2020-04-30

Development of a Clinical Care Pathway for Patients with Suspected Acute Coronary Syndromes in the Emergency Departmer

O'Rielly, Connor M.

UNIVERSITY OF CALGARY

Development of a Clinical Care Pathway for Patients with Suspected Acute Coronary Syndromes in the Emergency Department

by

Connor M. O'Rielly

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE
DEGREE OF MASTER OF SCIENCE

GRADUATE PROGRAM IN COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

APRIL, 2020

Abstract

Chest pain is a predominant reason for emergency department (ED) visits and hospitalizations in Canada. ED physicians use diagnostic tools (e.g., biomarkers) to identify patients with myocardial infarction (MI) requiring intervention, and prognostic tools (e.g., risk scores) to determine which patients without MI are eligible for discharge. While clinical guidelines recommend that these two portions of the assessment occur sequentially, the evidence for each has emerged in isolation. There is also a paucity of evidence on risk score use in the era of high-sensitivity cardiac troponin (hs-cTn) assays, adverse event risk factors for patients without MI, and appropriate timelines for follow-up. This project had three complimentary objectives:

(1) Synthesize available evidence on prognostic prediction score performance when hs-cTn assays are incorporated;
(2) Quantify the time course of major adverse cardiac events (MACE) in patients without index MI and identify characteristics with potential predictive value for MACE, and;
(3) Develop a sequential clinical pathway for the assessment of chest pain in the ED and measure the impacts on diagnostic and prognostic accuracy as well as ED patient flow.

A systematic review was conducted to synthesize evidence on the chest pain risk scores to be prioritized for integration into the clinical pathway. A time-to-event analysis was then conducted to measure timing of MACE in patients without index MI, as well as a stratified analysis to identify characteristics with predictive value for 30-day MACE to be used in the pathway for clinical stratification. Trial clinical pathways were developed and quantitatively compared. Pathways combined a validated 2-hour hs-cTn diagnostic algorithm with variable clinical pre-stratification, risk score types, and low-risk cut-offs. A sequential clinical pathway

using a validated hs-cTn algorithm and the HEART score can identify nearly 40% of ED chest pain patients as eligible for discharge without the need for further testing with **no missed MI or 30-day MACE.**

This thesis project contributed evidence necessary for the updating and advancing of the ED chest pain assessment and presents an evidence-based sequential clinical pathway that maximizes the efficiency of the ED chest pain assessment.

Preface

This thesis is original, unpublished, independent work by the author, C. M. O'Rielly. The time-to-event analysis and pathway development components of the thesis project reported in Chapters 3 and 4 were covered by Ethics Certificate number REB18-2098, issued by the University of Calgary Conjoint Health Research Ethics Board for the project "Development of a clinical tool to predict risk of short-term cardiac events" on February 11, 2019 and renewed on January 23, 2020.

Acknowledgements

This work was made possible only through the support of countless wonderful individuals and organizations. First and foremost, I would like to sincerely thank my supervisor, Dr. Andrew McRae. Despite dedicating endless hours to your own clinical, academic and family responsibilities, you somehow always made yourself available for meetings, expert feedback and encouragement. I am extremely grateful for the countless opportunities you have afforded me since day one. You have been (and continue to be) a caring, professional and diligent mentor – the type of mentor I could only hope to someday become- and for that I sincerely thank you.

I would like to thank my committee members, Dr. Paul Ronksley, Dr. Matthew James, Dr. Tolu Sajobi, and Dr. James Andruchow for providing the key insights that helped this project reach its' full potential. I consider myself lucky to have been part of this talented group of researchers and physicians and I hope to work with all of you again in the future.

This work was funded by the Canadian Institutes of Health Research, Alberta Innovates, the Libin Cardiovascular Institute of Alberta, The University of Calgary Department of Emergency Medicine, and the University of Calgary. It is thanks to these organizations that I was able to spend two years immersed in my studies, taking full advantage of the incredible teaching and professional programs the Department of Community Health Sciences had to offer.

Last but certainly not least, I am indebted to those behind the scenes. To Bailin Xie, for her unwavering support and ability to put things into perspective, always. To my parents and sister for always being there, no matter what. To my friends, new and old, for feigning interest in my research and letting me vent when it wasn't going quite right. I love you all and I consider myself very lucky to have gone through this with you on my team.

Table of Contents

List of Tables

List of Figures and Illustrations

Epigraph

"We're obsessed in medicine with having great components – the best drugs, the best devices, the best specialists- but pay little attention to how to make them fit together well."

-Atul Gawande

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 HEART DISEASE AND ITS IMPACT

Heart disease is a leading cause of death and hospitalization across the globe[1]. Specifically, in Canada, heart disease is the second leading cause of death and the leading cause of hospitalization[2,3]. In the United States, heart disease is the leading cause of death and the fourth leading reason for hospitalizations, causing 165 deaths per 100,000 and over a million hospital stays each year[4,5]. While heart disease serves as an umbrella term for a number of conditions such as congestive heart failure and atrial fibrillation, these statistics are largely driven by the subgroup of ailments known as ischemic heart disease. Ischemic heart disease is defined by cardiac ischemia, or blockage of coronary arteries that supply blood to the heart muscle resulting in necrosis (i.e., death) of cardiac tissue. This heart disease subgroup can be broken down further into three predominant acute coronary syndromes (ACS): ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA)[6]. Ultimately, ischemic heart disease is the leading cause of years of life lost and the second most common cause of disability-adjusted life years lost globally[1].

1.2 HEART DISEASE IN THE EMERGENCY DEPARTMENT

The aforementioned deaths and burdens secondary to ischemic heart disease and ACS are often preceded by chest pain. In fact, chest pain and symptoms of ACS are a leading cause of emergency department (ED) visits in developed countries across the globe[7]. Recent estimates suggest that over 8 million Americans and upwards of 500,000 Canadians present to the ED annually with a primary complaint of chest pain[7-9]. This high frequency of ED utilization for

chest pain contributes substantially to worsening ED overcrowding seen nationally[10], generates substantive direct and indirect costs[11,12], and fuels large amounts of clinical resource utilization[13].

1.3 ED ASSESSMENT OF CHEST PAIN

In order to optimize patient outcomes and healthcare resource utilization, efficient and accurate assessment of ED patients with suspected ischemic chest pain is critical. Ultimately, the goal is to provide a timely and accurate diagnosis to facilitate appropriate treatment or disposition. This assessment can be divided into two parts. The first portion of the assessment is the diagnosis or exclusion (i.e., "ruling in" or "ruling out") of STEMI and NSTEMI, both of which are associated with substantial morbidity and mortality[14]. This part of the assessment ensures that patients quickly receive the appropriate care that is required to intervene on these acute conditions (i.e., anticoagulant/antiplatelet/thrombolytic medications, coronary artery angioplasty and bypass surgery). The second part of the assessment, which is only completed in patients who have had a diagnosis of MI ruled-out, is the estimation of risk (prognostication) for any major adverse cardiovascular events (MACE) such as death, MI, or need for revascularization in the short period after ED discharge. At this stage physicians will also seek to identify patients with a high clinical likelihood of UA (i.e., acute cardiac ischemia without elevation of cardiac biomarkers) – itself a diagnostic dilemma discussed further below- or severe underlying coronary artery disease (CAD) that puts them at further risk for MACE. Attempting to identify patients with these more subtle forms of ACS on the index ED visit is a leading reason for hospital admissions and inpatient days[15,16]. This step also ensures that patients who have not had an MI on the index visit are sent home with an outpatient follow-up care plan (i.e.,

follow-up type, locale, and timing) that is well aligned with their UA or CAD status and corresponding risk of short-term MACE risk.

The technologies and procedures that are central to the two parts of the chest pain assessment are best understood in the context of the trajectory of a chest pain patient moving through a diagnostic evaluation in the ED. It should be noted, however, that the following pages will focus on a particular type of chest pain patient. Chest pain in the absence of trauma can still be of non-cardiac origin and could represent a number of other life-threatening conditions including pulmonary embolism (PE), aortic dissection, or spontaneous pneumothorax[17]. However, ACS is by far the most common high-risk explanation for chest pain and the attempt to identify a cardiac origin for the pain would likely be prioritized and completed first. Therefore, to represent the ED assessment of chest pain as closely as possible, the description below is assumed to have occurred in a patient whose pain is being treated as a **potential ACS.**

1.3.1 PART IA: RULING IN AND RULING OUT STEMI WITH ELECTROCARDIOGRAMS

Upon arrival to the ED, chest pain patients are triaged to an available area of the department that is aligned with the acuity and gravity of their chest pain. Since "time is muscle" when it comes to minimizing myocardial necrosis secondary to AMI, the primary focus of the treating ED physician and allied health professionals is to rule in or rule out such an event. This is first achieved using electrocardiograms (ECG) at arrival often corroborated by ECGs taken in the pre-hospital setting.

ECGs measure the electrical activity of the heart and provide treating clinicians with an interpretable tracing of that activity. This tracing shows P waves, T waves, and a segment known

as the 'QRS' complex, all of which make up a single heartbeat cycle. Abnormalities in these tracings, such as prolongations, shortenings, depressions, or elevations of a line or segment can represent changes in the heart's electrical conductivity that may be secondary to heart tissue death relating to ischemia. In the correct clinical context, elevation of the ST-segment (the area between the end of the QRS complex and the T-wave) is diagnostic of a complete coronary artery occlusion leading to STEMI[18]. Patients with diagnostic ECG showing STEMI must undergo reperfusion therapy immediately given the high morbidity potential[19].

While the presence of ST-segment elevation is diagnostic of STEMI in the appropriate clinical context, the absence of this specific ECG abnormality does not exclude the possibility of NSTEMI or other ACS. NSTEMI (i.e., AMI that is not characterized by ST-segment elevation on ECG) is also associated with high mortality whereby the relative risk for all-cause death is 30% higher in NSTEMI survivors than in the general population[20]. As such, patients without ST elevation on ECG will receive further investigations using cardiac biomarkers (specifically, cardiac troponin (cTn)) to rule out NSTEMI and temper this higher than normal risk of mortality. In accordance with treatment guidelines, patients who have cTn results suggestive of NSTEMI will be admitted to hospital for inpatient management with medical therapy (e.g., anticoagulant and antiplatelet therapy) and/or urgent revascularization (e.g., coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI))[21].

1.3.2 CARDIAC TROPONIN ASSAYS

In addition to cTn, many assays have been used to identify NSTEMI, including creatine kinase (CK), myoglobin, and Creatine Kinase-MB (CKMB). Both CKMB and **cTn assays** are cardiac specific, with cTn assays touting the highest diagnostic accuracy[22]. The two types of cTn,

cardiac troponin I (cTnI) and cardiac troponin T (cTnT) exist almost exclusively in the cardiac muscle and play a role in the contraction of heart muscle. Both cTnI and cTnT are released into the blood plasma following death of heart tissue, but there is some evidence to suggest that cTnI may be more cardiac specific[3,24]. Given that AMI is defined primarily by evidence of heart tissue necrosis in the appropriate clinical context[25], cTn assays are essential for clinicians to diagnose NSTEMI in the ED.

Cardiac troponin was established as the standard serologic biomarker for the diagnosis of MI in 1999 and reaffirmed as such in 2007 by the National Academy of Biochemistry[26]. In response to this and the growing evidence supporting the use of cTnI and cTnT for identifying AMI[27,28], a number of contemporary cTn assays were developed and made available for clinical use in EDs worldwide[29,30]. Guidelines for the ED management of chest pain and potential non-ST-elevation ACS recommended serial cTn testing at initial patient assessment and 6-12 hours after onset of chest pain or ACS symptoms[31,32]. A rise and/or fall in cTn concentration with at least one measurement above the 99th percentile upper reference limit (URL) of a healthy population is diagnostic of NSTEMI[32]. While the increased clinical availability of contemporary cTn assays and the guidelines standardizing their use did reduce short- and long-term mortality[33], the assays remained flawed in two ways: (1) they had poor sensitivity for AMI at patient presentation due to the delayed increase in circulating cTn levels[34], and (2) many were imprecise with coefficients of variation (CV) greater than 10% at the 99th percentile URL for healthy individuals[30]. As a result, to achieve diagnostic certainty with contemporary cTn assays requires ED stays of six to twelve hours with serial cTn testing. Further, with the high CV at the 99th percentile URL there remained a reasonable risk of misclassifying healthy patients as having

AMI (i.e., false positives) which can lead to costly, resource-intensive treatment for patients who are unlikely to benefit and can even experience iatrogenic harm as a result[35-37].

Gradual refinement of contemporary cTn assays has culminated in the current generation of **high-sensitivity cTn (hs-cTn) assays**. These novel hs-cTn assays can detect troponin at substantially lower concentrations and with much greater reliability compared with their conventional predecessors[38]. To be classified as "high-sensitivity" a hs-cTn assay should be able to measure concentrations less than the 99th percentile URL in at least 50% (ideally 95%) of healthy individuals, and should have a CV (i.e., total imprecision) ≤10% at the 99th percentile URL[30,39]. As a result of these analytical properties, hs-cTn assays can detect troponin release at an earlier time point compared to contemporary cTn assays[34,40]. In recent years, hs-cTn has become the primary ED biomarker for chest pain assessment in Europe, New Zealand, and Canada and is gaining traction in the United States[41].

1.3.3 PART IB: RULING IN AND RULING OUT NSTEMI WITH HIGH-SENSITIVITY TROPONIN

As previously mentioned, the next step for patients who have had STEMI ruled out by ECG is to undergo hs-cTn testing to rule in or rule out NSTEMI. The aforementioned analytic properties of these hs-cTn assays require an adapted clinical approach compared to contemporary cTn assays (i.e., timing of serial sampling, differing cut-offs and value interpretation). Their faster kinetics and improved precision allow ED physicians to achieve diagnostic certainty faster, within 1-2 hours for most patients. Moreover, research has shown that up to 30% of chest pain patients with normal ECG can have AMI ruled-out with high accuracy following a single undetectable hs-cTn measure at ED arrival, a strategy not previously possible with contemporary

cTn assays[42,43]. Patients without early diagnostic confirmation of NSTEMI by these single undetectable measure strategies will require serial sampling. To facilitate this, a number of protocols called rapid diagnostic or rapid rule-out algorithms (RDAs) that integrate and attempt to standardize serial hs-cTn sampling have emerged. These RDAs allow clinicians to rule in or rule out NSTEMI with sensitivities >95% using serial hs-cTn measures at 0, 1-, and 2-hour timepoints[44-46]. Some of these validated RDAs allow the achievement of diagnostic certainty for almost two thirds of chest pain patients within 2 hours of ED arrival[47], reducing the length of stay, costs, and resource utilization associated with their care while ensuring patients with NSTEMI receive necessary care (i.e., inpatient medical management) expeditiously[21,48,49].

The use of hs-cTn and associated RDAs rounds out the first part of the ED chest pain assessment. Approximately 60-70% of chest pain patients will have low risk hs-cTn testing and will emerge from the first part of the chest pain assessment without a diagnosis of AMI[47]. In keeping with our two-stage conceptualization of the chest pain assessment, these are the patients who would be risk stratified in the second part of the chest pain assessment, discussed below.

1.3.4 PART II: RISK STRATIFICATION

Patients who are not diagnosed with STEMI or NSTEMI at index ED visit may still have advanced underlying coronary disease or UA which increase their risk for potential MACE in the short and long-term following ED evaluation. To ensure that these discharge eligible patients with serious underlying CAD or incident UA (2-5% of whom will go on to have a MACE[50,51]) are identified through additional cardiac testing, many ED physicians use different risk scores to predict adverse event risk.

Although this is a prognostic task, many of these risk scores were derived to play a diagnostic role (i.e., to identify ACS including MI on the index visit). This discordance between derived purpose and clinical use may be attributable, in part, to the diagnostic difficulty of index UA. Specifically, 30-day revascularization (a component of MACE typical of risk score derivation studies) is often used as a surrogate outcome for diagnosis of UA, whereby subsequent revascularization without AMI could serve as the confirmation of a clinician's diagnostic suspicions that a patient did have UA at the initial ED presentation. The potential conflation of diagnosis and prognosis secondary to the use of a 30-day outcome as a proxy for the detection of index UA will be discussed in more detail later, following a description of some of the currently available chest pain risk scores.

The History, ECG, Age, Risk factors, and Troponin (HEART) score: The HEART score (based on 5 well described predictors of MI) was first validated in 2008 in a population of 122 undifferentiated chest pain patients 18 years and older (excluding those with STEMI) presenting to a community hospital in the Netherlands[52]. This risk score gives equal weight to the five predictors that make up its namesake, all of which receive a score from 0 to 2 and were selected based on perceived clinical merit. Despite being developed as a diagnostic tool for AMI, the validation study used a composite outcome combining index AMI with prognostic events such as PCI, CABG, or death within 3 months of the index visit. The longer follow-up period and mixed diagnostic/prognostic outcome used in the derivation study has led to the HEART score being used by most, whether appropriate or not, as a prognostic tool for MACE risk stratification. The HEART score has been prospectively validated with both contemporary and hs-cTn as a prognostic tool in a number of multicenter studies and has demonstrated its utility in many

randomized controlled trials (RCTs)[53,54]. According to a recent meta-analysis[53], a low-risk HEART score (≤3 points) has sensitivity for short-term MACE of approximately 96.0%.

The North American Chest Pain Rule (NACPR): The NACPR was developed collaboratively in 2012 by researchers in Canada and the United States[55]. The derivation study included 2,718 undifferentiated chest pain patients aged older than 24 years (excluding those with STEMI). The study used a composite primary outcome of AMI, coronary revascularization, or death of cardiac or unknown cause within 30 days of the index visit. Clinical predictor variables were selected from a list of 64 candidate measures and considered for inclusion through a consensus building process and multivariable analyses. Ultimately the rule quantified 30-day risk for the outcome using a listwise presentation of the absence of 5 predictors: ischemic ECG changes not known to be old, history of CAD, pain typical for acute coronary syndrome, initial or 6-hour troponin levels greater than the 99th percentile, and age greater than 50 years. The NACPR has been validated in external prospective cohorts of patients with a low-risk NACPR (i.e., having none of the criteria in the rule) consistently touting sensitivities for 30-day cardiac events of 100%, but only identifying <10% of patients as eligible for early discharge[56,57].

The Vancouver Chest Pain Risk (VCPR) score: The VCPR score was derived in Vancouver, Canada with patients enrolled between 2003 and 2006 and subsequently published in 2014[9]. The derivation study recruited 763 patients aged 25 years and older who presented to the ED with a primary complaint of chest pain. The primary outcome was 30-day diagnosis of ACS (AMI or UA). The VCPR is presented as a decision tree and includes a number of relevant clinical and demographic variables such as abnormal ECG, positive troponin at 2 hours, pain on palpation,

and age ≥50 years. The VCPR has been prospectively validated and boasts sensitivities for 30-day ACS >95%, but at best can only identify 20% of patients as eligible for discharge within 2 hours[58,59].

The No Objective Testing rule (NOTR): The NOTR was derived in a cohort of 2,396 patients aged 18 years or older who presented to EDs in Australia and New Zealand with a primary complaint of chest pain or symptoms of ACS[60]. Patients were only included if they had normal 0- and 2-hour troponin levels and no ischemic ECG findings. The primary outcome for the derivation study was a composite of 30-day ACS including AMI, cardiovascular death, UA, or urgent revascularization. The final rule included age, risk factors and previous myocardial infarction or coronary artery disease. The NOTR has been prospectively validated using both contemporary and hs-cTn with sensitivities >97% but identifies only a quarter of AMI ruled-out patients as eligible for early discharge[61,62].

The Emergency Department Assessment of Chest pain Score (EDACS): The EDACS was derived in a cohort of 1,974 patients from Australia and New Zealand aged 18 years or older with at least 5 minutes of symptoms consistent with ACS[63]. The primary outcome was MACE within 30-days of the ED visit, as defined by STEMI, NSTEMI, emergency revascularization, cardiac death, ventricular arrythmia, cardiac arrest, cardiogenic shock, or a high-grade atrioventricular block. Backwards elimination resulted in the inclusion of 5 predictor variables in the final score: age, sex, known CAD or ≥3 risk factors, diaphoresis, pain radiation to arm, shoulder, jaw, or neck, and pain worsening with inspiration. These factors have also been combined with normal 0- and 2-h troponin results to form the EDACS accelerated diagnostic

pathway (EDACS-ADP). The EDACS and EDACS-ADP have been internally and externally validated using conventional and hs-cTn assays with sensitivities as high as 100% and can safely identify over 40% of patients as low-risk (i.e., those without any of the included variables) and eligible for early discharge[63-65].

As mentioned and delineated above, many of these risk scores were derived in cohorts of undifferentiated chest pain patients as diagnostic tools for ACS, including MI on the index visit. However, the use of 30-day MACE in derivation as a surrogate outcome for ACS – likely to capture UA cases for which there is no objective case definition- these scores have become widely used as prognostic tools for risk stratification. And, while the scores perform well (i.e., sensitivities for the outcome >95%) when applied to other cohorts of undifferentiated chest pain patients, they tend to perform poorly (specificities for the outcome <45%) when applied to patients in whom MI has been ruled out[66,67]. This highlights how the mismatch between the diagnostic derivation purpose and prognostic clinical may be leading to an overestimation of their overall prognostic performance. Further, the conflation of diagnosis and prognosis in the development, application, and evaluation of the risk scores has led to confusion and variability between practitioners, whereby it becomes unclear for which patients the application of a risk score is most appropriate, and for what purpose.

While the intended use of the available scores was not to risk-stratify patients for whom AMI has already been ruled out, they may have a role in identifying which patients do not need further testing. Recent evidence suggests that when combined with a single hs-cTn measure the HEART and EDACS scores can identify 37.2% and 30% of patients as very low-risk for MACE and eligible for discharge without further outpatient follow-up, respectively[67,68]. It is possible

that the ability of the risk scores in these studies to rule out more patients without an increase in missed AMI was secondary to the heightened sensitivity of the novel assays and the application of the risk scores in a more restricted patient population (i.e., patients without index STEMI and NSTEMI). It should still be noted, however, that this evidence is limited because many studies still apply risk scores in undifferentiated chest pain populations, and the derivation of most of the available risk scores preceded the availability of hs-cTn assays. Instead, they were derived using less sensitive contemporary cTn assays. As such, a systematic review or meta-analysis is warranted to gain a better understanding of how the available risk scores perform when combined with hs-cTn and applied in a population who has already had an MI diagnosis at index ED visit ruled out **(see thesis project objective 1, below)**. The evidence synthesized in this review could provide clinicians with the up-to-date information necessary to optimize the use of chest pain risk scores in the hs-cTn era.

1.3.5 DISPOSITION DECISION MAKING

Following the ruling-out of STEMI and NSTEMI and the risk stratification of patients into low, intermediate and high-risk categories using clinical judgement or the aforementioned risk scores, ED physicians must still decide where and when discharge-eligible patients will undergo any required follow-up investigations. While the care locales and investigative procedures vary, consistent are the guideline recommendations that all but very low-risk patients undergo this testing prior to or within 72 hours of ED discharge (US, Europe), or within 2 weeks of the index ED encounter (Canada)[21,69,70]. These recommendations lead not only to between 35-40% of Canadian patients undergoing resource intensive follow-up but are also likely

contributors to higher than necessary rates of admission as clinicians avoid exceeding the recommended timeframes[72-73].

Academic support for these timing recommendations by the American College of Cardiology (ACC), European Society of Cardiology (ESC), and Canadian Cardiovascular Society (CCS) is scarce[74-76]. These are a Class IIa recommendation (Evidence level B), meaning the data has been derived from only a single randomized trial or non-randomized studies for which there is some conflicting evidence[74,76]. Further, the 1.5 week difference between CCS and other guidelines appears to be based less on true event timing and more on the fact that as few as 35% of Canadian patients will see a physician in follow-up within a week of discharge[77]. The substantial differences in the recommended timeframes for follow-up emphasizes the lack of supportive evidence and suggests that timing guidelines are based more on systems capacities than they are on concrete knowledge of when the short-term MACE is occurring. As such, an investigation of the true timing of MACE events in patients eligible for ED discharge is warranted to determine if these guideline-recommended timeframes for follow-up balance timely follow-up for at-risk patients with minimal unnecessary or untimely resource utilization **(see thesis project objective 2, below).**

1.4 THE CLINICAL GUIDELINES: EVIDENCE-BASED OR EVIDENCE-OUTPACED?

Overall, based on the evidence presented above it appears that ED clinicians are well equipped with the diagnostic tools necessary to make accurate diagnoses of STEMI and NSTEMI. And, while clinical gestalt and many risk scores are available to help physicians prognosticate, they may have poor specificity for short-term MACE and may contribute to the over-testing of many low risk patients[43]. Moreover, the evidence has historically evaluated the

effectiveness of these diagnostic and prognostic portions of this assessment in isolation. Almost no research has been conducted to determine how these two arms of the overall ED chest pain assessment might work best in concert to maximize the expedience and efficiency of this process. As such, there remains a clear need for the development and testing of a sequential clinical pathway that can distinguish patients with STEMI and NSTEMI from those without, can accurately identify risk of adverse events in patients requiring disposition, and can match the disposition of those patients to their short-term risk **(see thesis project objective 3, below).**

1.5 THESIS PROJECT OBJECTIVES

In response to the gap in the literature surrounding the prognostic performance of risk scores when used concurrently with hs-cTn, the minimal support for the guideline-recommended timing of follow-up care for discharge eligible chest pain patients, and the lack of evidence supporting the guideline-recommended sequential assessment of chest pain patients in the ED, the objectives of the proposed thesis project are three-fold:

1. To synthesize, through a systematic review, the available evidence on the performance of risk scores for MACE when hs-cTn assay results are incorporated, and;
2. To quantify, through time-to-event analysis, the elapsed time between ED discharge and MACE (up to 30 days) amongst chest pain patients without index AMI and to investigate the potential predictive capacities of predefined clinical characteristics for 30-day MACE in this population, and;

3. To develop a sequential clinical pathway for the assessment of chest pain in the ED and measure how this pathway might influence the care trajectory for chest pain patients within and beyond the ED.

Knowledge gained from the first objective of this project will provide the evidence necessary to make recommendations on best practices for clinical risk stratification in the hs-cTn era. Evidence emerging from the second objective may help clinicians identify what patients should receive follow-up investigations on a more prioritized basis and in what timeframe. Finally, the knowledge products of the third objective could provide ED clinicians with a clinical pathway that is aligned with current guidelines and maximizes the number of chest pain patients who can be quickly and safely discharged from the ED.

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CHAPTER 2: THESIS COMPONENT I SYSTEMATIC REVIEW

BACKGROUND

Chest pain and symptoms of ACS are a leading cause of ED visits in developed countries worldwide[1]. This pain is often attributable to some degree of cardiac ischemia and may manifest as a STEMI, NSTEMI, or UA[2], all of which are ACS and are associated with large disease burden[1] and substantive morbidity and mortality[3-6]. ED physicians must assess chest pain patients accurately and efficiently in order to avoid missed diagnoses while simultaneously reducing the ED overcrowding[7], healthcare costs[8,9] and resource utilization linked to their care[10].

Guidelines for the assessment of patients with suspected ACS have been outlined by leading medical bodies from Europe[11], the United States[12] and Canada[13]. Clinicians are advised to first use prehospital or arrival ECG to identify STEMI in all patients to ensure expeditious care for those with marked ST-changes. Patients without STEMI will then undergo serial hs-cTn assay sampling to detect any changes in cardiac biomarker concentration that may be secondary to NSTEMI. Finally, patients emerging from the former two steps without a clear diagnosis of AMI (or other clear acute ailment) will be stratified on the basis of their risk for adverse events – such as incident AMI, death or urgent revascularization- in the short-term following ED discharge.

The STEMI/NSTEMI rule-out portion of the assessment described above can be accomplished using ECG and hs-cTn assays in isolation or combined into more formalized RDAs[14-16]. Evidence suggests that 60-70% of patients will emerge from this process with index AMI ruled-out, eligible for discharge[17]. These patients have an approximate residual 2% MACE risk, though, and some may benefit from additional testing. ED clinicians can make such disposition decisions for these patients using validated clinical prognostic prediction scores. The

majority of these scores perform well and can identify patients as being at low-, intermediate- or high-risk for post-discharge MACE with high sensitivity and reasonable specificity[18-20]. However, these risk scores were derived in patient populations for whom MI remained a diagnostic consideration and prior to the availability of the hs-cTn assays currently used in most Canadian EDs, instead being developed using less sensitive contemporary cTn assays[21-24]. As such, there is limited evidence on the prognostic performance of these scores when used with the current generation of hs-cTn assays and for patients who have already had AMI ruled-out.

Therefore, the purpose of this component of the thesis project was to synthesize the available evidence on chest pain prognostic prediction scores when used concurrently with hs-cTn assays, and to determine their prognostic performance (i.e., ability to predict 30-day MACE) for suspected ACS patients **who have already had AMI ruled-out on the index ED visit.** The last distinction was made to ensure that risk scores were being applied in the population that would emerge from the AMI rule-out portion of the guideline-recommended chest pain assessment described above. Findings emerging from this study will advance the evidence on chest pain prognostic prediction score performance into the hs-cTn era and ensure disposition decisions are made using the best available tools.

METHODS

The methods of this study were developed and reported in alignment with the Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) and CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) reporting guidelines[25,26].

Study Design

This systematic review sought to answer the following question: what are the prognostic performances of chest pain risk prediction scores when used in conjunction with high-sensitivity cardiac troponin assays? Both mathematical risk prediction models and categorical risk prediction scores were eligible for inclusion in the review, granted all of the variables included in the prediction tool of interest were available to the treating physician at the time of the ED assessment. A study protocol describing the review methods, search methodology and analytical goals of the review was developed and registered to PROSPERO (CRD42019131264) prior to the commencement of the review.

Study Protocol

Search Strategy. An electronic search strategy was developed by the investigators (CO, AM) and further refined by a medical research librarian (HLR). The search strategy included terms describing the population, study designs, risk prediction scores and hs-cTn assays of interest (Appendix A). Headings and keywords were adapted for use in each database. To maximize the number of eligible articles identified, no publication date or publication language constraints were applied to the search.

A comprehensive search of six electronic databases (Ovid MEDLINE, EMBASE, CENTRAL, Scopus, Web of Science, CINAHL) was conducted to identify articles published between database inception and May 15, 2019. Reference lists of the included studies were also examined to identify any relevant articles not captured in the formal literature search.

Study Selection. Following the removal of duplicate records, two researchers (CO, TH) independently screened titles and abstracts identified in the database search to select articles with potential relevance to the research question. Inclusion criteria for the study were the following: (1) Studies must include adult (≥18 years) patients presenting to the ED with a primary complaint of chest pain or symptoms suggestive of ACS; (2) Studies had to assess risk score performance in the population of patients who have had MI ruled-out at the index visit; (3) Studies must assess the prognostic performance of one (or many) risk prediction scores applied in the ED, and; (4) Studies must evaluate these risk scores in reference to at least one of the outcomes described below. In accordance with CHARMS checklist, eligible study designs included prediction model development studies without external validation, prediction score model development studies with external validation, and external score validation studies (with or without model updating)[26]. Studies were excluded if they included only contemporary cardiac troponin results or assessed troponin-only prognostication tools (i.e., diagnostic and prognostic algorithms). The former exclusion was implemented as we judged risk scores including a number of clinical variables to be meaningfully different from those only assessing changes in cardiac biomarkers over time.

Full texts of the articles not excluded in the title and abstract phases were then reviewed in duplicate by the same researchers to ensure applicability to the research question. Articles meeting the pre-specified inclusion and exclusion criteria were included in the final review. A Cohen's kappa (κ) statistic and corresponding 95% confidence interval (CI) was calculated following the title and abstract phase of the selection process to quantify the level of agreement on included studies between the independent reviewers. At all stages of review, an unbiased third

party was available to mediate group discussions necessary to resolve sustained disagreement between article reviewers.

Outcomes of Interest. The primary outcome was the proportion of patients that could be categorized as low risk for 30-day MACE (i.e., ruled-out) by the prognostic prediction tool(s) of interest. Secondary outcomes included classification measures such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), as well as measures of discrimination (e.g., Area Under the Receiver Operating Characteristic Curve (AUC), C-statistic) and calibration (e.g., Hosmer-Lemeshow test result).

Data Extraction and Synthesis. Relevant study and outcomes data were collected by one researcher using a standardized data collection form. The data abstracted from each study included date of publication, country of origin, population characteristics, study type (derivation and internal validation, external validation), high-sensitivity troponin assay type (assay name, I or T), risk score being assessed, and relevant outcomes data.

Information describing study design, characteristics of the derivation and/or validation cohorts, and other relevant study details were discussed in the form of a narrative review and summarized in a data table. All of the synthesized outcomes data including proportion of patients ruled-out, classification characteristics, as well as discrimination and calibration results were presented semi-quantitatively in tabular form alongside written descriptions of their magnitude. Statistical significance of any direct comparisons of risk scores (i.e., comparisons of multiple risk scores within a single included study) was defined by a two-tailed p-value <0.05.

The *a priori* registered protocol for this study included plans for meta-analysis of the classification characteristics reported in the included studies. However, a prognostic meta-analysis requires the availability of the 2x2 contingency tables that correspond to each result reported in a study. The authors attempted to re-create these tables with data available in the included studies, but to ensure accurate interpretation contacted all authors for confirmation. Despite repeated follow-up, we were unable to receive responses from all authors and as such, the meta-analysis was rendered infeasible. This limitation is discussed further in the sections to follow.

Study Quality (risk of bias) Assessment. Study quality was appraised using the Prognostic model Risk of Bias ASsessment Tool (PROBAST)[27]. PROBAST is a novel, domain-based tool that enables the targeted and transparent assessment of risk of bias for derivation, validation or score updating studies. It should be noted that a single form is completed for each study with risk of bias ratings being made for all applicable designs (i.e., derivation/internal validation and external validation), resulting in two domain-based ratings and a single overall rating per study. One researcher (CO) completed a PROBAST form in full for each included study, with every form then being reviewed for completion and ROB rating appropriateness by a second researcher (TH).

RESULTS

Search Results. A total of 2217 articles were identified in the electronic database search, with 1350 articles remaining for assessment following the removal of duplicates. The title and abstract review yielded 325 texts for full-text review. Following the title and abstract screening phases

the level of agreement for study inclusion between independent reviewers was rated as good (κ=0.61 (95% CI: 0.56-0.67). The independent review of the 325 full texts led to the identification of 13 studies that met all pre-specified inclusion criteria and were included in the final review. The PRISMA flow diagram illustrating all stages of the reference management process, including reasons for full-text exclusion, is shown in Appendix B.

Study and Patient Characteristics. The included studies were published between 2014 and 2018 and were geographically diverse hailing from the United States[28,29], United Kingdom[30-32], Sweden[33], Argentina[34], Spain[35], Italy[36], New Zealand[37], Switzerland[38], the Netherlands[39] and Hong Kong[40]. All studies were published in English.

As detailed in Table 1, one derivation and internal validation study[33], two derivation studies with both internal and external validation[30,35], and ten external validation studies[28,29,31,32,34,36-40] were included assessing 751 patients, 2844 patients, and 17,348 patients, respectively. The reported mean ages in all studies ranged from 48.0 years to 63.5 years, with males representing between 44.0% and 64.6% of the study samples. The incidence of 30-day MACE varied largely between studies, ranging from 0.14% to 15.1%. Regardless of 30-day MACE incidence, this composite outcome was largely driven by urgent revascularizations with a contribution to the overall outcome as high as 93.4%[30].

The included studies evaluated risk score performance in concurrence with hs-cTnT assays (n=8)[29,30,32-36,39], hs-cTnI assays (n=2)[37,40], or both (n=3)[28,31,38]. Each study assessed the prognostic performance of between one and four individual risk scores. Among them were TIMI (n=6)[29,31,32,35,37,38], HEART (n=4)[32,34,36,39], HEAR (i.e., a HEART score calculated without the inclusion of the hs-cTn measure, which is considered separately, n=2)[28.29], GRACE (n=2)[32,35],

EDACS (n=1)[37], the troponin-only Manchester Acute Coronary Syndrome (T-MACS) decision aid (n=1)[30], the objective CORE score (n=1)[33], and an unnamed clinical score (n=1)[35]. One study assessed modified versions of the HEART, TIMI, GRACE and NACPR scores without the components that they deemed relied on clinical gestalt[32]. These are herein referred to as m-HEART, m-TIMI, m-GRACE and m-NACPR. Descriptions of the identified risk scores are shown in Table 2 including the patient populations in which they were derived, the outcomes they were developed to predict, as well as the items they contain and associated point systems. When applicable, studies often evaluated the prognostic performance of risk prediction scores at a variety of cut-offs (Table 1) allowing not only for comparisons between scores but also for a comparison across cut-offs of the same score.

Risk of Bias Assessment. All 13 studies were assessed in detail using PROBAST yielding low (n=5)[31,32,34,36,40], unclear (n=4)[28,29,37,38] and high (n=4)[30,33,35,39] risk of bias ratings. The majority of high overall risk of bias ratings were in studies with an internal validation component and were due to the limited use of the analytical techniques (e.g., bootstrapping) necessary to curb within-cohort optimism in derived model performance. Any bias secondary to this reason likely led to an overestimation of risk score performance within that study cohort. A single internal and external validation study had an overall high risk of bias stemming from the predictor domain. This emerged from concerns with the exclusion of all patients with ischemic ECGs, despite ischemia on ECGs being a model predictor. Otherwise, there was minimal concern with bias due to data source, participant selection, predictor selection, outcomes assessment or outcomes reporting. A more detailed visual summary of the domain-specific and overall risk of bias ratings is shown in Figure 1.

Outcomes. As previously mentioned, we were unable to confirm the composition of the necessary 2x2 contingency tables with all corresponding authors and had a maximum of two studies contributing to any outcome, thus making the planned meta-analysis and generation of pooled estimates infeasible. This was compounded by concerns about the use of the same patient cohort in more than one of the included studies, which without author confirmation would have been very challenging to manage and might have biased estimates. To ensure that the results reported were aligned with the predefined goals of the project (i.e., to measure prognostic performance of risks scores in patients with index MI ruled-out), we elected to report findings confirmed by authors separately from those without confirmation. Semi-quantitative summaries of performance within each score were performed and are reported separately. Similarly, results confirmed by corresponding authors to contain only patients with index AMI ruled-out are summarized in tables independently from results reported in the included studies without confirmation. Any differences between confirmed and unconfirmed results were underlined and acknowledged in the limitations section of the discussion. The inclusion and exclusion criteria for each individual study were also provided in Table 2 to make clear what specific types of chest pain patients were prognosticated in each study.

Due to the large variations in 30-day MACE incidence between studies and the dependence of NPV and PPV on this incidence, we chose post-hoc to exclude NPV and PPV as measures of interest for comparisons between scores. Instead, comparisons of risk scores were made on the basis of proportion of patients deemed low risk for 30-day MACE (i.e., ruled-out), sensitivity, specificity, and discriminative ability. Figure 2 shows the true positives, false positives, false negatives, true negatives and resulting sensitivities for the external validation studies confirmed by authors. These values allowed for the most rigorous comparison of

performance across the risk scores. Further, the results reported in each study for all predefined outcomes are summarized in Tables 3-5 (results confirmed by corresponding authors), Tables 6-10 (results as reported in the studies but not confirmed) and described for each identified risk score below in more detail.

HEART/HEAR Score. The prognostic performance of the HEART and HEAR scores was assessed by a number of studies at cut-offs ranging from a traditional low risk threshold of ≤3 points to less typical cut-offs of m-HEART where those with scores ≥1 and ≥2 were deemed not low-risk for 30-day MACE.

The single study with confirmed results for the cut-off of ≤3 points enabled the ruling out of 37.2% of patients when implemented concurrently with hs-cTnT, but no equivalent combination with hs-cTnI was available for comparison. This same study reported a sensitivity for 30-day MACE of 100% (95% CI: 98.2-100) and a specificity for the same outcome of 44.6% (95% CI: 41.7-47.5).

Results from the studies reporting on the HEART/HEAR score but whose populations were not confirmed by authors to exclude index MI were similar to those in the confirmed study. The ≤3 points low-risk cut-off enabled the ruling out of between 34.8% and 62.5% of patients when implemented concurrently with hs-cTnT, while the single study combining this cut-off with hs-cTnI ruled out 45.1% of patients. A comparison of this proportion with the other HEART cut-offs was not possible as the study testing them did not report on this outcome. The ≤3 point threshold for low-risk combined with hs-cTnT corresponded to sensitivities for 30-day MACE between 90.9% (95% CI: 58.7-99.8) and 97.6% (95% CI: 94.6-99.2), slightly underperforming compared to the same cut-off with hs-cTnI which achieved 100% sensitivity

(95% CI: 71.5-100). The 49.2% (95% CI: 40.0-58.4) specificity for 30-day MACE for HEART≤3 combined with hs-cTnI fell within the range of specificities for the equivalent cut-off in tandem with hs-cTnT (48.4% to 60.9%). The sensitivities for 30-day MACE relating to the atypical cut-offs of m-HEART ≥1 and ≥2 were similarly high at 98.8% (95% CI: 95.2-99.8) and 98.2% (95% CI: 94.3-99.5), respectively. However, the reported specificities for these cut-offs were much lower by comparison, with the highest of 32.8% (95% CI: 29.8-26.0) falling below the range of specificity values for HEART≤3. Four studies reported on the discriminative ability of the HEART score for 30-day MACE in combination with hs-cTnT and one reporting on the same outcome for HEART in combination with hs-cTnI, showing minimal difference. The AUC for HEART≤3 with hs-cTnT ranged from 0.748 (95% CI: NR) to 0.91 (95% CI: 0.89-0.93) with the AUC corresponding to m-HEART≥1 with hs-cTnI falling within this range at 0.845 (95% CI: 0.812-0.878). HEART/HEAR score calibration was not reported on in any of the included studies.

TIMI Score. The prognostic performance of the TIMI score was assessed at 5 distinct low risk thresholds: TIMI=0 (both hs-cTn assays), TIMI≤1 (both hs-cTn assays), TIMI≤2 (both hs-cTn assays), m-TIMI≥1 (hs-cTnI only), and m-TIMI≥2 (hs-cTnI only).

Confirmed data was available from 3 studies reporting on the TIMI score, with one study providing results separately for two of the distinct cohorts contained in the original manuscript[31]. In these studies, the proportion of patients identified as low-risk for 30-day MACE by TIMI=0 combined with hs-cTnT ranged from 20.4% to 30.4%, falling within the range for the same cut-off in combination with hs-cTnI (16.8% to 37.2%). Assay type aside, as the TIMI low-risk cut-off increased, so too did the proportion of patients identified as low risk for 30-day MACE,

reaching a maximum of 66.3% for TIMI≤2 with hs-cTnI. Sensitivities for 30-day MACE were 100% (95% CIs: 69.2-100, 29.2-100) for a TIMI=0 cut-off in both studies using hs-cTnT and ranged from 92.0% (95% CI: 72.5-98.6) to 100% (95% CI: 71.5-100) in studies using hs-cTnI. An estimate for sensitivity could not be calculated in one study[37] given that no MACE occurred at 30-days. Sensitivity for 30-day MACE typically decreased as TIMI cut-offs increased, reaching minimums of 33.3% (95% CI: 0.84-90.6) and 60.0% (95% CI: 38.9-78.2) for TIMI ≤1 with hs-cTnT and TIMI ≤2 with hs-cTnI, respectively. The range of specificities for 30-day MACE for TIMI=0 combined with hs-cTnT (20.6% to 30.5%) fell within the larger range of specificities for the score in concurrence with hs-cTnI (16.9% to 37.2%). Specificities expectedly increased as more patients were ruled-out by higher TIMI cut-offs, reaching a maximum of 66.6% (95% CI: 64.5-68.3) for TIMI ≤2 with hs-cTnI.

Results from studies without confirmation of index MI rule-out from authors did not differ meaningfully from the results above. A total of 30.8% of patients were deemed low-risk for 30-day MACE by TIMI=0 in combination with hs-cTnT, with no studies reporting on the same cut-off with hs-cTnI. Irrespective of hs-cTn assay type, the largest proportion of patients was ruled-out by TIMI≤1 (64.0%) followed closely by TIMI≤2 which identified up to 41.5% of patients as low risk for 30-day MACE (within the 29.5% to 66.3% range in confirmed studies). The study evaluating the m-TIMI≥1 and m-TIMI≥2 cut-offs did not report on this outcome. No studies reported on the sensitivity for 30-day MACE at the TIMI=0 cut-off, and no meaningful differences in sensitivity were seen between hs-cTn assays at the TIMI≤1 cut-off (range 91.0% to 100%). The specificities for 30-day MACE trended upwards with increases in the TIMI cut-off regardless of hs-cTn assay type, reaching notable highs of 63.7% (95% CI: 61.2-66.2) and 68.8 (95% CI: 65.7-71.8) for TIMI ≤1 with hs-cTnT and m-TIMI≥2 with hs-cTnI, respectively

tables 6 and 7). Four studies reported on the discriminative ability of the TIMI score. The AUCs of 0.77 (95% CI: NR) for TIMI=0 with hs-cTnT and 0.809 (95% CI: 0.777-0.841) for m-TIMI≥1 with hs-cTnI fell within the range of 0.677 (95% CI: NR) to 0.855 (95% CI: NR) for TIMI≤1 with hs-cTnT. No studies reported on the calibration of the TIMI score.

GRACE Score. A single study with a confirmed MI ruled-out population showed that low-risk cut-offs of GRACE>109 and GRACE>140 identified 82.6% and 98.2% of patients as ruled-out, respectively. However, they did so with sensitivities of 0% (95% CI: 0-70.8%). These results suggest that these score thresholds are unsuitable for clinical use in this population to risk stratify for 30-day MACE, and as such no further assessment or comparison of these combinations of GRACE and hs-cTnT was conducted.

In the remaining studies, only the one evaluating GRACE score performance in combination with hs-cTnT reported the proportion of patients deemed low risk for 30-day MACE, suggesting that 28.6% could be ruled out with GRACE<75. Notwithstanding hs-cTn assay type, lower cut-offs of the GRACE score such as ≥50 and <75 outperformed all others, with the former cut-off achieving a sensitivity for 30-day MACE of 99.4% (95% CI: 96.1-100). Among the GRACE cut-offs with sensitivities >90%, GRACE≥75 with hs-cTnI held a very slight 0.3% edge in specificity over GRACE<75 with hs-cTnT (32.5% versus 32.2%). Three studies reported on the discriminative abilities of this score giving GRACE<75 with hs-cTnT the highest AUC of 0.791. No measures of calibration were provided by any of the included studies with respect to the GRACE score.

Additional Scores. The remaining prognostic prediction scores (i.e., T-MACS[30], Core Score[33], EDACS[37], m-NACPR[40], and an unnamed Clinical Score[35]) were each evaluated by a single study and unlike above, within score comparisons using ranges of values could not be completed. These scores ruled-out between 24.0% and 46.0% of patients with the highest being achieved on internal validation by the unnamed clinical score with a cut-off of 1 point or less in combination with hs-cTnT (Table 5)[35]. Sensitivities for all of these scores were between 93.3% (95% CI: 66.0-99.7) and 100% (95% CI: 29.2-100) and specificities ranged from 23.6% (95% CI: 20.4-26.9) to 54.2% (95% CI: 50.4-57.9). While many of these additional scores performed strongly, it should be noted that the T-MACS was the only one of these scores to be both internally and externally validated. The T-MACS score maintained high performance in external validation ruling-out 40.4% of patients with sensitivity and specificity for 30-day MACE of 98.1% (95% CI: 95.2-99.5) and 47.0% (95% CI: 44.2-49.8), respectively. Information on discriminative ability was only available for T-MACS and the unnamed clinical score=0, showing the superiority of T-MACS with an AUC of 0.94 on internal validation (which was slightly reduced to 0.90 on external validation). No information on risk score calibration was available for these additional scores.

DISCUSSION

The purpose of this study was to evaluate the prognostic performance of chest pain risk scores when used concurrently with hs-cTn assays in patients with index MI already ruled out. We identified 13 low to moderate quality studies providing prognostic performance data on a number of risk scores across various cut-offs. The evidence synthesized in this study shows that

many common risk predictions scores can safely be used with hs-cTn assays for the prognostication of patients with suspected ACS.

The findings of our study suggest that, when used in conjunction with hs-cTn assays, HEART≤3 outperformed the most effective cut-off for the TIMI score (i.e., ≤1) which, in turn, was superior to GRACE≤75. To reach this conclusion we performed within (in the case of a risk score with multiple low risk thresholds) and between score comparisons based on three predominant components of prognostic performance: proportion deemed low-risk, sensitivity, and specificity (the former two are best seen compared in Figure 2). This ensured that we did not falsely conclude superiority of a risk score identifying more than 80% of patients as low risk for 30-day MACE, while ignoring a very low sensitivity and high likelihood for false negatives. The finding that HEART≤3 was the superior risk score is consistent with those of the direct comparison studies included in this review[28,32,40] and with available literature on prognostic prediction score performance in undifferentiated chest pain patients[18,19,41,42].

Regardless of which risk score was best for chest pain patient prognostication, almost all tested scores when combined with hs-cTn assays identified the same or more patients as low risk for 30-day MACE than they did with contemporary troponin assays. This was true for TIMI≤1 which in previous validation studies ruled-out 9.9% to 25.5%[43,44] (compared to only one study in this review ruling out <25% of patients), and for HEART≤3 which has historically ruled-out between 32% and 48% of patients[45,46], compared to 37.2% in this study. This is notable given that in the nascent days of hs-cTn assays, some researchers hypothesized that the ability to detect lower troponin concentrations due to other pathologies (i.e., pulmonary embolism, sepsis) might contribute to higher resource utilization[47]. Evidence on this claim is mixed whereby some studies have shown small increases in coronary revascularizations and others have shown no change[48,49].

The findings of our review add to this literature the consideration that a similar or higher proportion of patients can be ruled-out when risk scores are used in concurrence with hs-cTn assays compared to contemporary cTn, potentially creating an opportunity for reduced hospital and outpatient resource utilization attributable to follow-up testing.

It is important to note that the determination of HEART≤3 score superiority was based on the studies included in this review, but risk score appropriateness and preference will likely vary based on local workflow, resources, and medicolegal environment. This review merely provides a summary of the risk scores available and situates their performance in the era of hs-cTn assays in hopes that ED clinicians and administrators can identify a risk score well suited to their own clinical context.

STRENGTHS AND LIMITATIONS

To our knowledge this is the first systematic review to synthesize evidence on **risk score performance with hs-cTn assays specifically in patients who have already had AMI ruled-out at the index ED encounter**. We developed a comprehensive electronic search strategy in collaboration with clinical experts and a medical research librarian. The study was completed with strict adherence to the *a priori* protocol registered to PROSPERO, whose methods were developed in reference to recommendations from established methodological sources. Further, all procedures and findings were reported in accordance with PRISMA and CHARMS guidelines.

This study is not without its limitations. Firstly, we were unable to complete the planned meta-analysis given that we did not have access to the necessary data. As a result, our findings

were derived through semi-quantitative analyses and do not hold the same rigor as the pooled estimates that would have emerged from a formal prognostic meta-analysis.

Secondly, risk score calibration is a statistically important property of validation studies[50] that we intended to assess in this study. However, despite strong reporting on the equally important validation characteristic of discrimination, none of the included studies reported measures of calibration. Knowledge of calibration would have allowed us to comment on the tendency of certain risk scores to over or underestimate risk for 30-day MACE in this patient population, which in turn may have informed clinically important recalibration studies.

This study is also limited by the low to moderate methodological quality of the included studies. According to PROBAST, all of the included derivation and internal validation studies were at high risk of bias, typically due to a lack of analytical procedures to address within-cohort optimism in risk score performance. We recommend that the reported prognostic performance of the internally validated risk scores presented in this review be considered with this limitation in mind. To avoid a biased interpretation of the included studies, commentary around which risk scores perform best in this population of chest pain patients was focused on the external validation studies shown by PROBAST to be less susceptible to such biases.

FUTURE DIRECTIONS

Because hs-cTn assays have largely improved ED physician's ability to diagnose AMI, it is essential that further development and refinement of risk stratification tools focus on the post-AMI rule out population with the goal of maximizing their clinical utility for prognostication. Moreover, as we identified a universal lack of information on risk score calibration, future derivation, validation and updating studies should prioritize this aspect of reporting. In the case

that common risk scores are shown to consistently over- or underestimate patient risk for subsequent adverse events, re-calibration studies should be performed.

CONCLUSION

In the population of chest pain patients who have had index MI ruled-out, HEART≤3, TIMI≤1, and GRACE≤75 used concurrently with both hs-cTnT and hs-cTnI assays enable the ruling-out of large proportions of patients while maintaining clinically acceptable sensitivity and specificity for 30-day MACE. Future research should ensure that available risk scores are tailored to patients for whom AMI has already been ruled out with hs-cTn, given that a large proportion of these low risk patients likely continue to undergo low-yield and potentially harmful urgent objective testing.

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Tables.

Table 1. Characteristics of included studies and populations, by study design.

Study	Country	Sample Size	Mean Age (SD) or Median (Q1-Q3)	Male (%)	30D MACE (%)	Troponin assay(s)	Risk score(s) and cut-offs
Derivation and Internal Validation							
Borna, 2018[33]	Sweden	751	63.5 (49.6-74.1)	419 (55.8)	72 (9.59)	hs-cTnT	CORE Score
Derivation, Internal Validation, and External Validation							
Body, 2017[30]	England	D+IV: 703 EV: 1459	D+IV: 58.6 (14.3) EV: 59.6 (14.5)	D+IV: 430 (61.2) EV: 874 (59.9)	D+IV: 106 (15.1) EV: 143 (9.80)	hs-cTnT	T-MACS
Sanchis, 2016[35]	Spain	D+IV: 682 EV: 682	D+IV: 61.0 (14.0) EV: 61.0 (14.0)	D+IV: 371 (54.0) EV: 371 (54.0)	D+IV: 23 (3.37) EV: 23 (3.37)	hs-cTnT	New Score=0 New Score ≤1 TIMI=0 TIMI ≤1 GRACE >109 GRACE >140
External Validation Only							
Carlton, 2018[31]	England	7691	58.1 (13.2)	4830 (62.8)	19 (0.25)	hs-cTnT hs-cTnI	TIMI=0 TIMI ≤1 TIMI ≤2
Chew, 2018[32]	England	1642	59 (47-72)	858 (52.0)	88 (5.36)	hs-cTnT	TIMI ≤1 GRACE <75 HEART ≤3
Cortes, 2018[34]	Argentina	1464	52.8 (12.2)	352 (47.6)	2 (0.14)	hs-cTnT	HEART ≤3

(Continued)

Table 1 (Continued)							
Mahler, 2017[28]	USA	259	53.6 (12.0)	114 (44.0)	11 (8.27)	hs-cTnT hs-cTnI	HEART ≤3
McCord, 2017[29]	USA	661	58.3 (13.0)	385 (58.2)	6 (0.91)	hs-cTnT	HEART ≤3 TIMI=0 TIMI ≤1
Santi, 2017[36]	Italy	1378	60.0 (19.0)	778 (56.5)	33 (2.39)	hs-cTnT	HEART ≤3
Than, 2016[37]	New Zealand	558	58.7 (11.9)	340 (60.9)	3 (0.54)	hs-cTnI	TIMI=0 EDACS ≤16
Wildi, 2017[38]	Switzerland	2525	62 (50-74)	1632 (64.6)	NR	hs-cTnT hs-cTnI	TIMI ≤1
Willems, 2014[39]	Netherlands	89	61.0 (NR)	52 (58.4)	9 (10.1)	hs-cTnT	HEART ≤3
Wong, 2018[40]	Hong Kong	1081	48.0 (27.0)	565 (52.3)	6 (0.56)	hs-cTnI	m-TIMI ≥1 m-TIMI ≥2 GRACE ≥50 GRACE ≥75 GRACE ≥100 m-HEART ≥1 m-HEART ≥2 m-NACPR

SD= Standard deviation, USA= United States of America, D+IV= Derivation and Internal Validation, EV= External Validation, hs-cTnT= high-sensitivity cardiac troponin T, hs-cTnI= high-sensitivity cardiac troponin I, T-MACS= Troponin only Manchester Acute Coronary Score, TIMI= Thrombolysis in Myocardial Infarction, GRACE= Global Registry of Acute Coronary Events, HEART= History, ECG, Age, Risk Factors, Troponin, EDACS= Emergency Department Assessment of Chest Pain Score, NACPR= North American Chest Pain Rule, NR= Not Reported

Table 2. Description of prediction scores in the included studies

Prediction Score	Derivation Population and Outcome	Items	Score
TIMI score*	**Included:** • Patients presenting to the ED within 24 hours of an episode of UA/NSTEMI at rest. • Patients with at least one of the following: o ST-segment deviation on the qualifying ECG (either transient ST elevation or persistent ST depression ≥0.5 mV. o Documented history of CAD o Elevated serum cardiac markers **Excluded:** • Planned revascularization in ≤24 hours. • Correctable cause of angina. • Contraindications to anticoagulation. **Outcome:** 14-day composite of all-cause mortality, new or recurrent MI, or severe recurrent ischemia prompting urgent revascularization through (including during initial attendance/admission).	Age ≥65 years ≥3 CAD risk factors Hypertension Hypercholesterolemia Diabetes Family history of CAD Current Smoker Known CAD (stenosis ≥50%) ASA use in the past 7 days Severe angina (≥2 episodes in 24 hours) ECG ST changes ≥0.5mm Elevated cardiac biomarker	1 1 1 1 1 1 1
HEART score†	**Included:** • Patients admitted to the ED due to chest pain. • No age restrictions. • No restrictions on previous medical treatments. **Excluded:** • STEMI	History Slightly suspicious Moderately suspicious Highly suspicious ECG Normal Non-specific repolarization disturbance/LBBB/LVH Significant ST changes	 0 1 2 0 1 2

	Outcome: 3 month AMI, PCI, CABG, or death, plus a combined endpoint of AMI, PCI, CABG and death (including during initial attendance/admission).	Age <45 years 0 45-64 years 1 ≥65 years 2 CAD Risk Factors No known risk factors 0 1-2 risk factors 1 ≥3 risk factors or history of atherosclerotic disease 2 Troponin (including hs-cTnT) ≤normal limit 0 1-3x normal limit 1 >3x normal limit 2
GRACE score	**Included:** • Patients with a presumptive diagnosis of ACS. • Aged ≥18 years. **Excluded:** • ACS not precipitated by MVC, trauma, severe GI bleeding, operation, or procedure. • Inpatients at time of ACS symptom development. • Enrolled ≤6 months previously. **Outcome:** Six month all cause death or the composite measure of death or non-fatal myocardial infarction (including during initial attendance/admission).	Age 0-100 Heart rate 0-46 Systolic blood pressure 0-58 Creatinine 1-28 Congestive heart failure: Killip class I/II/III/IV 0-59 Cardiac arrest at presentation 39 ST-segment deviation 28 Elevated cardiac enzymes/biomarker 14
EDACS	**Included:** • Patients with ≥5 minutes of symptoms consistent with ACS such that physician planned to perform further investigations for this potential diagnosis.	Age 2-20 Male sex 6 Aged 18-50 years and either: 4 Known CAD or ≥3 risk factors

	• Aged ≥18 years. **Excluded:** • STEMI • Clear cause other than ACS for the symptoms. • Inability to provide informed consent. • Staff considered recruitment inappropriate (e.g., receiving palliative treatment). • Transfer from another hospital. • Pregnancy. • Previous enrollment. • Inability to be contacted after discharge. **Outcome:** 30-day MACE composed of death (unless clearly non-cardiac), cardiac arrest, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and AMI (including during initial attendance/admission)	Diaphoresis 3 Pain radiates to arm or shoulder 5 Pain occurred or worsened with palpation -4 Pain is reproduced by palpation -6	
NACPR‡	**Included:** • Patients presenting to the ED with a primary complaint of anterior chest pain, for whom cardiac troponin testing was ordered by the treating physician as a component of the assessment for ACS. • Aged ≥24 years. **Excluded:** • STEMI • Hemodynamic instability (pulse greater than 100 or less than 50 beats/min or systolic blood pressure persistently below 90 mm Hg).	New ischemia on initial ECG History of CAD Initial cardiac troponin is positive AND Age ≤ 40 years; or Pain is typical for ACS Age 41-50 years and repeat troponin at least 3h from symptom onset is negative	N/A, a patient is ruled-out if all items are absent.

	• Unreliable clinical history as determined by treating physician. • Clear traumatic cause of chest pain. • Clinical history of cocaine use or positive test result for cocaine. • Terminal noncardiac illness. • Pregnancy. • Previous enrollment within the past 30 days. • Inability to receive follow-up by telephone. **Outcome:** 30-day AMI, coronary revascularization, or death of cardiac or unknown cause (including during initial attendance/admission).		
T-MACS	**Included:** • Patients who presented to the ED with a primary complaint of chest pain that the treating physician suspected might be cardiac in nature and warranted investigation for a possible ACS. • Aged >25 years. **Excluded:** • Another medical condition requiring hospital admission. • Renal failure needing dialysis. • Significant chest trauma with suspicion of myocardial contusion. • Pregnancy. • Unable to speak English. • Prisoners.	ECG ischemia Worsening or crescendo angina Pain radiating to right arm or shoulder Pain associated with vomiting Sweating observed Hypotension (sBP<100 mmHg on ED arrival) hs-cTnT concentration on ED arrival	1 1 1 1 1 1 True value

	Outcome: 30-day diagnosis of AMI, and 30-day diagnosis of ACS (prevalent AMI or incident MACE). MACE was composed of incident AMI, death (from all causes) or coronary revascularization (not including initial attendance/admission).		
Objective CORE score	**Included:** • Patients who presented with non-traumatic chest pain/discomfort to the ED for whom a hs-cTnT was analyzed at presentation (0h). • Aged ≥18 years. **Excluded:** • STEMI • Missing 2h hs-cTnT samples or hemolysis in either the 0h or 2h sample. **Outcome:** 30-day MACE composed of AMI, unstable angina, cardiac arrest, cardiogenic shock, ventricular arrhythmia requiring intervention, atrioventricular block requiring intervention, unplanned PCI or CABG, or death of all causes. (including during initial attendance/admission)	Age <65 years No history of artierial disease (previous MI, PCI, or CABG) No history of hypertension No history of diabetes mellitus hs-cTnT ≤14 ng/L at 0 and 2h	N/A, a patient is ruled-out if all items are absent.
Unnamed Clinical score	**Included:** • Patients who presented with non-traumatic acute chest pain without ischemic ECG changes or hs-cTnT elevation. • Aged ≥18 years. **Excluded:**	Male gender Effort-related chest pain at admission or during previous week ≥2 episodes in 24 hours Prior coronary heart disease	1 1 2 2

	• Diagnosis of an obvious cardiac nonischemic or noncardiac cause after the initial assessment in the ED. • Any positive hs-cTnT or ECG result. **Outcome:** Long term (median 4.3 years) and 30-day MACE composed of death, MI, readmission for unstable angina, or coronary revascularization (including during initial attendance/admission).	

ED=Emergency department, CAD=Coronary artery disease, UA=Unstable angina, MACE=Major adverse cardiac events, NSTEMI=Non ST-elevation myocardial infarction, ASA=Acetyl salicylic acid, STEMI=ST-elevation myocardial infarction, ECG=Electrocardiogram, ACS=Acute coronary syndromes, AMI=Acute myocardial infarction, MVC=Motor vehicle collision, hs-cTnT=high-sensitivity cardiac troponin, TIMI= Thrombolysis in Myocardial Infarction, GRACE= Global Registry of Acute Coronary Events, HEART= History, ECG, Age, Risk Factors, Troponin, EDACS= Emergency Department Assessment of Chest Pain Score, NACPR= North American Chest Pain Rule, T-MACS= Troponin only Manchester Acute Coronary Syndrome decision aid.

*m-TIMI score differs by the removal of the "Severe Angina (≥2 episodes in 24 hours)" score item.
†m-HEART score differs by the removal of the categorical "History" score item.
‡m-NACPR differs by the removal of the "Pain is typical for

Table 3. Classification characteristics for 30-day MACE in external validation studies using hs-cTnT assays **as confirmed by corresponding authors**, stratified by risk score and cut-off.

Study	Ruled-out (%)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
TIMI=0					
Cartlon (NZ)	254 (20.4)	100 (69.2-100)	20.6 (18.3-22.9)	100 (98.6-100)	1.00 (0.1-1.8)
Sanchis	207 (30.4)	100 (29.2-100)	30.5 (27.0-34.1)	100 (97.7-100)	0.63 (0.60-0.66)
TIMI ≤1					
Carlton (NZ)	367 (29.5)	90.0 (55.5-99.7)	29.7 (27.2-32.3)	99.7 (98.5-100)	1.00 (0.50-1.90)
Sanchis	434 (63.6)	33.3 (0.84-90.6)	63.6 (59.9-67.3)	99.5 (98.9-99.8)	0.40 (0.08-1.97)
TIMI ≤2					
Carlton (NZ)	459 (36.8)	90.0 (55.5-99.7)	37.1 (34.4-39.8)	99.8 (98.8-100)	1.10 (0.50-2.20)
HEART ≤3					
Santi	512 (37.2)	100 (98.2-100)	44.6 (41.7-47.5)	100 (99.1-100)	24.5 (23.5-25.4)
GRACE >109					
Sanchis	563 (82.6)	0 (0-70.7)	82.5 (79.4-85.3)	99.5 (99.4-99.4)	0 (-)
GRACE >140					
Sanchis	670 (98.2)	0 (0-70.8)	98.2 (96.8-99.1)	99.6 (99.6-99.6)	0 (-)

NPV= Negative Predictive Value, PPV= Positive Predictive Value, NR= Not Reported, C1= Cohort 1, C2= Cohort 2, TIMI= Thrombolysis in Myocardial Infarction, HEART= History, ECG, Age, Risk Factors, Troponin, GRACE= Global Registry of Acute Coronary Events, T-MACS= Troponin only Manchester Acute Coronary Score

Table 4. Classification characteristics for 30-day MACE in external validation studies using hs-cTnI assays **as confirmed by corresponding authors**, stratified by risk score and cut-off.

Study	Ruled-out (%)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
TIMI=0					
Carlton (Aus)	576 (26.8)	92.0 (72.5-98.6)	27.0 (25.1-28.9)	99.7 (98.6-99.9)	1.46 (0.95-2.22)
Carlton (NZ)	263 (16.8)	100 (71.5-100)	16.9 (15.1-18.9)	100 (98.6-100)	0.80 (0.40-1.50)
Than	90 (37.2)	NA	37.2 (31.1-43.6)	100 (-)	0 (0.00-1.51)
TIMI ≤1					
Carlton (Aus)	1217 (56.6)	88.0 (67.7-96.8)	57.1 (54.9-59.2)	99.8 (99.2-99.9)	2.36 (1.52-3.61)
Carlton (NZ)	365 (23.3)	90.9 (58.7-99.8)	23.4 (21.3-25.6)	99.7 (98.5-100)	0.80 (0.40-1.50)
TIMI ≤2					
Carlton (Aus)	1425 (66.3)	60.0 (38.9-78.2)	66.6 (64.5-68.3)	99.3 (98.7-99.6)	2.07 (1.21-3.47)
Carlton (NZ)	451 (28.8)	90.9 (58.7-99.8)	28.9 (26.7-31.2)	99.8 (98.8-100)	0.90 (0.40-1.60)
EDACS ≤16					
Than	113 (48.5)	50.0 (1.26-98.7)	48.5 (41.9-55.1)	99.1 (96.5-99.8)	0.83 (0.00-3.27)

NPV= Negative Predictive Value, PPV= Positive Predictive Value, NR= Not Reported, C1= Cohort 1, C2= Cohort 2, TIMI= Thrombolysis in Myocardial Infarction, HEART= History, ECG, Age, Risk Factors, Troponin, GRACE= Global Registry of Acute Coronary Events, T-MACS= Troponin only Manchester Acute Coronary Score, EDACS= Emergency Department Assessment of Chest Pain Score, NACPR= North American Chest Pain Rule.

Table 5. Classification characteristics for 30-day MACE in internal validation studies using hs-cTnT assays **as confirmed by corresponding authors**, stratified by risk score and cut-off.

Study	Ruled-out (%)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
Clinical Score=0					
Sanchis	160 (23.5)	100 (29.2-100)	23.6 (20.4-26.9)	100 (-)	0.57 (0.55-0.60)
Clinical Score ≤1					
Sanchis	314 (46.0)	100 (29.2-100)	54.2 (50.4-57.9)	100 (-)	0.96 (0.88-1.04)

NPV= Negative Predictive Value, PPV= Positive Predictive Value, NR= Not Reported, T-MACS= Troponin only Manchester Acute Coronary Score

Table 6. Classification characteristics for 30-day MACE in external validation studies using hs-cTnT assays **as reported in the included studies (not confirmed to be non-index AMI only)**, stratified by risk score and cut-off.

Study	Ruled-out (%)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
TIMI=0					
McCord	200 (30.8)	-	-	-	-
TIMI ≤1					
Chew	931 (56.7)	91.0 (86.3-94.5)	63.7 (61.2-66.2)	27.0 (23.8-30.4)	98.0 (96.8-98.8)
McCord	366 (56.3)	-	-	-	-
Wildi (C1)	496 (36.2)	100 (98.5-100)	-	100 (99.3-100)	-
Wildi (C2)	469 (40.7)	94.7 (90.4-97.4)	-	99.4 (98.1-99.0)	-
HEART ≤3					
Chew	877 (53.4)	97.6 (94.6-99.2)	60.9 (58.4-63.5)	99.4 (98.7-99.8)	26.9 (23.8-30.2)
Cortes	739 (50.5)	-	-	-	-
Willems	31 (34.8)	-	-	-	-
HEAR ≤3 + 0h hs-cTnT<14 ng/L					
Mahler	60 (45.1)	90.9 (58.7-99.8)	48.4 (39.2-57.6)	98.3 (91.1-100)	13.7 (6.8-23.8)
McCord	413 (62.5)	93.8 (89.6-96.7)	-	99.8 (98.7-100)	-
GRACE <75					
Chew	470 (28.6)	95.7 (92.0-98.0)	32.2 (29.8-34.7)	98.1 (96.4-99.1)	17.2 (15.1-19.5)
T-MACS					
Body	590 (40.4)	98.1 (95.2-99.5)	47.0 (44.2-49.8)	99.3 (98.8-99.8)	23.9 (21.1-26.9)

NPV= Negative Predictive Value, PPV= Positive Predictive Value, NR= Not Reported, C1= Cohort 1, C2= Cohort 2, TIMI= Thrombolysis in Myocardial Infarction, HEART= History, ECG, Age, Risk Factors, Troponin, GRACE= Global Registry of Acute Coronary Events, T-MACS= Troponin only Manchester Acute Coronary Score

Table 7. Classification characteristics for 30-day MACE in external validation studies using hs-cTnI assays **as reported in the included studies (not confirmed to be non-index AMI only)**, stratified by risk score and cut-off.

Study	Ruled-out (%)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
TIMI ≤1					
Wildi (C1)	511 (37.2)	99.6 (97.7-100)	-	99.8 (98.8-100)	-
Wildi (C2)	492 (42.7)	94.1 (89.8-97.0)	-	99.6 (98.5-100)	-
m-TIMI ≥1					
Wong	-	97.0 (92.7-98.9)	45.7 (42.4-49.0)	98.8 (97.1-99.6)	24.2 (21.0-27.7)
m-TIMI ≥2					
Wong	-	76.8 (69.5-82.9)	68.8 (65.7-71.8)	94.3 (92.2-95.9)	30.6 (26.2-35.3)
HEAR ≤3 + 0h hs-cTnI <34 ng/L (men) or 16 ng/L (women)					
Mahler	60 (45.1)	100 (71.5-100)	49.2 (40.0-58.4)	100 (94.0-100)	15.1 (7.8-25.4)
m-HEART ≥1					
Wong	-	98.8 (95.2-99.8)	11.7 (9.7-14.0)	98.2 (92.9-99.7)	16.7 (14.4-19.2)
m-HEART ≥2					
Wong	-	98.2 (94.3-99.5)	32.8 (29.8-36.0)	99.0 (96.9-99.7)	20.7 (18.0-23.8)
GRACE ≥50					
Wong	-	99.4 (96.1-100)	7.5 (5.9-9.5)	98.6 (91.2-99.9)	16.1 (13.9-18.6)
GRACE ≥75					
Wong	-	92.1 (86.5-95.5)	32.5 (29.5-35.7)	95.8 (92.8-97.7)	19.6 (16.9-22.6)
GRACE ≥100					
Wong	-	76.2 (68.8-82.4)	61.9 (58.7-65.1)	93.6 (91.2-95.3)	26.4 (22.5-30.6)
EDACS ≤16					
Than	116 (41.6)	-	-	-	-
m-NACPR					
Wong	-	93.3 (66.0-99.7)	51.5 (44.9-58.0)	99.2 (94.8-100)	10.9 (6.3-18.0)

NPV= Negative Predictive Value, PPV= Positive Predictive Value, NR= Not Reported, C1= Cohort 1, C2= Cohort 2, TIMI= Thrombolysis in Myocardial Infarction, HEART= History, ECG, Age, Risk Factors, Troponin,

(Continued)

Table 7 (Continued)

GRACE= Global Registry of Acute Coronary Events, T-MACS= Troponin only Manchester Acute Coronary Score, EDACS= Emergency Department Assessment of Chest Pain Score, NACPR= North American Chest Pain Rule.

Table 8. Classification characteristics for 30-day MACE in internal validation studies using hs-cTnT assays **as reported in the included studies (not confirmed to be non-index AMI only)**, stratified by risk score and cut-off.

Study	Ruled-out (%)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
CORE Score					
Borna	248 (33.0)	98.9 (93.1-99.9)	37.4 (33.7-41.2)	99.6 (97.4-100)	17.7 (14.6-21.4)
T-MACS					
Body	265 (37.7)	98.7 (95.3-99.8)	47.6 (43.4-51.9)	99.3 (97.3-99.9)	34.0 (29.6-38.7)

NPV= Negative Predictive Value, PPV= Positive Predictive Value, NR= Not Reported, T-MACS= Troponin only Manchester Acute Coronary Score

Table 9. Discriminative ability according to AUC or C-statistic for 30-day MACE in external validation studies using hs-cTnT assays **as reported in the included studies (not confirmed to be non-index AMI only)**, stratified by risk score and cut-off (reporting studies only).

Study	AUC or C-statistic	95% CI
TIMI=0		
Sanchis	0.77	-
TIMI≤1		
Chew	0.86	-
McCord	0.68	-
HEART≤3		
Chew	0.91	-
Cortes	0.91	0.89-0.93
McCord	0.75	-
Santi	0.88	0.86-0.89
GRACE>75		
Chew	0.79	-
GRACE >109		
Sanchis	0.44	-
T-MACS		
Carlton	0.90	-
Clinical Score=0		
Sanchis	0.88	-

AUC= Area Under the Receiver Operating Characteristic Curve, C-statistic= Concordance Statistic, 95% CI= 95% Confidence Interval, TIMI= Thrombolysis in Myocardial Infarction, HEART= History, ECG, Age, Risk Factors, Troponin, GRACE= Global Registry of Acute Coronary Events, T-MACS= Troponin only Manchester Acute Coronary Score

Table 10. Discriminative ability according to AUC or C-statistic for 30-day MACE in external validation studies using hs-cTnI assays **as reported in the included studies (not confirmed to be non-index AMI only)**, stratified by risk score and cut-off (reporting studies only).

Study	AUC or C-statistic	95% CI
m-TIMI ≥1		
Wong	0.81	0.78-0.84
m-GRACE ≥50		
Wong	0.76	0.72-0.79
m-HEART≥1		
Wong	0.85	0.81-0.88

AUC= Area Under the Receiver Operating Characteristic Curve, C-statistic= Concordance Statistic, 95% CI= 95% Confidence Interval, TIMI= Thrombolysis in Myocardial Infarction, HEART= History, ECG, Age, Risk Factors, Troponin, GRACE= Global Registry of Acute Coronary Events, T-MACS= Troponin only Manchester Acute Coronary Score

Figures.

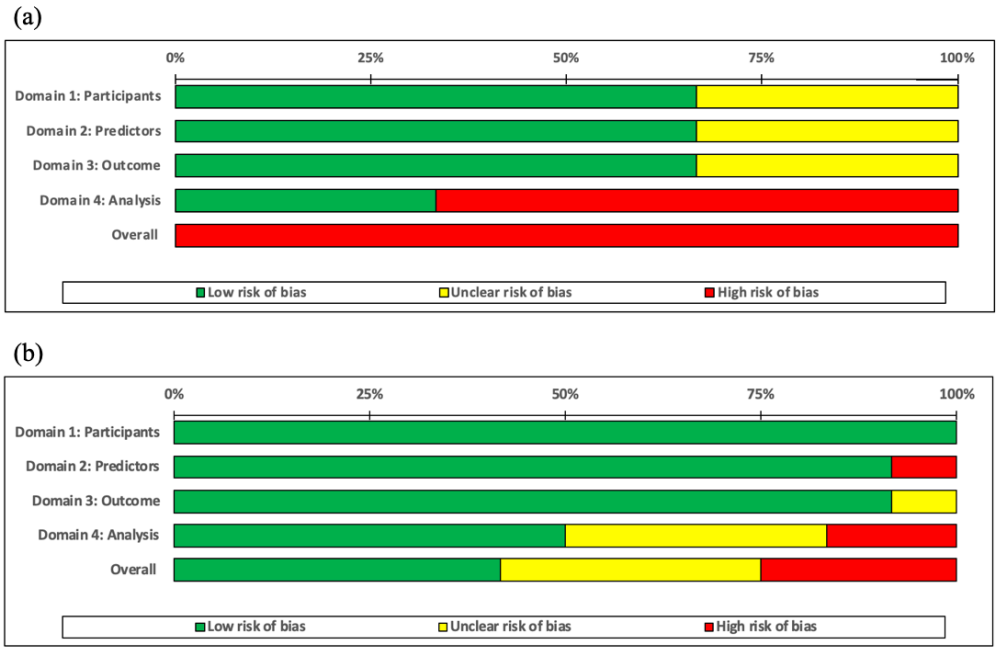

Figure 1. Risk of bias ratings per domain and overall as determined using PROBAST for studies (a) with an internal validation component (n=3), (b) with an external validation component (n=12).

Study	% Low-risk	TP	FP	FN	TN
HEART≤3 + hscTnT					
Santi	37.2	206	636	0	512
TIMI=0 + hscTnT					
Carlton (NZ)	20.4	10	982	0	254
Sanchis	30.4	3	472	0	207
TIMI=0 + hscTnI					
Carlton (Aus)	26.8	23	1557	2	574
Carlton (NZ)	16.8	11	1293	0	263
Than	37.2	0	152	0	90
TIMI≤1 + hscTnT					
Carlton (NZ)	29.5	9	869	1	367
Sanchis	63.6	1	247	2	432
TIMI≤1 + hscTnI					
Carlton (Aus)	56.6	22	911	3	1214
Carlton (NZ)	23.3	10	1192	1	364
TIMI≤2 + hscTnT					
Carlton (NZ)	36.8	9	778	1	458
TIMI≤2 + hscTnI					
Carlton (Aus)	66.3	15	710	10	1415
Carlton (NZ)	28.8	10	1106	1	450
GRACE>109 + hscTnT					
Sanchis	82.6	0	119	3	560
GRACE>140 + hscTnT					
Sanchis	98.2	0	12	3	667
EDACS≤16 + hscTnI					
Than	48.5	1	119	1	112

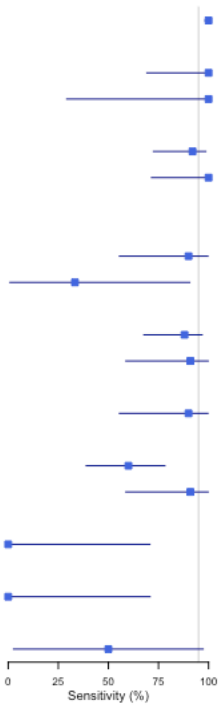

Figure 2. Forest plot showing classification characteristics and sensitivity (95% confidence interval) for 30-day MACE in external validation studies **as confirmed by corresponding authors**, stratified by risk score and cut-off.
TP=True Positive, FP=False Positive, FN=False Negative, TN=True Negative.

CHAPTER 3: THESIS PROJECT COMPONENT II TIME-TO-EVENT ANALYSIS

BACKGROUND

Upwards of 500,000 Canadians present to the ED with chest pain annually[1]. Following physician assessment with patient history, ECG, and serial cardiac biomarkers, as many as 70% of these patients will be deemed low-risk and will require further disposition prior to potential ED discharge[2]. The focal point of these disposition decisions is to ensure that the 2-5% of discharged patients who may experience 30-day MACE receive the timely inpatient or outpatient follow-up investigations (e.g., treadmill stress test, stress myocardial perfusion injury, stress echocardiography) necessary to prevent these unnecessary adverse events[3-5].

Recommended timelines for these follow-up investigations are available in current clinical guidelines from Europe, the USA and Canada. The former two countries suggest that patients undergo this testing prior to or within 72 hours of ED discharge[5,6], while Canadian guidelines propose that follow-up occur within 2 weeks of the index ED visit[7]. Evidence supporting these recommendations is scarce[8], however, whereby it is unclear if they are well aligned with the true timing of the short-term MACE that they are meant to intervene on. Further, the large difference in endorsed timelines between USA/Europe and Canada, where wait times for this type of follow-up are known to be longer[9], suggest that these recommendations are based as much on system capacity as they are on event timing.

Additionally, current guidelines recommend that all but very low risk patients undergo follow-up, without defining low risk in terms of probability of adverse events[5]. These guidelines also do not cite evidence as to what clinical characteristics identify patients as low risk or patients who might be at high risk for short-term MACE despite the absence of index AMI. This

leads to large proportions of low-value follow-up with poor diagnostic yield, high healthcare cost, increased radiation exposure for patients, and no clear benefit[10-12].

Given the above, the twofold purposes of this second component of the thesis project were; (1) To conduct a formal time-to-event analysis for MACE outcomes to inform guidelines for timing of follow-up testing, and (2): To identify clinical characteristics that might predict high risk of MACE among patients who have NSTEMI ruled-out using hs-cTn. The findings of this analysis may help inform follow-up disposition decisions that are more closely aligned with true MACE timing and could help ED physicians identify which discharge-eligible patients should be prioritized for follow-up.

METHODS

Data Source. This was a secondary analysis of data prospectively collected from a large urban level one trauma and regional percutaneous coronary intervention center in Calgary, AB, Canada between August 2014 and September 2016. The ED has an approximate volume of 80,000 visits, approximately 2,500 of which are for chest pain. This data has previously been used to identify and validate undetectable hs-cTnT concentrations for the ruling-out of AMI at ED arrival[13] and in a comparative evaluation of available 2-hour rapid diagnostic algorithms (RDA)[14]. The collection procedures for this data were approved by the University of Calgary Conjoint Health Research Ethics Board. Raw data were de-identified prior to delivery to the investigators and as such no further informed consent from the subjects was required.

Study Population. Patients aged 25 or older were eligible if they presented to the ED with Canadian Emergency Department Information System (CEDIS) standardized chief complaints[15]

of “chest pain- cardiac features” or “cardiac type pain” determined by the attending ED physician to require serial troponin (0h & 2h hs-cTnT) testing to rule out MI. Patients were excluded if they met any of the following criteria: diagnosis of STEMI, clear acute ischemic changes or new arrhythmia (not including sinus tachycardia, premature atrial contractions, premature ventricular contractions, paced rhythm, or rate-controlled atrial fibrillation/atrial flutter) on the initial ECG, evidence of ACS in the 30-days preceding the index ED visit, hemodynamic instability, advanced renal failure requiring dialysis or inability to provide consent secondary to language barriers or cognitive issues. Patients unable to have valid samples collected within the +/- 30-minute window of the specified 0h or 2h collection time were also excluded from the analysis.

Following the application of study inclusion and exclusion criteria, a validated 2-hour hs-cTnT RDA[16] was applied to all eligible patients. This algorithm utilizes a 5th generation hs-cTnT assay (Roche Elecsys® High-sensitivity) performed on cobas e601 instrument as per the manufacturer’s specifications. The analytical properties of this assay are shown in Appendix C. In the first 2 hours of the clinical assessment, the RDA yields three patient groups: patients with AMI ruled-out, patients with AMI ruled-in, and a group of patients with status not yet determined (Appendix D). For this analysis, only patients in the AMI ruled-out group were included and assessed given that this is the patient group that would be eligible for ED discharge and would require further prognostication prior to that discharge.

Study Outcomes. The primary outcome of interest for this study was the time (in days) to MACE occurring within 30 days of the index ED visit. MACE is a composite endpoint defined as: (1) MI as defined by the 4th Universal Definition of MI criteria[17], (2) all-cause death, or (3)

need for urgent revascularization surgery (non-elective coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). The secondary outcomes for this study were the demographic and clinical characteristics of patients with and without 30-day MACE. The *a priori* selected variables of interest for comparison included age, sex, 0h and 2h hs-cTnT concentrations, cardiac risk factors (e.g., hypertension, hypercholesterolemia, smoking, diabetes, family history of cardiac disease, personal history of MI/ACS), personal history of CAD, and degree that the history is suspicious for ACS (i.e., slightly, moderately, or highly; based on clinical gestalt judgement). These covariates were selected based on their availability at the index ED encounter and their presence in a number of chest pain risk scores with established utility for predicting 30-day MACE[18-22].

The procedures for collecting 30-day outcome data have been described in detail elsewhere[14]. In brief, outcome data were obtained using the ED and hospital administration databases, as well as Alberta vital statistics and the Alberta Provincial PRroject for Outcome Assessment in Coronary Heart Disease (APPROACH) registry[23]. Patients were also contacted by telephone 30 days after their index encounter to confirm outcomes. All outcomes were independently adjudicated by two emergency medicine physicians.

Statistical Analysis. We quantified the overall and sex-specific crude incidences of 30-day MACE among eligible patients. Information on the timing of these short-term events, specifically the overall time to MACE (in days) and the same specific to males and females was measured. The sex-specific incidence, Kaplan-Meier estimators, and distribution of MACE over the 30-day follow-up period were shown visually with a stratified Kaplan-Meier failure plot. Patients were censored in the Kaplan-Meier plot if they did not have complete follow-up at 7 or

30-days (i.e., lost to follow-up) or if MACE had not occurred at the end of the 30-day follow-up period. In the case that a single patient incurred multiple MACEs in 30-days (e.g., a patient experiencing AMI who subsequently undergoes a revascularization procedure or death, only the time of the first event was considered. The difference in Kaplan-Meier estimators for 30-day events between men and women was tested statistically using the log-rank test[24].

We compared the ruled-out patients who did experience MACE to those who did not across the aforementioned *a priori* defined variables to identify any distinctions that could be used to maximize the discrimination of the two groups. Further, once all patients experiencing 30-day MACE were identified a summary table was developed to allow for comparisons between these patients across the same demographic and clinical variables. This information was synthesized to identify any commonalities between these patients that may help identify predictors of short-term adverse events in the ruled-out population.

Data on 30-day MACE incidence is reported with corresponding 95% confidence intervals (95% CI). Given their inherently skewed nature, all data relating to the timing of events are reported as medians (range), with a unit of days. Continuous data are reported as means (SD) while categorical data are reported as proportions with corresponding binomial exact 95% CIs. The threshold for statistical significance of all differences was set at $p<0.05$ for a two-tailed test.

RESULTS

Study Population. Following the exclusion of patients without available hs-cTnT measurements at 0 or 2-hours (N=617), 550 patients were evaluated using the 2h hs-cTnT algorithm. After excluding patients ruled-in (N=60) or whose AMI status was not yet determined (N=140) by the 2-hour ADP, 350 (63.6%, 95% CI: 59.5-67.7) chest pain patients with AMI ruled-out were

included in the study (Figure 1). The RDA had 100% sensitivity for AMI (95% CI: 94.3-100) and as such there was no index AMI in the ruled-out population. All included patients had complete data at the end of the 30-day follow-up period with minimal missingness (1.14%, 95% CI: 0.31-2.90) in the prioritized variables.

A total of 13 patients experienced MACE at 30-days, corresponding to an overall incidence of 3.71% (95% CI: 1.99-6.27). Incidence was higher among men (2.86%, 95% CI: 1.38-5.19) than women (0.86%, 95% CI: 0.18-2.48). The majority of ruled-out patients with MACE had only urgent revascularizations (n=12) while one patient had cardiac arrest and died within 13 days after their index ED visit.

Time to MACE. In all ruled-out patients MACE occurred at a median time of 5 days (range: 0-23). MACE occurred slightly faster in females at a median of 5 days (range: 3-9) compared to a median of 5.5 days (range 0-23) among males. In all, 30.8% of patients experienced MACE within 24 hours of their index ED visit, 38.5% within 72 hours of their index ED visit, and 61.5% experienced MACE within 7 days. The distribution of these events over the 30-day follow-up period and the sex-specific Kaplan-Meier estimators are shown in the Kaplan-Meier failure curve (Figure 2). The estimators for 30-day MACE were shown by the log-rank test not to differ significantly between males and females (p=0.18). Each discontinuity in the respective lines on the Kaplan-Meier plot represents the occurrence of an adverse event at the time seen on the x-axis. The number of patients at risk and the number of events occurring within each 5-day segment from the index ED visit to the end of follow-up are shown in the risk table below the curve.

Comparison of Patients with and without 30-day MACE. A higher proportion of patients with MACE had a known history of CAD than their ruled-out counterparts who did not experience adverse events (92.3% versus 25.5%). The two groups also differed in how much their histories were suspicious for ACS, likely stemming from a higher proportion of patients with MACE having highly suspicious histories (69.2% versus 9.30%). A higher proportion of patients with hypertension also experienced 30-day MACE (69.2% versus 53.2%). To avoid spurious findings due to the low sample size of ruled-out patients experiencing MACE, none of these differences was assessed for statistical significance.

Characteristics of Ruled-Out Patients with MACE. The majority of ruled-out patients who suffered MACE were male (n=10) with a mean age of 59.7 years (SD: 9.30). A number of the *a priori* selected clinical features were consistent in this population (Table 2). Specifically, nearly all patients had a known history of CAD (n=12), the majority (n=9) had normal ECGs and detectable 0h and/or 2h hs-cTnT concentrations, and all had at least one classic cardiac risk factor (i.e., diabetes, smoking, hypertension, hyperlipidemia, family history of cardiac disease, and obesity). Most patients had clinical histories that were highly suspicious for ACS (n=9). Pain duration was the least consistent variable, varying widely from 1 hour to >24 hours. The only patient to experience a MACE that was not urgent revascularization did not clearly differ from the other patients with MACE.

DISCUSSION

The purposes of this second component of the thesis project were to assess the time course of 30-day MACE in chest pain patients with MI ruled-out in the ED and to identify any

demographic or clinical commonalities among these discharge eligible patients who do ultimately experience short-term MACE. We found that a low proportion of patients who have index MI ruled-out using a validated 2h hs-cTnT algorithm experience short-term MACE, and that the timing of many events falls beyond the 72-hour guidelines from Europe and the USA but prior to the 14-days recommended by Canadian guidelines. This calls into question their sufficiency for confident disposition decision making within these patients.

The incidence of 30-day MACE in all patients with AMI ruled-out by the 2h hs-cTnT algorithm was low at 3.71% (95% CI: 1.99-6.27). This is somewhat higher than 30-day MACE incidences among low risk chest pain patients reported in recent studies, which fall between 0.6% and 2.4%[10,25,26]. This discrepancy may stem from the use of a composite MACE outcome that, in our study, was driven almost entirely (91.7% of first 30-day MACE) by urgent revascularizations. While this is typical, there is ongoing debate surrounding the importance of including revascularization in MACE[27,28], specifically whether or not revascularization is an adverse event or an indicator of appropriate emergent care delivery. Since percutaneous coronary intervention in patients with stable angina and even modest ischemia has not been shown to reduce death or nonfatal MI[29], it could be argued that these revascularizations represent over-testing/overtreatment and that 30-day revascularization need not be included in the MACE outcome. It is also important to consider how variability in revascularization practices across countries based on resource availability and clinical practices might contribute to the differing incidences between our study and those previously published. Given the above, a justified omission of urgent revascularizations from the MACE definition in this study reduces incidence to 0.29%, falling closer to the ranges seen in the literature.

The 13 patients who experienced 30-day MACE did so at a median of 5 days (range: 0-23 days). While minimal evidence on MACE timing in the ED chest pain population is available, studies on patients following renal transplantation or elective CABG surgeries looking at longer term adverse events found that 20-25% of all recorded MACE occurred within 24 hours of the procedure, with 57% having occurred at 30 days[30,31]. The former finding is somewhat consistent with this study for patients with index AMI ruled-out whereby approximately 30% of MACE occurred within 24 hours of the index ED visit. While more than half of the adverse events in this cohort of low-risk patients occurred after the European and American 72-hour recommendations for follow-up, more than a quarter experienced the outcome before the end of 3 days and 85% occurred before the end of the 14 days recommended in Canada. As such, while European and American guidelines recommend very early testing within 72-hours, low-risk patients in all countries are still susceptible to incurring a MACE before the end of their country's guideline-based timeline for follow-up. These findings suggest that current guideline recommended timeframes for cardiac follow-up, especially those in Canada, may not be well aligned with the true timing of 30-day MACE. Of note, however, is that any adjustments to Canadian guidelines will be rendered difficult by resource scarcity and cost and would likely first require improved identification of patients at true risk of short-term adverse events to be prioritized for streamlined follow-up.

In this vein, the secondary purpose of this project was to characterize patients with index AMI ruled-out who experienced 30-day MACE to identify demographic or clinical characteristics that might serve as predictors of adverse events among them. It was determined that nearly all patients who experienced MACE had a known history of CAD, most had a clinical history that was deemed by the treating clinician to be highly suspicious for ACS, more were

male than female, most were older than 52 years. We chose *a priori* to evaluate the potential predictive utility of these variables, among others, given their established use in a number of clinical risk scores[18-22]. The finding that these *a priori* selected variables may have predictive capacity for 30-day MACE are consistent with their inclusion in a number of risk scores. Although these risk scores were largely derived in populations of undifferentiated chest pain patients and a number of the variables (e.g., ECG, pain or symptom duration, 0 and 2h hs-cTnT) did have clear prognostic utility in this population, it appears some variables assessed could play a role in identifying low-risk chest pain patients who will develop 30-day MACE. It is likely that ECG and serial hs-cTnT measurements did not emerge as predictors because the included population had already been assessed on the basis of these two clinical variables in the 2h RDA. These findings suggest that to maximize the prognostic utility of available risk scores in the low-risk chest pain population it might be appropriate to weigh certain variables more heavily and potentially omit variables already used in the preceding clinical assessment. Notably, a pragmatic risk score with less variables could be beneficial in the prediction of MACE in a population shown to have a low number of events[32,33].

STRENGTHS AND LIMITATIONS

This is one of the first studies to formally assess the time course of MACE in the low-risk cohort of discharge eligible chest pain patients without AMI in an attempt to provide evidence that might inform the development of future guidelines. A validated 2h algorithm using ECG and serial hs-cTnT was used to rule-out AMI and identify low-risk patients in a way that is reproducible and closely mimics the true ED assessment of chest pain. Further, the clinical and demographic variables evaluated as potential predictors were selected *a priori* based on available

evidence and availability at the time of the ED assessment to ensure transferability of findings to the clinical context.

This study is not without its limitations. Firstly, the lower-risk cohort of chest pain patients assessed in this study incurred very few MACE at 30 days. While this is a clinically positive finding and highlights the potential efficacy of a 2h validated RDA for ruling out MI, it reduced the precision of our estimates and prevented the use of methodologically favorable hazard modelling methods and statistical testing. As such the reliability of our findings surrounding potential predictors of MACE may be limited. However, the decision to avoid statistical testing prevents the propagation of potentially spurious findings, and the incidence of 30-day MACE (notwithstanding the impacts of including urgent revascularization) being similar to that of previous studies suggests these findings might still be generalizable.

FUTURE DIRECTIONS

It remains unclear if guideline recommended timelines for follow-up are well aligned with the time course of event occurrence. However, the need for follow-up that balances the timely assessment of those who require it with avoidance of unnecessary (and potentially harmful) testing in those who do not, cannot be understated. As such, larger studies using survival analysis methods are necessary to support or refute the findings of this study to ensure any potential changes to the guideline recommended timelines for follow-up are based on substantive evidence. These studies should also use formal hazard or regression modelling methods to test potential predictors statistically in hopes of potentially developing novel prognostic prediction tools derived for use in this low-risk population of chest pain patients.

CONCLUSIONS

The guideline recommended timelines for follow-up in low-risk chest pain patients following ED assessment, especially those from Canada, do not align well with the true time course for short term MACE. Further, given a very low incidence of 30-day MACE in this population driven primarily by revascularization (which is not necessarily an adverse outcome), the guideline recommendation that all but very-low risk patients undergo additional investigations is likely leading to substantial over-testing. Known CAD status, male sex and suspicion of clinical history for ACS might have value in identifying which low-risk patients should receive prioritized follow-up.

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Tables.

Table 1. Characteristics of all patients and patients with and without 30-day MACE.

Variable	Overall (n=350)	No 30-day MACE (n=337)	30-day MACE (n=13)
Mean Age (SD)	57.3 (12.4)	57.2 (12.5)	59.7 (9.30)
Males (%)	206 (58.9, 53.5-64.1)	196 (58.2, 52.7-63.5)	10 (76.9, 46.2-94.9)
Known CAD (%)	97 (28.0, 23.4-33.1)	85 (25.5, 20.9-30.6)	12 (92.3, 64.0-99.8)
History Suspicion level for ACS (%)			
Slightly	164 (47.4, 42.0-52.8)	164 (49.2, 43.8-54.8)	0 (0.0, 0.0-24.7)
Moderately	142 (41.0, 35.8-46.4)	138 (41.4, 36.1-46.9)	4 (30.8, 9.09-61.4)
Highly	40 (11.6, 8.39-15.4)	31 (9.31, 6.41-12.9)	9 (69.2, 38.6-90.9)
ECG Changes (%)			
Normal	240 (69.4, 64.2-74.2)	231 (69.4, 64.1-74.3)	9 (69.2, 38.6-90.9)
Non-Specific Changes	102 (29.5, 24.7-34.6)	99 (29.7, 24.9-34.9)	3 (23.1, 5.04-53.8)
Significant ST Changes	4 (1.16, 0.32-2.93)	3 (0.90, 0.19-2.60)	1 (7.69, 0.19-36.0)
Hypertension (%)	186 (53.8, 48.3-59.1)	177 (53.2, 47.6-58.6)	9 (69.2, 38.6-90.9)
Hyperlipidemia (%)	153 (44.2, 38.9-49.6)	143 (42.9, 37.6-48.5)	10 (76.9, 46.2-94.9)
Current Smoker (%)	54 (15.6, 11.9-19.9)	53 (15.9, 12.2-20.3)	1 (7.69, 0.19-36.0)
Diabetes (%)	52 (15.0, 11.4-19.2)	48 (14.4, 10.8-18.7)	4 (30.8, 9.09-61.4)
Family History of CAD (%)	76 (22.0, 17.7-26.7)	71 (21.3, 17.0-26.1)	5 (38.5, 13.9-68.4)
Obesity (%)	83 (23.9, 19.6-28.8)	79 (23.7, 19.3-28.7)	3 (23.1, 5.04-53.8)

Note. All proportions reported as point estimate followed by binomial exact 95% CI. Missing data in following predictors for overall (n=4) and no 30-day MACE (n=4) groups: Known CAD, History Suspicion, ECG Changes, Hypertension, Hyperlipidemia, Current Smoker, Diabetes, Family history, Obesity.
Abbreviations: SD= Standard deviation, MACE= Major adverse cardiac events, CAD= Coronary artery disease, ACS= Acute coronary syndromes, ECG= Electrocardiograms.

Table 2. Characteristics of individual ruled-out patients who experienced 30-day MACE.

Patient	Days to MACE	Age	Sex	ECG Description	Pain Duration	0h hs-cTnT	2h hs-cTnT	History	Risk Factors	Known CAD
30-day Urgent revascularizations (8 DES, 3 CABG, 1 POBA/DES)										Yes
1	9	64	F	Normal	3-6 hours	6 ng/L	6 ng/L	Highly	≥3	Yes
2	1	75	M	Normal	3-6 hours	10 ng/L	9 ng/L	Highly	1-2	Yes
3	5	57	M	Normal	6-12 hours	8 ng/L	6 ng/L	Moderately	≥3	Yes
4	23	52	M	Non-specific Δ	>24 hours	8 ng/L	5 ng/L	Moderately	≥3	Yes
5	1	65	M	Normal	1-3 hours	4 ng/L	4 ng/L	Highly	≥3	Yes
6	3	69	F	Non-specific Δ	6-12 hours	11 ng/L	10 ng/L	Moderately	1-2	Yes
7	<1	74	M	Normal	1-3 hours	9 ng/L	8 ng/L	Moderately	1-2	Yes
8	1	52	M	Normal	3-6 hours	9 ng/L	6 ng/L	Highly	≥3	Yes
9	14	53	M	Normal	3-6 hours	4 ng/L	3 ng/L	Highly	≥3	Yes
10	5	58	F	Normal	3-6 hours	4 ng/L	4 ng/L	Highly	≥3	Yes
11	8	44	M	Signif. ST Δ	1-3 hours	2.9 ng/L	4 ng/L	Highly	1-2	No
12	6	60	M	Non-specific Δ	3-6 hours	5 ng/L	5 ng/L	Highly	≥3	Yes
30-day AMI and Death										
13	13	53	M	Normal	3-6 hours	9 ng/L	8 ng/L	Highly	1-2	Yes

Abbreviations: MACE= Major adverse cardiac event, ECG= Electrocardiogram, hs-cTnT= High-sensitivity cardiac troponin, CAD= Coronary artery disease, DES= Drug eluting stent, CABG= Coronary artery bypass graft, POBA= Plain old balloon angiography, AMI= Acute myocardial infarction, F= Female, M= Male,

Figures.

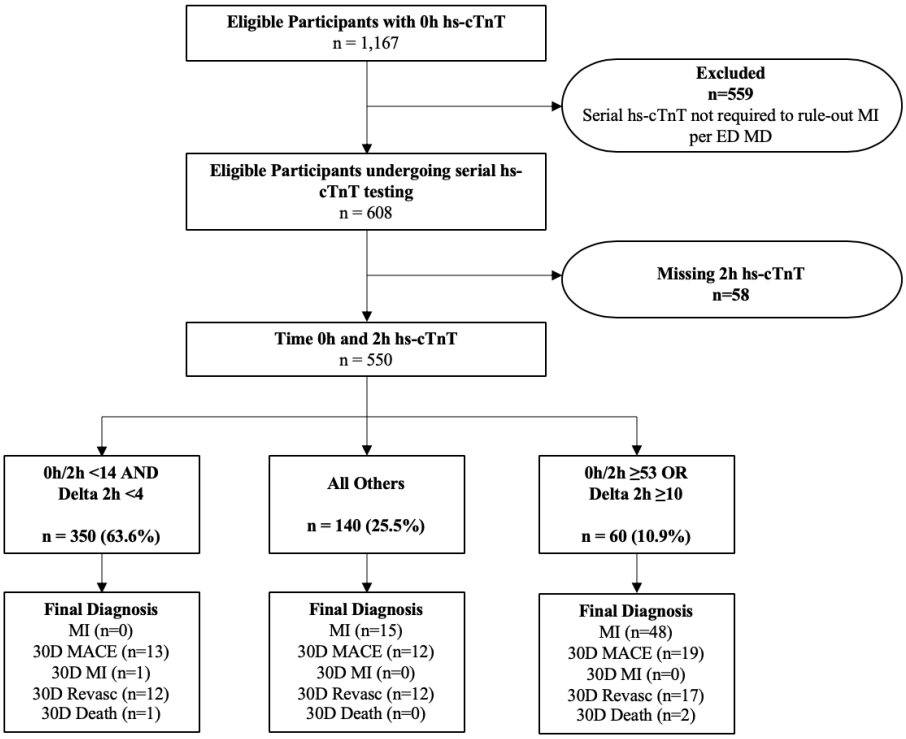

Figure 1. Patient inclusion/exclusion flow diagram. Patients included in this analysis are those with 0h/2h <14 AND Delta 2h <4 (n=350).

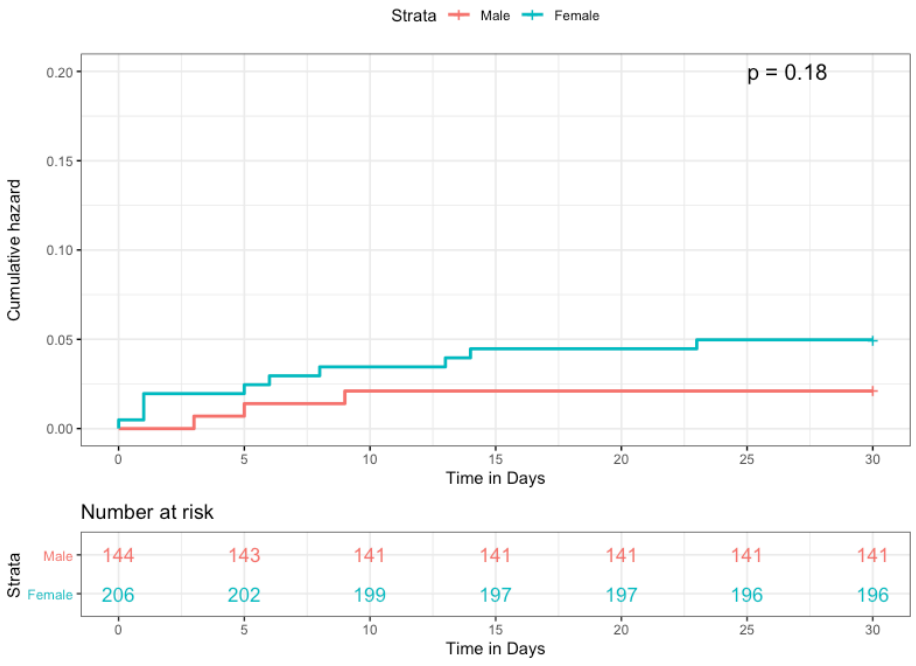

Figure 2. Kaplan-Meier failure curve and corresponding risk table showing sex-stratified baseline hazards and distribution of events over time for 30-day MACE.

CHAPTER 4 THESIS COMPONENT III PATHWAY DEVELOPMENT

BACKGROUND

Chest pain is a common physical manifestation of ischemic heart disease leading to frequent ED visits[1-3], substantial clinical resource utilization and costs[4-6], as well as high morbidity and mortality[7,8]. ED physicians and allied practitioners must assess these patients effectively to minimize poor outcomes at the patient and healthcare system levels.

Current clinical guidelines provide a framework for a sequential assessment of all chest pain patients in the ED[9-11]. Physicians are to first rule-out STEMI using serial ECG and evaluation of clinical history. They then assess remaining patients using serial cardiac biomarkers (e.g., hs-cTn) to identify NSTEMI. Finally, those emerging from the latter two steps without a clear diagnosis will be assessed for risk of UA or severe underlying CAD so that a disposition decision (i.e., admission for subsequent testing, discharge with or without outpatient follow-up) aligned with their risk for adverse events can be made.

The sequential nature of this assessment is not mirrored in the associated research, however, such that evidence on the first objective – ruling out STEMI and NSTEMI- has emerged in isolation from that for the second objective of patient prognostication and disposition. This can lead to inconsistencies in the chest pain assessment, especially in disposition decision making, which contributes to over-testing in many low-risk patients who are unlikely to benefit[12,13]. While there is an abundance of evidence on the use of ECG, hs-cTn assays and RDAs to rule-out index AMI[14-20], these studies do not typically go on to prognosticate patients without AMI. Further, most risk scores were developed as diagnostic tools for all ACS (including index MI and UA) in undifferentiated chest pain patients but are more often applied to this population as prognostic tools[21-23]. Given the state of this evidence, it remains unclear if

performing the diagnostic and prognostic procedures relevant to the ED assessment of chest pain in sequence is efficient and maximizes the number of patients that can be discharged while maintaining a high standard of patient safety.

Therefore, the purpose of this final component of the thesis project was to develop a sequential clinical pathway for the assessment of patients with chest pain and symptoms of ACS in the ED. Unlike the available evidence, this pathway will fulfill both a diagnostic and prognostic role with a focus on maximizing the number of patients identified as eligible for safe ED discharge without the need for follow-up testing. In addition to pathway derivation being informed by the clinical guidelines and clinical expertise, we will integrate knowledge on risk score performance and characteristics with predictive or discriminatory value gained in the preceding two thesis chapters.

METHODS

Data Source. This was a secondary analysis of prospectively collected data from a large urban level one trauma and regional percutaneous coronary intervention center in Calgary, AB, Canada. This data has been used previously for the identification of undetectable hs-cTnT concentrations for AMI rule-out on ED arrival[24] and in the development, comparison, and validation of 2-hour hs-cTnT rapid diagnostic algorithms (RDAs) for AMI[25]. The data collection procedures for these precedent projects were approved by the University of Calgary Conjoint Health Research and Ethics Board (CHREB). Patient-level data was de-identified prior to it being provided to the investigators of this analysis, and as such no further informed consent or ethics revisions were required.

Study Population. Patients aged 25 or older were eligible if they presented to the ED with Canadian Emergency Department Information System (CEDIS) standardized chief complaints[26] of "chest pain- cardiac features" or "cardiac type pain" determined by the attending ED physician to require serial troponin (0h & 2h hs-cTnT) testing to rule out MI. Patients were excluded if they met any of the following exclusion criteria: (1) diagnosis of STEMI, (2) clear acute ischemic changes or new arrhythmia (not including sinus tachycardia, premature atrial contractions, premature ventricular contractions, paced rhythm, or rate-controlled atrial fibrillation/atrial flutter) on the initial ECG, (3) evidence of ACS in the 30-days preceding the index ED visit, (4) hemodynamic instability, (5) advanced renal failure requiring dialysis, or (6) inability to provide consent secondary to language barriers or cognitive issues. Patients unable to have valid samples collected within the +/- 30-minute window of the specified 0h or 2h collection time were also excluded from the analysis.

Contrary to the previous component of the thesis project (see Chapter 3: Time-to-event analysis), patients with diagnosed NSTEMI at the index ED visit (within 24 hours of ED arrival including admission) were not excluded. This was done because the pathway to be developed is intended to facilitate the standardized assessment of chest pain patients from ED arrival onwards, and as such undifferentiated chest pain patients including those with an eventual diagnosis of NTEMI must be included. STEMI patients were still excluded because given clear ST-segment elevation on pre-hospital or arrival ECG their treatment course at ED arrival is typically pre-determined (i.e., immediate surgical intervention), and as a result they would not require a pathway-assisted clinical assessment.

Pathway Development. The pathway was conceived to mirror the sequential decision points involved in the ED assessment of chest pain, whereby the immediate focus is to identify and intervene on acute ischemic ailments, and the secondary goal is to risk stratify patient on the basis of future adverse events. The initial step in the first stage was derived to focus on the rule-out of STEMI or ACS identified by other ischemic changes using an immediate ECG assessment (within 10 minutes of patient arrival). Then, the use of serial hs-cTnT sampling in patients without diagnostic ECG is completed to identify NSTEMI. The second stage of the pathway focused on patients who had STEMI, NSTEMI or other acute ischemia ruled-out in the first stage, with the goal of stratifying these patients on the basis of their risk for 30-day MACE. This is the intuitive next step in the ED chest pain assessment, allowing clinicians to make the necessary disposition decisions for these patients that are more closely aligned with their short-term prognoses. The specific procedures followed for the development of both of the aforementioned pathway stages are discussed below in detail:

Stage 1: Ruling-out AMI. The primary focus of the ED assessment of chest pain is to identify AMI and limit the associated morbidity and mortality. This can be achieved using demographic and clinical variables available at the time of assessment, typically arranged into a type of RDA. While a number of troponin-only RDAs using hs-cTnT are available, it was decided that a validated 2h hs-cTnT (5th generation Roche Elecsys®) testing algorithm that utilized more of the data available to ED physicians at the time of the assessment was more reflective of the true clinical context. This decision was based largely on the expectation that physicians were unlikely to ignore important aspects of the clinical picture (i.e., ECG, pain duration, pain characteristics) and allow a single feature to determine disposition (as in a troponin-only RDA). Further, unlike

other 2h RDAs that require 2-hour hs-cTn measurements for all patients prior to rule-out, the selected 2h hs-cTnT testing algorithm allowed for very low-risk patients to be ruled-out prior to the 2-hour mark (Appendix D). Reflective of the temporality of the assessment described above, the 2h algorithm first stratifies patients based on their ECG interpretation on arrival (clear ischemic changes versus no clear ischemia), followed by further stratification by varying cut-offs of hs-cTnT at 0-hour and 2-hours. Since patients with ischemic ECGs were excluded from this study, the former stratification had already occurred and was not performed. When applied to the undifferentiated chest pain patients this algorithm yields three patient groups after 2 hours: (i) AMI ruled-in to be admitted to hospital for necessary medical intervention, (ii) a group with AMI status not yet determined to remain under observation with continued serial hs-cTnT sampling, and (iii) AMI ruled-out, who are potentially eligible for ED discharge and require further prognostication prior. For our purposes, this last group of patients with AMI ruled-out by the 2h algorithm will have their need for subsequent testing assessed by further clinical risk stratification in the next stage of the pathway.

Stage 2: Risk Stratification for 30-day MACE. Clinical risk scores are a prominent tool for the stratification of ruled-out patients on the basis of risk for adverse events following discharge, and as such we sought to identify clinical risk scores with established utility in this patient population. Through consultation with published evidence[21-23, 27,28], findings from preceding parts of the thesis project (see Chapter 2: systematic review), and local clinical experts, we chose to prioritize the HEART, TIMI, and Diamond and Forrester risk scores for trial in this portion of the clinical pathway. We first assessed the discrimination and calibration of these selected risk scores in the ruled-out population, using the same measures in the undifferentiated population as

a reference for performance (see statistical analysis plan below). This provided a brief external validation of the selection of the risk scores and a basis on which the scores could be objectively compared prior to their application in the pathway.

Following the assessments of risk score discrimination and calibration, the HEART, TIMI, and Diamond and Forrester risk scores were applied to all patients ruled-out in the pathway's first stage. Patients were identified as low, intermediate (for HEART and Diamond and Forrester only), or high-risk for 30-day MACE by these scores and placed into corresponding categories. The prognostic performance of each score was compared by quantifying the proportion of patients in each category and classification characteristics for those deemed low and not low risk were quantified (see statistical analysis plan below).

To determine if the prognostic performance and rule-out capacity of the including risk scores could be improved through prior separation of the ruled-out patient group, we stratified patients using the clinical variables that showed promise for discrimination of MACE in Chapter 3 of the thesis project (i.e., known history of CAD, suspicion of a patient's history for ACS) before risk score application. This yielded the same two or three 30-day MACE risk categories when applicable, but within each of the groups emerging from the prior stratification. Low, intermediate, and high-risk patients under each category were grouped together to allow quantification of the same measures of prognostic performance as the non-stratified trial pathways.

Statistical Analysis.

Pathway Stage 1 (Diagnostic, in all undifferentiated chest pain patients): The diagnostic performance of the 2h hs-cTnT algorithm was quantified using the proportion of patients with

AMI ruled-out as well as measures of sensitivity and NPV for those patients ruled-out, and measures of specificity and PPV amongst those ruled in. All classification characteristics were calculated in reference to the index AMI outcome. The diagnostic capacity of the 2h hs-cTnT RDA in the first stage of the pathway is presented in text with all measures and their respective 95% confidence intervals (95% CI).

Pathway Stage 2 (Prognostic, only in patients with MI ruled-out): To determine discrimination and calibration for the prediction of 30-day MACE probabilities it was necessary to first develop logistic regression models corresponding to each prioritized risk score. These models were developed to predict the binary outcome of 30-day MACE and had an explanatory variable (binary or factor, score dependent) for each predictor in the published score. For example, the logistic regression model for the HEART score had 5 explanatory variables (History, ECG result, Age, Risk factors, and Troponin result), all of which were factor variables with three levels. Coefficients and odds ratios of each of the constructed models applied in both the undifferentiated and AMI ruled-out chest pain populations are presented in Tables 1 and 2. It should be noted that when applied to the AMI ruled-out population, the explanatory variable in the HEART score related to troponin is changed from a factor variable with 3 levels to a dichotomous variable because all patients with hs-cTnT >53 ng/L have been ruled-in by the 2h algorithm. Both the troponin and ECG variables were removed from the TIMI logistic regression model when applied to the AMI ruled-out population, since the RDA only ruled-out patients with hs-cTnT <14 ng/L and with normal ECG (both TIMI criteria).

The discriminatory ability for 30-day MACE of the logistic regression models relating to each risk score was quantified using the area under the receiver-operative characteristic curve

(AUC), plotting the true positive rate against the true negative rate at various risk thresholds. To avoid spurious significance of results due to the established sensitivity of the Hosmer-Lemeshow goodness of fit test to small sample sizes[29,30], we chose to avoid a statistical test of score calibration and instead opted for a visual representation with calibration plots. These plotted the predicted probabilities for 30-day MACE generated by the aforementioned logistic regression models for each individual in the study sample against the events observed. To avoid the influence of sparse data on the interpretation of the calibration plots, locally estimated scatterplot smoothing (LOESS) techniques were used[31]. Calibration of a risk score was considered improved as the LOESS line more closely estimated the line of perfect calibration (i.e., diagonal line in plot).

Prognostic performance of the risk scores included in each trial pathway was measured similarly to the diagnostic capacity of the 2h hs-cTnT algorithm in the former pathway stage. The proportion of patients deemed low-risk for 30-day MACE (i.e., patients potentially eligible for discharge home without further outpatient cardiac investigation), sensitivity, NPV, specificity, and PPV for 30-day MACE were quantified. Notably, in the pathways with pre-stratification by discriminatory variables, as many as 9 distinct groups (e.g., 3 low risk, 3 intermediate risk, and 3 high risk) were created. In these cases, all low-risk groups were regrouped together to form a single low-risk for 30-day MACE group, and conversely all intermediate and high-risk groups were combined to form a single ‘not low-risk for 30-day MACE’ patient group. Sensitivity, specificity, NPV, and PPV for 30-day MACE could then be determined using these dichotomized patient groups.

The discrimination of each risk score for 30-day MACE in both the undifferentiated and ruled-out populations (as measured by AUC) is presented in a table with 95% CIs. Calibration

plots for all risk scores applied in both populations are shown side-by-side to allow reference and comparison. All measures of prognostic performance and corresponding 95% CIs are also presented in tabular form, with all values for each trial pathway. Finally, the second stages of each trial pathway are shown in a standardized visual format to demonstrate patient flow through the different stratifications by discriminatory variables and risk scores.

RESULTS

Study population. Following the exclusion of patients missing 2h hs-cTnT measurements (n=617), 550 patients were included in the analysis and were eligible for assessment using the clinical pathway. Included patients had a mean age of 62.2 (SD: 14.2) years and 62.0% (95% CI: 57.8-66.1) were male. A total of 63 patients (11.5%, 95% CI: 8.92-14.4) had an adjudicated diagnosis of AMI at the index ED visit, while 78 (14.2%, 95% CI: 11.4-17.4) patients experienced at least one MACE at 30-days. The patients with index AMI experienced a total of 92 MACE (63 AMI, 2 deaths, 27 revascularizations), while patients who did not have AMI at the index visit had 16 MACE (1 AMI, 1 death, 15 revascularizations). Clinical characteristics and outcomes experienced by included patients are detailed in Table 3 below.

Pathway Stage 1: Ruling-out AMI. All 550 patients were evaluated using the 2-hour hs-cTnT RDA (Figure 1). At presentation their baseline troponin concentrations were assessed, leading to immediate AMI rule-out and rule-in of 76 (13.8%, 95% CI: 11.0-16.9) and 31 (5.64%, 95% CI: 3.86-7.91) patients, respectively. The 443 patients not classified at baseline were reassessed using their 2h hs-cTnT concentrations, allowing the rule-out of an additional 274 (49.8%, 95% CI: 45.6-54.1) patients and AMI rule-in for 29 (5.27%, 95% CI: 3.56-7.49) more patients. In total

following the application of the 2h RDA 350 (63.6%, 95% CI: 59.5-67.7) of patients had AMI ruled-out, with zero missed index AMI yielding a sensitivity and NPV for AMI of 100% (95% CI: 92.6-100). Of the total 60 (10.9%, 95% CI: 8.43-13.8) patients who had AMI ruled-in, 48 had index AMI corresponding to a specificity and PPV for AMI of 96.7% (95% CI: 94.3-98.3) and 80.0% (95% CI: 69.6-87.5), respectively. In the ED, the 60 ruled-in patients would likely be sent for immediate intervention and the remaining 140 (25.5%, 95% CI: 21.9-29.3) patients not yet classified would undergo continued serial hs-cTnT sampling and observation. The 350 patients with AMI ruled-out are shuttled into the second stage of the pathway for further prognostication, described below.

Pathway Stage 2: Risk Stratification for 30-day MACE.

Discrimination and calibration of selected risk scores. Prior to their application in the second stage of the pathway, the discrimination of the prioritized risk scores for 30-day MACE when applied to all patients (as a reference) and the ruled-out patient population were assessed. All three risk scores had high discriminative ability for 30-day MACE according to AUC in the undifferentiated population and this increased when the scores were applied to the AMI ruled-out population. AUC ranged from 0.775 to 0.886 and 0.852 to 0.911 in the undifferentiated and ruled-out populations, respectively (Table 4). The ROC curves corresponding to all AUC values in Table 4 are shown in Figure 2.

It is important to consider the high AUCs seen for all scores concurrently with their calibration in each population. Calibration was assessed for all scores in both populations with the calibration plots and LOESS curves shown in Figure 3. The close proximities of the LOESS curves and line of perfect calibration for the HEART and TIMI scores in the undifferentiated

chest pain population suggest that these risk scores are well calibrated for use with these patients. Conversely, however, the LOESS curve for the Diamond and Forrester score appears to mirror the line of perfect calibration more closely when applied to ruled-out patients compared to all patients, suggesting better calibration in this population compared to HEART and TIMI whose calibration appears to deteriorate in this patient group.

Trial of non-stratified pathways. The pathways developed by applying all included risk scores to the ruled-out patients without pre-stratification are shown graphically in Figures 4-8, with corresponding classification characteristics summarized in Table 5. Among those achieving 100% sensitivity for 30-day MACE, the pathway using HEART≤3 identified the most AMI ruled-out patients as eligible for discharge without the need for subsequent follow-up (58.9%) and also had the leading specificity of 61.1% (95% CI: 55.7-66.4). The pathways using a modified version of the HEART score with a low-risk cut-off of 4 points or less and a TIMI with a low-risk threshold ≤2 points had sensitivities for 30-day MACE of 76.9% (95% CI: 46.2-94.9%) and 92.3% (95% CI: 63.9-99.8), respectively, indicating that they might be unsuitable for clinical use. However, their NPVs of 98.9% (95% CI: 97.0-99.6%) and 99.5 (95% CI: 96.9-99.9) and the imprecise 95% CIs surrounding the estimates suggest that the poor sensitivity is likely due to the low number of 30-day MACEs in the population and a high vulnerability to chance, and may not be a true reflection of score performance.

Trial of stratified pathway: Known CAD. The application of the binary variable of known CAD status to patients entering the second stage of the pathway created two groups of patients: patients with known CAD (n=97), and patients with no known CAD (n=249). Most AMI ruled-

out patients with MACE were classified in the known CAD group (n=12), demonstrating the high discriminative ability of this clinical characteristic in the AMI ruled-out population. The HEART, TIMI, and Diamond and Forrester risk scores were then applied independently in the two groups emerging from the stratification (Figures 9-13). The pre-stratification had a minimal effect on the performance of the pathways, only decreasing the proportion of patients identified as eligible for discharge without further investigation by TIMI≤2. However, given that the single missed MACE in the group of patients without known CAD came from a patient with a HEART score of 5, this type of stratification creates an opportunity for applying different low-risk thresholds between strata. A hypothetical pathway applying HEART≤3 to the higher risk subset of patients with known CAD and a HEART≤4 to those without CAD at lower baseline risk would have identified 68.3% of AMI ruled-out patients as eligible for discharge without follow-up with 100% sensitivity for 30-day MACE. The classification characteristics of all trial pathways with stratification by CAD status are shown in Table 5.

Trial of stratified pathway: Suspicion of history for ACS. Stratification of ruled-out patients by the categorical variable of level of suspicion of clinical history for ACS yielded three groups: slightly suspicious history (n=164), moderately suspicious history (n=142), and highly suspicious history (n=40). The included risk scores were once again applied to each of these groups independently, followed by the regrouping of all low-, intermediate-, and high-risk patients back together for the calculation of classification characteristics (Figures 14-18). These pathways classified patients in a way that very closely resembled the non-stratified pathways, with a maximum of 58.9% of patients being identified as eligible for discharge without

subsequent testing by the pathway using HEART≤3 with 100% sensitivity (95% CI: 75.3-100) and 61.1% specificity (95% CI: 55.7-66.4) for 30-day MACE (Table 5).

DISCUSSION

The purpose of this final component of the thesis project was to develop and test a sequential clinical pathway to guide the assessment of chest pain in the ED. Through a combined use of the available evidence and input from clinical experts, this pathway was derived to mirror the cognitive steps required in this assessment with the ultimate goal of maximizing the number of patients who could be discharged safely without the need for subsequent investigations. We determined that this goal was best achieved through the successive use of a validated 2h hs-cTnT algorithm for AMI and prognostication of patients with AMI ruled-out using a HEART score ≤3 points. This pathway ruled-out AMI in over 63.6% of undifferentiated chest pain patients and, within 2 hours of ED arrival, identified 58.9% of these ruled-out patients (i.e., 37.5% of the 550 included patients) as eligible for discharge **without the need for subsequent follow-up** with 0 missed index AMI or 30-day MACE.

Evidence on clinical pathways that allow the assessment of chest pain patients from ED arrival to potential discharge is scarce. Given the available studies, the best performing pathway in this study identified a similar proportion of patients as low-risk and eligible for discharge without subsequent testing than both the ADAPT-ADP and EDACS-ADP, which identified 30.5% and 41.6% of patients as such, respectively[32]. In a retrospective validation, the EDACS-ADP – a pathway that identifies patients as low risk if they had no new ischemic ECG changes, negative 0 and 2-hour hs-cTn measurements, EDACS<16, and no clinical red flags- identified 41.6% of all patients as low-risk with 100% sensitivity for 30-day MACE[33]. Notably, this

pathway does not allow clinical decisions to be made prior to the complete collection of all criteria. The best performing pathway in the current study identified slightly less patients as eligible for discharge without subsequent testing (37.5%), but leaves the opportunity for clinical decisions to be made at earlier time points for very low risk patients (e.g., following a single hs-cTn measurement at ED arrival), suggesting that our pathway may allow for a more expeditious assessment. The HEART pathway described by Mahler et al.[34] identified 46.8% of patients as low-risk, and while this is more than the pathway in this study, they utilized contemporary cTn and recommend stratification with the HEART score before 0 and 3-hour cTn measurement. This is not reflective of the cognitive steps taken in the ED and has a longer serial sampling schedule than the pathway herein described. Further, a recent study assessed the performances of risk scores with hs-cTn in chest pain patients without MI (similar to the second stage of the pathway in this study), but at best identified 60.6% of these patients as eligible for discharge without subsequent testing with an NPV for 60-day MACE of 98.88% (95% CI: 98.80-98.95)[21]. This was slightly more than the 58.9% of patients without AMI identified as low-risk in this study, but ours maintained sensitivity and NPV for 30-day MACE of 100%.

The 61.1% (95% CI: 55.7-66.4) specificity for 30-day MACE seen in the best performing pathways in this study is superior to those for the m-Goldman, TIMI, GRACE, HEART, and VCPR scores combined with hs-cTnT ≤14 ng/L[35]. This is especially notable given that the 30-day MACE definition in this study did not include any index MI. Despite only accounting for 11.5% of the chest pain population in this study, patients with index AMI account for 80.8% of all 30-day MACE. This is the case in most studies which focus on undifferentiated chest pain patients, and as such their reported specificities for MACE would likely decline when assessing a true prognostic outcome (i.e., no index events).

One thing should be noted about the performance of the pathway using a modified HEART score. As previously mentioned, the HEART score was derived and has most often been validated in a population of undifferentiated chest pain patients. We confirmed that this score had good discrimination and was well calibrated in the undifferentiated population, however we have since argued that this is not the population of interest when applying risk scores. When applying a regression model designed to mirror the HEART score to patients with AMI ruled-out by a 2h hs-cTnT algorithm, it shows poor calibration, overestimating risk for most patients that it is applied to. The same pattern of poor calibration was also shown for the TIMI risk score. Conversely, the Diamond and Forrester risk score which was derived in a population of patients more closely aligned to the ruled-out population (i.e., outpatients with stable ischemic disease) had improved calibration in this group. Overall, these findings suggest that re-calibration of established risk scores may be warranted to maximize their performance in the low-risk patient population.

From a methodological standpoint, two additional caveats to the performance of the pathways assessed in this chapter should be noted. The first stems from the low events per variable (EPV) value <1 in regression modelling, falling far below the recommended minimum of 10[36]. This is an unavoidable consequence of developing regression models with a relatively rare outcome in a small sample. Due to the low EPV, the performance and fit of the logistic regression models seen in this analysis may be overestimated and is unlikely to be maintained when applied outside of this training sample.

The second key consideration surrounds the lack of sex and gender-based analysis and reporting (SBGAR)[37] throughout pathway development. There are established differences in the ways that females and males present with, experience, and receive care for myocardial ischemia

and chest pain. This includes potential differences in disease aetiology and symptomology[38-40], cardiac troponin concentrations and kinetics[41,42], and ultimately contributes to females receiving less evidence-based investigations and treatments and having worse ischemia-related outcomes compared to males[41,42]. As such, the pathways presented in this chapter represent an average of performance across both biological sexes and if assessed in a sex-specific fashion, these performances may decline or be altered for one sex more than the other. Unfortunately given the low incidence of MACE among females in our sample we are not able to explore these potential sex differences with precision and must plan to do so in future work. Gender – referring to the spectrum of expressions of identities and socially constructed roles of men and women[37] – also influences cardiovascular outcomes. However, gender was not a variable available in the data used for these analyses. Further prospective work should evaluate the presence or absence of gender-specific factors in chest pain evaluation so they can be integrated into future pathways to ensure equitable ED care for all.

STRENGTHS AND LIMITATIONS

The prospectively validated 2h hs-cTnT diagnostic algorithm used in this study uses an up-to-date cardiac biomarker meaning it will translate well into hospitals across North America and much of the developed world. Also, the risk scores and discriminator variables prioritized and tested in this pathway were selected based on novel evidence (see Chapter 2: Systematic review and Chapter 3: Time-to-event analysis) showing their strong performance with these novel hs-cTn assays.

Development decisions for the pathway in this study were made with input from clinical experts and designed to be not only pragmatic, but reflective of the real clinical decision-making

process. Instead of creating and introducing novel diagnostic and prognostic tools, this pathway simply organizes a diagnostic algorithm and clinically available risk score into a structure that could maximize safe rule-out capacity. With the knowledge that uptake of previously introduced clinical pathways and guidelines in the ED has been poor[32,33,36-38], the pragmatic design and inclusion of the end-user in the development process may facilitate clinical uptake and adherence.

This study is not without its limitations. The small sample size of this study, especially the limited number of 30-day MACE in the ruled-out population, led to decreased precision of the estimates for sensitivity and specificity. As such, the findings of this study may not translate to larger chest pain cohorts.

Further, in order to compare the discriminatory capacity (using ROC curves) and calibration of risk scores, it was required that we developed logistic regression models for each risk score. It is important to note that this is not how the HEART and Diamond and Forrester risk scores were developed, and to have representation of all of the variables that these scores include we forced them into the models. The logistic regression models were well calibrated in the undifferentiated chest pain populations similar to those they were derived in, suggesting this methodological decision likely did not bias apparent score performance downwards. All of the associated coefficients are provided for transparency and reproducibility purposes.

FUTURE DIRECTIONS

Further testing and refinement of the exploratory clinical pathways presented in this study in larger, prospectively collected datasets is necessary. If performance is sustained in larger datasets, a randomized trial may be warranted to assess clinical uptake and results of the

standardized pathway on patient safety as well as downstream costs and resource utilization in follow-up testing. The risk scores used in this study, especially the HEART and TIMI scores, were shown to be poorly calibrated when applied to patients who have had AMI ruled-out by a validated 2h hs-cTnT algorithm. As such, recalibration of these risk scores in larger datasets with many MACE (excluding index MI) may be necessary to maximize their capacities for ED chest pain patient prognostication.

CONCLUSION

A sequential clinical pathway using a validated 2h hs-cTnT algorithm for AMI and using a HEART score ≤3 ruled-out index AMI in over 60% of presenting chest pain patients and identified 37.5% of all patients as eligible for discharge without the need for subsequent follow-up. Patients identified as such had zero missed index AMI or 30-day MACE. This exploratory pathway outperformed the few currently available and begins to bridge the gap between the evidence on the diagnostic and prognostic tools available to ED clinicians assessing chest pain patients.

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Tables.

Table 1. Description of logistic regression models for each risk score assessed in the study when applied to all patients.

	Unstandardized Coefficients			
HEART	Beta	Std. Error	Odds Ratio	Sig.
(Intercept)	-4.216	0.849	0.02	<0.001
History (1)	0.446	0.433	1.56	0.302
History (2)	2.710	0.436	15.0	<0.001
ECG (1)	-0.482	0.353	0.62	0.172
ECG (2)	2.464	0.838	11.8	0.003
Age (1)	0.184	0.739	1.20	0.804
Age (2)	-0.288	0.759	0.75	0.705
Risk Factors (1)	0.523	0.602	1.69	0.385
Risk Factor (2)	0.645	0.607	1.91	0.288
Troponin (1)	1.582	0.408	4.86	<0.001
Troponin (2)	3.653	0.493	38.6	<0.001
TIMI				
(Intercept)	-0.941	0.329	0.39	0.004
Age (1)	-0.536	0.326	0.58	0.099
Risk Factors (1)	0.289	0.320	1.34	0.366
Known CAD (1)	0.288	0.362	1.33	0.425
ECG (1)	2.903	0.713	18.2	<0.001
ASA Use (1)	0.063	0.357	1.06	0.861
Angina (1)	0.597	0.303	1.82	0.049
Troponin (1)	-2.144	0.325	0.12	<0.001
D&F				
(Intercept)	-2.954	0.418	0.05	<0.001
Age (1)	-0.449	0.516	0.64	0.384
Age (2)	-0.182	0.349	0.83	0.601
Age (3)	-0.197	0.361	0.82	0.585
Age (4)	0 (omitted)	-	-	-
Male Sex	0.415	0.296	1.52	0.160
Symptoms (1)	0.583	0.390	1.79	0.135
Symptoms (2)	2.764	0.381	15.9	<0.001

HEART= History, ECG, Age, Risk Factors, Troponin; TIMI=Thrombolysis in Myocardial Infarction; D&F=Diamond and Forrester; ECG=Electrocardiogram; CAD=Coronary artery disease; ASA=Acetylsalicylic Acid. D&F omission due to collinearity.

Table 2. Description of logistic regression models for each risk score assessed in the study when applied to all patients.

	Unstandardized Coefficients			
HEART	Beta	Std. Error	Odds Ratio	Sig.
(Intercept)	-0.768	1.462	0.46	0.599
History (1)	-2.286	0.664	0.10	0.001
History (2)	0 (omitted)	-	-	-
ECG (1)	-1.042	0.736	0.35	0.157
ECG (2)	1.348	1.424	3.85	0.344
Age (1)	0.082	1.412	1.09	0.954
Age (2)	0.069	1.416	1.07	0.961
Risk Factors (1)	-0.366	0.670	0.69	0.585
Risk Factor (2)	0 (omitted)	-	-	-
TIMI				
(Intercept)	-5.787	1.071	0.00	<0.001
Age (1)	-0.112	0.696	0.89	0.872
Risk Factors (1)	0.223	0.652	1.26	0.727
ECG (1)	0 (omitted)	-	-	-
Known CAD (1)	3.137	1.181	23.0	0.008
ASA Use (1)	0.523	0.884	1.69	0.554
Angina (1)	0.552	0.634	1.73	0.384
Troponin (1)	0 (omitted)	-	-	-
D&F				
(Intercept)	-2.298	0.970	0.10	0.018
Age (1)	-0.342	1.327	0.71	0.797
Age (2)	0.559	0.909	1.75	0.538
Age (3)	0.360	0.965	1.43	0.709
Age (4)	0 (omitted)	-	-	-
Male Sex	1.215	0.721	3.37	0.092
Symptoms (1)	-2.315	0.658	0.10	<0.001
Symptoms (2)	0 (omitted)	-	-	-

HEART= History, ECG, Age, Risk Factors, Troponin; TIMI=Thrombolysis in Myocardial Infarction; D&F=Diamond and Forrester; ECG=Electrocardiogram; CAD=Coronary artery disease; ASA=Acetylsalicylic Acid

HEART:
161 observations:

- 164 observations dropped because History (0) predicts failure perfectly.
- 21 observations dropped because Risk Factors (0) predicts failure perfectly.
- Omissions are because of collinearity

TIMI
350 observations:

- Omissions are because of collinearity.

(Continued)

Table 2 (Continued)

D&F:
173 observations:

- 27 observations dropped because Age (0) predicts failure perfectly.
- 146 observations dropped because Symptoms (0) predicts failure perfectly.
- Omissions because of collinearity.

Table 3. Characteristics of all patients and patients with AMI ruled-out by the 2h hs-cTnT algorithm in the first stage of the clinical pathway.

Variable	All Patients (n=550)	AMI Ruled-Out (n=350)
Mean Age (SD)	62.2 (14.2)	57.3 (12.4)
Males (%)	341 (62.0, 57.8-66.1)	206 (58.9, 53.5-64.1)
Known CAD (%)	190 (35.0, 31.0-39.2)	97 (28.0, 23.4-33.1)
History Suspicion level for ACS (%)		
Slightly	226 (41.6, 37.4-45.9)	164 (47.4, 42.0-52.8)
Moderately	225 (41.4, 37.3-45.7)	142 (41.0, 35.8-46.4)
Highly	92 (16.9, 13.9-20.4)	40 (11.6, 8.38-15.4)
ECG Changes (%)		
Normal	331 (61.0, 56.7-65.1)	240 (69.4, 64.2-74.2)
Non-Specific Changes	199 (36.6, 32.6-40.9)	102 (29.5, 24.7-34.6)
Significant ST Changes	13 (2.39, 1.28-4.06)	4 (1.16, 0.32-2.93)
Hypertension (%)	328 (60.4, 56.2-64.5)	186 (53.8, 48.3-59.1)
Hyperlipidemia (%)	262 (48.3, 44.0-52.5)	153 (44.2, 38.9-49.6)
Current Smoker (%)	77 (14.2, 11.4-17.4)	54 (15.6, 11.9-19.9)
Diabetes (%)	104 (19.2, 15.9-22.7)	52 (15.0, 11.4-19.2)
Family History of CAD (%)	115 (21.2, 17.8-24.9)	76 (21.9, 17.7-26.7)
Obesity (%)	126 (23.2, 19.7-27.0)	82 (23.7, 19.3-28.5)
Index AMI (%)	63 (11.5, 8.92-14.4)	0 (0.00, 0.00-1.051)
30-day MACE (pts with index, %)	63 (11.5, 8.92-14.4)	-
30-day AMI	63	-
30-day Death	2	-
30-day Revascularization	27	-
30-day MACE (pts without index, %)	16 (2.91, 1.67-4.68)	13 (3.71, 1.99-6.27)
30-day AMI	1	1
30-day Death	1	1
30-day Revascularization	15	12

Note. All proportions reported as point estimate followed by binomial exact 95% CI. Missing data in following predictors for all patients (n=7) and ruled-out (n=4) groups: Known CAD, History Suspicion, ECG Changes, Hypertension, Hyperlipidemia, Current Smoker, Diabetes, Family history, Obesity.

Abbreviations: SD= Standard deviation, MACE= Major adverse cardiac events, CAD= Coronary artery disease, ACS= Acute coronary syndromes, ECG= Electrocardiograms.

Table 4. Discriminative ability (as determined by AUC) of the prioritized risk scores for both the undifferentiated and ruled-out patient populations.

	AUC (95% Confidence Interval)	
Risk Score	**All Patients**	**Ruled-Out Patients**
HEART	0.886 (0.843-0.929)	0.898 (0.817-0.978)
TIMI	0.801 (0.747-0.856)	0.852 (0.745-0.958)
D&F	0.775 (0.708-0.841)	0.911 (0.847-0.974)

AUC=Area under the receiver-operating characteristic curve; HEART=History, ECG, Age, Risk factors, Troponin; TIMI=Thrombolysis in Myocardial Infarction; D&F=Diamond and Forrester.

Table 5. Summary of classification characteristics of all trial clinical pathways.

	Low-Risk (%)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
Non-stratified pathways					
HEART≤3	206 (58.9)	100 (75.3-100)	61.1 (55.7-66.4)	100 (-)	9.03 (7.99-10.2)
HEART≤4	265 (75.7)	76.9 (46.2-94.9)	77.7 (72.9-82.1)	98.9 (97.0-99.6)	11.8 (8.52-16.0)
TIMI≤1	127 (36.6)	100 (75.3-100)	37.7 (32.5-43.1)	100 (-)	5.83 (5.39-6.30)
TIMI≤2	207 (59.1)	92.3 (63.9-99.8)	61.1 (55.7-66.4)	99.5 (96.9-99.9)	8.39 (6.94-10.1)
D&F	60 (17.1)	100 (75.3-100)	17.8 (13.9-22.3)	100 (-)	4.48 (4.27-4.70)
Pre-stratification by Known CAD					
HEART≤3	206 (58.9)	100 (75.3-100)	61.1 (55.7-66.4)	100 (-)	9.03 (7.99-10.2)
HEART≤4	265 (75.7)	76.9 (46.2-94.9)	77.7 (72.9-82.1)	98.9 (97.0-99.6)	11.8 (8.52-16.0)
TIMI≤1	127 (36.6)	100 (75.3-100)	37.7 (32.5-43.1)	100 (-)	5.83 (5.39-6.30)
TIMI≤2	206 (58.9)	92.3 (63.9-99.8)	60.8 (55.4-66.1)	99.5 (96.9-99.9)	8.33 (6.89-10.1)
D&F	60 (17.1)	100 (75.3-100)	17.8 (13.9-22.3)	100 (-)	4.48 (4.27-4.70)
Pre-stratification by Suspicion level of History for ACS					
HEART≤3	206 (58.9)	100 (75.3-100)	61.1 (55.7-66.4)	100 (-)	9.03 (7.99-10.2)
HEART≤4	265 (75.7)	76.9 (46.2-94.9)	77.7 (72.9-82.1)	98.9 (97.0-99.6)	11.8 (8.52-16.0)
TIMI≤1	127 (36.3)	100 (75.3-100)	37.7 (32.5-43.1)	100 (-)	5.83 (5.39-6.30)
TIMI≤2	206 (58.9)	92.3 (63.9-99.8)	60.8 (55.4-66.1)	99.5 (96.9-99.9)	8.33 (6.89-10.1)
D&F	60 (17.1)	100 (75.3-100)	17.8 (13.9-22.3)	100 (-)	4.48 (4.27-4.70)

NPV=Negative predictive value; PPV=Positive predictive value; HEART=History, ECG, Age, Risk Factors, Troponin; TIMI=Thrombolysis in Myocardial Infarction; D&F=Diamond and Forrester; CAD=Coronary artery disease; ACS=Acute coronary syndrome.
Missing data for 4 patients in HEART pathways (non-stratified), and all stratified pathways.

Figures.

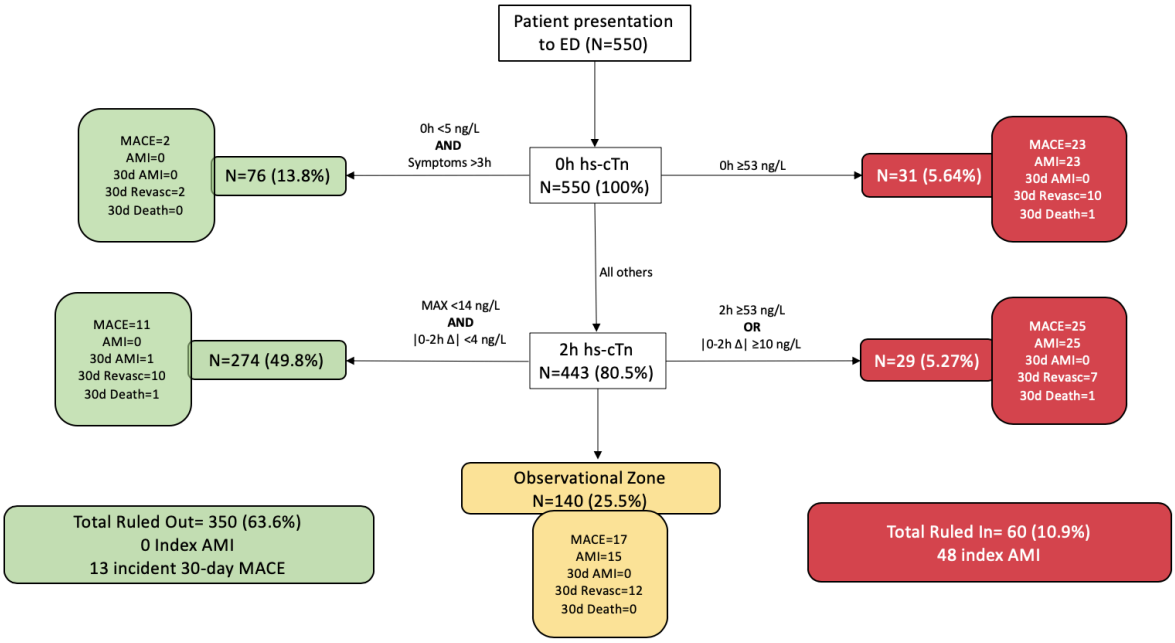


Figure 1. Patient flow diagram showing diagnostic and prognostic outcomes of patients following application of the validated 2h hs-cTnT algorithm for AMI. Patients continuing through pathway are those with AMI Ruled-Out.

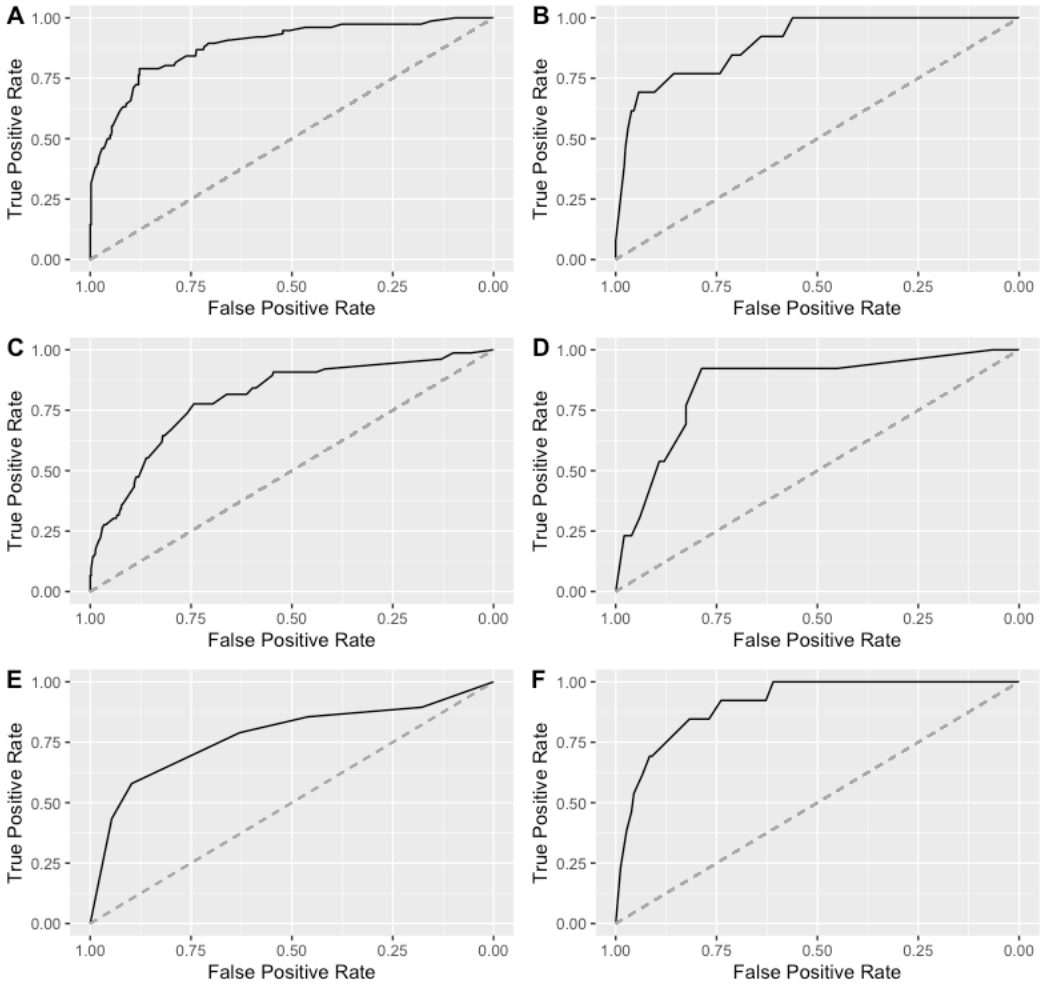


Figure 2. Receiver-operating characteristic curves for risk scores **a)** HEART score applied to full cohort, **b)** HEART score applied to population ruled-out with 2h hs-cTnT algorithm, **c)** TIMI score applied to full cohort, **d)** TIMI score applied to ruled-out cohort, **e)** Diamond and Forrester risk score applied to full cohort, **f)** Diamond and Forrester risk score applied to ruled-out cohort.

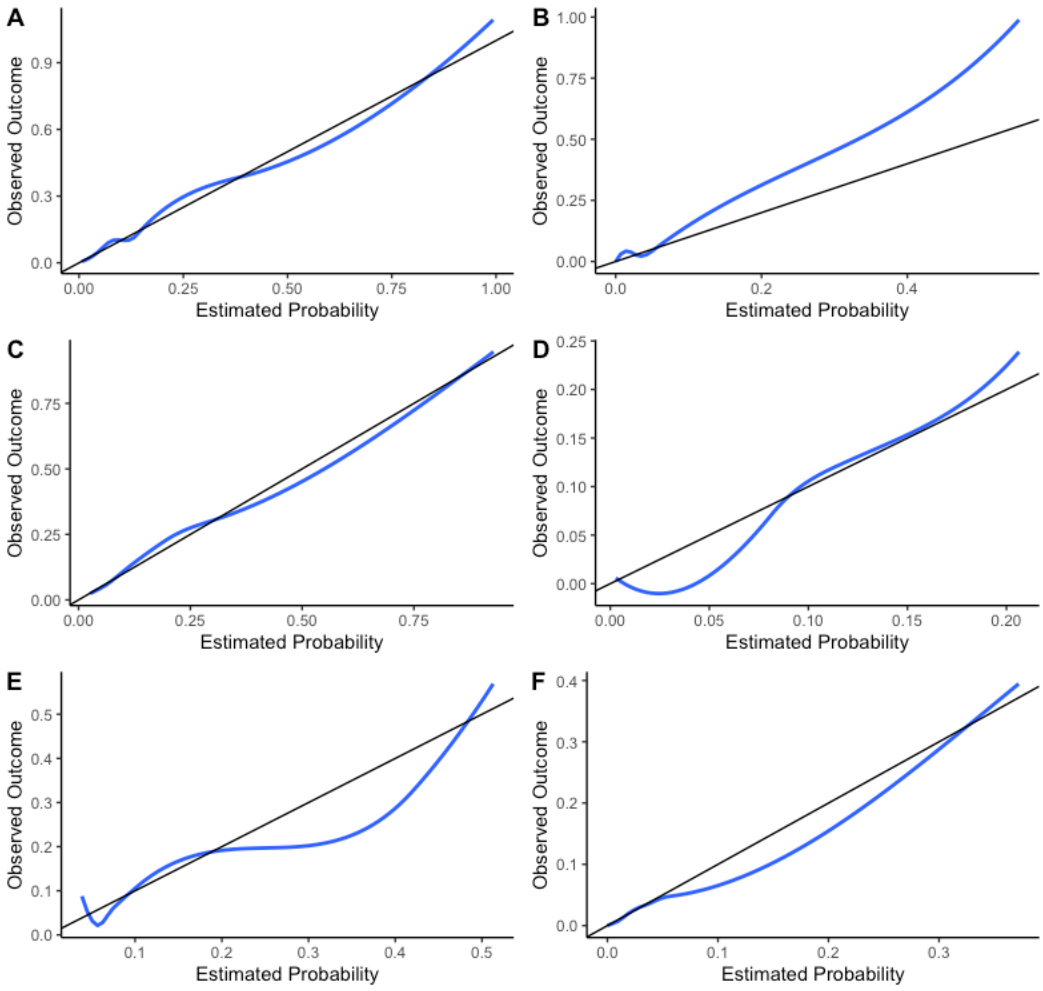
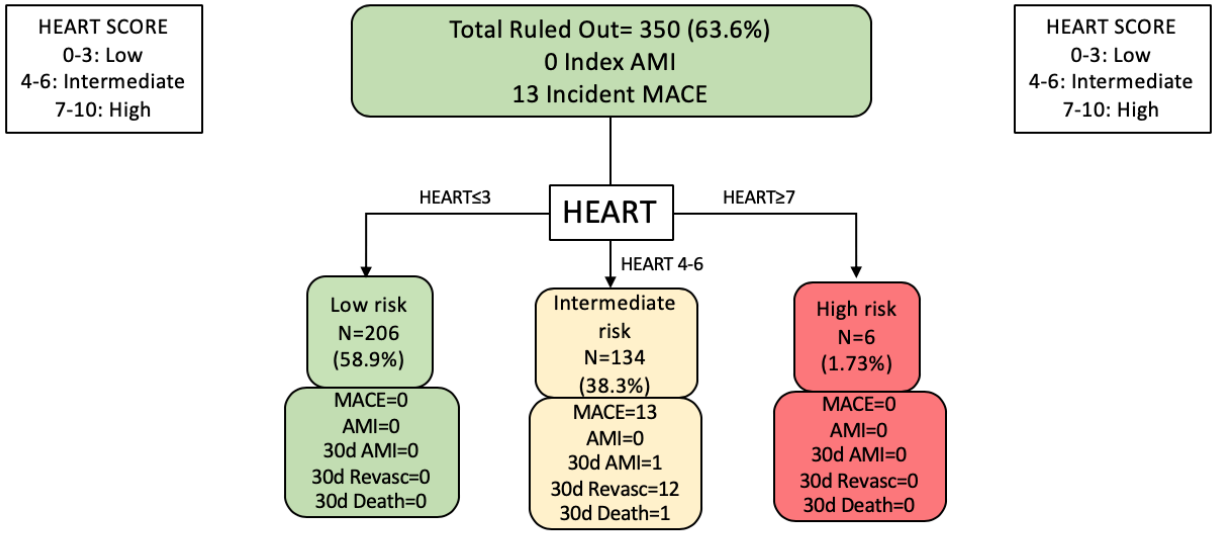


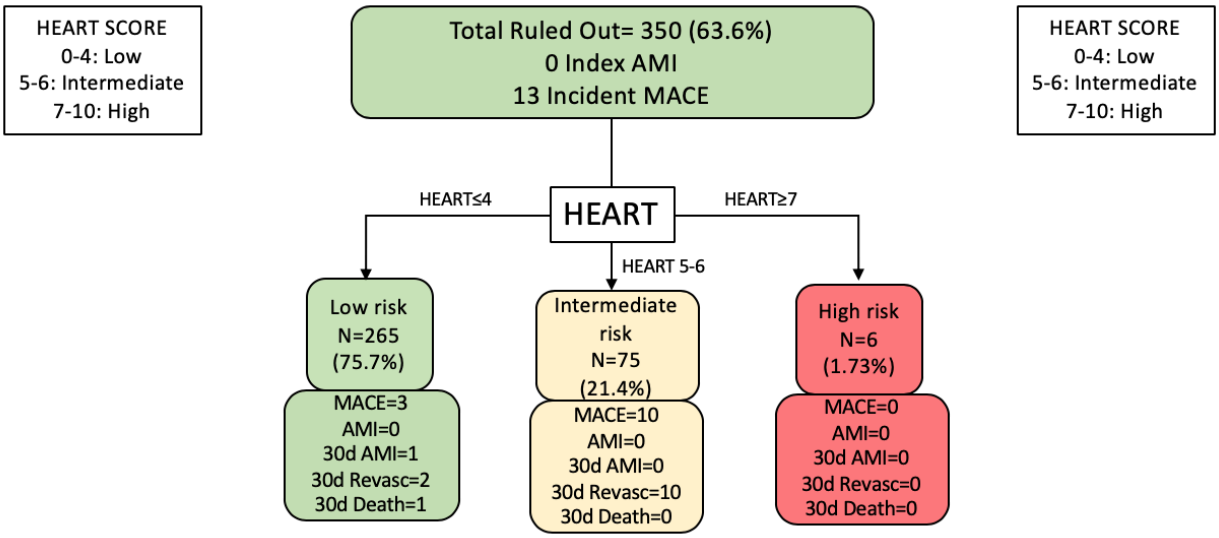
Figure 3. Calibration plots and LOESS curves for risk scores **a)** HEART score applied to full cohort, **b)** HEART score applied to population ruled-out with 2h hs-cTnT algorithm, **c)** TIMI score applied to full cohort, **d)** TIMI score applied to ruled-out cohort, **e)** Diamond and Forrester risk score applied to full cohort, **f)** Diamond and Forrester risk score applied to ruled-out cohort.



Ruled-out requiring no further testing: 206/350 (58.9%)

Sensitivity: 100% **Specificity:** 61.1% **NPV**: 100% **PPV:** 9.03%

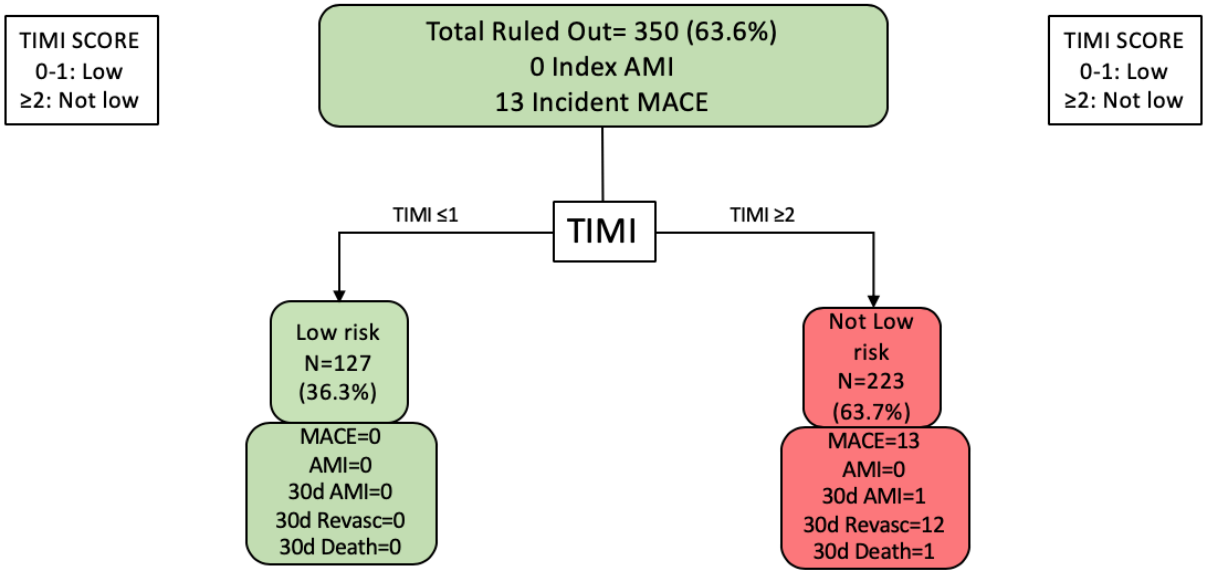
Figure 4. Trial pathway for HEART score with typical low (0-3), intermediate (4-6) and high-risk (7-10) cut-offs. Classification statistics for 30-day MACE shown. Missing HEART score data for 4 patients.



Ruled-out requiring no further testing: 265/350 (75.7%)

Sensitivity: 76.9% **Specificity:** 77.7% **NPV**: 98.9% **PPV:** 11.8%

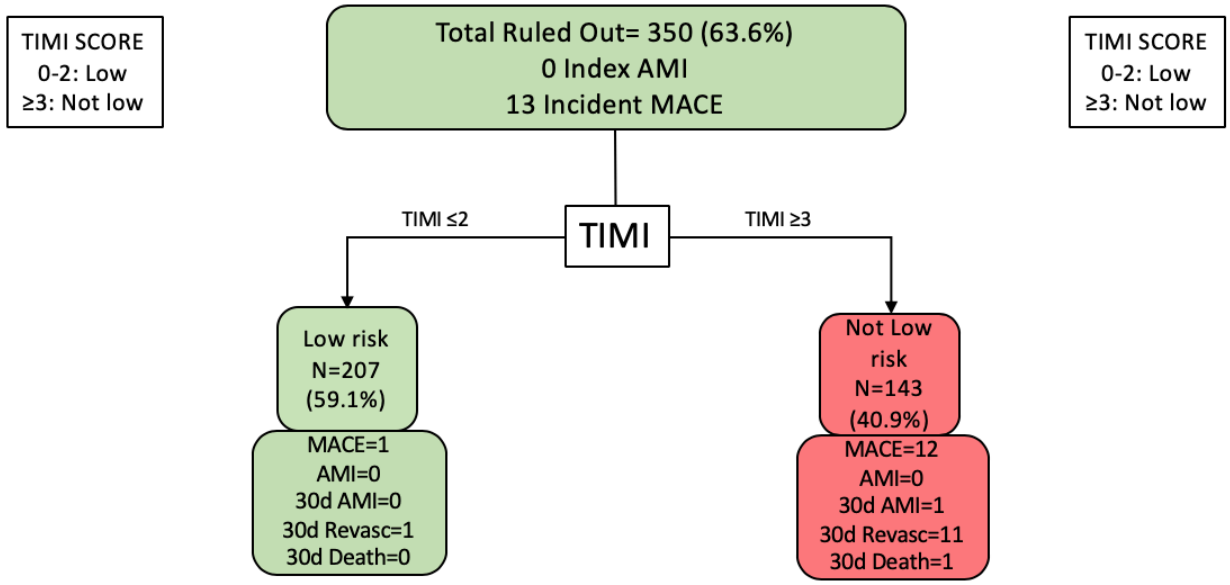
Figure 5. Trial pathway for HEART score with modified low (0-4), intermediate (5-6) and high-risk (7-10) cut-offs. Classification statistics for 30-day MACE shown. Missing HEART score data for 4 patients.



Ruled-out requiring no further testing: 127/350 (36.3%)

Sensitivity: 100% **Specificity:** 37.7% **NPV**: 100% **PPV:** 5.83%

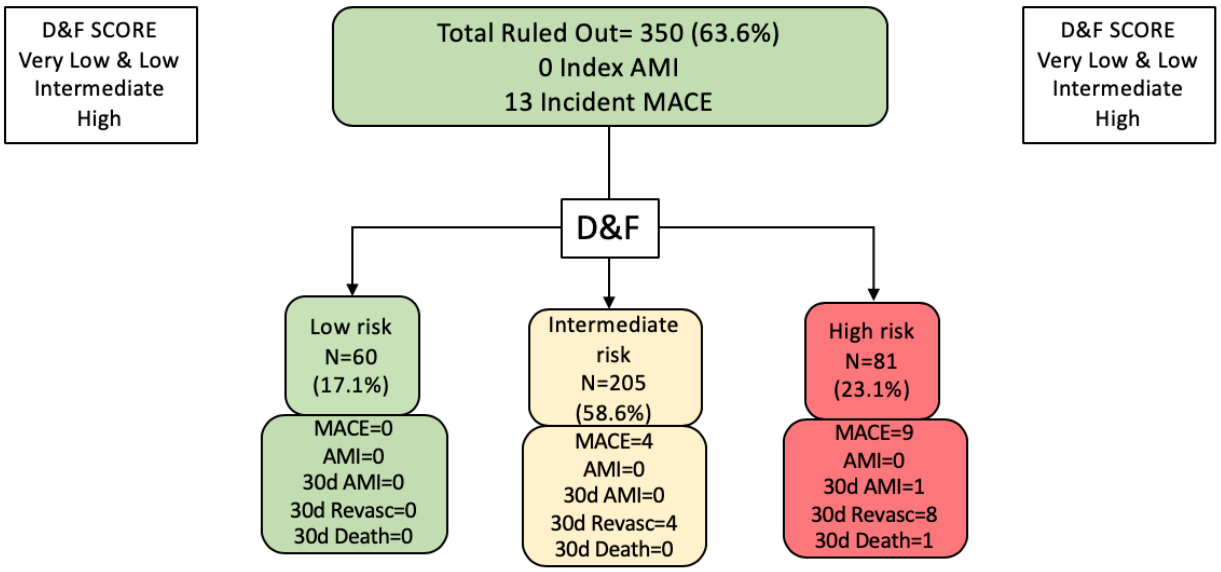
Figure 6. Trial pathway for TIMI score with typical low (0-1), and not low-risk (≥2) cut-offs. Classification statistics for 30-day MACE shown.



Ruled-out requiring no further testing: 207/350 (59.1%)

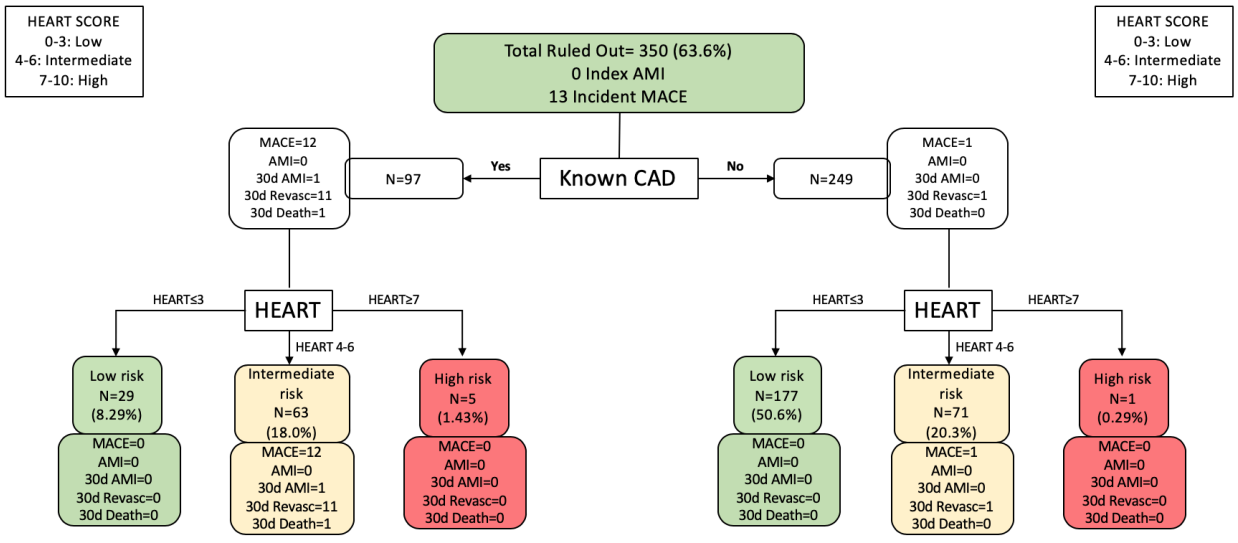
Sensitivity: 92.3% **Specificity:** 61.1% **NPV**: 99.5% **PPV:** 8.39%

Figure 7. Trial pathway for TIMI score with modified low (0-2), and not low-risk (≥3) cut-offs. Classification statistics for 30-day MACE shown.



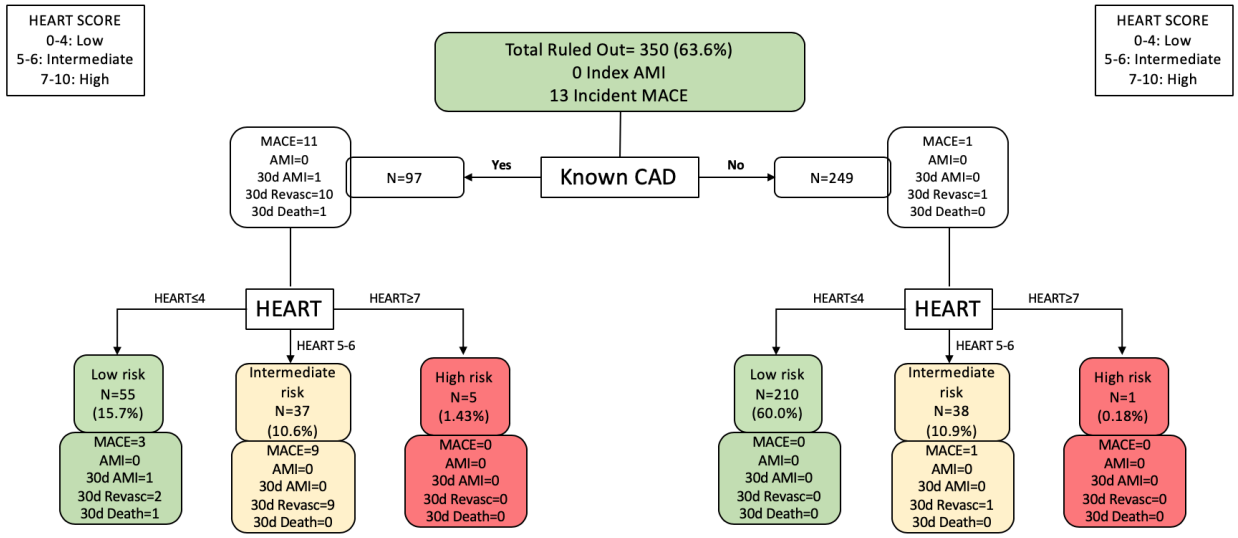
Ruled-out requiring no further testing: 60/350 (17.1%)
Sensitivity: 100% **Specificity:** 17.8% **NPV**: 100% **PPV:** 4.48%

Figure 8. Trial pathway for Diamond and Forrester score with very low and low, intermediate, and high-risk cut-offs. Classification statistics for 30-day MACE shown. Missing Diamond and Forrester data for 4 patients.



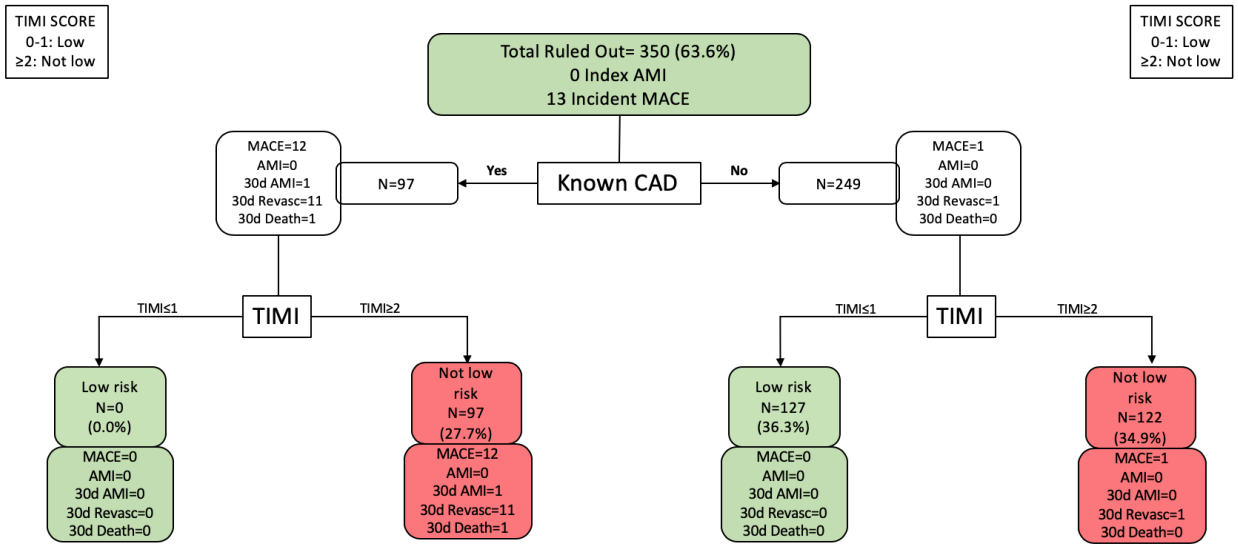
Ruled-out requiring no further testing: 206/350 (58.9%)
Sensitivity: 100% **Specificity:** 61.1% **NPV**: 100% **PPV:** 9.03%

Figure 9. Trial pathway for HEART score with typical low (0-3), intermediate (4-6) and high-risk (7-10) cut-offs following patient stratification by CAD status. Classification statistics for 30-day MACE shown. Missing HEART score/CAD status data for 4 patients.



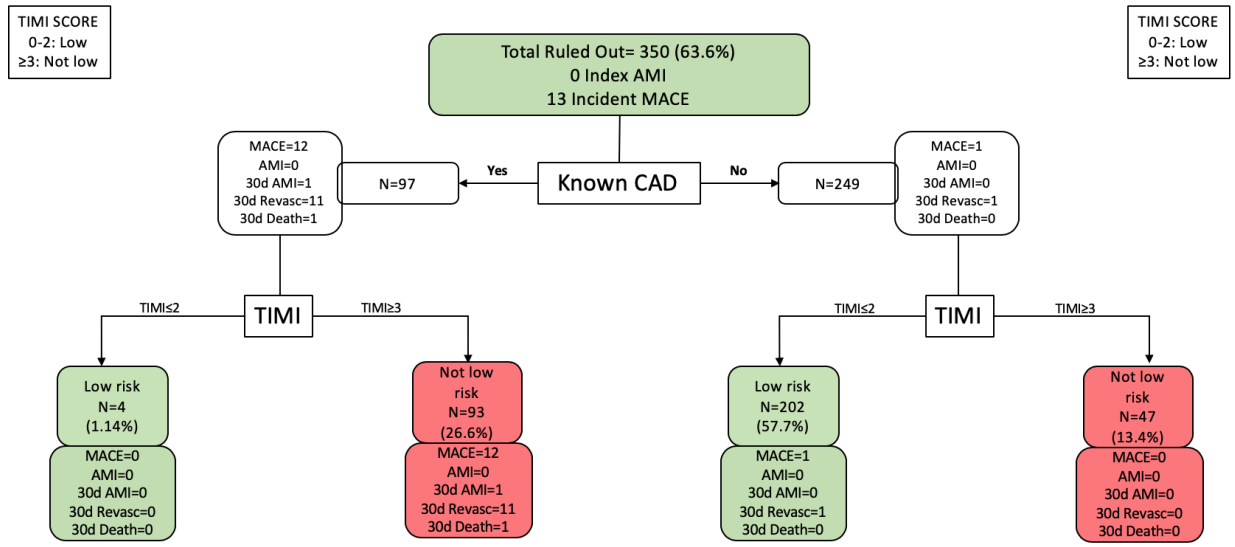
Ruled-out requiring no further testing: 265/350 (75.7%)
Sensitivity: 76.9% **Specificity:** 77.7% **NPV**: 98.9% **PPV:** 11.8%

Figure 10. Trial pathway for HEART score with modified low (0-4), intermediate (5-6) and high-risk (7-10) cut-offs following patient stratification by CAD status. Classification statistics for 30-day MACE shown. Missing HEART score/CAD status data for 4 patients.



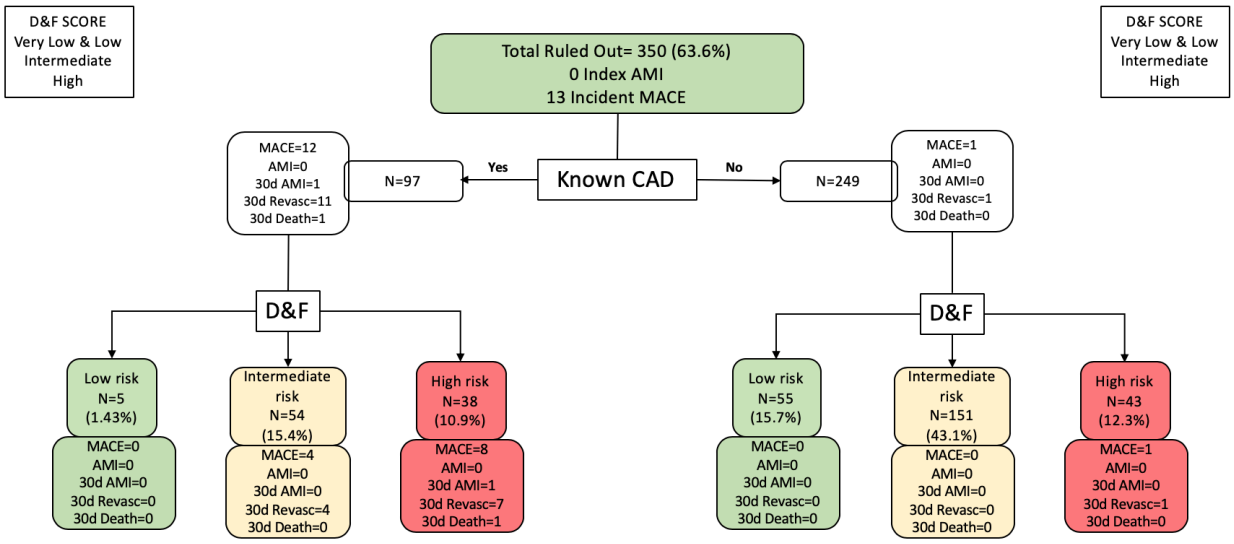
Ruled-out requiring no further testing: 127/350 (36.3%)
Sensitivity: 100% **Specificity:** 37.7% **NPV**: 100% **PPV:** 5.83%

Figure 11. Trial pathway for TIMI score with typical low (0-1), and not low-risk (≥2) cut-offs following patient stratification by CAD status. Classification statistics for 30-day MACE shown. Missing CAD status data for 4 patients.



Ruled-out requiring no further testing: 206/350 (58.9%)
Sensitivity: 92.3% **Specificity:** 60.8% **NPV**: 99.5% **PPV:** 8.33%

Figure 12. Trial pathway for TIMI score with modified low (0-2), and not low-risk (≥3) cut-offs following patient stratification by CAD status. Classification statistics for 30-day MACE shown. Missing CAD status data for 4 patients.



Ruled-out requiring no further testing: 60/350 (17.1%)
Sensitivity: 100% **Specificity:** 17.8% **NPV**: 100% **PPV:** 4.48%

Figure 13. Trial pathway for Diamond and Forrester score with very low and low, intermediate, and high-risk cut-offs following patient stratification by CAD status. Classification statistics for 30-day MACE shown. Missing Diamond and Forrester/CAD status data for 4 patients.

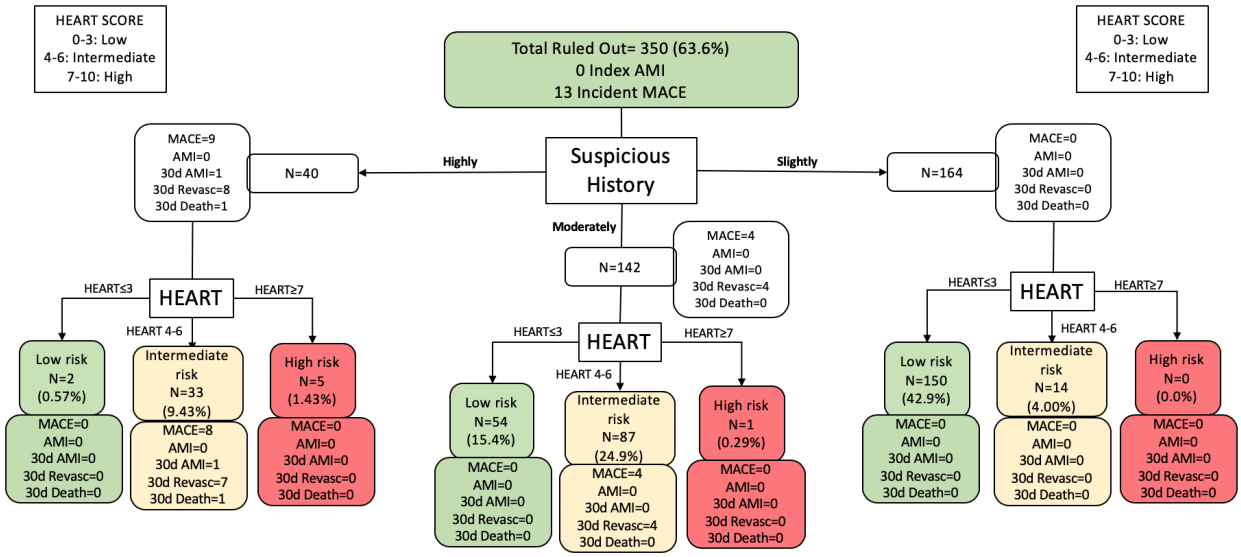


Figure 14. Trial pathway for HEART score with typical low (0-3), intermediate (4-6) and high-risk (7-10) cut-offs following patient stratification by suspicion of history for ACS (as determined through clinical gestalt judgement). Classification statistics for 30-day MACE shown. Missing HEART score/History data for 4 patients.

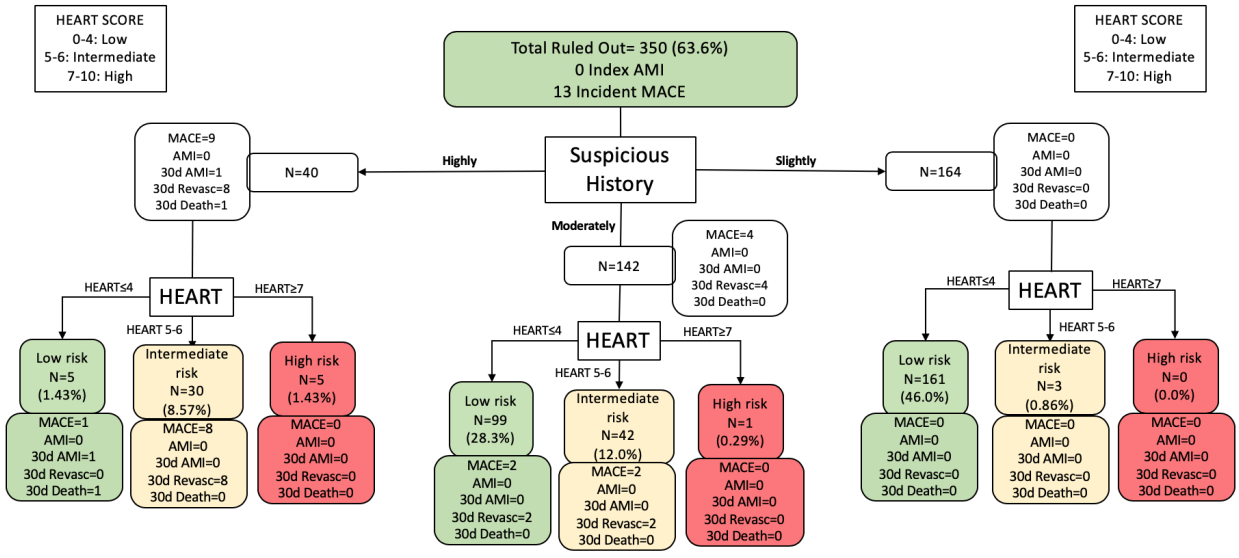
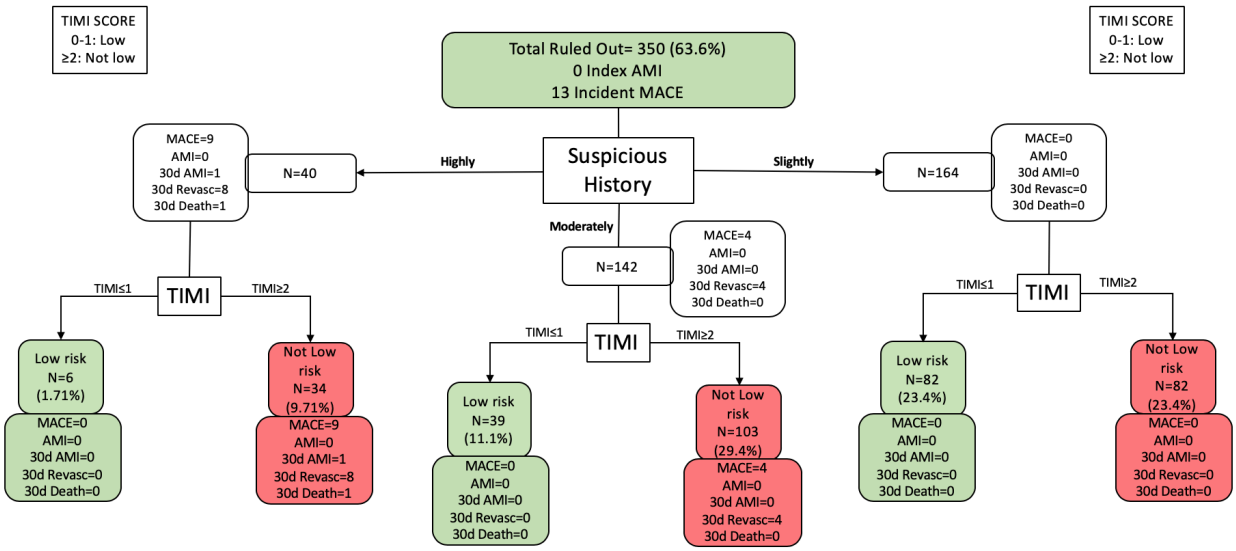


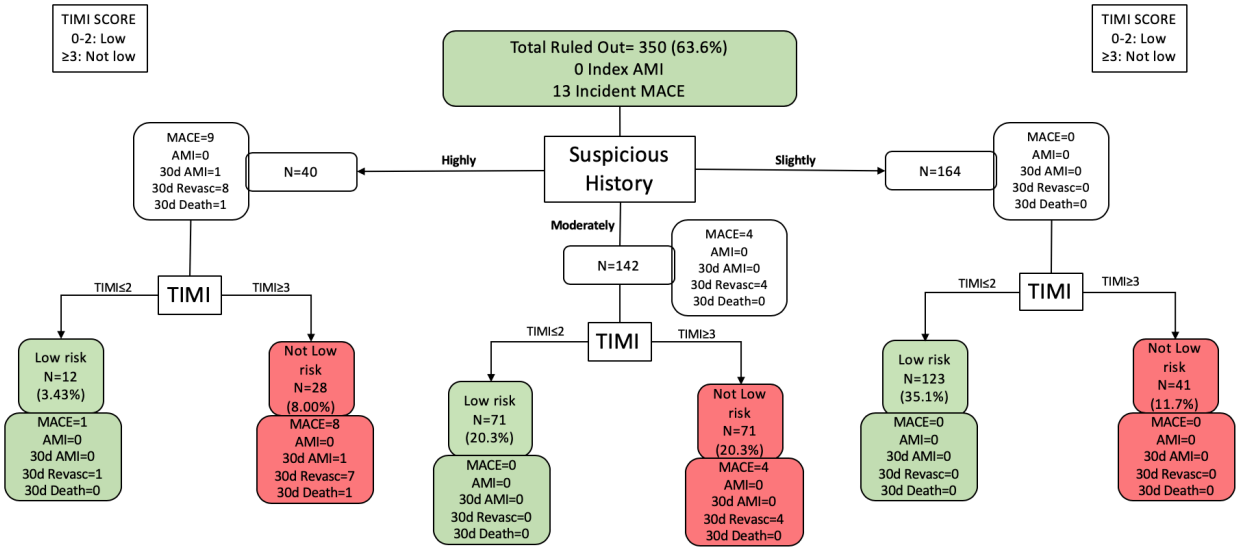
Figure 15. Trial pathway for HEART score with modified low (0-4), intermediate (5-6) and high-risk (7-10) cut-offs following patient stratification by suspicion of history for ACS (as

determined through clinical gestalt judgement). Classification statistics for 30-day MACE shown. Missing HEART score/History data for 4 patients.



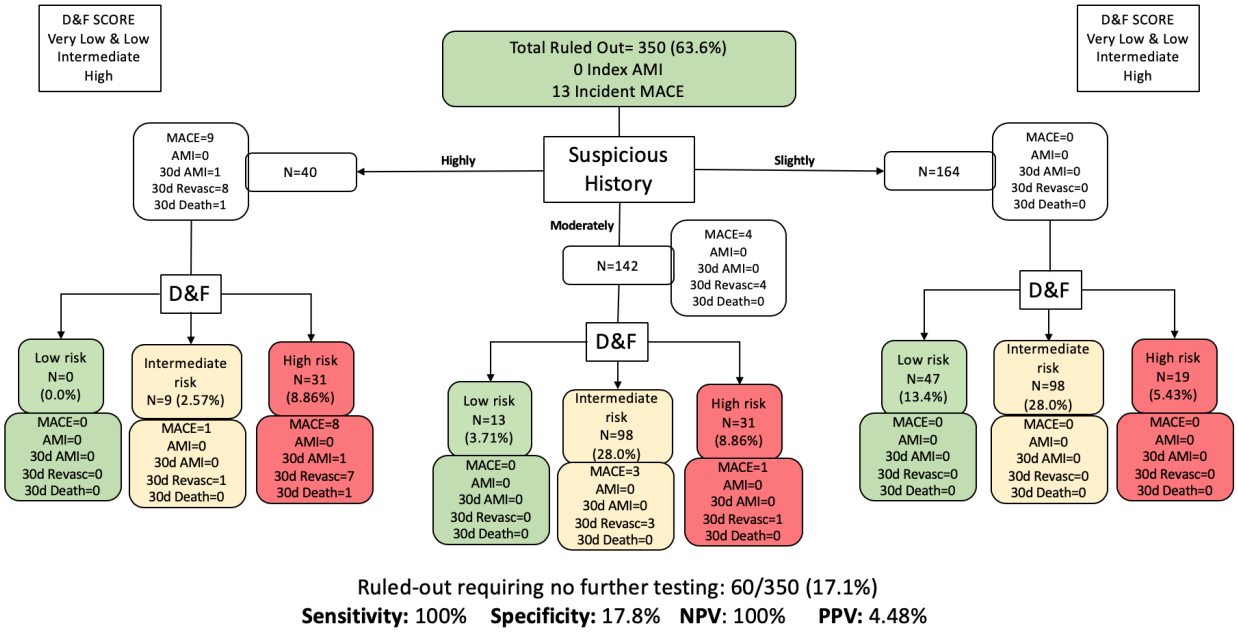
Ruled-out requiring no further testing: 127/350 (36.3%)
Sensitivity: 100% **Specificity:** 37.7% **NPV**: 100% **PPV:** 5.83%

Figure 16. Trial pathway for TIMI score with typical low (0-1), and not low-risk (≥2) cut-offs following patient stratification by suspicion of history for ACS (as determined through clinical gestalt judgement). Classification statistics for 30-day MACE shown. History data missing for 4 patients.



Ruled-out requiring no further testing: 206/350 (58.9%)
Sensitivity: 92.3% **Specificity:** 60.8% **NPV**: 99.5% **PPV:** 8.33%

Figure 17. Trial pathway for TIMI score with modified low (0-2), and not low-risk (≥3) cut-offs following patient stratification by suspicion of history for ACS (as determined through clinical gestalt judgement). Classification statistics for 30-day MACE shown. History data missing for 4 patients.



Ruled-out requiring no further testing: 60/350 (17.1%)

Sensitivity: 100% **Specificity:** 17.8% **NPV**: 100% **PPV:** 4.48%

Figure 18. Trial pathway for Diamond and Forrester score with very low and low, intermediate, and high-risk cut-offs following patient stratification by suspicion of history for ACS (as determined through clinical gestalt judgement). Classification statistics for 30-day MACE shown. History data missing for 4 patients.

CHAPTER 5 THESIS SUMMARY

This thesis project was organized around the accomplishment of three objectives: (1) To synthesize, through systematic review, the available evidence on the performance of risk scores for MACE when integrated with hs-cTn assay results; (2) To quantify, through time-to-event analysis, the elapsed time between ED discharge and MACE (up to 30 days) amongst chest pain patients without index AMI and to investigate the discriminatory capacities of predefined clinical characteristics for 30-day MACE in this population, and; (3) To develop a sequential clinical pathway for the assessment of chest pain in the ED and measure how this pathway might influence the care trajectory for chest pain patients within and beyond the ED.

Although these objectives were completed as distinct components, the overall project was designed to make them complimentary. The systematic review led to the determination that when used in combination with hs-cTn assays, HEART≤3 was superior to TIMI≤1 and GRACE≤75 for the purposes of patient prognostication. This finding informed the prioritization of risk scores that were subsequently integrated into the developed clinical pathway. The time-to-event analysis in Chapter 3 showed that the guideline recommended timeframes for follow-up care in low-risk patients were not well aligned with the true time course of MACE, such that most events fall beyond 72-hours (Europe, USA) and prior to 14-days (Canada). This portion of the thesis project also identified known CAD and clinical history highly suspicious for ACS as characteristics with the potential to distinguish low-risk patients who remained at risk for 30-day MACE from those who could likely be discharged without subsequent investigations. The latter finding informed the pre-stratification of low-risk patients by CAD status prior to the application of a risk score, which informed the development of a number of strongly performing pathways as the crux of the thesis project.

IMPLICATIONS FOR CLINICAL PRACTICE

While some are preliminary and exploratory, a number of findings from this thesis project have implications for current clinical practice. Firstly, knowledge emerging from the systematic review suggests that risk scores, especially the HEART, TIMI, and GRACE scores combined with hs-cTn assays can be used by ED physicians for the prognostication of patients without index MI. However, physicians should consider that study-cited specificities for these scores are likely to be inflated secondary to the inclusion of index MI in their 30-day outcomes, and by following them they may be sending more patients for follow-up than is necessary or beneficial. Clinicians should also note the lack of information on the calibration of these risk scores may be masking consistent under or overestimation of risk for adverse events among low-risk chest pain patients.

Much of the discussion in this thesis on the use of risk scores or clinical pathways to reduce unnecessary cardiac investigations has focused on the impacts that this reduction could have on resource availability and care costs. While this has certainly been demonstrated previously[1-4] and is further supported herein, a focus on institutional impacts fails to consider how reducing unnecessary testing could directly benefit individual patients and care quality. Although it is true that outpatient testing for very low-risk patients may allow the beneficial identification of coronary disease at its earliest stages, these tests have human costs and potential harms. These potential harms include ionizing radiation or intolerance to contrast agents following invasive and non-invasive cardiac imaging[5,6] and procedural risks (e.g., adverse cerebrovascular events and mortality) associated with both PCI and CABG[7-9]. All of this in addition to the added stress caused by an uncertainty of health status, additional hospital or clinic visits and, at worst, false positives that lead to inappropriate intervention[10,11]. As the

appropriateness of further outpatient testing decreases (it often does in non-acute chest pain patients[5,6]), these costs begin to outweigh any hypothetical benefit. It is thus even more important than previously stated for ED practitioners to use scores outlined in chapter two to reduce unnecessary referral and investigation.

Secondly, findings from the time-to-event component of this thesis suggest that physicians may be sending too many patients for follow-up at times that do not align well with the time course of MACE occurrence. As such, it may be of value for ED physicians to consider the timing of their follow-up recommendations more closely and to consider clinical characteristics (such as history of CAD or highly suspicious history for ACS) when deciding what discharge-eligible patients should be prioritized for expeditious follow-up.

Finally, the fourth chapter showed that ED physicians currently have at their disposure all of the diagnostic and prognostic tools necessary to assess chest pain. It demonstrated, however, that a structured implementation and use of these tools could maximize the efficiency of this assessment. ED physicians sequentially using a 2h hs-cTnT algorithm for AMI and the application of a modified HEART score might achieve diagnostic and prognostic certainty in more patients and faster than physicians using these tools in isolation. Stratification of ruled-out patients on the basis of CAD status also creates an opportunity to the application of risk scores with varying low-risk thresholds, further maximizing the proportion of patients eligible for discharge without need for subsequent testing. Most importantly, we have not introduced any new technologies or prognostic prediction tools that could overwhelm or slow down physicians, but instead have introduced a new approach for the consistent and efficient use of familiar (and currently available) resources. However, there are specific methodological concerns that remain including the potential overestimation of logistic regression model performance and the lack of

sex and gender-based analyses and reporting. Both of which should be considered prior to or during any clinical application of these pathways in the future. Any further methodological considerations and plans to mitigate them in future research are discussed below.

METHODOLOGICAL ISSUES IN CURRENT RESEARCH

We encountered a number of methodological issues while conducting this research. We had planned to perform a diagnostic/prognostic meta-analysis in addition to the systematic review in Chapter 2 but were not able to do so given that we could not reconstruct or confirm the 2x2 contingency tables needed from all included studies. As such, the conclusions of the study are based on a less rigorous semi-quantitative summary of the evidence.

Further, none of the studies included in the systematic review reported on risk score calibration which, as became clear when we assessed score calibration in the pathway development chapter, is an area of concern for chest pain risk score performance. Score calibration and re-calibration are important components of standard reporting guidelines for clinical risk prediction scores (e.g., Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis; TRIPOD statement)[1]. Until reporting in this area improves, we are unable to confirm if the poor calibration seen in our analyses is sustained across these other studies, reducing the immediate generalizability of these findings.

Also, the small sample size and low number of 30-day MACE in patients without index MI was a sustained concern throughout the time-to-event and pathway development analyses. Having only 13 MACE in low-risk patients leaves the measure of days-to-MACE susceptible to large change if in a larger dataset there are more events prior to or beyond the identified median of 5 days. And, while patients with known CAD are intuitively at higher risk of 30-day MACE,

the finding that nearly every low-risk patient who experienced 30-day MACE had a history of CAD is a potential artefact of the small sample size. Lastly, low sample size contributed to a lack of precision around the estimates for sensitivity, specificity, NPV and PPV used to quantify the performance of pathways in Chapter 4, limiting our confidence in the use of these pathways in the ED at this stage.

FUTURE DIRECTIONS

Despite the potential shortcomings of this research, we have contributed to the evidence base and laid a foundation for the improved evaluation of the thousands of chest pain patients who will continue to present to EDs across Canada each year. Going forward, researchers looking to derive, internally validate or externally validate risk scores must be clear if they are to be used for diagnostic or prognostic purposes and select their outcome measures accordingly (i.e., if prognostic, not to include with index MI who would not be prognosticated in practice). These authors must also assess risk score calibration when possible and if necessary, perform recalibration of these risk score to minimize the frequency of over- or underestimations of risk that contribute to both missed diagnoses and excessive downstream testing. Such recalibration studies should be performed in large datasets with many adverse events to limit within-sample optimism in performance and maximize generalizability. In this vain, the time-to-event and pathway development analyses performed in this thesis require reproduction in larger cohorts of patients prior to their introduction into the clinical context in the form of novel guidelines or recommendations for practice. These subsequent studies must include closer considerations of the EPV for logistic regression modelling and should contribute to the narrowing of sex and gender-related disparities in chest pain care by reporting and analysing data with these details in

mind. Future studies could take the form of a large prospective data collection effort or a large multi-centre collaborative meta-analysis, in order to gain a diverse population within which these preliminary findings can be tested further. Finally, should the developed and refined pathways show sustained performance in larger chest pain cohorts, a randomized controlled trial embedded within practice would allow an assessment of adherence and clinical uptake as well as an evaluation of the downstream impacts on patient outcomes, resource utilization and treatment costs.

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CHAPTER 6 CONCLUSION

This thesis project moves prognostic prediction score use into the high-sensitivity cardiac troponin era, contributes to the limited evidence base surrounding the need for and appropriate timing of follow-up investigations for low-risk chest pain patients, and provides a sequential clinical pathway that maximizes the accuracy and efficiency of the ED chest pain assessment. We have underlined the methodological shortcomings of the field and made recommendations for future researchers who want to reproduce, refine, and advance the findings of the thesis. Chest pain patients represent a large contingent of ED attendants globally and there is a tremendous opportunity to alleviate the impacts on the broader health system by optimizing their care. We hope that this thesis will act as a first step towards the achievement of this objective.

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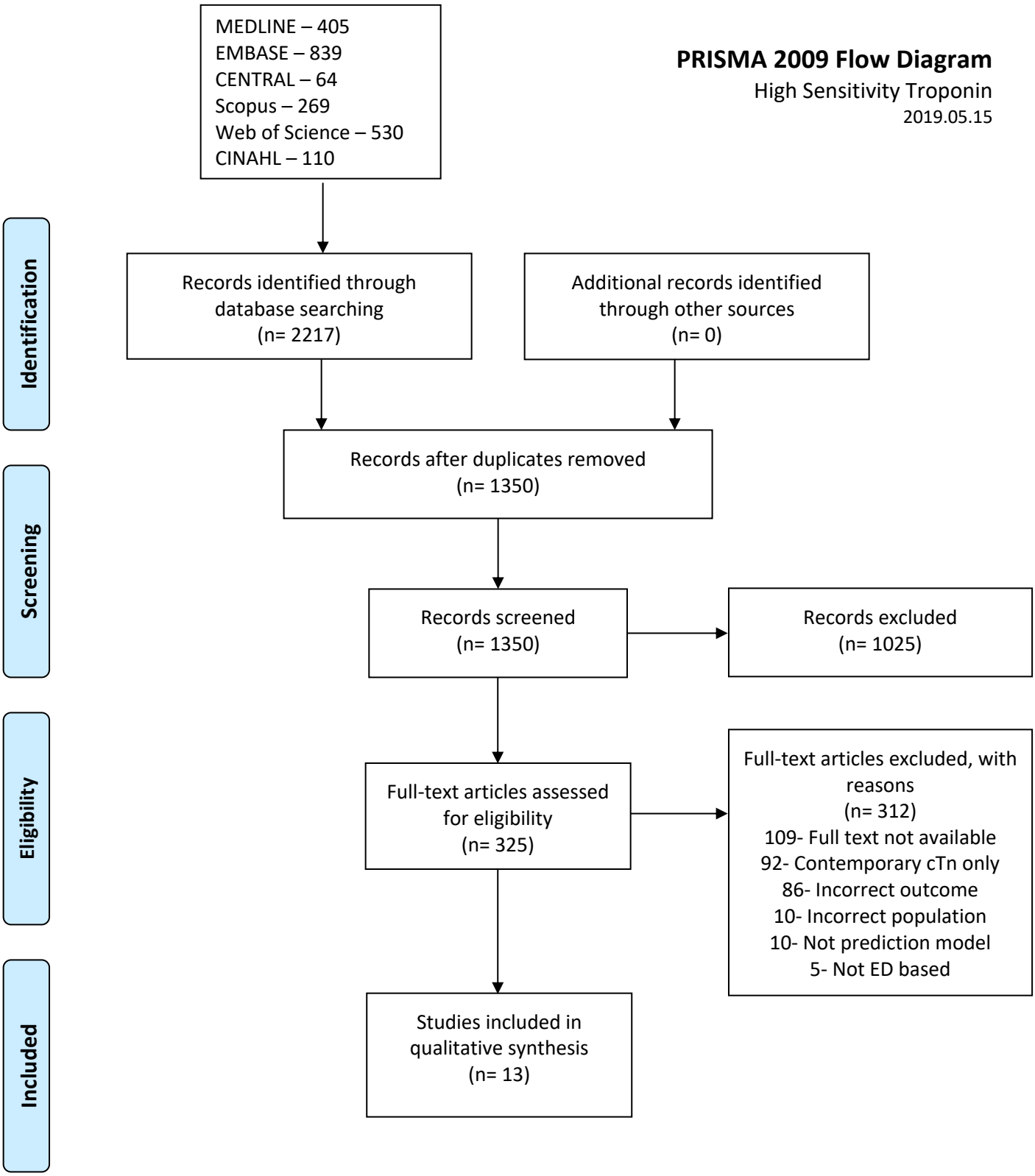
APPENDIX A: MEDLINE SEARCH STRATEGY

1 exp Emergency Medical Services/ or exp Emergency Service, Hospital/
2 ((emergency adj3 (department* or unit* or room* or service* or ward*)) or urgent care).mp.
3 (ED or ER).ti,ab.
4 or/1-3
5 exp Troponin/
6 (troponin* or ctn or ctns).mp.
7 ((high* sensitiv* or ultrasensitiv* or ultra-sensitiv*) adj3 troponin*).mp.
8 (hs-cTn or hs-cTns).mp.
9 troponin.rn.
10 or/5-9
11 Chest Pain/
12 ((chest or thoracic or thorax) adj2 (pain* or discomfort)).mp.
13 Angina Pectoris/
14 Angina, Unstable/ or Angina, Pectoris, Variant/ or Angina, Stable/
15 (angina* pectori* or stable angina* or preinfarct* angina* or pre-infarct* or angina at rest or variant angina* or prinzmetal*).mp.
16 Coronary Artery Disease/
17 ((coronary arter* adj2 (disease* or atheroscleros* or constrict* or dissect* or obstruct* or occlu* or thrombos*)) or CAD).mp.
18 Myocardial Ischemia/
19 ((myocardi* or cardiac or coronary or heart) adj3 (ischemi* or ischaemi* or anoxi* or hypoxi*)).mp.
20 Acute Coronary Syndrome/
21 acute coronary syndrome*.mp.
22 Myocardial Infarction/
23 ((myocardial or heart) adj2 (infarct* or reinfarct* or attack*)).mp.
24 exp Coronary Disease/
25 (coronary disease* or coronary heart disease* or coronary arterioscleros* or coronary atheroscleros*).mp.
26 or/11-25
27 Decision Support Techniques/
28 (decision adj2 (support or aid* or model*)).mp.
29 (clinical adj2 (decision or prediction) adj3 (aid* or model* or rule* or support*)).mp.
30 Risk assessment/ or risk assessment.mp.
31 (risk score or risk scores).mp.
32 or/27-31
33 ((heart adj2 score) or heartscore or heart tool or heart pathway).mp.
34 heart history ecg age risk factors troponin.mp.
35 vancouver chest pain.mp.
36 north american chest pain.mp.
37 emergency department assessment of chest pain.mp.
38 “accelerated diagnostic protocol with troponin”.mp.
39 “diamond and forrester risk score”.mp.
40 thrombolysis in myocardial infarction.mp.

41 global registry of acute coronary event.mp.
42 or/33-41
43 32 or 42
44 4 and 10 and 26 and 43

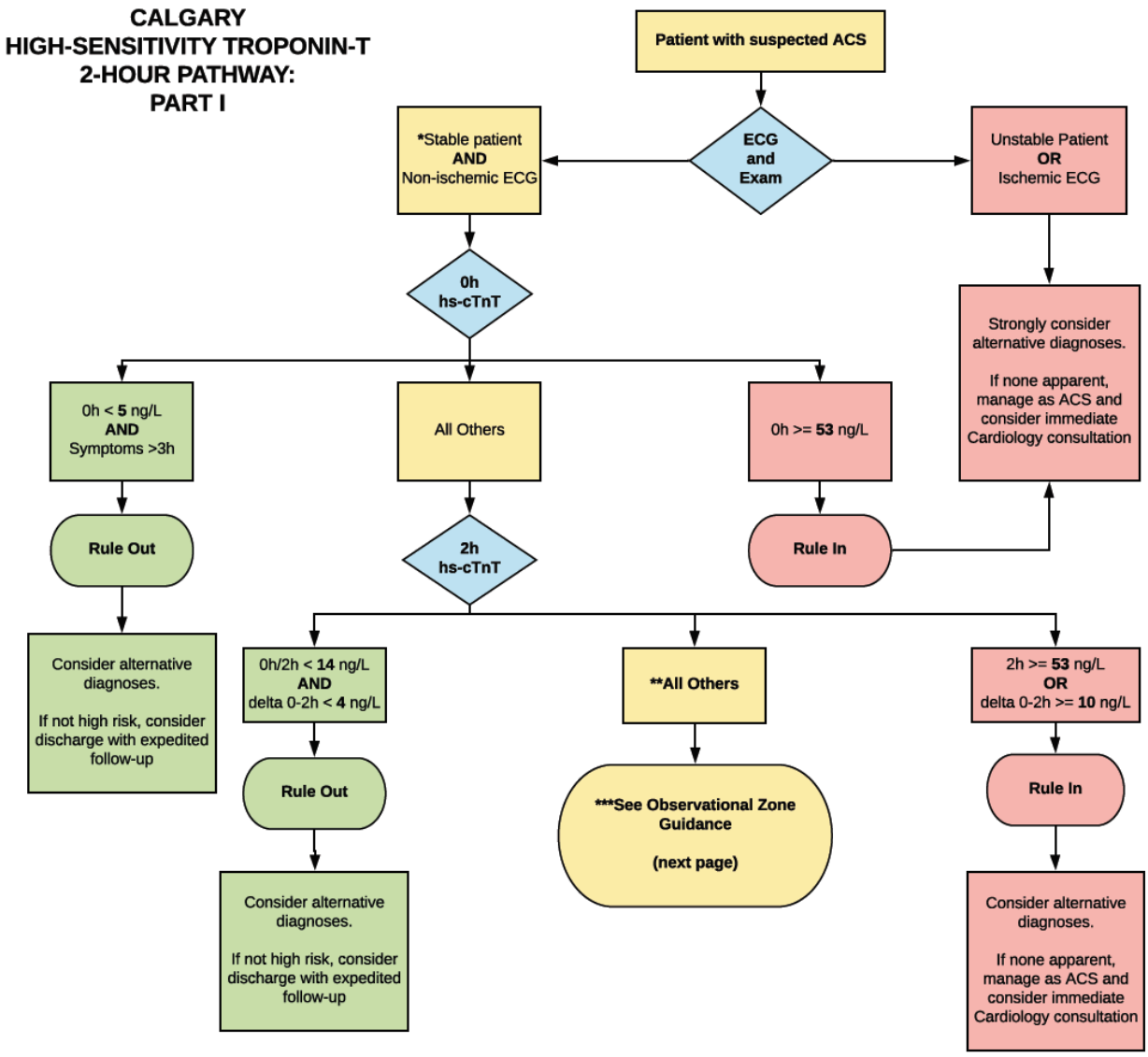
APPENDIX B: PRISMA FLOW DIAGRAM



APPENDIX C: ROCHE HS-CTNT ASSAY ANALYTICAL PROPERTIES

Name: Roche Diagnostics Elecsys® High-Sensitivity
Assay type: hs-cTnT:
Limit of Blank (LoB): 3 ng/L
Limit of Detection (LoD): 5 ng/L
99^{th} percentile/Upper Reference Limit (URL): 14 ng/L
10% Coefficient of Variation (CV): 13 ng/L

APPENDIX D: CALGARY 2H HS-CTNT RDA (USED WITH PERMISSION FROM DR. JAMES ANDRUCHOW).



Note:

* Consider using a structured risk assessment tool such as the HEART score to aid decision making for all patients.

** For all patients with abnormal hs-cTnT results, check the medical record for prior results. Many patients have stable abnomalities in hs-cTnT and measured concentrations similar to the patient's baseline are reassuring.

*** The observational zone pathway arm is based on expert opinion and has not been prospectively validated but does align with ESC 2017 recommendations.