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Biomarkers After Risk Stratification in Acute Chest Pain (from the BRIC Study)

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Abstract

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Current models incompletely risk-stratify patients with acute chest pain. In this study, N-terminal proeB-type natriuretic peptide and cystatin C were incorporated into a contemporary chest pain triage algorithm in a clinically stratified population to improve acute coronary syndrome discrimination. Adult patients with chest pain presenting without myocardial infarction (n = 382) were prospectively enrolled from 2008 to 2009. After clinical risk stratification, N-terminal proeB-type natriuretic peptide and cystatin C were measured and standard care was performed. The primary end point was the result of a clinical stress test. The secondary end point was any major adverse cardiac event at 6 months. Associations were determined through multivariate stratified analyses. In the low-risk group, 76 of 78 patients with normal levels of the 2 biomarkers had normal stress test results (negative predictive value 97%). Normal biomarkers predicted normal stress test results with an odds ratio of 10.56 (p = 0.006). In contrast, 26 of 33 intermediate-risk patients with normal levels of the 2 biomarkers had normal stress test results (negative predictive value 79%). Biomarkers and stress test results were not associated in the intermediate-risk group (odds ratio 2.48, p = 0.09). There were 42 major adverse cardiac events in the overall cohort. No major adverse cardiac events occurred at 6 months in the low-risk subgroup that underwent stress testing. In conclusion, N-terminal proeB-type natriuretic peptide and cystatin C levels predict the results of stress tests in low-risk patients with chest pain but should not be substituted for stress testing in intermediate-risk patients. There is potential for their use in the early discharge of low-risk patients after clinical risk stratification.

Accurate and efficient risk stratification for patients with acute chest pain remains a significant problem.^{1,2,3} In this study, we evaluated low- and intermediate-risk patients with acute chest pain presenting to the emergency department (ED) by measuring cystatin C^{4,5} and N-terminal pro-B-type natriuretic peptide (NT-proBNP)^{6,7} to determine if these biomarkers could substitute for the results of stress testing, potentially leading to more rapid, accurate, and cost-effective triage to hospital admission or ED discharge. No previous study has attempted to correlate biomarkers with stress test results. Secondarily, we assessed whether these biomarkers provide incremental benefit above clinical risk stratification in this population.

Methods

Patients presenting to the ED at a large urban tertiary care medical center triaged with a chief complaint of chest pain were consecutively enrolled from August 2008 to June 2009. After obtaining informed consent, history and physical examination information was collected using a protocol-specific questionnaire. Each patient's blood specimens were collected and stored. Patients were determined to be at high, intermediate, or low risk per Agency for Health Care Policy and Research (AHCPR) guidelines.⁸ The study was approved by the local institutional review board.

Eligible patients were aged ≥ 18 years with acute chest pain lasting ≥ 10 minutes and at low or intermediate risk per AHCPR guidelines without clinical, electrocardiographic, or biomarker evidence of myocardial infarction (MI). MI was defined per current guidelines to be a troponin I elevation ≥ 0.6 ng/ml along with the appropriate clinical, electrocardiographic, or imaging criteria.⁹ Patients with electrocardiographic evidence of ST-segment

elevation MI who underwent immediate cardiac catheterization without elevated troponin I were also counted in the MI group. Exclusion criteria included patients classified at high AHCPR risk, those with MIs, those without available blood samples, and those who failed to provide informed consent. Disagreements in classification of MI were resolved by the primary investigator. To allow adequate time to rule out acute MI, patients were observed for 9 hours in the chest pain or telemetry unit and until 2 sets of troponin I tests had been analyzed before enrollment.

Plasma was analyzed for troponin I, aliquoted, and stored at -20°C until testing for cystatin C and NT-proBNP. Conventional cardiac troponin I was measured by radial partition immunoassay using the Dade Stratus CS analyzer (Siemens Healthcare Diagnostics, Deerfield, Illinois). NT-proBNP was measured by chemiluminescent immunoassay on the Dade Dimension Xpand analyzer (Siemens Healthcare Diagnostics). Cystatin C was measured by immunoturbidimetry on the Roche DPP analyzer (Roche Diagnostics, Indianapolis, Indiana). An abnormal NT-proBNP level was defined as ≥ 125 pg/ml. An abnormal cystatin C level was defined as ≥ 1.19 mg/L. All patients included in the final analysis had NT-proBNP measured, but because of the lack of sufficient plasma sample, 37 patients did not have cystatin C measured.

After enrollment in the study, patients underwent standard clinical care as determined by their treating physicians. Telephone and medical chart follow-up occurred at 6 months. Measured end points included stress test results and any major adverse cardiac event (MACE). Stress tests included any noninvasive ischemic evaluation, including exercise treadmill testing, exercise or pharmacologic myocardial perfusion imaging, and exercise or pharmacologic echocardiography performed during the course of the index visit. All stress tests were performed per standard guideline-driven protocols.^{10,11} Stress test results were divided into normal, abnormal, or indeterminate on the basis of a review by a certified cardiologist. An abnormal stress test result was defined as electrocardiographic ST-segment depression >1 mm on exercise testing or abnormal myocardial perfusion on nuclear imaging. All interpretation and reports were on the basis of current consensus guidelines.¹⁰ This end point was chosen because of its use as the primary guideline-recommended ischemic evaluation for low- and intermediate-risk patients with chest pain. MACEs included the first occurrence of an MI, revascularization (percutaneous coronary intervention or coronary artery bypass grafting), or death from the time a patient left the ED (for discharge or admission) up to 6 months except for in-hospital MIs or staged percutaneous coronary intervention revascularization. Source documents of each MACE were reviewed by independent members of the team for accuracy (S.S.S. and K.S.). Reports of mortality were cross referenced with the Social Security Death Index.

Depending on the distribution, between-group differences for continuous variables were assessed using 2-sample Student's *t* tests (expressed as mean $\pm$ SD) or Wilcoxon's rank-sum tests (expressed as median [interquartile range]). Nominal variables are expressed as frequencies and percentages. For categorical variables, differences between groups were assessed using chi-square tests or Fisher's exact tests as appropriate. The primary outcome measure of the relation of NT-proBNP or cystatin C to stress test results was expressed as an odds ratio (OR) using chi-square analyses. Each biomarker was analyzed individually for

this relation, and then an analysis was performed with the 2 biomarkers. We stratified these analyses by low or intermediate risk using the Cochran-Mantel-Haenszel statistic to generate an adjusted OR. Secondary outcome measures are also expressed as ORs using chi-square or Fisher's exact tests as appropriate. Sensitivity, specificity, positive predictive value, and negative predictive value (NPV) were generated using frequencies. Statistical significance was defined as a p value <0.05 .

Results

Of the 524 patients who initially consented to the study, 382 patients were eligible for final analysis (Figure 1). Of these patients, nearly half ($n = 189$) underwent stress testing during their hospital visits. Patients who underwent stress testing were more likely to be younger, female, and at low AHCPR risk. Stress testing was less likely to be performed in patients with histories of MI, revascularization, diabetes, or heart failure.

Table 1 illustrates the baseline characteristics as stratified by AHCPR risk classification. Similar to the differences between patients who did and did not undergo stress testing, patients classified at low risk were younger and less likely to be men, to have hypertension, diabetes, heart failure, prior revascularization, to use aspirin, or to be prescribed typical cardiovascular medications.

In the stress test group ($n = 189$), there were 30 studies with abnormal results (15.9%). To confirm the accuracy of initial risk classification, intermediate-risk patients were statistically more likely to have abnormal stress test results compared to low-risk patients, with an unadjusted OR of 5.72 (95% confidence interval [CI] 2.38 to 13.75; Table 2).

Overall, 158 of 382 patients (41%) had elevated NT-proBNP levels. In contrast, 83 of 345 patients (24%) had abnormal cystatin C levels. Either value was abnormal in 172 patients (49%). When comparing by AHCPR risk classification, individually, NT-proBNP and cystatin C were statistically more likely to be elevated in intermediate-risk patients (Table 2). Likewise, elevation of either NT-proBNP or cystatin C was statistically more likely to be present in the intermediate-risk group compared to the low-risk group (OR 5.06, 95% CI 3.22 to 7.97).

In the stress test group ($n = 189$), 58 patients had either elevated cystatin C or NT-proBNP levels (30.7%; Table 3), with 19 having an abnormal stress test results. In contrast, 102 of 111 patients with normal cystatin C and NT-proBNP levels had normal stress test results, yielding an NPV of 92%. Therefore, biomarkers predicted the stress test results with an OR of 5.52 (95% CI 2.3 to 13.2, $p < 0.0001$).

Further analysis divided the 189 patients who underwent stress testing by risk classification and analyzed its relation to biomarkers. In the group at low AHCPR risk ($n = 101$), either marker was abnormal in 23 patients. Of these, 5 patients had abnormal stress test. However, in the 78 patients with normal biomarker levels, only 2 patients had abnormal stress test results (NPV 97.4%). In this stratified group, the OR for the biomarker level predicting the stress test result was 10.56 (95% CI 1.9 to 58.9, $p = 0.006$). In contrast, in the intermediate-risk group that underwent stress testing, 35 of 68 patients had abnormal NT-proBNP or

cystatin C levels. Of the patients with abnormal biomarker levels, 14 had abnormal stress test results, but 26 of 33 patients with normal biomarker levels had normal stress test results (NPV 79%). In contrast to the low-risk population, the association between biomarker levels and stress test results did not reach statistical significance (OR 2.48, 95% CI 0.845 to 7.25) in the intermediate-risk group.

For all patients included in the study, biomarker and MACE data were available for 332 patients (Table 4). In these patients, there were 42 events at 6 months after leaving the ED (whether discharged or admitted), a rate of 12.7%, with most consisting of revascularizations. Either NT-proBNP or cystatin C level was abnormal in 26 of these patients (62%), compared to 16 with normal biomarker levels (38%). As seen in Table 4, the association between biomarker levels and events did not reach statistical significance, regardless of risk stratification. In the subgroup of patients who underwent stress tests, there were no events in the low-risk group. The intermediate-risk group had 14 events: 7 marker positive and stress test positive, 5 biomarker negative and stress test positive, 0 biomarker negative and stress test positive, and 2 biomarker negative and stress test negative.

Discussion

In this cohort of 382 patients with acute chest pain at low to intermediate AHCPR risk, we evaluated the diagnostic utility of 2 relevant cardiac biomarkers (NT-proBNP and cystatin C) and showed that they may be useful in the triage of low-risk patients but do not substitute for stress testing in intermediate-risk patients. Few studies have evaluated the potential niche for biomarkers in low- and intermediate-risk patients that are heavy on resource utilization but lack clear algorithms for efficient and reliable triage.

When patients were stratified by low and intermediate risk, the NPV was 98% in the low-risk group but decreased to 79% in the intermediate-risk group. Low-risk patients with normal biomarkers were 10 times less likely to have abnormal stress test results compared to a patient at similar risk with elevated biomarkers. In addition, no low-risk patients who underwent stress tests (regardless of their results) had events at 6 months. This provides evidence that simply drawing a panel of admission biomarkers, including cardiac troponin, NT-proBNP, and cystatin C, after clinical risk stratification may allow more accurate discrimination between those patients needing further ischemia evaluation and those who can be discharged without the current guideline recommended stress testing within 24 to 72 hours of discharge.¹²

No previous study has associated biomarker results with the outcomes of stress tests, focusing instead on prognostic rather than diagnostic utility in high-risk populations.¹³⁻¹⁷ We purposefully chose a pure clinical risk classification scheme that predated the use of troponin,⁸ favoring a mechanism for immediate-risk stratification on arrival to the ED. The AHCPR guideline accurately identifies a low-risk population with a 2.5% event rate at 30 days,¹⁸ a rate similar to that in the low-risk cohort derived from risk stratification schemes incorporating conventional cardiac troponin.^{19,20}

If patients with low AHCPR risk and normal NT-proBNP and cystatin C levels can be confidently discharged earlier from the ED, there is tremendous potential for cost savings individually and for the health care system. Although stress tests have long been established as an effective method of refining clinical risk stratification, using biomarkers as a substitute may provide a less expensive and speedier alternative. Currently, an estimated \$6 billion are spent annually on negative chest pain evaluations.²¹ These costs increase in low-risk patients, who likely do not have acute coronary syndromes.²² With improved diagnostic classification, at a very modest cost, we have the opportunity to reallocate these resources to those patients with actual pathology.

Several trials have advocated the wholesale use of coronary computed tomography as a quick way to discharge patients with chest pain from the ED.²³⁻²⁵ However, the high NPV of this modality and potential for a quicker ED visit needs to be balanced with the radiation risk and cost of doing this procedure on most (especially low-risk) patients with chest pain. As another alternative, a recent analysis suggested potential discharge without further ischemic evaluation in low-risk patients on the basis of clinical risk stratification alone.²⁶ Although we believe that risk stratification is the cornerstone of diagnostic evaluation in patients with acute chest pain, the subsequent addition of NT-proBNP and cystatin C incrementally increases NPV, favoring more likely adoption of this strategy in the contemporary health care and medicolegal climate.

Aside from NT-proBNP and cystatin C, another intriguing new biomarker for ischemia or early infarction is high-sensitivity troponin.²⁷ Recent studies have confirmed a high NPV for this assay in excluding acute coronary syndromes applied across an entire ED cohort of patients with chest pain.^{28,29} Another study revealed the benefit of this test in the context of a clinically risk stratified population at 30 days.³⁰ Longer follow-up, such as the 6 months used in our study, is certainly needed.

The primary end point of a clinical stress test comprised a variety of modalities, each having its own sensitivity and specificity profile. However, this end point was specifically chosen because our aim was to evaluate whether the biomarkers had the ability to substitute for noninvasive testing as currently used in the clinical algorithm for these patients. Although certainly a subject of further inquiry, this particular study was not designed or powered to look at clinical outcomes. Although data were collected at 6 months, event rates were expectedly low. Furthermore, previous studies have demonstrated the association of worse outcome with abnormal NT-proBNP or cystatin C levels, providing evidence for prognostic implications. We instead sought to demonstrate clinical utility and diagnostic significance of that association by using stress test results as a surrogate. This preliminary study provides evidence for the importance of a larger randomized study to evaluate clinical outcomes.

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Figure 1.

Study flowchart. ACS = acute coronary syndrome; Cys C = cystatin C; NT-BNP = N-terminal proB-type natriuretic peptide.

Table 1

Characteristics by Agency for Health Care Policy and Research classification

Variable	n	Overall	Low AHCPR Risk (n = 191)	Intermediate AHCPR Risk (n = 191)	p Value
Men	382	162 (42%)	71 (37%)	91 (48%)	0.04
Smokers	345	137 (40%)	70 (41%)	67 (38%)	0.58
Previous MI	369	59 (16%)	1 (1%)	58 (31%)	<0.001
Previous percutaneous coronary intervention	379	89 (24%)	1 (1%)	88 (47%)	<0.001
Previous coronary artery bypass grafting	382	44 (12%)	0 (0)	44 (23%)	<0.001
History of heart failure	376	56 (15%)	3 (2%)	53 (28%)	<0.001
Previous stroke	337	26 (8%)	9 (5%)	17 (10%)	0.11
Hypertension	381	256 (67%)	107 (56%)	149 (78%)	<0.001
Diabetes mellitus	381	129 (34%)	50 (26%)	79 (41%)	0.002
Aspirin use (past 7 days)	349	207 (59%)	82 (49%)	125 (69%)	<0.001
Age (yrs)	382	58.3 ± 13.5	52.3 ± 9.6	64.3 ± 14.2	<0.001
Body mass index (kg/m ²)	213	29.9 ± 7.5	30.8 ± 7.0	29.0 ± 7.9	0.07
Heart rate (beats/min)	345	82.4 ± 18.5	83.1 ± 17.3	81.7 ± 19.6	0.49
Systolic blood pressure (mm Hg)	340	140.3 ± 24.4	140.0 ± 22.1	140.6 ± 26.5	0.85
Diastolic blood pressure (mm Hg)	340	81.0 ± 15.8	82.1 ± 14.5	79.9 ± 16.9	0.20
Antihypertensive medication	317	218 (69%)	88 (58%)	130 (79%)	<0.001
Antiplatelet therapy	309	171 (55%)	64 (43%)	107 (67%)	<0.001
Diabetes medication	298	94 (32%)	33 (22%)	61 (40%)	<0.001
Cholesterol medication	302	129 (43%)	38 (26%)	91 (59%)	<0.001
Creatinine (mg/dl)	380	1.0 (0.4)	1.0 (0.30)	1.1 (0.50)	0.002
NT-proBNP (ng/ml)	382	77.7 (322.4)	35.1 (90.2)	184.6 (1,064.0)	<0.001
Cystatin C (mg/L)	345	0.9 (0.4)	0.8 (0.3)	1.0 (0.5)	<0.001

Data are expressed as number (percentage), as mean ± SD, or as median (interquartile range).

Table 2

Stress test results and biomarker levels by Agency for Health Care Policy and Research classification

Variable	Overall	Low Risk	Intermediate Risk	OR	95% CI	p Value
Stress test results abnormal	30/184 (16%)	8 (7.1%)	22 (30.6%)	5.72	2.38–13.75	<0.001
NT-proBNP level abnormal	158/382 (41%)	45 (23.6%)	113 (59.2%)	4.70	3.02–7.31	<0.001
Cystatin C level abnormal	83/345 (24%)	19 (11.5%)	64 (35.8%)	4.31	2.44–7.59	<0.001
Either abnormal	172/353 (49%)	49 (28.8%)	123 (67.2%)	5.06	3.22–7.97	<0.001

Table 3

Biomarker levels by stress test results and Agency for Health Care Policy and Research risk classification

Abnormal Values	Stress Test Results Abnormal	Sensitivity	Specificity	PPV	NPV	OR	95% CI	p Value
Low AHCPR risk								
NT-proBNP	3/21 (14%)	37.5%	82.3%	14.3%	94.5%	2.87	0.63–13.09	0.160
Cystatin C	3/8 (38%)	42.9%	94.6%	37.5%	95.6%	13.05	2.27–74.90	<0.001
Either	5/23 (22%)	71.4%	80.8%	21.7%	97.4%	10.56	1.89–58.86	0.006
Intermediate AHCPR risk								
NT-proBNP	13/29 (45%)	59.1%	68.0%	44.8%	79.1%	3.07	1.09–8.66	0.032
Cystatin C	6/19 (32%)	30.0%	72.3%	31.6%	70.8%	1.12	0.36–3.54	0.845
Either	14/35 (40%)	66.7%	55.3%	40.0%	78.8%	2.48	0.845–7.25	0.094
Overall								
NT-proBNP	16/50 (32%)	53.3%	77.9%	32.0%	89.6%	4.03	1.79–9.09	<0.001
Cystatin C	9/27 (33%)	33.3%	87.1%	33.3%	87.1%	3.36	1.31–8.62	0.009
Either	19/58 (33%)	67.9%	72.3%	32.8%	91.9%	5.52	2.30–13.24	<0.001

PPV = positive predictive value.

Table 4

MACE frequencies classified by risk and by biomarker

AHCPR Risk Classification	n	Biomarker Level Normal	Biomarker Level Abnormal	OR	95% CI	p Value
All	42	16	26	1.79	0.92–3.47	0.08
Low	5	2	3	3.78	0.61–23.42	0.15
Intermediate	37	14	23	0.72	0.34–1.53	0.39

This table lists the number of MACEs stratified by AHCPR risk and by either normal or abnormal biomarker level (either cystatin C or NT-proBNP).