

RANDOMIZED COST COMPARISON OF CARDIAC MRI USE IN EMERGENCY
DEPARTMENT PATIENTS WITH CHEST PAIN

By

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ABSTRACT

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OBSERVATION UNIT CARE WITH STRESS CARDIAC MRI REDUCES HOSPITAL COST IN ED PATIENTS WITH INTERMEDIATE RISK CHEST PAIN

Dissertation under the direction of

W. Gregory Hundley, MD, Professor of Cardiology and Radiology

Objective

To compare the medical cost among patients with intermediate-risk chest pain managed with two diagnostic strategies: an observation unit (OU) cardiac MRI (CMR) strategy and inpatient care.

Methods

A single center clinical trial randomized 110 patients with intermediate-risk chest pain (TIMI ≥ 2 or clinical impression) to OU CMR (OU care, serial cardiac markers and stress CMR) or inpatient care (admission, care determined by the admitting provider). Outcomes included direct cost of the index hospital visit and correct cardiac dispositions.

Results

53 subjects were randomized to OU CMR and 57 to inpatient care; In the OU CMR group, 49/53 underwent stress CMR, 11/53 were admitted, 1 left against

medical advice (AMA), and 41 were discharged. Of inpatient care participants, 54/57 were admitted and 3 left AMA. ACS occurred in 2 patients in the OU CMR group and 6 in the inpatient care group. At 30 days no subjects experienced ACS after discharge. OU CMR was associated with reduced median index hospitalization cost (\$2062 vs \$2680, $p < 0.001$). OU CMR improved cardiac disposition decisions (83% vs 11%, $p < 0.001$).

Conclusion

In patients with intermediate-risk chest pain, an OU CMR strategy reduces cost and improves cardiac disposition decisions with similar outcomes at 30 days.

CHAPTER ONE

INTRODUCTION

Overview

Coronary Heart Disease Affects 15.8 Million People in the US¹ and Represents a Major Public Health Dilemma

The evaluation process for this disease is inefficient and must change. In the US, patients with symptoms of chest pain are generally evaluated in an emergency department (ED). As a result, EDs care for 6 million patients annually with a complaint of chest pain.² Of all patients presenting with chest pain, almost two thirds will be admitted to the hospital but only 15-25% will ultimately be diagnosed with a cardiac cause.³ This over-triage has been estimated to cost \$10-12 billion annually.⁴⁻⁶ Excessive admissions also contribute to hospital and emergency department crowding, which has been linked to an overall decrease in quality of care.^{7,8} This inefficiency also taxes the US in other ways such as lost productivity for affected patients and unnecessary invasive procedures. Equally important, this inefficiency consumes resources that could be diverted for other health interventions.

The Evaluation of Chest Pain Is a Major Clinical Problem

The cause of chest pain is notoriously difficult for physicians to diagnose. Despite a large increase in the rate of admissions for patients with chest pain, 4% of patients with acute coronary syndrome (ACS), consisting of the combination of myocardial infarction and unstable angina, are inadvertently

discharged from the emergency department.⁹ These patients inadvertently discharged home have higher mortality compared to those hospitalized⁹, emphasizing the importance of making the correct diagnosis. Due to limitations of the history, physical exam, and electrocardiogram, the ACC/AHA guidelines¹⁰ recommend serial cardiac markers and cardiac imaging for those with possible ACS. In response to guideline recommendations, and in attempt to decrease the rate of missed ACS, physicians have adopted a strategy of admitting most patients with possible ACS to observation units or inpatient beds for completion of their evaluation. These practices lead to lengthy hospital stays, further exacerbating hospital crowding, and increasing cost.

Current guidelines from the ACC/AHA¹¹ recommend risk stratification into low, intermediate, and high-risk based on the likelihood of coronary disease and the probability of short term death or infarction. Patients stratified as low-risk are often cared for in observation units (OUs) which have proven efficiency. In contrast, patients stratified as intermediate-risk are commonly admitted to the hospital. These intermediate-risk patients represent >50% of chest pain admissions¹², commonly have known coronary disease, are generally older, and are a growing segment due to aging of the US population. Care patterns involve lengthy evaluations consisting of serial ECG's, cardiac biomarkers, cardiology consultation, and stress testing or coronary angiogram leading to mean lengths of stay as long as 4.7 days¹³ yet only 5-19% of this subgroup of patients will have cardiac ischemia.^{5,14-16} A major opportunity exists to improve the delivery of care to patients with intermediate-risk chest pain.

Inefficiency in Health Care Delivery to Patients with Chest Pain Is
Exacerbated By Deviation from Established Guidelines and Inaccurate Tests

Deviation from Established Guidelines

The ACC/AHA guidelines provide a framework for managing patients with possible ACS. However, despite these recommendations, there is wide variability in management of these patients in the US. For example, the guidelines recommend admission to a telemetry monitored unit or chest pain observation unit for all subjects with possible cardiac ischemia.¹¹ In an analysis of 2,939 patients admitted to 35 hospitals in the US with chest pain, 48% of patients with intermediate-risk and 47% with low-risk were admitted to a non-telemetry bed. Paradoxically, subjects admitted to non-telemetry beds were more likely to undergo in-hospital procedures compared to those admitted to telemetry beds despite having a lower risk profile. Mean length of stay for intermediate-risk patients was 4.7 days.¹³

These care patterns have a significant impact on health care expenditures. For example, among low- and intermediate-risk patients with unstable angina or non-ST-segment elevation MI, routine cardiac catheterization does not definitively improve outcomes, but does prevent re-hospitalization. Unfortunately, the cost to prevent one re-hospitalization with this strategy approximates \$80,000, well above the cost of a re-hospitalization.¹⁷ However, despite this monetary difference, 37-56% of intermediate-risk chest pain patients undergo cardiac catheterization, but only about half of those require revascularization.^{13,15,16} Standardizing the chest pain evaluation process would

reduce deviations from established guideline-recommended care and likely result in improved health care efficiency and cost effectiveness.

Inaccurate Tests

Stress treadmill, stress echocardiography (echo), and nuclear medicine are the most commonly used cardiac imaging modalities. Stress treadmill is quick and convenient; however, in a meta-analysis of 24,000 patients, it had only 68% sensitivity and 77% specificity for significant coronary stenosis.¹⁸⁻²⁰ Stress echocardiography is also convenient and widely adopted, but a meta-analysis of 28 studies found that when used to evaluate coronary artery disease, stress echo demonstrated a suboptimal sensitivity of 80% and specificity of 84%²¹. Nuclear myocardial perfusion imaging has excellent sensitivity for acute myocardial infarction,²² but requires stress testing for unstable angina diagnosis^{23,24} and is limited by difficulties of radionuclide storage, injection, and time delays. In a prospective randomized trial of 2,475 subjects comparing resting sestamibi imaging to usual care, resting myocardial perfusion imaging did not reduce the 19% rate of discharge for subjects ultimately proven to have unstable angina²⁵. The delays associated with obtaining the much-needed stress images have made nuclear imaging less popular in chest pain diagnostic protocols.

Tests with sub-optimal sensitivity, such as stress treadmill, stress echo, or resting nuclear medicine testing, may lead to inadvertent discharge of patients with ACS. Because of worse outcomes, these patients represent a high medical-legal risk to emergency physicians and are a leading cause of malpractice payouts. A non-specific test (e.g. stress treadmill) leads to increased cardiac

catheterizations. Cardiac catheterization is a costly, invasive test with a major complication rate of 1-2%.²⁶ Thus, the ideal diagnostic protocol would minimize the number of diagnostic catheterizations that do not lead to revascularization. Current rates of catheterization among intermediate-risk chest pain patients admitted to the hospital are 37-56%, with only half of those leading to revascularization.^{13,15,16} These negative catheterizations represent a poor use of resources and carry significant cost. Therefore, a more accurate diagnostic test prior to cardiac catheterization could significantly improve health care efficiency.

Observation Units Represent a Solution to
Improving Health Care Efficiency

Observation Units (OU) Are Designed to Deliver Efficient Care

These specialized areas within hospitals, and often within emergency departments, deliver protocol driven care. Protocols are designed to further diagnose and treat the suspected illness, and have been developed for many different conditions including heart failure, chest pain, asthma, and cellulitis. Because care is protocol driven, variability in care patterns is reduced. These observation units have been demonstrated to improve the efficiency of health care delivery as highlighted in The Institute of Medicine report: “Hospital based emergency care: At the breaking point”. The report found observation unit care decreased length of stay and hospital cost relative to inpatient admission and may decrease ED over-crowding. The report stated: “Based on the foregoing evidence, the subcommittee concludes that CDUs (clinical decision units) reduce

boarding and diversion, avoid expensive hospitalization, and appear to contribute to improved management of common ambulatory-care sensitive conditions.”²⁷

Implementation of OU Protocols in Intermediate-Risk Patients With Chest Pain Has Been Limited by Suboptimal Testing Options

Because of the recognized efficiency benefits, it is common for patients with low-risk chest pain to be managed in an OU. However, two investigations of OU use in intermediate-risk patients emphasize the need for a more accurate stress testing method in this population. Using exercise treadmill testing, Farkouh et al were able to safely discharge 46% of patients without hospital admission.⁵ Although an improvement over standard admission for all patients, this approach still had poor specificity with 54% of patients being admitted, and only 7% having cardiac events at 30 days. Stowers et al implemented nuclear imaging in intermediate-risk patients and decreased length of stay by 2 days and decreased cost by \$1800 per patient.¹⁶ However, their results lack external validity as they excluded patients with known coronary artery disease which accounts for a substantial portion (14-30%) of those with intermediate-risk chest pain.^{5,14} They also implemented exercise treadmill testing in those with negative perfusion images. Among intermediate-risk patients, 18% are unsuitable to undergo exercise treadmill testing²⁸, further limiting the implementation of their approach. Observation units improve resource consumption, but their efficiency in managing patients with intermediate-risk chest pain is limited by suboptimal cardiac testing.

High Quality Care Can Be Provided in Observation Units

If a widespread OU policy is adopted for intermediate-risk patients with chest pain, a significant number of patients (5-19%) will prove to have ischemic heart disease and will require hospital admission. Given this relatively high prevalence of disease, it is important these patients receive the same level of care as that provided in the hospital. An Italian trial by Conti, et al²⁹ treated patients with ACS entirely in a chest pain unit. These patients had similar outcomes at less hospital cost compared to those treated in the coronary care unit. Although in the US these patients would be transferred to a coronary care unit once their cardiac biomarkers became positive, these results demonstrate that high-quality care can be provided in OUs.

Summary of Inefficiencies Relating to the

Evaluation of Patients with Chest Pain

Care patterns among patients with intermediate-risk chest pain commonly deviate from established guidelines. This variability decreases the efficiency of health care delivery. OUs may offer a solution to care variability and improve efficiency. However, conventional testing options are suboptimal for use in patients with intermediate-risk chest pain. Improved testing options are needed to increase health care efficiency.

Cardiac Magnetic Resonance Imaging

Cardiac Magnetic Resonance Imaging Has Superior Sensitivity and Specificity When Compared to Traditional Testing Modalities

Nagel et al evaluated the ability of stress CMR to detect clinically significant coronary stenosis (> 50% luminal diameter) and compared results to stress echocardiography in a highly selected group of 208 patients with suspected coronary artery disease³⁰. Study subjects underwent stress CMR testing, stress echocardiography, and cardiac catheterization. Stress CMR proved significantly more sensitive (86.2% versus 74.3%, $p < 0.05$) and specific (85.7 versus 69.8%, $p < 0.05$) than stress echocardiography. These findings were expanded by Plein et al³¹, who performed stress CMR exams in 72 patients with NSTEMI ACS within 72 hours of hospitalization and demonstrated a 96% sensitivity and 83% specificity in patients with coronary stenosis > 70%.

Preliminary Data in Stress CMR Suggests it Could Be an Ideal Test for ED and OU Patients

Magnetic Resonance Imaging Has Been Adapted to Cardiac Applications Over the Past Two Decades. During this time, evolutions in imaging techniques have allowed CMR to emerge as the superior imaging modality for cardiac function and ischemia. As a result, CMR has moved out of the research arena and is used daily in clinical care. However, the application of CMR has traditionally been limited to inpatients or outpatients. Recent developments allowing the imaging of ongoing myocardial ischemia and infarction³²⁻³⁴ over the past 5 years have made CMR an attractive option for ED and OU use.

CMR Accurately Detects Ongoing Myocardial Ischemia. Two techniques, perfusion imaging and T-2 weighted imaging, have recently proven extremely sensitive for ongoing myocardial ischemia. Kwong et al demonstrated resting myocardial perfusion imaging was 100% sensitive for ongoing myocardial ischemia in the subjects (n = 10) with ongoing ischemia in their analysis.²⁴ These findings were complimented by Plein et al who performed stress CMR exams in 72 patients with NSTEMI ACS within 72 hours of hospitalization. In these subjects, perfusion imaging alone (resting and stress) was 88% sensitive and 83% specific for significant coronary stenosis.³¹

T-2 weighted imaging has also shown great promise for detecting ongoing myocardial ischemia. Abdel-Aty et al³² first demonstrated the ability of T2-weighted imaging to detect acute ischemia. In their analysis of 73 patients with MI, T2-weighted images combined with delayed enhancement was able to distinguish acute from chronic MI with a specificity of 96%. Cury and colleagues further expanded this work by demonstrating that resting CMR incorporating T2-weighted images was able to detect 4 of 4 ED patients with myocardial infarction before cardiac markers were elevated.³³ Because CMR can detect ongoing myocardial ischemia, resting followed by stress imaging can be performed before serial cardiac markers are completed.

CMR Has an Acceptable Test Performance Time. Magnetic resonance imaging has been criticized for having long image acquisition times. Plein et al performed resting and stress perfusion, resting and stress wall motion, coronary angiography, and delayed enhancement with a mean image acquisition time of

62.5 minutes / subject.³¹ Although longer than some modalities, this acquisition time is shorter than nuclear medicine which often requires 1 or 2 days for resting and stress imaging.

CMR Results Correlate With Long Term Prognosis. Correlating stress CMR to clinical prognosis, members of this research team have previously shown the significant correlation between dobutamine stress CMR and long term prognosis.³⁵ This correlation holds true in ED patients as well, demonstrated when Ingkanisorn et al. performed stress CMR imaging in ED patients with negative troponin results.³⁶ In their population of ED patients, the sensitivity of stress CMR for significant coronary disease at 1 year was 100%, with 93% specificity.

CMR Testing Has Been Used in ED Subjects with Chest Pain

Several investigators have successfully implemented CMR testing in research protocols evaluating ED patients.^{24,33,36} These results demonstrate the feasibility of obtaining CMR imaging in this population, and provide estimates for technical efficacy and diagnostic accuracy. Importantly, these protocols have not evaluated the effect of CMR imaging when implemented in a clinical care algorithm on patient outcomes, efficiency, or resource consumption.

Resting CMR has been studied in 161 ED patients with chest pain by Kwong and colleagues.²⁴ Patients were evaluated by resting CMR followed by inpatient evaluations, including serial cardiac biomarkers. This protocol utilized measurement of wall motion abnormalities and incorporated information from gadolinium infusion to detect areas of decreased perfusion or delayed

enhancement. During hospitalization or follow-up, 25 patients (15.5%) had evidence of ACS. Resting CMR detected all 10 patients experiencing myocardial infarction, but only detected 12 of 15 patients who likely had unstable angina at presentation. The sensitivity and specificity of resting CMR to detect ACS in this population was 84% and 85%, respectively. More recently, Cury and colleagues³³ demonstrated that resting CMR incorporating T2-weighted images detected 4 of 4 ED patients with myocardial infarction before cardiac markers were elevated. However, similar to Kwong's findings, resting CMR only detected 7 of 9 patients with unstable angina, again underscoring the importance of stress imaging.

Although these results are encouraging, several points are noteworthy. Resting CMR was very sensitive for ongoing myocardial infarction, but less so for patients who likely had unstable angina. All 3 of the patients missed were detected at 6- to 8-week follow up: one returned with a ST-segment elevation MI, one returned with unstable angina, and one had significant left anterior descending coronary artery stenosis on a subsequent hospitalization. This finding highlights the need for stress imaging in the ED patient population to detect those with unstable angina, especially given that 2.3% of patients with unstable angina are inadvertently discharged home from the ED and are at high-risk for adverse events⁹.

Stress CMR was investigated by Ingkanisorn and colleagues among 135 ED patients with chest pain.³⁶ In this protocol, patients were first excluded from having myocardial infarction using serial troponin measurements and then

underwent adenosine stress CMR. This protocol demonstrated 100% sensitivity and 93% specificity for significant coronary disease at 1 year. These results demonstrate the added value of stress imaging to CMR in ED patients with chest pain. Additionally, these findings suggest that stress CMR in ED patients is feasible and safe. However, given that this is a single center investigation, repetition at other institutions is warranted. Importantly, this investigation did not measure the impact of stress CMR on efficiency of health care delivery, care patterns, resource utilization, or ED throughput.

Summary of CMR Advantages

In patients with chest pain, CMR testing has several potential advantages compared to traditional testing including superior accuracy for diagnosing significant coronary disease and a high sensitivity for detecting ongoing myocardial ischemia. However, in order to detect ED patients with unstable angina, stress imaging must be performed.

An OU-CMR Strategy Is Likely to Decrease Resource Utilization

Combining OU care and CMR testing capitalizes on the strengths of CMR testing while maintaining the efficiency of OU care. As discussed previously, OU care represents a highly efficient method for evaluating patients with chest pain, but implementation in the subset of patients with intermediate-risk chest pain has been hampered by suboptimal testing. The advantages of CMR testing likely represent a solution to this dilemma. Improvements in resource utilization are likely to result from the mechanisms listed below.

Increased Accuracy

High specificity and could reduce unnecessary testing resulting from false positive tests. Cardiac catheterization is an invasive test with a major complication rate of 1-2%.²⁶ Furthermore, an invasive approach incorporating cardiac catheterization increases costs by \$4320 when applied to low- and intermediate-risk patients with chest pain.¹⁷ Thus, the ideal diagnostic protocol would eliminate diagnostic catheterizations in patients not requiring revascularization. Current rates of catheterization among intermediate-risk chest pain patients admitted to the hospital are 37-56%, with only half of those leading to revascularization.^{13,15,16} This 50% rate of negative catheterizations represents a poor use of resources and carries significant cost. A more accurate diagnostic test prior to cardiac catheterization could dramatically improve efficiency. In support of this concept, Plein et al³¹ suggested their stress testing protocol incorporating cardiac magnetic resonance (CMR) could prevent cardiac catheterization in 33% of ACS patients with unstable angina and non-ST segment elevation.

Applying a high sensitivity test to patients with ACS can improve resource utilization by preventing the discharge of patients with ACS. Such patients, when inadvertently discharged from the ED, have poor outcomes compared to those hospitalized.⁹ In addition, these patients are a high medical-legal risk and represent a leading cause of malpractice pay-outs for emergency physicians. Additionally, a high sensitivity test may also lead to early diagnosis of ACS and earlier treatment which may confer better clinical outcomes.

Avoidance of Unnecessary Admissions

As previously discussed, as many as 85% of patients with intermediate-risk chest pain admitted to the hospital will not ultimately have ACS as a cause of their symptoms. Given the large number of patients admitted annually with chest pain, this “over-triage” represents a massive consumption of inpatient resources. As a solution, an OU-CMR strategy uses an accurate diagnostic testing protocol to determine the need for admission to the hospital. Reducing the proportion of patients with unnecessary hospital admissions is likely to improve efficiency.

Increased Speed

CMR appears to be extremely sensitive for ongoing myocardial ischemia. This attribute may allow cardiac imaging to be performed without waiting for serial cardiac markers. Therefore, although CMR images take longer to acquire than other techniques, high sensitivity for detecting ongoing ischemia may allow imaging to occur earlier and enhance efficiency. Additionally, the high sensitivity of CMR may completely remove the need for serial cardiac markers after cardiac testing, which would facilitate rapid discharge.

Summarizing the Limitations in the Existing Literature

The Data Supporting OU Implementation in ED Patients with Intermediate-Risk Chest Pain is Limited in Quantity and Depth

Importantly, OU management of these patients is accepted by the ACC/AHA guidelines.¹¹ However, as previously discussed in detail, the existing data have investigated highly selected subgroups of intermediate-risk patients

and have not addressed the broader subset of patients classified as intermediate-risk.

The Implementation of CMR in ED Patients with Chest Pain Has Not Been Investigated as Part of a Clinical Care Algorithm

The existing investigations have examined the diagnostic accuracy of CMR testing in ED patients. In these investigations, CMR has been used as a research intervention and has been additive to usual care. While this design provides an excellent assessment of diagnostic accuracy, these investigations have not examined the impact of implementing a CMR protocol as a component of a clinical care algorithm. As a result, the impact of CMR testing when used as a clinical test is unknown. Furthermore, the effect of CMR testing on the efficiency of health care delivery is also unexplored.

The Combination of Observation Unit Care with CMR Testing Has Not Been Previously Described

Based on the strengths of CMR imaging and OU care, the combination of these approaches intuitively should improve health care efficiency. However, descriptions of this approach to caring for ED patients with chest pain are lacking.

Moving Beyond the Current Limitations

In order to improve the efficiency of health care delivery to patients with intermediate-risk chest pain, we have designed a prospective randomized clinical trial comparing an OU-CMR approach to standard hospital admission.

The purpose of this research is to investigate the following hypotheses and specific aims among patients presenting to the ED with chest pain at intermediate-risk for ACS:

Research hypothesis 1

Patients with intermediate-risk chest pain in an OU CMR protocol will have lower direct cost for their index hospitalization compared to standard inpatient care.

Specific Aim 1:

Compare among groups the direct cost of care from the index hospital visit.

Research hypothesis 2

An OU CMR protocol for patients with intermediate-risk chest pain will significantly improve the accuracy of cardiovascular admission decisions when compared to standard care.

Specific Aim 2:

Compare the proportion of correct cardiovascular admission decisions between groups. Correct cardiovascular admission decisions are based on the premise that patients with ACS should be admitted to the hospital and those without ACS should be discharged home.

The long term objective is to improve the healthcare delivery process by informing patients, care providers, and policy makers of the most efficient models for evaluating ED patients with chest pain. The intent of this research is to provide preliminary data on the potential cost and admission accuracy improvements resulting from an OU-CMR strategy. These data will be used to

determine whether a large multi-center trial should be conducted and to inform the design of such a study.

Summary

Combining CMR with OU Care Is an Exciting Opportunity to Improve the Efficiency of Health Care Delivery to Patients with Intermediate-Risk Chest Pain.

OU care has been shown to be more efficient than standard hospital admission. However, achieving this increased efficiency has been challenging in intermediate-risk chest pain patients because of limitations of traditional cardiac testing. Recently CMR has emerged as a highly accurate imaging modality that may be well suited for use in the OU. Because of high sensitivity to ongoing cardiac ischemia, CMR can be performed early after the patient's presentation and in parallel to obtaining serial cardiac markers. Because of the increased accuracy of CMR, it can be expected that this testing may allow use in a broader definition of intermediate-risk patients and decrease unnecessary invasive testing rates. These effects are expected to increase efficiency which can be measured primarily as decreased cost of care and secondarily as an improvement in the accuracy of cardiovascular admission decisions. The proposed clinical trial will compare measures of efficiency among OU-CMR and inpatient care strategies.

REFERENCES

1. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y, for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics--2007 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2007;115:e69-171.
2. McCaig L, Nawar E. National Hospital Ambulatory Medical Care Survey: 2004 emergency department summary. Advance data from vital and health statistics; no 372. Hyattsville, MD: National Center for Health Statistics. 2006.
3. Christenson J, Innes G, McKnight D, Thompson CR, Wong H, Yu E, Boychuk B, Grafstein E, Rosenberg F, Gin K, Anis A, Singer J. A Clinical Prediction Rule for Early Discharge of Patients With Chest Pain. *Annals of Emergency Medicine* 2006;47:1-10.
4. Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A Randomized Controlled Trial of Multi-Slice Coronary Computed Tomography for Evaluation of Acute Chest Pain. *Journal of the American College of Cardiology* 2007;49:863-871.
5. Farkouh ME, Smars PA, Reeder GS, Zinsmeister AR, Evans RW, Meloy TD, Kopecky SL, Allen M, Allison TG, Gibbons RJ, Gabriel SE, The Chest Pain Evaluation in the Emergency Room (CHEER) Investigators. A Clinical Trial of a Chest-Pain Observation Unit for Patients with Unstable Angina. *N Engl J Med* 1998;339:1882-1888.
6. Heller GV, Stowers SA, Hendel RC, Herman SD, Daher E, Ahlberg AW, Baron JM, Mendes de Leon CF, Rizzo JA, Wackers FJ. Clinical value of acute rest technetium-99m tetrofosmin tomographic myocardial perfusion imaging in patients with acute chest pain and nondiagnostic electrocardiograms. *J Am Coll Cardiol* 1998;31:1011-7.
7. Sprivilis PC, Da Silva JA, Jacobs IG, Frazer AR, Jelinek GA. The association between hospital overcrowding and mortality among patients admitted via Western Australian emergency departments. *Med J Aust* 2006;184:208-12.
8. Miro O, Antonio MT, Jimenez S, De Dios A, Sanchez M, Borrás A, Milla J. Decreased health care quality associated with emergency department overcrowding. *Eur J Emerg Med* 1999;6:105-7.

9. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, Griffith JL, Selker HP. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000;342:1163-70.
10. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE, 3rd, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC, Jr. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2002;40:1366-74.
11. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr., Chavey WE, 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC, Jr., Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction). *Circulation* 2007.
12. Katz DA, Griffith JL, Beshansky JR, Selker HP. The use of empiric clinical data in the evaluation of practice guidelines for unstable angina. *Jama* 1996;276:1568-74.
13. Gomberg-Maitland M, Murphy SA, Moliterno DJ, Cannon CP. Are we appropriately triaging patients with unstable angina? *American Heart Journal* 2005;149:613-618.
14. Calvin JE, Klein LW, VandenBerg EJ, Meyer P, Parrillo JE. Validated risk stratification model accurately predicts low-risk in patients with unstable angina*1. *Journal of the American College of Cardiology* 2000;36:1803-1808.
15. Tatum JL, Jesse RL, Kontos MC, Nicholson CS, Schmidt KL, Roberts CS, Ornato JP. Comprehensive strategy for the evaluation and triage of the chest pain patient. *Ann Emerg Med* 1997;29:116-25.
16. Stowers SA, Eisenstein EL, Th Wackers FJ, Berman DS, Blackshear JL, Jones AD, Jr., Szymanski TJ, Jr., Lam LC, Simons TA, Natale D, Paige KA, Wagner GS. An economic analysis of an aggressive diagnostic strategy with single photon emission computed tomography myocardial perfusion imaging and early exercise stress testing in emergency department patients who present with

chest pain but nondiagnostic electrocardiograms: results from a randomized trial. *Ann Emerg Med* 2000;35:17-25.

17. Desai AS, Solomon DH, Stone PH, Avorn J. Economic consequences of routine coronary angiography in low- and intermediate-risk patients with unstable angina pectoris. *The American Journal of Cardiology* 2003;92:363-367.

18. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL Jr. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). 2002. American College of Cardiology Web site.

19. Detrano R, Gianrossi R, Froelicher V. The diagnostic accuracy of the exercise electrocardiogram: a meta-analysis of 22 years of research. *Prog Cardiovasc Dis* 1989;32:173-206.

20. Gianrossi R, Detrano R, Mulvihill D, Lehmann K, Dubach P, Colombo A, McArthur D, Froelicher V. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. *Circulation* 1989;80:87-98.

21. Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. *J Am Coll Cardiol* 1997;30:595-606.

22. Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA, Russell RO, Jr., Cerqueira MD, St John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, Williams KA, Antman EM, Smith SC, Jr., Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol* 2003;42:1318-33.

23. Hilton TC, Thompson RC, Williams HJ, Saylor R, Fulmer H, Stowers SA. Technetium-99m sestamibi myocardial perfusion imaging in the emergency room evaluation of chest pain. *J Am Coll Cardiol* 1994;23:1016-22.

24. Kwong RY, Schussheim AE, Rekhraj S, Aletras AH, Geller N, Davis J, Christian TF, Balaban RS, Arai AE. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. *Circulation* 2003;107:531-7.

25. Udelson JE, Beshansky JR, Ballin DS, Feldman JA, Griffith JL, Handler J, Heller GV, Hendel RC, Pope JH, Ruthazer R, Spiegler EJ, Woolard RH, Selker HP. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. *Jama* 2002;288:2693-700.
26. Bashore TM, Bates ER, Berger PB, Clark DA, Cusma JT, Dehmer GJ, Kern MJ, Laskey WK, O'Laughlin MP, Oesterle S, Popma JJ, O'Rourke RA, Abrams J, Brodie BR, Douglas PS, Gregoratos G, Hlatky MA, Hochman JS, Kaul S, Tracy CM, Waters DD, Winters WL, Jr. American College of Cardiology/Society for Cardiac Angiography and Interventions Clinical Expert Consensus Document on cardiac catheterization laboratory standards. A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001;37:2170-214.
27. Committee on the Future of Emergency Care in the United States Health System. 2006. *Hospital-Based Emergency Care: At the Breaking Point*. Washington, DC: The National Academies Press:420.
28. Ramakrishna G, Milavetz JJ, Zinsmeister AR, Farkouh ME, Evans RW, Allison TG, Smars PA, Gibbons RJ. Effect of exercise treadmill testing and stress imaging on the triage of patients with chest pain: CHEER substudy. *Mayo Clin Proc* 2005;80:322-9.
29. Conti A, Pieralli F, Sammiceli L, Camaiti A, Vanni S, Grifoni S, Dovellini E, Antonucci D, Squillantini G, Mazzuoli F, Colombo G. Updated management of non-ST-segment elevation acute coronary syndromes: selection of patients for low-cost care: an analysis of outcome and cost effectiveness. *Med Sci Monit* 2005;11:CR100-8.
30. Nagel E, Lehmkuhl HB, Bocksch W, Klein C, Vogel U, Frantz E, Ellmer A, Dreysse S, Fleck E. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. *Circulation* 1999;99:763-70.
31. Plein S, Greenwood JP, Ridgway JP, Cranny G, Ball SG, Sivananthan MU. Assessment of non-ST-segment elevation acute coronary syndromes with cardiac magnetic resonance imaging. *Journal of the American College of Cardiology* 2004;44:2173-2181.
32. Abdel-Aty H, Zagrosek A, Schulz-Menger J, Taylor AJ, Messroghli D, Kumar A, Gross M, Dietz R, Friedrich MG. Delayed enhancement and T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. *Circulation* 2004;109:2411-6.

33. Cury RC, Shash K, Nagurney JT, Rosito G, Shapiro MD, Nomura CH, Abbara S, Bamberg F, Ferencik M, Schmidt EJ, Brown DF, Hoffmann U, Brady TJ. Cardiac magnetic resonance with T2-weighted imaging improves detection of patients with acute coronary syndrome in the emergency department. *Circulation* 2008;118:837-44.
34. Arai AE. Using Magnetic Resonance Imaging to Characterize Recent Myocardial Injury: Utility in Acute Coronary Syndrome and Other Clinical Scenarios. *Circulation* 2008;118:795-796.
35. Hundley WG, Morgan TM, Neagle CM, Hamilton CA, Rerkpattanapipat P, Link KM. Magnetic resonance imaging determination of cardiac prognosis. *Circulation* 2002;106:2328-33.
36. Ingkanisorn WP, Kwong RY, Bohme NS, Geller NL, Rhoads KL, Dyke CK, Paterson DI, Syed MA, Aletras AH, Arai AE. Prognosis of Negative Adenosine Stress Magnetic Resonance in Patients Presenting to an Emergency Department With Chest Pain. *Journal of the American College of Cardiology* 2006;47:1427-1432.

CHAPTER TWO

OBSERVATION UNIT CARE WITH STRESS CARDIAC MRI REDUCES
HOSPITAL COST IN ED PATIENTS WITH INTERMEDIATE-RISK CHEST PAIN

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Abstract

Background

Emergency department (ED) patients with chest pain at intermediate-risk for acute coronary syndrome (ACS) often receive relatively expensive 23 hour observation visits that may include cardiac catheterization, stress echocardiography or radioisotope imaging. This clinical trial compares the medical cost among patients with intermediate-risk chest pain managed with two diagnostic strategies: an observation unit cardiac MRI (OU-CMR) strategy versus inpatient care.

Methods and Results

A single center clinical trial randomized 110 patients with intermediate-risk chest pain (TIMI ≥ 2 or clinical impression) to OU-CMR (OU care, serial cardiac markers and stress CMR) or inpatient care (admission, care determined by the admitting provider). The primary outcome was index hospital visit cost, including hospital and provider costs. The secondary outcome was correct cardiovascular disposition. Acute coronary syndrome (ACS) occurred in 8/110 (7%) participants. In the OU-CMR group, 49/53 underwent stress CMR, 11/53 were admitted, 1 left against medical advice (AMA), 41 were discharged, and 2 had ACS. In the usual care group, 39/57 subjects initially received stress testing. 54/57 were admitted, 3 left AMA, and 6 had ACS. At 30 days, no subjects in either group experienced ACS after discharge. OU-CMR participants had reduced median cost (\$2062 vs. \$2680, $p < 0.001$) and a higher rate of correct cardiac disposition decisions (83% vs. 11%, $p < 0.001$).

Conclusion

In comparison with tertiary care admissions, an OU-CMR strategy reduces cost and improves cardiac disposition decisions with similar patient outcomes at 30 days in ED patients presenting with chest pain at intermediate-risk for ACS.

Current guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA)(1) recommend risk stratification of patients with chest pain into low, intermediate, and high-risk based on the likelihood of coronary disease and the probability of short term death or myocardial infarction (MI). Patients stratified as intermediate-risk are commonly admitted for periods of observation. These individuals represent >50% of admissions for chest pain(2), commonly have known coronary disease(3), and are expected to represent a growing segment of the aging US population.

Cardiac magnetic resonance imaging (CMR) is a relatively new, sensitive testing modality for identifying ACS. CMR stress protocols have been found to be feasible and accurate for identifying ACS in patients presenting for emergent evaluation of chest pain in a research setting.(4-6) Stress CMR testing is appealing because it can detect ongoing and inducible myocardial ischemia and can differentiate between new and old myocardial infarctions.(5, 7) These attributes may facilitate more rapid observation unit (OU) care in place of admissions to hospital floor beds among patients with intermediate-risk chest pain.

Implementing a CMR stress testing program requires equipment purchases and personnel training; for these reasons, it is associated with “up-front” expenses. In order for this to be a worthwhile investment, a CMR strategy would have to represent an improvement over existing models of care delivery. To determine the impact of an OU-CMR approach on direct cost of medical care, we implemented a clinical trial in emergency department (ED) patients with

intermediate-risk chest pain to compare the cost of this strategy to admission to an inpatient telemetry unit. We hypothesized that the increased accuracy of CMR combined with the efficiency of an OU setting would reduce the direct cost of medical care compared to admission to an inpatient telemetry unit.

Methods

A single-center randomized clinical trial was conducted from January, 2008, to March, 2009, with the primary intent to compare the direct cost of medical care. Participants were recruited from the ED at Wake Forest University Baptist Medical Center, a tertiary care hospital in Winston-Salem, NC, with an annual ED volume of approximately 93,000 visits per year. All participants gave written informed consent. The study protocol was approved by the Institutional Review Board of the sponsoring institution and is registered on clinicaltrials.gov (NCT00678639).

Participants were recruited by study personnel from 8am to 11pm Monday through Thursday and 8am to 11am on Friday and when the CMR scanner had capacity to conduct examinations within approximately 24 hours. Initial participant screening was conducted using chief complaints or by discussion with care providers. Review of records and / or interviews were then conducted to determine eligibility criteria. Intermediate-risk was defined as Thrombolysis in Myocardial Infarction (TIMI) risk score(8) ≥ 2 or physician clinical impression of intermediate or high likelihood that the symptoms represented ACS (providers were encouraged to use the ACC/AHA framework to make this determination)(1). Additional inclusion criteria were age ≥ 18 years, symptoms consistent with possible ACS, care provider impressions that an inpatient evaluation was required, and that the patient could be discharged home if cardiac disease was excluded. Patients were excluded for an initial elevated troponin I (>1.0 ng/ml), new ST-segment elevation (≥ 1 mV) or depression

(≥ 2 mV), inability to lie flat, systolic blood pressure < 90 mm Hg, contraindications to MRI (pacemaker, defibrillator, cerebral aneurysm clips, metallic ocular foreign body, implanted devices, claustrophobia), refusal of follow up procedures, terminal diagnosis with < 3 months to live, pregnancy, renal insufficiency (glomerular filtration rate < 45 cc/min), chronic liver disease, or a history of heart, liver, or kidney transplant. Eligible patients were then approached to discuss participation.

Consenting participants were randomized to one of two study groups. Randomization was stratified based on the presence of known coronary artery disease and the time of presentation (6am-3pm or 3pm-6am). Randomization was blocked within strata. Treatment assignments were generated by research staff using a manual procedure previously described(9) and placed in opaque, sealed, sequentially numbered envelopes for the study coordinator to access.

Patients were randomized to one of two study groups:

1. OU-CMR patients received care in an ED observation unit staffed by nurse practitioners and/or physician assistants and supervised by a board certified / board eligible emergency physician. Participants had orders placed for cardiac biomarkers to be obtained at 4 and 8 hours from the initial blood draw, and a stress CMR exam. If the 4 hour biomarker determination was completed and below the upper limit of normal, patients could undergo the stress CMR exam. Care providers were able to change testing strategies if needed for optimal patient

care. Interpretation of the CMR results, ordering additional testing, and patient disposition were determined by the care providers.

2. Inpatient care participants were admitted to the hospital and were cared for on the internal medicine, family medicine, or cardiology services. Testing in this group was determined by the care providers and unaffected by the study protocol. CMR imaging was available to participants in this study arm.

Sources of data were determined prior to study initiation and were contained in a sources of data document. Data collection templates were used to capture data prospectively that was determined a priori to be either unreliable or unavailable in the medical record. Initial electrocardiogram interpretation was conducted after enrollment by a study investigator (CDM) blinded to study group allocation. Other information was gathered from the electronic medical record or billing records using a structured review.

CMR imaging in OU-CMR participants was similar to current imaging protocols used for clinical stress testing at the primary institution. All imaging was performed with a 1.5 Tesla Siemens Magnetom Avanto system with Total Imaging Matrix technology (Siemens Medical Solutions, Munich, Germany) using a 108-144 x 192 matrix, a 30 to 42 cm field of view (FOV) and a 75% phase FOV. The imaging protocol could be modified by the care providers if felt to be clinically indicated. Specific imaging parameters are detailed in Table 1. Stress images were obtained using an adenosine infusion unless contraindicated in which case a dobutamine infusion was used. CMR image interpretation was

conducted immediately after image acquisition by board certified radiology or cardiology faculty with specialty training in CMR. Results were posted to the electronic medical record. Interpreting care providers were not blinded to treatment assignment.

Table I. Cardiac Imaging Parameters

Component	Orientation	Slice Thick- -ness (mm)	Flip Angle (degrees)	Band- width (Hz/pixel)	Echo Time (ms)	Repe- tition Time (ms)
Resting wall motion	2, 3, 4 chamber and 3 short axis	8	90	930	1.16	38.5
T2-weighted dark blood	2, 3, 4 chamber and 3 short axis	15	180	180	87	800
Stress agent infusion (adenosine or dobutamine) and contrast injection (gadopentetate dimeglumine 0.1 mmol/kg)						
Stress perfusion	3 short axis	8	12	521	1.18	180
Contrast injection (gadopentetate dimeglumine 0.1 mmol/kg)						
Rest perfusion	3 short axis	8	12	521	1.18	180
Delayed enhancement	2, 3, 4 chamber and 10 short axis	8	25	130	3.32	800

Participants were contacted by telephone at 30 days using a scripted follow-up dialogue(10) to determine cardiac events since discharge. Hospitalization records were obtained for those reporting hospitalizations at any facility since discharge. The occurrence of ACS within 30 days of enrollment was determined by adjudication using a consensus of two board certified emergency physicians blinded to treatment assignment.

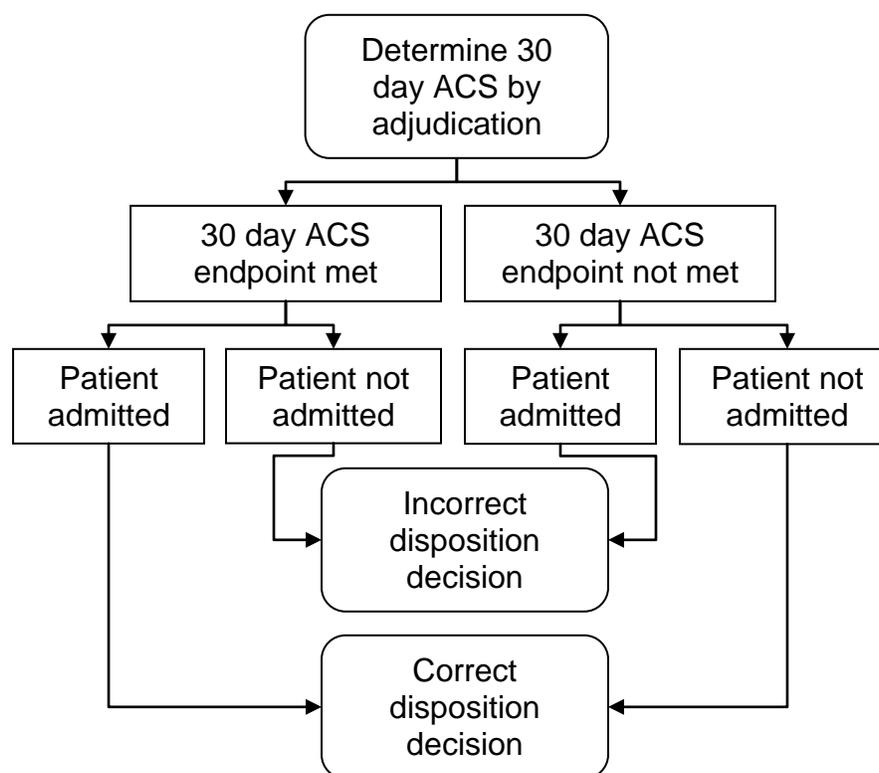
ACS was defined as one of the following: i. Acute myocardial infarction ii. Ischemia symptoms leading to revascularization iii. Death likely related to cardiac ischemia iv. Discharge diagnosis of definite or probable unstable angina with evidence of coronary stenosis > 70% or inducible ischemia on stress testing in participants not undergoing cardiac catheterization.

Acute myocardial infarction was defined as a troponin I > 1.0 ng/ml in the presence of ischemic symptoms. Troponin I was measured in the central lab using either the TnI-Ultra™ assay using the ADVIA Centaur platform (Siemens) or the Access® AccuTnI™ Troponin I Assay using the dxi800s platform (Beckman Coulter).

The primary outcome was direct medical cost of the index hospital visit. Direct medical cost was calculated as the sum of hospital and provider cost. For hospital cost, itemized patient charges were converted to cost using 2008 departmental specific cost:charge ratios used to file cost reports with Centers for Medicare and Medicaid Services (CMS) annually. Provider cost was determined by using current procedural terminology codes from each charged service, converting to physician work relative value units using the CMS physician fee

schedule, and subsequently converting to dollars using the Medicare conversion factor.(11) The secondary outcome of this trial was correct cardiac disposition, defined a priori as shown in Figure 1.

Figure 1. Determination of Correct Cardiac Disposition Decisions



Based on preliminary cost data collected from the study institution, we anticipated that we could detect an approximate \$2000 difference in direct cost of the index hospital visit (\$8000 vs \$6000) favoring the OU-CMR group. The standard deviation of cost in the preliminary data was \$3400. To detect a difference of \$2000 using a parametric approach, 47 participants per arm were required to provide 0.8 power (2 sided 0.05 level of significance), without attrition. Accounting for a conservative 15% attrition rate (unable to undergo CMR, missing data), sample size was set at 110. Data were reviewed after

enrollment of 40 and 80 participants by the study team with the safety monitor and an interim analysis was presented in abstract form on the first 50 participants. These analyses were not intended or used to determine study termination or adjust sample size and therefore no adjustment for multiple comparisons was made.

The primary outcome, cost, was analyzed as a continuous variable. First, the distribution of cost was analyzed and noted to be non-normally distributed. Additionally, cost data were incomplete for four patients (3 in the inpatient care group and 1 in the OU-CMR group) as they left before completion of their hospital evaluation. Log, log-log, and square root transformations were explored without adequate correction of the data's right skewness. Nonparametric comparisons were then implemented using the Wilcoxon rank-sum test to assess differences between the two groups including those with incomplete (censored) data. To understand the impact of censoring, an additional Wilcoxon rank-sum test was conducted after excluding the censored patients, and multiple imputation using propensity scores was implemented treating censored cost data as missing. Wilcoxon rank-sum tests were then conducted on each data set created. Additionally, since our hypothesis is that the OU-CMR group will have lower costs, we further analyzed the cost data by assigning the censored subjects in the inpatient care group the lowest cost ranks and the one censored subject in the OU-CMR group the highest cost rank. As an additional confirmatory analysis, we used Kaplan-Meier methods to estimate the median costs and a log rank test to compare the costs while accounting for the censored

data. All analyses gave similar results and conclusions, so only the results from the nonparametric analyses including the four censored individuals are presented. Since 3 of these were in the inpatient care group, comparisons will be conservative. Subsequently analysis of covariance (ANCOVA) using the rank transformation(12) was performed to adjust for covariates. In the ranked ANCOVA models, candidate covariates included the 4 levels of stratification at the time of randomization (known coronary disease as binary, time of day of presentation 6a-3p or 3p-6a), age (continuous and binary as ≥ 65 years), TIMI risk score, gender, race, confirmed prior heart failure, confirmed prior MI, confirmed prior coronary revascularization, and chest pain at ED arrival. First, interactions between treatment group and each covariate were examined. One significant interaction was present between age ≥ 65 and treatment group but not included in the final model as its effect had a quantitative effect only and complicated the interpretation of the main effects of the model. The effect of this interaction is shown in subgroup analysis in Appendix 1. The 4 stratification levels were then entered into the models. Confounding was evaluated by comparing the effect of treatment group between the full model (all covariates) to the reduced model (treatment group and strata). Further post-hoc comparisons were conducted using subgroup analyses and reported as differences in median costs per group. Correct cardiac disposition decision was analyzed as a binary outcome. Comparison of proportions among groups was made using a Fisher's exact test. Statistical analysis was conducted using SAS Enterprise Guide v4.1,

SAS v9.1.2, SAS Institute Inc, Cary, NC, and GraphPad InStat Version 3.06,
GraphPad Software Inc., San Diego, CA.

Results

Between January 7th, 2008, and March 4th, 2009, 967 patients were screened, 178 approached, and 110 enrolled with 57 participants randomized to inpatient care and 53 randomized to OU-CMR. (Figure 2) Baseline demographic information and past medical history were similar among study groups. (Table II) Study participants had a median age of 56 years, half were women, and 68% Caucasian. The prevalence of established coronary artery disease upon enrollment in the study was 25% with 22% of all participants confirmed to have had prior coronary revascularization. Most participants presented with a chief complaint of chest pain (92%), had multiple episodes of symptoms (59%), and had chest pain present on arrival to the ED (69%). (Table III) A minority of patients had pain that was reproducible on exam (7%) or described as pleuritic (10%). No significant differences in vital signs or physical exam findings were seen between groups.

Figure 2 Screening, Enrollment, Randomization, and Follow-up of Participants

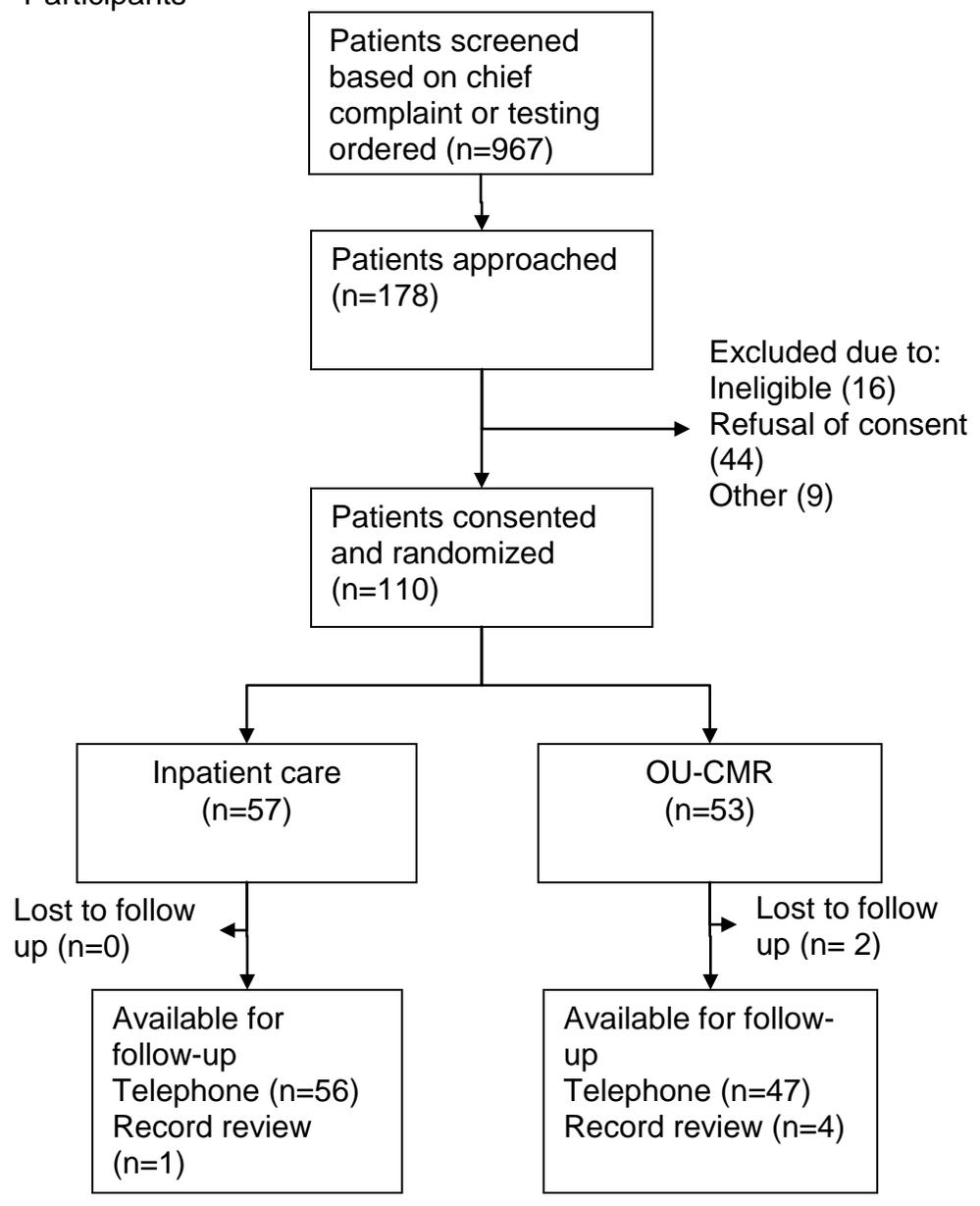


Table II. Participant Demographics and Past Medical History

Patient Characteristics	Inpatient care n / N (%)	OU-CMR n / N (%)	P value
Demographics			
Age (yrs)†	57 (47, 64)	55 (48, 61)	0.58
Age ≥ 65 years	10/57 (18)	8/53 (15)	0.80
Female sex	27/57 (47)	28/53 (53)	0.70
White race	40/57 (70)	35/53 (66)	0.69
Medical History			
Hypertension	43/57 (75)	36/53 (68)	0.40
Diabetes mellitus	23/57 (40)	20/53 (38)	0.92
Current smoking	18/57 (32)	18/53 (34)	0.84
Hyperlipidemia	44/57 (77)	39/53 (74)	1.00
Prior Heart Failure	3/57 (5)	2/53 (4)	1.00
Established CAD	16/57 (28)	11/53 (21)	0.38
Prior MI (%)	15/57 (26)	8/53 (15)	0.17
Prior revascularization	15/57 (26)	9/53 (17)	0.26
Prior CABG	3/57 (5)	2/53 (4)	1.00
† = data presented as median (1 st quartile, 3 rd quartile) OU-CMR = Observation unit cardiac magnetic resonance; CAD = Coronary artery disease; MI = myocardial infarction; CABG = Coronary artery bypass graft			

Table III. Presenting Characteristics and Physical Exam Findings

	Inpatient care n / N, (%)	OU-CMR n / N, (%)	P value
Presenting Characteristics			
Chest pain chief complaint	52/57 (91)	49/53 (92)	1.00
Chest pain at rest	49/57 (86)	43/53 (81)	0.61
Multiple episodes of symptoms within 24 hours	32/57 (56)	33/53 (62)	0.56
Chest pain present on arrival to the ED	45/57 (79)	31/53 (58)	0.02
Chest pain pleuritic	7/55 (13)	4/52 (8)	0.53
Canadian Cardiovascular Society Angina Severity Score†	0 (0, 2) n=53	0 (0, 2) n=51	0.44
Time from onset of last episode to arrival (h)†	2.5 (1.0, 8.0)	3.5 (1.0, 10.0)	0.59
Duration of last episode (h)†	2.0 (0.75, 5.5)	1.0 (0.25, 5.0)	0.53
Physical Exam			
Heart rate (beats/min)†	75 (70, 91)	77 (68, 86)	0.99
Systolic BP (mmHg)†	141 (128, 159)	139 (124, 155)	0.47
Murmor	0/57 (0)	0/53 (0)	-
Rales	0/57 (0)	1/53 (2)	0.48

JVD	0/57 (0)	0/53 (0)	-
Chest pain reproducible	4/56 (7)	4/53 (8)	1.00
† = data presented as median (1 st quartile, 3 rd quartile); OU-CMR = Observation unit cardiac magnetic resonance; ED = emergency department; BP = blood pressure; JVD = jugular venous distention			

Results of the ED evaluation are noted in Table IV. The ED care provider's unstructured assessment of the likelihood of ACS within 30 days was similar among both groups (inpatient care median 15% vs. OU-CMR median 10%, $p=0.20$). The ED physician's overall impression was most commonly atypical chest pain (50%) or unstable angina (41%) and did not vary by group (p value=0.85, Fisher's exact test). Most participants had a TIMI risk score of 2 (36%) or 3 (30%), and did not vary by group (p value = 0.58, Fisher's exact test).

Table IV. Emergency Department Evaluation Results

ECG findings	Inpatient care n / N (%)	OU-CMR n / N (%)	P value
ST segment depression	0/57 (0)	1/53 (2)	0.48
Known to be old	0/57 (0)	1/53 (2)	
ST segment elevation	0/57 (0)	0/53 (0)	-
T wave inversion	8/57 (14)	6/53 (11)	0.50
<2mm, old	4/57 (7)	3/53 (6)	
<2mm, not known to be old	1/57 (2)	0/53 (0)	
>2mm, old	3/57 (5)	1/53 (2)	
>2mm, not known to be old	0/57 (0)	2/53 (4)	
Left bundle branch block	0 (0)	0 (0)	-
Right bundle branch block	0/57 (0)	2/53 (4)	0.23
Pathological Q waves	6/57 (11)	6/53 (11)	0.52
Known to be old	5/57 (9)	3/53 (6)	
Overall ECG classification			0.96
Normal	24 (42)	25 (47)	
Nonspecific ST-T wave changes	22 (39)	17 (32)	
Early repolarization only	1 (2)	0 (0)	
Abnormal but not diagnostic of ischemia	3 (5)	4 (8)	
Infarction or ischemia known to be old	3 (5)	3 (6)	

Infarction or ischemia not known to be old	4 (7)	4 (8)	
Suggestive of acute MI	0 (0)	0 (0)	
Risk Stratification			
ED physician assessment of % likelihood of ACS within 30 days†	15 (10, 25)	10 (7.8, 20)	0.20
ED Physician overall impression:			0.85
Acute MI	0/57 (0)	0/50 (0)	
Unstable angina	25/57 (44)	19/50 (38)	
Atypical	27/57 (47)	26/50 (52)	
Non-ischemic	5/57 (9)	5/50 (10)	
TIMI risk score			0.58
0	1/57 (2)	1/53 (2)	
1	10/57 (18)	8/53 (15)	
2	18/57 (32)	22/53 (42)	
3	17/57 (30)	16/53 (30)	
4	11/57 (19)	5/53 (9)	
5	0/57 (0)	1/53 (2)	
<p>† = data presented as median (1st quartile, 3rd quartile); OU-CMR = Observation unit cardiac magnetic resonance; MI = myocardial infarction; ED = emergency department; ACS = acute coronary syndrome; TIMI = thrombolysis in myocardial infarction</p>			

During the index hospital visit, most participants had at least 3 serial troponin measurements (inpatient care 86% vs. OU-CMR 96%, $p=0.10$). More participants in the inpatient care group had stress echocardiography testing (54% vs. 4%, $p<0.001$) whereas more participants in the OU-CMR group had stress CMR testing (92% vs. 16%, $p<0.001$).

In the OU-CMR group, stress CMR imaging was accomplished over a median 53 minutes (Q1 44, Q3 58). No patients experienced ventricular arrhythmias, hypotension, cardiac arrest, persistent ST-segment elevation, or death during CMR imaging. Four subjects had CMR ordered but not completed due to leaving against medical advice (AMA) ($n=1$), troponin elevation before testing ($n=1$), development of ventricular tachycardia prior to testing ($n=1$), and care provider ordered another form of stress testing ($n=1$). Of the 49 patients who started CMR testing, 46 completed all planned imaging components. Early terminations were due to vomiting ($n=1$), patient request ($n=1$), and tachycardia with stress adenosine infusion ($n=1$). Of these three, two studies contained adequate information for disposition without additional testing and one participant was admitted for cardiac catheterization.

OU-CMR participants with CMR imaging had a median left ventricular ejection fraction of 61% (Q1 = 57%, Q3 = 65%). Resting wall motion abnormalities were present on 6/49 exams. No evidence of acute myocardial ischemia on any imaging component was noted on 43/49 exams. Inducible ischemia was present on 6/49 exams, all detected as an unmatched defect on myocardial perfusion imaging. Abnormal delayed enhancement suggestive of old

MI was present in 3/49 exams. No participants had abnormal T2-weighted imaging; however, frequent artifacts limited the clinical utility of this imaging component. Additional details on the diagnostic performance of CMR are provided in Appendix 2.

After randomization, 3/57 participants in the inpatient care group left against medical advice before cardiac imaging was performed and the remainder of participants were admitted to the hospital for care. (Table V) Admitting services included cardiology (n=29), internal medicine (n=16), family medicine (n=8), and geriatric medicine (n=1). In the OU-CMR group, 1/53 left against medical advice before cardiac imaging was performed, 11/53 were admitted after their OU evaluation, and the remainder were discharged home. Of the 11 who were admitted, 10 were admitted to cardiology, 1 was admitted to internal medicine. Median length of stay was shorter in the OU-CMR group (25.7h vs. 29.9h, $p=0.003$).

Table V. Cardiac Testing and Clinical Outcomes During Index Hospital Visit or Observation Unit Care

	Inpatient care n / N (%)	OU-CMR n / N (%)	P value
≥ 3 cardiac markers	49/57 (86)	51/53 (96)	0.10
Stress CMR	9/57 (16)	49/53 (92)	<0.001
Resting echo	1/57 (2)	1/53 (2)	1.00
Stress echo	31/57 (54)	2/53 (4)	<0.001
Nuclear medicine imaging	0/57 (0)	0/53 (0)	-
Cardiac catheterization	9/57 (16)	8/53 (15)	1.00
Cardiac catheterization without antecedent stress testing	8/57 (14)	1/53 (2)	0.03
≥ 3 cardiac markers and ≥ 1 stress test or cardiac catheterization	42/57 (74)	50/53 (94)	0.004
Clinical outcomes – index hospital visit			
Acute coronary syndrome	6/57 (11)	2/53 (4)	0.27
Cardiovascular death	0/57	0/53	-
Myocardial infarction	1/57 (2)	1/53 (2)	1.00
Revascularization	5/57 (9)	2/53 (4)	0.44
PCI	5/57 (9)	1/53 (2)	0.21

CABG	0/57 (0)	1/53 (2)	0.48
Unstable angina	2/57 (4)	0/53 (0)	0.50
Length of stay†	29.9 (26.7, 35.7)	25.7 (20.7, 31.3)	0.003
Hospital admission (defined by transfer to an inpatient bed)	54/57 (95)	12/53 (23)	<0.001
Correct cardiovascular disposition	6/54 (11)	43/52 (83)	<0.001
Unadjusted direct medical cost†	\$2680	\$2062	<0.001
Clinical outcomes – after discharge through 30 days			
Acute coronary syndrome	0/57 (0)	0/53 (0)	-
Cardiovascular death	0/57 (0)	0/53 (0)	-
Myocardial infarction	0/57 (0)	0/53 (0)	-
Revascularization	0/57 (0)	0/53 (0)	-
PCI	0/57 (0)	0/53 (0)	-
CABG	0/57 (0)	0/53 (0)	-
<p>† = data presented as median (1st quartile, 3rd quartile); OU-CMR = Observation unit cardiac magnetic resonance; MI = myocardial infarction; ED = emergency department; ACS = acute coronary syndrome; TIMI = thrombolysis in myocardial infarction</p>			

The incidence of ACS was similar among both groups (inpatient care 6/57 (11%) vs. OU-CMR 2/53 (4%), $p=0.27$). (Table V) Of the 6 patients experiencing ACS in the inpatient care group, 3 received PCI as the only qualifying ACS event, 1 met the definition of unstable angina and underwent PCI, 1 experienced MI and received PCI, and 1 only met the definition of unstable angina. Of the 2 patients in the OU-CMR group with ACS, 1 underwent CABG and 1 experienced a myocardial infarction and was treated with PCI. No patients in either group experienced ACS after discharge from the hospital.

The median direct cost of the index hospital visit was lower in OU-CMR participants (\$2062 vs. \$2680, Wilcoxon-Rank Sum $p<0.001$). (Tables V and VI) This difference remained significant when conducting the analysis excluding censored participants, when using multiple imputation techniques to estimate censored costs, and when using the most conservative assumptions about censored data in the ranked ANCOVA models. Kaplan-Meier survival curves using cost in place of time and “against medical advice” as censored were heterogeneous with median costs favoring OU-CMR (\$2088 vs. \$2717, Log-rank p value = 0.01). Analysis of covariance using a rank transformation of the data was conducted. In a full model containing all of the candidate covariates, OU-CMR was associated with a rank reduction of 18.5 and significantly contributed to the model ($p<0.001$). In a reduced model containing the 4 levels of randomization strata, OU-CMR was associated with a 22.4 rank reduction ($p<0.001$). This suggests that confounding is present but the confounding does not have a large impact on the main effect. The effect of covariates is

demonstrated in Table VI where the unadjusted median cost for each level of covariate (for class variables) is shown with the adjusted p value from the full model. In subgroup analysis, OU-CMR demonstrated a reduction in median cost across most subgroups examined. (Appendix 1)

Table VI. Median Cost Among Subgroups and Adjusted Statistical Significance			
Subgroup name	Number of participants	Median Cost	Adjusted p-value*
Treatment Group			0.002
Inpatient Care	53	\$2680	
OU-CMR	57	\$2062	
Age			0.96
Age ≥ 65	18	\$2607	
Age <65	92	\$2408	
Age (continuous)	110	-	0.51
TIMI Risk Score (continuous)	110	-	0.63
Gender			0.39
Male	55	\$2559	
Female	55	\$2344	
Race			0.20
Caucasian	75	\$2551	
Other	35	\$2311	
Time of presentation			0.30
6a-3p	90	\$2388	
3p-6a	20	\$2507	
Established CAD			0.56
Established CAD	28	\$2606	

No Established CAD	82	\$2356	
Prior Heart Failure (confirmed)			0.04
Prior Heart Failure	5	\$2367	
No Prior Heart Failure	105	\$3159	
Prior MI (confirmed)			0.48
Prior MI	22	\$2644	
No prior MI	88	\$2325	
Prior Revascularization (confirmed)			0.24
Prior Revascularization	24	\$2606	
No Prior Revascularization	86	\$2356	
Chest pain at ED arrival			0.04
Chest pain	76	\$2635	
No chest pain	34	\$2088	
OU-CMR = Observation unit cardiac magnetic resonance; TIMI = Thrombolysis in myocardial infarction; MI = myocardial infarction; ED = emergency department; * adjusted p value is derived from the full ranked ANCOVA model described in the text;			

Correct cardiovascular disposition, determined according to Figure 1, was more common in OU-CMR participants (83% vs. 11%, $p < 0.001$), excluding from analysis patients who left against medical advice. (Table V) In the inpatient care group, 6 participants were classified as having correct dispositions based on

being admitted and experiencing ACS; 48 participants were classified as having incorrect dispositions based on being admitted and not experiencing ACS. In the OU-CMR group, 43 were classified as correct dispositions based on 41 being discharged home and not experiencing ACS and 2 being admitted and experiencing ACS. The remaining 9 participants were incorrect dispositions based on being admitted to the hospital and not experiencing ACS within 30 days.

Discussion

Stress cardiac MRI has gained popularity in the past decade for evaluating patients with acute chest pain. Data in ED patients suggest that this imaging test can detect ongoing ischemia(6) and is highly accurate for diagnosing ACS and assessing long term prognosis.(4, 5) However, existing descriptions of CMR implementation in ED patients have been observational and have either blinded the CMR results to clinicians and / or have not used the results of CMR testing to make medical decisions.(4-6) As a result, it had been left unclear as to whether the reported potentially superior test characteristics would translate into decreased expenditures. In this investigation, participants with intermediate-risk chest pain managed in an OU and imaged with stress CMR accumulated lower direct medical cost during the index hospital visit. Furthermore, an OU-CMR strategy led to a large decrease in admission rates, an improvement in correct cardiovascular disposition decisions, and decreased hospital length of stay. Jointly, these findings suggest an improvement in efficiency relating to an OU-CMR approach in patients with intermediate-risk chest pain when compared to a strategy of inpatient care. Importantly, the increases in efficiency were not associated with a difference in cardiovascular outcomes at 30 days.

We hypothesized that an OU-CMR strategy would decrease cost relating to a decreased rate of cardiac catheterizations. In this investigation, the cardiac catheterization rates were nearly identical in both groups. However, more patients underwent revascularization in the usual care group (although not

statistically different). To determine if the cost differences were related to revascularization events, we excluded all patients who received revascularization and OU-CMR still had a lower median cost of care. Therefore, it is unlikely that the cost reduction seen in this trial is related to an unbalanced event rate among groups.

Further exploring revascularization decisions, a difference in revascularization rates could be related to the study intervention. Five patients in the inpatient care group received revascularization. All of these had negative serial cardiac markers and then underwent cardiac catheterization as their first cardiac imaging study, followed by PCI. One of these 5 patients had an elevated troponin after revascularization and was thus classified as having myocardial infarction. In contrast, two patients received revascularization in the OU-CMR group. One of these patients had an elevated troponin prior to CMR testing and went directly to cardiac catheterization and PCI. The other patient had a positive CMR and received a CABG surgery. Implementing an OU-CMR strategy could be impacting downstream care patterns. Following this theory, the highly accurate stress imaging results may change the pattern of referrals for catheterization, and impact the decision to perform revascularization once catheterization has been performed.

If an OU-CMR approach decreases coronary revascularization events, this could affect clinical outcomes. Examining this possibility, several arguments can be made to support an OU-CMR approach, even if coronary revascularization is reduced. However, it is first important to understand that if

revascularization is reduced, it is likely to be among patients with negative serial cardiac biomarkers, no significant findings on serial ECGs, and a negative stress CMR (previously shown to be 96% sensitive for >70% coronary stenosis on cardiac catheterization)(13). Most would agree that these patients are unlikely to have ACS as a cause of their symptoms and thus any interventions in these patients would amount to intervening in patients with stable coronary artery disease. Findings from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial support earlier findings that PCI does not prevent MIs or decrease mortality outside the setting of ACS.(14-17) As a result, ACC/AHA guidelines are heavily focused on noninvasive imaging results.(18) Extrapolating this to patients undergoing an OU-CMR approach, revascularization is unlikely to improve health outcomes in patients with negative serial cardiac markers and ECGs, and a negative stress CMR examination. Therefore, a reduction in revascularization among these patients would represent a reduction in resource consumption with expected equivalent clinical outcomes. Future investigations should determine the extent to which this occurs with an OU-CMR strategy.

Patients with chest pain at intermediate-risk for ACS are a diagnostic and management challenge. Although previous investigations of OU care have demonstrated an advantage to OU management,(3, 19) widespread adoption has not followed. Furthermore, these investigations have not evaluated OU care in a broadly defined intermediate-risk population. With aging of the population, the proportion of patients with chest pain classified as intermediate risk can be

expected to increase. One potential solution is coronary computed tomography angiography (CCTA). CCTA has been shown to reduce cost(20), but has been predominately tested in low risk ED patients where it accurately detects the presence of coronary disease.(21, 22) When testing intermediate risk patients with chest pain, determining the presence of coronary disease is not sufficient. Intermediate risk patients commonly have known coronary disease, and many have had prior ACS events. Furthermore, because intermediate risk patients are older, they are more likely to have artifacts on CCTA related to coronary calcifications. Therefore, the use of CCTA is unlikely to be adopted in intermediate risk patients due to reduced image quality from coronary calcifications and the absence of functional information obtained from stress imaging. In comparison, the success of a stress CMR approach in our intermediate risk population suggests that expansion of OU care to a more broadly defined population, including patients with prior revascularization, is feasible with stress CMR.

Limitations

The findings of this investigation should be tempered by several limitations. First, this investigation was a single center trial in a center with vast experience with CMR. It is uncertain whether these results can be duplicated at other centers with less experience in CMR stress testing. Second, we were only able to enroll participants when CMR was available within a reasonable time frame. This may have biased length of stay in favor the CMR group. Third, changes in care delivery can have many unanticipated downstream effects that are not reflected by index hospital visit expenditures. Future investigations should evaluate intermediate term clinical outcomes and resource consumption. Fourth, analyzing cost data is challenging due to the skewed nature of cost data, the controversies surrounding data transformations, and varying opinions on whether mean or median cost is of primary interest. We chose to use nonparametric techniques due to the highly skewed data. Costs for those who left against medical advice were included, but should make our comparison more conservative since 3 of the 4 who left were in the inpatient care arm. Fifth, this trial evaluated the cost of a care strategy rather than measuring the cost savings of a particular test. Therefore we are unable to ascertain whether the reduction in expenditures was the result of CMR, OU care, or both together. Finally, differences in the secondary outcome, correct cardiovascular disposition, should be interpreted with caution as some patients may have been properly admitted for other medical reasons. Moreover, one group was randomized to a care pathway that included admission (although care providers were not obligated to

admit the patient) while another was not. This biased the secondary outcome measurement in favor of the OU-CMR group. However, 77% of intermediate risk participants in the OU-CMR arm were discharged home without hospital admission. This discharge rate exceeds that seen previously demonstrated in intermediate risk observation unit patients managed with conventional testing.(3)

Conclusions

A diagnostic strategy implementing observation unit care coupled with stress CMR reduces index hospital cost when compared to a standard inpatient care strategy in patients with intermediate-risk chest pain in the emergency department. The OU-CMR strategy was also associated with an improvement in cardiac dispositions and a reduction in hospital length of stay, and was not associated with a difference in short-term cardiac events after discharge.

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References

1. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction). *Circulation* 2007.
2. Katz DA, Griffith JL, Beshansky JR, Selker HP. The use of empiric clinical data in the evaluation of practice guidelines for unstable angina. *Jama* 1996;276(19):1568-74.
3. Farkouh ME, Smars PA, Reeder GS, et al. A Clinical Trial of a Chest-Pain Observation Unit for Patients with Unstable Angina. *N Engl J Med* 1998;339(26):1882-8.
4. Kwong RY, Schussheim AE, Rekhraj S, et al. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. *Circulation* 2003;107(4):531-7.
5. Ingkanisorn WP, Kwong RY, Bohme NS, et al. Prognosis of Negative Adenosine Stress Magnetic Resonance in Patients Presenting to an Emergency Department With Chest Pain. *Journal of the American College of Cardiology* 2006;47(7):1427-32.
6. Cury RC, Shash K, Nagurney JT, et al. Cardiac magnetic resonance with T2-weighted imaging improves detection of patients with acute coronary syndrome in the emergency department. *Circulation* 2008;118(8):837-44.
7. Abdel-Aty H, Zagrosek A, Schulz-Menger J, et al. Delayed enhancement and T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. *Circulation* 2004;109(20):2411-6.
8. Antman EM, Cohen M, Bernink PJLM, et al. The TIMI Risk Score for Unstable Angina/Non-ST Elevation MI: A Method for Prognostication and Therapeutic Decision Making. *JAMA* 2000;284(7):835-42.
9. Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. *J Crit Care* 2005;20(2):187-91; discussion 91-3.
10. Kline JA, Mitchell AM, Runyon MS, Jones AE, Webb WB. Electronic medical record review as a surrogate to telephone follow-up to establish outcome for diagnostic research studies in the emergency department. *Acad Emerg Med* 2005;12(11):1127-33.

11. Puskas JD, Williams WH, Mahoney EM, et al. Off-Pump vs Conventional Coronary Artery Bypass Grafting: Early and 1-Year Graft Patency, Cost, and Quality-of-Life Outcomes: A Randomized Trial
10.1001/jama.291.15.1841. JAMA 2004;291(15):1841-9.
12. Conover WJ, Iman RL. Analysis of Covariance Using the Rank Transformation. Biometrics;38(3):715-24.
13. Plein S, Greenwood JP, Ridgway JP, Cranny G, Ball SG, Sivananthan MU. Assessment of non-ST-segment elevation acute coronary syndromes with cardiac magnetic resonance imaging. Journal of the American College of Cardiology 2004;44(11):2173-81.
14. Boden WE, O'Rourke RA, Teo KK, et al. Optimal Medical Therapy with or without PCI for Stable Coronary Disease
10.1056/NEJMoa070829. N Engl J Med 2007;356(15):1503-16.
15. Wood SICTCH, 2007. Accessed at http://www.medscape.com/viewarticle/562897_print on 6/9/2009.
16. Kereiakes DJ, Teirstein PS, Sarembock IJ, et al. The Truth and Consequences of the COURAGE Trial
10.1016/j.jacc.2007.07.063. J Am Coll Cardiol 2007;50(16):1598-603.
17. Diamond GA, Kaul S. COURAGE Under Fire: On the Management of Stable Coronary Disease
10.1016/j.jacc.2007.08.010. J Am Coll Cardiol 2007;50(16):1604-9.
18. Smith SC, Jr, Feldman TE, Hirshfeld JW, Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention)
10.1016/j.jacc.2005.12.001. J Am Coll Cardiol 2006;47(1):e1-121.
19. Stowers SA, Eisenstein EL, Th Wackers FJ, et al. An economic analysis of an aggressive diagnostic strategy with single photon emission computed tomography myocardial perfusion imaging and early exercise stress testing in emergency department patients who present with chest pain but nondiagnostic electrocardiograms: results from a randomized trial. Ann Emerg Med 2000;35(1):17-25.
20. Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A Randomized Controlled Trial of Multi-Slice Coronary Computed Tomography for

Evaluation of Acute Chest Pain. *Journal of the American College of Cardiology* 2007;49(8):863-71.

21. Hollander JE, Chang AM, Shofer FS, McCusker CM, Baxt WG, Litt HI. Coronary Computed Tomographic Angiography for Rapid Discharge of Low-Risk Patients With Potential Acute Coronary Syndromes. *Annals of Emergency Medicine* 2009;53(3):295-304.

22. Hoffmann U, Bamberg F, Chae CU, et al. Coronary Computed Tomography Angiography for Early Triage of Patients With Acute Chest Pain: The ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) Trial. *Journal of the American College of Cardiology* 2009;53(18):1642-50.

Appendix 1. Post-hoc Subgroup Analyses of Median Cost by Subgroup					
Subgroup name	Inpatient Care		Cardiac MRI		p value
	N	Cost	N	Cost	
Age					
Age ≥ 65	10	\$2661	8	\$2114	0.003
Age <65	47	\$3250	45	\$1985	0.012
Gender					
Male	30	\$2742	25	\$2150	0.12
Female	27	\$2662	28	\$2043	0.001
Race					
Caucasian	40	\$2799	35	\$2062	0.002
Other	17	\$2636	18	\$2090	0.076
Time of presentation					
6a-3p	46	\$2674	44	\$2057	0.003
3p-6a	11	\$2707	9	\$2129	0.034
Established CAD					
Established CAD	16	\$3212	12	\$2079	0.030
No Established CAD	41	\$2661	41	\$2062	0.005
Prior Heart Failure					
Prior Heart Failure	3	\$2661	2	\$5296	0.79
No Prior Heart Failure	54	\$2693	51	\$2051	<0.001
Prior Revascularization					
Prior Revascularization	15	\$3068	9	\$2044	0.023

No Prior Revascularization	42	\$2664	44	\$2088	0.005
OU-CMR = Observation unit cardiac magnetic resonance; CAD = coronary artery disease; ED = emergency department;					

Appendix 2. Imaging Results For OU-CMR Participants			
	CMR results		
	Inducible ischemia	No inducible ischemia	
ACS	1	0	1
No ACS	5	43	48
	6	43	49
No patients had ongoing ischemia or infarction on resting imaging			
Sensitivity	100% (95% CI 3% – 100%)		
Specificity	90% (95% CI 77%-97%)		
Stress agent:			
Adenosine	43/49		
Dobutamine	6/49		

CHAPTER THREE

EXPANDED DISCUSSION OF THE CLINICAL TRIAL

Summary of Research Findings

The primary objective of this research was to examine the expenditure differences associated with two diagnostic strategies when used in patients presenting to the emergency department with intermediate risk chest pain. The single center clinical trial presented in Chapter Two compared the direct cost of medical care during the index hospital visit between the two strategies of interest, OU-CMR and inpatient care. The results of this trial demonstrated that participants in an OU-CMR strategy had a reduction in the cost of the index hospital visit. A significant difference persisted when analyzed using several different statistical approaches.

The secondary objective of this research was to determine the difference in proper cardiovascular dispositions between the two strategies. Proper cardiovascular dispositions were determined based on the principle that patients with ACS should be admitted and those without ACS should be discharged. Using an adjudicated diagnosis of ACS, the OU-CMR strategy demonstrated an absolute improvement in proper cardiovascular admissions of 72%.

An OU-CMR strategy also demonstrated a reduction in other measures of health care efficiency including length of stay and inpatient bed utilization. These improvements in efficiency were achieved without any missed cases of ACS. In combination, these results suggest that an OU-CMR strategy represents an

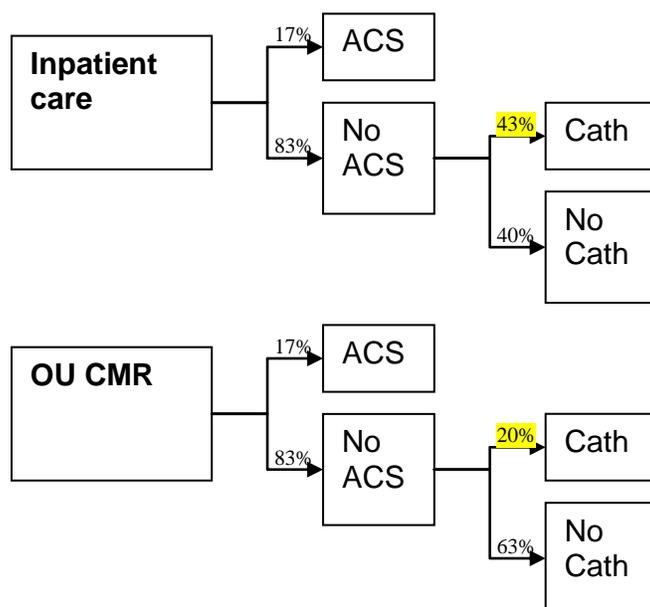
efficient model for diagnosing patients presenting to the emergency department with chest pain at intermediate risk for ACS.

Proposed Mechanism for the Research Results

When designing the research plan for this investigation, a model was generated to hypothesize how the intervention would impact cost. (Figure 3) In this model, we hypothesized that the major determinant in cost differences would be a differential cardiac catheterization rate relating to a higher specificity of CMR for significant coronary disease. Because cardiac catheterization adds significant cost to a hospital encounter, this difference would overcome the increased cost associated with obtaining a stress CMR.

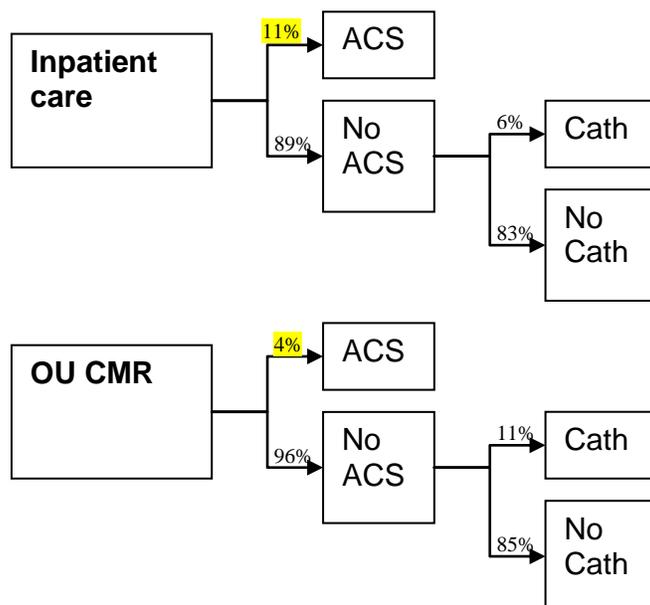
Note: The rate of ACS was assumed to be constant in both groups. In this model, the rate of catheterizations in the usual care arm was derived from literature review.¹⁻³ The rate of catheterizations in the OU CMR arm is based upon a conservative estimate of 75% specificity of CMR for coronary disease requiring intervention.⁴

Figure 3. Model of Anticipated Patient Flow



The actual patient flow through our clinical trial is represented in Figure 4. The rates of cardiac catheterization were not different among groups. However, a higher proportion of patients in the inpatient care group underwent revascularization and thus qualified as having ACS. Revascularization procedures are costly, and it was possible that our main findings of a cost reduction with OU-CMR related to this difference in revascularization rates. However, when eliminating participants receiving revascularization and reanalyzing the data, the difference persisted. These findings suggest that OU-CMR reduces cost even after removing the effect resulting from differences in revascularization rates.

Figure 4 Actual Patient Flow in the Clinical Trial



Although our results are not dependent on reducing revascularization in order to reduce cost, reducing revascularization events could be a major source of efficiency gain. To examine the mechanism of how an OU-CMR strategy could reduce revascularization, consider that in this trial 8/57 (14%) participants in the inpatient care group underwent cardiac catheterization as the initial cardiac imaging modality. In contrast, this only occurred in 1/53 (2%) participants in the OU-CMR group (p value for comparison 0.03). Of the 8 who underwent catheterization, 5 had PCI performed and none of these patients had stress testing performed during the index hospital visit. Had these patients undergone antecedent stress testing, it is likely that some would not have gone on to cardiac catheterization and therefore would not have received PCI.

Implications of the Research Results on Clinical Practice

These data suggest that an OU-CMR strategy is a more efficient diagnostic method for evaluating patients with intermediate risk chest pain in the ED. Efficiency endpoints measured for this investigation included direct cost, cardiovascular disposition, and length of stay, all of which favored an OU-CMR strategy. Importantly, these findings are from a single center and this investigation contains a relatively small number of participants. Therefore, before these results change clinical practice, the study results should be replicated in a multi-center trial. Simultaneously, such a trial should include measures of intermediate-term (i.e. 6 to 12 months) care utilization, intermediate-term clinical outcomes, health utilities, and include a formal cost-effectiveness analysis.

Areas of Uncertainty Relating to an OU-CMR Strategy

The Rate of Missed ACS When Implementing an OU-CMR Strategy is Likely Acceptable

In this trial, no patients in the short-term experienced ACS after discharge. However, this trial was not powered to detect a difference in short-term missed ACS. Whether a difference exists will need further exploration with future research. However, this area can be addressed conceptually using existing literature.

First, the rate of MI or cardiac death after a negative inpatient evaluation for this disease process is commonly cited as 0.5%-2.9% with follow-up lengths ranging from 6 months to 1 year.^{3,5,6} There are likely multiple causes of these events occurring after hospital discharge including initial misdiagnoses, new

lesions through plaque rupture or vasospasm, and complications of revascularization procedures (i.e. re-stenosis). Of these causes, initial misdiagnosis would most likely be impacted by diagnostic strategy during the index hospital visit.

Further discussion on reducing the initial misdiagnosis rate of ACS requires an exploration of testing thresholds. The testing threshold for patients with possible ACS has been previously calculated as 2%.⁷ When the probability of ACS is below this threshold, it is postulated that patients are more likely to be harmed than helped by further testing. Two percent also represents the most recent estimate of the proportion of patients with myocardial infarction discharged from the ED.⁸ Therefore, accepting 2% as a reasonable test threshold, the goal should be to arrive at a post-test probability of disease below this threshold. Using actual event rates from our investigation, 7% of our population can be expected to experience ACS. Using conservative estimates for CMR as having 90% sensitivity and 75% specificity for ACS⁴, it can be expected that at most 1.0% of the population with negative stress CMR exams would have missed ACS. (Table 6)

Table VII Calculation of Probability of ACS After a Negative Stress CMR

Pr disease = 7.2%

Sensitivity stress CMR 90%

Specificity stress CMR 75%

$\Pr(\text{Disease (+)} \mid \text{Test (-)}) = \Pr(\text{disease (+)} \cap \text{Test (-)}) / \Pr(\text{Test (-)})$

$= 0.007 / 0.703 = .0010 = 1.0\%$

	ACS (+)	No ACS	
CMR (+)	6.5%	23.2%	29.7%
CMR (-)	0.7%	69.6%	70.3%
	7.2%	92.8%	

However, of this 1.0%, it is also likely that a portion of these would be diagnosed via other modalities in the OU-CMR pathway such as serial cardiac markers and serial electrocardiograms. As such, the actual rate is likely below 1.0%, which is well below an acceptable 2% threshold. Therefore, it is unlikely that an unacceptable miss rate would be seen with an OU-CMR strategy, even with a larger investigation.

If an OU-CMR Approach Minimizes Cost by Reducing Revascularization

Procedures, the Impact on Long Term Health Must Be Examined

If a reduction in revascularization occurs after implementing an OU-CMR strategy, it would be among the participants who are biomarker negative and stress test negative. A clinical trial reported by Cannon et al⁹, commonly referred

to as the TACTICS - TIMI-18 trial, provides insight into the role of revascularization in patients with acute chest pain who are biomarker negative. In the Tactics TIMI-18 trial, patients with suspected non-ST-segment elevation ACS were treated with an early invasive strategy (early catheterization and revascularization based on coronary anatomy) or a conservative strategy (decision to perform catheterization based on clinical stability and stress testing). Patients in the early invasive strategy group had higher catheterization rates (97% vs 50%) and PCI rates (41 vs 24%). Importantly, no benefit to an early invasive strategy was seen among patients who were biomarker negative, with both groups having equivalent rates of death, nonfatal MI, and re-hospitalization for ACS at 6 months. Similar findings have been supported in a meta-analysis which demonstrated that an early invasive strategy is beneficial in patients with biomarker elevations, but not in those without elevations.¹⁰ Extrapolating these findings to our results, if a reduction in PCI occurred in patients with negative cardiac biomarkers, it is unlikely it would impact clinical outcomes. In addition, OU-CMR participants will also have stress CMR results, which will provide an additional level of scrutiny that coronary ischemia is not the cause of the presenting symptoms.

A second argument could be made that reducing revascularization through an OU-CMR approach could negatively impact long term outcomes because PCI has a preventative effect. As previously discussed in Chapter 2, the literature on revascularization of patients with stable coronary artery disease suggests that this intervention does not improve long term survival or infarction

rates when used in patients without ACS. Further, guidelines for coronary revascularization have been published by the ACC/AHA which are heavily focused on noninvasive imaging results.¹¹ Because OU-CMR participants undergo stress CMR testing, these results will be available to guide revascularization decisions should the patient require cardiac catheterization. Therefore, it is unlikely that a change in revascularization rates would lead to a detrimental change in clinical outcomes. Contrarily, in the US, as many as 68% of coronary angioplasty procedures are either of uncertain appropriateness or inappropriate.¹² Reducing inappropriate revascularizations could improve the efficiency of health care delivery.

Can the Research Findings Be Generalized to Other Institutions?

It has been previously suggested that the efficiency gains from observation unit care for patients with chest pain varies by institution and is a function of the admission rate.¹³ When the admission rate of patients presenting with chest pain is low, an OU has a smaller effect compared to that seen in EDs where a high proportion of patients with chest pain undergo an evaluation for ACS. This interaction between admission rate and OU care on efficiency is understandable for patients with low risk chest pain where the decision to conduct an evaluation is the most important determinant of resource consumption. Among intermediate-risk patients, the large majority undergo a comprehensive evaluation for ACS. Therefore, it would seem likely that OU care would be an efficient strategy.

Adding CMR to OU care intuitively should improve efficiency. The superior accuracy of CMR testing compared to other stress testing modalities should reduce unnecessary invasive testing resulting from false positive testing. Further, it stands to reason that using a stress modality to determine the need for invasive testing and subsequent revascularization would reduce the number of revascularization procedures. This effect should be consistent across centers. However, before widespread adoption of an OU-CMR strategy occurs, the effect across multiple centers on a broader scope of outcomes should be assessed.

Rationale for Research Methods

The research plan implemented a randomized clinical trial design

Alternatives to a randomized clinical trial were considered including a quasi-experimental and non-experimental design. It was felt that a non-experimental design, in which patients were cared for in an OU-CMR strategy without a comparison group, would allow an exploration of feasibility of an OU-CMR approach but would not allow comparisons of expenditures among groups. Because feasibility of CMR in ED patients had already been established¹⁴⁻¹⁶, and OU care had been previously established at the study site, a non-experimental design was not further considered. A quasi-experimental design could have been implemented by establishing a care pathway for OU-CMR and comparing patients receiving care in this new care pathway with patients receiving care in a usual care pathway. This design was not implemented because of concerns that selection bias would lead to residual confounding and subsequently biased results. Randomization eliminates the selection bias, creates 2 equal groups for

comparison, and allows for more robust conclusions. Therefore, it was felt that implementing an experimental design represents the most feasible, practical method to prospectively compare the expenditure differences between an OU-CMR and an inpatient care strategy.

The Primary and Secondary Endpoints are measures of Efficiency

The primary endpoint was chosen as direct medical cost of the index hospital visit. This endpoint was chosen because it had the best balance between validity and feasibility. We chose a macro costing approach to measure cost of medical care. This approach used departmental specific cost-to-charge ratios to determine inpatient hospital cost and work relative value units to determine provider cost. These methods are accepted, validated, and accurate.¹⁷⁻²¹

Mechanistically, it was reasoned that CMR was a more expensive test yet was also more accurate. This increase in accuracy was theorized to lead to a reduction in invasive testing and hence a reduction in cost. We felt the largest effect of the intervention would be measured closest in time to the intervention, with the effect waning after hospital discharge. Therefore, if a difference in cost was not seen during the index hospitalization, it would be unlikely to appear after discharge. If no difference was seen, it would also significantly limit the argument for choosing a diagnostic pathway implementing a more expensive test.

Alternatively, if a difference in index hospital visit cost was demonstrated favoring an OU-CMR group, a very strong argument could be made that more elaborate investigations should be conducted. Consideration was given to

conducting a long term expenditure analysis, examining long term clinical outcomes, or conducting a formal cost-effectiveness analysis. However, it was felt that examining these endpoints would require substantial resources and to have external validity will require a multi-center design. Given the stage of this research, a multi-center design seemed premature. In contrast, this investigation was able to be conducted with limited resources at a single center.

Selecting the Comparison and Intervention Groups

The clinical trial compared usual inpatient care to care provided in an observation unit coupled with stress CMR imaging. Both of these groups required careful consideration. The care provided to the inpatient care group was not controlled in this investigation. Not designing a protocol for care delivery in the control group complicates understanding the effect of an OU-CMR approach. However, this was preferred as the intent of this investigation was to compare an experimental care pathway to care provided daily in centers across the US. Chapter 1 discusses the heterogeneity in care patterns when evaluating patients with intermediate risk chest pain and demonstrated that this heterogeneity decreases efficiency (page 3). Designing a protocol for care in the inpatient care group would have eliminated the heterogeneity but does not accurately portray care in the US. The result would have been a reduction of external validity.

The OU-CMR group represents a dual intervention – first managing patients in an observation unit, and second implementing stress CMR testing. Implementing a dual intervention creates difficulty understanding which component of the intervention is responsible for the observed effect. Despite this

challenge, it was felt that OU-CMR should be implemented and viewed as a single intervention. Stress CMR is unique among stress testing modalities with respect to the comprehensiveness and accuracy of the information provided. Therefore it was felt that CMR would allow expansion of OU care into a population of patients defined by a broader interpretation of intermediate risk than previously investigated.

Consideration was given to creating an OU-conventional testing comparison group. However, the definition of intermediate risk used in this trial allowed inclusion of participants that might be considered high risk in many institutions (known coronary disease, classic cardiac history). A minority of these patients are managed in OUs in the US as most are admitted. Therefore, it was felt that an inpatient testing strategy represented a safer comparison group and more closely represented care patterns in the US.

The success of *expansion* into this more broadly defined population was confirmed by the relatively high proportion of patients with prior revascularization (22%) who were safely managed with this strategy. Each participant recruited for this trial was done so with the permission of the ED care providers. The success in recruiting this population demonstrates the confidence that the ED physicians had in the diagnostic ability of the OU- CMR strategy.

The success of the OU-CMR protocol in *managing* this more broadly defined intermediate risk cohort is demonstrated by high proportion of patients who had a proper cardiovascular disposition in the OU-CMR group (83%). Similarly, a high proportion of OU-CMR participants were safely managed without

hospital admission (77%). In comparison to prior literature, an OU protocol based on conventional testing in patients meeting a narrower definition of intermediate risk was able to discharge only 46%.⁶

Expansion on Statistical Methods and Analysis

Cost data are commonly right skewed which poses analytical challenges

It has been suggested that in large pragmatic randomized trials, the arithmetic mean is of most importance.²² Therefore, when large sample sizes are present, t-tests can be used and are relatively robust to violations of normality.²² It was not felt that the data in this trial were appropriate for this approach given the gross violations of normality apparent on graphical inspection of the data and our small number of study participants. In a small dataset, comparing means would allow a few participants with large cost accumulations to highly influence the results. For example, one participant in this trial had coronary artery bypass grafting. This expensive procedure led to a high accumulation of cost and could have undue influence on the overall results.

Attempts were made to convert the cost data to a normal distribution using log, log-log, and square root transformations. Using histograms for visual analysis, the distributions improved with both a log and a log-log transformation, but still appeared right skewed. Using statistical testing, the Kolmogorov-Smirnov test was conducted with a null hypothesis of normality, which was rejected for each transformation ($p < 0.010$).

Nonparametric approaches were then used to conduct the comparisons among groups. First, the median costs were compared without adjustment using

a Wilcoxon-rank sum test. As previously described, this test was highly significant and suggested a reduced cost associated with the OU-CMR group.

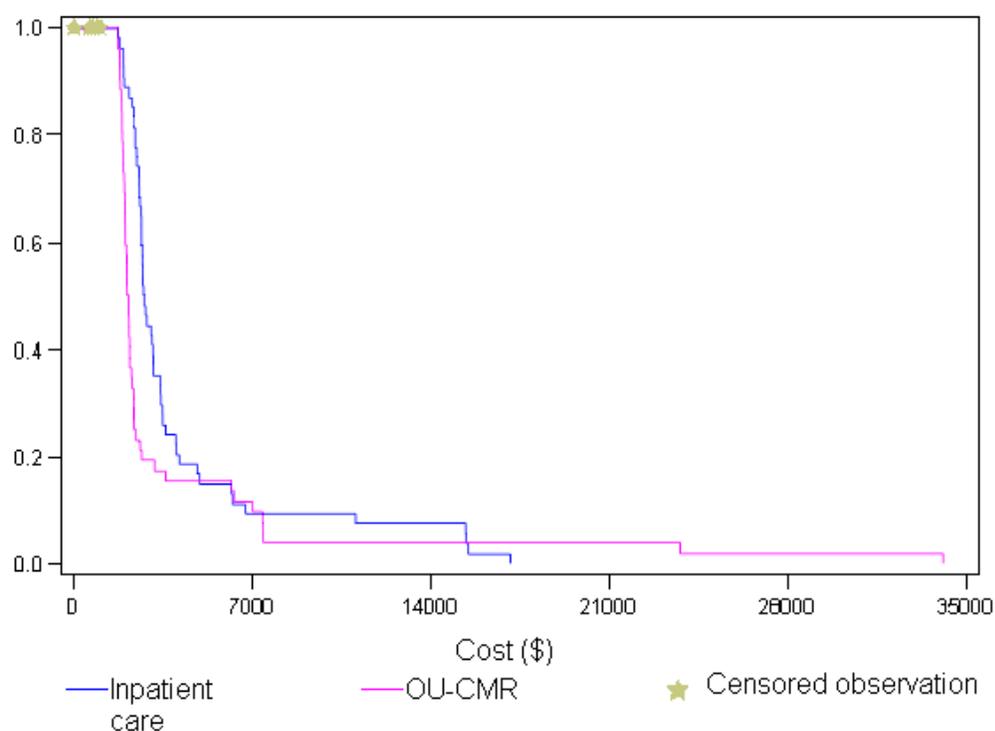
Censoring Was Noted To Exist for 4 Participants Who Left Against Medical Advice

Patients who left against medical advice did not accrue the full cost they would have accrued had they remained in the study. One could argue that the most appropriate analysis would be the one that included the actual costs incurred by those individuals, since those were their costs and in actual practice patients will leave against medical advice. And indeed, our primary analysis includes the actual costs realized by those four patients. However, we also wanted to explore the effect of this censoring on our estimates of cost and the difference in costs between the two arms. Several methods were used to account for the censoring (Table VIII). First, participants with censored data had their cost data treated as missing. A multiple imputation process was then used (SAS Procedure MI) to create 5 different data sets with different estimates for those with missing cost. Wilcoxon-rank sum tests comparing treatments were then conducted in each dataset. All 5 analyses were consistent with the original analysis in that they suggested a significant reduction in cost associated with the OU-CMR group. Finally, the most conservative method of accounting for censored data was conducted by giving censored participants in the inpatient care group the lowest cost rank and the participant in the OU-CMR group with the highest cost rank. Despite this relatively drastic replacement, the OU-CMR group continued to have a highly significant reduction in median cost.

Table VIII. Comparison of Median Costs Using Different Techniques to Account for Censored Data			
	OU-CMR median cost	Inpatient care median cost	p-value
Actual costs	\$2062	\$2680	<0.001
Multiple imputations 1	\$2114	\$2707	<0.001
Multiple imputations 2	\$2114	\$2707	<0.001
Multiple imputations 3	\$2114	\$2680	<0.001
Multiple imputations 4	\$2114	\$2680	<0.001
Multiple imputations 5	\$2114	\$2707	<0.001
Kaplan-Meier method	\$2088	\$2717	0.01
Treating censored as missing	\$2088	\$2717	<0.001
Replacing censored with low (inpatient care) and high (OU-CMR) ranks	\$2114	\$2680	<0.001

Accounting for censoring was also attempted using survival analysis techniques. Using survival analysis techniques for analysis of cost data is conducted by using cost as the time variable, hospital discharge as the event variable, and treating those leaving against medical advice as censored. The Kaplan-Meier approach was implemented using treatment group as a stratification variable. Hypothesis testing was conducted using the log-rank test with H_0 : the survival distribution functions are identical across strata. With this approach, a highly significant result was obtained for the log-rank test. The differences in survival function estimates are demonstrated in Figure 5. In conglomerate, these results suggest a reduction in cost among the OU-CMR group after accounting for censored observations.

Figure 5. Survivor Distribution Function By Treatment Group Using Kaplan-Meier Methods



The results obtained when accounting for censored observations using multiple imputations and Kaplan-Meier techniques are logical. Of the 4 censored participants, 3 were in the inpatient care group, all of whom had very low estimates for cost. Accounting for censoring in these participants had to increase their cost estimates. Therefore, it could be expected that the results of analyses would be at least as significant as those previously conducted without accounting for the censoring.

Adjustments for Covariates Were Attempted Using Two Approaches

First, Cox proportional hazards models were constructed. In order to implement Cox proportional hazard modeling, a key assumption is that of proportional hazards. This assumption was tested graphically by comparing log (-log) survival plots and using a time dependent covariate (cost*treatment group). Both methods suggested that treatment group violated the proportional hazard assumption. Therefore, adjustment for covariates was then conducted using a ranked analysis of covariance (ANCOVA) approach. Using this approach, costs were first ranked and these rankings were then modeled as the outcome variable using standard ANCOVA techniques. Candidate covariates included the 4 levels of stratification at the time of randomization (known coronary disease as binary, time of day of presentation 6a-3p or 3p-6a), age (continuous and binary as ≥ 65), TIMI risk score, gender, race, ethnicity, confirmed prior heart failure, confirmed prior MI, and confirmed prior coronary revascularization. Interactions between treatment group and each covariate were explored. One significant interaction was present between age ≥ 65 and treatment group and was further explored by

examining subgroups. (Appendix 1) This interaction was determined to be quantitative and had only a marginal impact on the results. This can be seen in Appendix 1 where OU-CMR is associated with a statistically significant reduction in cost among participants ≥ 65 or < 65 years. However, the magnitude of reduction is greatest among those < 65 years. In order to allow a clearer interpretation of the main effects, this interaction was not entered into the full model. Next, a full model was constructed with all of the remaining covariates and compared to a reduced model containing only treatment group and the randomization strata (entered as covariates). The difference in the treatment group effect estimate was then compared between the full and reduced models to examine the magnitude of confounding. A 21% difference was observed between models with randomization group being statistically significant in both models. Overall this suggests a small amount of confounding is present, but does not impact the interpretation of the findings.

As an exploratory analysis, post-hoc subgroup analyses were conducted

Because these analyses were exploratory and hypothesis generating, no adjustments were made for multiple comparisons. The direction of treatment effect remained similar and favored OU-CMR across all subgroup analyses except among participants with prior heart failure. However, the overall number of participants with heart failure is small ($n=5$) and among those with prior heart failure, the difference among treatment groups was not statistically different.

Data Analysis Summary

The cost data from this clinical trial were not normally distributed. Data transformations were not successful in converting the data to a normal distribution. Wilcoxon-rank sum tests were used to compare median cost among treatment groups. Adjustment for censored data was conducted by treating the data as missing and then using multiple imputations, by assigning the most conservative ranks, and by using a Kaplan-Meier technique to compare the cumulative survival functions. All techniques demonstrated a beneficial effect of OU-CMR in reducing cost. Finally, confounding was explored using Cox proportional hazard modeling and ranked ANCOVA analyses. Cox proportional hazard modeling was not used ultimately due to violation of the proportional hazard assumption. Ranked ANCOVA analyses suggested a small degree of confounding was present that did not change the significance of the findings and minimally impacted the magnitude of the treatment effect.

Comparison of Cost Data Using Survival Analysis

Techniques Must Be Used Cautiously

Survival analysis techniques are appealing for use with cost data because their use is not dependent on a normal distribution of the outcome variable and the models account for censored data. Censoring and non-normal distributions are common with cost data. However, the use of these techniques can lead to biased results.²³ We felt it was appropriate to use Kaplan-Meier techniques with our data for several reasons. First, the degree of censoring in our data was very small (4%). Second, the censored participants were not expected to vary from those

who were not censored. In all 4 scenarios, the censored participants left prior to cardiac testing and had negative cardiac markers prior to testing. We did not have reason to believe that the probability of being censored was related to cost, and therefore felt that the censoring mechanism was non-informative. Both of these assumptions have been shown to lead to less biased results with Kaplan-Meier methods when applied to cost data.²³ The use of Cox Proportional Hazard modeling has potential to impart even more bias due to the increased likelihood of proportional hazard violation with cost data. This was demonstrated in our data and therefore this technique was not implemented. Finally, although Kaplan-Meier methods can lead to biased results when used to examine cost data, our results obtained using these methods were consistent with those obtained using other analytical methods suggesting our observed difference represents a true effect.

Future Research Implications and Direction

The improvement in efficiency seen with an OU-CMR strategy should be examined in a broader context. Future trials should incorporate a larger number of patients observed over a longer period of time. This future trial should incorporate a primary endpoint driven by clinical outcomes (ex revascularization rates) and should be powered to detect a clinically important difference in the rates of ACS after discharge. In addition, health utilities should be collected in order to perform a formal cost-effectiveness analysis. This multi-center clinical trial is currently in the planning stages.

Consideration of Designing a Trial to Investigate Whether an OU-CMR Strategy Can Reduce the Incidence of Missed ACS

A trial examining missed ACS rates is appealing because missed ACS leads to higher morbidity and mortality.⁸ However, after careful consideration, it was felt that the current problem rests with the rate of invasive imaging and revascularization rather than missed ACS after discharge. As previously discussed, the rate of MI or cardiac death after a negative inpatient evaluation for this disease process is relatively low (commonly cited as 0.5%-2.9%) over the ensuing 6 months to 1 year.^{3,5,6} Substantially improving this event rate with a more accurate diagnostic protocol is unlikely.

In contrast, a more accurate diagnostic protocol could reduce the high catheterization rate. A catheterization rate of 37-56% exists among intermediate risk patients, half of whom undergo revascularization.¹⁻³ The high catheterization rate may relate to suboptimal accuracy of noninvasive tests leading care providers to choose cardiac catheterization as the first line imaging modality. However, data suggests that this is a flawed strategy. Among low- and intermediate-risk patients with unstable angina or non-ST-segment elevation MI, routine cardiac catheterization prevents re-hospitalization but does not definitively improve outcomes.²⁴ The cost to prevent one re-hospitalization with this strategy approximates \$80,000, well above the cost of a re-hospitalization.²⁴ Additionally, this high catheterization rate is likely a contributing factor to the excessive number of revascularization procedures in the US, many of which are of questionable appropriateness.¹² Therefore the study team concluded that

substantial gains are unlikely to result from decreasing the ACS rate after discharge in patients with intermediate risk chest pain; in contrast, a major opportunity exists to improve revascularization utilization in this population.

An Ongoing Trial Resulting from These Data is Examining the Differences Between an OU-CMR and an OU-Conventional Testing Strategy

To further examine the source of the observed treatment effect, we are currently conducting a second clinical trial. This second trial compares the differences in length of stay and diagnostic thinking efficacy between patients managed with an OU-CMR strategy and an OU-conventional testing strategy.

Conclusion

An OU-CMR strategy in ED patients with chest pain at intermediate risk for ACS reduces the cost of the index hospital visit. This reduction was accompanied by similar improvements in other measures of efficiency including length of stay and proper cardiovascular disposition. These improvements in efficiency were achieved without any participants experiencing missed ACS.

Designing this single center investigation required several difficult decisions regarding the intervention, the comparison group, and the outcomes. Similarly, analysis of the data was characterized by a non-normal distribution of the primary outcome and censoring of cost due to participants leaving against medical advice. However, the observed treatment effect remained stable across several techniques of comparison.

Future research should examine whether the results of this trial persist in a multi-center trial setting. In addition, the outcome endpoints should be

broadened to include clinical endpoints, measurements of safety, and a formal cost-effectiveness analysis.

REFERENCES

1. Gombert-Maitland M, Murphy SA, Moliterno DJ, Cannon CP. Are we appropriately triaging patients with unstable angina? *American Heart Journal* 2005;149:613-618.
2. Stowers SA, Eisenstein EL, Th Wackers FJ, Berman DS, Blackshear JL, Jones AD, Jr., Szymanski TJ, Jr., Lam LC, Simons TA, Natale D, Paige KA, Wagner GS. An economic analysis of an aggressive diagnostic strategy with single photon emission computed tomography myocardial perfusion imaging and early exercise stress testing in emergency department patients who present with chest pain but nondiagnostic electrocardiograms: results from a randomized trial. *Ann Emerg Med* 2000;35:17-25.
3. Tatum JL, Jesse RL, Kontos MC, Nicholson CS, Schmidt KL, Roberts CS, Ornato JP. Comprehensive strategy for the evaluation and triage of the chest pain patient. *Ann Emerg Med* 1997;29:116-25.
4. Plein S, Greenwood JP, Ridgway JP, Cranny G, Ball SG, Sivananthan MU. Assessment of non-ST-segment elevation acute coronary syndromes with cardiac magnetic resonance imaging. *Journal of the American College of Cardiology* 2004;44:2173-2181.
5. Manini AF, Gisondi MA, van der Vlugt TM, Schreiber DH. Adverse Cardiac Events in Emergency Department Patients with Chest Pain Six Months after a Negative Inpatient Evaluation for Acute Coronary Syndrome. *Acad Emerg Med* 2002;9:896-902.
6. Farkouh ME, Smars PA, Reeder GS, Zinsmeister AR, Evans RW, Meloy TD, Kopecky SL, Allen M, Allison TG, Gibbons RJ, Gabriel SE, The Chest Pain Evaluation in the Emergency Room (CHEER) Investigators. A Clinical Trial of a Chest-Pain Observation Unit for Patients with Unstable Angina. *N Engl J Med* 1998;339:1882-1888.
7. Kline JA, Johnson CL, Pollack CV, Jr., Diercks DB, Hollander JE, Newgard CD, Garvey JL. Pretest probability assessment derived from attribute matching. *BMC Med Inform Decis Mak* 2005;5:26.
8. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, Griffith JL, Selker HP. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000;342:1163-70.
9. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann F-J, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM,

Braunwald E, the TACTICS-Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of Early Invasive and Conservative Strategies in Patients with Unstable Coronary Syndromes Treated with the Glycoprotein IIb/IIIa Inhibitor Tirofiban
10.1056/NEJM200106213442501. *N Engl J Med* 2001;344:1879-1887.

10. Mehta SR, Cannon CP, Fox KAA, Wallentin L, Boden WE, Spacek R, Widimsky P, McCullough PA, Hunt D, Braunwald E, Yusuf S. Routine vs Selective Invasive Strategies in Patients With Acute Coronary Syndromes: A Collaborative Meta-analysis of Randomized Trials
10.1001/jama.293.23.2908. *JAMA* 2005;293:2908-2917.

11. Smith SC, Jr, Feldman TE, Hirshfeld JW, Jr, Jacobs AK, Kern MJ, King SB, III, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention)
10.1016/j.jacc.2005.12.001. *J Am Coll Cardiol* 2006;47:e1-121.

12. Schneider EC, Leape LL, Weissman JS, Piana RN, Gatsonis C, Epstein AM. Racial Differences in Cardiac Revascularization Rates: Does "Overuse" Explain Higher Rates among White Patients? *Ann Intern Med* 2001;135:328-337.

13. Goodacre S, Dixon S. Is a chest pain observation unit likely to be cost effective at my hospital? Extrapolation of data from a randomised controlled trial. *Emerg Med J* 2005;22:418-22.

14. Cury RC, Shash K, Nagurney JT, Rosito G, Shapiro MD, Nomura CH, Abbara S, Bamberg F, Ferencik M, Schmidt EJ, Brown DF, Hoffmann U, Brady TJ. Cardiac magnetic resonance with T2-weighted imaging improves detection of patients with acute coronary syndrome in the emergency department. *Circulation* 2008;118:837-44.

15. Kwong RY, Schussheim AE, Rekhraj S, Aletras AH, Geller N, Davis J, Christian TF, Balaban RS, Arai AE. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. *Circulation* 2003;107:531-7.

16. Ingkanisorn WP, Kwong RY, Bohme NS, Geller NL, Rhoads KL, Dyke CK, Paterson DI, Syed MA, Aletras AH, Arai AE. Prognosis of Negative Adenosine Stress Magnetic Resonance in Patients Presenting to an Emergency Department With Chest Pain. *Journal of the American College of Cardiology* 2006;47:1427-1432.

17. Shwartz M, Young DW, Siegrist R. The ratio of costs to charges: how good a basis for estimating costs? *Inquiry* 1995;32:476-81.
18. Smith LR, Milano CA, Molter BS, Elbeery JR, Sabiston DC, Jr., Smith PK. Preoperative determinants of postoperative costs associated with coronary artery bypass graft surgery. *Circulation* 1994;90:1124-8.
19. Gold MR, Siegel JE, Russell LB, Milton WC (eds) (1996). *Cost-Effectiveness in Health and Medicine*. Oxford University Press, New York.
20. Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, Staples JR, Glas KE, Marshall JJ, Leimbach ME, McCall SA, Petersen RJ, Bailey DE, Weintraub WS, Guyton RA. Off-Pump vs Conventional Coronary Artery Bypass Grafting: Early and 1-Year Graft Patency, Cost, and Quality-of-Life Outcomes: A Randomized Trial
10.1001/jama.291.15.1841. *JAMA* 2004;291:1841-1849.
21. Becker ER, Mauldin PD, Bernardino ME. Using physician work relative value units to profile surgical packages: methods and results for kidney transplant surgery. *Best Pract Benchmarking Healthc* 1996;1:140-6.
22. Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed? *Bmj* 2000;320:1197-200.
23. Etzioni RD, Feuer EJ, Sullivan SD, Lin D, Hu C, Ramsey SD. On the use of survival analysis techniques to estimate medical care costs. *J Health Econ* 1999;18:365-80.
24. Desai AS, Solomon DH, Stone PH, Avorn J. Economic consequences of routine coronary angiography in low- and intermediate-risk patients with unstable angina pectoris. *The American Journal of Cardiology* 2003;92:363-367.

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1997 *Summa cum laude*

PROFESSIONAL INTERESTS:

My research emphasis has focused on the clinical evaluation and treatment of patients presenting to the emergency department with chest pain. Completed efforts have led to publications on the prognosis of patients with non-cardiac chest pain, the importance of ethnicity in acute coronary syndrome presentations, the role of established and investigative treatments for patients with chest pain, and characterized a common yet poorly described population of ED patients with chest pain, those with myocardial infarctions in evolution at the time of presentation. As my independence as an investigator increased, I gravitated towards understanding the role of emergent cardiac imaging on patient outcomes and health care delivery. In September 2007 I was awarded a research training grant from the Wake Forest University Translational Science Institute. This grant allowed me to complete the coursework for a Master's degree in health sciences research at Wake Forest University Division of Public Health Sciences in 2008. Also as part of this grant, I conducted a randomized trial evaluating cardiac MRI stress testing in emergency department patients with chest pain and have several ongoing projects in both cardiac MRI and coronary computed tomography angiography. I have applied my research expertise in emergent chest pain to design and implement care pathways within our department for the diagnosis and treatment of patients with possible acute coronary syndromes. Over the next several years I intend to maintain my current research focus on emergent cardiac imaging and evaluating the most effective use of modalities such as cardiac MRI and coronary computed tomography angiography.

GRANTS:

- | | |
|------------|---|
| 2009-2011 | American Heart Association
National Clinical Research Program
Funding of "Efficacy Evaluation of Observational Unit Cardiac MRI in Patients with Intermediate Risk Acute Chest Pain"
Primary Investigator |
| 2007-2009 | Wake Forest University Translational Science Institute
K12 training grant providing 75% effort support for a Master's degree in Health Sciences Research through Wake Forest University Public Health Science. Grant funding also provided for "Randomized Cost Comparison of Cardiac MRI use in ED Patients with Chest Pain".
Primary Investigator |
| 2008– 2011 | 5 M01 RR07122-17 (Applegate)
National Center for Research Resources
General Clinical Research Center (GCRC)
Associate Director;
Director of the acute care research unit within the GCRC |
| 2006 | Intramural grant, Wake Forest University Baptist Medical Center
Intramural grant to investigate predictors of requiring a higher level of care among patients admitted from the emergency department |

Primary Investigator

- 2004 Inovise Medical, Inc
Unrestricted educational grant to educate about and investigate the importance of abnormal heart sounds in patients with chest pain.
Primary Investigator

RESEARCH SUPPORT:

Completed:

- 2003 - 2006 Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines (CRUSADE), Millennium Pharmaceuticals, Inc/Schering-Plough Research
Site Co-Investigator
- 2004 A Prospective, Open-Label, Randomized, Parallel-Group Investigation to Evaluate the Efficacy and Safety of Enoxaparin versus Unfractionated Heparin in Subjects who Present to the Emergency Department with Acute Coronary Syndrome (RESCUE-ACS), Aventis Pharmaceuticals
Site Co-Investigator
- 2004 - 2005 Rapid Assessment of Cardiac Markers for the Evaluation of Acute Coronary Syndromes (RACE-ACS), Biosite Inc.
Site Co-Investigator
- 2004 - 2006 Rapid emergency department heart failure outpatient trial (Red-Hot II), Biosite Inc.
Site Primary Investigator
- 2004 - 2008 Early Glycoprotein IIb/IIIa Inhibition in Non-ST-segment Elevation Acute Coronary Syndrome: A Randomized, Double-blind, Placebo-Controlled Trial Evaluating the Clinical Benefits of Early Front-loaded Eptifibatide in the Treatment of Patients with Non-ST-segment Elevation Acute Coronary Syndromes (Early-ACS), Millennium Pharmaceuticals, Inc/Schering-Plough Research
Site Primary Investigator
- 2007 Myeloperoxidase In The Diagnosis of Acute Coronary Syndrome (MIDAS), Biosite Inc.
Site Primary Investigator
- 2007 Multimarker Index for the Risk Assessment of Sepsis in the Emergency Department (MINDSET), Biosite Inc
Site Primary Investigator

- 2007 URGENT- Survey: A Prospective, Observational, Non-interventional Study of Patients Who Present with Acute Heart Failure Syndromes
Site Primary Investigator, PDL Biopharma
- 2007 - 2008 Blinded Observational Outcomes Study of PRIME ECG in the Emergency Department (OCCULT MI), Heartscape Inc.
Site Co-Investigator
- 2007 - 2008 Breathscreen Pivotal Trial, Breathquant Medical, LLC
Site Primary Investigator
- 2007 - 2009 Emergency Medicine Pulmonary Embolism in the Real world Registry: A National Quality Improvement Initiative for the ED (EMPEROR), University of Pennsylvania
Site Primary Investigator

Ongoing:

- 2007 - Present Acute Study of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure (ASCEND)
Scios Inc. and Johnson & Johnson Pharmaceutical Research and Development LLC
Site Co-Investigator

BIBLIOGRAPHY:

Chapters in books

1. **Miller CD.** Congestive heart failure and acute pulmonary edema. In: Ma OJ, Cline DM, Tintinalli JE, Kelen GD, Stapczynski JS, eds. *Emergency Medicine: Just the facts, 2nd ed.* New York: McGraw-Hill, 2004:99-101.
2. **Miller CD.** Infective Endocarditis. In: Ma OJ, Cline DM, Tintinalli JE, Kelen GD, Stapczynski JS, eds. *Emergency medicine manual , 6th ed.* New York : McGraw-Hill, 2004:419-421.
3. **Miller CD.** Congestive heart failure and acute pulmonary edema. In: Ma OJ, Cline DM, Tintinalli JE, Kelen GD, Stapczynski JS, eds. *Emergency medicine manual, 6th ed.* New York : McGraw-Hill, 2004: 140-141.
4. **Miller CD.** Infective Endocarditis. In: Ma OJ, Cline DM, Tintinalli JE, Kelen GD, Stapczynski JS, eds. *Emergency medicine: Just the facts, 2nd ed.* New York: McGraw-Hill, 2004: 313-315.

5. **Miller CD**, Hoekstra J. Acute Myocardial Infarction and Acute Coronary Syndrome: Combination Therapy for ST-Segment Elevation Myocardial Infarction. In: Peacock F, Tiffany B, eds. *Cardiovascular Emergencies, 1st ed.* New York: McGraw-Hill, 2006: 164-173.

Journal articles

1. Khandelwal S, **Miller CD**. Distinguishing dural sinus thrombosis from benign intracranial hypertension. *Emerg Med J* 2004; 21:245-247.
2. **Miller CD**, Lindsell CJ, Khandelwal S, Chandra A, Pollack CV, Tiffany BR, Hollander JE, Gibler WB, Hoekstra JW. Is the initial diagnostic impression of “noncardiac chest pain” adequate to exclude cardiac disease? *Ann Emerg Med* 2004; 44(6):565-574.
3. **Miller CD**, Lindsell CJ, Anantharaman V, Greenway J, Pollack CV, Tiffany BR, Hollander JE, Gibler WB, Hoekstra JW. Performance of a population-based cardiac risk stratification tool in asian patients with chest pain. *Acad Emerg Med* 2005; 12(5):423-30.
4. Hoekstra JW, Roe MT, Peterson ED, Menon V, Li Y, Milgund J, Pollack C, **Miller CD**, Palabrica T, Harrington RA, et al. Early Glycoprotein IIb/IIIa Inhibitor Use for Non–ST-Segment Elevation Acute Coronary Syndromes: Patient selection and associated treatment patterns. *Acad Emerg Med* 2005; 12(5):431-8.
5. Mehta RH, Newby LK, Patel Y, Hoekstra JW, **Miller CD**, Chen AY, Lytle BL, Diercks DB, Summers RL, Brogan GX, et al. The Impact of Emergency Department Structure and Care Processes in Delivering Care for Non-ST-Segment Elevation Acute Coronary Syndromes. *Am Heart J* 2006; 152:648-660.
6. Han JH, Lindsell CJ, Hornung RW, Lewis T, Storrow AB, Hoekstra JW, Hollander JE, **Miller CD**, Peacock WF, Pollack CV, et al. The Elder Patient with Suspected Acute Coronary Syndromes in the Emergency Department. 10.1197/j.aem.2007.04.008. *Acad Emerg Med* 2007:j.aem.2007.04.008.
7. **Miller CD**, Banerjee A, Mahaffey KW, Kontos MC, Fermann G, Pollack CV, Jr., Antman E, Aylward P, Goodman SG, Santos R, et al. Treatment and outcomes of patients with evolving myocardial infarction: experiences from the SYNERGY trial. *Eur Heart J* 2007; 28(9):1079-84.
8. **Miller CD**, Roe MT, Mulgund J, Hoekstra JW, Santos R, Pollack CV, Jr., Ohman EM, Gibler WB, Peterson ED. Impact of acute beta-blocker therapy for patients with non-ST-segment elevation myocardial infarction. *Am J Med* 2007; 120(8):685-92.

9. Boden WE, Hoekstra J, **Miller CD**. ST-elevation myocardial infarction: The role of adjunctive antiplatelet therapy. *Am J Emer Med* 2008; 26:212-220.
10. White HD, Chew DP, Hoekstra JW, **Miller CD**, Pollack Jr CV, Feit F, Lincoff AM, Bertrand M, Pocock S, Ware J, et al. Safety and Efficacy of Switching From Either Unfractionated Heparin or Enoxaparin to Bivalirudin in Patients With Non-ST-Segment Elevation Acute Coronary Syndromes Managed With an Invasive Strategy: Results From the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) Trial. *J Am Coll Cardiol* 2008; 51:1734-1741.
11. **Miller CD**, Kumar R, Storrow AB. Alignment of Emergency Medicine Research Efforts with Clinical and Translational Science Awards. *Academic Emergency Medicine* 2008; 15(7):672-7.
12. Society of Chest Pain Centers Recommendations for the Evaluation and Management of the Observation Stay Acute Heart Failure Patient: A Report From the Society of Chest Pain Centers Acute Heart Failure Committee. *Crit Pathw Cardiol* 2008; 7(2):83-6.

Trupp RJ, Hiestand B, Dodge G, Hayes CO, **Miller CD**, Selby E, Peacock WF, Fonarow GC. Patient Education. *Crit Pathw Cardiol* 2008; 7(2):116-21.
13. **Miller CD**, Fermann GJ, Lindsell CJ, Mahaffey KW, Peacock WF, Pollack CV, Hollander JE, Diercks DB, Gibler WB, J W Hoekstra on behalf of the EMCREG-International itrACS Investigators. Initial risk stratification and presenting characteristics of patients with evolving myocardial infarctions. 10.1136/emj.2007.052183. *Emerg Med J* 2008; 25(8):492-7.
14. Roe MT, Kikano G, **Miller CD**, Hoekstra JW. Continuum of Care in the Treatment of ST-Segment Elevation Myocardial Infarction (STEMI): Importance of Platelet and Coagulation Inhibition. *Postgrad Med* 2008; 120(2):67-78.
15. Pang PS, Mebazaa A, Collins SP, Cleland JG, Hollander JE, Nieminen M, **Miller CD**, Courtney DM, Kirk JD, Masip J, et al. Design and rationale of the URGENT Dyspnea study: an international, multicenter, prospective study. *Am J Ther* 2008; 15(4):299-303.
16. Diercks DB, **Miller CD**. Natriuretic peptide testing: a useful diagnostic test. *Ann Emerg Med* 2009; 53(3):386-7.

Journal articles forthcoming:

1. **Miller CD**, Blomkalns AL, Gersh BJ, Pollack CV, Brogan GX, Diercks DB, Peacock WF, Stone GW, Hollander JE, Manoukian SV, et al. Safety and Efficacy of Bivalirudin in High-Risk Patients Admitted Through the Emergency Department. *Acad Emerg Med* (forthcoming).

2. Collins SP, Levy PD, Lindsell CJ, Pang PS, Storrow AB, **Miller CD**, Naftilan AJ, Thohan V, Abraham WT, hiestand B, Filippatos G, Diercks DB, Hollander J, Nowak R, Peacock WF, Gheorghide M. The Rationale for an Acute Heart Failure Syndromes Clinical Trials Network. *Journal of Cardiac Failure* (forthcoming).
3. Heitz C, Gaillard J, Blumstein H, Case D, Messick C, **Miller CD**. Performance of the Maximum Modified Early Warning Score to Predict the Need for Higher Care Utilization Among Admitted Emergency Department Patients. *Journal of Hospital Medicine* (forthcoming).

Abstracts:

1. Bahner DP, **Miller CD**, Werman H, et al. "Prehospital Ultrasound Training – A 5-month pilot study" *Ann Emerg Med* 2002;40(4).
2. **Miller CD**, Lindsell CJ, Anantharaman V, et al. Validation of the ACI-TIPI Score in Asian Patients with Chest Pain. *Acad Emerg Med* 2004; 11(5):507.
3. Bozeman WP, Idris AH, Gabrielli A, **Miller CD**. Etomidate-based rapid sequence intubation does not change intracranial pressure and brain tissue oxygenation: evolution of a swine model. *Acad Emerg Med* 2004; 11(5):492.
4. **Miller CD**, Patel Y, Lytle BL. Emergency department factors that predict adherence to ACC/AHA Guidelines for treatment of patients with non-ST-Segment elevation acute coronary syndromes: Results from the CRUSADE initiative. *Ann Emerg Med* 2004; 44(4) p s46.
5. Peterson ED, Chen AY, Kontos MC, Smith SC Jr, **Miller C**, Pollack CV Jr, Ohman M, Roe MT. Associating changes in hospital non-ST-segment elevation acute coronary syndromes guidelines adherence with changes in patient outcomes: results from CRUSADE. *Circulation* 2004;110(17 Suppl III):III-785.
6. Han JH, Lindsell CJ, Hollander JE, Peacock WF, **Miller C**, Tiffany BR, Hoekstra JW, Gibler WB. The Emergency Evaluation of Chest Pain in the Elder Population. *Acad Emerg Med* 2005;12(5_suppl_1):28-b-9.
7. Lombardi AK, **Miller CD**, Johnson J, Chen N, Bahner D. Defining a Set of Criteria to Reduce Blood Redraws in Emergency Department Patients with Pseudohyperkalemia. *Acad Emerg Med* 2005;12(5_suppl_1):79-a-.
8. Pollack CV, Jr., Hollander JE, Diercks DB, **Miller CD**, Mahaffey KW, Ferguson JJ, Califf RM, Pieper KS, Hoekstra JW. Impact of Early Administration of Evidence-based Antithrombotic and Antiplatelet Therapy in Patients with High-risk Non-ST-segment Elevation Acute Coronary Syndrome. *Acad Emerg Med* 2005;12(5_suppl_1):85-a-.

9. **Miller CD**, Kontos M, Mahaffey KW, et al. Patients with Evolving Myocardial Infarction Have a Significant Missed Opportunity for Earlier Treatment: Experience from the SYNERGY Trial. *Annals of Emergency Medicine* 2005;46(3, Supplement 1):3.
10. Han JH, Lindsell CJ, Hollander JE, Peacock IV WF, **Miller CD**, Gibler WB. Determinants of Acute Coronary Syndromes in the Elderly Population. *Annals of Emergency Medicine* 2005;46(3, Supplement 1):9.
11. **Miller CD**, Mulgund J, Hoekstra JW, et al. Patterns and Correlates of Acute (<24 Hours) Use of Beta-Blockers for Non-ST-Segment Elevation Acute Coronary Syndromes: Results from the CRUSADE Initiative. *Annals of Emergency Medicine* 2005;46(3, Supplement 1):59-60.
12. **Miller CD**, Lindsell CJ, Fermann GJ, et al. After the First Negative Troponin: Distinguishing Patients with Evolving Myocardial Infarctions from Those Without Infarction in Emergency Department Patients with Chest Pain. *Annals of Emergency Medicine* 2005;46(3, Supplement 1):114-5.
13. **Miller CD**, Warner RA, Hoekstra JW. 147: The Utility of Electronically Recorded S3 and S4 Gallops to Predict Cardiac Events in Emergency Department Patients with Chest Pain. *Annals of Emergency Medicine* 2006;48(4, Supplement 1):46.
14. Chandra A, Cairns CB, **Miller C**, Lindsell CJ, Peacock WF IV, Hollander J, Hoekstra J, Pollack CV Jr, Gibler B. Emergency physician high pre-test probability for ACS predicts death, MI, or revascularization independent of initial ECG and cardiac biomarkers [abstract]. *Ann Emerg Med* 2006; 48(4 Suppl):S10-S11.
15. Hoekstra JW, Manoukian SV, **Miller CD**, et al. 95: Early, Upstream, and Consistent Antithrombotic Therapy in High Risk Non-ST-Elevation ACS: Should Bivalirudin Be Initiated in the ED Prior to Coronary Angiography? *Annals of Emergency Medicine* 2006;48(4, Supplement 1):30.
16. **Miller CD**, Hoekstra JW, Pollack CV, et al. Safety and Efficacy of Bivalirudin in High-Risk patients with Acute Coronary Syndrome Admitted through the Emergency Department: Implications for Upstream Management. *Journal of the American College of Cardiology* 2007;49(9, Supplement 1):208A.
17. White H, Chew DP, Hoekstra JW, Pollack CV, Feit F, Ohman EM, Mehran R, **Miller C**, Stone GW. Safety and efficacy of switching from either unfractionated heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor to bivalirudin monotherapy in patients with non-ST elevation acute coronary syndromes managed with an invasive strategy. *Am J Cardiol* 2007; 100(8A Suppl):63L.

18. Diercks D, **Miller C**, Eden S, Kirk JD. Kansas City Cardiomyopathy Questionnaire: Value in Heart Failure Patients Presenting to the Emergency Department. *Academic Emergency Medicine* 2008; Vol. 15(supplement 1):182.
19. Diercks D, **Miller C**, Eden S, Kirk JD. Can Dyspnea Measures Predict Length of Stay in Emergency Department Patients? *Acad Emerg Med* 2008; Vol. 15(supplement 1):523.
20. Diercks DB, Kontos M, Blomkalns A, Chen A, Owen K, **Miller C**, Wiviott S et al. Abstract 4993: Time from Symptom Onset to Hospital Presentation in Women with Myocardial Infarction: A Temporal Analysis from the CRUSADE and NCDR ACTION Registry. *Circulation* 2008;118:S_1127-a-.
21. **Miller C**, Hwang W, Hoekstra J, Lefebvre C, Case D, Hundley WG. Randomized comparison of observation unit plus stress cardiac MRI and hospital admission. *Journal of Cardiovascular Magnetic Resonance* 2009;11(Suppl 1):O103.
22. Pang P, Collins S, Kyriacou D, Hasa J, Nowak R, Storrow A, Hollander J, **Miller C**, Courtney DM, Tavares M, Mebazaa A, Gheorghide M. Factors Affecting Dyspnea Reduction in Emergency Department Patients with Acute Heart Failure Syndromes. *Academic Emergency Medicine* 2009; Vol 16 (Supplement 1):12.
23. Shundry SA, Martin DR, **Miller CD**, Weigand JV, Kuhn G, Beeson MS. Classification of Education Articles Published in Emergency Medicine Journals. *Academic Emergency Medicine* 2009; Vol 16 (Supplement 1):60.
24. Courtney DM, Klekowski N, **Miller C**, Smithline H, Hogg M, Kline J. Prospective Multi-Center Assessment of Interobserver Agreement for Radiologist Interpretation of 64-Channel CT Angiography for Pulmonary Embolism. *Academic Emergency Medicine* 2009; Vol 16 (Supplement 1):75.
25. McMullan J, Gallaher J, Askew K, Zhang Z, Hoekstra J, **Miller C**. The Association between Frontal Plane QRS/T Angle and Short-term Adverse Events in ED Patients with Chest Pain. *Academic Emergency Medicine* 2009; Vol 16 (Supplement 1):116.

Invited editorials and commentary

1. **Miller CD**, Hoekstra JW. Prospective validation of the San Francisco Syncope Rule: will it change practice? *Ann Emerg Med* 2006;47(5):455-6.
2. Diercks DB, **Miller CD**. Disparities in the care of chest pain 10.1503/cmaj.081190. *Can Med Assoc J* 2008;179(7):631-3.

Miscellaneous - Letters, non-refereed publications

1. **Miller CD**. Reply. *Annals of Emergency Medicine*. 2005; 46(1):96-97.

2. Hoekstra JW, Pollack CV, Roe MT, Peterson ED, **Miller CD**, Blomkalns A, Ohman M, Gibler WB. CRUSADE – A roadmap for change: 100,000 patients make a difference. EMCREG Monograph; Vol 2, March 2005.

Scientific presentations

Oral

1. **Miller CD**. “Patients with Evolving Myocardial Infarction Have a Significant Missed Opportunity for Earlier Treatment: Experience from the SYNERGY Trial.” Oral presentation (6th abstract) at the Research Forum, Scientific Assembly of the American College of Emergency Physicians, Washington, DC, 2005.
2. **Miller CD**. “Safety and Efficacy of Bivalirudin in High-Risk patients with Acute Coronary Syndrome Admitted through the Emergency Department: Implications for Upstream Management.” Oral presentation at the American College of Cardiology 56th Annual Scientific Session, New Orleans, LA, 2007.
3. **Miller CD**. “Randomized Comparison of Observation Unit Plus Stress Cardiac MRI and Hospital Admission” Oral presentation at the Society for Cardiac Magnetic Resonance Twelfth Annual Scientific Sessions, Orlando, FL 2009.

Poster

1. **Miller CD**. “Prehospital Ultrasound Training – A 5-month pilot study.” Poster presentation at the Research Forum, Scientific Assembly of the American College of Emergency Physicians, Seattle, 2002.
2. **Miller CD**. “Validation of the ACI-TIPI in Asian patients with chest pain.” Poster presentation at the Society for Academic Emergency Medicine Regional Meeting, Chapel Hill, NC, 2004.
3. **Miller CD**. “Validation of the ACI-TIPI in Asian patients with chest pain.” Poster presentation at the Society for Academic Emergency Medicine National Meeting, Orlando, Florida, 2004.
4. **Miller CD**. “Emergency department factors that predict adherence to ACC/AHA guidelines for treatment of patients with non-ST-segment elevation myocardial infarction: Results from the CRUSADE initiative.” Poster presentation at the Research Forum, Scientific Assembly of the American College of Emergency Physicians, San Francisco, 2004.
5. **Miller CD**. “Impact of Early Administration of Evidence-based Antithrombotic and Antiplatelet Therapy in Patients with High-risk Non-ST-segment Elevation Acute Coronary Syndrome.” Poster presentation at the Society for Academic Emergency Medicine National Meeting, New York, NY, 2005.

6. **Miller CD.** “Patterns and Correlates of Acute (<24 Hours) Use of Beta-Blockers for Non-ST-Segment Elevation Acute Coronary Syndromes: Results from the CRUSADE Initiative.” Poster presentation at the Research Forum, Scientific Assembly of the American College of Emergency Physicians, Washington, DC, 2005.
7. **Miller CD.** “After the First Negative Troponin: Distinguishing Patients with Evolving Myocardial Infarctions from Those Without Infarction in Emergency Department Patients with Chest Pain.” Poster presentation at the Research Forum, Scientific Assembly of the American College of Emergency Physicians, Washington, DC, 2005.
8. **Miller CD.** “The Utility of Electronically Recorded S3 and S4 Gallops to Predict Cardiac Events in Emergency Department Patients with Chest Pain.” Poster presentation at the Research Forum, Scientific Assembly of the American College of Emergency Physicians, New Orleans, LA, 2006.
9. **Miller CD.** “Early, Upstream, and Consistent Antithrombotic Therapy in High Risk Non-ST-Elevation ACS: Should Bivalirudin Be Initiated in the ED prior to Coronary Angiography?” Poster presentation at the Research Forum, Scientific Assembly of the American College of Emergency Physicians, New Orleans, LA, 2006.
10. **Miller CD.** “The Association Between Frontal Plane QRS/T Angle and Short Term Adverse Events in ED Patients with Chest Pain.” Poster presentation at the Society for Academic Emergency Medicine Annual Meeting, New Orleans, LA, 2009.