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Title: UTILITY OF OBSERVATION UNITS FOR YOUNG EMERGENCY CHEST PAIN PATIENTS.

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Submission Category: Original Contribution

Preliminary analyses of portions of this paper's data were presented as posters at the annual Society of Academic Emergency Medicine conference, in Phoenix, AZ June 2010 and at the 2010 American College of Emergency Physicians Scientific Assembly, in Las Vegas, NV on 28 Sep 2010. The associated abstracts appeared in the corresponding journal supplements. Statistical analyses performed by Alexander Limkakeng, MD.

This study was performed without any external financial support. Dr. Limkakeng has received research support from Brahms AG, Roche, and National Institute of General Medical Sciences for other studies, but does not have any financial conflicts of interest. Dr. Chandra has received research support from Abbott, Inc. and the National Institute of Aging, but does not have any financial conflicts of interest.

The authors do not have any other financial interest in or other relationships that would be perceived as a conflict of interest.

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Dear Editor,

In this paper, “Utility of Observation Units for Young Emergency Department Chest Pain Patients,” we attempt to demonstrate that current cardiac observation unit evaluation protocols are low-yield in the low-risk young adult age group. We are submitting it as an Original Contribution.

Thank you for the valuable feedback. We have addressed each concern in an itemized fashion in our detailed response to reviewers, as well as in the revisions of our manuscript.

Please do not hesitate to contact us with any questions that may arise.

Sincerely,

Sora Ely, BS

**Title:** Utility of Observation Units for Young Emergency Department Chest Pain Patients

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Running Title: Young Patient Cardiac Observation

1 **Title:** Utility of Observation Units for Young Emergency Department Chest Pain Patients

2 **Abstract**

3 **Background:** Determining which patients presenting to the emergency department (ED) require  
4 further workup for acute coronary syndrome (ACS) can be difficult. The utility of routine  
5 observation for cardiac testing in low-risk young adult patients has been questioned.

6 **Study Objectives:** We investigated the rate of positive findings yielded by routine cardiac  
7 observation unit workup in patients 40 years or younger.

8 **Methods:** This was a retrospective observational cohort study of patients aged 18 to 40 years  
9 who were evaluated for ACS in an ED-based observation unit. Data was collected by trained  
10 abstractors from electronic medical records.

11 **Results:** A total of 362 patients met inclusion criteria. Of those, 239 received stress testing,  
12 yielding 5 positive and 9 indeterminate results. One other patient had acute troponin elevation  
13 while under observation. The positive stress test patients and troponin-elevated patient  
14 underwent cardiac angiography. Only one positive stress test patient showed significant coronary  
15 stenosis and received coronary interventions. In follow-up data, one patient had an adverse  
16 cardiac outcome within one year of index visit but no coronary interventions. Thus only three  
17 patients had adverse cardiac events, with only one patient warranting intervention discovered by  
18 observation unit stress testing and a second via serial cardiac markers.

19 **Conclusion:** Routine observation of symptomatic young adults for ACS had low yield.  
20 Observation identified one patient with acute cardiac marker elevation and further stress testing  
21 identified only one patient with intervenable ACS, despite a high false positive rate. This  
22 suggests that observation and stress testing should not be routinely performed in this  
23 demographic absent other high-risk features.

24 **Keywords: chest pain; stress testing; provocative cardiac testing; cardiac observation**  
25 **protocols; young patients; youth; acute coronary syndrome; ACS; diagnostic utility;**  
26 **coronary artery disease; CAD; low-risk; youth; emergency department;**

**Introduction**

Cardiovascular disease remains the leading cause of morbidity and mortality in the United States, causing over 710,000 deaths per year (1). Patients presenting with acute coronary syndrome (ACS) represent a major health issue, accounting for 2.5 million hospitalizations annually in the United States alone (1). Determining which patients presenting to the emergency department (ED) require further workup can be difficult (1,3-6). Missed acute myocardial infarction in the emergency department represents a significant source of concern about morbidity, mortality, and associated malpractice burden (7). The prevalence and seriousness of potential consequences make identifying and effectively treating ACS in emergency department settings crucial.

A particularly important risk factor for ACS is age, with a prevalence of only 1% in patients under 40 years of age (8). The utility of routine observation and cardiac testing in low-risk young adult (40 years or younger) patients has been questioned. AHA/ACC Guidelines acknowledge that such patients have “very low short-term rates of major adverse cardiac events,” but include the caveats that the patients have “non-classical presentations and no significant past medical history,” “serial biomarkers and 12-lead ECGs are normal,” and “appropriate outpatient testing can be arranged within 72 hours” (9). Most ED patients cannot meet all of these criteria (10,11) and serial biomarkers and ECGs require several hours to complete. Accordingly, a large number of patients under the age of 40 are placed in ED-based observation units or admitted (12).

Identifying a cohort of patients who do not need stress testing would be clinically and practically helpful. Excluding patients who do not need further workup could reduce hospital admissions, thereby reducing exposure to the risks of provocative tests, reducing cost, and

50 decreasing patient inconvenience. Prior work suggests that the rate of adverse cardiac events in  
51 this demographic approaches 1% (8). We hypothesized that patients 40 years or younger placed  
52 in our observation unit would have a <1% rate of abnormal stress tests associated with  
53 significant coronary artery disease. We secondarily sought to determine the rate of adverse  
54 cardiac events, defined as proportion of patients with >50% stenosis on coronary angiography,  
55 stenosis requiring percutaneous coronary intervention, stenosis requiring coronary artery bypass  
56 graft (CABG), subsequent troponin elevations >0.1 ng/mL, or death (all-cause mortality) within  
57 one year.



## 58 **Materials and Methods**

### 59 Study Design

60 This was a retrospective observational cohort study of patients aged 18 to 40 years who  
61 were evaluated for acute coronary syndrome in an ED-based observation unit at an urban  
62 academic tertiary care hospital ED with an average annual census of 65,000 visits from 2004 to  
63 2007. Approximately 40% of patients seen during this time period were admitted.

### 64 Study Setting and Population

65 The population for this study consisted of patients presenting to the emergency  
66 department with symptoms leading to observation in an ED based observation unit for ACS. In  
67 this observation unit, patients with suspected ACS receive serial cardiac markers and cardiac  
68 stress testing (usually treadmill echocardiogram) according to defined protocol. The choice of  
69 stress test modality was defined within the protocol, with the treating emergency physician  
70 making any final decisions in consultation with the cardiologist performing the test. Patients  
71 were eligible for our observation unit if they had suspected ACS but no acute ST segment  
72 changes, positive biomarkers, unstable vital signs, nor unstable dysrhythmias, and were 18 or  
73 more years old. As per the standard protocol, all patients had serial cardiac biomarkers and  
74 ECGs. Most then underwent provocative cardiac stress testing at the discretion of the treating  
75 physician.

### 76 Study Protocol

77 This study received exemption from human subjects research review by our Institutional  
78 Review Board (IRB) on the basis that the data were drawn from an existing database created for  
79 quality assurance purposes. Patient data were abstracted from a registry that contains  
80 consecutive patients who were cared for in an emergency department-based observation unit.

81 We obtained data for the registry via retrospective monitored data abstraction from electronic  
82 medical records, as detailed in Figure 1. All abstractors were trained in a one-hour didactic  
83 session in which the data abstraction spreadsheet, data variable definitions, and electronic patient  
84 record format were reviewed. The abstractors also completed a practice set of ten records that  
85 had been previously reviewed by the senior investigator, and they thereafter used a standardized  
86 abstraction form. The codes for data abstracted were included in the spreadsheet. Ten percent of  
87 the patient records were independently abstracted by a second reviewer and outcomes were  
88 compared for inter-rater reliability. All patients' electronic medical charts were reviewed for at  
89 least 1 year after their index visit. We also checked our institutional financial billing records via  
90 a web-based portal for any International Classification of Disease-9 codes for acute myocardial  
91 infarction, coronary angioplasty, coronary stent placement, coronary artery bypass surgery, and  
92 death.

### 93 Measures

94 Our primary outcome was a positive cardiac stress test: either wall motion abnormalities  
95 during stress echo or reversible perfusion defect on nuclear imaging or cardiac magnetic  
96 resonance imaging. We secondarily assessed for evidence of coronary disease requiring  
97 intervention or other adverse cardiac outcomes. For follow-up data, we determined whether the  
98 patient had cardiac catheterization (either with lesion >50% or requiring percutaneous  
99 intervention) or CABG; a subsequent troponin elevations >0.1 ng/mL; or death within one year.  
100 All stress tests were performed by board-certified cardiologists according to standard guidelines.

### 101 Data Analysis

102 Patients with ECG findings diagnostic of myocardial infarction or ischemia or positive  
103 biomarkers in the ED were excluded. Binomial proportions with 95% confidence intervals for

104 the rate of positive or indeterminate stress tests were calculated using SAS Enterprise Guide 4.2  
105 (Cary, NC). Simple proportions were calculated as appropriate for secondary outcomes.

106 **Results**

107           A total of 362 patients met inclusion criteria, with a mean age of 34.2 years and median  
108 of 36. The gender distribution was nearly equal, with 49% male. The distribution of races  
109 represented in the sample was more skewed, with 54.5% African American. The full breakdown  
110 of race across the sample, as well as the overall characteristics of the sample, is given in Table 1.  
111 The most common cardiac risk factor was family history (39.9%) followed by smoking (35.9%)  
112 and hypertension (34.3%). Among our 10% of records double-abstracted, there was complete  
113 agreement on outcomes.

114           Of the total 362 patients who met inclusion criteria, 124 did not undergo stress testing,  
115 being discharged after serial markers only. Of the remaining 238 undergoing observation, the  
116 numbers of patients undergoing various stress test modalities were as follows: 1 cardiac CT,  
117 5 cardiac MRIs, 17 dipyridole nuclear studies, 1 adenosine echocardiogram, 20 dobutamine  
118 echocardiograms, and 193 exercise treadmill echocardiograms. One patient was directed to  
119 coronary catheterization. Among these patients, 15 had abnormal workups. There were 14  
120 patients (5.9%; 95% CI 3.4-9.7%) who had abnormal stress test results and 1 patient who had  
121 acute elevation of troponin. The 14 abnormal stress test results were broken down into 5 positive  
122 (2.1%; 95% CI 0.8-4.9%) and 9 indeterminate (3.8%; 95% CI 1.9-7.1%) results. Among the 9  
123 indeterminate patients, 5 were considered indeterminate due to failure to reach target HR, for the  
124 others it could not be determined from our registry why the test was indeterminate. Eight of the  
125 nine indeterminate patients had follow-up visits at least 30 days out indicating they were still  
126 alive, 7 had such visits one year out. For these patients, no diagnostic angiography was  
127 performed but no other outcomes of interest were noted in the medical or financial billing  
128 records at one year.

129           The outcomes for the 5 patients with positive stress tests were of greatest interest based  
130 on study criteria, and their specific characteristics are outlined in Table 2. The 5 positive stress  
131 test patients were all admitted and underwent cardiac angiography. Only 1 of those 5 showed  
132 significant coronary stenosis >50%, and this patient received a percutaneous coronary  
133 intervention, for a positive predictive value of only 20%. The 1 patient with acute troponin  
134 elevation had a normal cardiac angiography but was given the diagnosis of myocardial  
135 infarction. Another patient had chronic renal failure and chronically elevated troponins, and  
136 despite no acute elevation of troponins under observation was admitted for cardiac angiography  
137 and received a percutaneous coronary intervention. We excluded this patient from the outcome  
138 results as this was a deviation from our standard protocol.

139           The majority of patients (79%) who had undergone observation had some form of  
140 medical entry at one year or more. At one year follow-up, the only additional outcome of  
141 interest was one patient who was diagnosed 8 months later with myocardial infarction but  
142 without percutaneous intervention. Thus overall there were 3 patients (0.8%; 95% CI 0.1-2.5%)  
143 with any outcome at one year. Using angiography as a reference standard, only 1 patient  
144 (0.28%; 95% CI 0.01-1.5%) had a provocative test result that led to angiography showing  
145 coronary artery disease requiring intervention. In contrast, in the general population of our  
146 observation unit, 115 out of 1,870 patients had significant coronary disease requiring  
147 intervention (6.15%; 95% CI 5.1-7.3%) at 1 year.

148 **Discussion**

149           Determining which patients require work-up for obstructive coronary artery disease  
150 remains challenging. In this study, over 3 years we found a total of 2 patients under the age of  
151 40 with significant coronary disease amenable to intervention, only one of whom was discovered  
152 through observation for routine cardiac stress testing. Although these results do not allow  
153 rejection of our null hypothesis, they nonetheless strongly suggest that current observation unit  
154 evaluation protocols are low yield in young patient populations. To our knowledge, this study  
155 represents the largest cohort of symptomatic young adults undergoing observation and cardiac  
156 stress testing (12,13). The extremely low rate of cardiac outcomes in the entire patient sample  
157 (consistent with national data for CAD in this age group) combined with the particularly high  
158 rate of false positives (80%) yielded by provocative cardiac testing calls into question routine  
159 observation for stress testing in this age demographic. Our results confirm findings at other  
160 centers, including studies by Hermann, et al, and Hamilton, et al. They too found an extremely  
161 low overall positive rate for stress testing (2.7% and 2.4% respectively) as well as a high false  
162 positive rate (66% in Hermann et al.) (12,13). Hamilton et al noted that stress testing made no  
163 difference in rates of 30 day adverse outcomes in patients under the age of 40 years (12). Our  
164 replication of their findings strengthens the conclusions of both studies: stress testing in  
165 symptomatic young patients currently has very low diagnostic utility. Taken together, our  
166 combined studies represent 531 young adult symptomatic patients undergoing cardiac stress  
167 testing, with only 5 (0.9%) patients having adverse cardiac outcomes identified by it (12,13).

168 **Limitations**

169           This data does have some key limitations. Use of medical records from a single medical  
170 center allows the possibility of under-diagnosed and under-reported (or more accurately, under-

171 recorded) disease, particularly for follow-up data. Although there are 2 other health systems in  
172 an approximately 10 mile radius to our facility, the high proportion of patients who had at least  
173 one subsequent healthcare entry in our records database at one year suggests that the majority of  
174 our patients tended to stay within our healthcare system. Additionally, to help compensate for  
175 both of these issues, we allowed a generous follow-up period after index visits to allow for the  
176 occurrence and documentation of significant events within our system. Given the scarcity of  
177 outcomes, it does not appear a great number of outcomes were likely to have been missed. The  
178 sample was of course limited by our selected inclusion criteria; in particular, we limited the  
179 sample to patients placed in an observation unit for chest pain. We did not determine whether  
180 cocaine use was reported by patients, which limits our external validity and ability to compare  
181 our findings to other settings. This may have been the indication for some of our patients to be  
182 placed in observation. It is possible that cocaine use may explain the few events that did occur.  
183 It is also possible that some young patients presenting with chest pain were not included in this  
184 sample if they were admitted or discharged without being placed in the observation unit.  
185 However, our intent was to focus on those patients who were considered low risk, but not to the  
186 extent that the clinicians felt the patients could be sent home immediately. We wanted to focus  
187 on patients for whom decision-making is often difficult, not those with obvious need for in-  
188 patient admission or further testing. The retrospective, observational nature of the study  
189 precluded proactive follow-up of patients, and not all patients had any further information noted  
190 in their medical records. Fortunately, the loss to follow-up was lower than might have been  
191 expected, with only 21% of the patients observed lacking subsequent records, and a rigorous  
192 chart and billing review enabled us to examine follow-up in the majority of patients who had  
193 undergone observation. A more specific concern about loss to follow-up is the lack of further

194 diagnostic cardiac data for the 9 patients with indeterminate stress tests, but existing follow-up  
195 data did at least indicate survival for most of them, none of whom had any documented adverse  
196 events. Finally, although our confidence intervals do not allow us to safely conclude that  
197 existing evaluation protocols are as low-yield as we had hypothesized, reducing the size of the  
198 confidence intervals would have required a very large trial, on a scale that was not feasible  
199 within the scope of this study.



**Conclusion**

201 Our data on coronary artery disease in symptomatic young adults confirms that overall  
202 risk of adverse cardiac outcomes at one year is extremely low (1.1% in our sample) although  
203 cardiac stress testing results were positive >1% of the time. Additionally, over the course of 3  
204 years, routine stress testing managed to identify only 1 young patient with actionable obstructive  
205 coronary artery disease while producing 4 false positives. These false positives were subjected  
206 to subsequent cardiac catheterization, an invasive procedure that is not without costs and risks.  
207 This suggests that existing evaluation protocols, especially with regards to stress testing, are very  
208 low-yield and possibly inappropriate for these young patients.

209 This study and the few others like it point to difficult challenge in emergency medicine.  
210 The extremely risk adverse physician cannot totally exclude the possibility of ACS based on age,  
211 but routine observation for such patients appears to cause the potential for as much harm as  
212 good. Additional studies, perhaps pooling data across centers to strengthen findings, will be  
213 needed to more definitively address these questions and direct changes in diagnostic protocol.  
214 Although the overall prevalence of ACS and CAD is low in this population, serious cardiac  
215 outcomes do occur. Better diagnostic tools are needed to more accurately identify symptomatic  
216 young patients at risk for ACS.

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256 Cardiac Stress Testing in Emergency Department Chest Pain Patients Younger Than 40  
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258 **Figure Legends**

259 Figure 1: Patient Flow Diagram with Outcomes.

260 MI = myocardial infarction, PCI = percutaneous coronary intervention

261 **Article Summary**

262 1. Why is this topic important?

263 Evaluation of patients for CAD is important because of its prevalence and potential difficulty in  
264 risk stratification, and existing observation workup protocols have not yet been thoroughly  
265 evaluated for young adult patient populations.

266 2. What does this study attempt to show?

267 This study attempts to demonstrate that current cardiac observation unit evaluation protocols are  
268 low-yield in the low-risk young adult age group.

269 3. What are the key findings?

270 We found a very low rate of CAD requiring intervention (1 patient out of 362, or 1.1%) in  
271 cardiac observation unit patients aged 18-40 years. Routine stress testing managed to identify  
272 only 1 young patient with actionable obstructive coronary artery disease while producing 4 false  
273 positives. This suggests that existing evaluation protocols, especially with regards to stress  
274 testing, are very low-yield and possibly inappropriate for these young patient populations.

275 4. How is patient care impacted?

276 Our findings, especially when taken with corroborating studies, suggest that existing protocols  
277 for evaluating young patients for chest pain in an emergency setting are inefficacious.  
278 Emergency physicians may be immediately able to avoid some unhelpful diagnostic procedures  
279 and thus reduce exposure to procedure-associated risks, and once new protocols are developed  
280 they will be able to more accurately and efficiently diagnose ACS in these young patients.

**Table 1: Sample Population Characteristics**

<b>Table 1: Sample Population Characteristics</b>						
<b>Characteristics</b>	<b>N</b>	<b>%</b>	<b>Stress</b>		<b>No Stress<sup>†</sup></b>	
<b>Total</b>	362	N/A	237	N/A	124	N/A
<b>Age</b>	$\mu = 34.2$ years	N/A	$\mu = 35.3$ years		$\mu = 32.0$ years	
<b>Gender</b>	<b>N</b>		<b>Stress</b>		<b>No Stress<sup>†</sup></b>	
<i>Male</i>	177	49.0%	115	48.5%	64	52.0%
<i>Female</i>	185	51.0%	122	51.5%	60	48.0%
<b>Race</b>	<b>N</b>		<b>Stress</b>		<b>No Stress<sup>†</sup></b>	
<i>Black</i>	190	52.5%	123	51.9%	66	53.2%
<i>White</i>	133	36.7%	92	38.8%	41	33.1%
<i>Hispanic</i>	24	6.6%	13	5.5%	11	8.9%
<i>Indian</i>	1	0.3%	0	0.0%	1	0.8%
<i>Other</i>	14	3.9%	9	3.8%	5	4.0%
<b>Risk Factors</b>	<b>N</b>		<b>Stress</b>		<b>No Stress<sup>†</sup></b>	
<i>Family History CAD</i>	144	39.9%	110	46.4%	34	27.2%
<i>Smoking</i>	130	35.9%	86	36.3%	44	35.2%
<i>Hypertension</i>	124	34.3%	90	38.0%	34	27.2%
<i>Past History CAD</i>	28	7.7%	16	6.8%	12	9.7%
<i>Diabetes Mellitus</i>	54	14.9%	38	16.0%	16	12.8%
<i>Hyperlipidemia</i>	58	16.0%	45	19.0%	13	10.4%
<i>TIMI Score</i>	median = 0		median = 0		median = 0	
<i>TIMI Score = 0</i>	216	59.7%	151	63.7%	65	52.4%

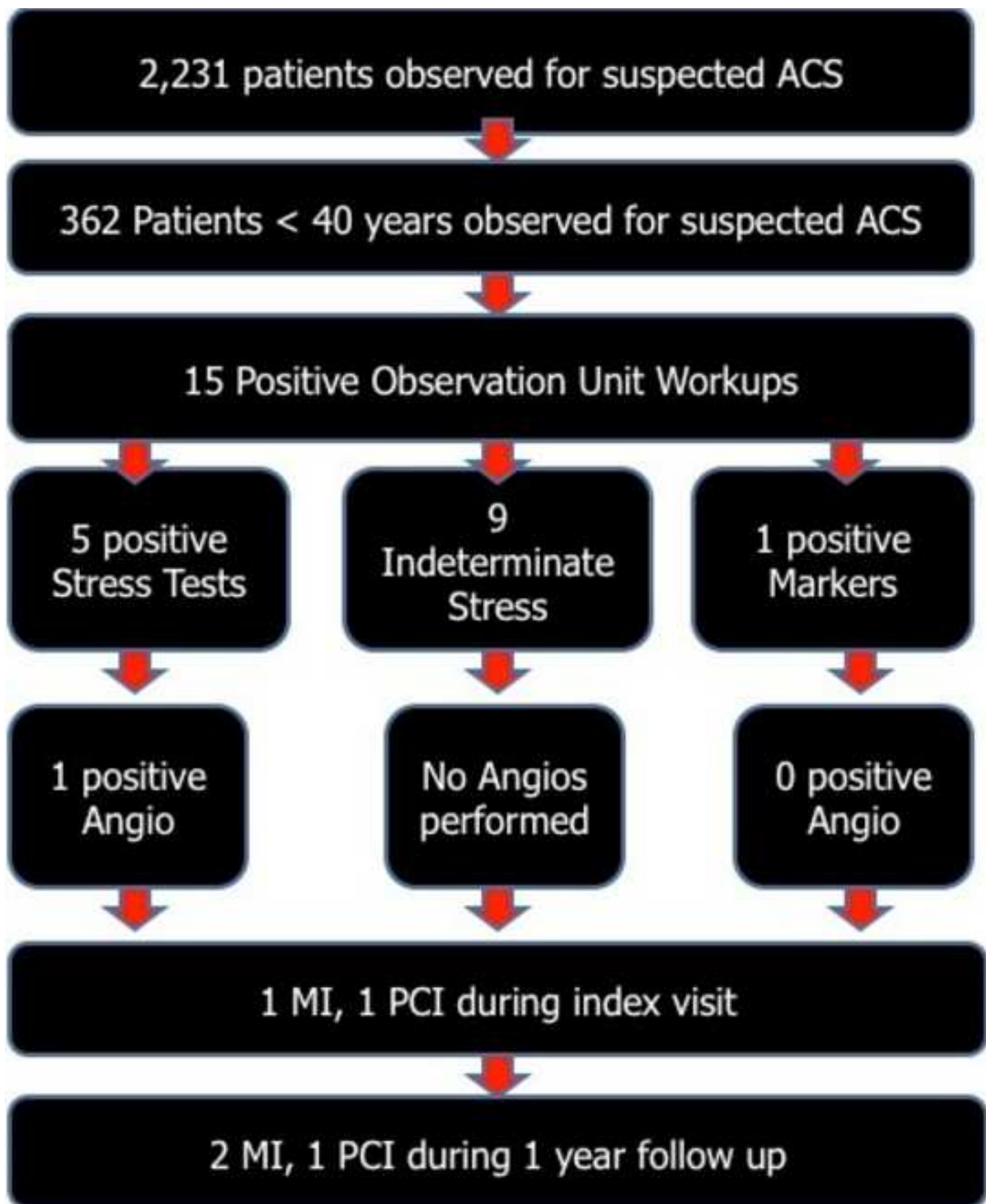
<i>TIMI Score =1</i>	109	30.1%	63	26.5%	46	37.1%
<i>TIMI Score =2</i>	34	9.4%	22	9.3%	11	8.9%
<i>TIMI Score =3</i>	3	0.8%	1	0.4%	2	1.6%
<i>3+ Cardiac Risk Factors</i>	51	14.1%	38	16.0%	13	10.5%
CAD = coronary artery disease; TIMI Score = Thrombolysis In Myocardial Infarction Risk Score						
†1 patient went straight to cath and was not included in the No Stress group						

**Table 2: Characteristics of Young Patients with Positive Stress**

<b>Table 2: Characteristics of Young Patients with Positive Stress Tests</b>				
<b>Age (years)</b>	<b>Cardiac Risk Factors</b>	<b>Stress Test Modality</b>	<b>Cardiac Angiography Results</b>	<b>TIMI Risk Score</b>
39	diabetes mellitus, hypertension	dobutamine echo	negative	0
36	hypertension, family history	exercise echo	negative	0
37	hyperlipidemia	dobutamine nuclear	negative	0
35	family history	exercise echo	negative	0
40	hypertension, hyperlipidemia, family history, coronary artery disease	exercise echo	positive	1



Figure 1: Patient Flow Diagram with Outcomes  
[Click here to download high resolution image](#)



We greatly appreciate the constructive criticisms of our manuscript and have made requested revisions as well as included these responses to each reviewer comment.

*Reviewer #1: The authors present a retrospective review examining the role of stress testing in an observation unit in young patients.*

*The authors need to decide if they are studying observation management or stress testing. The title suggests stress testing, the analysis reflects information from both stressed and non-stressed obs patients.*

We agree that the focus should really be on observation, not just stress testing. The manuscript has been edited appropriately.

*Also, I have concerns regarding the author's apparent contention that only interventionable CAD matters - MI is MI, regardless of whether a cardiologist can drop a stent somewhere.*

Agreed: Intervenable CAD is important if considering only stress testing, but considering observation, we have included discussion of MI as well as the broader category of adverse cardiac events.

*Specific concerns - highest concerns are marked with \**

*Line 39 - Provide citations to support this statement (which is accurate, yes, but should be supported)*

Done.

*\*Your primary hypothesis relates to a <1% rate of abnormal stress tests, although you cite literature with a prevalence of 2% ACS in patients under 40. This goes back to my concern regarding the nature of the study - are you studying stress tests or observation? Explain how you arrived at <1% as a target.*

This is really just a standard target, it being unreasonable to assume we will find a population with 0% prevalence, 1% has been suggested as low enough to be considered safe for discharge but high enough to be considered feasible to detect. Also, per the other reviewer: Dawson M et al. Crit Pathw Cardiol 2010 Sep;9(3):170-3 suggests this is the prevalence in this population.

*Line 48 - all cause mortality or cardiac related mortality? Please clarify.*

All cause mortality.

*\*Study setting and population - need more detail regarding your hospital and ED - annual census, admission percentage, academic vs. community.*

We did describe this in our methods ("urban academic tertiary care hospital ED with an average annual census of 65,000 visits") but have additionally included our admission percentage from the ER (approximately 40%).

*Also, it would be good to describe how many other health systems / hospitals are in the surrounding geographic area - your contention later that patients stay within one health system*

*flagrantly contradicts my own experience, but knowing how many other hospitals patients have to choose from in your area would help to inform that discussion.*

There are 2 other health systems in approximately 10 mile radius and this fact is now included in the limitations section.

*\*Line 63 - the ESRD patient with chronically elevated troponins is a protocol violation, and really should not be considered within this cohort.*

This patient was excluded from outcome results, we mention it only for clarity.

*Line 67 - But the study was still human subjects research, and received expedited review with a waiver of consent, correct? Exempt refers to non-human subjects research. Please clarify.*

This study received exemption from human subjects research review as it was drawn from an existing database created for quality assurance purposes.

*Study protocol- well done on the description of your training (and the training itself)!*

*Measures: Clarify that you did, or did not, consider the ECG portion of the stress imaging.*

We did not consider the ECG portion of the stress imaging because it is the practice of our cardiologists to follow the imaging results of the stress test over the ECG findings.

*\*Data analysis - how did you determine how many records you were going to review? Did you go back all the way to the inception of the obs unit? Given a binomial 95%CI, which conceivably could have been calculated as a single tail as there is a reasonable expectation that the event rate in <40 was 0, it would not be difficult to determine a denominator to review so that the upper limit of the 95% CI was <1%, as per your primary hypothesis. As you did not reject the null, power (expressible conceptually in this setting in 95%CI width) becomes an issue.*

Because we were drawing on existing quality assurance database, sample size was determined by the existing data. As such, we did not perform a retrospective power analysis. Our sample began at the earliest point at which we could obtain electronic medical records on patients from our quality assurance database. This also contributed to other limitations as noted below and in the manuscript section. Based on our IRB approval we could not, after our analysis, review more records to attempt to narrow our confidence intervals and scientifically this would amount to, essentially, multiple comparisons.

*Line 91 - this is why the ESRD / trop+ fellow should not be included in this analysis.*

Agreed; removed.

*\*Line 97 - 362 were observed, but only 239 met inclusion criteria for your primary hypothesis.*

*Again, this speaks to the study not having a clear direction - are you testing observation care or stress testing?*

As per the earlier concern, we have edited the manuscript to focus more broadly on observation.

*Line 107-108 - more about the indeterminate population, please. How were these indeterminate? Inadequate heart rate? Poor quality images? Positive ECG / negative imaging?*

As this was a retrospective observational study, we could not perform prospective follow-up. However, we were able to obtain existing follow-up and can provide some more details on the stress testing results (included in the manuscript). Among the 9 indeterminate patients, 5 were considered indeterminate due to failure to reach target HR; among the others, the data from our registry did not elucidate why the test was indeterminate. 8/9 of the indeterminate patients had follow-up visits at least 30 days after the index visit, indicating they were still alive, and 7 had such visits one year out. None had any adverse cardiac events noted by records or billing review.

*\*Line 112-113 - cath results are not actually dichotomous, although the decision to stent or not is. There is a substantial difference between clean coronaries and diffuse disease, and these results will inform the oft maligned "medical management." Please clarify the angio results, and I would be very interested to know if any of these patients had their medical regimens changed during the stay.*

Unfortunately, we do not have this level of detail in our registry, so we cannot clarify.

*\*118-129. This is the major limitation to the study. Leaving aside the possibility that subjects had MIs and were treated at other hospitals in the area (see above comment regarding Study Setting), the presence of an entry in the medical record provides at least an indication that the patient is still alive. In the absence of explicit documentation, though, that the patient had no further workup, no MI, no interventions, it is a reaching assumption to be making that the absence of documented events is equivalent to the absence of events.*

Agreed; we attempted to clarify this further in the limitations, in addition to addressing the earlier concern.

*\*Discussion. Given the lack of concrete follow up, and given that you did not meet your prespecified rejection of your null hypothesis, I would perhaps be less enthusiastic about how strongly the data suggests anything (line 141). Note that I don't disagree with the concept - we are working up way too much garbage chest pain in young people, in my opinion. However, this study as a retrospective cohort is hypothesis generating at best, and can serve mainly to inform a prospective cohort in terms of potential event rates.*

Agreed; we have deleted these 2 statements entirely.

*Line 147-148 - help the reader out, provide the event rates for the Hamilton and Hermann studies.*

Done.

*Line 158 - I will admit to my own bias here, but at the various health care systems I have worked at, patients flit between healthcare systems like butterflies on speed. Even in a strongly locked in HMO system like Kaiser, substantial numbers of patients presented to external facilities. I would reconsider the strength of this statement here.*

Edited accordingly.

*\*Line 171 -174 - This is a failure of study design, and a failure to incorporate basic statistical principles when deciding how many charts to examine, or whether to pool data with other*

centers with observation units. Failing to reject your null was almost a given with this sample size.

It would be difficult, perhaps nearly impossible, to obtain a sufficiently large sample size of young chest pain patients who received workup in a reasonable time frame. We have added a suggestion for future directions that might help address this (pooling data with other centers).

*Reviewer #2: The authors describe a retrospective chart review of 362 under-40 CPU patients with stress test results (n=239) as primary outcome, with additional use of a 1-year standard composite endpoint (MI, death, revasc/CABG). Stress testing utilized multiple different modalities (eg echo, nuclear, etc). Angio data was available as a gold-standard in only 6 patients (1 pos markers, 5 pos stress) and only 4 patients had + composite endpoints at 1 yr. The authors found that 4/5 pos stress tests were false positives. The authors conclude that stress testing is very low-yield and possibly inappropriate for young patients with cp.*

*In general the paper is well written. The authors carried out the largest retrospective study I can find of <40 CPU pts to date and should be commended. There were several limitations of the study, most of which the authors conceded. Probably the largest weaknesses are functions of the retrospective nature of the study (ie multiple different stress modalities, possible loss to followup, misclassification, and lack of a gold standard on the majority of patients). I have tried to provide constructive feedback to the authors arranged by section below:*

*Intro:*

*1. Interesting study question in light of recent AHA guidelines that exonerate ED docs from stressing <40. To quote verbatim, AHA/ACC Guidelines (Nov 2010) stipulate "Patients younger than 40 years-of-age with non-classical presentations and no significant past medical history have very low short-term rates of major adverse cardiac events when serial biomarkers and 12-lead ECGs are normal. These patients may be discharged directly from the ED/CPU if appropriate outpatient testing can be arranged within 72 hours." Would include this reference in your intro and defend your decision to conduct study despite this. (The answer should probably focus on the issues of "non-classical" presentations and barriers to "outpatient testing can be arranged within 72 hours".)*

We have edited accordingly.

*Methods:*

*1. Cocaine use excluded? If not this is a limitation.*

It was not excluded and we have included this in our limitations.

*2. Many different stress test modalities are a major source of confounding. Who chose the stress test modalities? Needs to be addressed in limitations. In an ideal study, everyone gets the same stress test to minimize variability. Can you break the numbers down better for us in terms of who got what provoc test?*

The choice of stress test modality was protocol-driven but ultimately determined by the treating ED physician ("In this observation unit, patients with suspected ACS receive serial cardiac markers and cardiac stress testing (usually treadmill echocardiogram) according to defined protocol"). We have added: "The choice of stress test modality was defined within the

protocol, with the treating emergency physician making any final decisions in consultation with the cardiologist performing the test” to our methods, as well as the modality breakdown within our results (1 cardiac CT, 5 cardiac MRIs, 1 adenosine echo, 17 dypramidole nuclear, 20 dobutamine echos, 193 exercise echos, 1 cath).

*3. Inclusion criteria appear to be a source of bias - enrollment of <40 CPU patients leaves out <40 cp patients who did NOT go to the CPU (and thus were overlooked by the protocol). Were there many of these latter patients during the study period?*

We chose to focus on patients placed in observation and so we discuss this self-imposed limitation in our limitations section.

*Results:*

*1. Please report positive predictive value (PPV) of stress test using angio as gold standard. Excluding the one patient with pos markers, there were 5 outright positive stress tests with only 1 pos angio. This leads to PPV = 20% for stress testing in this population, which is dismal. This should really be the headline of this paper. In other words, positive stress tests were rare and overwhelmingly likely to be false positives - when put with this spin, it begs the question even better in my opinion.*

Excellent point; added.

*2. Lacking stress results on 1/3 of your initial sample is a concern and a major limitation. Need to list general characteristics (risk factors, "classic" cp story, etc) to see if there were any major differences between the stressed and not-stressed groups. See comments ion Table 1.*

Unfortunately, we do not have access to the descriptive features of the chest pain symptoms in our database, but we do have access to the traditional risk factors and have now reported them in the manuscript (included below, as well).

In stressed group:

38/237 (16%) patients with 3 or more risk factors

median TIMI = 0

63 (26.5%) patients with TIMI =1

22 (9.3%) with TIMI =2

1 (0.4%)with TIMI = 3

rest were TIMI = 0

In unstressed group:

13/124 (10.5%) patients with 3 or more risk factors

median TIMI = 0

46 (37.1%) patients with TIMI =1

11 (8.9%) with TIMI =2

2 (1.6%) with TIMI = 3

rest were TIMI = 0

*3. Missed outcomes - what was loss to follow up rate at 1 yr? Loss to followup can lead to misclassification and is a threat to validity in the 1-yr reporting. To the authors credit, this was not a major thrust of the paper.*

We expanded the discussion of this limitation in the corresponding section and had already included the percentage of patients for whom data was available in our results section.

*Discussion:*

1. We know that the population of chest pain patients younger than 40 years with no history of coronary disease, a nondiagnostic ECG, and negative serial biomarkers may not benefit from provocative testing. Please discuss your results in light of the following paper - Dawson M et al. *Crit Pathw Cardiol* 2010 Sep;9(3):170-3.

We added specific discussion of this paper (see responses above to reviewer #1 as well). Despite its points, many patients are still being placed in observation for fear of liability (see Hamilton et al.).

2. Prior data has yielded similar findings (Reference #7 Hermann et al). In the prior study, 100% of the time (4 out of 4) the initial positive provocative study was angiographically proven to be falsely positive. How is your study similar/different?

Our study is similar; our results are in agreement with their findings and add to the evidence base.

3. Similarly prior data has looked at differences between those who were and weren't stressed (Reference #8 Hamilton et al). Those data showed 30-day cardiovascular complication rates were no different between the stress and no-stress groups. Do you have data on your "no-stress" group?

Yes, these patients' follow-up was performed in the same manner as the stress test group with no outcomes of interest, as noted.

4. There exist "rules" for cp pts <40 years of age (Marsan et al): *Acad Emerg Med* 2005;12:26-32. These authors identified <2% risk without need for stress testing.

This is true. However, some of our patients would not have met these rules; only 31% of the patients under age 40 would have met all the requirements of the rule, leaving the question of optimal disposition of the remaining patients. Additionally, this highlights the reluctance on the part of providers to discharge these patients despite the evidence.

5. Another cp rule in a <40 subgroup: (Christenson et al: *Ann Emerg Med*. 2006 Jan;47(1):1-10). Patients have very low risk of acute coronary syndrome if they have a normal initial ECG, no previous ischemic chest pain, and age younger than 40 years.

Similar case to above; only 25% of the patients under 40 would have met the rule.

6. "Nondiagnostic/Indeterminate" stress results from the CPU are problematic because no one really knows what to do with them. None of your 9 "nondiagnostic" patients went to angio which I find an interesting/concerning practice since these patients have well-demonstrated higher rates of cv events at followup. Not having a gold standard (ie angio) for these patients needs to be discussed as a major limitation unfortunately. For example, if they all had obstructive CAD this would completely change the flavor of the study, which appears to suggest not to stress cp patients under 40.

We could not perform prospective follow up of course, but we were able to obtain existing follow up and can provide some more details on the indeterminate stress test patients. Among the 9 indeterminate patients, we found that 5 were considered indeterminate due to failure to reach target HR, but it could not be determined from our registry why the rest were considered

indeterminate. 8/9 of the indeterminate patients had follow-up visits at least 30 days out indicating they were still alive; 7 had such visits one year out. We also added this specific concern explicitly to the limitations section.

*Conclusions:*

1. *Why the word choice "used sparingly" - this appears to be an intentional hedge and should be re-worded.*

Done.

2. *Final "future studies" paragraph should be reworded or eliminated. Confused that the authors want to look for new tools to identify risk for adverse events when they had very low rates in this study. If you buy the paper's results, then it seems like a poor use of research resources to now embark on that witch hunt. In other words, your data did not reassure you that this is indeed a low risk population, so I want to ask you why not?*

This is a good point, but we did feel we had to concede that there were some patients with adverse events and we did not reject our null hypothesis. Elucidating ways to identify these very rare patients would seem to be worthwhile so that the rest of the patients under the age of 40 could be discharged from the ED. We have re-worded it to clarify this point and to better reflect the state of the literature.

*Tables:*

1. *Table 1: would add columns for those stressed (n=239) vs not stressed (n=123). This way we can eyeball for any bias between groups.*

Done.

*Figures:*

1. *Consider changing (+), which is confusing, to just writing out "positive"*

Done.