Novel Protein Markers of Acute Coronary Syndrome Complications in Low-Risk Outpatients: A Systematic Review of Potential Use in the Emergency Department

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Background: Published literature was systematically reviewed to determine the diagnostic accuracy of new protein markers of acute coronary syndromes (ACS) in symptomatic outpatients at low risk of ACS and related complications, compared with patients evaluated in emergency department chest pain units.

Methods: Studies were identified by a MEDLINE® (1966 to May week 3, 2005) search. Abstracts were reviewed for relevance, and manuscripts were included by the independent consensus of 2 observers based on explicit criteria restricting the analysis to studies relevant to screening ambulatory patients with symptoms suggesting ACS. Publication bias was identified by a modified funnel plot analysis [study size (y) vs the inverse of the negative likelihood ratio (x)]. Results of individual markers were reported separately. When 3 or more eligible studies were identified, data were aggregated by use of the summary ROC (SROC) curve.

Results: Twenty-two protein markers in 10 unique populations met the inclusion criteria. Data required for SROC analysis (true- and false-positive rates) were available for 17 markers, in 9 unique populations, from publications and personal communications. Of these, only C-reactive protein was published in more than 2 populations to allow aggregation (6 studies total). C-Reactive protein demonstrated poor diagnostic performance on SROC curve analysis, with an area under the curve of 0.61 and a pooled diagnostic odds ratio of 1.81 (95% confidence interval, 1.06–3.07).

Conclusion: Published evidence is not sufficient to support the routine use of new protein markers in screening for ACS in the emergency department setting.

An accurate, noninvasive, and efficient method of detecting substantial coronary artery disease in otherwise apparently low-risk patients remains an unmet need. In the emergency department setting, the subpopulation of patients who represent the greatest challenge in decision making are these low-risk patients. These patients generally present with nonspecific chest discomfort, a population risk factor, and are at low risk of an acute coronary syndrome (ACS) and related complications. However, reports by Goldman et al. (1) and Lee et al. (2) indicated that 2% to 5% of patients with myocardial infarctions are initially missed and are discharged from the emergency department. On the other hand, <5% of patients in this emergency department population category of “atypical chest pain” are ultimately diagnosed with ACS (3). A developing standard in care is to evaluate low-risk patients with possible ACS by use of emergency department chest pain units that incorporate serial markers of myocardial necrosis (e.g., serum troponin, creatine kinase, and myoglobin concentrations), telemetry, and a provocative test. This strategy may increase the sensitivity for detecting incipient ACS, but at the cost of an overnight stay, possible false/positive testing, and the requirement of other resources. Even with a well-conceived chest-pain unit protocol approach, as many as 4% to 14% of patients

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4 Nonstandard abbreviations: ACS, acute coronary syndrome; LR, negative likelihood ratio; CI, confidence interval; SROC, summary ROC; TPR, true-positive rate; FPR, false-positive rate; and CL, confidence interval.
with negative studies go on to have a serious cardiac event (4, 5).

Recent research has focused on circulating proteins that increase before the development of cardiomyocyte death. For example, markers of inflammation are the most well studied, and some of these have received considerable attention in the both the medical and lay press. These markers may be found to be accurate predictors of adverse outcomes in high-risk populations, or they may serve as markers of arterial inflammation, which might help to predict long-term prognosis (6). Additionally, C-reactive protein, for example, is currently being used in emergency department chest pain unit protocols (Chandra A., personal communication, April 8, 2005). However, when applied to emergency department populations with lower disease severity, the test characteristics of each biomarker may differ from the population in which the initial diagnostic performance was measured.

The primary objective of this systematic review was to determine whether a set of markers can be identified that has been studied sufficiently and that demonstrates diagnostic utility in the evaluation of ACS in low-risk emergency department–derived populations.

Materials and Methods

SEARCH STRATEGY

A comprehensive search of the medical literature was used to identify protein-based biological markers with potential application to a low-risk population. Potential markers were first identified by a MEDLINE® search (January week 1, 1966 through May week 3, 2005) using the following search string: “biological markers (explode) AND myocardial ischemia (explode) OR chest pain (explode)”. A keyword search was performed for each identified marker using the marker name and the term “myocardial ischemia (explode) OR chest pain (explode)”.

Relevance screen. Abstracts were reviewed independently by 2 reviewers to identify studies performed in humans with suspected ACS for full-length manuscript review. Reviewers excluded abstracts if the studies were performed only in patients with well-documented coronary artery disease before the measurement of the marker, patients with myocardial infarction immediately diagnosed at arrival to the hospital, postoperative patients whose chest pain was unrelated to coronary artery disease and ACS, and animal models. Secondary analysis studies, in which studies were clearly performed as part of a large epidemiologic cohort, were also excluded. The complete manuscripts of all other studies were reviewed.

Inclusion and exclusion of manuscripts. Remaining studies were examined by 2 independent assessors using a data collection form. Studies were included in the final analysis based on the following criteria: (a) The biological marker specimen was obtained before criterion standard testing in an acutely symptomatic, emergency department (or approximate outpatient) population; (b) The primary outcomes included acute myocardial infarction, death, and/or need for revascularization; (c) The prevalence of positive outcomes was ≤40%; and (d) The study included a minimum 30-day follow-up. Studies that did not meet these criteria were excluded. Data to determine the sensitivity, specificity, and the negative likelihood ratio (LR) were extracted by 2 independent investigators, and discrepancies were resolved by consensus and by a third, independent investigator when needed. When the data necessary to determine these diagnostic indices were not available in the published manuscript, the authors were contacted and asked to provide the necessary data. The final collection of manuscripts was also screened for duplications in populations, and authors were contacted if clarifications were necessary.

DATA ANALYSIS

Study quality was assessed numerically (1–5) by use of a proposed scale, which is a modification of the Jadad scale for treatment studies (7) (Table 1). This proposed quality score is a nonstandardized score defined for the purposes of this study because no validated quality score exists for the review of diagnostic studies.

A modified funnel plot analysis of sample size vs the inverse of the LR was used to visually identify publication bias. Similarly, an analogous plot was used to identify spectrum bias. Results of individual studies are also reported separately. Unique populations for each marker were used; duplicate populations were excluded.

Markers were considered for further analysis if they were represented in more than 2 qualifying studies using unique populations. Eligible data were analyzed with a summary ROC curve (SROC) using MetaTest (Ver. 0.6) and MathCAD (Ver. 2001i Professional®, 1986–2001; MathSoft Engineering & Education, Inc.) software. The SROC curve analysis was based on a regression analysis of logit transformation of the data that plots the difference between the logit of the true-positive rate (TPR) and the logit of the false-positive rate ([FPR); \( D = \logit(\text{TPR}) - \logit(\text{FPR}) \)] on the y axis and the sum \( (S = \logit(\text{TPR}) + \logit(\text{FPR}) \) on the x axis (8). The y axis \( (D) \) is equivalent to the log diagnostic odds ratio, and the x axis \( (S) \) is a measure of how the test characteristics vary with the test threshold. A regression equation \( (D = \alpha + \beta \times S) \) derived from the SROC curve analysis can be used to assess the heteroge-

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Test threshold defined at start of study</td>
<td>1 point</td>
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<tr>
<td>Consecutive or random sample of a defined outpatient population</td>
<td>1 point</td>
</tr>
<tr>
<td>Acceptable criterion standard including follow-up</td>
<td>1 point</td>
</tr>
<tr>
<td>Test performed prior to criterion standard</td>
<td>1 point</td>
</tr>
<tr>
<td>Criterion standard interpreted independently</td>
<td>1 point</td>
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</table>
neity among study results. If the $\beta$ coefficient is near zero and is not statistically significant, then significant heterogeneity is not present.

In the absence of significant heterogeneity, a quantitative summary of results can be reported as pooled sensitivity and specificity using a random effects model. However, if there are considerable differences in the test thresholds used among studies, the overall diagnostic odds ratio provides the best summary estimate of test performance. A random-effects model was used.

**Results**

The results of the literature search are summarized in Fig. 1. The initial literature search identified 56 markers published in 5463 citations. Of these, 4462 citations were of publications of human studies in the clinical setting. Approximately one half of these studies were studies related to chronic disease states such as stable angina, chronic congestive heart failure, chronic cardiomyopathies, posttransplantation conditions, and other diseases not directly related to ACS. Approximately 500 studies were of non–protein-based or non–plasma-based markers. Because this review is focused primarily on novel markers that are not considered “typical” of the diagnosis of coronary artery disease, 912 studies limited to troponin (I or T), creatinine kinase, and myoglobin were not considered relevant to this review. An additional 64 studies of markers sampled directly in coronary artery circulation were also eliminated for lack of relevance. Of the remaining 1004 publications, 712 did not prospec-

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**Fig. 1.** Literature search strategy used to identify potential studies, followed by the application of inclusion and exclusion criteria.

Studies were included based on the following, predetermined criteria: (a) The biologic markers were measured prospectively, before the application of the criterion standard; (b) Study prevalence of acute myocardial infarction, death, or the need for revascularization procedure is $\leq 40\%$; (c) The study included more than 400 patients; and (d) The study protocol included a minimum 30-day follow-up. All other studies were excluded.
tively measure markers in an acutely symptomatic population, 122 did not include any of the target outcomes, 974 were of study populations with >40% prevalence of ACS, and 862 did not have a minimum of 30-day follow-up. Thus, most studies had more than one reason for exclusion (average of 2.5 exclusions per study). Fourteen published manuscripts of 22 protein markers, comprising 10 unique populations, were identified after completion of the abstract relevance screen and full-length manuscript review for inclusion and exclusion criteria (9–22).

The goal of this study is to compare and potentially to aggregate data for each biomarker. Toward this aim, reported data for each of the 22 markers were assessed for prevalence of ACS, sensitivity, specificity, and LR. Data necessary to determine diagnostic indices [i.e., data sufficient to determine the TPR (sensitivity) and FPR (1 – specificity) needed for SROC curve analysis] were reported for only 8 markers (9–17). In some cases, data were sufficient for some, but not all of the markers studied in a single publication (11, 14, 16, 17). In 3 publications, data were insufficient for all markers reported in this study (18, 19, 22). The authors of these manuscripts were contacted for these data, and data were provided by 3 authors for an additional 9 markers. (Heeschen C., personal communication, June 7, 2005; Menown I., personal communication, June 3, 2005; Lund J., personal communication, June 13, 2005). Thus, using the combination of published data and personal communication in Table 2, we report sensitivity and specificity data for 17 markers in 9 unique populations. Studies with quality scores of 3 or 4 out of 5 lost points for not using a predetermined test threshold, for selecting only patients with troponin concentrations within reference values before the measurement of the study markers, or both. Five of the studies did not use the full composite outcome of death, acute myocardial infarction, or the need for revascularization (10, 11, 14, 16, 17); in 2 studies the outcome was death alone (10, 15).

C-Reactive protein was the most frequently studied of these markers. However, the diagnostic threshold used for C-reactive protein varied by more than 10-fold among studies. Overall, the mean prevalence of ACS was 16% with a range of 3% to 40%. Diagnostic performance for all markers, estimated by the LR, ranged from 0.16 to 3.75. Among these studies, only 2 studies of 2 different markers (pro-B-type natriuretic peptide and C-reactive protein) demonstrated an LR <0.40 (12, 15), a value well above the suggested threshold required for a test to rule out a potentially fatal disease, even in a low-prevalence population (23).

A modified funnel plot (Fig. 2) of study population size vs the inverse of the LR was used to screen for publication bias. All populations for each marker are represented. The studies clustered around an LR near unity, suggesting the absence of substantial publication bias.

A similar plot was used to examine the group of studies for possible spectrum bias. This plot (Fig. 3) shows the relationship between the prevalence of ACS vs the inverse of the LR. Among the studies included in this systematic review, prevalence of disease did not appear to influence the LR, suggesting the absence of spectrum bias.

As shown in Table 2, only C-reactive protein had data from more than 2 populations, including 6 in total: 4 obtained from published literature, and 2 from personal communications. Therefore, C-reactive protein was the only marker for which data could be aggregated by SROC curve analysis (Fig. 4). There was no evidence of statistical heterogeneity [β = 0.07; 95% confidence interval (CI), −0.53 to 0.67]. However, because of the wide range of test thresholds used among the studies, simple pooling of the results to provide an overall estimate of test sensitivity and specificity is inappropriate. Therefore, the random-effects model was used to estimate the overall diagnostic odds ratio. The pooled diagnostic odds ratio was 1.81 (95% CI, 1.06–3.07) and the area under the curve was 0.61, demonstrating diagnostic equivalence.

**Discussion**

We submit that emergency department patients with chest pain represent a very heterogeneous and poorly defined population in terms of underlying risk factors for ACS. Many emergency department patients have no regular medical care, and their risks of ACS are vaguely defined. Many have multiple confounding factors that alter the test performance of any protein marker, including the presence of inflammation from other nonvascular sources (e.g., periodontitis), or coronary artery disease that is mediated by poorly understood mechanisms such as chronic cocaine use. A protein marker (or set of markers) that accurately reflects the underlying pathophysiology of ACS would theoretically improve the clinical evaluation of this population, used either alone or in combination with standard necrosis markers. Unfortunately, from the present systematic analysis, we must conclude that the appropriate cutoff and diagnostic reliability for a “positive” C-reactive protein, B-type natriuretic peptide, or fibrinogen in the emergency department population remains unknown. Likewise, the role of these markers, and others reported in this systematic review, as complementary diagnostic tests to be used in concert with standard necrosis markers remains undefined for the emergency department population. Accordingly, before any protein marker is used in a chest pain unit protocol, the cutoff for a positive test must be quantitatively set to a sensitivity and specificity that can be tolerated by the medico-legal interests, that accommodates resource availability, and that can be tested prospectively in a population analogous to this low-risk population. In many cases in this review, a predefined diagnostic threshold had not been established before the study; several markers were simply untested in low-risk patients before these studies. This issue is reflected in the quality score.

This systematic literature review identified only a small number of markers studied in populations that approximate a low-risk emergency department popula-
tion. Studies with good diagnostic performance are conspicuously absent. In fact, only 2 studies, one of pro-B-type natriuretic peptide and the other an isolated study of C-reactive protein had an LR/11021

\[
LR = 0.4 \quad (12, 15)
\]

The plots in Figs. 2 and 3 suggest that the generally poor diagnostic performance did not result from spectrum or publication bias, respectively.

Only C-reactive protein was studied sufficiently to allow pooling of data. The pooled diagnostic odds ratio and the SROC curve demonstrate a lack of discriminatory power. Additionally, there is a more than 10-fold difference in the diagnostic thresholds used in these studies. This difference is not accounted for by the assays used or the normal and abnormal values recommended by the

<table>
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<tr>
<th>Study (Ref.)</th>
<th>Diagnostic threshold</th>
<th>n</th>
<th>ACS, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>LR</th>
<th>Quality score</th>
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<tbody>
<tr>
<td>Myeloperoxidase</td>
<td>Brennan et al. (9)</td>
<td>198 pmol/L</td>
<td>604</td>
<td>40</td>
<td>66</td>
<td>61</td>
<td>0.55</td>
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<tr>
<td>C-Reactive protein</td>
<td>Sabatine et al. (10)a</td>
<td>15 mg/L</td>
<td>1840</td>
<td>3</td>
<td>46</td>
<td>78</td>
<td>0.70</td>
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<td></td>
<td>Thompson et al. (11)b</td>
<td>1 mg/L</td>
<td>2960</td>
<td>4</td>
<td>83</td>
<td>20</td>
<td>0.83</td>
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<td>Brennan et al. (9)</td>
<td>10 mg/L</td>
<td>604</td>
<td>40</td>
<td>32</td>
<td>69</td>
<td>0.99</td>
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<tr>
<td></td>
<td>Magadale et al. (12)</td>
<td>7 mg/L</td>
<td>226</td>
<td>9</td>
<td>80</td>
<td>69</td>
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<td></td>
<td>Menown IBd</td>
<td>7.1 mg/L</td>
<td>188</td>
<td>19</td>
<td>26</td>
<td>75</td>
<td>0.99</td>
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<td></td>
<td>Lund Jd</td>
<td>2.0 mg/L</td>
<td>136</td>
<td>19</td>
<td>62</td>
<td>52</td>
<td>0.74</td>
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<td>CD40 ligand</td>
<td>Heeschen Cb,c</td>
<td>5 µg/L</td>
<td>626</td>
<td>10</td>
<td>64</td>
<td>80</td>
<td>0.46</td>
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<td>D-Dimer</td>
<td>Menown IBd</td>
<td>0.58 g/L</td>
<td>195</td>
<td>19</td>
<td>25</td>
<td>74</td>
<td>1.01</td>
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<td>B-Type natriuretic peptide</td>
<td>Morrow et al. (13)</td>
<td>80 ng/L</td>
<td>1676</td>
<td>14</td>
<td>51</td>
<td>13</td>
<td>3.75</td>
</tr>
<tr>
<td></td>
<td>de Lemos et al. (14)b</td>
<td>80 ng/L</td>
<td>2525</td>
<td>10</td>
<td>72</td>
<td>52</td>
<td>0.54</td>
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<td>Pro-B-type natriuretic peptide</td>
<td>Jernberg et al. (15)a</td>
<td>400 ng/L</td>
<td>775</td>
<td>22</td>
<td>90</td>
<td>62</td>
<td>0.16</td>
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<td>Fibrinogen</td>
<td>Thompson et al. (11)b</td>
<td>3.31 g/L</td>
<td>2960</td>
<td>4</td>
<td>47</td>
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<td>Menown IBd</td>
<td>4.6 g/L</td>
<td>195</td>
<td>19</td>
<td>22</td>
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<td>1.05</td>
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<td>Heart-type fatty acid–binding protein</td>
<td>Menown IBd</td>
<td>5.0 µ/L</td>
<td>195</td>
<td>19</td>
<td>11</td>
<td>73</td>
<td>1.21</td>
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<td>Interleukin-6</td>
<td>Menown IBd</td>
<td>10.7 ng/L</td>
<td>146</td>
<td>16</td>
<td>25</td>
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<td>1.01</td>
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<tr>
<td>Monocyte chemoattractant protein-1</td>
<td>de Lemos et al. (16)b</td>
<td>238 ng/L</td>
<td>2270</td>
<td>16</td>
<td>33</td>
<td>55</td>
<td>1.21</td>
</tr>
<tr>
<td>Peripheral leukocyte count</td>
<td>Sabatine et al. (10)a</td>
<td>10 × 10^9/L</td>
<td>1840</td>
<td>3</td>
<td>32</td>
<td>76</td>
<td>0.90</td>
</tr>
<tr>
<td>Placental growth factor</td>
<td>Heeschen et al. (17)b</td>
<td>27 mg/L</td>
<td>646</td>
<td>10</td>
<td>63</td>
<td>74</td>
<td>0.50</td>
</tr>
<tr>
<td>Pregnancy-associated plasma protein</td>
<td>Heeschen Cb,c</td>
<td>7 mIU/L</td>
<td>644</td>
<td>10</td>
<td>54</td>
<td>73</td>
<td>0.63</td>
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<td>Soluble E-selectin</td>
<td>Menown IBd</td>
<td>68 µg/L</td>
<td>195</td>
<td>19</td>
<td>14</td>
<td>27</td>
<td>3.16</td>
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<td>Soluble intercellular adhesion molecule-1</td>
<td>Menown IBd</td>
<td>834 µg/L</td>
<td>195</td>
<td>19</td>
<td>8</td>
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<td>Soluble P-selectin</td>
<td>Menown IBd</td>
<td>152 µg/L</td>
<td>195</td>
<td>19</td>
<td>29</td>
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<td>0.84</td>
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<tr>
<td>Soluble vascular adhesion molecule-1</td>
<td>Menown IBd</td>
<td>1897 µg/L</td>
<td>195</td>
<td>19</td>
<td>25</td>
<td>75</td>
<td>1.00</td>
</tr>
</tbody>
</table>

a Outcome includes death only.

b Outcome includes death and acute myocardial infarction only.

c Personal communication, June 7, 2005.

d Personal communication, June 3, 2005; marker threshold defined as 75th percentile.
e Personal communication, June 13, 2005.
In the entire group of studies, only 3 were able to test a diagnostic threshold defined before the onset of the study; there were simply no preexisting data to define the threshold. Our data emphasize the need for more research of these and other potential markers of ACS in this important population.

Research efforts into novel protein markers of ACS have focused on 3 broad categories of proteins: (a) proteins that diffuse from the myocyte in response to ischemia; (b) proteins that undergo posttranslational modification as a result of ischemia; and (c) other proteins that reflect the numerous biochemical pathways that are activated during ischemia. This third class includes proteins that increase in response to the presence of arterial inflammation, an important step in the transformation of a stable to unstable plaque. It is this class of proteins that represents the majority of potential markers currently being studied. A large and well-developed theoretical rationale has fueled this enthusiasm for the use of inflammatory markers to screen for developing ACS (6, 24). Essentially, these markers mirror the underlying mechanisms that produce coronary artery stenosis, and they increase sharply with plaque rupture (25). A substantial body of literature has demonstrated that C-reactive protein performed as well as a risk-stratification instrument in patients with population risk factors for coronary artery disease (26, 27). We believe that it is essential to clearly distinguish between research that was applied to patients with known coronary artery disease and research applied to patients with symptoms that raise the suspicion of ACS. For many reasons, an inflammatory protein marker that demonstrates good utility as a risk-stratification test in high-risk populations may not perform well in a symptomatic, ambulatory population with unknown status for coronary artery disease. For example, the in vivo biology of C-reactive protein suggests that this marker would be a very nonspecific marker of coronary artery disease in a population that is not well selected. Hepatic transcription and translation of C-reactive protein increase in response to inflammation from virtually any cause, including infection, cancer, depression, connective tissue diseases, venous thrombosis, and many others (28–31).

Our results underscore the fundamental concept that the accuracy of a diagnostic test that performs well in a relatively homogeneous, high-risk population may shift unfavorably when the test is applied to a low-risk, heterogeneous population (32). Despite this important issue, several markers have received approval from the US Food and Drug Administration and are currently marketed for use in screening low-risk patients for ACS, with no investigation of these markers specifically in these popu-
Ischemia-modified albumin has been studied prospectively in 7 acutely symptomatic populations evaluated for ACS (33–39). Only 1 study reported an ACS prevalence <40% (39), with most reporting an ACS prevalence of 45% to 71% (33–38). The largest of these studies enrolled 256 patients, but a positive outcome was limited to the development of an increased troponin I within 24 h of enrollment (39). Additionally, none of these studies included follow-up beyond emergency department or hospital discharge. The lack of follow-up concerns us for 2 reasons: (a) most low-risk patients will be discharged within a relatively short time period (4–72 h); and (b) emergency department patients notoriously have limited access to outpatient follow-up (40). For these reasons, the durability of a “negative outcome” remains questionable in these studies.

Several limitations warrant discussion. We designed this systematic review to estimate the diagnostic utility of the new markers for the outcomes of death, acute myocardial infarction, or the need for a revascularization procedure. These complications represent the primary concern of emergency physicians in evaluating patients for potential ACS (41). Our review does not address the utility of these new markers to screen for coronary stenoses amenable to treatment. We acknowledge that we did not use a cost-effectiveness analysis, which might have revealed different conclusions. We did not use a structured method to determine the optimal heuristics for clinical use of the new markers. It could be argued that specific sequencing of the tests, using different thresholds, would offer good diagnostic performance. We restricted our study to low-risk patients, explicitly defined as having a prevalence of ACS <40% and implicitly defined as patients who present with an overall clinical constellation atypical for angina pectoris, few or undefined population risk factors, and routine or nondiagnostic electrocardiograms. Our results indicate a lack of research focused on populations that fit this description. Although it would be ideal to review studies of populations with a prevalence of disease that is closer to 2% to 10%—the prevalence of ACS in most chest pain units—we found no such study in our search. The remaining selection criteria were also intended to select studies with a degree of rigor that would justify their current use. These criteria led to the selection of studies in which the study populations were not exactly matched; whereas some studies had enrolled a general emergency department population (9, 10, 12, 17, 19–21), others were more focused on populations with potential ACS (11, 13–16, 18, 22). Because we are unaware of any scoring system to quantify the rigor of diagnostic studies, we derived a scoring system using the Jadad score for therapeutic studies as a model. Obviously, our modification of the Jadad score has not been widely adopted. This study is also limited to published literature and related unpublished data, when available, but we do not expect that there are a large number of unpublished studies that would change our conclusions.

**Conclusion**

Despite considerable attention and major research efforts, novel protein markers of inflammation remain largely unstudied in the emergency department or analogous outpatient populations. The most important observation of this review is that there are very few studies that address the address the prognostic value of these markers specifically in the low-risk general emergency department population. In studies of low-risk symptomatic patients, no serum protein marker demonstrated good diagnostic performance (e.g., an LR < 0.4) (23) in more than 1 study. Only C-reactive protein has been used sufficiently to allow aggregation of the data, and these results demonstrate no better test performance than would be expected by random allocation of diagnosis. The threshold for a positive C-reactive protein remains unknown. These results show the need for research conducted in low-risk ambulatory patients before these markers can be used to routinely screen for ACS in the emergency department setting.

We thank Joseph Lau, MD, who provided the MetaTest software used in the analysis of the data presented in this review. We also acknowledge Drs. Christopher Heeschen and Juha Lund for providing unpublished data used in this review.

**References**


