uOttawa

L'Université canadienne
Canada's university

FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTOCTORALES

uOttawa

L'Université canadienne
Canada's university

FACULTY OF GRADUATE AND POSDOCTORAL STUDIES

Erik Hess

AUTEUR DE LA THÈSE / AUTHOR OF THESIS

M.Sc. (Epidemiology)

GRADE / DEGREE

Department of Epidemiology and Community Medicine

FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

A Study to Derive a Preliminary Clinical Decision Rule for Investigation of Patients Suspected of Having Acute Coronary Syndrome

TITRE DE LA THÈSE / TITLE OF THESIS

Ian Stiell

DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

George Wells

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS

Alan Forster

Dean Fergusson

Gary W. Slater

Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

A Study to Derive a Preliminary Clinical Decision Rule for Investigation of Patients Suspected of Having Acute Coronary Syndrome

By

Dr. Erik Paul Hess

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirements for the MSc degree in Epidemiology

Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa

Date Final Revisions Submitted: November 25, 2008

Your file Votre référence
ISBN: 978-0-494-48635-1
Our file Notre référence
ISBN: 978-0-494-48635-1

ABSTRACT

Objective: We derive a preliminary clinical decision rule to identify which patients with chest pain can be safely discharged without cardiac stress testing.

Methods: We prospectively enrolled patients over 24 years of age with chest pain. The primary outcome was acute myocardial infarction, revascularization, or 30-day mortality.

Results: We enrolled 640 patients. Characteristics were: mean age 59.6 years, 40.2% female and 21.9% history of acute myocardial infarction. There were 87 positive outcomes. We derived a rule which consisted of 5 variables: known coronary artery disease, age $\geq$ 55 years, acute ischemic changes on electrocardiogram, cardiac troponin T $\geq$ 0.01 ng/mL, and diaphoresis. The rule was 100% (95% CI 96-100%) sensitive and 25% (22-25%) specific for adverse cardiac events.

Conclusion: We derived a preliminary decision rule that is highly sensitive for adverse cardiac events. Additional research is required to derive a definitive decision rule.

Acknowledgements:

There are many who contributed to this thesis project who I would like to acknowledge. Dr. Ian Stiell, my thesis supervisor, made the study possible, took me on as a research fellow from the US, assisted with immigration and obtaining funding, and provided all the support needed to develop my career as a young investigator. Dr. George Wells, my thesis co-supervisor, provided professional and personal guidance, assisted with the methodological design, statistical analysis plan and conduct of the study, and constantly made himself available as a sounding board throughout the project. Dr. Jeff Perry assisted with trouble-shooting the project as it was conducted, supported the project, and provided constructive feedback throughout the study and thesis writing process. Dr. Allan Jaffe, a cardiologist at my home institution, the Mayo Clinic, provided valuable feedback and content expertise in study design. Pam Ladouceur, our study nurse coordinator, worked tirelessly to carry the study out and bring it to completion, constantly going above and beyond the call of duty to achieve our goals. I am also deeply grateful for the unwavering support of my wife, Dr. Jennifer Hess, who immigrated to Canada with our children to make this next step in my development as a career investigator possible. She made the journey a joy and supported me through the long hours needed to complete the thesis. Finally, I would most like to acknowledge God, who gave me the talent and passion needed to complete the process and sustains me in ways more significant than I comprehend.

Table of Contents

List of Tables

List of Figures and Illustrations

List of Appendices

CHAPTER 1: BACKGROUND AND REVIEW OF THE LITERATURE

Patients with acute chest pain often undergo extensive diagnostic testing and risk stratification to detect acute coronary syndrome and determine the likelihood of future adverse cardiac events. Chest pain can be either cardiac or noncardiac in etiology and represents a continuum of risk from benign self-limiting conditions to life-threatening illness requiring rapid diagnosis and treatment. Currently it is not well established which patients require additional investigation. The goal of this thesis is to derive a preliminary clinical decision rule that is highly sensitive for predicting adverse cardiac events within 30 days of the emergency department visit.

1.1 Introduction to Acute Coronary Syndromes

1.1.1 Pathophysiology of Acute Coronary Syndromes

Understanding the pathophysiology of acute coronary syndromes facilitates the differentiation of each of its subtypes as defined in section 1.1.2. The current paradigm emphasizes the gradual buildup of fatty deposits, or plaque, within the walls of coronary arteries followed by plaque destabilization and rupture. Over 3-5 decades, cholesterol-laden plaque is deposited in arterial vessel walls. The arterial wall initially remodels outwardly, with little impairment of blood flow. When this adaptive mechanism is exhausted, the plaque protrudes into the lumen, causing restriction of blood flow under conditions of increased demand. This results in cardiac ischemia, an absolute or relative shortage of blood supply to cardiac muscle cells (myocytes). The classic risk factors for coronary artery disease (e.g., hypertension, smoking, hyperlipidemia, diabetes mellitus, and family history) subsequently contribute to activation of endothelial intranuclear transducing pathways, endothelial dysfunction, and vascular inflammation. A complex

interplay of inflammatory mediators leads to activation of macrophages which breakdown structural components of the plaque. This renders the plaque unstable and vulnerable to rupture. Rupture of an unstable plaque disrupts the local balance of thrombosis and endogenous fibrinolysis, leading to platelet activation and aggregation, thrombus formation and, ultimately, acute cardiac ischemia.[1,2] Acute cardiac ischemia can manifest as characteristic clinical symptoms, changes on the surface electrocardiogram (ECG, a graphic representation of the electrical activity of the heart over time), and/or abnormalities on biochemical tests or imaging.

1.1.2 Definition of Acute Coronary Syndromes

Acute coronary syndrome is an umbrella term that encompasses unstable angina (UA) and two types of myocardial infarction classified on the basis of the surface ECG – non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). Unstable angina denotes cardiac ischemia without biochemical evidence of cardiac myocyte death, with or without new ST-segment depression or T-wave inversions on the surface ECG.[3] STEMI indicates death of cardiac myocytes accompanied by ST-segment elevation on the ECG, and NSTEMI indicates biochemical evidence of cardiac myocyte death without ST-segment elevation.

1.1.3 Epidemiology of Acute Coronary Syndromes

For many years cardiovascular disease has been the leading cause of death in Canada. According to recent data from Statistics Canada (2004), 72,338 deaths annually were due to major cardiovascular diseases, accounting for over one-third of the total. Of these, 39,311 were due to ischemic heart disease, with the subset acute myocardial infarction accounting for 18,125 deaths.[4]

Data from the 2005 National Hospital Ambulatory Medical Care Survey identify chest pain as the second most common chief complaint in North American Emergency Departments, accounting for 6 million (5.0%) patient visits.[5] Approximately 565,000 patients are ultimately diagnosed with acute myocardial infarction, and nearly twice as many are diagnosed with unstable angina pectoris.[6-8] Similar Canadian statistics on emergency department visits are scarce.

1.1.4 Presentation of Acute Coronary Syndromes

Acute coronary syndrome classically presents with substernal or left anterior chest pain, often radiating to the arm or jaw. The pain is usually described as a pressure or squeezing sensation that is exacerbated by exertion and unaffected by body position or movement of the muscles in the affected region. It is often associated with symptoms of nausea or vomiting, shortness of breath, and/or diaphoresis. The discomfort is not typically exacerbated by palpation of the affected region. Physical examination may reveal abnormal heart sounds, indicative of systolic or diastolic cardiac dysfunction, or a heart murmur. Auscultation of the lungs may reveal wheezing or rales, signs of pulmonary edema from heart failure.

Although patients often manifest symptoms like those described above, acute coronary syndrome can present in a variety of ways, adding to the challenge of diagnosis. The pain can come on at rest or with exertion. It often has resolved prior to emergency department arrival, and can recur during the evaluation. The discomfort can develop anywhere on the chest, or it can be located solely in the epigastrium, neck, jaw, arm, or back. It may be experienced as a burning sensation or feeling of indigestion. Patients often have difficulty clearly describing the discomfort, and it may not radiate to another

body region. Symptoms such as nausea, vomiting, shortness of breath, and diaphoresis may be absent, and the physical examination is often normal. Acute coronary syndrome can also occur without clinical symptoms, the diagnosis being evident only on the electrocardiogram, biochemical tests, or other studies.[9,10]

Patients with coronary artery disease can present with stable or unstable angina. Stable angina is characterized by chest pain that occurs in a predictable pattern, is brought on at approximately the same level of physical exertion or emotional stress, and is relieved by rest or rescue medications. New or unexpected chest pain that develops at lower levels of exertion or persists despite rescue medications is characteristic of unstable angina, a condition associated with a higher risk of adverse cardiac events.

1.1.5 Prognosis of Acute Coronary Syndromes

Patients who present with symptoms suggestive of acute coronary syndrome represent a wide spectrum of risk. Unfortunately, data stratifying prognosis according to acute coronary syndrome subtype are scarce. Rather, prognosis for patients with suspected acute coronary syndrome can be determined using a risk stratification model, with subsequent treatment tailored to individual patient risk.

Current guidelines recommend risk stratification of patients with acute coronary syndrome using any one of three risk stratification models – the Thrombolysis in Myocardial Infarction (TIMI) risk score, the Global Registry of Acute Coronary Events (GRACE) risk score, or the Platelet Glycoprotein IIb/IIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) risk score.[11]

Antman et al. derived and validated the TIMI risk score retrospectively from the databases of two phase III international clinical trials.[12] Using multivariable logistic

regression, the investigators identified seven independent predictors of the composite outcome acute myocardial, revascularization, or death within 30-days. These predictors can be summed to classify patients into risk strata, stratifying risk of 30-day adverse outcome from 4.7%-40.9%. Granger et al. derived the GRACE risk score from 11,389 patients enrolled in an international acute coronary syndromes registry and validated the score both internally on 3,972 registry patients and externally from the database of a large international clinical trial (GUSTO IIb).[13] These investigators identified 8 independent risk factors for in-hospital mortality that can be summed to provide an overall score, stratifying a patient's risk for in-hospital mortality from < 0.2%-44%. Finally, Boersma et al. derived the PURSUIT score from 9,461 patients enrolled in the PURSUIT trial and validated the model internally using bootstrapping techniques.[14] These investigators identified 7 independent predictors of 30-day mortality and 30-day mortality or acute myocardial infarction using multivariable logistic regression, stratifying a patient's risk from 0.6%-8.9% for 30-day mortality and 8.2%-24.1% for 30-day mortality or acute myocardial infarction. After stratifying a patient's risk using one of these 3 models, subsequent treatment can be tailored to coincide with risk level.

1.1.6 Investigation of Acute Coronary Syndromes

A clinical suspicion of acute myocardial infarction can be confirmed by any one of the following: 1) serial cardiac troponin levels exceeding the 99th percentile of a reference control group[15] with a rising or falling pattern (defined as a 20% relative change[16,17]), 2) development ST segment elevation in two or more contiguous leads (STEMI) or pathological Q-waves on the ECG, 3) coronary artery intervention (e.g., angioplasty or coronary artery bypass grafting) accompanied by elevations in cardiac

biomarkers above the 99th percentile of a reference control group (at least three times the 99th percentile for angioplasty and five times the 99th percentile for coronary artery bypass grafting)[18], or 4) histologic evidence of myocardial cell death on post-mortem examination. The diagnosis of UA can be confirmed in the setting of new or changing cardiac symptoms with serial cardiac troponin levels below the 99th percentile and any one of the following: 1) new or presumed new ST segment depression or T-wave inversions in two or more contiguous leads on the ECG or 2) new perfusion defects or wall motion abnormalities on cardiac stress testing.[3]

1.1.7 Treatment of Acute Coronary Syndromes

Acute coronary syndrome is a medical emergency that often requires urgent intervention. Patients who develop acute chest pain suggestive of cardiac ischemia should immediately receive supplemental oxygen, aspirin, nitroglycerin, and morphine if needed to relieve chest pain. Emergency medical service providers often administer many of these treatments prior to emergency department arrival, depending on local treatment protocols.

The need for additional emergency treatment is dictated by risk stratification using the initial 12-lead electrocardiogram. Patients with **STEMI** should receive antiplatelet therapy with clopidogrel, anticoagulation with heparin, and a glycoprotein IIb/IIa inhibitor as indicated. If the symptoms have been present for $\leq$ 12 hours, immediate reestablishment of myocardial perfusion is indicated. This can be done with percutaneous coronary intervention (PCI) or with fibrinolytic agents, procedures that reestablish coronary flow mechanically by use of percutaneously inserted arterial catheters or biochemically by administration of medications that lyse clots. If the

symptoms have been present for >12 hours, hospital admission to a monitored bed with additional risk stratification by a cardiologist and consideration for early PCI is indicated.

Patients with ST segment depression or dynamic T-wave inversion on the ECG are at high risk for UA and **NSTEMI** and should receive nitroglycerin, antiplatelet therapy with clopidogrel and a glycoprotein IIb/IIa inhibitor, and anticoagulation with heparin as indicated. This should be followed by hospital admission, additional risk stratification by a cardiologist, and consideration for early PCI. After hospital admission and stabilization, patients with STEMI, NSTEMI, or UA should receive additional treatment with an angiotensin converting enzyme inhibitor and an HMG CoA reductase inhibitor (statin) as indicated, medications that facilitate myocardial remodeling and lower cholesterol, respectively.

Patients with normal or nondiagnostic ST segment or T-wave changes on ECG are at intermediate or low risk for **UA** or NSTEMI. If the cardiac troponin is positive, they should be considered as having a NSTEMI and be treated as such. If the cardiac troponin is negative, they should undergo additional diagnostic investigation and risk stratification in an emergency department chest pain observation unit,[11] in the hospital or on an outpatient basis.

1.2 Statement of the Problem in the Emergency Department

Chest pain is a diagnostic dilemma for the emergency physician. Data from a recent Canadian study suggest that 4.6% of patients with acute myocardial infarction and 6.4% of patients with UA are misdiagnosed in the emergency department,[19] with lower rates reported in the United States (2.1% and 2.3%, respectively).[20] The differences in the rate of misdiagnosis of acute coronary syndrome between countries may be due to

different clinical practice patterns. Many emergency departments in the U.S. have chest pain observation units in which patients at low risk for acute coronary syndrome routinely undergo prolonged observation, serial cardiac enzyme testing, and early cardiac stress testing. Although this approach may decrease the rate of missed diagnosis, it is cost intensive and has not been broadly adopted in Canada.[19] In Canada few emergency department-based observation units exist, and immediate access to cardiac stress testing is uncommon. Most patients at low risk for acute coronary syndrome are evaluated on an individualized basis, and cardiac stress testing, if obtained, occurs in the outpatient setting. Patients at low risk for acute coronary syndrome are often discharged from the emergency department with outpatient subspecialty referral to cardiology, at which time cardiac stress testing is obtained.

Current practice guidelines provide little guidance in resolving this issue. Neither the 2007 American College of Cardiology/American Heart Association (AHA) guidelines for the management of patients with UA/NSTEMI nor the practical implementation of the AHA guidelines for the emergency department proposed by Gibler et. al. identify a group of patients at very low risk for acute coronary syndrome who can be safely discharged without cardiac stress testing.[11,21,22] As a result, many patients at very low risk for acute coronary syndrome undergo prolonged emergency department observation and cardiac stress testing based on an unstructured assessment of pretest probability and perceived legal risk.[23] High sensitivity is ensured at the expense of specificity, with increased likelihood of false positive cardiac stress testing and significant cost to the healthcare system.

Given that chest pain is the second most common chief complaint in North American emergency departments, the resource implications of diagnostic investigation for patients with possible acute coronary syndrome are substantial. Overcrowding, a situation where the demand for emergency services exceeds the ability to provide care in a reasonable amount of time, was cited as a major or severe problem by 62% of Canadian emergency department directors in a recent survey conducted by the Canadian Agency for Drugs and Technology in Health (CADTH).[24] Overcrowding is a problem in the U.S. as well; 91% of emergency department directors cited it as a problem in a survey conducted in all 50 U.S. states.[25] Correctly identifying high risk patients for whom additional investigation is indicated and low risk patients who can be safely discharged for further outpatient evaluation is a dilemma commonly faced by practicing emergency physicians. There is a clear need for valid and reliable guidelines to allow physicians to be more selective in their ordering of diagnostic tests and triage of patients to chest pain units without jeopardizing the quality of patient care.

1.3 Emergency Physicians' Recognition of a Need for a Decision Rule

In a recent international survey of emergency physicians, the need for a clinical decision rule on anterior chest pain was recognized as the fourth most commonly requested clinical guideline overall.[26] Moreover, a recent survey of Canadian emergency physicians indicated that most (94%) would use a clinical prediction rule for acute coronary syndrome provided it did not increase the miss rate above 2%.[27]

1.4 Review of Ottawa Hospital Database

To determine if an adequate number of patients were available for recruitment into our study, we reviewed an Ottawa Hospital clinical database of emergency

department visits. At The Ottawa Hospital Civic emergency department, 3,611 patients received diagnoses of chest pain, acute myocardial infarction, or angina pectoris in 2006. Five hundred sixty-two (15.6%) were admitted to the hospital. One hundred eighty-three (5.1%) received a diagnosis of acute myocardial infarction and 462 (12.8%) angina pectoris. Of those diagnosed with angina pectoris, 260 (56.3%) were classified as unstable. At The Ottawa Hospital General emergency department, 2,504 patients received diagnoses of chest pain, acute myocardial infarction, or angina pectoris in 2006. Three hundred fifty (14.0%) were admitted to the hospital. One hundred nine (4.4%) received a diagnosis of acute myocardial infarction and 305 (12.2%) angina pectoris. Of those diagnosed with angina pectoris, 154 (50.5%) were classified as unstable. Further specification of acute myocardial infarction cases into STEMI and NSTEMI was not possible given International Classification of Disease coding standards in 2006.

Clinical decision (or prediction) rules are clinical tools designed to reduce the uncertainty of medical decision making by standardizing the collection and interpretation of clinical data.[28] They are derived from original research and incorporate variables from the history, physical examination, and basic laboratory tests.[29] Prior decision rules developed by The Ottawa Hospital emergency department clinical epidemiology program have guided physicians in appropriately selecting patients for whom the ordering of ankle x-rays to detect ankle fractures or head computed tomography to detect traumatic intracranial injury is both medically indicated and cost-effective. The current study seeks to derive a preliminary rule to detect adverse cardiac events in patients with possible acute coronary syndrome, and data obtained by reviewing an Ottawa Hospital clinical

database suggest that such a rule would have broad applicability and potentially impact the care of a substantial number of patients in our practice setting.

1.5 Methodological Standards for Clinical Decision Rules

Concomitant with the reporting of various decision rules has been an interest in the methodological standards for their development and validation.[29,30] These standards may be summarized as follows:

1. The **outcome** or **diagnosis** to be predicted must be clearly defined and the assessment of this outcome should be made in a blinded fashion.

2. The clinical findings to be used as **predictors** must be clearly defined and standardized and their assessment must be done without knowledge of the outcome.

3. The **reliability** or reproducibility of the clinical findings used as predictors must be demonstrated.

4. The **subjects** in the study should be selected without bias and should represent a wide spectrum of clinical and demographic characteristics to increase the generalizability of the results.

5. The **mathematical techniques** for deriving the rules must be identified.

6. Clinical decision rules should be **sensible**: have a clear purpose, be relevant, demonstrate content validity, be concise, and be easy to use in the intended clinical application.

7. The **accuracy** of the decision rule in classifying patients with (sensitivity) and without (specificity) the targeted outcome should be demonstrated.

8. **Prospective validation** on a new set of patients is an essential test of accuracy because misclassification is commonly higher when decision rules are tested on a population other than the original derivation set.

9. **Implementation** to demonstrate the true effect on patient care is the ultimate test of a decision rule; the impact on clinical practice can be assessed at this stage.

1.6 Review of Previous Studies

1.6.1 Rationale for selection of combination protocols

A recent systematic review of studies evaluating the diagnostic utility of the chest pain history reported the positive and negative likelihood ratios of chest pain characteristics, with likelihood ratios ranging from 0.2 to 4.7.[9] Given the limited magnitude of the likelihood ratios for individual components of the chest pain history, no individual historical characteristic is strong enough to enable safe discharge of emergency department patients without additional diagnostic testing. Combination protocols, decision tools that incorporate combinations of components of the chest pain history with other information initially available to the clinician, have the greatest potential for guiding physician decision-making.[9] Clinical decision (prediction) rules are a specific type of combination protocol. Using an established methodology,[29] they use original data obtained from the history, physical examination, and basic laboratory tests to create a concise algorithm with a very high sensitivity and the highest possible specificity. The discussion below reviews all combination protocols potentially relevant to the current investigation, including studies variably indexed as clinical prediction rules, clinical decision rules, risk scores, algorithms, prediction guides, or risk stratification tools.

1.6.2 Methodological assessment of combination protocols

Currently, there is no decision rule that is widely used in Canadian and U.S. emergency departments. Although a number of studies have been published that risk stratify patients who present to the emergency department with chest pain, none that directly address the clinical question at hand could be considered methodologically robust according to the criteria described in section 1.5.[31] Some of the methodological deficiencies will be described in the following paragraphs.

The specific **outcome** measures varied considerably among the studies, consisting of acute myocardial infarction alone,[32-44] acute myocardial infarction and unstable angina,[45-49] acute myocardial infarction and death,[50-52] all-cause mortality, acute myocardial infarction, and need for revascularization,[12,14,53-61] and similar composite outcomes with slight variations.[31,62-74] Most studies did not report assessing the outcome without knowledge of the predictor variables.

Fourteen studies reported assessing the **predictor** variables in a standardized fashion with a data collection sheet specifically designed for a prediction rule study.[31,34,35,37,38,43,45,46,58,61,67-70] However, only four explicitly reported collecting the predictor variables without knowledge of the outcome.[31,61,67,68]

Only one study assessed the **reliability** of the clinical findings to be used as predictors in the rule.[31] However, this study did not report specific kappa values for the predictor variables considered for inclusion in the rule.

The definition of **subjects** in previous studies has been extremely variable making it difficult for physicians to interpret and apply the findings to their own patients. Several studies did not specify age criteria for enrolment.[12,14,35,39-43,45,47,51,52,55,56,59,61,63,66,67,69,71]

Among those that did specify age criteria, different criteria were used: over the age of 18,[33,34,46,50,65,70,74] over the age of 20,[54,57] over the age of 24,[36,58,60] over the age of 25,[31,37,38,64] over the age of 30,[44,48,53,62,72] between 20 and 80 years of age,[73] and between 24 and 39 years of age.[68,75] In some studies all patients with a primary complaint of chest pain were eligible for enrolment,[31,33,34,36-41,43-46,54,55,57,59,64,65] whereas others required additional or different eligibility criteria.[12,14,35,36,42,47,48,50-53,56,58,60-63,65-74,76] Exclusion criteria varied greatly among the studies as well.

The **mathematical techniques** were described in all of the studies except one.[43] Several studies developed prediction rules that lacked clinical **sensibility** and were not easily used in the intended clinical application.[33-43,45,46,48,61,63,70,72,73] Twenty-four studies reported the **accuracy** of the decision rule in terms of sensitivity and specificity in diagnosing the predicted outcome.[31,33-42,44-47,56,59-61,65,70,71,73,76]

Twelve prediction rules have been **prospectively validated** on a different set of patients from which the rule was derived.[33,34,37,38,46,49,53,64,66,68,72,76] None of these have consistently performed with sensitivities of $\geq 98\%$.[27] Only three prediction rules have been **implemented** to demonstrate their true effect on patient care.[37,48,67] The clinical decision rule developed by Goldman et al.[37] had a sensitivity of 88% documented in the implementation phase, and the outcome was limited to acute myocardial infarction. Sensitivities as low as 62% have been reported for the decision rule by Selker et al.[48] Finally, the decision rule developed by Reilly et al.[67] addressed the decision of whether to admit emergency department patients with chest pain to the hospital ward or intensive care unit, not whether to discharge a patient home or arrange additional observation and diagnostic testing.

1.6.3 Summary of Previous Studies

Figures 1-4 summarize combination protocols that assess risk for adverse cardiac events, divided into groups based on the hierarchy of evidence for clinical prediction rules.[28] Figure 1 summarizes studies that have been derived only (level 4). Figures 2-4 summarize studies that have been validated in only one narrow prospective sample (level 3), those that have been validated broadly in multiple clinical settings (level 2), and those that have undergone impact analysis (level 1), respectively. Studies that have undergone impact analysis are considered to be the highest level of evidence because they demonstrate that uptake of the rule can both change clinician behavior and improve patient outcomes.

Studies describing performance of emergency department chest pain algorithms or observation units that did not explicitly identify variables to include in a prediction model were not reviewed. Also, studies incorporating results of cardiac stress testing, coronary multidetector computed tomography (CT), or coronary angiography into the prediction model were not reviewed, as these tests are costly, not readily available in all clinical settings, and are common reference standards of diagnosis.

1.7 Potential Predictor Variables Identified from Literature Review

We conducted a rigorous literature review to identify predictor variables to prospectively collect in the current investigation. Section 1.7 summarizes the results of our search.

1.7.1 Risk Factors associated with Acute Coronary Syndrome

Several independent risk factors associated with acute coronary syndrome have been identified in the literature. A recent study analyzed the association between several

variables immediately available at emergency department presentation and acute coronary syndrome using multivariate techniques.[47] These investigators identified eight variables outside of the ECG as independent predictors of acute coronary syndrome: age, chest discomfort at presentation, symptom duration, and history of hypertension, angina pectoris, acute myocardial infarction, congestive heart failure, or coronary revascularization. Three other studies in emergency department patients reported the association between patient characteristics and acute coronary syndrome or myocardial infarction and 30-day mortality using multivariable logistic regression.[14,77,78] These variables are summarized in Figure 5.

1.7.2 Variables from the History of the Present illness

Certain variables from the history of the present illness have been identified as independent predictors of acute coronary syndrome. Patients with unstable angina or acute myocardial infarction often present with typical symptoms such as substernal chest pressure radiating to the left arm with associated symptoms such as nausea, vomiting, and diaphoresis. For a patient with typical symptoms and appropriate demographic characteristics and risk factors, diagnostic investigation will be appropriately extensive in all cases. However, patients often present with a combination of typical and atypical symptoms, may have difficulty describing their symptoms, or have symptoms suggestive of acute coronary syndrome and few risk factors. The pre-test probability of acute coronary syndrome is more difficult to quantify in patients who present in this fashion, and the extensiveness of diagnostic investigation often varies between clinicians and practice locales.

Swap et al. conducted a systematic review to identify the elements of the history that would be most useful to the clinician in identifying acute coronary syndrome in patients with chest pain .[9] These investigators conducted a Medline search from 1970 to 2005 to identify all potentially relevant articles using several keywords and medical subject heading terms for acute coronary syndrome and the medical history. Data from retrospective and prospective studies as well as systematic reviews were included. They identified several variables of potential diagnostic utility (Figure 6).

1.7.3 Variables from the Physical Examination

Few variables from the physical examination are diagnostically useful to identify acute coronary syndrome. Patients may have a cardiac murmur detected on auscultation of the heart, a decrease in systolic blood pressure, or crackles on pulmonary auscultation suggestive of congestive heart failure due to acute myocardial infarction. Chest pain due to noncardiac causes may be reproduced upon palpation of the chest. A systematic review by Panju et al. quantified the diagnostic utility of these variables (Figure 7).[79]

1.7.4 Variables from Diagnostic Tests

Several diagnostic tests are routinely obtained when evaluating patients with chest pain, including chest x-ray, hematology, and biochemical tests. Although occasionally helpful, results of these tests are not specific for acute coronary syndrome. The diagnostic tests of greatest utility in the diagnosis of acute coronary syndrome in the emergency setting are the ECG and cardiac troponin. Several findings on the ECG may indicate acute cardiac ischemia, including ST-segment elevation or depression, T-wave inversions and bundle branch blocks (Figures 10-12).[18]

When acute cardiac ischemia results in death of cardiac myocytes, several proteins are released into the circulation, including cardiac troponin, creatine kinase, and lactate dehydrogenase, among others. Cardiac troponin is the preferred marker for myocardial necrosis as it has high clinical sensitivity as well as nearly absolute myocardial tissue specificity.[80] After onset of acute cardiac ischemia and death of cardiac myocytes, cardiac troponin elevations can be detected as early as 2-4 hours after the onset of symptoms and remain elevated for 7-14 days.[81]

An elevated cardiac troponin is defined as a measurement exceeding the 99th percentile of a normal reference population.[18,82] Optimal precision is defined as the lowest concentration at which 10% imprecision is achieved (10% coefficient of variation).[83] Low level elevations of cardiac troponin can occur in the absence of overt cardiac ischemia. Conditions such as chronic renal failure, sepsis, and pulmonary embolism have been associated with such low level elevations. Because of this, detecting a rise or fall in cardiac troponin in the appropriate clinical setting is essential for accurate diagnosis of acute myocardial infarction.[17]

The cardiac biomarker used at The Ottawa Hospital is cardiac troponin T (Elecsys Troponin T, Roche Diagnostics, Indianapolis, Indiana). The 99th percentile of the reference range is < 0.01 ng/mL, and the 10% coefficient of variation is 0.03 ng/mL.

1.8 Current Investigations for Suspected Acute Coronary Syndrome

Initial evaluation of emergency department patients with suspected acute coronary syndrome is relatively uniform in Canada and the United States. One or more ECG's are obtained to detect acute cardiac ischemia, followed by serum cardiac troponin. If the ECG shows ST-segment elevation, the patient is classified as having a STEMI.

Treatment is rapidly initiated and emergency PCI is performed. If the ECG is nondiagnostic and cardiac troponin elevated, the patient is classified as having a NSTEMI, emergency treatments are administered, and the patient is admitted to the hospital for consideration of early PCI. If the initial ECG shows ST-segment depression and cardiac troponin levels are normal, the patient is considered to have UA. Treatments are administered as appropriate, and the patient admitted to the hospital. In patients with normal or nondiagnostic electrocardiograms and normal cardiac troponin levels, further diagnostic options include cardiac stress testing, computed tomography coronary angiography, invasive coronary angiography or discharge from the emergency department with close follow-up with a cardiologist or general practitioner.

In the U.S., many emergency departments have dedicated observation units in which patients with normal or non-diagnostic ECG's and normal cardiac troponin levels can undergo observation and cardiac stress testing. In Canada and other countries, however, observation units and immediate access to cardiac stress testing are relatively uncommon. As a result, disposition decisions for this group of patients consist of either discharge home or admission to hospital rather than admission to an emergency department observation unit. Figure 13 illustrates the diagnostic pathways commonly followed in the U.S. and Canada.

1.9 Use of Cardiac Stress Testing

1.9.1 Overview

In patients at low to moderate risk for acute coronary syndrome, stress testing is performed to more precisely assess risk for future ischemic events. Stress testing is based on the rationale that cardiac physiology and function under conditions of stress determine

risk better than knowledge of coronary anatomy alone. Diagnostic options for stress testing at The Ottawa Hospital consist of noninvasive stress ECG testing or stress myocardial perfusion imaging utilizing a radionuclide tracer to assess myocardial perfusion and function.

1.9.2 Treadmill Electrocardiogram Stress Testing

During a treadmill ECG stress test, a patient's heartbeat is monitored at rest and during exercise with ECG electrodes. The degree of ST-segment deviation during exercise, exercise duration, and occurrence of angina are recorded and incorporated into an index called the Duke treadmill score.[84] Depending on the score, patients are stratified into low, intermediate, or high risk for adverse cardiac events. In a long-term follow-up study by Shaw et al., the 5-year mortality rates for patients with low, intermediate, and high risk Duke treadmill scores were 3.1%, 9.5% and 35%, respectively.[85]

1.9.3 Disadvantages of Treadmill Electrocardiogram Stress Testing

First, a substantial number of patients who undergo treadmill ECG stress tests fall into the intermediate risk group. In the study by Shaw et al., 55% of patients had intermediate risk Duke treadmill scores. In addition, ST-segment depression on ECG correlates poorly with findings on myocardial perfusion imaging or coronary angiography. Several patients who undergo exercise ECG testing have an uninterpretable exercise ECG response. Finally, false-positive results are obtained in a substantial proportion of patients. In a study of 251 patients referred for evaluation of chest pain by Sketch et al., false-positive results were observed in 8% of men and 67% of women.[86]

1.9.4 Myocardial Perfusion Imaging

In myocardial perfusion imaging a radiotracer is injected intravenously and preferentially extracted by viable cardiac myocytes. Photons are emitted from the myocardium in proportion to the magnitude of tracer uptake, indicating adequacy of myocardial perfusion and enabling assessment of cardiac function. Gamma ray photons are emitted, captured by a gamma camera, and converted into digital images. The final images are displayed as multiple tomograms or slices that reflect adequacy of perfusion throughout the entire myocardium. This technique is referred to as single-photon emission computed tomography (SPECT).[87]

Exercise and pharmacologic radionuclide stress imaging provide additional prognostic information over that obtained from treadmill ECG stress testing alone.[88] Abnormal myocardial perfusion scans indicate both the region of inadequate perfusion and the degree of myocardial dysfunction, information that is not available with treadmill ECG stress testing. Patients with normal stress SPECT images have a combined annual event rate of death and nonfatal myocardial infarction of < 1%, and patients with abnormal scans have an annual event rate of 7.4%.[89]

The results of treadmill ECG stress testing can be integrated with SPECT imaging to more precisely define risk for future cardiac events. For these reasons, patients referred to the Acute Cardiac Referral Clinic at The Ottawa Hospital routinely undergo a protocol that includes treadmill ECG stress testing with rest and stress myocardial perfusion imaging using technetium-99m. The combination of the Duke treadmill score and results of myocardial perfusion imaging are integrated to assess patient risk and guide

management strategies. Patients at low risk for future adverse cardiac events are managed medically, whereas patients at high risk are referred for coronary angiography.

1.9.5 Disadvantages of Myocardial Perfusion Imaging

The most important limitation of radionuclide myocardial perfusion imaging is difficulty in distinguishing defects due to attenuation artifact from those due to regional ischemia or myocardial scar. This can be especially problematic in obese individuals and women. In addition, although radionuclide imaging has greater diagnostic accuracy than treadmill exercise ECG stress testing, its test characteristics are not perfect. In a meta-analysis of 82 studies comparing the diagnostic accuracy of pharmacologic stress testing to coronary angiography for diagnosis of coronary artery disease, sensitivities for radionuclide imaging ranged from 72-90% and specificities ranged from 65-91%, depending on the specific pharmacologic agent used.[90]

1.10 Use of Percutaneous Coronary Angiography

Coronary angiography is the gold standard test to determine the presence or absence of coronary artery disease.[91] The purpose of the procedure is to define coronary anatomy, determine the degree of luminal obstruction, and assess the need for revascularization, either by percutaneous or surgical means. Specialized intravascular catheters are threaded through the femoral or brachial artery and directed centrally to the origin of the coronary arteries. Injection of radiopaque contrast media into the ostia of the left and right coronary arteries enables radiographic visualization of the coronary vasculature.

1.10.1 Disadvantages of Percutaneous Coronary Angiography

Coronary angiography is an invasive procedure that is not without risk. Data from a centralized database of cardiac catheterization laboratories representing 63 laboratories and 59,792 patients reported the total risk of all major complications of coronary angiography at 1.7%.[92] Given the potential seriousness of the complications – including mortality, myocardial infarction, cerebrovascular accident, arrhythmia, contrast reaction, contrast nephropathy, and perforation of a heart chamber, among others – the benefits of coronary angiography should outweigh potential risks. For this reason, coronary angiography is reserved for patients at high risk for acute cardiac ischemia, with noninvasive stress testing performed in those who are low to moderate risk.

1.11 Rationale for the Study

Patients frequently present to the emergency department complaining of chest pain, with etiologies ranging from benign to life-threatening. Acute coronary syndrome, although often classic in presentation, can present with atypical signs and symptoms, adding to the challenge of diagnosis. In the absence of guidelines to assist physicians' triage decisions, patients at low risk for acute coronary syndrome often undergo extensive testing unnecessarily, and patients with acute coronary syndrome are inappropriately discharged. At the same time, Canadian and U.S. hospitals suffer from a shortage of inpatient beds and severe overcrowding in the emergency department. We believe there is a strong need to develop a decision rule that will guide physicians' triage decisions and allow them to be more selective in their ordering of diagnostic tests for patients with possible acute coronary syndrome. This will ultimately improve and standardize triage

and diagnostic practices for these patients, decreasing both unnecessary investigations and unsafe discharge decisions.

CHAPTER 2: GOALS AND OBJECTIVES

2.1 Derivation of a Preliminary Decision Rule

The goal was to derive a preliminary clinical decision rule for identifying patients at very low risk for acute coronary syndrome for whom additional diagnostic testing or admission is unnecessary. Based on time constraints available for the thesis, we aim to derive a preliminary decision rule based on 6 months of data. Future plans are to derive a definitive decision rule after a longer period of data collection. Specific objectives are:

2.1.1 To develop and pretest standardized clinical assessment methods for patients with acute chest pain, incorporating results of initial cardiac testing.

2.1.2 To apply these standardized clinical assessments to patients with chest pain.

2.1.3 To determine the interobserver reliability of the clinical findings.

2.1.4 To determine the association between the clinical findings and acute coronary syndrome.

2.1.5 To use multivariate techniques to derive a highly sensitive preliminary clinical decision rule for patients with chest pain to guide selection of further diagnostic testing.

2.1.6 To assess the classification performance of the derived decision rule.

2.1.7 To determine emergency physicians' accuracy in predicting acute coronary syndrome without a decision rule.

CHAPTER 3: METHODS

3.1 Study design

The study was a prospective cohort study in which a convenience sample of emergency department patients with a chief complaint of chest pain and possible acute coronary syndrome were enrolled.

3.2 Study period

This preliminary study collected data for the 6-month period from July 9, 2007 to January 9, 2008.

3.3 Study Center

The study center consisted of a full-service emergency department located at the Civic Campus of The Ottawa Hospital. It is a tertiary care emergency department with an annual census of approximately 60,000 patient visits. Data management and analysis were performed at the University of Ottawa, Ottawa Health Research Institute, Clinical Epidemiology Program, Ottawa Hospital Civic Campus.

3.4 Study Population

3.4.1 Inclusion Criteria

All adult patients at least 25 years of age with a primary complaint of anterior chest pain and possible acute coronary syndrome were eligible for enrolment. Eligible patients were considered to be at risk of acute coronary syndrome if they underwent a 12-lead electrocardiogram and were placed on continuous cardiac monitoring.

3.4.2 Exclusion Criteria

Patients were excluded if any of the following criteria were met:

1. Acute ST-segment elevation ($\geq$ 0.1mV in limb leads or $\geq$ 0.2mV in precordial

leads) on the initial electrocardiogram (ST-segment elevation acute myocardial infarction, a known high risk subgroup to whom the rule will not apply).

2. Hemodynamic instability or tachycardia (systolic blood pressure < 90mmHg, bradycardia < 50 beats/min, tachycardia > 100 beats/min) (too ill for this study).

3. Pulmonary edema on chest x-ray (too ill for this study).

4. A history of cocaine use or positive test for cocaine (known high risk patient population).

5. Severe communication problems such that a reliable history cannot be obtained (clinical predictors unreliable).

6. A clear traumatic etiology of chest pain (non-cardiac etiology of pain).

7. A radiologically-evident cause of chest pain on chest x-ray such as pneumonia or pneumothorax (noncardiac etiology of pain).

8. Prior enrolment in the study within the past 30 days (confounds assessment of 30-day outcome).

9. Terminal non-cardiac illness (may confound assessment of 30-day outcome).

10. No available phone contact (phone follow-up not possible).

11. Pregnancy (many standard therapies for acute coronary syndrome are potentially harmful to the fetus, and pregnant patients with possible acute coronary syndrome require additional considerations that preclude early discharge from the emergency department).

3.5 Design of Case Record Forms and Study Database

Prior to beginning patient enrolment, case record forms were designed for data collection (described in more detail in section 3.7). After we designed the case record forms, a SAS database was created. It consisted of data entry screens that were similar in

appearance to each case record form, facilitating ease of data entry. The data entry screens were also programmed to flag extreme values and missing data fields, ensuring accurate and complete data entry.

3.6 Patient selection

Designated physicians enrolled a convenience sample of patients who met eligibility criteria when time permitted completion of the data form.

3.7 Study Flow

When a patient with a primary complaint of chest pain presented to the Civic emergency department of The Ottawa Hospital, a triage nurse, registration clerk, or emergency physician attached the physician case record form to the patient chart (Appendix 1). The treating physician determined patient eligibility, completed the data collection form, and ordered diagnostic investigations as appropriate. Cardiac Troponin T was measured at emergency department arrival and $\geq$ 6 hours from pain onset, with at least 4 hours between samples.

At a later point in time after patient discharge, a study nurse attached the emergency department record of treatment to the physician case record form along with a copy of the first interpretable ECG, laboratory results, and results of cardiac stress testing, if available. A study nurse extracted additional data from the medical record of eligible enrolled patients and recorded it on the designated case record form (Appendix 2). To determine the potential number of missed eligible patients, a study nurse reviewed the patient log for all patient visits with a primary complaint of chest pain and completed the case record form for missed eligible patients (Appendix 3). The primary investigator, blinded to both predictor variables and patient outcome, interpreted ECG's

of all enrolled patients according to current standardized reporting guidelines (Appendix 4).[93] A study nurse conducted telephone follow-up one month from the emergency department visit for all enrolled patients (Appendix 5). We also reviewed the medical record for all patients at one month to determine the occurrence of adverse outcomes. Professional data entry personnel then entered data recorded on case record forms into a SAS database. The primary investigator monitored patient recruitment and data integrity on a regular basis throughout the duration of the study.

3.8 Standardized Patient Assessment

3.8.1 Patient Assessment

All patient assessments were made by staff physicians certified in emergency medicine by the Royal College of Physicians and Surgeons in Canada and/or the College of Family Physicians of Canada and supervised emergency medicine residents in at least the second post-graduate year. The primary investigator oriented each of the physician assessors and emergency medicine residents individually and provided one-on-one training to ensure uniform data collection. All physicians completed data collection forms after assessing the patient and before obtaining results of diagnostic tests, without knowledge of the outcome.

3.8.2 Quality Assurance

Throughout the duration of the study, the completeness of data collection and compliance in patient enrolment were monitored. Physicians were given regular feedback regarding their completeness of data collection and percentage of eligible patients enrolled. No feedback regarding the reliability or accuracy of each of the predictor variables was given.

3.8.3 Selection of Variables

The variables selected for assessment in the study were chosen from a comprehensive review of the literature, input from all the investigators, and solicited feedback from the designated study physicians. We limited the number of variables collected to ensure efficient completion of data forms in the context of patient care and to optimize physician compliance. The data collection forms were then shared with Dr. Alan Jaffe, a Professor of Cardiology at the Mayo Clinic, to obtain subspecialty expert feedback on the appropriateness of each individual variable. The variables collected are listed in Figures 8 and 9.

3.8.4 Run-in Period

We evaluated the data collection forms, patient assessment techniques, and patient follow-up questions during an 8-week run-in period prior to the actual study. This allowed time for training of the physician assessors and revision of the data collection forms as appropriate. Because only minor modifications were necessary, we included data from the initial 8-week run-in period in the analysis.

3.8.5 Interobserver Reliability

A subset of patients was assessed by a second emergency physician who was blinded to the results of the first assessment. These second assessments were performed on a feasibility basis whenever two study physicians were available.

3.9 Outcome measures

3.9.1 Outcome Definitions

We defined acute myocardial infarction as any one of the following: (1) a cardiac Troponin T $\geq$ 0.01 ng/mL with a rising or falling pattern (defined as a change of $\geq$ 0.03

ng/mL for values that were initially < 0.2 ng/mL; for levels ≥ 0.20 ng/mL, a positive cardiac Troponin T was defined as a change of ≥ 20% between samples)[18,94] or (2) development of pathological Q-waves on the ECG or ECG evolution consistent with acute myocardial infarction. Revascularization was defined as reestablishment of coronary artery patency by percutaneous coronary angioplasty with or without stent placement or coronary artery bypass graft (CABG) surgery. The final component of the primary outcome was death of cardiac or unknown cause within 30 days of the emergency department visit.

Outcomes were determined by investigators blinded to the knowledge of the predictor variables. If a diagnosis could not be assigned, 2 co-investigators reviewed all clinical data and assigned an adjudicated outcome diagnosis. If a consensus could not be reached between two co-investigators, an adjudicated diagnosis was assigned by the primary investigator. If all 3 disagreed, the final diagnosis was the most significant diagnosis. The reliability of the primary outcome determination was assessed by having all positive outcomes and 10% (randomly selected) of patients with negative outcomes reviewed by an investigator blinded to the first interpretation.

3.9.2 Primary outcome

We defined the **primary outcome** as **acute myocardial infarction, death of cardiac or unknown cause, or revascularization within 30 days** of the emergency department visit. This includes all outcomes that occurred after patient assessment, whether in the emergency department, in the hospital, or after emergency department discharge. We selected this composite outcome to facilitate comparison with the extant literature[13] and to comply with the core recommendation that the 30-day interval be

reported in emergency department-based risk stratification studies for patients with possible acute coronary syndrome.[93]

3.9.3 Secondary outcome

We defined the secondary outcome as acute myocardial infarction, death of cardiac or unknown cause, or revascularization occurring after hospital admission or emergency department discharge but within 30 days of the index visit. We chose outcomes occurring outside of the emergency department as the secondary outcome because these are the outcomes that are the most challenging to predict clinically. A clinical decision rule developed on these outcomes would have the greatest utility for clinicians.

3.9.4 Proxy Outcome

With the current pattern of practice at The Ottawa Hospital emergency department, many patients with chest pain considered to be at low risk for acute coronary syndrome are not referred to the University of Ottawa Heart Institute for outpatient stress testing or coronary angiography. Rather, after initial evaluation in the emergency department with ECG and cardiac enzymes, further cardiac risk stratification is left to the purview of the patient's primary care physician. The study protocol did not alter current practice. As such, the study nurse contacted all enrolled patients one month from the emergency department visit to ensure that they did not experience any subsequent adverse events. We also reviewed the medical record to determine if any additional visits or diagnostic investigations occurred within 30 days of the index visit. If the patient had difficulty understanding the questions, the study nurse clarified the patient's queries as appropriate. The study nurse asked the following questions:

1. Since your initial emergency department visit, have you returned to see a physician?
2. If yes, did the physician tell you that you had a myocardial infarction or heart attack?
3. Since your initial emergency department visit, have you had a cardiac stress test?
4. If yes, where was it performed?
5. If yes, what was the result?
6. Since your initial emergency department visit, have you undergone angioplasty/stent placement in your coronary arteries or cardiac bypass surgery?

3.10 Data Analysis

To identify outliers we explored the data by examining frequency reports and stem and leaf plots. We also reviewed patient characteristics and outcomes in simple descriptive tables. We further investigated outliers by reviewing the original data collection forms and the medical record.

3.10.1 Interobserver Agreement

We determined the interobserver agreement for each variable by calculating the kappa coefficient, the proportion of potential agreement beyond chance, along with 95% confidence intervals. Variables with kappa values ≥ 0.6 were considered to represent "substantial agreement" and considered for inclusion in the clinical rule.

3.10.2 Univariate Analysis

Univariate analysis was used to determine the strength of association between each variable and the primary outcome. The appropriate univariate technique was chosen for the type of data: for nominal data, the chi-square test with continuity correction; for ordinal variables, the Mann-Whitney U test; and, for continuous variables, the unpaired 2-tailed t-test, using pooled or separate variance estimates as appropriate. For select

continuous variables, we assessed the univariate association of various cut-points with the primary outcome. We also created combination variables and assessed the association with the primary outcome. To be included as a component of a combination variable, each variable had to be both significantly associated with the primary outcome ($p < 0.05$) and have a kappa value of at least 0.6.

3.10.3 Multivariate Analysis

We used multivariate analysis to derive a model to predict the primary outcome. The objective was to find the best combination of predictor variables that were highly sensitive for detecting the primary outcome while achieving the maximum possible specificity. To be clinically acceptable, the model must be nearly 100% sensitive and contain the fewest number of predictor variables to facilitate ease of use by clinicians.

Variables found to be both reliable (kappa ≥ 0.6) and associated with the primary outcome ($p < 0.2$) were evaluated with two different statistical techniques: logistic regression and recursive partitioning. Clinically sensible composite variables were considered for incorporation in the multivariate analyses. Cut points were sought for continuous variables in order to provide a simpler model for clinicians.

To ensure stability of the regression coefficients, we restricted the number of variables entered into any given logistic regression model to maintain an event-per-variable ratio of approximately 10:1.[95] Model building proceeded with forward stepwise selection until no variables met the entry (0.05) or removal (0.10) criteria for the significance level of the likelihood ratio test. Because it is possible for a set of variables to have considerable predictive ability though any particular subset may not, we also used

backward elimination with a removal criterion of 0.10 to identify a set of predictors for possible inclusion in a prediction rule.[96]

We performed recursive partitioning using KnowledgeSEEKER Version 5.2 software (Angoss Software International, Toronto).[97-99] In recursive partitioning, the relationship between a dependent outcome variable (Y) and a series of predictor variables (X) is defined by a series of binary splits, resulting in a decision tree in which data are partitioned into several nodes or leaves along branches. We developed a model by evaluating the statistical impact of a series of candidate predictor variables. Variables were selected based on both clinical sensibility and diagnostic accuracy.

We also conducted a **secondary analysis** predicting outcomes occurring outside of the emergency department using multivariate logistic regression. We conducted this analysis to identify potentially important predictor variables in patients who did not experience outcomes during emergency department evaluation, a particularly challenging subgroup of patients to predict clinically. We allowed the event-per-variable ratio to approach 5:1 in this part of the analysis, as the purpose was to identify potentially important predictor variables rather than derive a preliminary rule.

3.10.4 Classification Performance

We cross-validated the derived decision rule by comparing the classification of each patient to their actual status for the primary outcome. This enabled an estimate of the sensitivity and specificity of the rule, with 95% confidence intervals.

3.10.5 Physicians' Judgment

Data relating to physicians' predictions were tabulated and presented in descriptive format. The predicted probability was used to calculate a receiver operating

characteristic (ROC) curve for determining the patient's probability of developing an acute coronary syndrome within 30 days of the emergency department visit.

3.10.6 Sample Size for Study

We collected data for a 6 month period in order to acquire sufficient cases for the purposes of the thesis. We aimed to have a minimum of 60 positive outcomes. This enabled inclusion of a maximum of 6 variables in the preliminary decision rule while maintaining an event-per-variable ratio of 10:1 in multivariate analyses.

It is recognized that more patients would be required to derive a definitive decision rule. To derive a rule that is 100% sensitive with upper and lower 95% confidence limits of 100% and 97.0%, 120 positive outcomes are needed.

3.11 Patient Recruitment

Data sheet completion rates of 80% have occurred with prior clinical decision rule studies and it was anticipated that this would continue. Patient recruitment continued after the 6 month period to obtain the requisite sample size for study completion.

3.12 Ethical Concerns

We obtained Research Ethics Board approval, without the need for written informed consent, from The Ottawa Hospital prior to beginning data collection (Appendix 6). As the study did not affect usual practice, there were no specific ethical concerns. At enrollment, participants were informed that they would be contacted by phone in one month to determine their status, and verbal consent was obtained at the time of the follow-up phone call. We kept all personal identifiers strictly confidential and stored them separately from the clinical data collected.

CHAPTER 4: RESULTS

4.1 Study Flow

A total of 1,089 potentially eligible patients were identified as having chest pain as a chief complaint. Figure 14 illustrates the study flow. There were 1,021 eligible patients, of which 676 (66.2%) were enrolled. Thirty-six (5.3%) patients could not be reached by phone for the proxy outcome measure at 30 days, leaving 640 enrolled patients with complete outcome data. Eighty-seven (13.6%, 95% CI 11.2-16.5) of the 640 enrolled patients were positive for the primary outcome. Of the 345 eligible patients not enrolled, 60 (17.4%, 95% CI 13.8-21.7) were positive for the primary outcome.

4.2 Missing Data

4.2.1 Physician Case Record Form (Appendix 1)

Cardiac risk factor data – with the exception of smoking history – was missing in 1(0.16%) patient. Smoking history was missing in 78 (12.2%) patients. The number of missing variables for the remaining data from the history and physical examination ranged from 2 (0.3%) for the question, "Present at time of ED arrival?" to 18 (2.8%) for the variable "chest wall tenderness." The physician judgment question, "What is the patient's pre-test probability of unstable angina or MI?" had the greatest amount of missing data. This data point was missing in 104 (16.3%) cases.

4.2.2 Study Nurse Case Record Forms (Appendices 2 and 3)

The remaining variables were extracted from the medical record by the study nurse after patient enrollment. The variable with the greatest amount of missing data was cardiac troponin. Cardiac troponin T was not obtained in 42 (6.56%) patients. The

frequency of missing data for the other variables extracted from the medical record ranged from 0.6% to 1.25%.

4.3 Descriptive Statistics

After verifying the accuracy and completeness of the data set, we analyzed all of the variables by generating descriptive statistics (Tables 1-5). Table 1 displays demographic, cardiac risk factor, and cardiovascular history characteristics. The mean age (SD) was 59.6 (13.8), and 40.2% were female. Patients transferred to The Ottawa Hospital for cardiac evaluation are as a policy seen directly by the cardiology consulting service rather than the on-duty emergency physician; thus no patients transferred from another emergency department were enrolled. Nineteen percent of patients were admitted to the hospital. Approximately 25% of patients had a history of acute myocardial infarction, angina, or known coronary artery disease.

Table 2 displays characteristics from the medication history. Thirty-nine percent of the patients were currently taking aspirin and 19.4% nitroglycerin or other nitrates. Thirty-seven percent of the patients were on a cholesterol-lowering medication.

Table 3 displays characteristics from the chest pain history. The mean (S.D.) duration of chest pain prior to physician evaluation was 6 (20.3) hours. Sixty-three percent of patients had chest pain on arrival to the emergency department, and 31.1% described their pain as worse with exertion. Forty-five percent of patients had at least 2 episodes of chest pain in the previous 24 hours. Seventy-six percent of patients described their pain as abrupt in onset, and 60.5% described the pain as being located in the center of the chest. Emergency physicians considered the patient's symptoms to be typical for acute coronary syndrome in 45.4% of cases.

Table 4 displays descriptive characteristics from the physical examination. Emergency physicians detected a third or fourth heart sound (indicative of a failing left ventricle or stiff left ventricle, respectively) in only 0.5%. Ninety percent of patients had no abnormalities detected on lung auscultation.

Table 5 shows characteristics of the first readable electrocardiogram and cardiac troponin T values. Of the 640 patients, 4.7% had ST-segment depressions and 7.0% T-wave inversions. Eight percent of electrocardiograms demonstrated ischemic changes not known to be old. At least one serial cardiac troponin T value was $\geq$ 0.01 ng/mL in 14.0% of patients.

Table 6 demonstrates management for all eligible enrolled patients. Thirty-one percent underwent cardiac stress testing, with radionuclide imaging the most common modality (23.4%). Three percent underwent cardiac computed tomography, and 16.7% had coronary angiography. Of these, 79.4% had at least one stenosis constituting $\geq$ 70% of the vessel lumen.

Table 7 shows patient outcomes. Of the 640 eligible enrolled patients, 13.6 (11.2-16.5)% experienced at least one component of the primary outcome acute myocardial infarction, death of cardiac or unknown cause, or revascularization within 30 days of the emergency department visit. There were 36 (5.6%) patients with outcomes that occurred outside of the emergency department, 13 (2.0%) of which occurred in the out-of-hospital setting.

4.4 Missed Eligible Patients

Table 8 displays characteristics of the 345 missed eligible patients. Mean age (SD) was 62.1 (12.8), 41.7% were female and 24.9% underwent cardiac stress testing.

Twenty-four percent underwent coronary angiography, and 17.4 (13.8-21.7)% were positive for the primary outcome.

Eligible enrolled patients were similar to the missed eligible patients with respect to mean age and sex. There were slight differences between eligible enrolled and missed eligible cases in regard to the percentage of patients who underwent stress testing (31.4% vs. 24.9%) and coronary angiography (16.7% vs. 24.9%). However, a similar percentage of patients were positive for the primary outcome in the eligible enrolled cases (13.6%, 95% CI 11.2-16.5) and the missed eligible cases (17.4%, 95% CI 13.8-21.7).

4.5 Univariate Analysis

Table 9 shows the univariate association of demographic, cardiac risk factor, and cardiovascular history features with the primary outcome. (Kappa values will be discussed in section 4.5.) Patients who were positive for the primary outcome were significantly older (64.5 vs. 58.8, $p < 0.01$), more frequently admitted to the hospital (80.5% vs. 9.4%, $p < 0.01$), and had a shorter emergency department length of stay (4.9 vs. 6.2 hours, $p < 0.01$). A greater proportion of patients with known coronary artery disease experienced the primary outcome (41.4% vs. 24.4%, $p = 0.02$).

Table 10 shows the univariate association of variables from the medication history with the primary outcome. Aspirin was the only medication significantly associated with the primary outcome ($p = 0.02$), with clopidogrel and nitrates demonstrating a marginal association ($p = 0.16$ and $p = 0.11$, respectively).

Table 11 displays the univariate association of features from the chest pain history with the primary outcome. A greater proportion of patients with pain at rest were negative for the primary outcome (91.7% vs. 79.3%, $p < 0.01$), whereas a greater

proportion of patients who reported a change in their usual pattern of angina within the past 24 hours (24.1% vs. 14.3%, p = 0.04) or described their pain as similar to previously diagnosed ischemia (35.6% vs. 20.3%, p = 0.01) were positive for the primary outcome. A greater proportion of patients who localized their pain to the center of the chest (72.4% vs. 58.6%, p = 0.02) or described it as a pressure or squeezing sensation (63.2% vs. 50.3%, p = 0.01) were positive for the primary outcome. A greater proportion of patients who described their pain as radiating to the left arm or shoulder (43.7% vs. 29.7%, p = 0.01) or both arms or shoulders (11.5% vs. 4.9%, p = 0.01) were positive for the primary outcome. Although a third heart sound (S3) was associated with the primary outcome, only one patient had this finding (Table 12). No other characteristics from the physical examination were associated with the primary outcome.

Table 13 shows the univariate association of ECG findings and cardiac troponin T values with the primary outcome. A greater proportion of ECG's classified as "infarction or ischemia not known to be old" were positive for the primary outcome (26.4% vs. 6.0%, $p < 0.01$). A greater proportion of patients with cardiac troponin T values ≥ 0.01 ng/mL were positive for the primary outcome (63.2% vs. 6.1%, $p < 0.01$).

Table 14 shows the univariate association of continuous variables at various cut-points and selected combination variables with the primary outcome. All cut-points between 45 and 70 years of age were significantly associated with the primary outcome. There was a marginal association between the absence of cardiac risk factors and the primary outcome (21.2% vs. 12.6%, 0.08). When smoking history was evaluated as a dichotomous variable (ever smoked versus never smoked), it was marginally associated with the primary outcome (56.3% versus 47.6%, p = 0.05). Patients with various

combinations of features from the cardiovascular history (history of acute myocardial infarction, angina, and/or known coronary disease) or associated shortness of breath or diaphoresis more frequently experienced the primary outcome. Patients with pre-test probability cut-points of $\geq 10\%$ and $\geq 20\%$ more frequently experienced the primary outcome.

4.6 Interobserver Agreement

Tables 9, 11, and 12 display kappa values for the 49 cases where interobserver data were available. Cardiac risk factor and cardiovascular history characteristics demonstrated near perfect agreement (0.88-1.00, Table 9). Twenty-one variables from the chest pain history had kappa values ≥ 0.6 (Table 11). Kappa values for the questions "Pain worse with exertion?" and "Pain worse with movement?" were low (kappa = 0.51 and 0.28, respectively). Interobserver agreement for the variable "Overall assessment: typical or atypical" was substantial (kappa = 0.71). Four variables from the physical examination had kappa values ≥ 0.6 (Table 12). Interobserver agreement for physician assessment of pre-test probability for acute coronary syndrome at cut points of $\geq 20\%$ and $\geq 10\%$ was 0.63 and 0.78, respectively (Table 14).

4.7 Multivariate Analysis

Given that there were 87 cases positive for the primary outcome, the number of variables entered into any given multivariate logistic regression model was restricted to 9 to ensure stability of regression coefficients. We analyzed different combinations of individual variables that were both associated with the outcome ($p < 0.2$) and of at least substantial interobserver agreement (kappa ≥ 0.6). We also assessed the impact of different combination variables on the predictive ability of the model. Finally, we

explored the impact of different clinically important cut points of continuous variables on the model.

Using forward stepwise selection with a p to enter of 0.05 and p to remove of 0.10, the regression model included 7 variables: acute ischemic changes on electrocardiogram, cardiac troponin T $\geq$ 0.01 ng/mL, pain present at rest, $\geq$ 2 episodes of pain in the past 24 hours, pain described as a pressure or squeezing sensation, pain radiating to the left or both shoulders, and pain atypical for acute coronary syndrome. The Hosmer and Lemeshow test p-value for this model was 0.810 and the C-statistic was 0.92, indicating a well-calibrated model with good fit (Table 15).[100] However, the model contained 7 variables, which is not as parsimonious as clinically desired. After removing the least significant variable "pain described as a pressure or squeezing sensation" the forward stepwise procedure selected 5 variables. This model also had a nonsignificant Hosmer and Lemeshow p-value of 0.239 and a C-statistic of 0.91, indicating that removing the least significant variable did not substantially impact the calibration or fit of the model.

Using backward stepwise selection with a p to remove of 0.10 identified the same 7 variables selected using forward selection. After removing the least significant variable "pain described as a pressure or squeezing sensation," the same 5 variables remained.

4.7.1 Final Logistic Regression Model

The final model included the following terms: acute ischemic changes on ECG, cardiac troponin T $\geq$ 0.01 ng/mL, pain present at rest, $\geq$ 2 episodes of pain in the past 24 hours, and pain atypical for acute coronary syndrome. The regression coefficients with their corresponding odds ratios and 95% confidence intervals are displayed in Table 16.

We selected this model based on clinical sensibility, diagnostic accuracy, and outstanding discrimination.

4.7.2 Interaction Terms for the Logistic Regression Model

Interaction terms were not added to the model given that there were no combinations known to interact with each other on literature review.

4.7.3 Assessment for Multicollinearity

We assessed for the presence of multicollinearity by fitting the same model using linear regression and specifying options to calculate the tolerance and variance inflation factor for each independent variable.[101] The tolerance and variance inflation factors did not approach 0.1 and 10, respectively, indicating the absence of multicollinearity (Table 17).

4.7.4 Sensitivity and Specificity of the Logistic Regression Model

We determined the sensitivity and specificity of the regression model using probability classification cut points from 0.01 to 0.95. Table 18 shows the respective sensitivities and specificities for these cut points. Figure 15 shows the receiver operating characteristic curve (ROC) for the final logistic regression model. The area under the curve was 0.91.

4.7.5 Multivariate Analysis of Patient Subgroup with Outcomes Occurring Outside of the Emergency Department

Fifty-one of the 87 positive outcomes occurred in the emergency department. We conducted a subgroup analysis excluding these outcomes to explore the impact on the model. As done in the primary analysis, we analyzed different combinations of

individual variables that were both associated with the outcome ($p < 0.20$) and of at least moderate interobserver agreement (kappa ≥ 0.6).

The multivariable logistic regression model using forward stepwise selection (p to enter 0.05, p to remove 0.10) selected the following five variables: pain present at rest, resolution of the pain prior to physician evaluation, ≥ 2 episodes of chest pain in the past 24 hours, current aspirin use, and pretest probability for acute coronary syndrome $\geq 20\%$ (Table 19). The Hosmer and Lemeshow test p-value was 0.945. Repeating the analysis using backward stepwise selection (p to remove = 0.10) resulted in a model with 7 variables: resolution of the pain prior to physician evaluation, ≥ 2 episodes of chest pain in the past 24 hours, current aspirin use, pain present at rest, radiation of pain to left or both shoulders, pain location in the center of the chest, and pretest probability for acute coronary syndrome $\geq 20\%$. The Hosmer and Lemeshow test p-value was 0.246.

4.7.5.1 Final Logistic Regression Model

The final model included the following terms: pain present at rest, resolution of the pain prior to physician evaluation, ≥ 2 episodes of chest pain in the past 24 hours, current aspirin use, and pretest probability for acute coronary syndrome $\geq 20\%$. The regression coefficients with their corresponding odds ratios and 95% confidence intervals are displayed in Table 20. The model fit using forward stepwise selection was more parsimonious (5 versus 7 variables) and had a higher sensitivity at the lowest probability cut point than the model fit using backward stepwise selection (93.1% vs. 89.7%). It was therefore selected as the final model.

4.7.5.2 Interaction Terms for the Logistic Regression Model

Interaction terms were not added to the model given that there were no combinations known to interact with each other on literature review.

4.7.5.3 Assessment for Multicollinearity

We fit the final model using linear regression and specified options to calculate the tolerance and variance inflation factor for each independent variable. None of the tolerance or variance inflation factors for each of the independent variables approached 0.1 or 10, respectively, indicating the absence of multicollinearity (Table 21).

4.7.5.4 Sensitivity and Specificity of the Logistic Regression Model

We determined the sensitivity and specificity of the regression model using probability classification cut points from 0.01 to 0.95. Table 22 shows the respective sensitivities and specificities for these cut points. Figure 16 shows the ROC curve for the final logistic regression model. The area under the curve was 0.89.

4.7.6 Recursive Partitioning

Table 23 shows the candidate prediction models derived using recursive partitioning. The first model has an age cut-off of ≥ 55 years and does not incorporate any combination variables. The second model has an age cut-off of ≥ 60 years. In order to achieve 100% sensitivity, the combination variables "history of acute myocardial infarction or known coronary artery disease" and "shortness of breath or diaphoresis" were included in the model. Including these combination variables resulted in a slightly lower specificity (22%) relative to the first model (25%). The third model also has an age cut-off of ≥ 60 years. Rather than including the combination variable "shortness of breath or diaphoresis" as in the second model, the third model includes the variables

"history of diabetes," "current nitrate use" and "diaphoresis." This resulted in a slightly higher specificity (27%) relative to the first and second models (25% and 22%, respectively). However, the third model includes 7 variables, which is not as parsimonius as clinically desired.

Figure 17 shows the classification and flow of patients in the final recursive partitioning model. Figure 18 displays the proposed preliminary model from the study data. This model was chosen based on considerations of clinical sensibility, diagnostic accuracy, and statistical features (100% sensitivity and 25% specificity). Figure 19 shows the classification performance, sensitivity, specificity, and proportion of patients who would require further testing in this cohort of patients.

4.7.7 Physicians' Accuracy in Predicting Acute Coronary Syndrome

The results of the question asking physicians to estimate the pre-test probability that their patient had acute coronary syndrome are shown in Table 24. There were 2 patients with acute coronary syndrome with a pre-test probability $\leq 1\%$, 6 patients with acute coronary syndrome with a pre-test probability of 2%, and 5 patients with acute coronary syndrome with a pre-test probability of 3%. Overall, 20 patients with a pre-test probability $\leq 5\%$ had an acute coronary syndrome. The remainder of the enrolled patients had a pre-test probability of $\geq 10\%$. This is graphically displayed with a ROC curve in Figure 20. The area under the curve was 0.81.

CHAPTER 5: DISCUSSION

5.1 Enrollment

Six hundred and forty patients with chest pain were enrolled in the study between July 9, 2007 and January 9, 2008. Despite regular communication with the designator physicians, regular physician reminders and incentives for registration clerks and nurses to attach data collection forms to potentially eligible patients, only 66% of eligible patients were enrolled. This lack of complete capture is partly because emergency departments are busy environments, with many demands on physicians' time.

It is important to note, however, that the eligible enrolled cases and missed eligible cases were similar with respect to mean age, sex, and the proportion of patients who were positive for the primary outcome (13.6%, 95% CI 11.2-16.5 vs. 17.4%, 95% CI 13.8-21.7). Although selection bias is a possibility, the overlapping 95% confidence intervals suggest that the difference in the proportion of positive cases in each group could be due to chance alone. Furthermore, even if a greater proportion of higher acuity cases were missed, the study was designed to derive a preliminary decision rule for low risk patients. It is also possible that some patients classified as missed were actually ineligible due to information not documented on the medical record. For these reasons, it is unlikely that selection bias impacted study findings.

5.2 Potentially Important Predictor Variables

We identified several potentially important predictor variables. There were 23 variables that were both significantly associated with the outcome ($p < 0.05$) and had kappa values ≥ 0.6 on univariate analysis (Tables 9-11, 13). There were 11 variables independently associated with the outcome on multivariate analysis (Tables 15, 19). The

large number of statistically and clinically significant variables on both univariate and multivariate analyses indicate that derivation of a definitive clinical decision rule for emergency department patients with chest pain is feasible.

One unexpected observation is that the variable "pain present at rest" was negatively associated with the primary outcome. For patients with chest pain due to cardiac ischemia, rest pain is considered to be a high risk feature. For this reason we expected to observe a positive association between rest pain and the primary outcome. One potential explanation for this observation is that in our broad cohort of emergency department patients with chest pain the proportion of patients with noncardiac chest pain was relatively greater than the proportion with cardiac disease. It is likely that many patients with noncardiac chest pain had pain at rest. So, in our broadly inclusive patient population, pain at rest was more often associated with low risk chest pain.

5.3 Interobserver Reliability of Predictor Variables

Thirty-five variables had kappa values ≥ 0.6 and were thus of sufficient reliability to be considered for inclusion in the prediction rule. It is important to keep in mind, however, that the kappa estimates were derived from only 49 interobserver cases. We aim to obtain at least 100 interobserver cases for the definitive study, and the final kappa estimates may differ slightly from the current calculations.

5.4 Models Derived from Multivariate Analysis

5.4.1 Logistic Regression Model Predicting All Outcomes

5.4.1.1 Classification Performance

The logistic regression model predicting all 87 outcomes was 100% sensitive and 29% specific at the lowest probability cut-point. As all of the variables were

dichotomous, a given patient would need to have a value of zero for each of the predictor variables to be at the lowest probability cut-point.

5.4.1.2 Interobserver Reliability

The kappa values for the 5 variables included in the final model ranged from 0.60 to 0.88. The variable "≥ 2 episodes of pain in the past 24 hours" had the lowest kappa value at 0.60. Although this indicates at least moderate interobserver agreement, it may negatively impact the reliability of the rule. We plan on specifying this variable more precisely in the future.

5.4.1.3 Clinical Sensibility

As this prediction model includes only 5 dichotomous variables, it is concise and likely to be easily used by practicing clinicians. The variable "pain present at rest," however, lacks face validity, as it is considered a high risk feature by most clinicians. In addition, the variable "pain atypical for acute coronary syndrome" requires clinical judgment and experience to assess. It may be less acceptable to physicians with fewer years of experience.

5.4.1.4 Potential Impact

If this model were applied to our patient population, 61.4% of enrolled patients would require additional investigation. In our cohort, 300 (46.9%) of patients underwent cardiac stress testing, cardiac computed tomography, or coronary angiography within 30 days, and 13 (14.9%) outcomes occurred in patients discharged home from the emergency department. These data suggest that current practice is 85.1% sensitive for predicting adverse cardiac events within 30 days. So, application of the rule to our

setting would increase the sensitivity from 85% to 100% and require a 14.5% absolute increase in testing.

5.4.2 Logistic Regression Model Predicting Outcomes Occurring Outside of the Emergency Department

5.4.2.1 Classification Performance

The logistic regression model predicting the 36 outcomes that occurred outside of the emergency department was 93.1% sensitive and 49.7% specific at the lowest probability cut-point. As all of the variables are dichotomous, a given patient would need to have a value of zero for each of the predictor variables to be at the lowest probability cut-point.

5.4.2.2 Interobserver Reliability

The kappa values for the 5 variables included in the final model ranged from 0.60 to 0.88. As in the model predicting all outcomes, the variable "$\geq$ 2 episodes of pain in the past 24 hours" had the lowest kappa value at 0.60. This variable may negatively impact the reliability of the model were it to be applied. We intend to more clearly specify this variable in the future.

5.4.2.3 Clinical Sensibility

The model includes 5 dichotomous variables and would likely be easy to use by practicing emergency physicians. However, as discussed previously, the variable "pain present at rest" lacks face validity and may be less acceptable to end users. The variable "pretest probability for acute coronary syndrome $\geq$ 20%," however, requires clinical experience and judgment to assess and may be less acceptable to physicians with fewer years of experience.

5.4.2.4 Potential Impact

Application of this rule to our cohort would increase the sensitivity for predicting adverse cardiac events from 85.1% to 93.1%, an 8% absolute increase in sensitivity. Were this model to be applied 44.4% of patients would require additional investigation, a 2.5% absolute decrease relative to the 46.9% baseline testing rate. So, an absolute increase in sensitivity of 8% could be achieved while simultaneously decreasing the testing rate by 2.5%.

5.4.3 Recursive Partitioning Model

5.4.3.1 Classification Performance

The final recursive partitioning model including all 87 outcomes was 100.0% sensitive and 25.3% specific. The answer to each of the questions in the decision tree would need to be "no" to achieve this degree of diagnostic accuracy.

5.4.3.2 Interobserver Reliability

The kappa values for the variables included in the final model ranged from 0.89 to 0.91, indicating near perfect agreement. We would anticipate a very high degree of reliability were this rule to be applied in clinical practice.

5.4.3.3 Clinical Sensibility

The model derived with recursive partitioning contains 5 dichotomous variables and is concise. When evaluating patients with chest pain, emergency physicians commonly take into account patient age and coronary artery disease history when assessing the risk for adverse outcome. Clinicians routinely incorporate ECG findings and cardiac troponin results when managing patients with chest pain. The variable

"diaphoresis" has face validity, as it is classically associated with acute cardiac ischemia. For these reasons, the model derived with recursive partitioning is clinically sensible.

5.4.3.4 Potential Impact

Were this decision rule to be applied to our cohort, it would increase the sensitivity for predicting adverse cardiac events from 85.1% to 100.0%, a 14.9% absolute increase in sensitivity. 70.5% of patients would require additional investigation, a 23.6% increase relative to the 46.9% baseline testing rate. So, increasing the sensitivity from 85% to 100% would require a 23.6% absolute increase in testing.

5.4.4 Overall Assessment of Models Derived from Multivariate Analysis

All of the final models include 5 variables, are concise, and would be user friendly for the intended application. The logistic regression model predicting all 87 outcomes is 100% sensitive and 29% specific and would achieve a high degree of sensitivity while increasing the testing rate by 14.5%. The logistic regression model predicting outcomes occurring outside of the emergency department is 93.1% sensitive. As a clinical decision rule for chest pain must be nearly 100% sensitive to be used by clinicians, this model is suboptimal. Both models derived using logistic regression include variables that lack face validity. This would likely result in the models being less acceptable to clinicians.

The final model derived using recursive partitioning is 100% sensitive and clinically sensible. The kappa values of each of the individual variables indicate near perfect agreement, suggesting minimal variability in the model were it to be applied. Although application of the rule to clinical practice would be expected to increase the rate of testing by 23.6%, this would not likely be the case in all practice settings. In the U.S.,

the medicolegal implications of missing an adverse cardiac outcome are substantial, and current treatment guidelines do not identify a low risk patient group who can be safely discharged without additional cardiac testing.[11] For these reasons, we would expect the baseline testing rate to be substantially higher in the U.S., nearly 100% in some settings. Application of the rule in the U.S. may increase the sensitivity for predicting adverse cardiac events and decrease the testing rate. For these reasons, we selected the final model derived using recursive partitioning as the preliminary decision rule.

5.5 Comparison to Other Models Predicting Adverse Cardiac Events in Emergency Department Patients with Chest Pain

A recent systematic review assessed the diagnostic accuracy of clinical prediction rules that exclude acute coronary syndrome in the emergency department setting.[102] Studies of sufficient methodological quality to warrant consideration for use in clinical practice were included. We will compare the findings of these studies to the current investigation.

5.5.1 Bassan et al.[45]

Bassan et al. derived a clinical decision rule to predict acute coronary syndrome (acute myocardial infarction or unstable angina) using a neural diagnostic tree. These investigators prospectively enrolled 566 consecutive patients with chest pain and no ST-segment elevation on electrocardiogram. After enrolment, patients were classified according to the likelihood of acute coronary syndrome. Subsequent diagnostic testing was based on this clinical assessment.

Using multivariate logistic regression and recursive partitioning, 5 variables were identified for inclusion in the rule: chest pain type, history of coronary artery disease,

CK-MB level, and the presence of ST-segment depression or T-wave inversions on electrocardiogram. The neural diagnostic tree was 97% sensitive and 57% specific for acute coronary syndrome.

In this study 117 (20.7%) of patients were discharged home based on clinical and electrocardiographic assessment alone. This increases the risk of verification bias (i.e., failure to use the same gold standard on all patients), potentially leading to overestimation of diagnostic performance. The duration of follow-up was not reported, so it is possible that some outcomes were missed. It is unclear whether outcomes were assessed without knowledge of the patient's chest pain classification, and vice versa (inadequate blinding). Even if these methodological weaknesses did not impact diagnostic accuracy, the prediction tool is insufficiently sensitive (97%) to consider for incorporation in clinical practice. In addition, it has been derived but not validated and would constitute level 4 evidence according to the hierarchy of evidence for clinical prediction rules.[28]

5.5.2 Fernandez Portales et al.[63]

Fernandez Portales and colleagues derived a risk score to predict recurrent cardiac ischemia, death, or heart failure within 15 days of emergency department presentation. Cardiology residents identified potentially eligible patients based on a presumed diagnosis if acute coronary syndrome. Three hundred twenty-one emergency department patients with chest pain and no ST-segment elevation on electrocardiogram were consecutively enrolled. Clinical and electrocardiogram findings were recorded in addition to serial cardiac markers at 6, 12, and 18 hours after the onset of chest pain.

Using logistic regression, they identified 5 independent predictors of recurrent cardiac ischemia: age > 70, history of coronary artery disease, prolonged chest pain at rest in the preceding 15 days, ST-segment changes on electrocardiogram during pain, and cardiac troponin T > 0.1 ng/mL 12 hours after the onset of chest pain. This prediction model was 98% sensitive and 45% specific.

The investigators derived a prediction model that is highly sensitive ($\leq$ 2% miss rate). However, cardiology residents enrolled patients based on a presumed diagnosis of acute coronary syndrome. As emergency physicians rather than cardiology specialists evaluate emergency patients with possible acute coronary syndrome in many settings, this reduces the generalizability of the study. In addition, the model has been derived but not validated (level 4 evidence).

5.5.3 Christenson et al.[31]

Christenson et al. derived a clinical decision rule that is most similar in design and purpose to the current investigation. Research assistants enrolled 769 patients at a single Canadian tertiary care emergency department in 2 separate periods between June 2000 and January 2003. The study was conducted using established methodology for clinical prediction rules.[29] The primary outcome was acute coronary syndrome within 30 days of the emergency department visit. There were 2 separate decision rules: one for patients < 40, and one for patients $\geq$ 40. Patients < 40 with no history of acute myocardial infarction, angina, previously prescribed nitroglycerin, or a history of effort-related angina were considered safe for discharge. Patients $\geq$ 40 with chest pain that is nonradiating, pleuritic, or increases on palpation and either have an initial CK-MB < 3.0 ug/L or a CK-MB $\geq$ 3.0 ug/L and no electrocardiographic, CK-MB, or troponin rise

within 2 hours of the emergency department visit are safe for discharge. Two cases of acute coronary syndrome within 30 days were missed, resulting in a sensitivity of 98% and a specificity of 32.5%.

The study by Christenson et al. (i.e. Vancouver chest pain rule) differs from the current study in at least 2 ways. One difference is the choice of primary outcome. The Vancouver chest pain rule defines a positive exercise electrocardiographic stress test as indicative of acute coronary syndrome. False positive exercise electrocardiographic stress tests have been reported to occur in 8% of men and 67% of women.[86] We intentionally excluded results of cardiac stress testing from our primary outcome for this reason. Another difference is the inclusion of the combination variable "prior ischemic chest pain" in the final model. "Prior ischemic chest pain," consists of a past diagnosis of acute myocardial infarction or angina, previous nitroglycerin use, or a history of effort-related angina. In our study the variable "chest pain worse with exertion" had a kappa statistic of 0.51 and thus was not of sufficient interobserver reliability to be considered for inclusion in the rule. This difference may be due to differences in data collection. Physicians collected data in our study, and research assistants collected data in the study by Christenson et al. The Vancouver chest pain rule has been derived only and constitutes level 4 evidence according to the hierarchy of evidence for clinical prediction rules.

5.5.4 Lyon et al.[57]

Lyon et al. validated the Global Registry of Acute Coronary Events (GRACE) risk score in emergency department patients. The GRACE is a multicenter international registry of patients admitted to the hospital with acute coronary syndrome.[103]

Investigators derived and validated a model predicting the 6-month risk of death and acute myocardial infarction in 43,810 patients (21,688 derivation set, 22,122 validation set) enrolled in the registry.[51] The following model was developed using logistic regression: age, pulse rate at presentation, systolic blood pressure at presentation, serum creatinine level at presentation, Killip class (a classification system for the degree of heart failure after acute myocardial infarction), ST-segment depression on presenting electrocardiogram, elevated initial cardiac biomarker level, and cardiac arrest on admission. As the model was developed on patients admitted to the hospital with known acute coronary syndrome, its applicability to emergency department patients is less well established.

To determine its diagnostic accuracy in predicting short-term (30-day) risk for adverse cardiac events in emergency department patients, Lyon and colleagues validated the GRACE risk score. One thousand patients presenting with chest pain were consecutively enrolled over 2 months. Data needed to calculate a GRACE score were collected on each patient, and GRACE scores were calculated retrospectively. The prediction model was 100% sensitive and 13% specific.

Although the GRACE risk score was highly sensitive, the study has many limitations. First, data needed to calculate the GRACE score were missing in 240 (24%) patients. This is not surprising, as some of the variables incorporated in the GRACE score such as Killip class are not routinely available on emergency department presentation. Second, Killip class is not routinely used by emergency physicians to guide management decisions. Third, the prediction model has 8 variables and would likely be cumbersome to use in clinical practice. Some of the variables are continuous, and the

model requires use of an on-line calculator to determine an individual patient's risk. This is likely to negatively impact the acceptability of the rule to emergency physicians.[104] Finally, the GRACE score was only 13% specific and would likely lead to a substantial increase in testing were it to be implemented in clinical practice.

5.5.5 Marsan et al.[68]

Marsan and colleagues validated a clinical decision rule in young adult patients with chest pain. These investigators prospectively enrolled 1,023 consecutive patients between 24 and 39 years of age who received an ECG for chest pain. Data were collected in a structured fashion with prospective hospital and 30-day phone follow-up. The primary outcome was acute myocardial infarction, revascularization, or death within 30 days.

The investigators derived a decision rule using recursive partitioning. The following variables were included: known cardiac history, no cardiac risk factors, normal electrocardiogram, and negative initial cardiac markers. The rule was 98% sensitive and 31% specific. Although the prediction rule was highly sensitive, only adults between 24 and 39 years of age were enrolled, restricting its generalizability. In addition, the investigators did not report whether outcomes were assessed without knowledge of the predictor variables, and vice versa (inadequate blinding), increasing the risk for overly optimistic estimates of diagnostic performance. Finally, the rule was retrospectively refined to include normal initial cardiac markers and requires additional validation before incorporation in clinical practice (level 4 evidence).

5.5.6 The Thrombolysis in Myocardial Infarction (TIMI) Risk Score

The most rigorously developed risk score that predicts adverse cardiac events in emergency department patients is the TIMI risk score. It was originally derived from the databases of two large clinical trials and has subsequently been validated in multiple settings (level 2evidence).[12,53,54,57,62] It incorporates 7 clinical variables: "age ≥ 65 years," "> 3 risk factors for coronary artery disease," "known coronary artery disease," "aspirin use in the past 7 days," "≥ two anginal events in the past 24 hours," "ST-segment changes > 0.5mm," and "elevated cardiac marker." Among studies that have validated the TIMI risk score and reported the diagnostic accuracy of the instrument with risk scores of 0, sensitivities and specificities have ranged from 91-100% and 13-38%, respectively. Two studies reported sensitivities < 98%.[53,58] Despite extensive validation, the TIMI risk score has not been broadly adopted by emergency physicians. The suboptimal sensitivity is one potential explanation for its lack of uptake in clinical practice.

5.6 Study Strengths

One of the major strengths of this study is that it was conducted according to current methodological standards for clinical prediction rules, thus decreasing the risk of bias.[29] We clearly defined the primary outcome as acute myocardial infarction, death of cardiac or unknown cause, or revascularization within 30 days. The predictors to be considered for inclusion in the rule were clearly defined and assessed without knowledge of the outcome (adequate blinding). We demonstrated the reliability of the clinical findings used as predictors by calculating kappa values. We selected subjects without bias and included a wide spectrum of patients, increasing the generalizability of the

results. We clearly identified the mathematical techniques used to derive the preliminary rule. The final model derived by recursive partitioning was clinical sensible, concise, and highly sensitive (100%).

In addition, we collected and reported data in a format consistent with current standardized reporting guidelines for emergency department studies stratifying risk of patients with potential acute coronary syndromes, facilitating comparison of our results with the extant literature.[93] The composite outcome of acute myocardial infarction, revascularization, or death within 30 days is objective and used by many other emergency department studies on patients with potential acute coronary syndromes.[12,53,54,56,57,68] We defined acute myocardial infarction according to current guidelines.[18] Data were prospectively collected and all enrolled patients were contacted by phone 1 month from the date of visit, ensuring that no important outcomes were missed.

5.7 Study Limitations

While our sample size was excellent for the purpose of a thesis, it is not sufficient for a definitive study. There were a limited number of outcomes that occurred outside of the emergency department. Physicians do not need a clinical decision rule for patients who develop high risk findings in the emergency department such as ST-segment depression on electrocardiogram or an elevated cardiac Troponin T value. Patients with normal or nondiagnostic electrocardiograms and normal serial cardiac troponin T values are the most difficult to manage; a clinical decision rule derived for these patients would have the greatest utility. Data from the current study suggest that deriving a clinical decision rule based on outcomes that occur outside of the emergency department is feasible.

Another limitation of the study is the number of interobserver cases. We aim to have at least 100 interobserver forms completed for derivation of a definitive rule. As we have collected nearly 50 interobserver cases, we believe this goal is feasible.

5.8 Future Research

We aim to derive a clinical decision rule predicting outcomes that occur outside of the emergency department. Developing a rule based on these outcomes would have the greatest clinical utility for practicing emergency physicians and be more robust than other published prediction models.

Previous clinical decision rule studies have found that approximately 120 cases are needed to derive a decision rule that is 100% sensitive with upper and lower confidence limits of 100% and 97%, respectively. Given the medical and legal implications of missing a serious adverse cardiac event, narrow confidence intervals are needed. Based on the data collected, we anticipate a 5.6% rate of positive outcomes occurring outside of the emergency department. Approximately 2,150 patients will be needed for a definitive clinical decision rule study. As we have enrolled 640 cases over a 6 month time period, we anticipate meeting sample size goals within two years.

Many variables were significantly associated with the primary outcome. Also, estimates of interobserver reliability may vary slightly once 100 interobserver forms are completed. For these reasons, we will not drop any variables for the definitive study. We plan on conducting the multivariate analysis using recursive partitioning.

5.9 Importance and Relevance

Our data suggest that derivation of a highly sensitive clinical decision rule for triage of emergency department patients with chest pain is feasible. This supports

ongoing research in this area to obtain a sufficient sample size to derive a definitive rule. Given that chest pain is the second most common chief complaint in North American emergency departments,[5] development of a clinical decision rule for chest pain could substantially impact the care of a large number of patients. Results of an international survey of emergency physicians indicate that development of a clinical decision rule for anterior chest pain is an important priority.[105] Development of a highly sensitive clinical decision rule has potential to decrease the rate of misdiagnosis, decrease costs, and improve the efficiency of care in emergency departments across North America. This study represents the first step toward development of such a rule.

5.10 Conclusions

There were 87 patients who experienced acute myocardial infarction, death, or revascularization among the 640 prospectively enrolled emergency department patients. Of these 87 positive outcomes, 36 occurred outside of the emergency department. One hundred twenty-two (19.1%) patients were admitted to the hospital.

We found several variables that were highly correlated with the primary outcome that were sufficiently reliability to be considered for inclusion in a clinical decision rule. Using recursive partitioning, we derived a preliminary rule that was 100% sensitive and 25% specific for predicting acute myocardial infarction, death, or revascularization within 30 days of the emergency department visit. With a larger sample size, deriving a definitive rule that predicts outcomes occurring outside of the emergency department is feasible and has potential to decrease the rate of missed diagnosis, decrease costs, and enhance flow in our busy and overcrowded emergency departments.

Table 1. Demographic, Cardiac Risk Factor, and Cardiovascular History Characteristics of 640 Emergency Patients with Chest Pain

Characteristics	Number of Patients (N=640)
Demographics	
Mean Age (SD)	59.6 (13.8)
Range*	26-99
Interquartile range**	49.5-69.0
Female (%)	257 (40.2)
Arrival by Ambulance (%)	135 (21.1)
Transfer from Another ED (%)	0 (0)
Admitted to the hospital (%)	122 (19.1)
Interobserver Case (%)	49 (7.7)
Mean length of stay in Department in hours (SD)	6.0 (2.9)
Range	0.6-23.5
Interquartile range	4.0
Cardiac Risk Factors	
Hypertension (%)	327 (51.1)
Diabetes mellitus (%)	121 (18.9)
Hypercholesterolemia (%)	304 (47.5)
Family history of cardiac disease (%)	221 (34.5)
Smoking history (%) (n = 561)	
Current	115 (20.5)
Former (<1 year)	37 (6.6)
Former (>1 year)	159 (28.3)
Never	250 (44.6)
No cardiac risk factors (%)	128 (20.0)
Cardiovascular History	
Acute myocardial infarction (%)	140 (21.9)
Angina (chest pain on exertion) (%)	137 (21.4)
Known coronary artery disease (%)	171 (26.7)
Congestive heart failure (%)	26 (4.1)
Cardiac arrest (%)	4 (0.6)
Ventricular tachycardia (%)	3 (0.5)
Atrial fibrillation (%)	33 (5.2)
Stroke or transient ischemic attack (%)	19 (3.0)
Peripheral vascular disease (%)	13 (2.0)
None (%)	353 (55.2)

*The range is expressed as minimum – maximum.

**The interquartile range is expressed as the first quartile – third quartile.

Table 2. Characteristics from the Medication History in 640 Emergency Patients with Chest Pain

Medication	Number of Patients (N=640)
Aspirin (%)	250 (39.1)
Clopidogrel (%)	62 (9.7)
Beta blocker (%)	176 (27.5)
Calcium channel blocker (%)	95 (14.8)
Nitrates (%)	124 (19.4)
Angiotensin Converting Enzyme Inhibitors (%)	137 (21.4)
Other anticoagulants (e.g. Coumadin, Aspirin/Dipyridamole) (%)	33 (5.2)
Cholesterol-lowering drugs (%)	238 (37.2)

Table 3. Characteristics from the Chest Pain History in 640 Emergency Patients with Chest Pain

Characteristic	Number of Patients (N=640)
Mean duration of chest pain in hours (SD)	6.0 (20.3)
Range	0.08-168
Interquartile range	3.9-7.9
Present on ED arrival (%)	404 (63.1)
Present at rest (%)	576 (90.0)
Resolution of pain prior to evaluation (%)	368 (57.5)
Worse with exertion (%)	199 (31.1)
Pleuritic (%)	60 (9.4)
Similar to previously diagnosed ischemia (%)	143 (22.3)
Change in usual pattern of angina in past 24 hours (%)	100 (15.6)
$\geq$ 2 episodes of pain in the past 24 hours (%)	293 (45.8)
Recurred during the ED visit (%)	93 (14.5)
Onset (n = 633)	
Abrupt (< 1hr) (%)	481 (76.0)
Gradual (>1hr) (%)	152 (24.0)
Location on chest*	
Center (%)	387 (60.5)
Left anterior (%)	238 (37.2)
Left lateral (%)	39 (6.1)
Right anterior (%)	31 (4.8)
Right lateral (%)	8 (1.3)
Pain description*	
Pressure/squeezing (%)	333 (52.0)
Heavy (%)	122 (19.1)
Sharp (%)	130 (20.3)
Indigestion/burning quality (%)	63 (9.8)
Radiation*	
Right arm/shoulder (%)	29 (4.5)
Left arm/shoulder (%)	202 (31.6)
Both arms/shoulders (%)	37 (5.8)
Neck/jaw (%)	111 (17.3)
Back (%)	92 (14.4)
Abdomen (%)	8 (1.3)
Associated symptoms*	
Nausea or vomiting (%)	134 (20.9)
Shortness of breath (%)	257 (40.2)
Diaphoresis (%)	148 (23.1)
None (%)	259 (40.5)
Worse with movement (%)	77 (12.0)
Overall assessment (n = 637)	
Typical for acute coronary syndrome (%)	289 (45.4)
Atypical for acute coronary syndrome (%)	348 (54.6)

*Some patients reported pain in more than one location, used more than one descriptor for the pain, reported radiation of the pain to more than one location, and reported one or more associated symptoms.

Table 4. Characteristics from the Physical Examination in 640 Emergency Patients with Chest Pain

Characteristic	Number of Patients (N=640)
Physical examination	
Cardiac auscultation (n = 639)	
S3 (%)	1 (0.2)
S4 (%)	2 (0.3)
Systolic murmur (%)	39 (6.1)
Diastolic murmur (%)	1 (0.2)
Normal (%)	596 (93.2)
Lung auscultation*	
Crackles/rales at bases (%)	41 (6.4)
Crackles/rales to scapulae (%)	5 (0.8)
Wheezes (%)	15 (2.3)
Normal (%)	582 (90.9)
Chest wall tenderness (%)	76 (11.9)
Pitting edema (%)	40 (6.3)

*Some patients had more than one finding on lung auscultation.

Table 5. Interpretation of First Readable ECG and Cardiac Troponin T Measurements in 640 Emergency Patients with Chest Pain

Characteristics	Number of Patients (N=640)
ECG abnormalities	
ST-segment depression (%)	30 (4.7)
≤ ½ mm	5 (16.7)
½ to 1 mm	11 (36.7)
>1mm	14 (46.7)
Old (%)	9 (30.0)
Not known to be old (%)	21 (70.0)
T-wave inversions (%)	45 (7.0)
≥0.2 mm (%)	17 (37.8)
<0.2mm (%)	28 (62.2)
Old (%)	25 (55.6)
Not known to be old (%)	20 (44.4)
Q-waves	86 (13.4)
Old (%)	53 (61.6)
Not known to be old (%)	33 (38.4)
Left bundle branch block (%)	21 (3.3)
Old (%)	17 (90.0)
Not known to be old (%)	4 (19.0)
Right bundle branch block (%)	25 (3.9)
Old (%)	14 (56.0)
Not known to be old (%)	11 (44.0)
Overall interpretation	
Nonspecific ST-T wave changes (%)	229 (35.8)
Abnormal but not diagnostic of ischemia (%)	156 (24.4)
Infarction or ischemia known to be old (%)	68 (10.6)
Infarction or ischemia not known to be old (%)	56 (8.8)
*Consistent with acute myocardial infarction (ST-segment elevation or new left bundle branch block) (%)	0 (0)
Normal (%)	131 (20.5)
Cardiac Troponin T (n = 634)	
Cardiac Troponin T < 0.01	545 (86.0)
Cardiac Troponin T ≥ 0.01 ng/mL	89 (14.0)

* Patients ST-segment elevation were excluded from the study, as the prediction rule would not apply to this group of high risk patients.

Table 6. Management of 640 Emergency Patients with Chest Pain

Outcome	Number of Patients (N=640)
Cardiac stress testing (%)	201 (31.4)
Stress/rest radionuclide imaging (%)	150 (23.4)
Positive for ischemia (%)	31 (20.7)
Negative for ischemia (%)	118 (78.7)
Equivocal (%)	0 (0)
Inconclusive (%)	1 (0.7)
Exercise ECG (%)	41 (6.4)
Positive for ischemia (%)	2 (4.9)
Negative for ischemia (%)	38 (92.7)
Equivocal (%)	0 (0)
Inconclusive (%)	1 (2.4)
Stress echo (%)	0 (0)
Other (%)	8 (1.3)
Positive for ischemia (%)	3 (37.5)
Negative for ischemia (%)	3 (37.5)
Equivocal (%)	0 (0)
Inconclusive (%)	2 (25.0)
Cardiac computed tomography (%)	22 (3.4)
Stenosis $\geq$ 70% (%)	5 (22.7)
Coronary angiography (%)	107 (16.7)
Stenosis $\geq$ 70% (%)	85 (79.4)

Table 7. Outcomes of 640 Emergency Patients with Chest Pain

Outcome	Number of Patients (N=640)
Positive for primary outcome* (%)	87 (13.6)
Outcome location	
Emergency Department	51 (8.0)
In-hospital	23 (3.6)
Out-of-hospital	13 (2.0)
Acute myocardial infarction† (%)	48 (7.5)
Revascularization (%)	69 (10.8)
Percutaneous coronary intervention†† (%)	55 (79.7)
Coronary artery bypass grafting (%)	14 (20.3)
Death of cardiac/unknown cause (%)	0 (0)
New perfusion defect on radionuclide imaging (%)	31 (4.8)

* Acute myocardial infarction, revascularization, or death within 30 days of the emergency department visit.

† 30 of 48 patients with acute myocardial infarction underwent revascularization.

††Angioplasty and/or stent placement.

Table 8. Characteristics of the 345 Missed Eligible Emergency Patients with Chest Pain

Characteristics	Number of Patients (N=345)
Mean age (SD)	62.1 (12.8)
Range*	27-90
Interquartile range**	52-72
Female (%)	144 (41.7)
Cardiac stress testing (%)	86 (24.9)
Cardiac computed tomography (%)	8 (2.3)
Coronary angiography (%)	86 (24.9)
Positive for primary outcome (%)	60 (17.4)

*The range is expressed as minimum – maximum.

**The interquartile range is expressed as first quartile – third quartile.

Table 9. Univariate correlation and κ values of Demographic, Cardiac Risk Factor, and Cardiovascular History variables for the Primary Outcome Acute Myocardial Infarction, Revascularization, or Death within 30 days in 640 Emergency Patients with Chest Pain

Characteristics	Negative for primary outcome (n=553)	Positive for primary outcome (n=87)	p-value	κ (n=49)
Demographics				
Mean Age (SD)	58.8 (13.8)	64.5 (12.4)	<0.01	....
Female (%)	236 (42.7)	21 (24.1)	<0.01	....
Arrival by Ambulance (%)	116 (20.9)	19 (21.8)	0.90	....
Transfer from Another ED (%)	0 (0)	0 (0)	....	....
Admitted to the hospital (%)	52 (9.4)	70 (80.5)	<0.01	....
Mean length of stay in department in hours (SD)	6.2 (2.8)	4.9 (2.9)	<0.01	....
Cardiac Risk Factors				
Hypertension (%)	280 (50.6)	47 (54.0)	0.99	1.00
Diabetes mellitus (%)	100 (18.1)	21 (24.1)	0.28	1.00
Hypercholesterolemia (%)	256 (46.3)	48 (55.2)	0.27	0.90
Family history of cardiac disease (%)	192 (34.7)	29 (33.3)	0.48	0.96
Smoking history (%)			0.02	0.88
Current	102 (18.4)	13 (14.9)		
Former (<1 year)	27 (4.9)	10 (11.5)		
Former (>1 year)	133 (24.1)	26 (29.9)		
Never	225 (40.7)	25 (28.7)		
No cardiac risk factors (%)	117 (21.2)	11 (12.6)	0.08	....
Cardiovascular history				
Acute myocardial infarction (%)	116 (21.0)	24 (27.6)	0.90	0.95
Angina (chest pain on exertion) (%)	110 (19.9)	27 (31.0)	0.20	0.95
Known coronary artery disease (%)	135 (24.4)	36 (41.4)	0.02	0.91
Congestive heart failure (%)	20 (3.6)	6 (6.9)	0.37	1.00
*Cardiac arrest (%)	4 (0.7)	0 (0)	1.00	....
*Ventricular tachycardia (%)	3 (0.5)	0 (0)	1.00	....
Atrial fibrillation (%)	32 (5.8)	1 (1.1)	0.02	0.88
*Stroke or transient ischemic attack (%)	16 (2.9)	3 (3.4)	1.00	....
*Peripheral vascular disease (%)	10 (1.8)	3 (3.4)	0.46	....
No cardiovascular history (%)	315 (57.0)	38 (43.7)	0.03	....

* None of the interobserver cases had a cardiovascular history of cardiac arrest, ventricular tachycardia, stroke, transient ischemic attack, or peripheral vascular disease.

Table 10. Univariate correlation of Variables from the Medication History for the Primary Outcome Acute Myocardial Infarction, Revascularization, or Death within 30 days in 640 Emergency Patients with Chest Pain

Medication	Negative for primary outcome (n=553)	Positive for primary outcome (n=87)	p-value
Aspirin	204 (36.7)	46 (52.9)	0.02
Clopidogrel	49 (8.9)	13 (14.9)	0.16
Beta blocker	146 (26.4)	30 (34.5)	0.33
Calcium channel blocker	83 (15.0)	12 (13.8)	0.46
Nitrates	100 (18.1)	24 (27.6)	0.11
Angiotensin Converting Enzyme Inhibitor	119 (21.5)	18 (20.7)	0.45
Other anticoagulants (Coumadin, aspirin/dipyridamole)	30 (5.4)	3 (3.4)	0.32
Cholesterol-lowering drugs	199 (36.0)	39 (44.8)	0.38

Table 11. Univariate Correlation of Variables from the Chest Pain History with the Primary Outcome Acute Myocardial Infarction, Revascularization, or Death within 30 Days in 640 Emergency Patients with Chest Pain

Characteristics	Negative for primary outcome (n=553)	Positive for primary outcome (n=87)	p-value	κ (n=49)
Mean duration of chest pain in hrs (SD)	6.3 (20.0)	4.4 (22.1)	0.52	....
Present on ED arrival (%)	355 (64.2)	49 (56.3)	0.14	0.85
Present at rest (%)	507 (91.7)	69 (79.3)	<0.01	0.88
Resolution of pain prior to evaluation (%)	309 (55.9)	59 (67.8)	0.06	0.80
Worse with exertion (%)	154 (27.8)	45 (51.7)	<0.01	0.51
Pleuritic (%)	58 (10.5)	2 (2.3)	<0.01	0.73
Similar to previous ischemia (%)	112 (20.3)	31 (35.6)	0.01	0.83
Change in usual pattern of angina in past 24 hours (%)	79 (14.3)	21 (24.1)	0.04	0.65
≥ 2 episodes of pain in past 24 hrs (%)	233 (42.1)	60 (69.0)	<0.01	0.60
Recurred during the ED visit (%)	81 (14.6)	12 (13.8)	0.34	0.75
Onset			<0.01	0.43
Abrupt (<1hr) (%)	401 (72.5)	80 (92.0)		
Gradual (>1hr) (%)	145 (26.2)	7 (8.0)		
Location on chest				
Centre (%)	324 (58.6)	63 (72.4)	0.02	0.62
Left anterior (%)	212 (38.3)	26 (29.9)	0.12	0.59
Left lateral (%)	35 (6.3)	4 (4.6)	0.53	-0.03
Right anterior (%)	30 (5.4)	1 (1.1)	0.08	0.65
Right lateral (%)	8 (1.4)	0 (0)	0.61	....
Pain description				
Pressure/squeezing (%)	278(50.3)	55 (63.2)	0.01	0.62
Heavy (%)	103 (18.6)	19 (21.8)	0.39	0.34
Sharp (%)	123 (22.2)	7 (8.0)	<0.01	0.62
Indigestion/burning quality (%)	55 (9.9)	8 (9.2)	0.90	0.91
Radiation				
Left arm/shoulder (%)	164 (29.7)	38 (43.7)	0.01	0.67
Right arm/shoulder (%)	24 (4.3)	5 (5.7)	0.57	-0.02
Both arms/shoulders (%)	27 (4.9)	10 (11.5)	0.01	0.88
Neck/jaw (%)	92 (16.6)	19 (21.8)	0.24	0.45
Back (%)	82 (14.8)	10 (11.5)	0.40	1.00
Abdomen (%)	7 (1.3)	1 (1.1)	1.00	1.00
Associated symptoms				
Nausea or vomiting (%)	116 (21.0)	18 (20.7)	0.93	0.87
Shortness of breath (%)	211 (38.2)	46 (52.9)	0.01	0.70
Diaphoresis (%)	116 (21.0)	32 (36.8)	<0.01	0.89
Worse with movement (%)	71 (12.8)	13 (14.9)	0.28	0.28
Overall assessment			<0.01	0.71
Typical for acute coronary syndrome (%)	216 (39.1)	73 (83.9)		
Atypical for acute coronary syndrome (%)	334 (60.4)	14 (16.1)		

Table 12. Univariate correlation of Variables from the Physical Examination with the Primary Outcome Acute Myocardial Infarction, Revascularization, or Death within 30 days in 640 Emergency Patients with Chest Pain

Characteristics	Negative for primary outcome (n=553)	Positive for primary outcome (n=87)	p-value	κ (n=49)
Cardiac auscultation				
S3 (%)	0 (0)	1 (1.1)	0.01	....
S4 (%)	2 (0.4)	0 (0)	0.57	....
Systolic murmur (%)	33 (6.0)	6 (6.9)	0.73	0.64
Diastolic murmur (%)	1 (0.2)	0 (0)	0.69	....
Systolic/diastolic murmur (%)	1 (0.2)	0 (0)	0.69	....
Normal (%)	516 (93.3)	80 (92.0)	0.64	0.64
Lung auscultation				
Crackles/rales at bases (%)	34 (6.1)	7 (8.0)	0.50	0.45
*Crackles/rales to scapulae (%)	4 (0.7)	1 (1.1)	0.52	....
Wheezes (%)	11 (2.0)	4 (4.6)	0.13	....
Normal (%)	506 (91.5)	76 (87.3)	0.20	0.33
Chest wall tenderness (%)	70 (12.7)	6 (6.9)	0.12	0.63
Pitting edema (%)	33 (6.0)	7 (8.0)	0.44	0.77

No interobserver cases were reported as having an S3, S4, diastolic murmur, or systolic and diastolic murmur on cardiac auscultation, or crackles/rales to the scapulae or wheezes on lung auscultation.

Table 13. Univariate Correlation of Electrocardiographic (ECG) Findings and Cardiac Troponin T with the Primary Outcome Acute Myocardial Infarction, Revascularization, or Death within 30 days in 640 Emergency Patients with Chest Pain

Characteristics	Negative for primary outcome (n=553)	Positive for primary outcome (n=87)	p-value
ECG finding			
Normal (%)	118 (21.3)	13 (14.9)	0.17
Nonspecific ST-segment changes (%)	207 (37.4)	22 (25.3)	0.03
Abnormal but not diagnostic of ischemia (%)	138 (25.0)	19 (21.8)	0.53
*Infarction or ischemia known to be old (%)	57 (10.3)	11 (12.6)	0.51
Infarction or ischemia not known to be old (%)	33 (6.0)	23 (26.4)	<0.01
**Cardiac Troponin T ≥ 0.01 (%)	34 (6.1)	55 (63.2)	<0.01

*Infarction or ischemia on electrocardiogram is defined as T-wave inversions ≥ 0.2 mm or ST-segment depression ≥ 0.5mm in at least 2 contiguous leads.
**Any serial cardiac troponin T value ≥ 0.01.
ECG, electrocardiogram.

Table 14. Univariate correlation of Cut-point and Combination Variables with the Primary Outcome Acute Myocardial Infarction, Revascularization, or Death within 30 days in 640 Emergency Patients with Chest Pain

Characteristics	Negative for primary outcome (n=553)	Positive for primary outcome (n=87)	p-value
Age ≥ 35 (%)	536 (96.9)	87 (1.0)	0.10
Age ≥ 40 (%)	518 (93.7)	84 (96.6)	0.29
Age ≥ 45 (%)	474 (85.7)	83 (95.4)	0.01
Age ≥ 50 (%)	403 (72.9)	77 (88.5)	<0.01
Age ≥ 55 (%)	333 (60.2)	70 (80.5)	<0.01
Age ≥ 60 (%)	252 (45.6)	56 (64.4)	<0.01
Age ≥ 65 (%)	172 (31.1)	43 (49.4)	<0.01
Age ≥ 70 (%)	126 (22.8)	30 (34.5)	0.02
Age ≥ 75 (%)	84 (15.2)	20 (23.0)	0.07
No cardiac risk factors (%)	117 (21.2)	11 (12.6)	0.08
1 cardiac risk factor (%)	137 (24.8)	20 (23.0)	0.72
2 cardiac risk factors (%)*	157 (28.4)	27 (31.0)	0.61
3 cardiac risk factors (%)*	125 (22.6)	20 (23.0)	0.94
4 cardiac risk factors (%)*	53 (9.6)	9 (10.3)	0.82
5 cardiac risk factors (%)*	11 (2.0)	5 (5.7)	0.04
Ever a smoker (%)	263 (47.6)	49 (56.3)	0.05
No cardiovascular history (%)	315 (57.0)	38 (43.7)	0.03
History of acute myocardial infarction or angina (%)*	177 (32.0)	40 (46.0)	0.01
History of acute myocardial infarction or known coronary artery disease (%)*	168 (30.4)	40 (46.0)	<0.01
History of acute myocardial infarction, angina, or known coronary artery disease (%)*	206 (37.3)	45 (51.7)	0.01
Associated shortness of breath or diaphoresis (%)*	263 (47.6)	59 (67.8)	<0.01
Pre-test probability ≥ 20%**	63 (11.4)	42 (48.3)	<0.01
Pre-test probability ≥ 10%***	86 (15.6)	49 (56.3)	<0.01

* To be included as part of a combination variable, the kappa value of each component had to be ≥ 0.6 where assessed.
**Kappa = 0.63.
***Kappa = 0.78.

Table 15. Hosmer and Lemeshow Goodness of Fit of Final 2 Regression Models in Patients Presenting to the Emergency Department with Chest Pain

Model (Variables included)	Significance
7 variables	0.810
Acute ischemic changes on electrocardiogram	
Troponin T ≥ 0.01 ng/mL	
Pain present at rest	
≥ 2 episodes of pain in the last 24 hours	
Pain described as a pressure or squeezing sensation	
Radiation of the pain to the left or both shoulders	
Pain atypical for acute coronary syndrome	
5 variables	0.239
Acute ischemic changes on electrocardiogram	
Troponin T ≥ 0.01 ng/mL	
Pain present at rest	
≥ 2 episodes of pain in the last 24 hours	
Pain atypical for acute coronary syndrome	

Table 16. Final model Developed by Stepwise Logistic Regression Analysis to Predict Acute Myocardial Infarction, Revascularization, or Death within 30 Days in Patients Presenting to the Emergency Department with Chest Pain

Variable	Coefficient	Odds Ratio (95% CI)
Intercept	-2.24	< 0.0001
Acute ischemic changes on electrocardiogram (T-wave inversions or ST-depressions in at least 2 contiguous leads)	1.14	3.13 (1.33-7.39)
Troponin T ≥ 0.01 ng/mL	3.36	28.83 (14.22-58.43)
Pain present at rest	-1.32	0.27 (0.12-0.59)
≥ 2 episodes of pain the last 24 hours	1.71	5.51 (2.73-11.15)
Pain atypical for acute coronary syndrome	-1.57	0.21 (0.10-0.42)

Table 17. Assessment for Multicollinearity in Final Logistic Regression Model

Variable	Tolerance	Variance Inflation Factor
Intercept	....	0
Acute ischemic changes on electrocardiogram (T-wave inversions or ST-depressions in at least 2 contiguous leads)	0.92106	1.08571
Troponin T $\geq$ 0.01 ng/mL	0.88207	1.13369
Pain present at rest	0.97597	1.02463
$\geq$ 2 episodes of pain the last 24 hours	0.98856	1.01157
Pain atypical for acute coronary syndrome	0.91161	1.09696

Table 18. Sensitivity and Specificity of Proposed Logistic Regression Model at Varying Cut Points to Determine which Patients with Chest Pain Require Further Investigation

Classification Cut Off	Sensitivity (%)	Specificity (%)
0.95	1.1	100.0
0.9	12.6	99.8
0.8	32.2	98.7
0.7	35.6	98.0
0.6	43.7	98.0
0.5	43.7	97.4
0.4	59.8	95.5
0.3	72.4	92.6
0.2	77.0	92.2
0.1	89.7	75.5
0.05	89.7	72.9
0.04	89.7	72.9
0.03	89.7	49.6
0.02	98.9	30.5
0.01	100.0	29.0

Table 19. Hosmer and Lemeshow Goodness of fit of Final 2 Regression Models Predicting Outcomes Occurring Outside of the Emergency Department

Model (Variables included)	Significance
Forward stepwise selection	
5 variables	0.945
Pain present at rest	
Resolution of the pain prior to physician evaluation	
≥ 2 episodes of chest pain in the past 24 hours	
Current aspirin use	
Pretest probability for acute coronary syndrome ≥ 20%	
Backward stepwise selection	
7 variables	0.246
Resolution of the pain prior to physician evaluation	
≥ 2 episodes of chest pain in the past 24 hours	
Current aspirin use	
Pain present at rest	
Radiation of pain to left or both shoulders	
Pain location in the center of the chest	
Pretest probability for acute coronary syndrome ≥ 20%	

Table 20. Final model Developed by Stepwise Logistic Regression to Predict Outcomes Occurring Outside of the Emergency Department

Variable	Coefficient	Odds Ratio (95% CI)
Intercept, p-value	-6.0511	< 0.01
Pain present at rest	-1.0359	0.36 (0.13-0.96)
Resolution of the pain prior to physician evaluation	2.1840	8.88 (1.85-42.65)
≥ 2 episodes of chest pain in the past 24 hours	1.5790	4.85 (1.56-15.12)
Current aspirin use	1.3408	3.82 (1.50-9.77)
Pre-test probability for acute coronary syndrome ≥ 20%	1.8559	6.40 (2.57-15.95)

Table 21. Assessment for Multicollinearity in Final Model Predicting Outcomes Occurring Outside of the Emergency Department

Variable	Tolerance	Variance Inflation Factor
Intercept, p-value	....	0
Pain present at rest	0.89731	1.11444
Resolution of the pain prior to physician evaluation	0.92408	1.08216
≥ 2 episodes of chest pain in the past 24 hours	0.95245	1.04993
Current aspirin use	0.96863	1.03238
Pre-test probability for acute coronary syndrome ≥ 20%	0.94237	1.06116

Table 22. Sensitivity and Specificity of Proposed Logistic Regression Model Predicting Outcomes Occurring Outside of the Emergency Department at Varying Cut Points to Determine which Patients with Chest Pain Require Further Investigation

Classification Cut Off	Sensitivity (%)	Specificity (%)
0.95	0.0	100.0
0.90	0.0	100.0
0.8	0.0	100.0
0.7	0.0	99.6
0.6	31.0	99.6
0.5	31.0	99.6
0.4	41.4	98.2
0.3	41.4	98.0
0.2	48.3	96.9
0.1	72.4	86.2
0.05	79.3	80.8
0.04	79.3	78.8
0.03	79.3	66.8
0.02	86.2	55.0
0.01	93.1	49.7

Table 23. Recursive Partitioning Models to Predict which Patients with Chest Pain Develop Acute Myocardial Infarction, Revascularization, or Death within 30 days (n = 640)

Recursive Partitioning Model	Sensitivity	Specificity
5 variables Age ≥ 55, known coronary artery disease, Acute ischemic changes on electrocardiogram*, cardiac Troponin T > 0.01 ng/mL, diaphoresis	100% (96-100)	25% (22-29)
5 variables Age ≥ 60, history of acute myocardial infarction or known coronary artery disease, Acute ischemic changes on electrocardiogram*, cardiac Troponin T > 0.01 ng/mL, shortness of breath or diaphoresis	100% (96-100)	22% (19-26)
7 variables Age ≥ 60, history of acute myocardial infarction or known coronary artery disease, Acute ischemic changes on electrocardiogram*, cardiac Troponin T > 0.01 ng/mL, history of diabetes, current nitrate use, diaphoresis	100% (96-100)	27% (24-31)

* T-wave inversions ≥ 0.2 mm or ST-segment depression ≥ 0.5mm in at least 2 contiguous leads.

Table 24. Physician's Assessment of the Pre-test Probability that Their Patient had Acute Coronary Syndrome

Pretest Probability of Patient Having Acute Coronary Syndrome (%)*	Negative for Acute Coronary Syndrome	Positive for Acute Coronary Syndrome
≤ 1	90	2
2	94	6
3	43	5
4	11	1
5	89	6
10	45	9
20	21	9
30	17	8
50	23	10
75	14	22
100	3	8

* We defined acute coronary syndrome as acute myocardial infarction, revascularization, death, or a new perfusion defect on radionuclide imaging within 30 days.

Figure 1. Summary of Clinical Decision (Prediction) Rules that Have been Derived Only (Level 4 Evidence)

First author, year	Type of Clinical Prediction Tool	Outcomes	Duration of follow-up	Sensitivity, Specificity	Comments
Bjork, 2006[47]	Logistic regression model	Acute myocardial infarction, Unstable angina	Duration of hospitalization	0.95, 0.43	Retrospective; Limited duration of follow-up
Christenson, 2006 [31]	Clinical prediction rule	Cardiac-cause mortality, Acute myocardial infarction , Unstable angina	30 days	0.99, 0.33	Data on interobserver reliability of variables not reported
Lorenzoni, 2006[70]	Computer-derived algorithm	Cardiac-cause mortality, AMI, revascularization, significant coronary artery disease (>50% stenosis)	30 days	0.90, 0.87	Insufficient Sensitivity
Martinez-Selles, 2005[69]	Risk score	"Significant" coronary disease defined as: 1. >70% stenosis 2. Cardiac stress test positive for ischemia	3 months	0.94, 0.32	
Bassan, 2004[45]	Classification diagnostic tree	Acute myocardial infarction, Unstable angina	Unclear	0.97, 0..57	
Fernandez Portales, 2003[106]	Risk score	All-cause mortality, Ischemic recurrence, congestive heart failure	15 days	0.98, 0.45	
Baxt, 2002[36]	Artificial Neural Network	Acute myocardial infarction	30 days	0.95, 0.96	Outcome limited to Acute myocardial infarction
Baxt, 2002[107]	Artificial Neural Network	Acute myocardial infarction	30 days	0.88, 0.86	Retrospective
Domanovitz, 2002[59]	Diagnostic algorithm	Cardiac-cause mortality, acute myocardial infarction, revascularization	6 months	0.97, 0.86	
Limakeng, 2001[60]	Computer-derived algorithm	Acute myocardial infarction, revascularization, or death	30 days	0.71, 0.72	Relatively poor sensitivity
Ng, 2001[42]	Clinical diagnostic pathway	Acute myocardial infarction	30 days	1.0, 0.94	Outcome limited to Acute myocardial infarction
Porela, 2000[71]	Predictive instrument	All-cause mortality, Acute myocardial infarction	Duration of hospitalization	0.90, 0.61	
Mair, 1995[108]	Classification diagnostic tree	Acute myocardial infarction	Duration of hospitalization	0.91, 0.90	Convenience sample
Mair, 1995[41]	Classification diagnostic tree	Acute myocardial infarction	Duration of hospitalization	0.96, 0.90	Limited duration of follow-up
Baxt, 1991[32]	Artificial Neural Network	Acute myocardial infarction	Duration of hospitalization	0.92, 0.96	Retrospective
Poretsky, 1985[43]	Computer-derived algorithm	Acute myocardial infarction	Duration of hospitalization	0.81, 0.53	Limited duration of follow-up

Figure 2. Summary of Clinical Decision Rules that have been Validated in only 1 Narrow Prospective Sample (Level 3 Evidence)

First author, year	Type of Clinical Prediction Tool	Outcomes	Duration of follow-up	Sensitivity, Specificity	Comments
Mitchell, 2006[109]	Computer-derived probability assessment, Risk Score	All-cause mortality, Acute myocardial infarction, Revascularization	45 days	0.98, 0.26 (attribute matching) 1.0, 0.06 (ACI-TIPI)	Validation of attribute matching and **ACI-TIPI** instrument. Probability of adverse outcome >1%.
Harrison, 2005[46]	Artificial Neural Network	Acute myocardial infarction, Unstable angina	30 days	0.93, 0.93	Insufficient sensitivity
Marsan, 2005[68]	Clinical prediction rule	All-cause mortality, acute myocardial infarction, revascularization, unstable angina	30 days	0.98, 0.31	Clinical decision rule retrospectively refined to increase sensitivity; requires additional validation.
Diercks, 2004[76]	Risk Score	Acute myocardial infarction, unstable angina, death	30 days	Not reported (derivation) 0.76, 0.78 (validation)	Applicable to women only (men excluded)
Baxt, 1996[110]	Artificial Neural Network	Acute myocardial infarction	21 days	0.96, 0.96	Outcome limited to Acute myocardial infarction
Baxt, 1991[111]	Artificial Neural Network	Acute myocardial infarction	Duration of hospitalization	0.97, 0.96	Outcome limited to Acute myocardial infarction
Tierney, 1985[44]	Clinical Prediction Rule	Acute myocardial infarction	7 days	0.81, 0.86 (for combined derivation and validation data sets)	Outcome limited to acute myocardial infarction; limited follow-up; validated on same patient population from which the rule was derived

Figure 3. Summary of Clinical Decision Rules that Have Been Validated Broadly in Multiple Clinical Settings (Level 2 Evidence)

First author, year	Type of Clinical Prediction Tool	Outcomes	Duration of follow-up	Sensitivity, Specificity	Comments
Jaffery, 2007[56]	Risk score	All-cause mortality, acute myocardial infarction, revascularization	30 days	0.82, 0.58	Retrospective validation of the **TIMI risk score**
Lyon, 2007[112]	Risk score	All-cause mortality, Acute myocardial infarction, revascularization	30 days	1.00, 0.13	Prospective validation of the **TIMI risk score**
Chase, 2006[53]	Risk Score	All-cause mortality, Acute myocardial infarction, Revascularization	30 days	0.94, 0.35	Prospective validation of the **TIMI risk score**
Conway Morris, 2006[113]	Risk Score	All-cause mortality, Acute myocardial infarction, Revascularization	30 days	1.0, 0.28	Prospective Validation of the **TIMI risk score**
Fox, 2006	Risk Score	Acute myocardial infarction, acute myocardial infarction and death		Not reported; C-statistic 0.70 (derivation) and 0.73 (validation)	Retrospective; **GRACE risk score**; sensitivity of the model likely < 99%
Pollack, 2006[58]	Risk Score	All-cause mortality, Acute myocardial infarction, revascularization	30 days	0.91, 0.38	Retrospective validation of the **TIMI risk score**; convenience Sample
Chandra, 2005[49]	Clinical prediction instrument	Acute myocardial infarction, Unstable angina	45 days	0.62, 0.59	Relatively poor sensitivity
Garcia Almagro, 2005[114]	Risk Score	All-cause morality, acute myocardial infarction, death	6 months	0.83, 0.72	Prospective Validation of the **TIMI risk score**; scores ≤ 1 considered low risk
Goncalves, 2005	Risk scores (3)	Acute myocardial infarction, acute myocardial infarction and death	30 days	Not reported; C-statistic 0.59 (TIMI risk score); 0.72 (GRACE), and 0.63 (PURSUIT)	Retrospective validation of the TIMI, GRACE, and PURSUIT risk scores
Miller, 2005[109]	Risk Score	All-cause mortality, Acute myocardial infarction, Unstable Angina, Revascularization	30 days	Not reported	Diagnostic performance of the **ACI-TIPI** instrument differed between the United States and Singapore
Tong, 2005[115]	Risk Score	All-cause mortality, Acute myocardial infarction, Revascularization, Unstable Angina	30 days	0.98, 0.19	Prospective validation of the **TIMI risk score**

Eagle, 2004[50]	Risk Score	Acute myocardial infarction, acute myocardial infarction and death	6 months	Not reported; C-statistic 0.81 (derivation) and 0.75 (validation)	Retrospective; **GRACE risk score**; sensitivity of the model was not reported and likely <99%
Seyal, 2002[73]	Risk Score	Acute myocardial infarction, Unstable angina, Stable angina	Duration of hospitalization	0.98, 0.06	Validation of the **ACI-TIPI** instrument; limited follow-up
Durairaj, 2001[116]	Clinical Decision Rule	Major cardiac events defined as ventricular fibrillation, cardiac arrest, new complete heart block, insertion of a temporary pacemaker, emergency cardioversion, cardiogenic shock, use of an intraaortic balloon pump, intubation, or recurrent ischemic chest pain requiring revascularization	24-72 hours	Not reported	Predicts adverse cardiac events within 72 hours of admission
Antman, 2000[117]	Risk Score	All-cause mortality, Acute myocardial infarction, Revascularization	30-days	0.99, 0.05 (derivation) 0.99, 0.05 (validation)	Retrospective derivation and validation of the **TIMI risk score**
Boersma, 2000[14]	Risk Score	Acute myocardial infarction, acute myocardial infarction and death	30 days	Not reported; C-statistic 0.67 (derivation), 0.66 (validation)	Retrospective; **PURSUIT risk score**; sensitivity and of the model was not reported and likely <99%
Reilly, 1999[118]	Clinical Prediction rule	Major cardiac events defined as ventricular fibrillation, cardiac arrest, new complete heart block, insertion of a temporary pacemaker, emergency cardioversion, cardiogenic shock, use of an intraaortic balloon pump, intubation, or recurrent ischemic chest pain requiring revascularization	24-72 hours	1.0 , 0.55	Predicts adverse cardiac events within 72 hours of admission
Goldman, 1996[64]	Clinical Prediction Rule	Major cardiac events defined as ventricular fibrillation, cardiac arrest, new complete heart block, insertion of a temporary pacemaker, emergency cardioversion, cardiogenic shock, use of an intraaortic balloon pump, intubation, or recurrent ischemic chest pain requiring revascularization	24-72 hours	Not reported	Predicts adverse cardiac events within 72 hours of admission; results reported in terms of relative risk
Selker, 1991[72]	Clinical Prediction Instrument	Acute myocardial infarction, Unstable angina, in-hospital mortality	Duration of hospitalization	Not reported	Initial study of the **ACI-TIPI** predictive instrument.
Goldman, 1988[119]	Computer-derived Algorithm (refined)	Acute myocardial infarction	8 months	0.98, 0.66 (derivation) 0.88, 0.74 (validation)	Outcome limited to acute myocardial infarction

Figure 4. Summary of Clinical Decision Rules that Have Undergone Impact Analysis (Level 1 Evidence)

First author, year	Type of Clinical Prediction Tool	Outcomes	Duration of follow-up	Sensitivity, Specificity	Comments
Reilly, 2002[120]	Clinical Prediction Rule	Major cardiac events defined as ventricular fibrillation, cardiac arrest, new complete heart block, insertion of a temporary pacemaker, emergency cardioversion, cardiogenic shock, use of an intraaortic balloon pump, intubation, or recurrent ischemic chest pain requiring revascularization	24-72 hours	Not reported	Predicts adverse cardiac events within 72 hours of admission; use of the rule increased efficiency without decreasing patient safety
Selker, 1998[48]	Clinical Prediction Instrument	Acute myocardial infarction, Unstable angina	30 days	Not reported	Use of the **ACI-TIPI** instrument significantly decreased hospital admissions and increased the proportion of patients discharged from the Emergency Department
Goldman, 1982[37]	Computer-derived Algorithm	Acute myocardial infarction	8 months	1.0, 0.80 (derivation) 0.91, 0.70 (validation) 0.88, 0.77 (implementation)	Outcome limited to AMI; limited sensitivity in validation and implementation phases

Figure 5. Risk Factors Associated with Acute Coronary Syndrome on Multivariate Logistic Regression Analysis[14,47,77,78]

Demographic variable	Odds Ratio, 95% CI
Age > 71	1.23 (1.17-1.28)
Congestive heart failure	1.73 (1.31-2.28)
Coronary artery disease	3.2 (2.17-4.71)
Diabetes mellitus	1.18 (1.03-1.36)
Female sex	0.56 (0.45-0.69)
Hypertension	2.3 (1.3-4.1)
Peripheral vascular disease	1.29 (1.06-1.56)
Smoker (current)	3.7 (1.9-7.0)
Smoker (previous)	5.1 (2.4-11)

Figure 6. Diagnostically Useful Variables Obtained From the History of the Present Illness[9]

First author, year	Variable	Likelihood ratio (95% CI)
Increased likelihood of acute myocardial infarction		
Chun, 2004[121]	Radiation to right arm or shoulder	4.7 (1.9-12)
	Worse than previous angina	1.8 (1.6-2.0)
	Similar to previous MI	1.3 (1.2-1.5)
	Described as pressure	1.3 (1.2-1.5)
Goodacre, 2002[122]	Radiation to both arms or shoulders	4.1 (2.5-6.5)
	Associated with exertion	2.4 (1.5-3.8)
Panju, 1998[123]	Radiation to left arm	2.3 (1.7-3.1)
	Associated with diaphoresis	2.0 (1.9-2.2)
	Associated with nausea or vomiting	1.9 (1.7-2.3)
Decreased likelihood of acute myocardial infarction		
Chun, 2004[121]	Described as pleuritic	0.2 (0.1-0.3)
	Described as positional	0.3 (0.2-0.5)
	Described as sharp	0.3 (0.2-0.5)
	Reproducible with palpation	0.3 (0.2-0.4)
Everts, 1996[124]	Inframmamary location	0.8 (0.7-0.9)
Goodacre, 2002[122]	Not associated with exertion	0.8 (0.6-0.9)

Figure 7. Diagnostically Useful Variables Obtained from the Physical Examination[79]

First author, year	Variable	Likelihood ratio (95% CI)
Increased likelihood of acute myocardial infarction		
Tierney, 1986[125]	Third heart sound on auscultation (S3)	3.2 (1.6-6.5)
	Pulmonary crackles on lung auscultation	2.1 (1.4-3.1)
Decreased likelihood of acute myocardial infarction		
Lee, 1985,[126] Solomon 1989,[126] Tierney, 1986[125]	Chest pain reproduced on palpation	0.2-0.4*

*In studies considered to be heterogeneous, the likelihood ratios were reported as ranges.

Figure 8. List of Historical Variables Collected by Physician or Research Nurse

	Variables to be Collected	
Demographics	• Age (years) • Date of emergency visit (d/m/y) • Physician status (full-time, part-time, house staff) • Physician (code)	• Gender (male/female) • Interobserver case, if yes second physician (code) • Transfer from another emergency department • Arrival by ambulance
Cardiac medications	• Aspirin • Clopidogrel • Other anticoagulants (warfarin, aspirin/dipyridamole) • Beta blockers • Calcium channel blockers	• Nitroglycerin (or other nitrates) • Angiotensin converting enzyme inhibitors • Cholesterol-lowering drugs
Cardiac risk factors	• Hypertension • Diabetes Mellitus • Hypercholesterolemia • Renal insufficiency	• Family history of cardiac disease • Smoking history
Cardiac history	• Acute myocardial infarction • Cardiac arrest • Peripheral vascular disease • Angina • Ventricular tachycardia	• Known coronary artery disease • Atrial fibrillation • Congestive heart failure • Stroke or transient ischemic attack
Chest pain characteristics	• Duration of longest episode (days, hours, minutes; a.m., p.m.) • Was the pain present on arrival to the emergency department? • Is the pain worse with exertion? • Is the pain similar to previously diagnosed ischemia? • 2 or more episodes of pain in the last 24 hours? • Where on the chest is the pain located? • Does the pain radiate? • Is the pain worse with movement?	• Has the pain completely resolved? • Is the pain present at rest? • Is the pain pleuritic (sharp, worse with deep breathing)? • Has there been a change in the usual pattern of angina within the last 24 hours? • Did the pain recur during the ED visit? • How would you describe the pain? • Is the pain associated with nausea, vomiting, or diaphoresis?

Figure 9. List of Variables Obtained from the Physical Examination and Diagnostic Tests Collected by Physician or Research Nurse

	Variables to be Collected	
Physical Examination	• Temperature (degrees Celsius) • Heart rate (beats per minute) • Systolic blood pressure (mm of Hg) • Diastolic blood pressure (mm of Hg) • Cardiac auscultation findings (S3, S4, Systolic murmur, diastolic murmur)	• Lung auscultation findings (crackles/rales at bases, crackles/rales to scapulae, wheezes) • Chest wall tenderness (reproducing presenting symptom) • Pitting edema in lower extremities
Diagnostic tests	• Interpretation of first ECG (normal, nonspecific ST-T wave changes, abnormal known to be old, abnormal not known to be old) • Interpretation of chest x-ray (normal, pulmonary edema, other) • Cardiac stress test done • If yes, type of stress test (nuclear, exercise, stress echo, other) • If yes, result (positive for ischemia, negative for ischemia, equivocal) • If equivocal, mild ischemia, moderate ischemia, or severe ischemia?	• Time and values of first and second creatinine kinase and cardiac troponin T • Cardiac CT done • If yes, any stenosis > 70%? • Coronary angiography done? • If yes, any stenosis > 70%? • Did the patient undergo revascularization? • If yes, stent placement or coronary artery bypass grafting?
Physician judgment	• Pre-test probability of unstable angina or acute myocardial infarction (to the closest percent)	

Figure 10. Electrocardiogram Demonstrating ST-segment Elevation (arrows) and Q-waves (circles)

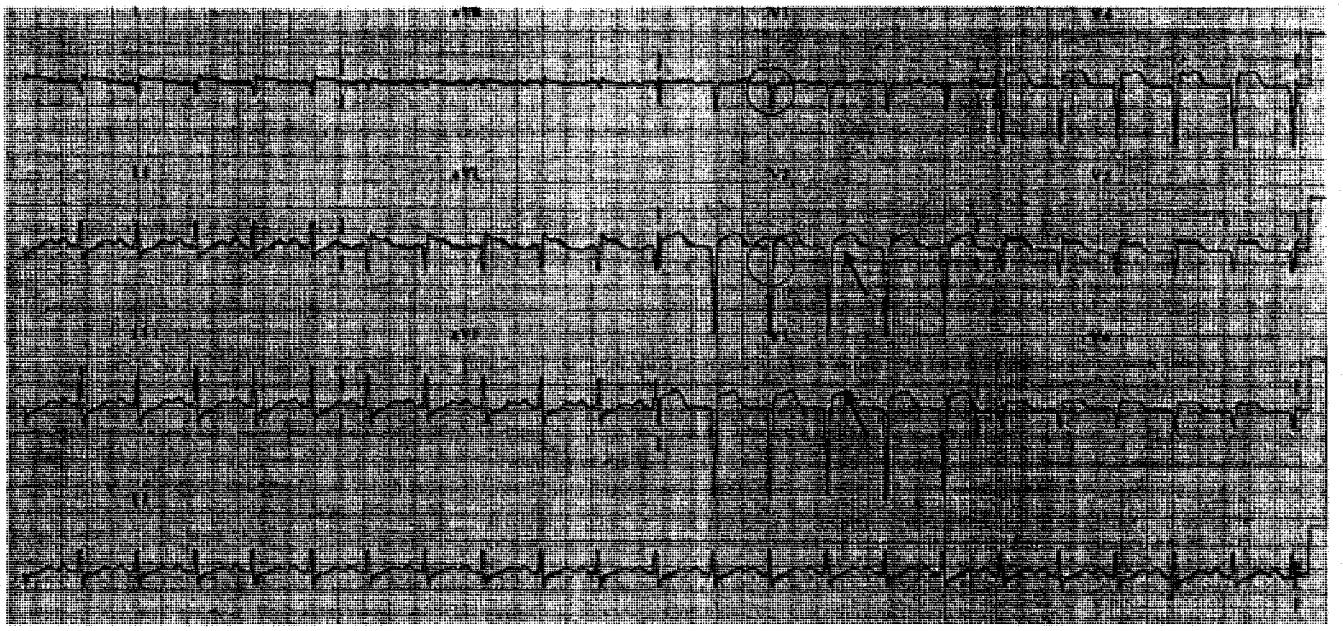


Figure 11. Electrocardiogram Demonstrating ST-segment Depression (arrows)

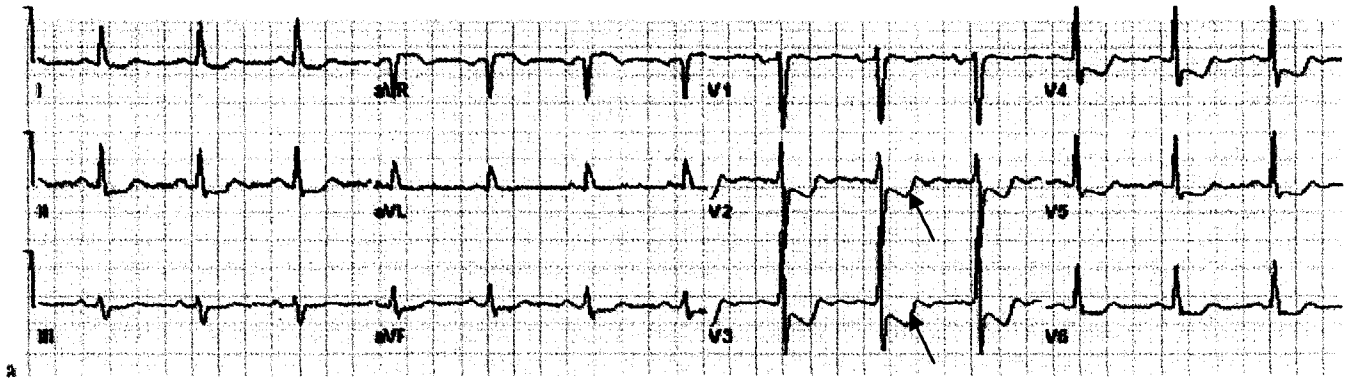


Figure 12. Electrocardiogram Demonstrating T-wave Inversions (arrows)

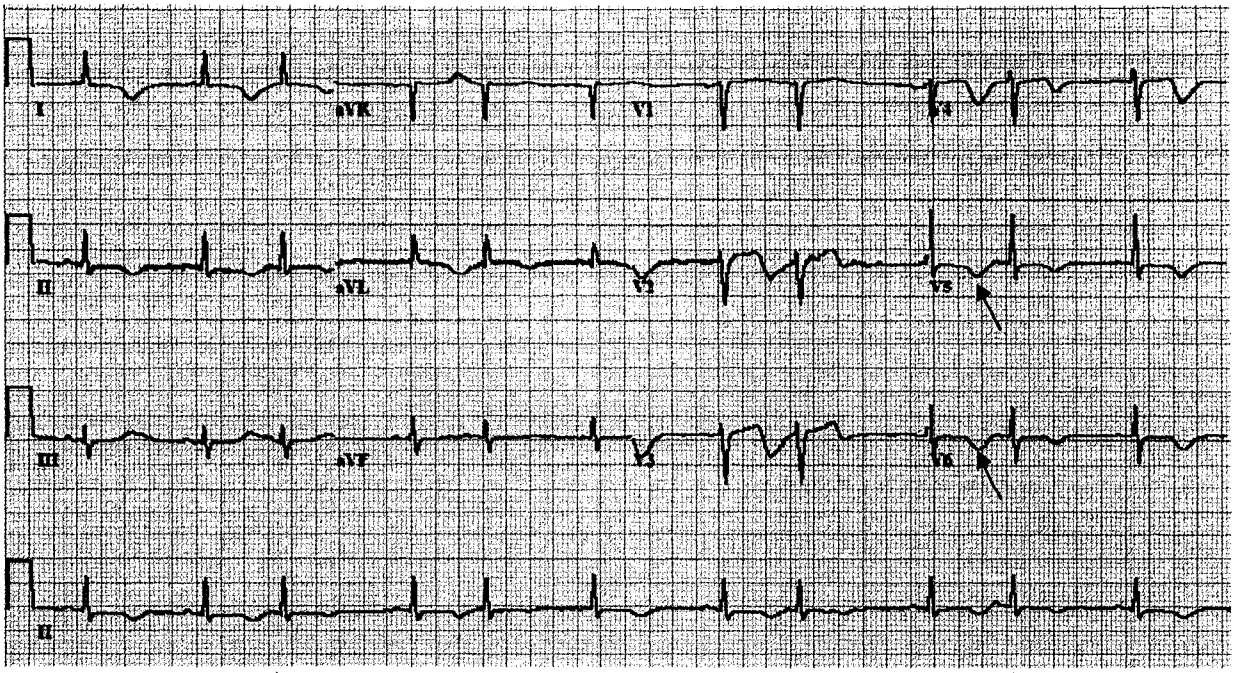
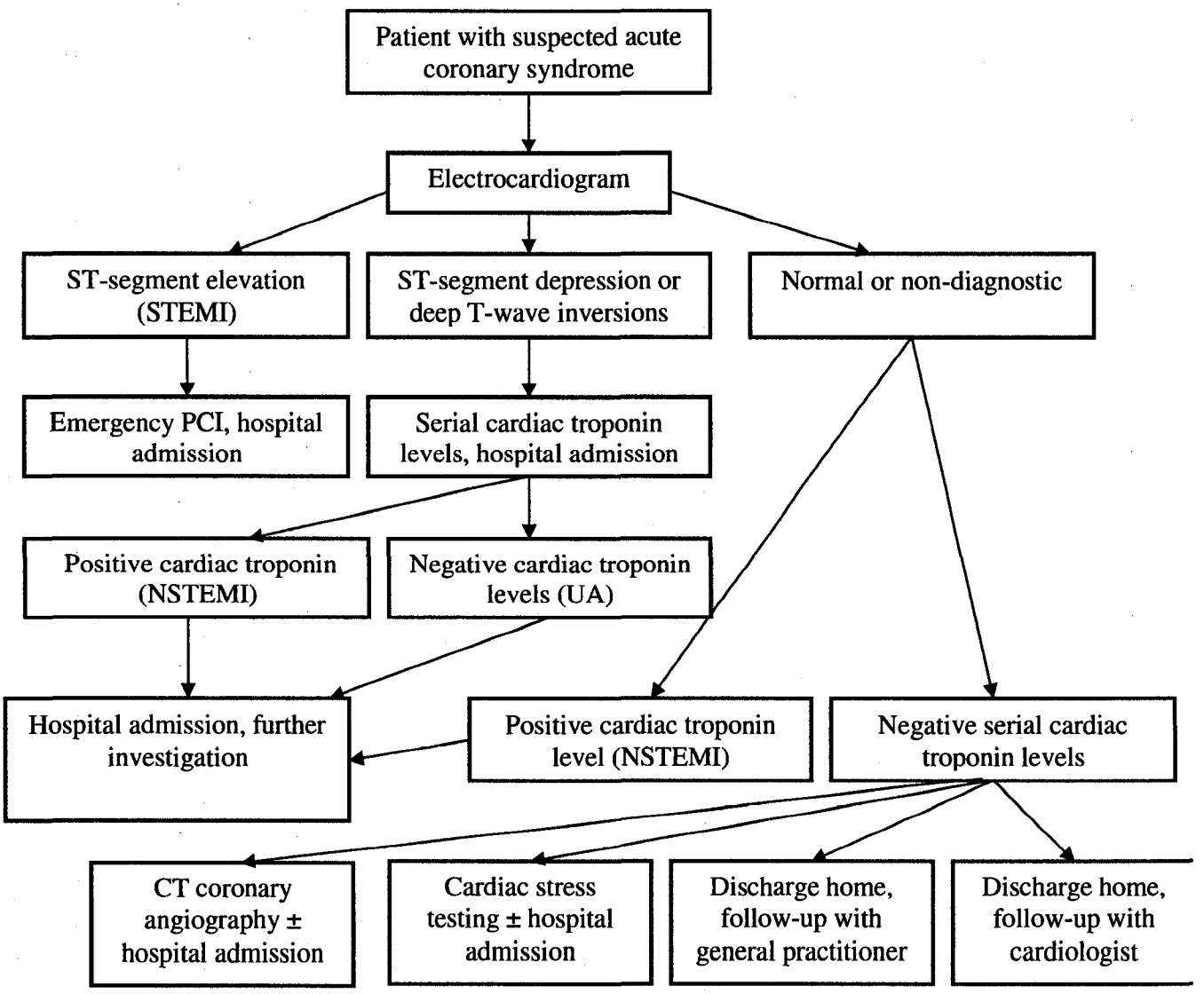
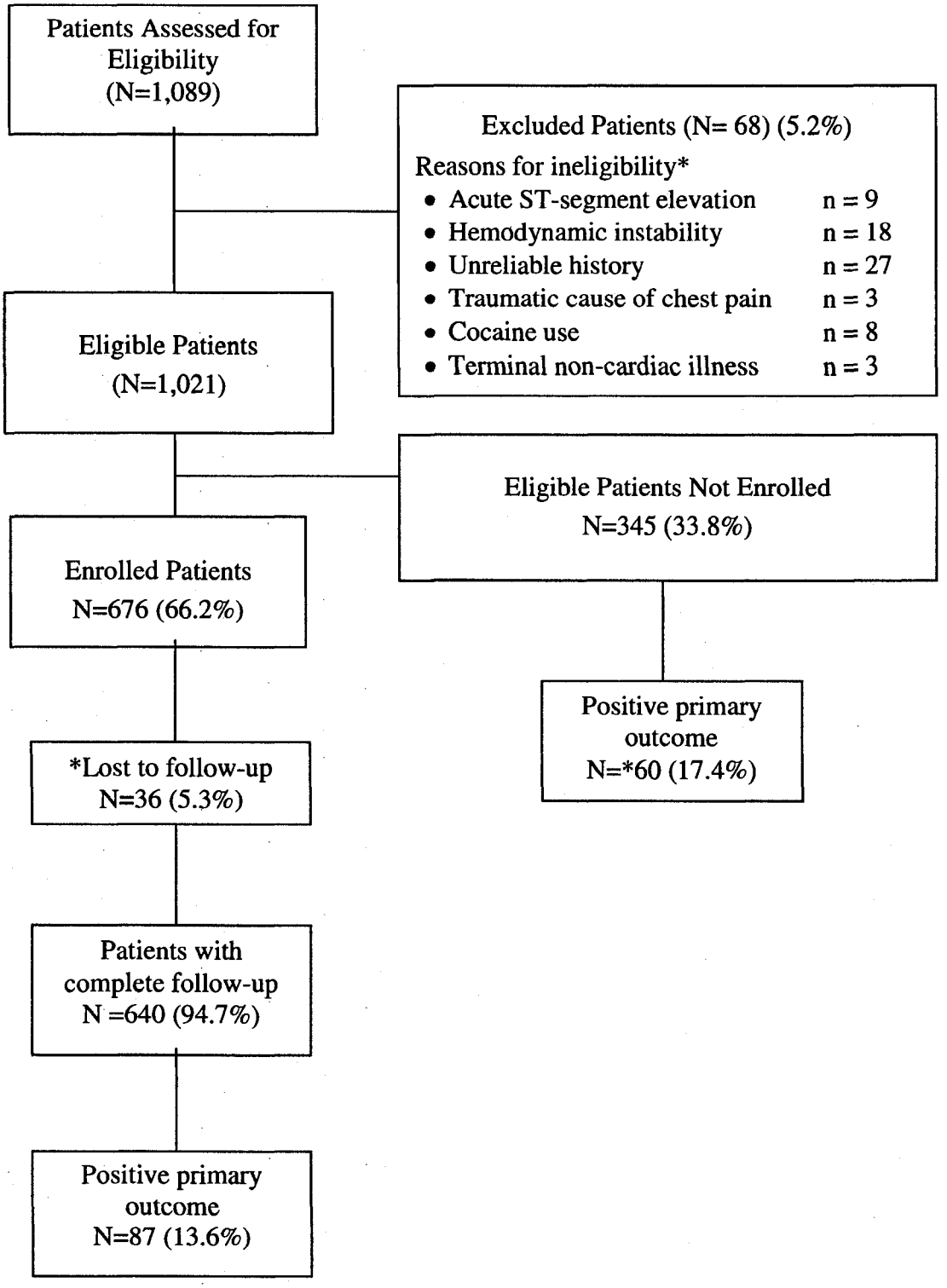


Figure 13. Potential Diagnostic Pathways for Patients Evaluated in the Emergency Department for Suspected Acute Coronary Syndrome



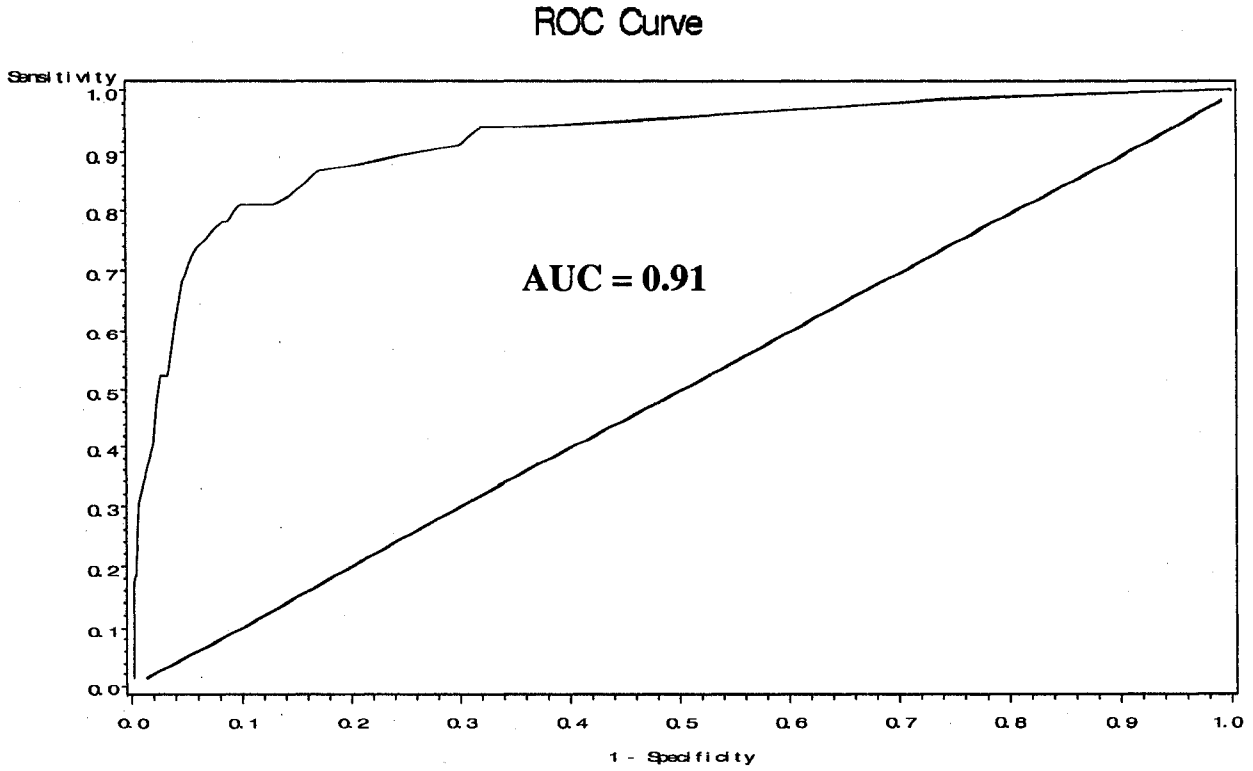
STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; UA, unstable angina; PCI, percutaneous coronary intervention; CT, computed tomography

Figure 14. Flow Diagram of 6-month Prospective Cohort Study of Emergency Department Patients with Chest Pain



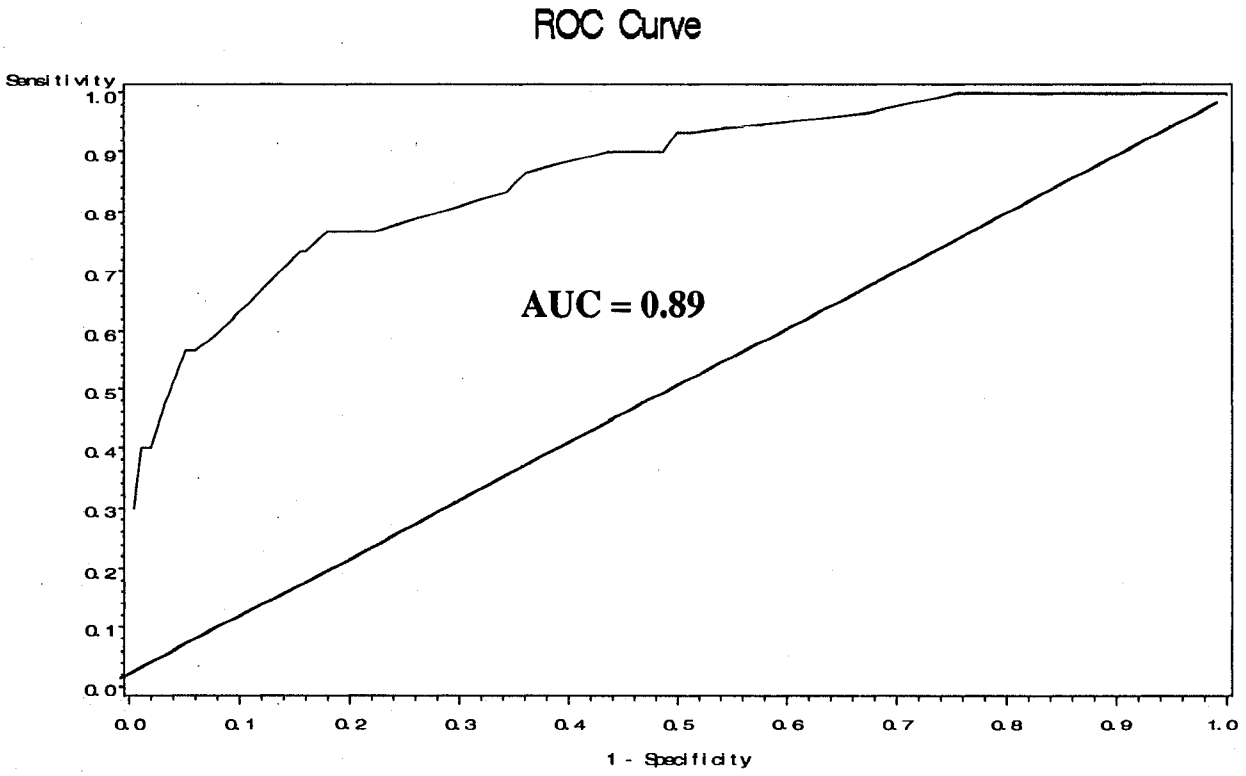
*All 36 patients were unable to be reached by phone for proxy outcome assessment.

Figure 15. Receiver Operator Characteristic (ROC) Curve for the Composite Outcome Acute Myocardial Infarction, Revascularization, or Death within 30 Days Using the Multivariable Logistic Regression Model Applied to the Patients Presenting to the Emergency Department with Chest Pain



AUC = area under the curve.

Figure 16. Receiver Operator Characteristic (ROC) Curve for the Composite Outcome Acute Myocardial Infarction, Revascularization, or Death within 30 Days Using the Multivariable Logistic Regression Model Applied to the Patient Subgroup with Outcomes Outside of the Emergency Department



AUC = area under the curve.

Figure 17. Flow Diagram of the Final Recursive Partitioning Model

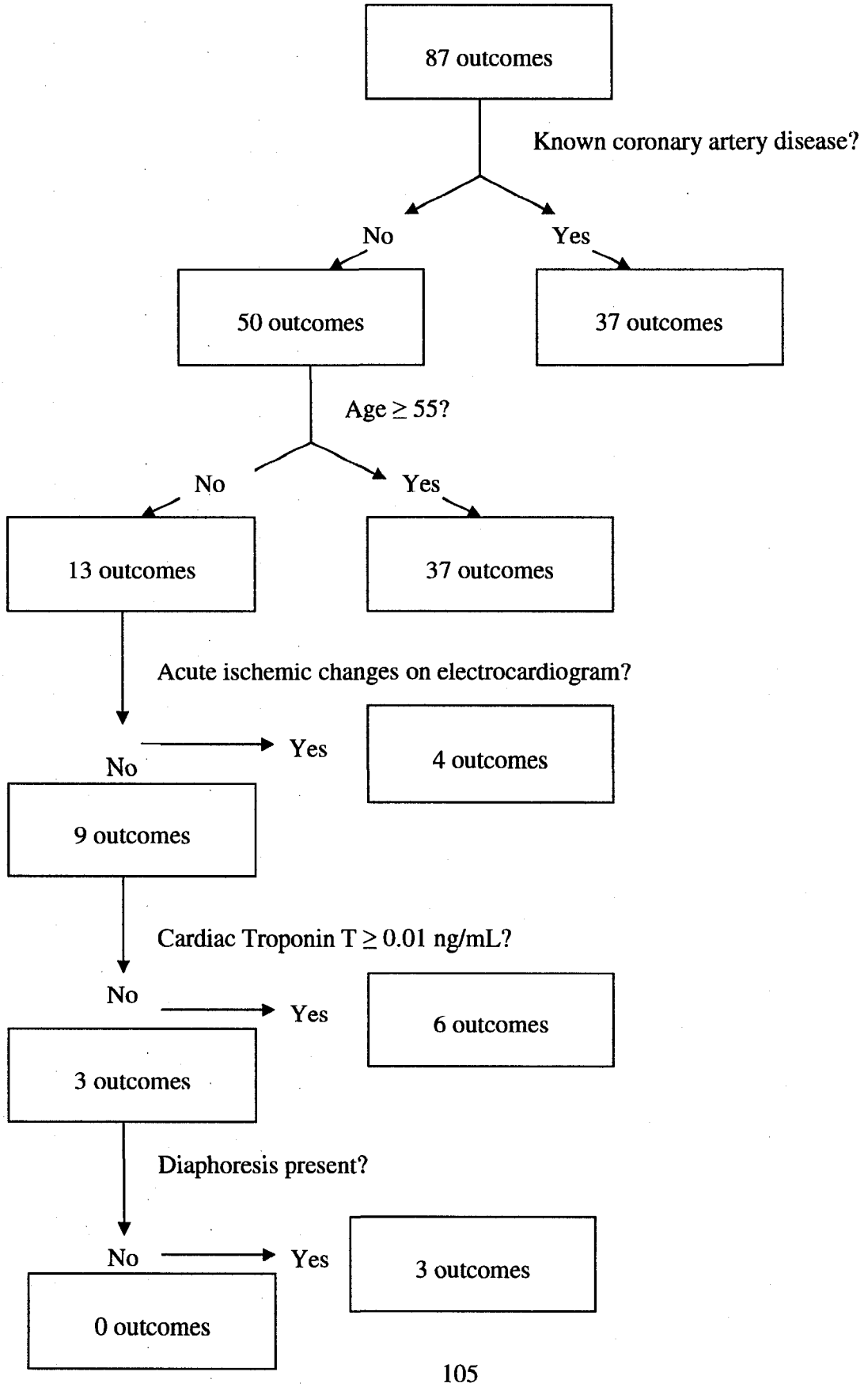


Figure 18. Preliminary Clinical Decision Rule to Determine which Emergency Department Patients with Chest Pain Require Additional Investigation Derived by Recursive Partitioning
(n = 640)

Patients with any of the following characteristics require additional investigation:

1) Known coronary artery disease

2) Age $\geq$ 55 years

3) Acute ischemic changes on electrocardiogram (T-wave inversions $\geq$ 0.2 mm or ST-segment depressions $\geq$ 0.5mm in at least 2 contiguous leads)

4) Cardiac Troponin T $\geq$ 0.01 ng/mL

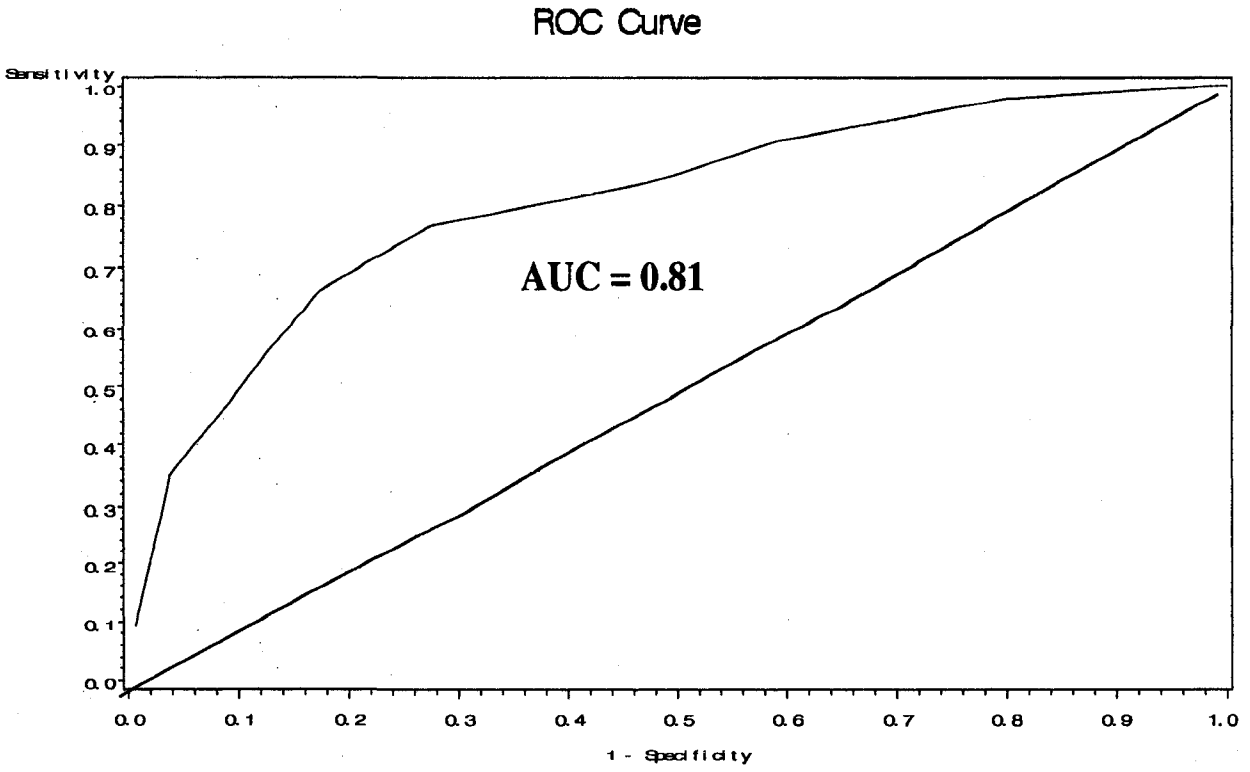
5) Presence of diaphoresis (on physical examination or by patient history)

Figure 19. Classification Performance of the Preliminary Prediction Model to Determine Which Patients with Chest Pain Require Additional Investigation Prior to Emergency Department Discharge

Decision Rule	Positive for Primary Outcome	Negative for Primary Outcome	
Yes	87	413	451
No	0	140	189

Sensitivity 100.0% (96-100)
Specificity 25% (22-29)
Percent Requiring Testing 70.5%

Figure 20. Receiver Operating Characteristic (ROC) Curve of Physicians' Pre-test Probability that Their Patient had Acute Coronary Syndrome



AUC = area under the curve.

6.0 REFERENCES

1. Brener SJ. Insights into the pathophysiology of ST-elevation myocardial infarction. *American Heart Journal.* 2006;151:S4-10.

2. Gelfand EV, Cannon CP. Myocardial infarction: contemporary management strategies. *Journal of Internal Medicine.* 2007;262:59-77.

3. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation.* 2003;108:2543-2549.

4. Statistics Canada. Mortality, Summary List of Causes. Ottawa; 2004. Released 2007:20.
5. Nawar EW, Niska RW, Xu J. National Hospital Ambulatory Medical Care Survey: 2005 emergency department summary. *Adv Data.* 2007:1-32.

6. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics--2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2007;115:e69-171. Epub 2006 Dec 2028.

7. Kontos MC, Jesse RL. Evaluation of the emergency department chest pain patient. *American Journal of Cardiology.* 2000:32B-39B.

8. Pope JH, Ruthazer R, Beshansky JR, Griffith JL, Selker HP. The clinical presentation of patients with acute cardiac ischemia in the emergency department: a multicenter controlled clinical trial. *Journal of Thrombosis and Thrombolysis.* 1998:63-74.

9. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. *JAMA.* 2005;294:2623-2629.

10. Gupta M, Tabas JA, Kohn MA. Presenting complaint among patients with myocardial infarction who present to an urban, public hospital emergency department. *Annals of Emergency Medicine.* 2002;40:180-186.

11. Anderson JL, Adams CD, Antman EM, 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 (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation.* 2007;116:e148-304. Epub 2007.

12. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA.* 2000;284:835-842.

13. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Archives of Internal Medicine.* 2003;163:2345-2353.

14. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation.* 2000;101:2557-2567.

15. 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. *Journal of the American College of Cardiology.* 2000;36:959-969.

16. Kavsak PA, MacRae AR, Lustig V, et al. The impact of the ESC/ACC redefinition of myocardial infarction and new sensitive troponin assays on the frequency of acute myocardial infarction. *American Heart Journal.* 2006;152:118-125.

17. Jaffe AS. Chasing troponin: how low can you go if you can see the rise? *J Am Coll Cardiol.* 2006;48:1763-1764.

18. Thygesen K, Alpert JS, White HD. Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation.* 2007;116:1-20.

19. Christenson J, Innes G, McKnight D, et al. Safety and efficiency of emergency department assessment of chest discomfort. *CMAJ.* 2004:1803-1807.

20. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *New England Journal of Medicine.* 2000;342:1163-1170.

21. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--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). *Journal of the American College of Cardiology.* 2002;40:1366-1374.

22. Gibler WB, Cannon CP, Blomkalns AL, et al. Practical implementation of the guidelines for unstable angina/non-ST-segment elevation myocardial infarction in the emergency department: a scientific statement from the American Heart Association Council on Clinical Cardiology (Subcommittee on Acute Cardiac Care), Council on Cardiovascular Nursing, and Quality of Care and Outcomes Research Interdisciplinary Working Group, in Collaboration With the Society of Chest Pain Centers. *Circulation.* 2005;111:2699-2710.

23. Zalenski RJ, Rydman RJ, Ting S, Kampe L, Selker HP. A national survey of emergency department chest pain centers in the United States. *American Journal of Cardiology.* 1998;81:1305-1309.

24. Bond K, Ospina MB, Blitz S, et al. Frequency, determinants and impact of overcrowding in emergency departments in Canada: a national survey. *Healthc Q.* 2007;10:32-40.

25. Derlet R, Richards J, Kravitz R. Frequent overcrowding in U.S. emergency departments. *Acad Emerg Med.* 2001;8:151-155.

26. Eagles D, Stiell IG, Clement CM, et al. International survey of emergency physicians' priorities for clinical decision rules. *Acad Emerg Med.* 2008;15:177-182.

27. Macgougan CK, Christenson JM, Innes GD, Raboud J. Emergency physicians' attitudes toward a clinical prediction rule for the identification and early discharge of low risk patients with chest discomfort. *CJEM.* 2001;3:89-94.

28. McGinn TG, Guyatt GH, Wyer PC, et al. Users' Guides to the Medical Literature: XXII: How to Use Articles About Clinical Decision Rules. *JAMA.* 2000;284:79-84.

29. Stiell IG, Wells GA. Methodologic standards for the development of clinical decision rules in emergency medicine. *Annals of Emergency Medicine.* 1999;33:437-447.

30. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. *JAMA.* 1997;277:488-494.

31. Christenson J, Innes G, McKnight D, et al. A clinical prediction rule for early discharge of patients with chest pain. *Annals of Emergency Medicine.* 2006;47:1-10.

32. Baxt WG. Use of an artificial neural network for data analysis in clinical decision-making: the diagnosis of acute coronary occlusion. *Neural Computation.* 1991;2:480-489.

33. Baxt WG. Use of an artificial neural network for the diagnosis of myocardial infarction. *Annals of Internal Medicine.* 1991;115:843-848.

34. Baxt WG, Skora J. Prospective validation of artificial neural network trained to identify acute myocardial infarction. *Lancet.* 1996;347:12-15.

35. Baxt WG, Shofer FS, Sites FD, Hollander JE. A neural network aid for the early diagnosis of cardiac ischemia in patients presenting to the emergency department with chest pain. *Annals of Emergency Medicine.* 2002;40:575-583.

36. Baxt WG, Shofer FS, Sites FD, Hollander JE. A neural computational aid to the diagnosis of acute myocardial infarction. *Annals of Emergency Medicine.* 2002;39:366-373.

37. Goldman L, Weinberg M, Weisberg M, et al. A computer-derived protocol to aid in the diagnosis of emergency room patients with acute chest pain. *New England Journal of Medicine.* 1982;307:588-596.

38. Goldman L, Cook EF, Brand DA, et al. A computer protocol to predict myocardial infarction in emergency department patients with chest pain. *New England Journal of Medicine.* 1988;318:797-803.

39. Kennedy RL, Burton AM, Fraser HS, McStay LN, Harrison RF. Early diagnosis of acute myocardial infarction using clinical and electrocardiographic data at presentation: Derivation and evaluation of logistic regression models. *European Heart Journal.* 1996;17:1181-1191.

40. Mair J, Smidt J, Lechleitner P, Dienstl F, Puschendorf B. A decision tree for the early diagnosis of acute myocardial infarction in nontraumatic chest pain patients at hospital admission. *Chest.* 1995;108:1502-1509.

41. Mair J, Smidt J, Lechleitner P, Dienstl F, Puschendorf B. Rapid accurate diagnosis of acute myocardial infarction in patients with non-traumatic chest pain within 1 h of admission. *Coronary Artery Disease.* 1995;6:539-545.

42. Ng SM, Krishnaswamy P, Morissey R, Clopton P, Fitzgerald R, Maisel AS. Ninety-minute accelerated critical pathway for chest pain evaluation. *American Journal of Cardiology.* 2001;88:611-617.

43. Poretsky L, Leibowitz IH, Friedman SA. The diagnosis of myocardial infarction by computer-derived protocol in a municipal hospital. *Angiology.* 1985;36:165-170.

44. Tierney WM, Roth BJ, Psaty B, et al. Predictors of myocardial infarction in emergency room patients. *Critical Care Medicine.* 1985;13:526-531.

45. Bassan R, Pimenta L, Scofano M, Soares JF. Accuracy of a neural diagnostic tree for the identification of acute coronary syndrome in patients with chest pain and no ST-segment elevation. *Critical Pathways in Cardiology: A Journal of Evidence-Based Medicine.* 2004;3:72-78.

46. Harrison RF, Kennedy RL. Artificial neural network models for prediction of acute coronary syndromes using clinical data from the time of presentation. *Annals of Emergency Medicine.* 2005;46:431-439.

47. Bjork J, Forberg JL, Ohlsson M, Edenbrandt L, Ohlin H, Ekelund U. A simple statistical model for prediction of acute coronary syndrome in chest pain patients in the emergency department. *BMC Medical Informatics & Decision Making.* 2006;6:28.

48. Selker HP, Beshansky JR, Griffith JL, et al. Use of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) to assist with triage of patients with chest pain or other symptoms suggestive of acute cardiac ischemia. A multicenter, controlled clinical trial. *Annals of Internal Medicine.* 1998;129:845-855.

49. Chandra A, Jones FM, Beam D, Promes SB, Kline JA, Cairns CB. Limited Utility of the Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) in the Evaluation of Chest Pain Unit Patients. *Acad Emerg Med.* 2005;12:30-b-31.

50. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA.* 2004;291:2727-2733.

51. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ.* 2006;333:1091. Epub 2006.

52. de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. *Eur Heart J.* 2005;26:865-872. Epub 2005.

53. Chase M, Robey JL, Zogby KE, Sease KL, Shofer FS, Hollander JE. Prospective validation of the Thrombolysis in Myocardial Infarction Risk Score in the emergency department chest pain population. *Annals of Emergency Medicine.* 2006;48:252-259.

54. Conway Morris A, Caesar D, Gray S, Gray A. TIMI risk score accurately risk stratifies patients with undifferentiated chest pain presenting to an emergency department. *Heart.* 2006;92:1333-1334.

55. Garcia Almagro FJ, Gimeno JR, Villegas M, et al. Use of a coronary risk score (the TIMI Risk Score) in a non-selected patient population assessed for chest pain at an emergency department. *Revista Espanola de Cardiologia.* 2005;58:775-781.

56. Jaffery Z, Hudson MP, Jacobsen G, Nowak R, McCord J. Modified Thrombolysis in Myocardial Infarction (TIMI) risk score to risk stratify patients in the emergency department with possible acute coronary syndrome. *J Thromb Thrombolysis.* 2007;24:137-144. Epub 2007.

57. Lyon R, Morris AC, Caesar D, Gray S, Gray A. Chest pain presenting to the Emergency Department-to stratify risk with GRACE or TIMI? *Resuscitation.* 2007;74:90-93.

58. Pollack CV, Jr., Sites FD, Shofer FS, Sease KL, Hollander JE. Application of the TIMI risk score for unstable angina and non-ST elevation acute coronary syndrome to an unselected emergency department chest pain population. *Academic Emergency Medicine.* 2006;13:13-18.

59. Domanovits H, Schillinger M, Paulis M, et al. Acute chest pain-a stepwise approach, the challenge of the correct clinical diagnosis. *Resuscitation.* 2002;55:9-16.

60. Limkakeng A, Jr., Gibler WB, Pollack C, et al. Combination of Goldman risk and initial cardiac troponin I for emergency department chest pain patient risk stratification.[see comment]. *Academic Emergency Medicine.* 2001;8:696-702.

61. Mitchell AM, Garvey JL, Chandra A, Diercks D, Pollack CV, Kline JA. Prospective multicenter study of quantitative pretest probability assessment to exclude acute coronary syndrome for patients evaluated in emergency department chest pain units. *Annals of Emergency Medicine.* 2006;47:447.

62. Tong KL, Kaul S, Wang XQ, et al. Myocardial contrast echocardiography versus Thrombolysis In Myocardial Infarction score in patients presenting to the emergency department with chest pain and a nondiagnostic electrocardiogram. *Journal of the American College of Cardiology.* 2005;46:920-927.

63. Fernandez Portales J, Perez Reyes F, Garcia Robles JA, et al. Risk stratification using combined ECG, clinical, and biochemical assessment in patients with chest pain without ST-segment elevation. How long should we wait? *Revista Espanola de Cardiologia.* 2003;56:338-345.

64. Goldman L, Cook EF, Johnson PA, Brand DA, Rouan GW, Lee TH. Prediction of the need for intensive care in patients who come to the emergency departments with acute chest pain. *New England Journal of Medicine.* 1996;334:1498-1504.

65. Reilly B, Durairaj L, Husain S, et al. Performance and potential impact of a chest pain prediction rule in a large public hospital. *American Journal of Medicine.* 1999;106:285-291.

66. Durairaj L, Reilly B, Das K, et al. Emergency department admissions to inpatient cardiac telemetry beds: a prospective cohort study of risk stratification and outcomes. *Am J Med.* 2001;110:7-11.

67. Reilly BM, Evans AT, Schaider JJ, et al. Impact of a clinical decision rule on hospital triage of patients with suspected acute cardiac ischemia in the emergency department. *JAMA.* 2002;288:342-350.

68. Marsan RJ, Jr., Shaver KJ, Sease KL, Shofer FS, Sites FD, Hollander JE. Evaluation of a clinical decision rule for young adult patients with chest pain. *Academic Emergency Medicine.* 2005;12:26-31.

69. Martinez-Selles M, Ortiz J, Estevez A, Andueza J, de Miguel J, Bueno H. A new risk score for patients with a normal or non-diagnostic ECG admitted to a chest pain unit. *Revista Espanola de Cardiologia.* 2005;58:782-788.

70. Lorenzoni R, Ebert AG, Lattanzi F, et al. A computer protocol to evaluate subjects with chest pain in the emergency department: a multicenter study. *Journal of Cardiovascular Medicine.* 2006;7:203-209.

71. Porela P, Pulkki K, Helenius H, et al. Prediction of short-term outcome in patients with suspected myocardial infarction. *Annals of Emergency Medicine.* 2000;35:413-420.

72. Selker HP, Griffith JL, D'Agostino RB. A time-insensitive predictive instrument for acute myocardial infarction mortality: a multicenter study. *Medical Care.* 1991;29:1196-1211.

73. Seyal JM, Clark EN, Macfarlane PW. Diagnosis of acute myocardial ischaemia using probabilistic methods. *Journal of Cardiovascular Risk.* 2002;9:115-121.

74. Miller CD, Lindsell CJ, Anantharaman V, et al. Performance of a population-based cardiac risk stratification tool in Asian patients with chest pain. *Academic Emergency Medicine.* 2005;12:423-430.

75. Walker NJ, Sites FD, Shofer FS, Hollander JE. Characteristics and outcomes of young adults who present to the emergency department with chest pain. *Academic Emergency Medicine.* 2001;8:703-708.

76. Diercks DB, Hollander JE, Sites F, Kirk JD. Derivation and validation of a risk stratification model to identify coronary artery disease in women who present to the emergency department with potential acute coronary syndromes. *Academic Emergency Medicine.* 2004;11:630-634.

77. Gorelik O, Almoznino-Sarafian D, Yarovoi I, et al. Patient-related variables predicting acute coronary syndrome following admission for chest pain of possible coronary origin. *Coronary Artery Disease.* 2006;17:15-21.

78. Goodacre SW, Angelini K, Arnold J, Revill S, Morris F. Clinical predictors of acute coronary syndromes in patients with undifferentiated chest pain. *Qjm.* 2003;96:893-898.

79. Panju AA, Hemmelgarn BR, Guyatt GH, Simel DL. Is This Patient Having a Myocardial Infarction? *JAMA.* 1998;280:1256-1263.

80. Jaffe AS, Ravkilde J, Roberts R, et al. It's time for a change to a troponin standard. *Circulation.* 2000;102:1216-1220.

81. Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: the present and the future. *Journal of the American College of Cardiology.* 2006;48:1-11.

82. Apple FS, Parvin CA, Buechler KF, Christenson RH, Wu AH, Jaffe AS. Validation of the 99th percentile cutoff independent of assay imprecision (CV) for cardiac troponin monitoring for ruling out myocardial infarction. *Clinical Chemistry.* 2005;51:2198-2200.

83. Panteghini M, Pagani F, Yeo KT, et al. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. *Clinical Chemistry.* 2004;50:327-332.

84. Mark DB, Shaw L, Harrell FE, Jr., et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *New England Journal of Medicine.* 1991;325:849-853.

85. Shaw LJ, Peterson ED, Shaw LK, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation.* 1998;98:1622-1630.

86. Sketch MH, Mohiuddin SM, Lynch JD, Zencka AE, Runco V. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. *Am J Cardiol.* 1975;36:169-173.

87. Braunwald E, Zipes DP, Libby P, Bonow R. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* 7th ed. Philadelphia: Elsevier Saunders; 2005:2259.

88. Wackers FJ, Brown KA, Heller GV, et al. American Society of Nuclear Cardiology position statement on radionuclide imaging in patients with suspected acute ischemic syndromes in the emergency department or chest pain center. *Journal of Nuclear Cardiology.* 2002;9:246-250.

89. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. *J Am Coll Cardiol.* 1998;32:57-62.

90. Kim C, Kwok YS, Heagerty P, Redberg R. Pharmacologic stress testing for coronary disease diagnosis: A meta-analysis. *American Heart Journal.* 2001;142:934-944.

91. Scanlon PJ, Faxon DP, Audet A-M, et al. ACC/AHA guidelines for coronary angiography: A report of the American College of Cardiology/American Heart Association Task Force on Practice

Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol.* 1999;33:1756-1824.

92. Noto TJ, Jr., Johnson LW, Krone R, et al. Cardiac catheterization 1990: a report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I). *Catheterization & Cardiovascular Diagnosis.* 1991;24:75-83.

93. Hollander JE, Blomkalns AL, Brogan GX, et al. Standardized reporting guidelines for studies evaluating risk stratification of ED patients with potential acute coronary syndromes. *Academic Emergency Medicine.* 2004;11:1331-1340.

94. Macrae AR, Kavsak PA, Lustig V, et al. Assessing the requirement for the 6-hour interval between specimens in the American Heart Association Classification of Myocardial Infarction in Epidemiology and Clinical Research Studies. *Clinical Chemistry.* 2006;52:812-818.

95. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology.* 1996;49:1373-1379.

96. Harrell FE, Jr. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis.* New York: Springer; 2001.

97. Friedman JH. A recursive partitioning decision rule for nonparametric classification. *IEE.Trans.Comput.* 1977;16:404-408.

98. Ciampi A, Hogg SA, McKinney S, Thiffault J. RECPAM: a computer program for recursive partition and amalgamation for censored suvival data and other situations frequently occurring in biostatistics. I. Methods and program features. *Comput.Meth.Prog.Biomed.* 1988;26:239-256.

99. Ciampi A, Thiffault J, Nakache JP, Asselain B. Stratification by stepwise regression, correspondence analysis and recursive partition: a comparison of three methods of analysis for survival data with covariates. *Comput.Stat.Data.Anal.* 1986;4:185-204.

100. LaValley MP. Logistic regression. *Circulation.* 2008;117:2395-2399.

101. Allison PD. *Logistic Regression Using SAS: Theory and Application.* Cary, North Carolina: SAS Institute Inc.; 1999:288.

102. Hess EP, Thiruganasambandamoorthy V, Wells GA, et al. Diagnostic accuracy of clinical prediction rules to exclude acute coronary syndrome in the emergency department setting: a systematic review. *CJEM.* 2008;10:373-382.

103. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J.* 2001;141:190-199.

104. Brehaut JC, Stiell IG, Graham ID. Will a new clinical decision rule be widely used? The case of the Canadian C-spine rule. *Acad Emerg Med.* 2006;13:413-420.

105. Eagles D, Stiell IG, Clement C, et al. International Survey of emergency physicians' priorities for clinical decision rules. *Acad Emerg Med.* 2008;15:177-82.

106. Fernandez Portales J, Perez Reyes F, Garcia Robles JA, et al. [Risk stratification using combined ECG, clinical, and biochemical assessment in patients with chest pain without ST-segment elevation. How long should we wait?]. *Revista Espanola de Cardiologia.* 2003;56:338-345.

107. Baxt WG, Shofer FS, Sites FD, Hollander JE. A neural network aid for the early diagnosis of cardiac ischemia in patients presenting to the emergency department with chest pain. *Annals of Emergency Medicine.* 2002;40:575-583.

108. Mair J, Smidt J, Lechleitner P, Dienstl F, Puschendorf B. A decision tree for the early diagnosis of acute myocardial infarction in nontraumatic chest pain patients at hospital admission. *Chest.* 1995;108:1502-1509.

109. Miller CD, Lindsell CJ, Anantharaman V, et al. Performance of a population-based cardiac risk stratification tool in Asian patients with chest pain. *Academic Emergency Medicine.* 2005;12:423-430.

110. Baxt WG, Skora J. Prospective validation of artificial neural network trained to identify acute myocardial infarction.[see comment]. *Lancet.* 1996;347:12-15.

111. Baxt WG. Use of an artificial neural network for the diagnosis of myocardial infarction. *Annals of Internal Medicine.* 1991;115:843-848.

112. Lyon R, Morris AC, Caesar D, Gray S, Gray A. Chest pain presenting to the Emergency Department-to stratify risk with GRACE or TIMI? *Resuscitation.* 2007.

113. Conway Morris A, Caesar D, Gray S, Gray A. TIMI risk score accurately risk stratifies patients with undifferentiated chest pain presenting to an emergency department. 2006.

114. Garcia Almagro FJ, Gimeno JR, Villegas M, et al. [Use of a coronary risk score (the TIMI Risk Score) in a non-selected patient population assessed for chest pain at an emergency department]. *Revista Espanola de Cardiologia.* 2005;58:775-781.

115. Tong KL, Kaul S, Wang XQ, et al. Myocardial contrast echocardiography versus Thrombolysis In Myocardial Infarction score in patients presenting to the emergency department with chest pain and a nondiagnostic electrocardiogram. *Journal of the American College of Cardiology.* 2005;46:920-927.

116. Durairaj L, Reilly B, Das K, et al. Emergency department admissions to inpatient cardiac telemetry beds: a prospective cohort study of risk stratification and outcomes. *American Journal of Medicine.* 2001;110:7-11.

117. Antman EM, Cohen M, Bernink P, et al. The TIMI risk score for unstable angina/non-ST elevation MI - A method for prognostication and therapeutic decision making. *Jama-Journal of the American Medical Association.* 2000;284:835-842.

118. Reilly B, Durairaj L, Husain S, et al. Performance and potential impact of a chest pain prediction rule in a large public hospital.[see comment]. *American Journal of Medicine.* 1999;106:285-291.

119. Goldman L, Cook EF, Brand DA, et al. A computer protocol to predict myocardial infarction in emergency department patients with chest pain. *New England Journal of Medicine.* 1988;318:797-803.

120. Reilly BM, Evans AT, Schaider JJ, et al. Impact of a clinical decision rule on hospital triage of patients with suspected acute cardiac ischemia in the emergency department. *JAMA.* 2002;288:342-350.

121. Chun AA, McGee SR. Bedside diagnosis of coronary artery disease: a systematic review. *American Journal of Medicine.* 2004;117:334-343.

122. Goodacre S, Locker T, Morris F, Campbell S. How useful are clinical features in the diagnosis of acute, undifferentiated chest pain? *Academic Emergency Medicine.* 2002;9:203-208.

123. Panju AA, Hemmelgarn BR, Guyatt GH, Simel DL. The rational clinical examination. Is this patient having a myocardial infarction?[see comment]. *JAMA.* 1998;280:1256-1263.

124. Everts B, Karlson BW, Wahrborg P, Hedner T, Herlitz J. Localization of pain in suspected acute myocardial infarction in relation to final diagnosis, age and sex, and site and type of infarction. *Heart & Lung.* 1996;25:430-437.

125. Tierney WM, Fitzgerald J, McHenry R, et al. Physicians' estimates of the probability of myocardial infarction in emergency room patients with chest pain. *Medical Decision Making.* 1986;6:12-17.

126. Lee TH, Cook EF, Weisberg M, Sargent RK, Wilson C, Goldman L. Acute chest pain in the emergency room. Identification and examination of low-risk patients. *Archives of Internal Medicine.* 1985;145:65-69.

Appendix 1. Physician Case Record Form

ACUTE CHEST PAIN STUDY - PHASE I

Name of clerk/RN attaching sheet to chart:_____
Pt. Initials:_____ **Chart No.**_____
Visit Date (y/m/d) ____/____/____ **Physician:**_____
Inter-observer O **Yes** O **No** **If 'yes', physician's name:**_____

Patient Stamp or Label Here

****Staff Physicians/Emergency Medicine Residents (PGY2 or greater) Please complete while assessing patient****
****Please inform patient that they may be contacted by telephone for follow up****

Inclusion Criteria

O ≥25 years of age O Chief Complaint is **Chest Pain** O **Possible ACS** (unstable angina/AMI)
Does the patient meet ALL inclusion criteria? O **Yes** O **No (IF 'NO' STOP HERE)**

Exclusion Criteria

O Acute ST-segment elevation **in at least 2 contiguous leads** (≥ 1mm in limb leads or ≥ 2mm in precordial leads)
O Hemodynamic instability **(SBP < 90 mmHg, HR < 50 bpm or > 100 bpm)**
O **Current or past** cocaine use or **positive for cocaine (if tested)**
O **Unreliable history** due to communication/language issues
O Chest pain has a **traumatic cause**
O Patient has a **terminal noncardiac illness**
O Patient is **pregnant**
Is the patient excluded by ANY exclusion criteria? O **Yes** O **No (IF 'YES' STOP HERE)**

Cardiac Risk Factors (previously diagnosed or on medication)

O **HTN** O **Hypercholesterolemia**
O **Diabetes mellitus** O **Family history** of cardiac disease (AMI, angina, or sudden cardiac death in a direct relative <60 years)
Smoking history O Never O Current O Former (<1 year ago) O Former (>1 year ago)
O **None**

Cardiovascular History

O **Acute MI** O **Angina** (chest pain on exertion) O **Known coronary artery disease** O **Congestive Heart Failure**
O **Cardiac arrest** O **Ventricular tachycardia** O **Atrial fibrillation** O **Stroke or TIA**
O **Peripheral vascular disease** O **Other CVS**_____ O **None**

Characteristics of the Chest Pain

Time course (of longest episode): Time of onset __:__ O AM O PM O Today O Yesterday O____day(s) ago
Has the pain **completely resolved?** O Yes O No
If yes, **total duration** of the chest pain _____minutes, **or** _____hours, **or** _____days
Present at time of ED arrival? O Yes O No
Present at rest? (at home or in ED) O Yes O No
Worse with exertion? O Yes O No O Unknown
Is the pain **pleuritic (sharp, worse with deep breathing)?** O Yes O No
Similar to previously diagnosed ischemia? O Yes O No O Not applicable
Change in the usual pattern of angina within the past 24 hours? O Yes O No O Not applicable
Has there been **2 or more episodes of chest pain** in the past 24 hours? O Yes O No
Did the pain **recur during the ED visit?** O Yes O No O Did not resolve during ED visit

Onset: O Abrupt (<1hr) O Gradual (≥1hr)
Location on chest: O Centre O Lt anterior O Lt lateral O Rt anterior O Rt lateral
Pain Description: O Pressure/Squeezing O Heavy O Sharp O Indigestion/Burning quality O Other
Radiation: O None O Rt arm/shoulder O Lt arm/shoulder O Both arms/shoulders O Neck/jaw O Back O Abdomen
Associated symptoms: O Nausea or vomiting O Shortness of breath O Diaphoresis O None
Worse with movement? O Yes O No O Unclear
Your overall assessment: O Typical O Atypical

Physical Examination/ECG interpretation/Cardiac Biomarkers

Cardiac auscultation O Normal O S3 O S4 O Systolic murmur O Diastolic murmur
Lung examination O Normal O Crackles/rales at bases O Crackles/rales to scapulae O Wheezes
Chest wall tenderness (reproducing presenting symptom) O Yes O No
Pitting edema in lower extremities O Yes O No
Interpretation of first ECG:
O normal O nonspecific ST-T wave changes O Abnormal but not diagnostic of ischemia
O Infarction/ischemia known to be old O Infarction/ischemia *not* known to be old O Consistent with AMI (ST-segment elevation or new LBB)

What is this patient's pre-test probability of unstable angina or AMI?
O ≤1% O 2% O 3% O 4% O 5% O 10% O 20% O 30% O 50% O 75% O 100%

****If Found on Ward, Please return to Emergency Department****

MayuApr2008

Appendix 2. Data Form Completed by Study Nurse for All Eligible Enrolled Patients

Subject No. _____

ACUTE CHEST PAIN STUDY - PHASE I

Eligible Patient with Completed MD Enrolment Form

VERIFICATION Research Assistant _____ Coordinator _____ Principal Investigator_____ Data Entry _____

VISIT HISTORY

Patient Initials _____ **Chart No.**_____ **Gender** O Male O Female
Date of Visit (yy/mm/dd)___/___/___ **Date of Birth** (yy/mm/dd) ___/___/___
Physician Code _____ **Physician status** O Full Time O Part Time
Interobserver O Yes O No **If 'yes', Physician Code:**_____
Arrived by Ambulance O Yes O No **Transfer from another ED** O Yes O No
Time of Registration _____:_____ O Not documented
Time of initial assessment by physician _____:_____ O Not documented
Time of discharge / referral _____:_____ O Not documented
Admitted O Yes O No **Requires Follow-up** O Yes O No

PHYSICAL EXAM

Temperature _____° C **Heart Rate** _____BPM **SBP** _____mmHg **DBP** _____mmHg **SaO2**_____

CXR INTERPRETATION

O normal O pulmonary edema O other

LABORATORY RESULTS (From OASIS):

CK ____ cTNT_____ Time 1: _____:_____ CK ____ cTNT_____ Time 2: _____:_____

MEDICATION LIST

O Aspirin
O Plavix (clopidogrel)
O Beta blockers (e.g., metoprolol, atenolol)
O Calcium channel blockers (e.g., diltiazem, verapamil)
O Nitroglycerin (or other nitrates)
O ACE-inhibitors
O Other anticoagulants (e.g., coumadin, aggrenox)
O Cholesterol-lowering drugs
O None of the above

CARDIAC RISK FACTORS

O HTN (O ROT only O medical record)
O Diabetes mellitus (O ROT only O medical record)
O Family history of cardiac disease (O ROT only O medical record)
O Hypercholesterolemia or Hyperlipidemia (O ROT only O medical record)
O Renal insufficiency (O ROT only O medical record)
(Creatinine > 221 umol/L for men or > 176.8 umol/L for women)

Smoking history
O Never O Current O Former (<1 year ago) O Former (>1 year ago)
O None

CARDIOVASCULAR HISTORY

O Acute MI (O ROT only O medical record)
O Angina (O ROT only O medical record)
O Congestive Heart Failure (O ROT only O medical record)
O Cardiac arrest (O ROT only O medical record)
O Known coronary artery disease (O ROT only O medical record)
O Ventricular tachycardia (O ROT only O medical record)
O Atrial fibrillation (O ROT only O medical record)
O Stroke or TIA (O ROT only O medical record)
O Peripheral vascular disease (O ROT only O medical record)
O None

(at least one 50% stenosis on coronary angiography, ECG with ST-segment elevation, perfusion defects on nuclear stress test, or previous MI?)

Follow-up data:

Cardiac Stress Test O Yes O No
If Yes, Type of test O nuclear O exercise O stress echo O other _____ **Date**(yy/mm/dd)___/___/___
Result O positive for ischemia O negative for ischemia O equivocal
If equivocal, O mild ischemia, O moderate ischemia or O severe ischemia?
Cardiac CT O Yes O No If yes, **Any stenosis ≥70%** O Yes O No O unclear **Date**(yy/mm/dd)___/___/___
Coronary Angiography O Yes O No If yes, **Any stenosis ≥70%** O Yes O No **Date**(yy/mm/dd)___/___/___
Did the patient undergo revascularization O Yes O No
If yes, O Stent placement or O CABG If yes, date (yy/mm/dd) ___/___/___
Did the patient die? O Yes O No If yes, date (yy/mm/dd) ___/___/___
If yes, was it due to a cardiac cause? O Yes O No O Unknown

OHRIOctober2007

Appendix 3. Data Form for Missed Eligible Patients

Subject No. _____

ACUTE CHEST PAIN STUDY - PHASE I

Eligible Patient with *NO* Completed MD Enrolment Form

VERIFICATION Research Assistant _____ Coordinator _____ Principal Investigator_____ Data Entry _____

VISIT HISTORY

Patient Initials _____ **Chart No.**_____ **Gender** O Male O Female
Date of Visit (yy/mm/dd)___/___/___ **Date of Birth** (yy/mm/dd) ___/___/___
Physician Code _____ **Physician status** O Full Time O Part Time
Arrived by Ambulance O Yes O No **Transfer from another ED** O Yes O No
Time of Registration _____:_____ O Not documented
Time of initial assessment by physician _____:_____ O Not documented
Time of discharge / referral _____:_____ O Not documented
Admitted O Yes O No

PHYSICAL EXAM

Temperature _____° C **Heart Rate** _____BPM **SBP** _____mmHg **DBP** _____mmHg **SaO2**_____

CXR INTERPRETATION

O normal O pulmonary edema O other

LABORATORY RESULTS (From OASIS):

CK ____ cTNT_____ Time 1: _____:_____ CK ____ cTNT_____ Time 2: _____:_____

MEDICATION LIST

O Aspirin
O Plavix (clopidogrel)
O Beta blockers (e.g., metoprolol, atenolol)
O Calcium channel blockers (e.g., diltiazem, verapamil)
O Nitroglycerin (or other nitrates)
O ACE-inhibitors
O Anticoagulants (e.g., coumadin, aggrenox)
O Cholesterol-lowering drugs
O None of the above

CARDIAC RISK FACTORS

O HTN (O ROT only O medical record)
O Diabetes mellitus (O ROT only O medical record)
O Family history of cardiac disease (O ROT only O medical record)
O Hypercholesterolemia or Hyperlipidemia (O ROT only O medical record)
O Renal insufficiency (O ROT only O medical record)
(Creatinine > 221 umol/L for men or > 176.8 umol/L for women)
O Smoker
O None

CARDIOVASCULAR HISTORY

O Acute MI (O ROT only O medical record)
O Angina (O ROT only O medical record)
O Congestive Heart Failure (O ROT only O medical record)
O Cardiac arrest (O ROT only O medical record)
O Known coronary artery disease (O ROT only O medical record)
O Ventricular tachycardia (O ROT only O medical record)
O Atrial fibrillation (O ROT only O medical record)
O Stroke or TIA (O ROT only O medical record)
O Peripheral vascular disease (O ROT only O medical record)
O None
(at least one 50% stenosis on coronary angiography, ECG with ST-segment elevation, perfusion defects on nuclear stress test, or previous MI?)

Follow-up data:

Cardiac Stress Test O Yes O No
If Yes, Type of test O nuclear O exercise O stress echo O other _____ **Date**(yy/mm/dd)___/___/___
Result O positive for ischemia O negative for ischemia O equivocal
Cardiac CT O Yes O No If yes, **Any stenosis ≥70%** O Yes O No O unclear **Date**(yy/mm/dd)___/___/___
Coronary Angiography O Yes O No If yes, **Any stenosis ≥70%** O Yes O No **Date**(yy/mm/dd)___/___/___

Did the patient undergo revascularization O Yes O No
If yes, O Stent placement or O CABG If yes, date (yy/mm/dd) ___/___/___
Did the patient die? O Yes O No If yes, date (yy/mm/dd) ___/___/___
If yes, was it due to a cardiac cause? O Yes O No O Unknown

OHRIJuly2007

Appendix 4. Standardized ECG Interpretation Form Completed by Primary Investigator

Subject No._____

Study Investigator to complete

Patient Initials _____ **Chart No.:**_____
Date of Visit:(yy/mm/dd)___/___/___ **Date of Birth:**(yy/mm/dd) ___/___/___

ECG interpretation

Rate:____

Rhythm: O NSR O sinus bradycardia O atrial fibrillation O atrial flutter O other

Morphology:

O ST-segment depression (O < ½ mm O ½ to 1mm O > 1mm) in at least 2 contiguous leads
O old O not known to be old

O T-wave inversion (O ≥ 0.2 mm or O < 0.2 mm in 2 or more contiguous leads with dominant R waves)
O old O not know to be old

O Left bundle branch block
O old O not known to be old

O Right bundle branch block
O old O not known to be old

O Pathological Q-waves
O old O not known to be old

Overall interpretation:

O Normal
O Nonspecific ST-T wave changes
O Abnormal but not diagnostic of ischemia
O Infarction or ischemia known to be old
O Infarction or ischemia not known to be old
O Consistent with AMI (ST-segment elevation or new LBBB)

30 Day outcomes O positive O negative

If positive, which outcome criteria were met in the Emergency Department?
O AMI O positive stress test O New ischemia on ECG O positive angiogram O Revascularization
O VF/VT O cardiac arrest O cardiac/unknown death

Within 4 days?
O AMI O positive stress test O New ischemia on ECG O positive angiogram O Revascularization
O VF/VT O cardiac arrest O cardiac/unknown death

Within 14 days?
O AMI O positive stress test O New ischemia on ECG O positive angiogram ORevascularization
O VF/VT O cardiac arrest O cardiac/unknown death

Within 30 days?
O AMI O positive stress test O New ischemia on ECG O positive angiogram ORevascularization
O VF/VT O cardiac arrest O cardiac/unknown death

Appendix 5. Telephone Follow-up Form

Subject No.:_____ 30 day Follow Up: (y/m/d) ____/____/____
Patient Initials:_____

ACUTE CHEST PAIN STUDY - PHASE I
30 Day Follow-up

Hello, my name is_____ and I am a research nurse working at the_____ emergency department. I am calling you because of your recent visit on (date). Our hospital is following all patients who present with chest pain, to determine how people who present to the emergency department with these symptoms are treated. I would like to ask you a few short questions in follow up to your visit.
Is this alright with you? O Yes O No
Do you recall receiving a handout or seeing a poster during your emergency department visit informing you about receiving a follow-up telephone call? O Yes O No

---

Date and times of attempts: _____
Date reached: (y/m/d) _____/_____/_____

Dead O Yes O No **If yes, Date of Death** (y/m/d) ____/____/_____
If yes, was it due to a cardiac cause? O Yes O No O Unknown
Lost Follow-Up O Yes O No
Refused O Yes O No

1) Since your initial emergency department visit, have you returned to see a physician? O Yes O No

2) If yes, did the physician tell you that you had a myocardial infarction or heart attack?
O Yes (y/m/d) ____/____/_____ O No

3) Since your initial emergency department visit, have you had a cardiac stress test?
O Yes (y/m/d) ____/____/_____ O No

4) If yes, where was it performed? _____

5) If yes, what was the result? O positive for ischemia O normal

6) Since your initial emergency department visit, have you undergone angioplasty/stent placement in your coronary arteries or cardiac bypass surgery?
O Yes (y/m/d) ____/____/_____ O No

Thank you very much for your participation. Please remember that all of your answers will be kept confidential and will be used for statistical research only.

OHRI July 2007