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A Double-Blind, Multicentered Study Comparing the Accuracy of Diagnostic Markers to Predict Short- and Long-Term Clinical Events and Their Utility in Patients Presenting with Chest Pain

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Summary

Background: Millions of patients present annually with chest pain, but only 10% have myocardial infarction (MI). We recently reported comparative sensitivity and specificity of available markers in the diagnosis of MI; however, optimum interpretation of marker results requires prognostic follow-up data.

Hypothesis: The study was undertaken to study the accuracy of CK-MB subforms, troponin I and T, myoglobin, and CK-MB in predicting clinical events at 30 days and 6 months.

Methods: In all, 955 consecutive patients with chest pain were enrolled in a prospective, multicenter, double-blind study to test the prognostic accuracy of these markers.

Results: Myocardial infarction was diagnosed in 119 by CK-MB mass criteria and unstable angina (UA) in 203 patients by clinical criteria. Follow-up at 30 days and 6 months was available in 824 and 724 patients, respectively, with mortalities of 2.8 and 4.14%, respectively. Cumulative 6-month mortality was 5.6% in MI, 4.4% in UA, and 3.0% in others. Revascularization was reported in 9.3% of patients by 6 months. A positive test on each of the markers except myoglobin was predictive of revascularization. The composite endpoint of death or revascularization occurred in 107 patients by 6 months and a positive result on each of the markers was predictive of this composite endpoint ($p < 0.05$). The relative risk of death or revascularization for patients who did not have MI but tested positive on each of the markers was > 1.0 but did not reach statistical significance.

Conclusions: With the possible exception of myoglobin, each of the diagnostic markers displayed similar prognostic performance in patients with chest pain presenting to emergency departments. The most appropriate markers to triage patients with chest pain, which has both adequate early diagnostic sensitivity and prognostic accuracy, are the CK-MB subforms.

Key words: diagnostic markers, prognosis, creatine kinase-MB, troponin I, troponin T, myoglobin

Introduction

Traditionally, the diagnosis of myocardial infarction (MI) was determined from the history, physical examination, electrocardiogram (ECG), and the evaluation of serum creatine kinase-MB (CK-MB). Recently, new markers thought to be more sensitive and specific for cardiac injury have been introduced into clinical practice. These diagnostic markers were introduced, at least in part, for their potential to provide a basis on which to select earlier and more appropriate therapy, as well as to be more cost effective.

Over five million patients present each year to emergency departments (EDs) with chest pain while only approximately 10% are subsequently proven to have MI. Physical findings and symptoms do not permit a specific diagnosis in many patients, and the ECG is diagnostic in only 40%.[1] Since 90% of patients with chest pain will not have infarction, one requires a

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diagnostic marker that both reliably confirms MI early after onset or excludes it in patients presenting to the ED. Total CK-MB, troponin T or I are elevated in only about 50 to 60% of patients with MI at 6 to 7 h from onset of symptoms. The remainder (95% of patients with chest pain) would require sampling for another 6 to 8 h before MI can be excluded or confirmed.[2] Thus, these tests are not very useful in reducing unnecessary hospital admissions for chest pain syndromes. This is a concern, since over $12 billion[3] are spent on evaluating these patients, with only a fraction ultimately diagnosed as having MI. In contrast, the rapid CK-MB subforms assay has been shown to provide a reliable diagnosis of MI within 6 h of onset of chest pain.[4] Similarly, myoglobin is an early marker of cardiac injury, albeit somewhat less specific.

The new markers, cardiac troponin I and cardiac troponin T, have been shown to be highly effective in stratifying patients with unstable angina into high and low risk for clinical events.[5,6] Large prospective studies of CK-MB subforms and myoglobin for risk stratification are lacking. While most patients in the United States presenting with unstable angina are admitted to hospital, those classified as low or intermediate risk may not necessarily benefit from hospital admission.[7–9] The use of markers to risk stratify patients with unstable angina is increasing rapidly. Since there are multiple markers, cost and time prohibits using all of them. Selecting the more appropriate marker would be greatly facilitated by a comparison of not just their sensitivity and specificity, but also their relative prognostic accuracy. We recently completed a multicenter, double-blinded, prospective study of diagnostic markers in 955 patients presenting with chest pain.[2] In this paper, we report their relative prognostic accuracy in a 6-month follow-up analysis of adverse events.

Methods

Study Design

A multicenter, prospective, double-blind study was performed involving Baylor College of Medicine and the University of Texas Health Science Center. Enrollment was consecutive 24 h a day, 7 days per week, at four affiliated teaching hospitals in Houston, Texas: Ben Taub General Hospital, Hermann Hospital, The Methodist Hospital, and Veterans Affairs Medical Center. Data analysis and statistics were performed by an independent Biostatistics Core in the School of Public Health, University of Texas Heath Science Center, Houston. Patients were required to be 21 years of age, with chest pain of at least 15 min duration suspected to be myocardial in origin and occurring within 24 h of presentation.

Blood samples were obtained on arrival, 1 h after arrival, then every 2 h up to 6 h from onset of chest pain and every 4 h thereafter for up to 24 h. The attending physician determined the final clinical diagnosis and disposition of the patient. Attending physicians and investigators did not have access to the results of the Core Laboratory cardiac markers, but did have available total CK-MB provided by the clinical laboratory.

Assays for Cardiac Markers

Blood for CK-MB subforms was collected in ethylene diamine tetraacetic acid (EDTA), and the plasma recovered, while for all other markers blood was clotted and serum recovered. Total serum CK activity was quantitated using a spectrophotometric enzymatic assay (Sigma Diagnostics, St. Louis, Mo., USA) with upper normal limit of 120 IU/l. Total plasma CK-MB mass was measured with Stratus CK-MB Flurometric Enzyme Immunoassay (Dade International, Inc., Miami, Fla., USA) with an upper normal limit of 7 ng/ml. Creatine kinase-MB subforms (MB and MB2) and total CK-MB activity were quantified using Cardio REP CL Isoforms Procedure (Helena Laboratories, Beaumont, Texas, USA). Creatine kinase-MB subforms of MB2 $\geq$2.6 and a ratio of MB2/MB1 $\geq$ 1.7 and a total CK-MB activity of >9 IU/l were accepted as abnormal. Myoglobin was determined by the Stratus Myoglobin Flurometric Enzyme Immunoassay (Dade International, Inc.) with an upper limit of normal of 85 ng/ml. Cardiac troponin T was assayed using the cardiac troponin T assay (Boehringer Mannheim Corp, Indianapolis, Ind., USA) which has an upper limit of normal of 0.1 ng/ml. Cardiac troponin I was assayed by the Stratus Cardiac Troponin-I Flurometric Enzyme Immunoassay (Dade International, Inc.) which has an upper limit of normal of 1.5 ng/ml.

Definition of Clinical and Laboratory Endpoints

Confirmation of MI was based on a CK-MB mass $\geq$ 7ng/ml and a CK-MB index (CK-MB mass/CK) $\geq$2.5% in two or more samples obtained in the first 24 h after hospital arrival, or in one sample if only one sample was available for analysis. Unstable angina was a clinical diagnosis determined by the investigators as follows: chest pain occurring at rest or with increased frequency or severity within the preceding 24 h.

Collection of In Hospital and Follow-Up Data at 1 and 6 Months

The outcome of patients from admission to hospital discharge was determined from the medical records. Data from 30-day and 6-month follow-up were obtained by mail, telephone interviews, or review of medical records. Multiple attempts were made to contact each patient lost to follow-up.

Results

In all, 955 patients were enrolled into the study. Myocardial infarction was confirmed by MB-CK (mass) criteria in 119 patients (12.5%), and 203 (21.3%) patients were diagnosed as having unstable angina by the study criteria. ST-segment elevation occurred in 45% of the 119 patients with MI. Reperfusion therapy was administered to 34.4% of the patients, 30 (25.2%)receiving thrombolysis and 11 (9.2%) direct angioplasty. A detailed analysis of the sensitivity and specificity of each of the diagnostic markers as a function of time from onset

TABLE I Sensitivity and specificity at 6 and 10 hours for each of the diagnostic markers

	Early diagnosis	Late diagnosis
Time (h)	6	10
Marker		
Total CK-MB activity		
Sensitivity (%)	74.5	96.2
Specificity (%)	97.5	97.5
Myoglobin		
Sensitivity (%)	78.7	86.5
Specificity (%)	89.4	90.2
Cardiac troponin T		
Sensitivity (%)	61.7	86.5
Specificity (%)	96.1	96.4
Cardiac troponin I		
Sensitivity (%)	57.5	92.3
Specificity (%)	94.3	94.6
CK-MB subforms		
Sensitivity (%)	91.5	96.2
Specificity (%)	89.0	90.2

Abbreviation: CK-MB = creatine kinase-MB.

of pain is provided in another report, therefore only the sensitivity and specificity for each of the markers at 6 and 10 h after pain onset were included (Table I).

Follow-up at 30 days was available in 825 patients. Myocardial infarction had been diagnosed in 106 of these patients, unstable angina in 181, and other conditions in the remaining 538 patients. Six-month follow-up was available in 724 patients. Overall mortality rates for 30 days and 6 months were 2.8 and 4.1%, respectively. Using the last follow-up data point for all 825 patients in the follow-up data set, mortality by 6 months was 5.6% in the MI group, 4.4% in the UA group, and 3.0% in all others. Revascularization occurred in 9.3% of the 825 patients by 6 months. A positive test on each of the markers except myoglobin was predictive of revascularization by 6 months. The relative risk of revascularization along with its 95% confidence limits and p value is shown in Table II.

The composite endpoint of death or revascularization occurred in 101 of the 825 follow-up patients by 6 months. A positive test on each of the diagnostic markers was predictive of death or revascularization by 6 months. The confidence limits for relative risk and the p values for the composite endpoint of revascularization or death are shown in Table III. The point estimate of the relative risk of death or revascularization in patients who were not diagnosed with MI was > 1.0 for each of the diagnostic markers although none of these estimates individually reached statistical significance. These relative risks are shown in Table IV. Recurrent symptoms were also common during the follow-up period, with 40% of the population experiencing recurrent chest pain.

TABLE II Relative risk of revascularization by 6 months of follow-up and its 95% confidence limits and p value for a positive diagnostic marker

Marker	Relative risk	95% CI lower limit	95% CI upper limit	p Value
CK-MB activity	2.29	1.49	3.55	0.0002
Myoglobin	1.36	0.87	2.12	0.18
Cardiac troponin T	2.41	1.53	3.77	0.001
Cardiac troponin I	1.80	1.16	2.81	0.009
CK-MB Subforms	1.58	1.02	2.44	0.039

Abbreviations: CI = confidence interval, CK-MB = creatine kinase-MB.

TABLE III Relative risk of revascularization or death by 6 months of follow-up and its 95% confidence limits and p value for a positive diagnostic marker

Marker	Relative risk	95% CI lower limit	95% CI upper limit	p Value
Total CK-MB activity	2.0	1.34	2.38	0.0002
Myoglobin	1.65	1.15	2.91	0.007
Troponin T	2.21	1.52	3.22	0.0001
Troponin I	1.68	1.16	2.44	0.0066
CK-MB subforms	1.79	1.25	2.55	0.0014

Abbreviations as in Table II.

Discussion

While most of the diagnostic markers have been shown to be prognostic,[5,6] at least in select populations, comparative data are not available, particularly in the unselected ED setting. Accordingly, CK-MB, myoglobin, cardiac troponin T, cardiac troponin I, and CK-MB subforms performed in 955 patients presenting to the ED with chest pain and enrolled consecutively in a prospective double-blind study were compared for their accuracy in predicting death and revascularization 6 months later. The relative risk of death or revascularization by 6 months of follow-up for CK-MB activity, myoglobin, cardiac troponin T, cardiac troponin I, and CK-MB subforms was 2.0, 1.65, 2.21, 1.68, and 1.79, respectively. With the possible ex-

TABLE IV Relative risk of death or revascularization by 6 month for a positive diagnostic marker in patients not diagnosed with myocardial infarction

Marker	Relative risk
Total CK-MB activity	1.47
Myoglobin	1.17
Troponin T	1.07
Troponin I	1.72
CK-MB subforms	1.51

Abbreviations as in Table I.

ception of myoglobin, our results show that each of the markers was positively associated with similar increases in risk of adverse outcomes. Our data do not suggest a specific diagnostic marker, when positive, is superior to the others based on prognostic performance alone. However, since CK-MB subforms are positive 90% of the time within 6 h of onset of symptoms as opposed to troponins which are positive in only about 60% during this interval, CK-MB subforms are the preferred diagnostic and prognostic marker in the ED. Clinicians requiring prognostic information after 12 to 24 h from onset of symptoms may rely upon either CK-MB mass, cardiac troponin I, cardiac troponin T, CK-MB activity, or CK-MB subforms. The assays for each marker are automated, have similar cost, and require about 25 min to perform.

Since there are no large studies comparing the relative prognostic significance of all the markers, we can only compare our data to studies assessing an individual marker or subsets of the available markers. Troponin T was examined as a prognostic marker in a large cohort of patients with unstable angina enrolled in the Global Use of Strategies To open Occluded coronary arteries II (GUSTO IIa) trial.[5] In this study of 801 patients with baseline troponin T measurements, elevated troponin T was associated with increased 30-day mortality. The relative risk of death at 30 days for those with high troponin T levels was 3.0 compared with those with a low troponin T level. This value is somewhat greater than we observed but reflects the higher overall 30-day mortality (6.7%) in this select population of unstable angina and non-Q-wave infarction. Troponin I was assessed as a prognostic indicator in 1,404 patients with unstable angina and non-Q-wave infarction enrolled in the Thrombolysis In Myocardial Infarction (TIMI) IIIb trial.[6] Samples were obtained at the time of enrollment with 845 patients presenting > 6 h after onset of symptoms. These investigators found that the 42-day mortality rate was increased for patients with a troponin I level ≥ 0.4 ng/ml, and increased significantly with increased troponin I levels. This study did not report CK-MB subforms or myoglobin and, thus, a comparative performance of the markers is not possible.

The results of our study have several diagnostic and therapeutic implications. Physicians are under increased pressure to use health care resources efficiently. Faced with patients with chest pain in the ED, the physician must determine whose condition warrants admission to the coronary care unit, to other hospital beds, and who may be safely discharged. He must also decide what therapies to employ. To be of value to the physician in the ED, the diagnostic marker should have good prognostic utility and be positive early enough to help the physician make decisions about admission and therapy. Our study shows all of the markers except myoglobin, when positive, have similar prognostic utility. However, the results of the comparative diagnostic sensitivity of the markers within 6 h of onset of symptoms[2,4] highlights CK-MB subforms as the most appropriate diagnostic and prognostic marker in the ED since it is the only marker that provides > 90% diagnostic sensitivity within the first 1 to 2 h after presentation. Myoglobin also has high diagnostic sensitivity but, as shown in this study and that of de Winter *et al.*,[10] lacks desirable prognostic significance.

Conclusion

Published guidelines for the management of acute ischemic syndromes advocate treatment based on risk stratification.[9] These guidelines suggest patients with unstable angina who have clinical characteristics suggesting low risk, be managed in less intense environments or even discharged home. Given the excess risk of adverse outcomes associated with a positive marker, it seems prudent that they be considered in the admission triage. Another potential role for these markers is in selecting patients with non-Q-wave MI and UA for newer therapies, particularly the glycoprotein IIb/IIIa inhibitors.[11] These agents are expensive and will contribute substantially to the cost of managing acute ischemic syndromes. The need for improved therapies for these syndromes is clear from the 28% 1-year clinical event rate in the medically treated group in the VA Non-Q-Wave Infarction Strategies in Houston trial (VANQUWISH).[12] The precise population in whom these agents are warranted has yet to be determined, but clinical trials are now ongoing to evaluate their administration, at least in part, on the basis of the results of diagnostic markers (Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network [PARAGON B], Thrombolysis And Counterpulsation To Improve Cardiogenic shock Survival [TACTICS]). Reserving IIb/IIIa inhibitors for patients with UA and elevated diagnostic markers has the potential to maximize cost effectiveness of anti-ischemic therapy and decrease the incidence of adverse clinical events.

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