# The Role Of Early Stress Testing In Assessing Low Risk Chest Pain Patients Admitted Through The Emergency Department

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## LAY ABSTRACT

**A. Study purpose**

Cardiac stress testing has been recommended in prior studies for assessing cardiac ischemia in low risk patients that present to the emergency departments with chest pain. These low risk or Level 3 patients are defined as patients with chest pain with either normal electrocardiograms or with non-specific ST segment or T wave changes, and with negative cardiac enzymes (such as Troponin I or Creatinine kinase MB). These are patients considered to be low risk for acute cardiac ischemia and fall into a "probably not" category of risk stratification. They fall into a low to moderate pretest probability for acute cardiac ischemia and need to be differentiated from the emergency department between those requiring admission and further invasive and extensive cardiac workup, and those who may be safely discharged.

This study aims to show that early stress testing during the initial presentation of such Level 3 patients described above, would prove beneficial by reducing cardiac ischemic events, decreasing revisits, and decreasing costs of assessment of chest pain patients in New York Presbyterian Hospital (NYPH).

**B. Study subjects and method of recruitment**

Approximately, 1200 patients would be enrolled from NYPH. Possible enrollees are Level 3 chest-pain patients, who the primary physicians plan to discharge from the hospital without a stress test in the emergency department or in the hospital while admitted. These are strictly adult patients admitted to the Milstein hospital. Patients will be recruited by their admitting physician, who would present this study protocol as an option, upon planned discharge from the hospital. Enrollees would be consented and randomized to stress testing (study subjects) or no stress testing (control subjects).

**C. Study procedures**

Study subjects would undergo a form of cardiac stress testing such as Exercise stress testing +/- thallium (based on baseline EKG), OR pharmacologic stress testing with either adenosine, dobutamine or Dipyridamole , OR stress echocardiography. Based on the results of the stress test, the study subjects' primary physician would be notified of the results of these tests, allowing appropriate management to be instituted. Subjects would be contacted via telephone or mailed-in questionnaires in 3 months intervals to assess for further symptoms, or hospitalizations. Subjects would also be given a telephone contact to report symptoms or hospital visits in the interim. Follow up visits at the 3-months and 6-months interval is required for electrocardiograms.

**D. Issues**

1) A practical problem is that of adequate follow-up in this patient. This can be minimized by collecting contact information from subjects, prior to enrolling in this study.

2) Randomizing subjects to a standard protocol testing procedure may be considered unethical, however, since the decision not to stress had already been made by the patient's primary physicians, this plays a minimal role.

## IRB PROTOCOL

### A. Study purpose and Rationale

Every year, 6 million patients with chest pain suggestive of acute cardiac ischemia (ACI) go to hospital emergency departments (EDS). While a majority of these patients are admitted to the hospital, to rule out AMI, only 25% of such patients receive a diagnosis of confirmed ACI, either acute myocardial infarction (MI) or unstable angina (*1*). Between 2-10% of patients with acute MI in the United States are inadvertently discharged home without proper diagnosis (*4*).

Two thirds of these 5-6 million chest-pain patients present with non-diagnostic electrocardiogram (ECG) findings. It has been shown that among patients presenting with acute chest pain a low–risk group of patients with less than 5% probability of coronary event can be identified by the proper clinical assessment (*3*). These population of patients with non-diagnostic ECG and negative serial cardiac enzyme, are a heterogeneous class of patients, and distinguishing the 5% with potential coronary event can be challenging.

In a study of low risk patients discharged home directly from a short-stay coronary observation unit without stress testing, 1.2% sustained MI within 72 hours (*5*). This was attributed to the lack of uniform exercise testing prior to discharge. In another study by *Hillis et al*, to assess the incidence of coronary artery disease in low risk patients with chest pain, they found 33.3 % had objective evidence of coronary heart disease (*6*).

Chest pain centers were established in 1981 to help risk stratify and expedite rapid evaluation of all chest pain patients with appropriate stream-lining of care. The rationale of provocative testing or stress testing is to make a diagnosis of cardiac ischemia in low risk patients with probable cardiac ischemia (*3*). More and more, stress testing is becoming part of the protocol for chest pain centers in hospitals to help risk stratification, prognostification, treatment and disposition.

There have been studies showing a cost benefit to stress testing patients in the setting of chest pain centers (*4*). It also has been shown to be safe, reliable, and to reduce length of stay, and hospitalizations (*3*). However, there have not been randomized studies showing clear decrease in cardiac ischemic events (infarction or angina), and decrease in revisits to hospitals for chest pain.

The primary endpoint of this study is to test the hypothesis that early cardiac stress testing (during first visit) of low risk (Level 3) patients decreases cardiac ischemic events. Ischemic events specified by fatal and non-fatal acute myocardial infarction, recurrent angina symptoms and silent myocardial infarctions.

The secondary endpoint of this study is test the hypothesis that early stress testing of Level 3 patients on the initial presentation for chest pain would decrease revisits to the hospital for recurrent chest pain.

Lastly, a tertiary endpoint is to demonstrate that there is a cost benefit to this institution, of stress testing level 3 patients during their first presentation for chest pain, by preventing multiple admissions of patients for chest pain.

These endpoints are based on the assumption that evidence of coronary artery disease shown by a stress test would ensure that patients are aggressively treated, or assessed by their physicians. Aggressive medical management include Beta-blockers, cholesterol-lowering agents, aspirin, nitrates. Also, evidence of ischemia on stress testing indicates necessity for cardiac catherization to assess anatomy of coronary disease, +/- angioplasty or coronary artery bypass.

In summary, the purpose of this study is to show a clear benefit of early stress testing (i.e at initial presentation) on subsequent incidence of cardiac ischemia, recurrent chest pain and revisits to our institution. Ultimately, we hope having achieved this goal, the need for better facilities for provocative stress testing at initial presentation in the chest pain unit would be demonstrated.

### B. Study Design

Subjects would be patients admitted as Level 3 chest pain patients (as per the current chest pain protocol) on presenting to the New York Presbyterian Hospital emergency department. Eligibility criteria include: 1) prior decision by patient's primary physician or admitting team not to acquire stress test in the hospital or within 1 week of discharge. 2) hospital admission . 3) Level 3 patients (low risk, with normal or nonspecific ECG findings + negative troponin. 4) no clinical or radiological evidence of heart failure, hypotension (systolic blood pressure < 90 mmHg or requirement for inotropes +/- IV volume expansion. 5) no cardiac arrhythmia.

All enrollees would be required to provide clinical history, demographic information, and contact information. All enrollees must sign consent for release of medical records accessible via Web-Cis or charts and also consent for stress test procedures.

Subjects would be randomized in block to appropriate cardiac stress test procedure or no stress test. All stress testing would be done within 24- 72 hours of subject's admission.

The subject's primary physician or admission team would be informed of the

results of the stress test on completion. This would allow the primary physicians to make arrangement of further testing, procedures (such as cardiac catherization), or medical management based on the results of the stress test.

Approximately 1200 patients would be enrolled into this study over a 12 months period. This number was derived for the Chi square test formulae of two proportions. This was estimated in order to detect a 60% difference between the proportion of events among the two arms of the study, assuming the incidence of ischemic events among non stressed patients to be 6.4% as per prior studies. The data would be analysed using chi-square test, to achieve power of 80% and p-value of $\leq$ 0.05 would be considered significant.

**C. Study procedures**

All referred enrollees would be required to give a clinical history, provide demographic and future contact information.

Patients randomized to the stressed arm of the study, would undergo a form of stress test based on variable factors. The standard form of stress testing would be the exercise stress test +/- perfusion scanning. However, for patients who can no undergo exercise stress test, alternative forms of stress test would be utilized as outlined below:

*Exercise stress testing*: patients would be required to fast for 2-3 hours prior to the test. They may take their medications. The Bruce protocol would be followed in this study. This consists of walking on a treadmill with 7 incremental changes in speed and grade every 3 minutes. The patient's vital signs, symptoms and ECG would be monitored. The study would be terminated when the patient achieves 85% of their target HR (220-age), when protocol is completed, or if the patient develops concerning symptoms. Exercise stress testing is indicated for patients able to exercise, and at a low risk for acute cardiac ischemia. It has been proven to be a safe test, with incidence of adverse effects of AMI or death of 1 per 2500 tests (7). Possible side effects are recurrence of chest pain, dizziness, near syncope, arrhythmias, fatigue and shortness of breath.

*Pharmacologic stress test*: would be utilized for patients who are unable to perform dynamic exercises secondary to arthritis, peripheral vascular diseases, musculoskeletal problems, asthma, COPD, or other systemic diseases that preclude exercise testing. The pharmacologic agents work by vasodilatation, or by affecting the inotrope and chronotropic myocardial parameters, thereby increasing oxygen demand. Common types of pharmacologic agents used include: Dipyridamole, adenosine, or dobutamine. Adenosine is administered via intravenous pump, it has transient side effects of flushing, chest pain, shortness of breath and headache. However, it is contraindicated in patients with asthma, severe COPD, and sick sinus syndrome. Dipyridamole is also an intravenous infusion, and has serious side effects of AMI and bronchospasm which are rare, but common side effects include chest pain, flushing, nausea, dizziness, headache. Dobutamine is a potent cardiac inotropic agent, that is given by intravenous infusion, and has possible side effects of chest pain, palpitations, headache, and flushing.

Dobutamine is contraindicated in severe hypertension or hypotension, or uncontrolled atrial fibrillation, aortic stenosis or hypertrophic obstructive cardiomyopathy, and therefore would not be used in those patients with these medical problems.

Myocardial perfusion imaging with thallium 201 or technetium –99m sestamibi would be used in a selection of patients to enhance the sensitivity and specificity of the appropriate stress test.

*Stress echocardiography :* would be indicated in a sub-population of patients with baseline abnormal ECG (eg, bundle branch block), women, or when the treadmill exercise test result is thought to be false positive. Stress can be induced by exercise or intravenous infusion of pharmacologic stress inducing agents as outlined above.

Subjects would participate in the initial assessment, and stress testing. Subsequently, participants would be contacted via telephone and questionaires in 3 months interval for a period of 6 months to assess for recurrent chest pain and admissions to outside hospitals for chest pain/ischemic events.

The duration of recruitment of the study would be 12 months. Each subject would be expected to participate for the initial assessment (+/- stress testing depending on arm of the study), two 3 months-interval questionnaires, which would be mailed to them, and two follow-up visits at the 3-months and 6-months intervals for follow up electrocardiograms.

**D. Study Subjects**

Subjects would include patients admitted to the New York Presbyterian hospital through the emergency department, and classified as Level 3 chest pain patients.

*Exclusion criteria*:

Troponin I level > 0.3ng/ml
ST segment depression fulfilling ischemic criteria +/- ST segment elevations.
Clinical or radiological evidence of congestive heart failure or dilated cardiomyopathy.
Hypotension (systolic blood pressure < 90 mmHg or requirement +/- IV fluid volume expansion.
unstable atrial or ventricular rhythm.
co-morbid diseases preventing stress testing or adequate assessment symptoms.

**E. Recruitment of Subjects**

All Level 3 chest pain patients admitted to the hospital would be monitored from the Medicine-Admitting-Resident records. All physicians within the New York Presbyterian Hospital would be informed about the study via questionnaires and announcements at the commencement of the study.

Primary Physicians would be contacted within 24 hours, if stress test had not been ordered, to assess plans for potential subjects. Subjects would be then be referred by their primary physicians, prior to planned discharge if in hospital stress testing is not planned. Study stress test will be performed within 72 hours of admission.

**F. Confidentiality of study data**

Confidentiality would be ensured by coding of all subjects. Data would be kept secure and accessible only to investigators.

**G. Location of the Study**

All studies would be conducted in the nuclear cardiology laboratory of the New York Presbyterian Hospital.

**H. Potential risks and Benefits**

Exercise stress testing has been estimated has relatively safe tests, with incidence of AMI or deaths estimated as 1 out of every 2500 to 5000 subjects depending on the source. The potential side effects of each type of stress testing modality as outlined in the procedure section, is mostly self-limited, and transient. The risk associated with the non-stressed arm of the study comes from prior data showing that low risk patients without stress test, have about 6% incidence of coronary events within a few months. Since subjects are randomized after their primary physician's decision to discharge them without an in-patient stress test, this study can therefore only benefit, or not make a difference, but it certainly should not pose any additive risk to subjects.

## I. Costs to Subjects

Subjects would incur the expense of any medical treatment or intervention that is required, based on the results of their stress test.

## J. References


1. Ryan TJ: Refining the classification of chest pain: A logical next step in the Evaluation of patients for acute cardiac ischemia in the emergency department. *Ann Emerg Med 29: 166-168, 1997.*
2. Chandra A, Rudraiah L, Zalenski RJ: Stress Testing for Risk Stratification of Patients with Low to Moderate Probability of Acute Cardiac Ischemia. *Emerg Med Clin of North Am Vol 19: 2001*.
3. Lateef F, Geber WB: Provocative testing for chest pain. *Am J Emerg Med 18: 793-801, 2001.*
4. Mikhail MG, Smith FA, Gray M, et al: Cost-effectiveness of mandatory stress testing in chest pain center patients. *Ann Emerg Med 29: 88-98, 1997*.
5. Gaspoz JM, Lee TH, Weinstein MC, et al: Cost-effectiveness of a new short stay unit to 'rule out' acute myocardial infarction in low risk patients. *J Am Coll Cardiol 24: 1249-1259, 1994*.
6. Hillis GS, Oliner C, O'neil BJ, et al: Coronary artery disease in patients with Chest pain who have low-risk clinical characteristics and negative cardiac troponin I. *Am J Emerg Med 19: 118-121, 2001*.

**Columbia Presbyterian Medical Center**
**Consent to Participate in a Research Study**

**The purpose of this consent form is to provide you with the information you need to consider in deciding whether to participate in this research study.**

**Study title:** Role of early stress testing in decreasing cardiac ischemic events in low risk coronary disease chest pain patients.

**Study Purpose**

You are invited to participate in a research study of the role of early cardiac stress testing in reducing the risk of cardiac ischemic events such as myocardial infarction, recurrent cardiac chest pain, and asymptomatic myocardial infarctions, in low risk chest pain patients admitted to the New York Presbyterian Hospital.

The hypothesis is that early cardiac stress testing of low risk patients would decrease eventual cardiac ischemic events, recurrent angina symptoms, and need for revisits to the medical center. This hypothesis is based on prior data showing approximately 6% risk of coronary events within 3 months among this sub-population of patients.

You qualify as a possible participant in this study because you have been admitted to the Presbyterian hospital as a level 3 chest pain patient, and the decision has been made by your primary physician (s) not to have you undergo cardiac stress testing while admitted to the hospital. There would the a total of 1200 subjects enrolled in CPMC.

**Study Procedures**

If you decide to participate, you may have to undergo cardiac stress testing. The most common is the exercise stress test. This entails walking on a treadmill while the heart is monitored with a electrocardiogram. The elevation and speed of the treadmill would be increased incrementally every 3 minutes as per a Bruce protocol to achieve 85% of maximal heart rate. Study may also be ended if you feel chest pain, or shortness of breath, or fatigue. For subjects who cannot undergo exercise stress testing, pharmacologic stress test with adenosine, or dobutamine would be utilized. These agents work by increasing blood flow to the heart or increasing the heart rate and pumping function without exercise. Lastly, for patients who have abnormal baseline electrocardiograms, stress echocardiograms would be used to assess heart function. This also uses the same modalities outlined above, but instead of monitoring heart function with electrocardiograms, the pumping function of the heart can be visualized with a ultrasound.

All participants would be required to provide medical history, demographic information, and contact information to enroll into this study. All participants would receive questionnaires twice in this study to assess interim events and episodes of chest pain. You would be required to make the study investigators aware of any cardiac related events that take place during the 6 months of your participation in this study.

Subjects would be assigned by chance to stress test or no stress test. All stress testing would be done as in-patients during the initial admission for chest pain. Your participation would require two additional visits to CPMC for electrocardiograms. These would be at the 3-month and 6 month intervals. A total time of about 1 hour each visit would be required. You would need to participate for 6 months.

**Study Risks**

Your The risk of cardiac stress testing include acute myocardial infarction, however, this only occurs in participation in this study involves the following risks:

1) 1 in 2500 to 1 in 5000 patients. Other possible side effects are recurrent chest pain, dizziness, syncope, arrhythmias, fatigue and shortness of breath. Dipyridamole may cause bronchospasm but also very rare.

2) There is risk that subjects in the unstressed arm of this study may have increased cardiac ischemic events such as myocardial infarction, and chest pain, because their coronary disease is not recognized.

**Study Benefits**

You may not benefit personally from this study or you may benefit by having your coronary artery disease diagnosed. Society would benefit by the contribution this study may bring towards better stratification and management of patients who are admitted to hospitals for chest pain.

**Costs**

All studies done pertaining to this study would not be at cost to you. However, other costs that may accrue from other procedures or medications recommended by your physician would be at cost to you or your health insurer.

**Compensation**

There would not be compensation for participating in this study.

**Confidentiality**

Any information obtained during this study and identified with you will remain confidential.

**Participation is Voluntary**

Your participation in this study is completely voluntary. You can refuse to participate, or withdraw from the study at any time, and such a decision will not affect your medical care at Columbia – Presbyterian Medical Center, now or in the future. Signing this for does not waive any of your legal rights.

**Questions**

For any additional questions, you can reach Dr. Simbo Chiadika at 212 –305-5880. If you have any question on your rights as a research subject, you can call the Institutional Review Board at (212)-305-5883 for information.

**Statement of Consent**

I have discussed this study with Dr Chiadika to my satisfaction. I understand that my participation is voluntary and that I can withdraw from this study at any time without prejudice. I have read the above and agree to enter this research study. Signing this form does not waive any of my legal rights.

I have been informed that if I believe that I have sustained injury as a result of participating in a research study, I may contact the Principal Investigator, Dr. Simbo Chiadika at 212-305-5880, or the Institutional Review Board at (212)-305-5883, or that I can review the matter and identify the medical resources which may be available to me.

I understand that:

a) The Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital;
b) I will be responsible for the cost of such care, either personally or through my medical insurance or othr form of medical coverage;
c) No monetary compensation for wages lost as a result of injury will be paid b the Columbia-Presbyterian Medical Center, and;
d) I will receive a copy of this consent form.

Signatures: