate the data from all three imperfect tests and to allow for possible conditional dependence between the two interpretations of the prehospital ECG (by the computer and the cardiologists) within disease categories (Dendukuri et al., 2009). Appendix D presents a visual representation of the "two latent variable, 3 test" model. In this case, the computer and the cardiologists measure the prehospital ECG latent variable (which can in turn be thought of as a proxy for the true disease status) and the hospitals measure the disease latent variable. These latent variables represent a total of four classes, since each variable can be positive or negative. In order to assign the Dirichlet parameters for the prior information on disease prevalence in the "two latent variable, 3 test" model, the α and β were scaled as specified in Table C1.

The proportions used for the scaling were chosen in the following manner. Based on my reading of the literature and Kudenchuk et al. (1991) in particular, I chose *a priori* an estimate of 70% (Class 1) for the proportion of prehospital ECGs that would be positive when the true disease status was positive (and thus 30% for negative prehospital ECGs among true STEMI patients, Class 3). I chose an estimate of 5% for the proportion of positive prehospital ECGs when the true disease status was negative (Class 2), based on Kudenchuk et al. (1998) (and thus 95% for Class 4).

Table C1. Designation of prevalence parameters in models with two latent variables

Class	Latent variable 1	Latent variable 2	Scaling
1	prehospital ECG data positive	true disease status positive	70% of β
2	prehospital ECG data positive	true disease status negative	5% of α
3	prehospital ECG data negative	true disease status positive	30% of β
4	prehospital ECG data negative	true disease status negative	95% of α

Hierarchical multivariate logistic regression of test sensitivity

Hierarchical analysis operates at multiple levels. At the lowest level, a multinomial model is used in this thesis to express the probabilities of being positive or negative for each of the tests of interest. Since each of the three tests in this thesis is binary there are eight combinations of possibilities for testing positive or negative (i.e., 2 x 2 x 2) and, for each of these, there is the possibility of being a true positive or negative (the latter known as the "latent", unknown data). These 16 possibilities can be defined as products of the probability of being truly positive (or truly negative), which is related to the prevalence (or 1-prevalence), and the probabilities of having a positive (or negative) result on each of the three tests, which is related to the sensitivity (or 1-specificity).

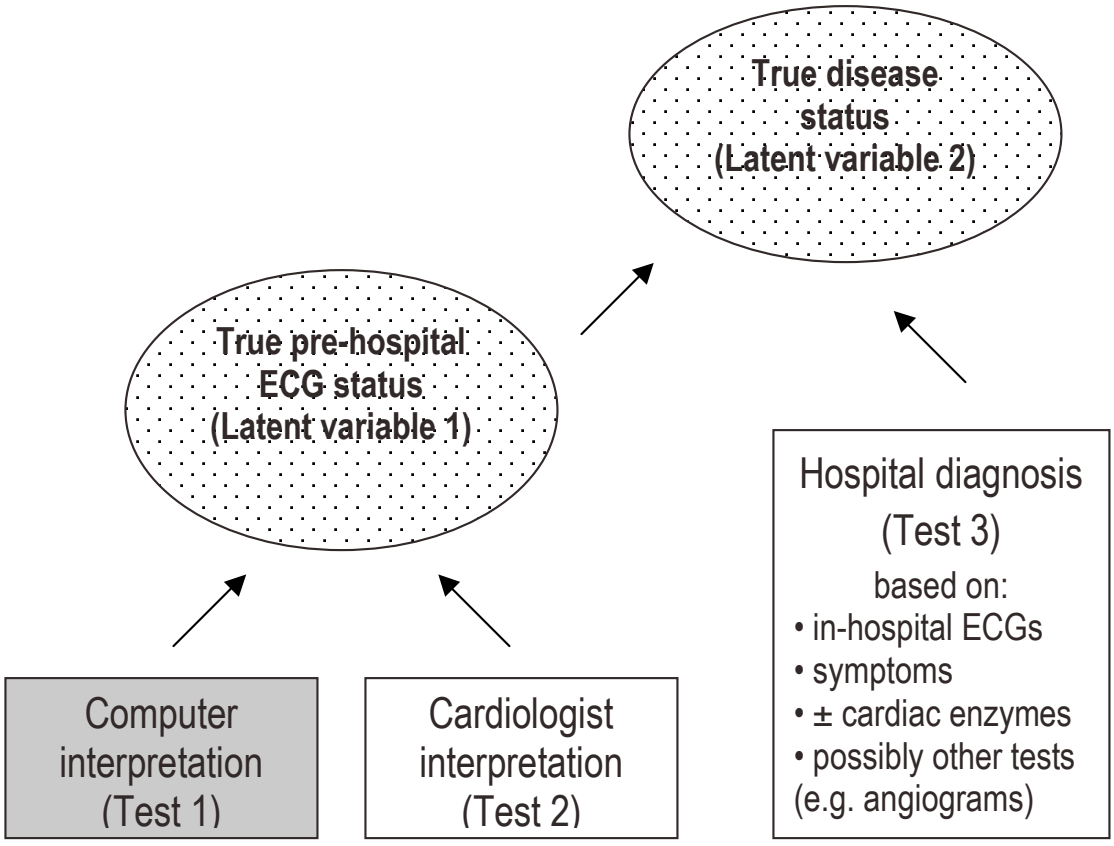
At the second level of this analysis, a logistic regression model was used to find factors which may affect the sensitivity of the computer (test 1), whereby

$$\text{logit (sensitivity of test 1)} = \beta_0 + \beta_1 (\text{age}) + \beta_2 (\text{sex}) + \beta_3 (\text{cardiac history}) + \beta_4 (\text{infarct territory dummy variable 1}) + \beta_5 (\text{infarct territory dummy variable 2}) + \beta_6 (\text{infarct territory dummy variable 3}) + \text{correlation term (sensitivity of test 1 and sensitivity of test 2)}$$

The correlation term in the regression was used to allow for conditional dependence between the results of test 1 and test 2.

APPENDIX D: BAYESIAN MODEL INCORPORATING 3 TESTS, 2 LATENT VARIABLES AND CONDITIONAL DEPENDENCE

(adapted from Dendukuri et al., 2007)



Tests 1 and 2 are conditionally dependent (interpretations of the same data), with a common latent variable (pre-hospital ECG status)

APPENDIX E: RESEARCH COMPLIANCE LETTERS

The "Montreal Urban Prehospital Electrocardiographic Transmission (MUPET) Trial" was launched in 2003 by *Urgences-santé* in collaboration with the *Institut de Cardiologie de Montréal*, which granted research ethics approval. This pilot project was intended to examine various aspects of the prehospital ECG program, including diagnostic performance and safety. Before my involvement in the study in April 2007, ECG tracings were collected and computer interpretations were entered in a database at *Urgences-santé*. In June 2007, the *Institut de Cardiologie de Montréal* renewed its ethics approval for the study (see scan of letter), following a request by Dr. Alain Vadeboncoeur, head of the Emergency Care Service at the *Institut* and a founding member of the MUPET research team. This approval was extended in June 2009 (see scan of letter), and thus covered the period April 2007 to June 2010. The hospital chart data was requested from each institution through an established quality assurance process with *Urgences-santé*, and did not require patient consent in accordance with the *Loi sur l'accès*, article 125.

Note: The scans of the research compliance letters are presented in a separate PDF file, in accordance with McGill University standards for electronic thesis format.

APPENDIX F: RAW TEST PERFORMANCE DATA

1. Two Tests: Computer and Cardiologists (for Tables 9 and 10)

All patients

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	70	18	88
	No STEMI	54	1303	1357
		124	1321	1445

Chest pain only

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	68	15	83
	No STEMI	49	1092	1141
		117	1107	1224

No posterior infarct

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	69	18	87
	No STEMI	52	1303	1355
		121	1321	1442

2. Two Tests: Computer and Hospitals (for Tables 9 and 10)

All patients

		Hospitals		
		STEMI	No STEMI	
Computer	STEMI	60	21	81
	No STEMI	26	1187	1213
		86	1208	1294

Chest pain only

	Hospitals		
	STEMI	No STEMI	
Computer STEMI	59	19	78
No STEMI	26	1009	1035
	85	1028	1113

3. Three Tests (for Table 11)

In the tables below, + = STEMI; - = No STEMI

All patients (N=1258)

Computer	**Cardiologists**	**Hospitals**	**N**
+	+	+	54
+	+	-	7
+	-	+	4
+	-	-	12
-	+	+	16
-	+	-	32
-	-	+	9
-	-	-	1124

Chest pain only (N=1070)

Computer	**Cardiologists**	**Hospitals**	**n**
+	+	+	53
+	+	-	7
+	-	+	4
+	-	-	10
-	+	+	16
-	+	-	29
-	-	+	9
-	-	-	942

4a. Stratified Analysis: Computer and Cardiologists (for Table 13)

Females

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	21	8	29
	No STEMI	18	630	648
		39	638	677

Males

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	49	10	59
	No STEMI	36	673	709
		85	683	768

65 years and older

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	33	11	44
	No STEMI	34	781	815
		67	792	859

64 years and younger

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	37	7	44
	No STEMI	20	522	542
		57	529	586

Anterior infarct

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	30	18	48
	No STEMI	34	1303	1337
		64	1321	1385

Inferior infarct

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	34	18	52
	No STEMI	13	1303	1316
		47	1321	1368

Cardiac disease history

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	21	10	31
	No STEMI	36	684	720
		57	694	751

No cardiac disease history

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	40	6	46
	No STEMI	15	474	489
		55	480	535

0-29 minutes between symptom onset and ECG time

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	8	0	8
	No STEMI	5	94	99
		13	94	107

30-59 minutes between symptom onset and ECG time

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	9	3	12
	No STEMI	14	175	189
		23	178	201

60-119 minutes between symptom onset and ECG time

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	14	4	18
	No STEMI	7	158	165
		21	162	183

120 minutes or more between symptom onset and ECG time

		Cardiologist		
		STEMI	No STEMI	
Computer	STEMI	16	6	22
	No STEMI	13	294	307
		29	300	329

4b. Stratified Analysis: Three Tests (for Table 14)

Females (N=580)

Computer	Cardiologists	Hospitals	n
+	+	+	15
+	+	-	2
+	-	+	1
+	-	-	6
-	+	+	7
-	+	-	10
-	-	+	1
-	-	-	538

Males (N=678)

Computer	Cardiologists	Hospitals	n
+	+	+	39
+	+	-	5
+	-	+	3
+	-	-	6
-	+	+	9
-	+	-	22
-	-	+	8
-	-	-	586

65 years and older (N=760)

Computer	Cardiologists	Hospitals	n
+	+	+	24
+	+	-	4
+	-	+	2
+	-	-	9
-	+	+	9
-	+	-	22
-	-	+	4
-	-	-	686

64 years and younger (N=498)

Computer	Cardiologists	Hospitals	n
+	+	+	30
+	+	-	3
+	-	+	2
+	-	-	3
-	+	+	7
-	+	-	10
-	-	+	5
-	-	-	438

Anterior infarct (N=1187)

Computer	Cardiologists	Hospitals	n
+	+	+	21
+	+	-	1
+	-	+	0
+	-	-	12
-	+	+	4
-	+	-	22
-	-	+	3
-	-	-	1124

Inferior infarct (N=1179)

Computer	Cardiologists	Hospitals	n
+	+	+	25
+	+	-	3
+	-	+	2
+	-	-	12
-	+	+	5
-	+	-	5
-	-	+	3
-	-	-	1124

Cardiac disease history (N=733)

Computer	Cardiologists	Hospitals	n
+	+	+	19
+	+	-	2
+	-	+	1
+	-	-	9
-	+	+	8
-	+	-	25
-	-	+	4
-	-	-	665

No cardiac disease history (N=525)

Computer	Cardiologists	Hospitals	n
+	+	+	35
+	+	-	5
+	-	+	3
+	-	-	3
-	+	+	8
-	+	-	7
-	-	+	5
-	-	-	459

0-29 minutes between symptom onset and ECG time (N=99)

Computer	Cardiologists	Hospitals	n
+	+	+	7
+	+	-	0
+	-	+	0
+	-	-	0
-	+	+	2
-	+	-	3
-	-	+	0
-	-	-	87

30-59 minutes between symptom onset and ECG time (N=172)

Computer	Cardiologists	Hospitals	n
+	+	+	7
+	+	-	0
+	-	+	1
+	-	-	2
-	+	+	5
-	+	-	8
-	-	+	1
-	-	-	148

60-119 minutes between symptom onset and ECG time (N=167)

Computer	Cardiologists	Hospitals	n
+	+	+	9
+	+	-	4
+	-	+	2
+	-	-	2
-	+	+	0
-	+	-	6
-	-	+	1
-	-	-	143

120 minutes or more between symptom onset and ECG time (N=297)

Computer	Cardiologists	Hospitals	n
+	+	+	13
+	+	-	2
+	-	+	0
+	-	-	6
-	+	+	4
-	+	-	8
-	-	+	2
-	-	-	262

5a. Two Tests: Computer and Cardiologists, expanding interpretations for positive diagnosis (for Table 15)

Add "infarct, possibly acute" and "infarct, age undetermined"

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	89	232	321
	No STEMI	35	1089	1124
		124	1321	1445

Also add "possible infarct, age undetermined"

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	93	272	365
	No STEMI	31	1049	1080
		124	1321	1445

Also add "cannot rule out infarct, age undetermined"

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	99	330	429
	No STEMI	25	991	1016
		124	1321	1445

Also add “ST elevation, consider early repolarization, pericarditis or injury” and “ST elevation, probably due to early repolarization, etc.”

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	103	331	434
	No STEMI	21	990	1011
		124	1321	1445

Also add “marked ST elevation, possible subendocardial injury, etc.”

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	105	363	468
	No STEMI	19	958	977
		124	1321	1445

Also add “ST abnormality and T wave abnormality, consider ischemia, etc.”

		Cardiologists		
		STEMI	No STEMI	
Computer	STEMI	111	472	583
	No STEMI	13	849	862
		124	1321	1445

5b. Two Tests: Computer and Hospitals, expanding interpretations for positive diagnosis

Add “infarct, possibly acute” and “infarct, age undetermined”

		Hospitals		
		STEMI	No STEMI	
Computer	STEMI	67	220	287
	No STEMI	19	988	1007
		86	1208	1294

Also add “possible infarct, age undetermined”

		Hospitals		
		STEMI	No STEMI	
Computer	STEMI	70	259	329
	No STEMI	16	949	965
		86	1208	1294

Also add “cannot rule out infarct, age undetermined”

		Hospitals		
		STEMI	No STEMI	
Computer	STEMI	71	319	390
	No STEMI	15	889	904
		86	1208	1294

Also add “ST elevation, consider early repolarization, pericarditis or injury” and “ST elevation, probably due to early repolarization, etc.”

		Hospitals		
		STEMI	No STEMI	
Computer	STEMI	73	321	394
	No STEMI	13	887	900
		86	1208	1294

Also add “marked ST elevation, possible subendocardial injury, etc.”

		Hospitals		
		STEMI	No STEMI	
Computer	STEMI	76	348	424
	No STEMI	10	860	870
		86	1208	1294

Also add “ST abnormality and T wave abnormality, consider ischemia, etc.”

		Hospitals		
		STEMI	No STEMI	
Computer	STEMI	79	444	523
	No STEMI	7	764	771
		86	1208	1294

REFERENCES

Achar SA, Kundu S, Norcross WA. Diagnosis of acute coronary syndrome. Am Fam Physician. 2005;72(1):119-26.

Adams J, Trent R, Rawles J. Earliest electrographic evidence of myocardial infarction: implications for thrombolytic treatment. BMJ. 1993;307(6901):409-13.

Adams GL, Campbell PT, Adams JM, Strauss DG, Wall K, Patterson J et al. Effectiveness of prehospital wireless transmission of electrocardiograms to a cardiologist via hand-held device for patients with acute myocardial infarction (from the Timely Intervention in Myocardial Emergency, NorthEast Experience [TIME-NE]). Am J Cardiol. 2006;98(9):1160-4.

Aehlert B. ECGs Made Easy. 3rd edition. St. Louis: Mosby Elsevier.

AETMIS. *Evaluation sur le terrain du traitement de l'infarctus aigu du myocarde avec élévation du segment ST (ETIAMEST) : portrait des délais du cheminement des soins.* Report prepared by Laurie Lambert, Peter Bogaty, Céline Carroll-Bilodeau, Maude Giguère, Lucy Boothroyd and Jean Morin. Montreal: *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS); 2008a. Available: http://www.aetmis.gouv.qc.ca/site/phpwcms_filestorage/090d5d43b6382b3f2737329df5a2ada2.pdf. In French.

AETMIS. *Infarctus aigu du myocarde avec élévation du segment ST (IAMEST) : enjeux organisationnels et économiques de la prise en charge.* Report prepared by Peter Bogaty, Lucy J. Boothroyd, Laurie Lambert, Jean-Marie R. Lance and Daniel Paquette. Montreal: *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS); 2008b. Vol. 4 No. 2. In French.

AETMIS. *Introduction des soins médicaux avancés dans les services préhospitaliers d'urgence au Québec.* Report prepared by Reiner Banken, Brigitte Coté, François de Champlain and André Lavoie. Montreal: *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS); 2005. Vol. 1 No 1. In French.

Afolabi BA, Novaro GM, Pinski SL, Fromkin KR, Bush HS. Use of the prehospital ECG improves door-to-balloon times in ST segment elevation myocardial infarction irrespective of time of day or day of week. Emerg Med J. 2007;24(8):588-91.

AHA. Part 8: Stabilization of the patient with acute coronary syndromes. Circulation. 2005;112(24 Suppl):IV89-110.

Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol. 2000;36(3):959-69.

American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of adult patients presenting with suspected acute myocardial infarction or unstable angina. Ann Emerg Med. 2000;35(5):521-5.

Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2007;50(7):e1-e157.

Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2008;51(2):210-47.

Antman EM. ST-elevation myocardial infarction: Management. In: Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's heart disease: A textbook of cardiovascular medicine. 7th ed. Philadelphia, PA: Elsevier Saunders; 2005. p. 1167-226.

Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol. 2004;44(3):E1-E211.

Armstrong PW, Bogaty P, Buller CE, Dorian P, O'Neill BJ. The 2004 ACC/AHA Guidelines: A perspective and adaptation for Canada by the Canadian Cardiovascular Society Working Group. Can J Cardiol. 2004;20(11):1075-9.

Arntz H-R, Koenen O, Schnitzer L, Müller D, Breckwoldt J, Schultheiss H-P. Diagnostic superiority of the pre-hospital electrocardiogram compared to the electrocardiogram on hospital admission in patients with acute coronary syndrome. Eur Heart J. 2004;25(Suppl):473 [abstract P2860].

Aufderheide TP, Hendley GE, Thakur RK, Mateer JR, Stueven HA, Olson DW et al. The diagnostic impact of prehospital 12-lead electrocardiography. Ann Emerg Med. 1990;19(11):1280-7.

Bång A, Grip L, Herlitz J, Kihlgren S, Karlsson T, Caidahl K, Hartford M. Lower mortality after prehospital recognition and treatment followed by fast tracking to coronary care compared with admittance via emergency department in patients with ST-elevation myocardial infarction. Int J Cardiol. 2007;129(3):325-32.

Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F et al.; Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2007;28(13):1598-660.

Blomström-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). Circulation. 2003;108(15):1871-909.

Bradley EH, Curry LA, Webster TR, Mattera JA, Roumanis SA, Radford MJ et al. Achieving rapid door-to-balloon times: how top hospitals improve complex clinical systems. Circulation. 2006a;113(8):1079-85.

Bradley EH, Herrin J, Wang Y, Barton BA, Webster TR, Mattera JA et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. N Engl J Med. 2006b;355(22):2308-20.

Bradley EH, Roumanis SA, Radford MJ, Webster TR, McNamara RL, Mattera JA et al. Achieving door-to-balloon times that meet quality guidelines: how do successful hospitals do it? J Am Coll Cardiol. 2005;46(7):1236-41.

Brainard AH, Raynovich W, Tandberg D, Bedrick EJ. The prehospital 12-lead electrocardiogram's effect on time to initiation of reperfusion therapy: A systematic review and meta-analysis of existing literature. Am J Emerg Med. 2005;23(3):351-6.

Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Circulation. 2002;106(14):1893-900.

Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine. 5th ed. Philadelphia: WB Saunders; 1997.

Brooks SC, Allan KS, Welsford M, Verbeek PR, Arntz HR, Morrison LJ. Prehospital triage and direct transport of patients with ST-elevation myocardial infarction to primary percutaneous coronary intervention centres: a systematic review and meta-analysis. CJEM. 2009;11(5):481-92.

Brown JP, Mahmud E, Dunford JV, Ben-Yehuda O. Effect of prehospital 12-lead electrocardiogram on activation of the cardiac catheterization laboratory and door-to-balloon time in ST-segment elevation acute myocardial infarction. Am J Cardiol. 2008;101(2):158-61.

Byrt T. How good is that agreement? Epidemiology. 1996;7(5):561.

Cannon CP, Battler A, Brindis RG, Cox JL, Ellis SG, Every NR et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). J Am Coll Cardiol. 2001;38(7):2114-30.

Carstensen S, Nelson GC, Hansen PS, Macken L, Irons S, Flynn M et al. Field triage to primary angioplasty combined with emergency department bypass reduces treatment delays and is associated with improved outcome. Eur Heart J. 2007;28(19):2313-9.

Caudle JM, Piggott Z, Dostaler S, Graham K, Brison RJ. Impact of a rapid access protocol on decreasing door-to-balloon time in acute ST elevation myocardial infarction. CJEM. 2009;11(1):29-35.

CCORT. Canadian Cardiovascular Outcomes Research Team: Canadian Cardiovascular Atlas. Toronto: Pulsus Group Inc and the Institute for Clinical Evaluative Sciences; 2006.

Christenson J, Innes G, McKnight D, Boychuk B, Grafstein E, Thompson CR et al. Safety and efficiency of emergency department assessment of chest discomfort. CMAJ. 2004;170(12):1803-7.

Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. 3rd edition. York, England: CRD, University of York; 2009.

Clemmensen P, Sejersten M, Sillesen M, Hampton D, Wagner GS, Loumann-Nielsen S. Diversion of ST-elevation myocardial infarction patients for primary angioplasty based on wireless prehospital 12-lead electrocardiographic transmission directly to the cardiologist's handheld computer: a progress report. J Electrocardiol. 2005;38(4 Suppl):194-8.

Curtis JP, Portnay EL, Wang Y, McNamara RL, Herrin J, Bradley EH et al.; National Registry of Myocardial Infarction-4. The pre-hospital electrocardiogram and time to reperfusion in patients with acute myocardial infarction, 2000-2002: findings from the National Registry of Myocardial Infarction-4. J Am Coll Cardiol. 2006;47(8):1544-52.

De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation. 2004;109(10):1223-5.

de Villiers JS, Anderson T, McMeekin JD, Leung RC, Traboulsi M; Foothills Interventional Cardiology Service; Calgary STEMI QIHI group. Expedited transfer for primary percutaneous coronary intervention: a program evaluation. CMAJ. 2007;176(13):1833-8.

Dendukuri N, Hagdu A, Wang L. Modeling conditional dependence between diagnostic tests: A multiple latent variable model. Stat. Med. 2009;28(3):441-61.

Dendukuri N, Bélisle P, Joseph L. BayesLatentClassModels: A program for estimating diagnostic test properties and disease prevalence. Version 1.3; 2007.

Dhruva VN, Abdelhadi SI, Anis A, Gluckman W, Hom D, Dougan W et al. ST-segment analysis using wireless technology in acute myocardial infarction (STAT-MI) trial. J Am Coll Cardiol. 2007;50(6):509-13.

Diercks DB, Kontos MC, Chen AY, Pollack CV Jr, Wiviott SD, Rumsfeld JS et al. Utilization and impact of pre-hospital electrocardiograms for patients with acute ST-segment elevation myocardial infarction: data from the NCDR (National Cardiovascular Data Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry. J Am Coll Cardiol. 2009;53(2):161-6.

Dorsch MF, Greenwood JP, Priestley C, Somers K, Hague C, Blaxill JM et al. Direct ambulance admission to the cardiac catheterization laboratory significantly reduces door-to-balloon times in primary percutaneous coronary intervention. Am Heart J. 2008;155(6):1054-8.

Drew BJ, Sommargren CE, Schindler DM, Zegre J, Benedict K, Krucoff MW. Novel electrocardiogram configurations and transmission procedures in the prehospital setting: Effect on ischemia and arrhythmia determination. J Electrocardiol. 2006 Oct;39(4 Suppl):S157-60.

Drew BJ, Pelter MM, Lee E, Zegre J, Schindler D, Fleishmann KE. Designing prehospital ECG systems for acute coronary syndromes. Lessons learned from clinical trials involving 12-lead ST-segment monitoring. J Electrocardiol. 2005;38(4 Suppl):180-5.

Drew BJ, Dempsey ED, Joo TH, Sommargren CE, Glancy JP, Benedict K et al. Pre-hospital synthesized 12-lead ECG ischemia monitoring with trans-telephonic transmission in acute coronary syndromes: Pilot study results of the ST SMART trial. J Electrocardiol. 2004;37(Suppl):214-21.

Dubin D. Rapid interpretation of EKG's. 6th ed. Tampa: Cover Publishing, 2000.

Eckstein M, Cooper E, Nguyen T, Pratt FD. Impact of paramedic transport with prehospital 12-lead electrocardiography on door-to-balloon times for patients with ST-segment elevation myocardial infarction. Prehosp Emerg Care. 2009;13(2):203-6.

Elko PP, Weaver WD, Kudenchuk P, Rowlandson I. The dilemma of sensitivity versus specificity in computer-interpreted acute myocardial infarction. J Electrocardiol. 1992;24(Suppl):2-7.

Erling BF, Perron AD, Brady WJ. Disagreement in the interpretation of electrocardiographic ST segment elevation: a source of error for emergency physicians? Am J Emerg Med. 2004;22(2):65-70.

Eskola MJ, Nikus KC, Voipio-Pulkki LM, Huhtala H, Parviainen T, Lund J et al. Comparative accuracy of manual versus computerized electrocardiographic measurement of J-, ST- and T-wave deviations in patients with acute coronary syndrome. Am J Cardiol. 2005;96(11):1584-8.

Feldman MJ, Verbeek PR, Lyons DG, Chad SJ, Craig AM, Schwartz B. Comparison of the medical priority dispatch system to an out-of-hospital patient acuity score. Acad Emerg Med. 2006;13(9):954-60.

Feldman JA, Brinsfield K, Bernard S, White D, Maciejko T. Real-time paramedic compared with blinded physician identification of ST-segment elevation myocardial infarction: results of an observational study. Am J Emerg Med. 2005;23(4):443-8.

Frendl DM, Palmeri ST, Clapp JR Jr, Hampton D, Sejersten M, Young D et al.; Journal of Electrocardiology Prehospital 12-lead ECG Working Group. Overcoming barriers to developing seamless ST-segment elevation myocardial infarction care systems in the United States: recommendations from a comprehensive Prehospital 12-lead Electrocardiogram Working Group. J Electrocardiol. 2009;42(5):426-31.

Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114(7):e257-354.

Garvey JL, MacLeod BA, Sopko G, Hand MM. Pre-hospital 12-lead electrocardiography programs: A call for implementation by emergency medical services systems providing advanced life support--National Heart Attack Alert Program (NHAAP) Coordinating Committee; National Heart, Lung, and Blood Institute (NHLBI); National Institutes of Health. J Am Coll Cardiol. 2006 Feb;47(3):485-91.

GE Medical Systems. 12SL™ statement of validation and accuracy for the physician's guide. Revision A, 23 October 2000. Milwaukee, Wisconsin: GE Medical Systems Information Technologies; 2000.

Gibler WB, Cannon CP, Blomkalns AL, Char DM, Drew BJ, Hollander JE et al.; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Nursing; Quality of Care and Outcomes Research Interdisciplinary Working Group; Society of Chest Pain Centers. Practical implementation of the guidelines for unstable angina/non-ST-segment elevation myocardial infarction in the emergency department. Ann Emerg Med. 2005;46(2):185-97.

Goldman L, Kirtane AJ. Triage of patients with acute chest pain and possible cardiac ischemia : the elusive search for diagnostic perfection. Ann Intern Med. 2003;139(12):987-95.

Gross BW, Dauterman KW, Moran MG, Kotler TS, Schnugg SJ, Rostykus PS et al. An approach to shorten time to infarct artery patency in patients with ST-segment elevation myocardial infarction. Am J Cardiol. 2007;99(10):1360-3.

Gupta M, Tabas JA, Kohn MA. Presenting complaint among patients with myocardial infarction who present to an urban, public hospital emergency department. Ann Emerg Med. 2002;40(2):180-6.

Hahn SA, Chandler C. Diagnosis and management of ST elevation myocardial infarction: A review of the recent literature and practice guidelines. Mt Sinai J Med. 2006;73(1):469-81.

Harris IM. Clinical presentation of acute coronary syndrome: does age make a difference? Implications for emergency nursing. Master's thesis, Wright State University, USA; 2006.

Herlitz J, Starke M, Hansson E, Ringvall E, Karlson BW, Waagstein L. Early identification of patients with an acute coronary syndrome as assessed by dispatchers and the ambulance crew. Am J Emerg Med. 2002 May;20(3):196-201.

Huynh T, O'Loughlin J, Joseph L, Schampaert E, Rinfret S, Afilalo M et al.; AMI-QUEBEC Study Investigators. Delays to reperfusion therapy in acute ST-segment elevation myocardial infarction: results from the AMI-QUEBEC Study. CMAJ. 2006;175(12):1527-32.

Jacobs AK, Antman EM, Faxon DP, Gregory T, Solis P. Development of systems of care for ST-elevation myocardial infarction patients: executive summary. Circulation. 2007;116(2): 217-30.

Johnston S, Brightwell R, Ziman M. Paramedics and pre-hospital management of acute myocardial infarction: Diagnosis and reperfusion. Emerg Med J. 2006;23(5):331-4.

Joseph L, Gyokos T, Coupal L. Bayesian estimation of disease prevalence and the parameters of diagnostic tests in the absence of a gold standard. Am J Epidemiol. 1995;141(3):263-72.

Kordish C, Albinger D, Crouch S, Kerwin P. Cardiac alert: decreasing door-to-balloon time for ST elevation myocardial infarction. J Emerg Nurs. 2008;34(2):116-20.

Kudenchuk PJ, Maynard C, Cobb LA, Wirkus M, Martin JS, Kennedy JW et al. Utility of the prehospital electrocardiogram in diagnosing acute coronary syndromes: The Myocardial Infarction Triage and Intervention (MITI) Project. J Am Coll Cardiol. 1998;32(1):17-27.

Kudenchuk PJ, Ho MT, Weaver WD, Litwin PE, Martin JS, Eisenberg MS et al. Accuracy of computer-interpreted electrocardiography in selecting patients for thrombolytic therapy. MITI Project Investigators. J Am Coll Cardiol. 1991;17(7):1486-91.

Larson DM, Menssen KM, Sharkey SW, Duval S, Schwartz RS, Harris J et al. "False-positive" cardiac catheterization laboratory activation among patients with suspected ST-segment elevation myocardial infarction. JAMA. 2007;298(23):2754-60.

Le May MR, So DY, Dionne R, Glover CA, Froeschl MP, Wells GA et al. A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2008;358(3):231-40.

Le May MR, Davies RF, Dionne R, Maloney J, Trickett J, So D et al. Comparison of early mortality of paramedic-diagnosed ST-segment elevation myocardial infarction with immediate transport to a designated primary percutaneous coronary intervention center to that of similar patients transported to the nearest hospital. Am J Cardiol. 2006;98(10):1329-33.

Massel D. Observer variability in ECG interpretation for thrombolysis eligibility: experience and context matter. J Thromb Thrombolysis. 2003;15(3):131-40.

McLean S, Egan G, Connor P, Flapan AD. Collaborative decision-making between paramedics and CCU nurses based on 12-lead ECG telemetry expedites the delivery of thrombolysis in ST elevation myocardial infarction. Emerg Med J. 2008;25(6):370-4.

McNamara RL, Wang Y, Herrin J, Curtis JP, Bradley EH, Magid DJ et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2006;47(11):2180-6.

Mirvis DM and Goldberger AL. Electrocardiography. In: Libby P, Bonow RO, Mann DL, Zipes DP, Braunwald E, editors. Braunwald's heart disease: a textbook of cardiovascular medicine. 8th ed. Philadelphia, PA: Elsevier Saunders; 2008. p. 149-193.

Morris F, Brady WJ. ABC of clinical electrocardiography: Acute myocardial infarction-Part I. BMJ. 2002;324(7341):831-4.

Morrison LJ, Brooks S, Sawadsky B, McDonald A, Verbeek PR. Prehospital 12-lead electrocardiography impact on acute myocardial infarction treatment times and mortality: A systematic review. Acad Emerg Med. 2006;13(1):84-9.

Moyer P, Ornato JP, Brady WJ Jr, Davis LL, Ghaemmaghami CA, Gibler WB et al. Development of systems of care for ST-elevation myocardial infarction patients: the emergency medical services and emergency department perspective. Circulation. 2007; 116(2):43-8.

Nallamothu B, Fox KA, Kennelly BM, Van de Werf F, Gore JM, Steg PG et al.; GRACE Investigators. Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention. The Global Registry of Acute Coronary Events. Heart. 2007;93(12):1552-5.

NAEMSP (National Association of EMS Physicians). Prehospital management of acute myocardial infarction [position paper]. Prehosp Emerg Care. 2008;12(3):393-394.

Nicoll D and Detmer WM. Basic principles of diagnostic test use and interpretation. Chapter 1 in Tierney LM Jr, McPhee SJ, Papadakis MA (editors): Current Medical Diagnosis & Treatment 1997. Norwalk, Connecticut: Appleton & Lange, 1996.

Pope JH, Aufderheide TP, Rothazer R, Woolard RH, Feldman JA, Beshansky JR et al. Missed diagnoses of acute cardiac ischemia in the emergency department. NEJM. 2000;342(16):1163-70.

Provo TA and Frascone RJ. 12-lead electrocardiograms during basic life support care. Prehosp Emerg Care. 2004;8(2):212-16.

Ransohoff DF and Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. NEJM. 1978;299(17):926-30.

RQCT. *Le développement de l'hémodynamie au Québec: Rapport du comité d'experts en hémodynamie du Réseau québécois de cardiologie tertiaire (RQCT)*: *Gouvernement du Québec;* 2005.

Schull MJ, Vaillancourt S, Donovan L, Boothroyd LJ, Andrusiek D, Trickett J et al. and the Canadian Cardiovascular Outcomes Research Team. Underuse of prehospital

strategies to reduce time to reperfusion for ST-elevation myocardial infarction patients in 5 Canadian provinces. CJEM. 2009;11(5):473-80.

Schull MJ, Vermeulen MJ, Stukel TA. The risk of missed diagnosis of acute myocardial infarction associated with emergency department volume. Ann Emerg Med. 2006;48(6):647-55.

Sejersten M, Sillesen M, Hansen PR, Nielsen SL, Nielsen H, Trautner S et al. Effect on treatment delay of prehospital teletransmission of 12-lead electrocardiogram to a cardiologist for immediate triage and direct referral of patients with ST-segment elevation acute myocardial infarction to primary percutaneous coronary intervention. Am J Cardiol. 2008;101(7):941-6.

Sejersten M, Young D, Clemmensen P, Lipton J, VerSteeg D, Wall T et al. Comparison of the ability of paramedics with that of cardiologists in diagnosing ST-segment elevation acute myocardial infarction in patients with acute chest pain. Am J Cardiol. 2002;90(9):995-8.

Sekulic M, Hassunizadeh B, McGraw S, David S. Feasibility of early emergency room notification to improve door-to-balloon times for patients with acute ST segment elevation myocardial infarction. Catheter Cardiovasc Interv 2005;66(3):316-9.

Sillesen M, Sejersten M, Strange S, Nielsen SL, Lippert F, Clemmensen P. Referral of patients with ST-segment elevation acute myocardial infarction directly to the catheterization suite based on prehospital teletransmission of 12-lead electrocardiogram. J Electrocardiol. 2008;41(1):49-53.

Sivagangabalan G, Ong AT, Narayan A, Sadick N, Hansen PS, Nelson GC et al. Effect of prehospital triage on revascularization times, left ventricular function, and survival in patients with ST-elevation myocardial infarction. Am J Cardiol. 2009;103(7):907-12.

Strauss DG, Sprague PQ, Underhill K, Maynard C, Adams GL, Kessenich A et al. Paramedic transtelephonic communication to cardiologist of clinical and electrocardiographic assessment for rapid reperfusion of ST-elevation myocardial infarction. J Electrocardiol. 2007;40(3):265-70.

Swan PY, Nighswonger B, Boswell GL, Stratton SJ. Factors associated with false-positive emergency medical services triage for percutaneous coronary intervention. West J Emerg Med. 2009;10(4):208-12.

Swor R, Hegerberg S, McHugh-McNally A, Goldstein M, McEachin CC. Prehospital 12-lead ECG: efficacy or effectiveness? Prehosp Emerg Care 2006;10(3):374-7.

Swor R, Anderson W, Jackson R, Wilson A. Effects of EMS transportation on time to diagnosis and treatment of acute myocardial infarction in the emergency department. Prehosp Disaster Med 1994;9(3):160-4.

Terkelsen CJ, Lassen JF, Norgaard BL, Gerdes JC, Poulsen SH, Bendix K et al. Reduction of treatment delay in patients with ST-elevation myocardial infarction: impact of pre-hospital diagnosis and direct referral to primary percutanous coronary intervention. Eur Heart J 2005;26(8):770-7.

Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173-95.

Ting HH, Krumholz HM, Bradley EH, Cone DC, Curtis JP, Drew BJ et al. Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: a scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. Circulation. 2008;118(10):1066-79.

Turnipseed SD, Amsterdam EA, Laurin EG, Lichty LL, Miles PH, Diercks DB. Frequency of non-ST-segment elevation injury patterns on prehospital electrocardiograms. Prehosp Emerg Care. 2010;14(1):1-5.

Urgences-santé. Rapport annuel 2006-2007. Montreal: *Corporation d'Urgences-santé;* 2007.

Vaught C, Young DR, Bell SJ, Maynard C, Gentry M, Jacubowitz S et al. The failure of years of experience with electrocardiographic transmission from paramedics to the hospital emergency department to reduce the delay from door to primary coronary intervention below the 90-minute threshold during acute myocardial infarction. J Electrocardiol 2006;39(2):136-41.

Williams DM. 2006 JEMS 200-city survey: EMS from all angles. JEMS. 2007;32(2):38-54.

Youngquist ST, Kaji AH, Lipsky AM, Koenig WJ, Niemann JT. A Bayesian sensitivity analysis of out-of-hospital 12-lead electrocardiograms: implications for regionalization of cardiac care. Acad Emerg Med. 2007;14(12):1165-71.

Zanini R, Aroldi M, Bonatti S, Buffoli F, Izzo A, Lettieri C et al. Impact of prehospital diagnosis in the management of ST elevation myocardial infarction in the era of primary percutaneous coronary intervention: reduction of treatment delay and mortality. J Cardiovasc Med (Hagerstown). 2008;9(6):570-5.