9-2-2015

Diagnosis in Myocardial Infarction: Prehospital Troponin for the Non-Diagnostic Electrocardiogram

Timothy Riddell

DIAGNOSIS IN MYOCARDIAL INFARCTION: PREHOSPITAL TROPONIN FOR THE NON-DIAGNOSTIC ELECTROCARDIOGRAM

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

September 2, 2015

Timothy Riddell, PA-SII
Class of 2015
Yale Physician Associate Program

David Cone, MD
Professor
Dept. of Emergency Medicine

Table of Contents

Abstract

Rapid prehospital electrocardiographic diagnosis of myocardial infarction in the setting of left bundle branch block and artificially paced rhythms is clinically challenging. Electrocardiographic findings of these conditions can mask classic findings of myocardial infarction, which can lead to significant treatment delays in these patient populations. We propose a randomized controlled trial evaluating prehospital measurement of troponin, in patients with left bundle branch block or paced rhythms, presenting with symptoms of acute coronary syndrome. We hypothesize that this prehospital measurement will reduce delays to percutaneous coronary intervention in patients with myocardial infarction. We will implement the use of point-of-care troponin assays to be completed by paramedics, with findings relayed to receiving facilities. Improving rates of early intervention in myocardial infarction has been shown to be beneficial in reducing morbidity and mortality. Prehospital measurement of troponin could be uniquely beneficial in patient populations who have low rates of early intervention.

Chapter 1: Introduction

Background

Myocardial infarction (MI) is a common, life-threatening illness worldwide. It is a major cause of death and disability throughout the world.[1] The World Health organization predicts that coronary-related deaths will increase 100% for each gender in the next 2 decades.[2] In the United States, it is estimated that an MI is experienced once every 43 seconds in the adult population.[3] The estimated annual incidence of MI is 730,000 events including new and recurrent attacks.[3] MI is defined as myocardial cell death due to prolonged ischemia.[1] It is caused by blockage of coronary arteries, which supply the muscle of the heart. This blockage can occur by multiple causes, including plaque rupture, thrombus, atherosclerotic changes, ischemic imbalance, or procedure-related causes.[1] MI is defined within the umbrella term acute coronary syndrome (ACS), which includes ST segment elevation myocardial infarction (STEMI), non-ST Segment elevation myocardial infarction (NSTEMI), and unstable angina (UA).[4]

Myocardial infarction can be recognized by clinical features, including electrocardiographic changes, elevated biochemical markers, imaging, and pathology.[1] STEMI and NSTEMI are distinguished from one another by characteristic changes on a 12-lead electrocardiogram (ECG).[4,5] STEMI and NSTEMI can indicate different levels of severity, and thus have different treatment and management guidelines.[5] The role of early reperfusion in STEMI patients is well established.[6-8] Current recommendations from the American Heart Association (AHA) stipulate that door-to-balloon times for percutaneous coronary intervention (PCI) should be under 90 minutes in STEMI patients.[6]

The need for early diagnosis, and the creation of new technology, has resulted in changes in the diagnosis and treatment of MI. In many EMS systems, STEMIs can be identified in the field, and 12-lead ECGs are acquired, and in some cases transmitted to receiving facilities.[8] In a systematic review of 16 studies, this has been shown to significantly reduce delays to treatment and short-term mortality in the setting of percutaneous intervention.[8] It is clear that decreasing delays to treatment in the acute phase of MI can lead to better outcomes for patients. System delay in the treatment of MI can be considered a modifiable risk factor.[9] However, ECG is not always the most appropriate diagnostic tool. The ECG is often insufficient to diagnose MI, as ST segment changes can be seen in other conditions.[1] Some of these conditions include pericarditis, left ventricular hypertrophy, left bundle branch block, Brugada syndrome, stress cardiomyopathy, and early repolarization.[1,5] The electrocardiographic findings of MI can also be masked in the presence of an implanted pacemaker.[10] For these situations, in which the ECG alone is not diagnostic of MI, other diagnostic tools become necessary.

Measurement of cardiac biomarkers such as troponin have become essential in the diagnosis of MI. An analysis of diagnostic data showed that the diagnosis of MI via ECG has decreased 50% over 40 years, while the amount of MIs diagnosed by cardiac biomarkers has increased 2 fold.[3] Troponin I and T are present in cardiac myocytes, and are detectable in the blood when myocytes necrose.[1] Serial measurements of troponin can reveal trends which are highly suggestive of evolving cardiac events.[11] Sensitive troponin assays have significantly improved the early diagnosis of MI.[12] However, central laboratory troponin measurements often take about 1 hour to run.[13] This amount of time can be certainly deleterious in the setting of an MI. The measurement of troponin is now

available via rapid point-of-care devices, which have reasonable correlation with central laboratory values.[13] Point-of-care devices are generally used in the emergency department of hospitals, however their use has been shown to be feasible in the prehospital setting.[14,15]

Patients with bundle branch block (BBB) have ECG findings that can confound the diagnosis of MI.[16] The presence of BBB is increasing as the US population ages.[16] It is estimated that about 100,000 patients with bundle branch block experience MI annually.[17] Bundle branch block can occur in 1-15% of MIs, and in one study of almost 300,000 patients, BBB was found in one out of every 8 patients presenting with MI.[18] BBB can present as a de novo finding in acute MI, however BBB is most often a pre-existing factor in those experiencing MI.[16] Patients with BBB and MI have a 2-fold increased risk of in-hospital death.[18] Furthermore, this increased mortality risk is seen in all BBB patients, regardless of time of onset or location of the conduction block.[19] Patients with BBB and MI have decreased rates of appropriate reperfusion therapy and experience longer delays to treatment.[20]

Similarly to BBB, the presence of a paced rhythm from an implantable pacemaker can make the diagnosis of MI difficult. In 2004, 178,000 pacemakers were implanted in the US, which was a 19% increase from 1997.[21] Pacemakers do not use the natural conduction system of the heart, causing the QRS complex to appear widened on ECG.[22] The characteristic ECG findings of MI can be accentuated, cancelled, or reversed by changes due to pacing.[23] Furthermore, the addition of new types of pacemakers and variability of pacemaker lead placement make ECG findings less predictable.[24] Patients with pacemakers are generally older and at a higher risk for coronary events.[10] In one

study of over 100,000 patients with MI, 1.9% had paced rhythms, and were found to have higher rates of crude mortality, and were less likely to receive reperfusion treatment.[25]

Statement of the Problem

Myocardial infarction is a common life-threatening event in the US and worldwide, and the incidence is increasing.[1-3] The role of early reperfusion, especially in STEMI patients, has created a need for rapid diagnosis and triage of ACS patients.[6-8] The prehospital ECG has improved rapid diagnosis, triage, and outcomes for patients presenting with MI.[8] However, this rapid diagnosis and triage is not possible for patients with underlying conditions that confound the electrocardiographic diagnosis of MI. Patients with BBB and paced rhythms have higher mortality, longer delays to treatment, and lower rates of overall treatment.[18,19,25] These patients require additional diagnostic modalities, such as the measurement of troponin. Measurement of prehospital point-of-care troponin in ACS has been studied, but not in a trial of select patients with difficult prehospital ECGs which may mask characteristic findings of MI. These patients, such as those with BBB or paced rhythms, could have significant benefit of prehospital troponin measurement in the rapid diagnosis of MI.

Goals and Objectives

The proposed study is a randomized controlled trial. The study aims to evaluate the use of point-of-care measurement of troponin in the prehospital phase for ACS patients with underlying BBB or paced rhythm. The intervention group will have troponin measured in the prehospital setting, with the value reported to the receiving facility, and the control group will receive no prehospital labs. The primary outcome for the study is door to balloon time for percutaneous coronary intervention, to be measured

in minutes for both the intervention and control groups. Secondary outcomes include: EMS transport time, symptom onset to first medical contact, diagnosis of MI, qualitative troponin, PCI status, and stent placement. This study will help determine whether prehospital measurement of troponin can reduce delays to treatment in a patient population that is at risk for significant treatment delays and high mortality.

Hypothesis

We hypothesize that in patients with BBB or paced rhythms, and symptoms consistent with acute coronary syndrome, prehospital measurement of troponin will significantly reduce delays to treatment, measured in door to balloon time for percutaneous coronary intervention, compared to a similar population receiving no prehospital troponin measurement.

References:

1. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third Universal Definition of Myocardial Infarction. *Circulation.* October 16, 2012 2012;126(16):2020-2035.
2. Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation.* May 15 2007;115(19):2549-2569.
3. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics—2015 Update: A Report From the American Heart Association. *Circulation.* January 27, 2015 2015;131(4):e29-e322.
4. Health CAfDaTi. CADTH Optimal Use Reports. *High-Sensitivity Cardiac Troponin for the Rapid Diagnosis of Acute Coronary Syndrome in the Emergency Department: A Clinical and Cost-Effectiveness Evaluation*. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health Copyright (c) 2013 Canadian Agency for Drugs and Technologies in Health.; 2013.
5. Nikus K, Pahlm O, Wagner G, et al. Electrocardiographic classification of acute coronary syndromes: a review by a committee of the International Society for Holter and Non-Invasive Electrocardiology. *Journal of electrocardiology.* Mar-Apr 2010;43(2):91-103.
6. Jacobs AK, Antman EM, Faxon DP, Gregory T, Solis P. Development of Systems of Care for ST-Elevation Myocardial Infarction Patients: Executive Summary. *Circulation.* July 10, 2007 2007;116(2):217-230.
7. Boden WE, Eagle K, Granger CB. Reperfusion strategies in acute ST-segment elevation myocardial infarction: a comprehensive review of contemporary management options. *Journal of the American College of Cardiology.* Sep 4 2007;50(10):917-929.
8. Nam J, Caners K, Bowen JM, Welsford M, O'Reilly D. Systematic review and meta-analysis of the benefits of out-of-hospital 12-lead ECG and advance notification in ST-segment elevation myocardial infarction patients. *Annals of emergency medicine.* Aug 2014;64(2):176-186, 186.e171-179.
9. Terkelsen CJ, Sorensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *Jama.* Aug 18 2010;304(7):763-771.
10. Kilic H, Atalar E, Ozer N, et al. Early electrocardiographic diagnosis of acute coronary ischemia on the paced electrocardiogram. *International journal of cardiology.* Oct 30 2008;130(1):14-18.
11. Mahajan VS, Jarolim P. How to interpret elevated cardiac troponin levels. *Circulation.* Nov 22 2011;124(21):2350-2354.
12. Gravning J, Smedsrud MK, Omland T, et al. Sensitive troponin assays and N-terminal pro-B-type natriuretic peptide in acute coronary syndrome: prediction of significant coronary lesions and long-term prognosis. *American heart journal.* May 2013;165(5):716-724.

13. Loten C, Attia J, Hullick C, Marley J, McElduff P. Validation of a point of care troponin assay in real life Emergency Department conditions. *Emergency medicine Australasia : EMA.* Aug 2009;21(4):286-292.
14. Sorensen JT, Terkelsen CJ, Steengaard C, et al. Prehospital troponin T testing in the diagnosis and triage of patients with suspected acute myocardial infarction. *The American journal of cardiology.* May 15 2011;107(10):1436-1440.
15. Stengaard C, Sorensen JT, Ladefoged SA, et al. Quantitative point-of-care troponin T measurement for diagnosis and prognosis in patients with a suspected acute myocardial infarction. *The American journal of cardiology.* Nov 1 2013;112(9):1361-1366.
16. Neeland IJ, Kontos MC, de Lemos JA. Evolving considerations in the management of patients with left bundle branch block and suspected myocardial infarction. *Journal of the American College of Cardiology.* Jul 10 2012;60(2):96-105.
17. Shlipak MG, Lyons WL, Go AS, Chou TM, Evans GT, Browner WS. Should the electrocardiogram be used to guide therapy for patients with left bundle-branch block and suspected myocardial infarction? *Jama.* Feb 24 1999;281(8):714-719.
18. Go AS, Barron HV, Rundle AC, Ornato JP, Avins AL. Bundle-branch block and in-hospital mortality in acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *Annals of internal medicine.* Nov 1 1998;129(9):690-697.
19. Sorensen JT, Stengaard C, Sorensen CA, et al. Diagnosis and outcome in a prehospital cohort of patients with bundle branch block and suspected acute myocardial infarction. *European heart journal. Acute cardiovascular care.* Jun 2013;2(2):176-181.
20. Shlipak MG, Go AS, Frederick PD, Malmgren J, Barron HV, Canto JG. Treatment and outcomes of left bundle-branch block patients with myocardial infarction who present without chest pain. National Registry of Myocardial Infarction 2 Investigators. *Journal of the American College of Cardiology.* Sep 2000;36(3):706-712.
21. Zhan C, Baine WB, Sedrakyan A, Steiner C. Cardiac device implantation in the United States from 1997 through 2004: a population-based analysis. *Journal of general internal medicine.* Jan 2008;23 Suppl 1:13-19.
22. Rosner MH, Brady WJ. The electrocardiographic diagnosis of acute myocardial infarction in patients with ventricular paced rhythms. *The American journal of emergency medicine.* Mar 1999;17(2):182-185.
23. Madias JE. The nonspecificity of ST-segment elevation > or =5.0 mm in V1-V3 in the diagnosis of acute myocardial infarction in the presence of ventricular paced rhythm. *Journal of electrocardiology.* Apr 2004;37(2):135-139.
24. Karumbaiah K, Omar B. ST-elevation myocardial infarction in the presence of biventricular paced rhythm. *The Journal of emergency medicine.* Aug 2013;45(2):e35-40.
25. Rathore SS, Weinfurt KP, Gersh BJ, Oetgen WJ, Schulman KA, Solomon AJ. Treatment of patients with myocardial infarction who present with a paced rhythm. *Annals of internal medicine.* Apr 17 2001;134(8):644-651.

Chapter 2: Review of the Literature

Introduction

A thorough literature review was conducted between July 2014 and August 2015. Relevant articles were accessed via Ovid MEDLINE and PubMed NCBI databases. Key search phrases included: prehospital troponin, troponin, cardiac biomarkers, point of care device, STEMI activation, STEMI, acute coronary syndrome, myocardial infarction, AHA guidelines, left bundle branch block (LBBB), bundle branch block, paced rhythm, electrocardiogram, electrocardiographic diagnosis of myocardial infarction, paramedic interpretation, paramedic skill, ventricular conduction delay, clinical outcomes, prehospital research, door to balloon time, treatment delay, and system delay. Preference was given to recent articles less than 10 years from publication date, however, older articles were included if they were considered essential to the scientific discourse. A textbook regarding prehospital research was also included.

Left Bundle Branch Block and Myocardial Infarction

The Electrocardiogram in Myocardial Infarction with Bundle Branch Block

The rapid diagnosis of myocardial infarction (MI) in the presence of left bundle branch block (LBBB) has been studied for over 60 years, due to the unique clinical challenge it presents.[1] A large retrospective study conducted in 1999 by Sgarbossa and colleagues, evaluated the electrocardiogram (ECG) in the diagnosis of MI.[2] The study was based on existing ECGs of patients with confirmed MI and BBB, compared to controls of patients with LBBB and no acute MI. The authors created several diagnostic criteria for diagnosing MI in the context of LBBB. These criteria involve ST segment changes including ST segment depression, ST segment elevation >1mm in precordial

leads, and ST segment elevation >5mm discordant with the QRS complex.[2] The individual criteria have low sensitivity and specificity when used alone, but when used as part of the index score proposed in the study, the sensitivity and specificity improved. The sensitivity and specificity were reported as 78% and 90%, respectively, in a derivation sample. However, the sensitivity dropped to 36% in a validation sample.[2]

The criteria proposed by Sgarbossa et al. provide an index scale for diagnosing MI on ECG in the presence of LBBB. However, a sensitivity of only 36% in the validation sample means that by these criteria alone, many patients with BBB and MI will not be identified by the criteria. The false negative rate of these criteria may be unacceptable in many settings. Also, in this study, all ECGs were interpreted by cardiologists. The authors acknowledge that the proposed interpretation may be more difficult by generalists, paramedics, or emergency physicians.[2] This has large implications in a real-world setting, where the rapid availability of a cardiologist is not always commonplace.

The index score outlined by Sgarbossa et al. has been evaluated by multiple studies since, and is referred to as the Sgarbossa criteria. A 1999 retrospective study evaluated the use of the Sgarbossa criteria and several other ECG findings in 103 presentations of acute cardiopulmonary symptoms, 83 of which were in patients with LBBB.[3] 30% of the patients evaluated met criteria for MI.[3] The authors found that using the Sgarbossa criteria, less than 10% of MIs would have been identified in the cohort, and the sensitivity of the algorithm was found to be 10% in this study.[3] Again, this study shows that the use of characteristic ECG findings of MI in LBBB patients is difficult, and the sensitivities of specific criteria or algorithms are low. This study is limited by small

sample size, only evaluating about 100 patients and 30 MIs. Furthermore, the ECGs were all read by a single physician, which may limit the external validity of the study.

A similar 2001 study included 182 patients with LBBB on initial presentation, and receiving workup for MI, 24 of whom were eventually diagnosed with MI.[4] This study revealed that the index score had a sensitivity of 46% and a specificity of 93%.[4] The study divided patients into high, moderate, and low risk groups based on initial presentation. Of note, only 29% of the patients who were diagnosed with MI were initially placed in the high risk group.[4] This suggests that determining risk in LBBB patients is difficult, further suggesting the need for quality diagnostic tests. The reported ECG sensitivity is higher than in previous studies, however, this was again a small study and external validity is questionable.

A prospective study in 2001 was carried out to establish the diagnostic accuracy of previously proposed ECG criteria.[5] This study included 148 patients with LBBB and suspected acute MI, and of these patients 48% had confirmed MI.[5] Interestingly, this study aimed to measure the ECG criteria against clinical judgment of providers. Clinical judgment was defined by decision-making, most notably the initiation of reperfusion by thrombolysis. The criteria used in this study, based on the work by Sgarbossa et al., had a sensitivity of 17.1% and specificity of 94%.[5] This was compared to clinical judgment, which had a sensitivity of 15.8% and specificity of 96%, which was noted by the authors to be not significantly different from the ECG criteria.[5] The sensitivities and specificities reported in this study are certainly lower than those reported in previous studies.[5] The authors explain that this may be due to a lower pretest probability in their study, versus a pre-test probability of almost 90% in prior, retrospective studies.[5] This reveals that

studies based on the ECG criteria performed in a retrospective manner are prone to selection bias. The lower pretest probability in this prospective study is likely more indicative of the ECG criteria performance in a real-world setting. All ECGs in the study were read by three separate clinicians experienced in ECG interpretation. The criteria were found to be unsatisfactory for a diagnostic test.[5]

A meta-analysis performed in 2008 evaluated studies evaluated methods including the Sgarbossa criteria in the diagnosis of MI in LBBB patients.[6] This meta-analysis included all of the above-described studies by Sgarbossa et al., Gunnarson et al., Shilpak et al., and Kontos et al. It also included several other studies that included at least one point of the Sgarbossa index score. The meta-analysis included 2,100 patients total and found that when a Sgarbossa index score of 3 was met, there was a summary sensitivity of 20% (95% CI 18% to 23%), and specificity of 98% (95% CI 97% to 99%).[6] Due to the high positive likelihood ratio of 7.9, the authors conclude that an index score of 3 is useful in diagnosing MI.[6] It is suggested that when a score of 3 or greater is met, in the right clinical setting, treatment for MI should be initiated.[6] Furthermore, the study found great intraobserver agreement between studies, suggesting that the criteria can be used uniformly.

Although the meta-analysis includes the strongest amount of evidence compiled, there remain some limitations. Sensitivies and specifities for the Sgarbossa criteria declined significantly when less than 3 criteria were met. When a score of 2 or less occurred, sensitivities ranged from 20% to 79% and specificities ranged from 61% to 100%.[6] Therefore, MI cannot always be ruled out using the criteria. Patients with a lower index score require more diagnostic testing, which can certainly delay treatment. The

authors report that a score of 2 or less does not have sufficient diagnostic accuracy.[6] Furthermore, in the included studies, ECGs were interpreted by experienced cardiologists and ED providers, all of whom were prepared to apply the criteria in the study.[6] Though the intraobserver agreement may be great in controlled settings within studies, it may not be as applicable in settings where providers are less likely to use the criteria on a regular basis. No study included in the meta-analysis evaluated the criteria in a prehospital setting.

A 2012 study looked to increase the accuracy of the Sgarbossa criteria, with the modification of one criterion.[7] In lieu of looking at ST segment elevation discordant with the QRS complex of >5 mm, the study used a proportional measure comparing the ratio of S segment with ST elevation.[7] The study included 162 patients, 129 of whom were in a control group, and used angiographic endpoints as the criterion standard to evaluate the presence of MI.[7] The authors found that the modified rule significantly increased the diagnostic accuracy of the ECG in LBBB patients. The sensitivity using the modified criteria was improved to 91% from 52% using the previous criteria, however, the specificity declined to 90% from 98%.[7] This indicates that the modified rule may improve ECG criteria to a more realistic and useful diagnostic tool. However, the authors reveal limitations to the study that limit the use of the more sensitive criterion. First, the study was small and underpowered to detect small differences in sensitivity.[7] Furthermore, the measurement of ratios on ECGs is difficult and not routine for most providers. These methods may not be feasible in a fast-paced emergency department or prehospital setting. The authors suggest that the proposed modified rule would need to be

validated in a larger prospective study.[7] Even with more specific ECG findings of MI in LBBB patients, electrocardiographic diagnosis remains challenging and time-consuming.

Outcomes and Complications in MI and Left Bundle Branch Block

A 1998 retrospective study examined the prevalence and outcomes of patients with MI and BBB.[8] The study was conducted using the National Registry of Myocardial Infarction 2 which includes over 200,000 patients. The study found that in the database, RBBB was found in 6.2% (95% CI 6.1-6.3%) of patients, and LBBB was found in 6.7% (95% CI 6.6-6.8%) of patients presenting with MI.[8] Surprisingly, BBB of any location was found in 1 out of every 8 patients presenting with myocardial infarction. Patients with BBB and MI were much less likely to receive reperfusion therapy. Patients with no BBB were 1.7 fold more likely to receive reperfusion therapy over patients with RBBB ($p < 0.001$), and 4.2 fold more likely to receive therapy over LBBB patients ($p < 0.001$).[8] BBB patients were also significantly less likely to receive other medical therapies such as aspirin, beta blockers, heparin, and IV nitroglycerin ($p < 0.001$ for all associations).[8] Furthermore, patients with LBBB were found to have significant delays to thrombolytic therapy.[8] The authors suggest that physicians may not understand the benefit of reperfusion of BBB patients, and may have difficulty in establishing the diagnosis of MI in these patients. Perhaps the most important finding of the study is related to the in-hospital mortality of BBB patients. The in-hospital mortality rates of RBBB and LBBB was not significantly different ($p = 0.2$). However, the in hospital mortality rate of BBB (RBBB 23%, LBBB 22.6%) patients was almost 2 fold higher than patients with no BBB (13.1%) ($p < 0.001$).[8]

This study by Go et al. demonstrates the increased risk associated with the diagnoses of RBBB of LBBB. Both were associated with increased risk of in-hospital mortality, and decreased rates of treatment. This is a strong study including over 200,000 patients, representing a diverse population from 1571 US hospitals.[8] The study does, however, have some limitations. Notably, the study was not able to determine how many patients presented with new BBB over pre-existing BBB. New BBB can be seen in acute MI, but other studies have suggested that it is more often a result of underlying structural disease.[1] The authors suggest that this limitation is perhaps generalizable, as many patients presenting for care will have BBB of unknown timing.[8] High mortality in the BBB patients may be due to the fact that they are more likely to have predisposing risk factors such as prior MI, congestive heart failure, coronary artery disease, stroke, diabetes mellitus, and hypertension.[8] However, the lower rates of treatment for treatment-appropriate patients seen in this study, as well as the significant delays for those who received treatment, could certainly play a role in the higher morbidity and mortality seen.

A 2000 study again used the National Registry of Myocardial Infarction 2 to understand rates of treatment, specifically in LBBB patients.[9] The study found that patients with LBBB and MI had a low rate of treatment, at 8.4%.[9] The rate of treatment for LBBB patients who presented with chest pain was 4 fold higher than those who presented without chest pain; however, treatment rates remained low at 13.6%.[9] This suggests that clinical impression is important for physicians in choosing treatment. However, the most common reason that providers did not choose reperfusion therapy was due to undiagnostic ECG, which was the reasoning for avoiding therapy in 57% of those who did not receive treatment.[9] Similar to Go et al., the authors found that patients were

less likely to receive reperfusion therapy, or other therapies standard to the treatment of MI, within 24 hours of presentation.[9] The study also found that patients who were admitted to the hospital with an initial diagnosis of MI were more likely to receive reperfusion therapy and had less delay to treatment.[9] This suggests that early diagnosis is associated with higher treatment rates and less delay. However, the authors explain that patients could not be interviewed, so the presence or absence of chest pain on a chart may have been entered in error.[9] Also, new versus old LBBB could not be determined in this study. The study does build to the evidence, establishing further that patient presentation complicates diagnosis and treatment. Notably, undiagnostic ECG was found to be the most common reason for non-treatment of MI.

A 2011 prospective study was completed to examine the relationship between LBBB and outcomes in patients with possible acute MI.[10] The study involved 401 patients with LBBB, admitted for the rule out of acute MI. Due to the high availability of prior ECGs seen in this study, the authors were able to estimate new or presumed new LBBB versus old LBBB. The proportion of new LBBB was 36%, presumed new 28%, and old 36%.[10] Neither the frequency of MI, nor the size of MI, was different among new, presumed new or old LBBB.[10] MI was diagnosed in 116 patients total, 93 of whom had elevations in troponin and CK-MB.[10] As part of the rule-out protocol, all patients were subject to measurement of cardiac biomarkers as well as use of a routine ECG. Of the patients diagnosed with MI, only 12 had concordant ST changes on ECG.[10] ST changes used in this study were those outlined by the Sgarbossa criteria. The study had high treatment rates: 152 patients underwent angiography, 43 had significant disease, and 16 had revascularization.[10]

Kontos et al conclude that MI among LBBB patients is rare, and the size of the MI is relatively small.[10] However, the authors did not compare LBBB patients to controls without LBBB in this study. ST changes were rare in this study, but were associated with a high likelihood of MI and larger disease.[10] The authors conclude that the ECG can be a good indicator of patients most likely to benefit from reperfusion therapy. This conclusion is interesting, given that significant disease was present on angiography in 43 patients with positive troponin, while only 12 were found to have ST changes in the entire study. What is clear, is that a universal activation of the catheterization laboratory ("cath lab") for all patients presenting with LBBB and acute coronary syndrome symptoms would not be cost-effective or beneficial. This study is helpful due to the prospective nature, as well as the ability to determine new versus old MI. However, LBBB patients were not compared to controls, and treatment rates were high in the study, which is not consistent with large registry trials.

LBBB and MI Conclusions

The above reviewed articles suggest that there remains a challenge of diagnosis of MI in the context of LBBB. LBBB on ECG remains a frequent reason for treatment delays or false activation of the catheterization laboratory.[1] The need for rapid diagnosis in MI puts pressure on providers to move patients to treatments quickly, but false activations are costly.[11] Criteria have been proposed to aid the diagnosis of MI in the context of LBBB, but sensitivity for MI has remained low.[2-6] The diagnosis of MI in the context of RBBB is generally more feasible for providers.[12] Measurement of S and ST segment ratios yields higher sensitivity, however this skill is not routinely used in ED providers.[7] Therefore, reliance on ECG alone in the diagnosis of MI would result in many

missed cases. Patients with LBBB and MI are underserved; they have lower overall rates of treatment, and higher mortality.[8,9] A frequent reason for non-treatment in BBB patients in the presence of an undiagnostic ECG.[3] Diagnosis and treatment in this population remains challenging, and the use of further diagnostic testing, such as the measurement of cardiac biomarkers may be necessary.[13]

Artificially Paced Rhythm and Myocardial Infarction

The Electrocardiogram and Artificially Paced Rhythm in Myocardial Infarction

Early electrocardiographic diagnosis of myocardial infarction in the setting of an artificial pacemaker is difficult. Similarly to the electrocardiographic morphology LBBB, the QRS complex is often widened with a paced rhythm, potentially masking characteristic changes associated with ischemia.[14] A study in 2008 examined the paced electrocardiogram in the setting of ischemia.[15] The small study of 15 patients with temporary pacing compared baseline ECGs to those acquired intraoperatively during percutaneous coronary intervention (PCI). The authors inflated a balloon in a coronary artery for one minute, blocking blood flow and mimicking the pathophysiology of a myocardial infarction.[15] Temporary pacing alone, without inflation of the balloon, created ST changes in 3 out of the 15 patients in the study.[15] The study found significant ST segment deviations during induced ischemia, when compared to pre-PCI ECGs.[15] This study shows that ST segment changes can be seen in the paced rhythm, either as a result of ischemia or as a secondary change due to pacing alone. However, the real-world application of this study may be limited. The study used temporary pacing, which may not be indicative of potential changes during permanent pacing. Another limitation is that ischemia was only induced for one minute with balloon inflation.[15] One minute of

ischemia is not typical of patient presentation in MI. This study only examined ECG changes seen in very early ischemia, and cannot necessarily characterize ECG patterns in patients experiencing prolonged ischemia.

A 1996 study by Sgarbossa et al. used the GUSTO-1 database to examine patients with paced rhythm. They found that of the 41,021 patients in the database, only 32 (0.1%) had ventricular paced rhythms and enzymatically confirmed MI.[16] The ECGs of these patients were compared to those of randomly selected patients with confirmed stable coronary artery disease and ventricular pacing. The authors found that the ECG finding most predictive of acute MI in paced patients was ST segment elevation >5 mm in leads with predominantly negative QRS complexes. This finding had a sensitivity of 53% and specificity of 88% (positive likelihood ratio 4.41, $p = 0.025$, relative risk 2.35, 95% confidence interval 1.26 to 4.39).[16] The sensitivity and specificity are reasonable and the authors suggest that it is a useful diagnostic tool. However, the study involves a very small number of patients from a large database. The small incidence of pacing in this outdated database is likely not representative of the general population, as the placement of pacemakers has increased.[17] Furthermore, ECGs in this study were compared to controls, not previous ECGs. Varied placement of pacemaker leads results in different QRS morphology in each patient.[18] As a result, comparison of ECGs to controls is less accurate than comparison to baseline ECGs, which was not possible in this study.

A 2004 case report discussed the potential downfall of relying on the above-discussed ST segment changes in the setting of paced rhythms. The case report discusses two cases of patients with pacemakers, both shown to have ST segment elevation >5 mm in at least one lead.[19] However, these patients were not experiencing MI, and had ST

segment elevations at baseline.[19] The use of ST segment elevation alone in the diagnosis of MI in these patients could result in unnecessary treatment and cost. Identification of MI is difficult, as ECG changes induced by ischemia can be accentuated, cancelled, or even reversed by secondary changes due to pacing.[19] A 1999 case report examined two patients with pacemakers, who were found to have MI by examining serial ECGs.[14] In these cases, providers had access to previous ECGs, which proved helpful in the eventual diagnosis of MI. The authors explain that because the majority of paced rhythms originate in the right ventricle and do not travel through the normal conduction system, their morphology is similar to that of LBBB.[14] The authors conclude that the diagnosis of MI by ECG in paced rhythms is difficult, and relies on experienced providers.

The electrocardiographic diagnosis of MI can be further complicated in the setting of a paced rhythm due to the variability of pacemakers, intermittent pacing, or biventricular pacing.[18,20] A 2012 case report discussed the ECG in a biventricular paced individual presenting with MI.[20] ST changes were seen when compared to baseline ECG and an eventual diagnosis of MI was made.[20] However, the diagnosis was aided by high suspicion of MI due to cardiogenic shock, characteristic symptoms, and availability of a prior ECG. The authors note that criteria outlined by Sgarbossa et al. likely do not translate to patients with biventricular pacing.[20] The variability of pacing methods, as well as differing patient presentations, confounds the diagnosis of MI in many cases.

A 2010 study aimed to build on the 1996 data by Sgarbossa et al. The authors reviewed a total of 159 ECGs, 57 of which were paced rhythms with confirmed MI, and 101 of which were controls.[21] The most specific criterion was found to be ST segment elevation >5 mm discordant with the QRS complex. The authors found that for this

criterion, sensitivity was 10% (95% CI 5% to 21%), and specificity 99% (95% CI 93% to 99%).[21] The specificity of this finding is strong, making the test useful for a diagnosing MI, but it is not useful as a rule-out test due to the very low sensitivity.[21] This is consistent with prior studies on ECG and paced rhythm in MI, where some findings are highly suggestive of MI but are not seen in a large number of patients. The study adds to the literature due to its larger sample size. However, it remains a retrospective study which relies on accurate data entry, and the ECGs were read by experienced users. The application of specific ECG criteria in a real-world emergency department is more difficult than in a controlled retrospective study.

Outcomes and Complications in Paced Patients with Myocardial Infarction

A retrospective analysis of over 100,000 patients with confirmed MI found a prevalence of pacemakers in 1,954 patients (1.9%) presenting with MI.[22] The study was completed in 2001, with data pulled from patients presenting for care from 1994 to 1996. The study found that patients with paced rhythms were more likely to be older and male, and more likely to have a previous diagnosis of MI and cerebrovascular disease.[22] Paced patients were significantly less likely to receive aspirin at admission (relative risk (RR) 0.91, 99% CI 0.88 to 0.94), or beta-blockers at admission (RR 0.89 99% CI 0.82 to 0.96).[22] These patients were also significantly less likely to receive reperfusion therapy (RR 0.27, 99% CI, 0.22 to 0.33).[22] The authors examined these treatment rates in treatment-appropriate patients. It is clear that they are less likely to receive the standard of care when compared to patients presenting without paced rhythms.

The above study also evaluated hospital outcomes in the cohort of patients presenting with MI and paced rhythm. Paced patients were more likely to experience

death in the hospital, at 30 days, and at 1 year ($P \leq 0.002$ for all associations).[22] Paced patients were also more likely to experience congestive heart failure or reinfarction during initial hospital stay ($P < 0.001$ for both associations).[22] It is reasonable that patients who are generally sicker and older on presentation, as was seen in the paced patients, had higher rates of mortality and complications. However, increased risk for mortality was adjusted for illness severity and treatment, including admission and discharge medication. The risk of 30-day mortality remained significant when adjusted for illness severity (RR 1.10, 95% CI 1.00 to 1.20), but fell slightly below sigificance when adjusted for illness severity and all treatment (RR 1.03, 95% CI 0.93 to 1.14). Risk of long-term mortality remained significant when adjusted for illness severity and all treatment (RR 1.12, 95% CI 1.06 to 1.18).[22] The authors suggest that some differences in treatment are potentially due to the difficulty in rapid diagnosis of MI in the setting of a paced rhythm. The decreased mortality risks when adjusted for treatment indicate that mortality rates could be improved by better and more consistent treatment of individuals with paced rhythms and MI.[22]

The above study is important and helpful in quantifying the prevalence of paced rhythms in MI, as well as the treatment and outcomes of these patients. However, as a retrospective study, data accuracy is not within the control of the writers. Furthermore, the data presented in this study were from 1994 to 1996, and may not be representative of the current population, as the incidence of pacemakers has increased. The study was also not able to determine differences between ventricular and atrial pacing, and it could not be determined whether all patients were paced during acute MI.[22] However, large study numbers, and adjustment for illness severity and treatment, aids analysis.

Pacemaker and MI Conclusions

As in LBBB, the electrocardiographic findings of paced rhythm complicate the diagnosis of MI.[14,15,17] Incidence of MI in paced patients is difficult to quantify given an increasing amount of pacemaker placements.[17] Above reviewed studies indicate the incidence of paced rhythm in MI to be around 0.1% to 1.9%.[16,22] There are findings on ECG of a paced rhythm that are highly suggestive of MI, but are seen in a low number of patients.[16,21] This means that use of ECG only in the triage of paced patients, like in LBBB, would lead to missed MIs or delayed treatment. Furthermore, the application of specific ECG criteria is difficult for general physicians.[23] Patients with paced rhythms and MI have lower rates of standard treatments, are significantly less likely to receive reperfusion therapy, and have a higher risk of mortality.[22] Difficulty in the diagnosis of MI in these patients and reduced overall treatment indicates a need for diagnostic tests other than the ECG.

Prehospital Triage in Myocardial Infarction

The Prehospital ECG in STEMI

Prehospital diagnosis and triage of STEMI has advanced greatly due to the availability of the ECG in a larger number of settings. A study conducted between 2004 and 2007 examined the use of prehospital ECGs in STEMI patients presenting from both rural and urban environments.[24] The study involved 1049 patients, 875 of whom presented to the hospital via EMS transport.[24] In the prehospital cohort, ECGs were transmitted to receiving hospitals and read by physicians. Physicians and EMS had the option to re-route EMS transport directly to centers for PCI in patients with high suspicion of STEMI on ECG. The study evaluated a performance measure of EMS to

balloon time of <120 minutes. Eighty six percent of patients with prehospital diagnosis met the <120 minute guideline, compared to only 32% of patients without prehospital diagnosis ($p<0.001$).[24] Long term all-cause mortality was lower in patients with prehospital diagnosis compared to those without, 18% vs 31% (log-rank P = 0.003), an association that remained when the authors adjusted for patient characteristics (hazard ratio 0.68, 95% CI 0.48 - 0.96, P = 0.028).[24]

The above study is strong evidence to support the prehospital diagnosis of STEMI in reducing delays to treatment and mortality. In the course of the study, the proportion of patients who were diagnosed prehospitally increased, indicating a quick adoption of the new technology.[24] However, the impact of this changing treatment environment on the results of the study is difficult to determine. The authors also reveal that mortality data in the study is inherently limited due to a selection bias between groups.[24] The study presents strong evidence for the prehospital diagnosis of MI.

Multiple studies have examined the expansion of prehospital diagnosis of STEMI to include a direct activation of PCI laboratories by EMS, and a bypass of the emergency department. A 2011 prospective study included 195 patients transported by EMS who received PCI.[25] Ninety-five of these PCI patients were transported to the ED, and 80 were transported directly to the PCI center by bypassing the ED.[25] For the group triaged directly to the PCI center, door to balloon time was 35 minutes (95% CI 31 to 36), compared to 83 minutes (95% CI 79 to 89) in the group without ED bypass ($p<0.001$).[25] The proportion of patients meeting the 90 minute door to balloon guidelines increased from 28.4% to 91.3% through implementation of the direct referral to PCI.[25] The study included ECG training for paramedics participating in the study, and a maximum of 3

paramedic interpreted ECGs. Notably, the number of false activations for PCI activation in this study was 12, the majority of which were due to pre-existing ECG abnormalities.[25] This indicates that the activation is inappropriate for patients with pre-existing conditions which may mimic STEMI, such as BBB and paced rhythm. This is a small study that was conducted in a single geographic area with a group of highly trained paramedics. The reproducibility of these results may be limited in areas and systems with fewer resources. However, the study is further strong evidence of how prehospital diagnosis and triage can significantly improve in-hospital delays.

Another study published in 2013 evaluated STEMI patients presenting to a single emergency department by multiple means including EMS transport with PCI activation, EMS transport without PCI activation, and self-presentation to ED.[26] The study included 38 EMS activations of the PCI lab, 47 non-activation STEMIs, and 28 walk-in STEMIs.[26] The mean door to balloon times were 37 (±17) in the PCI activation group, 87 (±40) in the non-activation group, and 80 (±23) minutes for walk-ins.[26] Also, compliance with 90 minute door to balloon times were 100%, 72% and 68%, respectively. This study used the paramedic as the decision maker in activation of the cath lab. The authors did take measures to control for false positive activations. In this study protocol, patients with widened QRS complexes > 0.12 seconds were ineligible for prehospital cath lab activation. This protocol was to avoid false positive activation due to STEMI mimics such as BBB. Therefore, the benefits of paramedic-centered early activation of PCI seen in this study are not available to patients presenting with pre-existing ECG abnormalities. The study does however indicate the potential of a paramedic-centered system in the rapid diagnosis and triage of MI.

Several other studies have evaluated the use of paramedics as the main decision-makers in STEMI triage. A 2014 study retrospective study of 1933 cases compared prehospital cath lab activation versus cath lab activation within 5 minutes of first in-hospital ECG.[27] The study found prehospital activation associated with door to balloon times 14 minutes shorter (95% CI 11 to 17 minutes) than in-hospital activation.[27] The prehospital false activation rate was 33%.[27] Computerized ECG interpretation aided paramedics in diagnosis of STEMI, so evaluating paramedic skill in ECG interpretation is difficult. The high prehospital false activation rate in this study may deter systems from adopting similar methods due to cost. STEMI mimics such as BBB or paced rhythms may be excluded from activation criteria, again demonstrating limited access to early diagnosis of MI in patients with pre-existing ECG abnormalities. A 2011 study evaluating prehospital triage showed false activation rates of 25% even when paramedics received additional training focusing on STEMI identification and differentiation of STEMI mimics.[28] The authors cite paramedic ability to distinguish presence or absence of ST elevation in ECG with LBBB as a specific concern.[28]

To review prehospital ECG in the treatment of STEMI, a meta analysis was conducted in 2014.[29] The review included data from 16 studies, comprising about 14,000 patients. The analysis included studies from differing geographic locations, and EMS protocols. Notably, the studies comprised multiple methods of advanced notification of STEMI.[29] The authors found that prehospital 12-lead ECG and advanced notification was associated with a 39% relative risk reduction in short-term mortality when compared to standard or no prehospital cardiac monitoring (risk ratio 0.61, 95% CI 0.42 to 0.89; P=.01).[29] For this outcome measure, low heterogeneity was observed between studies.

The 39% relative risk reduction in short term mortality is strong evidence for the use of early diagnosis and advanced notification of STEMI by EMS personnel. 12-lead ECG and advanced notification was associated with a mean 38.66 minute reduction in door to balloon time (95% CI -50.75 to -26.57, P<0.000001).[29] Door to balloon times were heterogeneous between studies, but significant reductions were seen in all but one study. This analysis presents a large pool of significant data supporting the use of prehospital notification in reducing delays to treatment. Methods varied between individual studies, which potentially threaten the internal validity of the analysis. However, study variability may aid the external validity of the analysis, due to a variety of EMS and hospital protocols that currently exist.

Limitations of the Prehospital ECG

As discussed above, the benefit of the prehospital ECG and advanced notification to hospitals is well established. However, prehospital diagnosis and triage is difficult, and challenges remain. Multiple studies have assessed paramedic ability to identify true ST segment elevation on 12-lead ECG. A 2008 study assessed the ability of paramedic students to distinguish ST elevation on isolated leads.[30] The survey included four isolated ECG tracings, three of which showed ST segment elevation. Only 10% of students correctly interpreted all four tracings, and recognition of ST elevation varied from 38-80% in the different tracings.[30] These reported accuracies are not ideal and could lead to poor performance of prehospital ECG and advanced notification. However, this study was conducted on students only, and did not allow for paramedic interpretation of a 12-lead ECG.

Paramedic assessment of STEMI becomes more complicated when confounding factors such as STEMI mimics are present on the ECG. A 2002 study showed that the paramedic true positive rate for STEMI was 60% when no confounding factors were present, and dropped to 36% when confounders were present.[31] ECG confounders were defined as prior acute MI, poor ECG quality, BBB, fascicular block, left ventricular hypertrophy, and paced rhythm. The study found that cardiologists were significantly more likely to be accurate when confounders were present.[31] A 2013 study evaluated ST segment elevation recognition in almost 500 practicing paramedics.[32] Paramedics were asked to evaluate 10 12-lead ECGs, which included STEMI, normal ECGs, and STEMI mimics such as LBBB and paced rhythms. Overall STEMI detection sensitivity was 75% (95% CI 73% to 77%) and specificity was 53% (95% CI 51% to 54%).[32] Much of the inaccuracy in this study was due to misinterpretation of STEMI mimics as STEMIs. Furthermore, the paramedics included reported recent ECG training and generally high confidence in interpreting ECGs.[32] The authors suggest that the results of this study show the potential for many STEMIs missed in the field, as well as many false activations of the cath lab.[32] This study did not assess paramedic ability to recognize MI superimposed on pre-existing ECG abnormalities such as LBBB or paced rhythms.

Prehospital ECG and Triage Conclusions

It is clear that the development of prehospital systems including implementation of 12-lead ECG, advanced notification of STEMI, and activation of PCI are associated with reduced delays to treatment.[25-29] System delay in the treatment of MI can be considered a modifiable risk factor.[33] Longer door to balloon times are associated with increased risk of mortality.[34] A meta-analysis showed that the prehospital 12-lead ECG is

also associated with a significant reduction in risk of short-term mortality.[29] However, paramedic recognition of ST elevation on ECG is difficult, and sensitivities are relatively low.[30-32] Furthermore, paramedics are less accurate in diagnosing STEMI when confounding factors are present, such as LBBB or paced rhythm.[31] Many systems currently exclude BBB and paced rhythms from PCI activation protocols, due to the difficulty in interpreting the ST segment. Therefore, paced patients and LBBB patients do not benefit from the early activation and improved treatment noted in STEMI patients.

Cardiac Biomarkers in the Diagnosis of MI

In-Hospital Troponin Assays

The ability to measure levels of sensitive cardiac biomarkers has certainly improved the diagnosis of MI. The enzyme CK-MB has been used for years, however troponin has overtaken its use, with even the earliest generations of troponin assays having a higher sensitivity than CK-MB.[35] However, multiple troponin assays exist, mainly troponin I (TnI) and troponin T (TnT). A large meta-analysis conducted in 2013 evaluated the diagnostic accuracy of multiple cardiac biomarkers.[36] The analysis used 21 studies regarding TnI to estimate the pooled sensitivity for MI as 77% (95% predictive interval 29% to 96%) and the sensitivity as 93% (95% predictive interval 46% to 100%).[36] The authors also evaluated TnT using 11 studies, reporting sensitivity for MI as 80% (95% predictive interval 33% to 97%) and specificity as 91% (95% predictive interval 53% to 99%).[36] These values show troponin to be a valuable diagnostic tool. Measurement of CK-MB, troponin I, or troponin T is currently a Class I recommendation for all patients presenting with signs and symptoms suggestive of MI.[37]

The development of sensitive troponin assays has allowed for earlier detection of more modest elevations in troponin.[38] In most cases, a positive troponin is defined as a qualitative value above the 99th percentile of a reference adult population.[38] The measurement of troponin is useful in populations with a high pre-test probability of MI.[38] An isolated measurement of troponin is not often used as the sole marker of MI. Troponin values are combined with signs, symptoms, and other diagnostic measurements such as the ECG. Furthermore, troponin is most often repeated, as rise or fall in troponin is highly suggestive of an evolving cardiac event.[38] Troponin can be elevated in other disease processes such as chronic kidney disease or congestive heart failure, however troponin rises more rapidly in acute MI than in these other conditions.[38]

Point-of-care Troponin Assays

Measurement of sensitive cardiac biomarkers is helpful in the diagnosis of MI. However, a reliance on hospital central laboratories to measure troponin can lead to significant delays to treatments in patients, usually taking about one hour to run.[39] Acute MI can evolve rapidly, and an effort has been made to measure troponin more quickly without sending blood samples to a central laboratory.[40] Point-of-care (POC) devices are now used in many emergency departments to speed diagnosis and triage. A 2009 retrospective study examined the care of patients in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) database to determine usage patterns of POC troponin measurement.[40] The authors found that hospitals using POC had significantly shorter ED stays ($p<0.0001$).[40] This may be due to reduced delays to admission or discharge as a result of quicker troponin results. Patients with positive POC troponins

were also more likely to receive standard treatment such as aspirin, beta-blockers, and heparin ($p<0.0001$ for all associations).[40] The study did not directly measure door to balloon time or specific treatment time measurements. Patients with positive troponin in this study were less likely to receive PCI than those with negative troponin ($p<0.0001$).[40] However, the CRUSADE database involves patients with NSTEMI and UA, for whom the care is less time-sensitive. The data from this study are likely not generalizable to STEMI or STEMI-equivalent patients. Another study in ACS patients without ST segment elevation showed that POC troponin was associated with a decreased time to anti-ischemic therapies of about 45 minutes ($p<0.001$).[41]

A potential danger of using point-of-care devices in the diagnosis of MI is the potential for inaccuracy. The performance of POC devices has been the focus of multiple studies. A 2013 retrospective trial assessed the accuracy of four POC devices versus central laboratory results.[42] The authors found that devices differed significantly with respect to sensitivity and specificity in the diagnosis of MI.[42] POC assays were less accurate than central laboratory results, but sensitivities improved with multiple spaced measurements and all four POC devices had strong negative predictive values.[42] This study is an important look at POC device accuracy. However, the study used banked heparinized plasma rather than whole blood, which does not represent typical use in the ED. A 2013 study looked to improve sensitivity of POC devices by reducing the cutoff of positive results to 50% of the 99th percentile value.[43] The authors found that reducing the cutoff did significantly improve sensitivity of the assays, but it also contributed to a significantly higher rate of false positives ($p<0.0001$).[43] While the improvement in sensitivity contributes to fewer missed MIs, a higher rate of false positives can add

significant cost and treatment-associated morbidity. This study did not assess the accuracy of POC devices at multiple time points, and rather used single draws.

A 2009 prospective study evaluated the use of POC troponin assays in an emergency department.[39] Loten et al. examined data from 474 uses of an Abbott i-Stat POC device, by both trained and untrained operators. The authors found that occasional users of the i-Stat can obtain accuracy similar to trained users (Spearman correlation 0.82).[39] The accuracy of the i-Stat when compared to central laboratory was not ideal, but acceptable with Spearman values of 0.76 to 0.83.[39] With a positive troponin cutoff set at 0.01 ng/dL, the specificity of the device was compared to central laboratory was 91%.[39] Subject numbers in this study were relatively small, but the study is useful in that it can be considered a more accurate representation of a real emergency department. It is clear that the i-Stat is not as accurate as central laboratory, but this study revealed reasonable correlation and acceptable accuracy among a variety of experienced and inexperienced users.

Use of POC Troponin Assays in the Prehospital Setting

Due to the rapid and portable nature of POC devices, their use has been studied on ambulances. The use of troponin measurement in the prehospital phase of care has the potential to speed triage and allow for quicker treatment for patients with MI.[44] POC devices were not designed with the intent to be used in moving ambulances, therefore their use in this setting requires validation. A 2013 study aimed to examine correlation between POC troponin measurement in a moving ambulance and POC values obtained in an emergency department.[44] The researchers simultaneously ran 42 sets of whole blood samples in two separate settings: in a moving ambulance and in an ED. There was no

significant difference between the two groups (intraclass correlation coefficient 0.997; 95% confidence interval 0.994 to 0.998; $p < 0.005$).[44] This study did not assess the clinical application of prehospital troponin assays, but is strong evidence to support high correlation with in-hospital POC assays.

A study conducted from 2008-2009 included prehospital troponin assays on almost 1000 patients presenting to an emergency department in Denmark.[45] The POC troponin assays were completed by 11 paramedics trained on the device and rotated between 70 ambulances. Results of the qualitative prehospital assay were reported to an on-call cardiologist. Nine hundred and fifty eight patients received prehospital troponin measurements, and of these patients 208 were eventually diagnosed with MI.[45] Of the patients eventually diagnosed with MI, positive prehospital troponin was reported in 32% of STEMIs, 30% of NSTEMIs, and 26% of BBB MIs.[45] These results are much less accurate than in-hospital measurements within the same group which identified 73% of STEMIs, 82% of NSTEMIs, and 83% of BBB MIs.[45] The most likely factor relating to the low sensitivity of the prehospital measurement is that a cutoff of 0.1 ng/dL was used. Sensitivities have been shown to improve with much lower cutoffs such as 0.01 ng/dL.[39] Furthermore, a large number of patients in this study had less than 6 hours of symptoms prior to the prehospital draw. Notably, nine patients in the study were referred directly for PCI based on positive prehospital troponin due to equivocal ECG or BBB on ECG.[45] The authors explain that the benefit of the test is most important in this population. This study is an important demonstration of the feasibility of implementing POC devices prehospitally.

A 2011 study evaluated the use of prehospital troponin measurement in a group of suspected ACS patients.[46] Paramedics were trained to complete the test, and were instructed to do so on all willing patients receiving prehospital ECGs for suspected ACS. Overall, 985 patients received prehospital troponin measurements in one year.[46] The results of the measurement were not used in triage or patient managment decisions. The prehospital troponin had a sensitivity of 39% (95% CI, 32% to 46%).[46] However, again the sensitivity of the assays may have been improved by lower detection cutoffs, as this cutoff in this study was set at 50 ng/L. The study did find that positive prehospital troponin was associated with higher mortality.[46] The authors conclude that the low sensitivity observed in this study does not justify the use of prehospital troponin as a tool for triage, but that the measure should be further studied in high risk patients.[46] The study does again demonstrate that the use of POC devices in the prehospital setting is feasible.

Troponin and MI Conclusions

The use of troponin assays in the diagnosis of MI is commonplace, and its use as a diagnostic tool is well supported.[36] Serial measurement of troponin can reveal trends that are diagnostic of cardiac events.[38] Point-of-care devices that measure troponin have been implemented in many emergency departments to aid in the diagnosis of MI. Accuracy of POC devices varies among manufacturers.[42] However, sensitivity of the devices increases when cutoffs for positive results are decreased.[43] Because this is associated with a higher rate of false positives, troponin results should be considered in clinical context. The use of POC troponin devices has been studied in the prehospital setting, where their use has been shown to be feasible.[44-46] Sensitivities of prehospital troponin have been low in these studies, but could be improved with lower troponin

cutoffs. The benefit for prehospital troponin is likely strongest in patients with MI and non-diagnostic ECG.[46]

Review of Additional Relevant Methodology

PCI Superiority

In the treatment of acute MI, primary PCI is generally superior to fibrinolysis.[47] An American Heart Association executive summary contains a Class 1 recommendation for the use of PCI in STEMI patients.[37] Primary PCI has also been shown to be superior to thrombolysis in a study of patients with paced rhythm.[48]

Considerations in Prehospital Research

Prehospital research entails a unique set of challenges, but the potential to investigate complex, system-based questions.[49] However, research in the prehospital setting occurs in an inherently less controlled environment than in-hospital research.[49] Due to these challenges, prehospital research is often less understood or accepted by the research community. However, research is very important to the field of emergency medicine. High-quality prehospital research requires a clear and simple question to be answered, and an appropriate study design.[49] A majority of prehospital research has focused on the treatment of cardiac arrest and trauma, but the potential exists for studying many other aspects of care; notably in systems-based research.[50]

Prehospital Randomization

Randomization of patients into control and intervention groups is difficult in the prehospital setting, but there are multiple methods available to researchers.[51] Studies have used computerized randomization, dispatch-controlled randomization, or pseudorandom techniques such as using even or odd days for group assignment.[51] A study of automated

versus manual chest compressions in cardiac arrest used a method of cluster randomization.[51,52] In this study, randomization was achieved through the allocation of the automated chest compression device to certain ambulances. It is possible to achieve randomization through this technique, though there is potential for bias in the selection of certain ambulances.[51] In the above study, the researchers used a cross-over design to reduce bias.[52]

Prehospital Consent

Obtaining consent for inclusion in a study is one of the most challenging aspects of prehospital research.[51,53] In some cases, prehospital consent can be obtained by EMS providers, provided that they are trained in this protocol.[53] There are challenges with bias when consent is obtained in the prehospital setting. Providers may feel uncomfortable obtaining consent, and may choose to avoid enrolling patients.[53] Patients may feel pressured to agree to enroll, feeling that they may receive inferior care if they do not.[53] There are modified consent structures when obtaining consent is not possible or unnecessary. A waiver of informed consent may be applied when inclusion the study implies minimal risk of harm.[53] This is generally applied to observational studies, as determining risk is often the goal of prospective trials. Exception of informed consent can be applied when a life-threatening condition is present and the patient is not able to provide consent.[53] All consent structures require approval from an IRB.

Conclusions

It is clear that the diagnosis of MI is difficult in the context of LBBB and paced rhythm.[2-6] LBBB patients with MI have also been shown to have lower rates of treatment, longer delays to treatment, and higher overall risk of mortality.[8,9] Patients with implanted

pacemakers and MI have also been found to have lower treatments and higher risk of mortality.[14,15,17] Undiagnostic ECG in these circumstances is problematic, as delays to treatment have been found to be detrimental to patient outcomes.[22] Prehospital care has contributed greatly in the care of STEMIs, but paramedic ability to recognize STEMI varies, and is especially difficult when ECG confounders are present.[30-32] As a result, patients with pre-existing ECG abnormalities are undertreated and experience more delays to treatment. The use of troponin aids diagnosis of MI, and has been studied in the prehospital setting.[44-46] However, the most obvious group that may benefit from prehospital troponin measurements are those without diagnostic ECGs due to pre-existing abnormalities. No study has evaluated prehospital troponin specifically in this population.

References

1. Neeland IJ, Kontos MC, de Lemos JA. Evolving considerations in the management of patients with left bundle branch block and suspected myocardial infarction. *Journal of the American College of Cardiology.* Jul 10 2012;60(2):96-105.
2. Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block. GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Investigators. *The New England journal of medicine.* Feb 22 1996;334(8):481-487.
3. Shlipak MG, Lyons WL, Go AS, Chou TM, Evans GT, Browner WS. Should the electrocardiogram be used to guide therapy for patients with left bundle-branch block and suspected myocardial infarction? *Jama.* Feb 24 1999;281(8):714-719.
4. Kontos MC, McQueen RH, Jesse RL, Tatum JL, Ornato JP. Can myocardial infarction be rapidly identified in emergency department patients who have left bundle-branch block? *Annals of emergency medicine.* May 2001;37(5):431-438.
5. Gunnarsson G, Eriksson P, Dellborg M. ECG criteria in diagnosis of acute myocardial infarction in the presence of left bundle branch block. *International journal of cardiology.* Apr 2001;78(2):167-174.
6. Tabas JA, Rodriguez RM, Seligman HK, Goldschlager NF. Electrocardiographic criteria for detecting acute myocardial infarction in patients with left bundle branch block: a meta-analysis. *Annals of emergency medicine.* Oct 2008;52(4):329-336.e321.
7. Smith SW, Dodd KW, Henry TD, Dvorak DM, Pearce LA. Diagnosis of ST-elevation myocardial infarction in the presence of left bundle branch block with the ST-elevation to S-wave ratio in a modified Sgarbossa rule. *Annals of emergency medicine.* Dec 2012;60(6):766-776.
8. Go AS, Barron HV, Rundle AC, Ornato JP, Avins AL. Bundle-branch block and in-hospital mortality in acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *Annals of internal medicine.* Nov 1 1998;129(9):690-697.
9. Shlipak MG, Go AS, Frederick PD, Malmgren J, Barron HV, Canto JG. Treatment and outcomes of left bundle-branch block patients with myocardial infarction who present without chest pain. National Registry of Myocardial Infarction 2 Investigators. *Journal of the American College of Cardiology.* Sep 2000;36(3):706-712.
10. Kontos MC, Aziz HA, Chau VQ, Roberts CS, Ornato JP, Vetrovec GW. Outcomes in patients with chronicity of left bundle-branch block with possible acute myocardial infarction. *American heart journal.* Apr 2011;161(4):698-704.
11. Larson DM, Menssen KM, Sharkey SW, et al. "False-positive" cardiac catheterization laboratory activation among patients with suspected ST-segment elevation myocardial infarction. *Jama.* Dec 19 2007;298(23):2754-2760.
12. Wellens HJ. Acute myocardial infarction and left bundle-branch block--can we lift the veil? *The New England journal of medicine.* Feb 22 1996;334(8):528-529.

13. Madias JE. Left bundle branch block and suspected acute myocardial infarction. *Journal of electrocardiology.* Jan-Feb 2013;46(1):11-12.
14. Rosner MH, Brady WJ. The electrocardiographic diagnosis of acute myocardial infarction in patients with ventricular paced rhythms. *The American journal of emergency medicine.* Mar 1999;17(2):182-185.
15. Kilic H, Atalar E, Ozer N, et al. Early electrocardiographic diagnosis of acute coronary ischemia on the paced electrocardiogram. *International journal of cardiology.* Oct 30 2008;130(1):14-18.
16. Sgarbossa EB, Pinski SL, Gates KB, Wagner GS. Early electrocardiographic diagnosis of acute myocardial infarction in the presence of ventricular paced rhythm. GUSTO-I investigators. *The American journal of cardiology.* Feb 15 1996;77(5):423-424.
17. Zhan C, Baine WB, Sedrakyan A, Steiner C. Cardiac device implantation in the United States from 1997 through 2004: a population-based analysis. *Journal of general internal medicine.* Jan 2008;23 Suppl 1:13-19.
18. Karumbaiah K, Omar B. ST-elevation myocardial infarction in the presence of biventricular paced rhythm. *The Journal of emergency medicine.* Aug 2013;45(2):e35-40.
19. Madias JE. The nonspecificity of ST-segment elevation > or =5.0 mm in V1-V3 in the diagnosis of acute myocardial infarction in the presence of ventricular paced rhythm. *Journal of electrocardiology.* Apr 2004;37(2):135-139.
20. Ukena C, Mahfoud F, Buob A, Bohm M, Neuberger HR. ST-elevation during biventricular pacing. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology.* Apr 2012;14(4):609-611.
21. Maloy KR, Bhat R, Davis J, Reed K, Morrissey R. Sgarbossa Criteria are Highly Specific for Acute Myocardial Infarction with Pacemakers. *The western journal of emergency medicine.* Sep 2010;11(4):354-357.
22. Rathore SS, Weinfurt KP, Gersh BJ, Oetgen WJ, Schulman KA, Solomon AJ. Treatment of patients with myocardial infarction who present with a paced rhythm. *Annals of internal medicine.* Apr 17 2001;134(8):644-651.
23. Ayer A, Terkelsen CJ. Difficult ECGs in STEMI: lessons learned from serial sampling of pre- and in-hospital ECGs. *Journal of electrocardiology.* Jul-Aug 2014;47(4):448-458.
24. Sorensen JT, Terkelsen CJ, Norgaard BL, et al. Urban and rural implementation of pre-hospital diagnosis and direct referral for primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction. *European heart journal.* Feb 2011;32(4):430-436.
25. Cheskes S, Turner L, Foggett R, et al. Paramedic contact to balloon in less than 90 minutes: a successful strategy for st-segment elevation myocardial infarction bypass to primary percutaneous coronary intervention in a canadian emergency medical system. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors.* Oct-Dec 2011;15(4):490-498.

26. Cone DC, Lee CH, Van Gelder C. EMS activation of the cardiac catheterization laboratory is associated with process improvements in the care of myocardial infarction patients. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors.* Jul-Sep 2013;17(3):293-298.
27. Squire BT, Tamayo-Sarver JH, Rashi P, Koenig W, Niemann JT. Effect of prehospital cardiac catheterization lab activation on door-to-balloon time, mortality, and false-positive activation. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors.* Jan-Mar 2014;18(1):1-8.
28. Young DR, Murinson M, Wilson C, et al. Paramedics as decision makers on the activation of the catheterization laboratory in the presence of acute ST-elevation myocardial infarction. *Journal of electrocardiology.* Jan-Feb 2011;44(1):18-22.
29. Nam J, Caners K, Bowen JM, Welsford M, O'Reilly D. Systematic review and meta-analysis of the benefits of out-of-hospital 12-lead ECG and advance notification in ST-segment elevation myocardial infarction patients. *Annals of emergency medicine.* Aug 2014;64(2):176-186, 186.e171-179.
30. Williams B, Boyle M, Lord B. Paramedic identification of electrocardiograph J-point and ST-segments. *Prehospital and disaster medicine.* Nov-Dec 2008;23(6):526-529.
31. Sejersten M, Young D, Clemmensen P, et al. Comparison of the ability of paramedics with that of cardiologists in diagnosing ST-segment elevation acute myocardial infarction in patients with acute chest pain. *The American journal of cardiology.* 11/1/ 2002;90(9):995-998.
32. Mencl F, Wilber S, Frey J, Zalewski J, Maiers JF, Bhalla MC. Paramedic ability to recognize ST-segment elevation myocardial infarction on prehospital electrocardiograms. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors.* Apr-Jun 2013;17(2):203-210.
33. Terkelsen CJ, Sorensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *Jama.* Aug 18 2010;304(7):763-771.
34. Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation.* Nov 7 2006;114(19):2019-2025.
35. McCord J. Will high-sensitivity troponin assays lead to improved outcomes in patients with acute coronary syndrome? *Coronary artery disease.* Dec 2013;24(8):713-715.
36. Goodacre S, Thokala P, Carroll C, et al. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. *Health technology assessment (Winchester, England).* 2013;17(1):v-vi, 1-188.
37. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and

Interventions. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* Feb 15 2012;79(3):453-495.
38. Mahajan VS, Jarolim P. How to interpret elevated cardiac troponin levels. *Circulation.* Nov 22 2011;124(21):2350-2354.
39. Loten C, Attia J, Hullick C, Marley J, McElduff P. Validation of a point of care troponin assay in real life Emergency Department conditions. *Emergency medicine Australasia : EMA.* Aug 2009;21(4):286-292.
40. Takakuwa KM, Ou FS, Peterson ED, et al. The usage patterns of cardiac bedside markers employing point-of-care testing for troponin in non-ST-segment elevation acute coronary syndrome: results from CRUSADE. *Clinical cardiology.* Sep 2009;32(9):498-505.
41. Renaud B, Maison P, Ngako A, et al. Impact of Point-of-care Testing in the Emergency Department Evaluation and Treatment of Patients with Suspected Acute Coronary Syndromes. *Academic Emergency Medicine.* 2008;15(3):216-224.
42. Palamalai V, Murakami MM, Apple FS. Diagnostic performance of four point of care cardiac troponin I assays to rule in and rule out acute myocardial infarction. *Clinical biochemistry.* Nov 2013;46(16-17):1631-1635.
43. Schneider HG, Ablitt P, Taylor J. Improved sensitivity of point of care troponin I values using reporting to below the 99 th percentile of normals. *Clinical biochemistry.* Aug 2013;46(12):979-982.
44. Venturini JM, Stake CE, Cichon ME. Prehospital point-of-care testing for troponin: are the results reliable? *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors.* Jan-Mar 2013;17(1):88-91.
45. Sorensen JT, Terkelsen CJ, Steengaard C, et al. Prehospital troponin T testing in the diagnosis and triage of patients with suspected acute myocardial infarction. *The American journal of cardiology.* May 15 2011;107(10):1436-1440.
46. Stengaard C, Sorensen JT, Ladefoged SA, et al. Quantitative point-of-care troponin T measurement for diagnosis and prognosis in patients with a suspected acute myocardial infarction. *The American journal of cardiology.* Nov 1 2013;112(9):1361-1366.
47. Boden WE, Eagle K, Granger CB. Reperfusion strategies in acute ST-segment elevation myocardial infarction: a comprehensive review of contemporary management options. *Journal of the American College of Cardiology.* Sep 4 2007;50(10):917-929.
48. Rathore SS, Gersh BJ, Weinfurt KP, Oetgen WJ, Schulman KA, Solomon AJ. The role of reperfusion therapy in paced patients with acute myocardial infarction. *American heart journal.* Sep 2001;142(3):516-519.
49. Cone DC, Lerner EB, Yealy MY. Prehospital Care Research-The Basics. In: Lerner EB, Pirrallo RG, Swor RA, White L, eds. *Evaluating and Improving Quality in EMS.* Vol 2009: National Association of EMS Physicians; 2009.
50. Spaite DW, Criss EA, Valenzuela TD, Guisto J. Emergency Medical Service System Research: Problems of the Past, Challenges of the Future. *Annals of emergency medicine.* 1995;26(2):146-152.

51. Sayre M, Gausche-Hill M. Conducting Randomized Trials in the Prehospital Setting. In: Lerner EB, Pirrallo RG, Swor RA, White L, eds. *Evaluating and Improving Quality in EMS.* Vol 3: National Association of EMS Physicians; 2009.
52. Hallstrom A, Rea TD, Sayre MR, et al. Manual chest compression vs use of an automated chest compression device during resuscitation following out-of-hospital cardiac arrest: a randomized trial. *Jama.* Jun 14 2006;295(22):2620-2628.
53. Moscati RM, Lerner EB, Pirrallo RG. Protection of Human Subjects in Prehospital Research. In: Lerner EB, Pirrallo RG, Swor RA, White L, eds. *Evaluating and Improving Quality in EMS.* Vol 3: National Association of EMS Physicians; 2009.

Chapter 3: Study Methods

Study Design

The proposed study is a prospective, randomized clinical trial to examine the efficacy of implementing prehospital troponin measurement in reducing delays to treatment for chest pain patients with pre-existing electrocardiographic abnormalities.

Study Population and Sampling

Inclusion Criteria

Paramedics will use the following inclusion and exclusion criteria to assess patient eligibility for study inclusion. Eligible patients will be over the age of 18, presenting to EMS with symptoms of acute coronary syndrome (ACS). ACS symptoms in this study are defined as paramedic impression of ACS including any combination the following: chest pain or pressure, shortness of breath, jaw pain, dizziness, nausea, or sweating. Eligible patients will have evidence of left bundle branch block (LBBB) or paced rhythm on prehospital 12-lead ECG. LBBB in this study is defined as: known history of LBBB or paramedic interpretation of LBBB with or without the aid of computerized ECG interpretation. Paced rhythm will be defined as known history of pacemaker placement, or paramedic interpretation of paced rhythm with or without the aid of computerized ECG interpretation.

Exclusion Criteria

Exclusion criteria include lack of any inclusion criterion, prehospital death, or cardiac arrest.

Catchment Area and Statistics

Patients will present to a single EMS agency, American Medical Response (AMR), in the greater New Haven and Bridgeport, Connecticut areas. Patients will be transported to Yale New Haven Hospital (YNHH) in New Haven, Connecticut, or Bridgeport Hospital (BH), in Bridgeport, Connecticut. AMR provides ambulance transport for eight towns in the greater New Haven area (New Haven, East Haven, North Haven, Hamden, West Haven, Orange, Woodbridge, Bethany) with a combined population of 330,000. AMR provides primary EMS service for Bridgeport and Fairfield Connecticut, as well as mutual aid services for Stratford, Monroe, Trumbull, Easton and surrounding communities. The Bridgeport/Fairfield division of AMR accounts for about 45,000 calls annually. YNHH and BH each account for around 200 PCI procedures per year from STEMI activations alone.

Baseline Characteristics

Both intervention and control groups will be assessed for baseline characteristics including: age, sex, cardiovascular medical history, cardiovascular risk factors, presence of LBBB, and presence of paced rhythm. Baseline characteristics will be assessed via patient electronic medical record.

Subject Protection and Confidentiality

Subject Protection and Confidentiality

The study design and protocol will be reviewed by the Yale University Human Investigation Committee (HIC), which governs studies at both YNHH and BH. See Appendix A for human investigation consent form. Enrollment in the study is voluntary, and the need to obtain consent will not be waived for any reason. Patients will be

assigned a unique identification number. Investigators tasked with analyzing study data will not have access to patient names or identifiers, and will use only the unique identification number. Patient data will be analyzed using locked computers compliant with Health Insurance Portability and Accountability Act (HIPAA) regulations. All investigators will be required to complete online training regarding HIPAA and Human Investigations. Patients will have the ability to withdraw from the study at any point during the study period.

Recruitment

Because this proposed study involves patients in the prehospital setting, paramedics will be used to obtain consent from patients. As this is not a common practice for paramedics, all paramedics involved in the study will receive supplemental training regarding HIPPA and Human Investigations. See Appendix B for an outline of supplemental paramedic training. Each paramedic will also be required to demonstrate ability to obtain informed consent, outlining risks and benefits to patients, in the presence of the principal investigator (PI). Once in the hospital, each patient will meet with a member of the research team. At this time, if it becomes apparent that a prehospital explanation of consent did not correctly outline all risks and benefits, patients will be given the opportunity to immediately withdraw from the study, and the paramedic who obtained consent will be re-trained.

Study Protocol

Sampling and Randomization

Paramedics will assess eligibility for the study using the above inclusion and exclusion criteria. Following successful training of all New Haven and Bridgeport AMR

paramedics, Abbott i-Stat devices will be distributed. The i-Stat is the same POC device used to measure troponin in the YNHH and BH EDs. The majority of AMR advanced life support (ALS) units are ambulances staffed by one paramedic and one EMT. Other ALS vehicles include "fly cars" and supervisor vehicles, of which three to four are staffed at any time. The i-Stat device will be placed on half of the vehicles assigned to paramedics. If a vehicle has an i-Stat on board, paramedics will complete a prehospital troponin draw on eligible patients, comprising the intervention group. Paramedics will not complete a prehospital troponin draw on eligible patients if their vehicle does not contain the i-Stat device, and these patients will be entered into the control group. The i-Stat devices will be pulled and tested every 6 months during the study, and at these time points they will be switched to the eligible paramedic vehicles that were without an i-Stat device during the previous 6 months of study, in a cross-over design. This switch will aid in reducing selection bias by allowing for intervention and control group patients to be enrolled simultaneously, by varied providers in a larger geographic area. 12-lead ECG and computerized interpretation will be acquired using LIFEPAK models 12 or 15; the only models currently in use by AMR in Connecticut.

Control Group

The control group in this study will comprise patients with LBBB or paced rhythm and ACS as interpreted by a paramedic. The control group will receive routine care, including acquisition of 12-lead ECG, and ACS care according to state EMS guidelines.

Intervention Group

The intervention group will comprise patients with LBBB or paced rhythm and ACS as interpreted by paramedics. The intervention group will receive a prehospital blood draw and troponin T measurement performed by a trained paramedic using the Abbott i-Stat device. Paramedics will receive training on the i-Stat device as outlined in Appendix B and C. The patients in the intervention group will also receive routine care as in the control group. Once the POC troponin assay has been completed, the quantitative result will be immediately relayed to the receiving ED. EMS will not activate the cath lab based on positive troponin, to avoid false positive activation of PCI. Further care will be determined and provided by ED providers or consulting physicians should they become involved.

Outcome Measures

As the primary goal of the study is to assess potential reduction in delays to treatment, patients will be followed only during the admission in which they were enrolled in the study. There will be no long-term follow-up for patients. The primary outcome is door to balloon time, to be measured in minutes. Door to balloon time will be assessed by data in the electronic medical record. Door time will be defined as time of ED entrance (the time at which the triage nurse creates the patient record immediately upon entry into the ambulance bay), balloon time will be defined as the time of balloon inflation during PCI (as recorded by the cath lab staff), and door to balloon time will be defined as the difference between these time points. Secondary outcomes include: PCI status, diagnosis of MI, in-hospital mortality, prehospital troponin, in-hospital troponin and EMS arrival at scene to balloon time. PCI status will be operationalized as a

dichotomous variable, indicating PCI procedure or no procedure. Prehospital troponin and in-hospital troponin will be operationalized as positive or negative using the YNHH cutoff of 0.01ng/dL.

Sample Size Calculation

The sample size calculation for this study was based on the effect size noted in STEMI EMS protocols, as no study has evaluated the primary outcome measure through use of prehospital troponin. The calculation is based on Nam et al., van de Loo et al.[1,2] Average door to balloon time with prehospital 12-lead ECG: 62 minutes. Average door to balloon time control group: 96 minutes. Standard Deviation: 55. Power 80%. Type I Error: 5%. Calculated Sample Size: 42 patients in each group. Although loss to follow-up should be minimal within this study, accounting for loss to follow-up due to death is an important component of prehospital research. Fifteen percent will be added to the sample size calculation for each group; total sample size will be 49 patients in each group.

Data Collection and Analysis

Data will be collected in the EPIC electronic medical record at YNHH and BH, as well as the computerized electronic medical record used by AMR. Paramedics will be required to record accurate run times, 12-lead ECG, and prehospital troponin result. Because of the potential use of the intervention in the care of the patient, blinding is not possible for providers or patients; however, the researcher reviewing the hospital record for data acquisition will be blinded to study group. Data will be compiled by a member of the research team who will extract information from the medical record and assign each patient a unique study identification number. The principal investigators will perform subsequent analysis. Blinding of intervention and control groups will occur during

analysis for the following outcome measures: door to balloon time, EMS contact to balloon time, PCI status, in-hospital troponin and diagnosis of MI. Analysis of prehospital troponin data will not be blinded.

Statistical Analysis

Analysis will be conducted using an intention-to-treat protocol. The primary outcome measure, door to balloon time, is a continuous unpaired variable reported in means (minutes). The statistical test for door to balloon time will be a Student's t-test. Statistical analysis for the secondary outcome, EMS arrival at scene to balloon time, similarly will use the student t-test for statistical analysis. Secondary outcomes of PCI status, diagnosis of MI, prehospital troponin, in-hospital troponin, and in-hospital mortality are all categorical variables in this study, reported in proportions. The statistical test for these variables will be the chi-square test. Statistical significance for all outcomes will use a p level of 0.05.

Timeline and Resources

Upon approval by the HIC, the entire training period, data collection, and data analysis, will be completed within two years. The Yale University School of Medicine will provide funding for the study. Abbott i-Stat devices will be purchased and provided to AMR for use during the study. i-Stat cartridges will also be provided by the research team. Paramedics will be compensated at their normal hourly rate for the training required to participate in the study, and will be awarded Continuing Medical Education credit by the Yale-New Haven Sponsor Hospital Program. The principal investigator for the study is Timothy N Riddell PA-SII. The faculty advisor is David Cone MD. One independent researcher will be hired to compile data for analysis. Care of patients will be

provided by paramedics and other EMS personnel, YNHH ED staff, and consulting physicians.

Sample Size References:

1. Nam J, Caners K, Bowen JM, Welsford M, O'Reilly D. Systematic review and meta-analysis of the benefits of out-of-hospital 12-lead ECG and advance notification in ST-segment elevation myocardial infarction patients. *Annals of emergency medicine.* Aug 2014;64(2):176-186, 186.e171-179.
2. van de Loo A, Saurbier B, Kalbhenn J, Koberne F, Zehender M. Primary percutaneous coronary intervention in acute myocardial infarction: direct transportation to catheterization laboratory by emergency teams reduces door-to-balloon time. *Clinical cardiology.* Mar 2006;29(3):112-116.

Chapter 4: Conclusion

Advantages

The study is designed to examine delays to care in MI, the reduction of which have been shown to decrease mortality. The primary outcome, door to balloon time, is a well-established outcome measure.[1] Door to balloon times are also easily acquired data which do not require long-term follow-up. All data points will be collected during a single hospital admission, and in most cases in a single day. Due to this, loss to follow-up or patient dropout should be minimal. The proposed randomization scheme allows control group and intervention group patients to be enrolled at the same time. Furthermore, the cross-over design, to be completed at multiple time points within the study, ensures that patients in both groups will be enrolled by a variety of providers and a larger geographic area. The inclusion of both YNHH and BH also aids in the inclusion of a more varied population. There are no obvious health risks for those involved in the study. The prehospital troponin draw does not carry significant risk of complication, and both control and intervention groups will receive routine EMS care.

Disadvantages

Because a prehospital activation of the cath lab based solely on positive troponin may result in a high rate of false positives, we have elected for only a notification of the prehospital troponin result to the receiving ED. This may limit the impact of the intervention, but this is not unlike many of the initial studies that were conducted on STEMI patients. Consent of patients in the prehospital settings is challenging, but a necessary component of this study. However, we have taken measures to train paramedics in this endeavor, and do not believe that challenges to prehospital consent

will significantly alter the results of the study. Patients will also interact with researchers while in the hospital, to assess whether consent was appropriately attained. Cost is also a challenge within this study, due to the training of a large number of paramedics and the purchasing of expensive i-Stat devices and cartridges. However, the i-Stat devices may be repurposed at the conclusion of the study, as many hospital units are now adopting POC devices into everyday practice.

We have elected to allow ED providers to interpret the prehospital troponin result and decide further care independently. There will be some variability between providers, which may affect results, however, this may be a strength in replicating the workings of a real-world ED. It is not possible to predict the effect of including providers from both hospitals in this study. The inclusion of two hospitals is not without challenge. However, this is mitigated by the inclusion of BH under the YNHH HIC, as well as AMR's coverage of both metropolitan areas.

Clinical and Public Health Significance

It is clear that the patients with LBBB and pacemakers are undertreated and experience more delays to treatment than those presenting with STEMI.[2-4] Prehospital troponin measurement has the potential to advance care for these patients similar to the advent of the 12-lead ECG in the care of STEMI patients. The technology has the potential to advance more patients to quicker life-saving treatment. The implementation of prehospital troponin has been shown to be feasible in multiple studies.[5,6] However, the most obvious potential benefit for the measurement is in patients for whom the ECG is unhelpful, which is the focus of this study.

Prehospital research has unique challenges, but can result in a great improvement of care for many acute illnesses. This study is proposed as a randomized clinical trial, a study design that is underutilized in the prehospital setting due to its perceived challenges.[7] Our study could serve as another example of the feasibility of clinical trials in this setting. Should this study yield significant results, it may influence further study of prehospital troponin in a similar population. Furthermore, the study will be another test of prehospital POC laboratory tests in general, which have the ability to aid in early diagnosis of many acute illnesses.

References:

1. Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation.* Nov 7 2006;114(19):2019-2025.
2. Go AS, Barron HV, Rundle AC, Ornato JP, Avins AL. Bundle-branch block and in-hospital mortality in acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *Annals of internal medicine.* Nov 1 1998;129(9):690-697.
3. Rathore SS, Weinfurt KP, Gersh BJ, Oetgen WJ, Schulman KA, Solomon AJ. Treatment of patients with myocardial infarction who present with a paced rhythm. *Annals of internal medicine.* Apr 17 2001;134(8):644-651.
4. Shlipak MG, Go AS, Frederick PD, Malmgren J, Barron HV, Canto JG. Treatment and outcomes of left bundle-branch block patients with myocardial infarction who present without chest pain. National Registry of Myocardial Infarction 2 Investigators. *Journal of the American College of Cardiology.* Sep 2000;36(3):706-712.
5. Sorensen JT, Terkelsen CJ, Norgaard BL, et al. Urban and rural implementation of pre-hospital diagnosis and direct referral for primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction. *European heart journal.* Feb 2011;32(4):430-436.
6. Stengaard C, Sorensen JT, Ladefoged SA, et al. Quantitative point-of-care troponin T measurement for diagnosis and prognosis in patients with a suspected acute myocardial infarction. *The American journal of cardiology.* Nov 1 2013;112(9):1361-1366.
7. Sayre M, Gausche-Hill M. Conducting Randomized Trials in the Prehospital Setting. In: Lerner EB, Pirrallo RG, Swor RA, White L, eds. *Evaluating and Improving Quality in EMS.* Vol 3: National Association of EMS Physicians; 2009.

Appendices:

Appendix A: HIC Consent Form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 1 (2014-4)

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL
YALE UNIVERSITY SCHOOL OF MEDICINE – BRIDGEPORT HOSPITAL

Study Title: Prehospital Quantitative Troponin for the Non-Diagnostic ECG
Principal Investigator: Timothy Riddell PA-SII; David Cone MD (Faculty Advisor)
Funding Source: Yale University School of Medicine

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to look at the effect of a prehospital troponin measurement in reducing delays to treatment for myocardial infarction (MI). You have been asked to participate because you have presented to emergency medical services, and your electrocardiogram is not diagnostic of MI, though you are experiencing symptoms which may be consistent with MI.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to participate in this study, you will be assigned to one of two possible groups. In one group, no additional tests are taken, and you will receive routine care from EMS and in the hospital. There is no additional medical risk of being assigned to this group versus opting out of the study.

The second possible group will receive one additional test before arriving at the hospital. Your paramedic will start an intravenous (IV) line during your routine care. This line will be used to draw a small amount of blood (5 to 10 mL, or 1 to 2 teaspoons). Your blood will not be mixed with other blood, and you will receive no blood products as a result of this blood draw. This blood will be applied to a testing device called the Abbott i-Stat. This machine will be used to test your blood for troponin, an enzyme that is released by

the heart when it is not receiving enough blood, such as during a heart attack (MI). The paramedic will relay the result of this test to the hospital to which you are being transported. The result of this test will not trigger any specific treatment. Your emergency providers will determine how to use the result of the test to determine your further treatment, and you will be informed of all treatment decisions.

For both study groups, we will only use information from this trip to the hospital. If you are admitted to the hospital, we will follow you during the course of this admission only. You will receive no long-term follow-up, and we will not ask you for any additional information once you are discharged.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Risks and Inconveniences

Group One: No Additional Prehospital Testing
There are no known physical risks associated with this arm of the study. However, your hospital course will be compared to patients assigned to group two, which may have better outcomes. There is the possible risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Group Two: Prehospital Troponin Measurement
Physical risks associated with this group involve additional bleeding from IV site, and injury to vessels as a result of the blood draw. However, an IV will be placed as part of your routine care regardless of your participation in this study. We do not know how this measurement will affect your care. Your hospital course will be compared to patients assigned to group one, which may have better outcomes. There is the possible risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Benefits

Should you be assigned to receive the prehospital troponin test, it is possible that this may affect your care. You may have quicker treatment and better outcomes as a result of the test. However, this association is unknown and is the reason for the study.

Economic Considerations

You will not be compensated for your inclusion in this study. However, there is no additional cost to you should you decide to be included. If you receive a prehospital

troponin test, you will not be charged for this test. The supplies for the IV, as well as the cartridge used in completing the test will be provided by the research team. The remainder of your care in the ambulance and in the hospital will be billed normally according to your diagnosis, treatment, and any procedure you may encounter. You will still be responsible for any co-pays required by your insurance company for standard treatment.

American Medical Response will receive no financial benefit from inclusion in the study. Individual paramedics have been trained by the principal investigators, and were compensated at their normal hourly rate for the training. Paramedics also received continuing education credit for their training.

Treatment Alternatives/Alternatives

The only alternative is to decline participation in the study. All patients in the study will receive routine prehospital and in-hospital care.

Confidentiality

Every effort will be made to protect your confidentiality within this study. Information will be collected from your Electronic Medical Record (EMR). Information about your inclusion in the study will not be entered into the EMR. All HIPAA guidelines will be followed during the course of this study. Your information will be collected by a member of the researcher no more than one week following your emergency visit. Once your information is collected, you will be assigned a unique identification number for further data analysis. At this point, only the de-identified information will be used. Your personal information, as well as any potential identifying factors, will be removed from our records.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

In Case of Injury

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine, Yale-New Haven Hospital and Bridgeport Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course, which includes your time in the emergency department and your time in the hospital should you be admitted. However, the result of the test may be used if you receive it, and the test cannot be undone.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. The researchers may withdraw you from participating in the research if necessary.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital, Bridgeport Hospital, or American Medical Response.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject:_____

Signature:_____

*Relationship:*_____

Date:_____

_____ _____
Signature of Principal Investigator Date

or

_____ _____
Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator Timothy Riddell (xxx-xxx-xxxx). If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED BY THE HIC OFFICE

THIS FORM IS VALID ONLY THROUGH: _____.
INITIALED: _____

Appendix B: Paramedic Training Outline

Course to be completed prior to research start date.

Course Directors: Timothy Riddell PA-SII, David Cone MD

Course Resources: One Abbott i-Stat device, payment for paramedics (normal hourly rate).

This course is a 6-hour course, for which you will be compensated at your normal hourly rate and receive 6 hours of continuing medical education credit.

Session One: 2 Hours
- Outline of Study Protocol
- HIPAA outline (supplemental HIPAA training to be completed online)
- Review of ECG: STEMI, LBBB, Paced Rhythm
- Simulated ECG Examples using Lifepak 12 and 15
- Written Quiz

Session Two: 2 Hours
- Outline of Abbott i-Stat Machines
- Outline of communication of result to receiving ED
- Outline of acquiring informed consent
- Demonstration of acquiring informed consent
- Written Quiz

Session Three: 2 Hours
- In-ED experience with i-Stat machines and ED techs
- Completed at YNHH ED only
- Paramedics must complete 3 troponin draws and tests using i-Stat machine

See Appendix C for training checklist

Appendix C: Paramedic Training Checklist

Paramedics must complete all training to be eligible to enroll patients. Check off and sign all completed elements.

Paramedic Name, Date _____
Rank at AMR _____

Circle Area of Employment: New Haven Area Bridgeport Area

Completion of Training Course and Demonstration of Informed Consent

☐ PI Signature _____

3 In-ED troponin draws with i-Stat

☐ ED Tech Signature _____

☐ ED Tech Signature _____

☐ ED Tech Signature _____

Completion of Online HIPAA Training

☐ PI Signature _____

I certify that I have met all training requirements as outlined above.

_____ _____
(Signature of Paramedic, Date) (Signature of PI, Date)

Bibliography:

1. Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation.* May 15 2007;115(19):2549-2569.
2. Ayer A, Terkelsen CJ. Difficult ECGs in STEMI: lessons learned from serial sampling of pre- and in-hospital ECGs. *Journal of electrocardiology.* Jul-Aug 2014;47(4):448-458.
3. Boden WE, Eagle K, Granger CB. Reperfusion strategies in acute ST-segment elevation myocardial infarction: a comprehensive review of contemporary management options. *Journal of the American College of Cardiology.* Sep 4 2007;50(10):917-929.
4. Cheskes S, Turner L, Foggett R, et al. Paramedic contact to balloon in less than 90 minutes: a successful strategy for st-segment elevation myocardial infarction bypass to primary percutaneous coronary intervention in a canadian emergency medical system. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors.* Oct-Dec 2011;15(4):490-498.
5. Cone DC, Lee CH, Van Gelder C. EMS activation of the cardiac catheterization laboratory is associated with process improvements in the care of myocardial infarction patients. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors.* Jul-Sep 2013;17(3):293-298.
6. Cone DC, Lerner EB, Yealy MY. Prehospital Care Research-The Basics. In: Lerner EB, Pirrallo RG, Swor RA, White L, eds. *Evaluating and Improving Quality in EMS.* Vol 2009: National Association of EMS Physicians; 2009.
7. Go AS, Barron HV, Rundle AC, Ornato JP, Avins AL. Bundle-branch block and in-hospital mortality in acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *Annals of internal medicine.* Nov 1 1998;129(9):690-697.
8. Goodacre S, Thokala P, Carroll C, et al. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. *Health technology assessment (Winchester, England).* 2013;17(1):v-vi, 1-188.
9. Gravning J, Smedsrud MK, Omland T, et al. Sensitive troponin assays and N-terminal pro-B-type natriuretic peptide in acute coronary syndrome: prediction of significant coronary lesions and long-term prognosis. *American heart journal.* May 2013;165(5):716-724.
10. Gunnarsson G, Eriksson P, Dellborg M. ECG criteria in diagnosis of acute myocardial infarction in the presence of left bundle branch block. *International journal of cardiology.* Apr 2001;78(2):167-174.
11. Hallstrom A, Rea TD, Sayre MR, et al. Manual chest compression vs use of an automated chest compression device during resuscitation following out-of-hospital cardiac arrest: a randomized trial. *Jama.* Jun 14 2006;295(22):2620-2628.

12. Health CAfDaTi. CADTH Optimal Use Reports. *High-Sensitivity Cardiac Troponin for the Rapid Diagnosis of Acute Coronary Syndrome in the Emergency Department: A Clinical and Cost-Effectiveness Evaluation*. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health Copyright (c) 2013 Canadian Agency for Drugs and Technologies in Health.; 2013.
13. Jacobs AK, Antman EM, Faxon DP, Gregory T, Solis P. Development of Systems of Care for ST-Elevation Myocardial Infarction Patients: Executive Summary. *Circulation.* July 10, 2007 2007;116(2):217-230.
14. Karumbaiah K, Omar B. ST-elevation myocardial infarction in the presence of biventricular paced rhythm. *The Journal of emergency medicine.* Aug 2013;45(2):e35-40.
15. Kilic H, Atalar E, Ozer N, et al. Early electrocardiographic diagnosis of acute coronary ischemia on the paced electrocardiogram. *International journal of cardiology.* Oct 30 2008;130(1):14-18.
16. Kontos MC, Aziz HA, Chau VQ, Roberts CS, Ornato JP, Vetrovec GW. Outcomes in patients with chronicity of left bundle-branch block with possible acute myocardial infarction. *American heart journal.* Apr 2011;161(4):698-704.
17. Kontos MC, McQueen RH, Jesse RL, Tatum JL, Ornato JP. Can myocardial infarction be rapidly identified in emergency department patients who have left bundle-branch block? *Annals of emergency medicine.* May 2001;37(5):431-438.
18. Larson DM, Menssen KM, Sharkey SW, et al. "False-positive" cardiac catheterization laboratory activation among patients with suspected ST-segment elevation myocardial infarction. *Jama.* Dec 19 2007;298(23):2754-2760.
19. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* Feb 15 2012;79(3):453-495.
20. Loten C, Attia J, Hullick C, Marley J, McElduff P. Validation of a point of care troponin assay in real life Emergency Department conditions. *Emergency medicine Australasia : EMA.* Aug 2009;21(4):286-292.
21. Madias JE. The nonspecificity of ST-segment elevation > or =5.0 mm in V1-V3 in the diagnosis of acute myocardial infarction in the presence of ventricular paced rhythm. *Journal of electrocardiology.* Apr 2004;37(2):135-139.
22. Madias JE. Left bundle branch block and suspected acute myocardial infarction. *Journal of electrocardiology.* Jan-Feb 2013;46(1):11-12.
23. Mahajan VS, Jarolim P. How to interpret elevated cardiac troponin levels. *Circulation.* Nov 22 2011;124(21):2350-2354.
24. Maloy KR, Bhat R, Davis J, Reed K, Morrissey R. Sgarbossa Criteria are Highly Specific for Acute Myocardial Infarction with Pacemakers. *The western journal of emergency medicine.* Sep 2010;11(4):354-357.
25. McCord J. Will high-sensitivity troponin assays lead to improved outcomes in patients with acute coronary syndrome? *Coronary artery disease.* Dec 2013;24(8):713-715.

26. Mencl F, Wilber S, Frey J, Zalewski J, Maiers JF, Bhalla MC. Paramedic ability to recognize ST-segment elevation myocardial infarction on prehospital electrocardiograms. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors.* Apr-Jun 2013;17(2):203-210.
27. Moscati RM, Lerner EB, Pirrallo RG. Protection of Human Subjects in Prehospital Research. In: Lerner EB, Pirrallo RG, Swor RA, White L, eds. *Evaluating and Improving Quality in EMS.* Vol 3: National Association of EMS Physicians; 2009.
28. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics—2015 Update: A Report From the American Heart Association. *Circulation.* January 27, 2015 2015;131(4):e29-e322.
29. Nam J, Caners K, Bowen JM, Welsford M, O'Reilly D. Systematic review and meta-analysis of the benefits of out-of-hospital 12-lead ECG and advance notification in ST-segment elevation myocardial infarction patients. *Annals of emergency medicine.* Aug 2014;64(2):176-186, 186.e171-179.
30. Neeland IJ, Kontos MC, de Lemos JA. Evolving considerations in the management of patients with left bundle branch block and suspected myocardial infarction. *Journal of the American College of Cardiology.* Jul 10 2012;60(2):96-105.
31. Nikus K, Pahlm O, Wagner G, et al. Electrocardiographic classification of acute coronary syndromes: a review by a committee of the International Society for Holter and Non-Invasive Electrocardiology. *Journal of electrocardiology.* Mar-Apr 2010;43(2):91-103.
32. Palamalai V, Murakami MM, Apple FS. Diagnostic performance of four point of care cardiac troponin I assays to rule in and rule out acute myocardial infarction. *Clinical biochemistry.* Nov 2013;46(16-17):1631-1635.
33. Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation.* Nov 7 2006;114(19):2019-2025.
34. Rathore SS, Gersh BJ, Weinfurt KP, Oetgen WJ, Schulman KA, Solomon AJ. The role of reperfusion therapy in paced patients with acute myocardial infarction. *American heart journal.* Sep 2001;142(3):516-519.
35. Rathore SS, Weinfurt KP, Gersh BJ, Oetgen WJ, Schulman KA, Solomon AJ. Treatment of patients with myocardial infarction who present with a paced rhythm. *Annals of internal medicine.* Apr 17 2001;134(8):644-651.
36. Renaud B, Maison P, Ngako A, et al. Impact of Point-of-care Testing in the Emergency Department Evaluation and Treatment of Patients with Suspected Acute Coronary Syndromes. *Academic Emergency Medicine.* 2008;15(3):216-224.
37. Rosner MH, Brady WJ. The electrocardiographic diagnosis of acute myocardial infarction in patients with ventricular paced rhythms. *The American journal of emergency medicine.* Mar 1999;17(2):182-185.
38. Sayre M, Gausche-Hill M. Conducting Randomized Trials in the Prehospital Setting. In: Lerner EB, Pirrallo RG, Swor RA, White L, eds. *Evaluating and*

Improving Quality in EMS. Vol 3: National Association of EMS Physicians; 2009.

39. Schneider HG, Ablitt P, Taylor J. Improved sensitivity of point of care troponin I values using reporting to below the 99 th percentile of normals. *Clinical biochemistry.* Aug 2013;46(12):979-982.
40. Sejersten M, Young D, Clemmensen P, et al. Comparison of the ability of paramedics with that of cardiologists in diagnosing ST-segment elevation acute myocardial infarction in patients with acute chest pain. *The American journal of cardiology.* 11/1/ 2002;90(9):995-998.
41. Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block. GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Investigators. *The New England journal of medicine.* Feb 22 1996;334(8):481-487.
42. Sgarbossa EB, Pinski SL, Gates KB, Wagner GS. Early electrocardiographic diagnosis of acute myocardial infarction in the presence of ventricular paced rhythm. GUSTO-I investigators. *The American journal of cardiology.* Feb 15 1996;77(5):423-424.
43. Shlipak MG, Go AS, Frederick PD, Malmgren J, Barron HV, Canto JG. Treatment and outcomes of left bundle-branch block patients with myocardial infarction who present without chest pain. National Registry of Myocardial Infarction 2 Investigators. *Journal of the American College of Cardiology.* Sep 2000;36(3):706-712.
44. Shlipak MG, Lyons WL, Go AS, Chou TM, Evans GT, Browner WS. Should the electrocardiogram be used to guide therapy for patients with left bundle-branch block and suspected myocardial infarction? *Jama.* Feb 24 1999;281(8):714-719.
45. Smith SW, Dodd KW, Henry TD, Dvorak DM, Pearce LA. Diagnosis of ST-elevation myocardial infarction in the presence of left bundle branch block with the ST-elevation to S-wave ratio in a modified Sgarbossa rule. *Annals of emergency medicine.* Dec 2012;60(6):766-776.
46. Sorensen JT, Stengaard C, Sorensen CA, et al. Diagnosis and outcome in a prehospital cohort of patients with bundle branch block and suspected acute myocardial infarction. *European heart journal. Acute cardiovascular care.* Jun 2013;2(2):176-181.
47. Sorensen JT, Terkelsen CJ, Norgaard BL, et al. Urban and rural implementation of pre-hospital diagnosis and direct referral for primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction. *European heart journal.* Feb 2011;32(4):430-436.
48. Sorensen JT, Terkelsen CJ, Steengaard C, et al. Prehospital troponin T testing in the diagnosis and triage of patients with suspected acute myocardial infarction. *The American journal of cardiology.* May 15 2011;107(10):1436-1440.
49. Spaite DW, Criss EA, Valenzuela TD, Guisto J. Emergency Medical Service System Research: Problems of the Past, Challenges of the Future. *Annals of emergency medicine.* 1995;26(2):146-152.
50. Squire BT, Tamayo-Sarver JH, Rashi P, Koenig W, Niemann JT. Effect of prehospital cardiac catheterization lab activation on door-to-balloon time,

mortality, and false-positive activation. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors.* Jan-Mar 2014;18(1):1-8.
51. Stengaard C, Sorensen JT, Ladefoged SA, et al. Quantitative point-of-care troponin T measurement for diagnosis and prognosis in patients with a suspected acute myocardial infarction. *The American journal of cardiology.* Nov 1 2013;112(9):1361-1366.
52. Tabas JA, Rodriguez RM, Seligman HK, Goldschlager NF. Electrocardiographic criteria for detecting acute myocardial infarction in patients with left bundle branch block: a meta-analysis. *Annals of emergency medicine.* Oct 2008;52(4):329-336.e321.
53. Takakuwa KM, Ou FS, Peterson ED, et al. The usage patterns of cardiac bedside markers employing point-of-care testing for troponin in non-ST-segment elevation acute coronary syndrome: results from CRUSADE. *Clinical cardiology.* Sep 2009;32(9):498-505.
54. Terkelsen CJ, Sorensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *Jama.* Aug 18 2010;304(7):763-771.
55. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third Universal Definition of Myocardial Infarction. *Circulation.* October 16, 2012 2012;126(16):2020-2035.
56. Ukena C, Mahfoud F, Buob A, Bohm M, Neuberger HR. ST-elevation during biventricular pacing. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology.* Apr 2012;14(4):609-611.
57. van de Loo A, Saurbier B, Kalbhenn J, Koberne F, Zehender M. Primary percutaneous coronary intervention in acute myocardial infarction: direct transportation to catheterization laboratory by emergency teams reduces door-to-balloon time. *Clinical cardiology.* Mar 2006;29(3):112-116.
58. Venturini JM, Stake CE, Cichon ME. Prehospital point-of-care testing for troponin: are the results reliable? *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors.* Jan-Mar 2013;17(1):88-91.
59. Wellens HJ. Acute myocardial infarction and left bundle-branch block--can we lift the veil? *The New England journal of medicine.* Feb 22 1996;334(8):528-529.
60. Williams B, Boyle M, Lord B. Paramedic identification of electrocardiograph J-point and ST-segments. *Prehospital and disaster medicine.* Nov-Dec 2008;23(6):526-529.
61. Young DR, Murinson M, Wilson C, et al. Paramedics as decision makers on the activation of the catheterization laboratory in the presence of acute ST-elevation myocardial infarction. *Journal of electrocardiology.* Jan-Feb 2011;44(1):18-22.
62. Zhan C, Baine WB, Sedrakyan A, Steiner C. Cardiac device implantation in the United States from 1997 through 2004: a population-based analysis. *Journal of general internal medicine.* Jan 2008;23 Suppl 1:13-19.