Bedside Multimarker Testing for Risk Stratification in Chest Pain Units: The Chest Pain Evaluation by Creatine Kinase-MB, Myoglobin, and Troponin I (CHECKMATE) Study

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Background—Earlier, rapid evaluation in chest pain units may make patient care more efficient. A multimarker strategy (MMS) testing for several markers of myocardial necrosis with different time-to-positivity profiles also may offer clinical advantages.

Methods and Results—We prospectively compared bedside quantitative multimarker testing versus local laboratory results (LL) in 1005 patients in 6 chest pain units. Myoglobin, creatine kinase-MB, and troponin I were measured at 0, 3, 6, 9 to 12, and 16 to 24 hours after admission. Two MMS were defined: MMS-1 (all 3 markers) and MMS-2 (creatine kinase-MB and troponin I only). The primary assessment was to relate marker status with 30-day death or infarction. More patients were positive by 24 hours with MMS than with LL (MMS-1, 23.9%; MMS-2, 18.8%; LL, 8.8%; $P=0.001$, all comparisons), and they became positive sooner with MMS-1 (2.5 hours, $P=0.023$ versus LL) versus MMS-2 (2.8 hours, $P=0.026$ versus LL) or LL (3.4 hours). The relation between baseline MMS status and 30-day death or infarction was stronger (MMS-1: positive, 18.8% event rate versus negative, 3.0%, $P=0.001$; MMS-2: 21.9% versus 3.2%, $P=0.001$) than that for LL (13.6% versus 5.5%, $P=0.038$). MMS-1 discriminated 30-day death better (positive, 2.0% versus negative, 0.0%, $P=0.007$) than MMS-2 (positive, 1.8% versus negative, 0.2%; $P=0.055$) or LL (positive, 0.0% versus negative, 0.5%; $P=1.000$).

Conclusions—Rapid multimarker analysis identifies positive patients earlier and provides better risk stratification for mortality than a local laboratory-based, single-marker approach. **(*Circulation*. 2001;103:1832-1837.)**

Key Words: prognosis ■ risk factors ■ angina

Each year, more than 5 million patients are seen in emergency departments (ED) for evaluation of symptoms of myocardial ischemia. Initial evaluation, including a history and physical examination and 12-lead ECG, is conclusive in only a minority of patients.[1,2] The use of cardiac markers has become standard to further risk-stratify such patients. Often this is done in a chest pain unit (CPU), following protocols for marker testing over 6 to 12 hours.[3] Creatine kinase-MB (CK-MB), cardiac troponin (I [cTnI] or T [cTnT]), and in some cases, myoglobin, are the most commonly measured cardiac markers.

Each marker can risk-stratify patients with chest pain,[4–11] but their specificities for myocardial injury and release and clearance characteristics differ.[12] Furthermore, patients with chest pain arrive at EDs at various times after symptom onset. Testing for multiple markers of myocardial necrosis, in a manner that emphasizes temporal patterns, could enhance the prompt recognition of high-risk patients and improve risk stratification across a range of patients with chest pain syndromes. This strategy, used at the point of care, making test results more readily available to treating physicians, could improve the efficiency of chest pain management and treatment and triage decisions.

We designed the Chest Pain Evaluation by Creatine Kinase-MB, Myoglobin, and Troponin I (CHECKMATE) study to evaluate the ability of quantitative bedside measurement of combinations of markers with different time-to-positivity characteristics (myoglobin, CK-MB, and cTnI) to risk-stratify patients with chest pain without ST-segment elevation. Our

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primary goals were to evaluate the relation of the results of such multimarker strategies with 30-day clinical outcomes and to examine the effect of bedside multimarker testing on time to detection of positive results.

Methods

Study Population

We enrolled 1005 patients with possible myocardial ischemia from the ED of 6 US hospitals that also had functional CPUs. Individuals ≥18 years old were eligible if they had chest pain or equivalent symptoms thought to represent possible myocardial ischemia. Patients were excluded if the initial ECG showed ST-segment elevation or left bundle-branch block (LBBB) that led to acute reperfusion therapy or its consideration.

The protocol was approved by the institutional review board of each participating hospital, and all patients gave written informed consent to participate. The study was conducted by the Duke Clinical Research Institute, independent of the trial's sponsor.

12-Lead ECG

All patients underwent standard 12-lead ECG at baseline. The sites followed their usual practices for follow-up ECGs. Tracings were read centrally by reviewers blinded to patient identity, marker status, and other clinical data. Baseline and all additional ECGs were classified as either "normal" (normal or nonspecific ECG changes) or "abnormal" (ST-segment elevation, ST-segment depression, T-wave inversion, or confounding factors [LBBB, paced rhythm, or left ventricular hypertrophy with strain]).

Cardiac Markers

Blood samples collected in 5-mL lithium-heparin tubes were obtained at enrollment (baseline), 3 hours, and 6 hours for analysis with the Dade-Behring Stratus CS STAT near-patient instrument. Additional samples at 9 to 12 and 16 to 24 hours were collected from patients remaining in the hospital at those times. Blood collection tubes were inserted directly into the instrument for automated testing. Blood also was collected according to the site's usual CPU "rule-out" protocol and analyzed by the hospital's laboratory. All sites performed CK-MB testing, and 4 of the sites also tested for cTnT or cTnI.

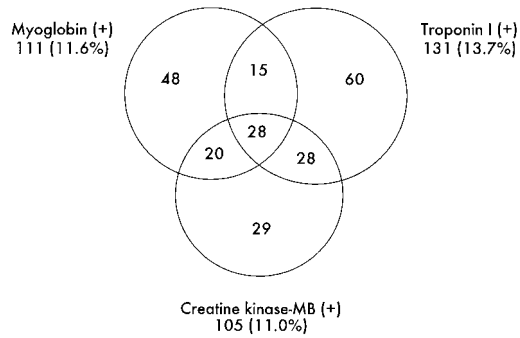
The Stratus CS instrument assays 3 serum cardiac markers from 1 blood sample in 15 to 20 minutes: myoglobin, CK-MB, and cTnI. The lower limits of detection are 1 ng/mL for myoglobin, 0.3 ng/mL for CK-MB, and 0.03 ng/mL for cTnI. The upper limits of normal are 105 ng/mL for myoglobin, 4.0 ng/mL for CK-MB, and 0.1 ng/mL for cTnI. A multimarker strategy (MMS) was considered positive if the level of any marker in the strategy was above the upper limit of normal. Two MMS were prospectively defined: MMS-1 (all 3 markers) and MMS-2 (CK-MB and cTnI).

A single-marker local laboratory strategy (LL) was defined by the site-laboratory result for CK-MB because it was available at all sites and considered the primary marker necessary to diagnose myocardial infarction (MI). If CK-MB data were unavailable, the cTnT or cTnI result, if available, was used for the LL status. LL results were considered positive if above the upper limit of normal for the assay at that site. Total CK was used for LL status in 31 patients who lacked other markers, with a level twice the upper limit of normal considered positive. Sites recorded assay reference ranges on the data collection form for all assays used.

Statistical Methods

The primary assessment was the relation between MMS status (positive or negative) and the composite rate of death or MI at 30 days. This relation was explored for baseline and overall MMS status from serial testing. Important secondary assessments included time from ED arrival to positive status, and the relations between MMS status and the rates of death, MI, revascularization, and their composite at 30 days. MI was defined as an elevation in CK-MB to above the local upper limit of normal after enrollment, the development of new, significant Q waves in ≥2 leads, or if the investigator specified MI during follow-up on the data collection form. Descriptive data and clinical outcomes were summarized as medians with 25th and 75th percentiles or as percentages. Tests for significance between groups were 2-tailed and used the χ^2 test. A value of $P<0.05$ defined statistical significance. To compare time to positivity in patients positive by both LL and either MMS-1 or MMS-2, we used paired t testing with a significance level of $P<0.05$.

To determine the best predictors of 30-day death or MI, we performed stepwise multivariable logistic regression modeling by using selected clinical and ECG variables with MMS status. Variables were selected on the basis of our previous work and by using the strength of univariable associations in the current study; they were retained in the models at a value of $P<0.05$. Models were validated by bootstrap techniques. Concordance (C)-index values describe the robustness of the models.



Overlap of myoglobin, CK-MB, and troponin I positivity during sampling.

Results

The median time from symptom onset to ED arrival was 3.3 (1.3, 9.5) hours for the 1005 enrolled patients. Data for marker and 30-day mortality status were available for 968 patients for LL testing (96%), 953 for MMS-1 (95%), and 955 for MMS-2 (95%). Patients who were lost to follow-up were younger, more often men and smokers, and less often diabetic.

Both MMS strategies identified more positive patients than did LL testing. At baseline, 18.9% of patients were positive by MMS-1, 14.3% by MMS-2, and 5.2% by LL ($P=0.001$, all comparisons). By serial testing, 23.9% of patients were positive by MMS-1, 18.8% by MMS-2, and 8.8% by LL ($P=0.001$, all comparisons). When we considered the results

TABLE 1. Chest Pain Duration by Baseline Marker Status

	Symptom Onset to Baseline Sample, h
Myoglobin	
Positive	4.4 (1.9, 12.5)
Negative	5.5 (2.5, 11.0)
CK-MB	
Positive	5.6 (2.9, 11.1)
Negative	5.4 (2.4, 11.6)
Troponin I	
Positive	6.4 (3.0, 14.3)
Negative	5.3 (2.4, 11.0)

Data are median (25th, 75th percentiles).

TABLE 2. Baseline Characteristics

	MMS-1		MMS-2		LL Single Marker	
	Positive (n=149)	Negative (n=641)	Positive (n=114)	Negative (n=684)	Positive (n=44)	Negative (n=807)
Age, y	57 (46, 70)	50 (43, 63)	56 (46, 70)	51 (43, 64)	52 (46, 66)	51 (43, 64)
Female, %	36.9	53.7	34.2	52.9	34.1	51.2
Race, %						
White	47.4	58.1	52.5	56.8	48.7	55.4
Black	48.9	38.4	43.6	39.8	58.7	41.1
Prior angina, %	40.7	31.7	41.8	32.3	27.3	33.5
Prior infarction, %	20.1	12.2	20.2	12.6	20.5	13.4
Prior percutaneous intervention, %	16.8	12.8	14.0	13.6	13.6	14.4
Prior bypass surgery, %	12.8	6.1	10.5	6.7	11.4	6.9
Diabetes, %	32.0	18.2	27.4	19.3	27.9	19.9
Hypertension, %	68.2	49.8	62.3	51.1	60.5	53.4
Cigarette smoking, %						
Current	42.3	38.0	44.4	37.7	46.5	37.9
Past	26.8	25.0	26.9	25.1	25.6	25.6
Hypercholesterolemia, %	25.9	28.2	26.4	28.0	30.2	27.4
Family history, coronary disease, %	42.6	52.3	44.4	51.5	50.0	50.5
Heart failure, %	20.8	8.6	15.8	9.8	9.1	10.9
Chronic renal insufficiency, %	17.5	1.9	8.8	4.4	13.6	5.0
Systolic blood pressure, mm Hg	146 (128, 163)	138 (120, 154)	143 (128, 160)	138 (120, 154)	140 (127, 160)	139 (121, 155)
Heart rate, bpm	84 (72, 98)	78 (69, 90)	84 (72, 98)	79 (69, 90)	85 (72, 100)	80 (70, 92)
Killip class, %						
I	88.3	97.3	89.2	96.9	85.7	96.0
II	10.3	2.7	9.9	3.0	14.3	3.8
III or IV	1.4	0.0	0.9	0.2	0	0.3
Baseline ECG category, %						
ST-segment elevation	12.4	10.5	13.4	10.6	19.1	12.3
ST-segment depression	7.6	4.9	8.9	4.7	9.5	4.8
T-wave inversion	13.1	9.2	11.6	9.6	16.7	9.5
Normal/nonspecific changes	41.4	65.8	42.9	64.3	35.7	62.3
Confounders*	25.5	9.7	23.2	10.8	19.1	12.3

Data are median (25th, 75th percentiles) or percent.
*LBBB, left ventricular hypertrophy, or paced rhythm.

of LL testing for either marker available at sites where more than 1 assay was run, 11.1% of patients were positive on serial testing, still significantly lower than by MMS testing.

The Figure shows the relations of positivity among the individual markers during serial testing of MMS-1. Only 40% of patients were identified as positive by more than 1 marker. The greatest redundancy was for CK-MB with 1 of the other 2 markers. Individually, cTnI (26%) and myoglobin (21%) detected more patients who were not detected as positive by any other marker.

The median times to positivity were similar with MMS-1 (2.5 hours) and MMS-2 (2.8 hours), and both were shorter than with LL testing (3.4 hours; $P=0.0001$ versus MMS-1 and MMS-2). Comparing only patients who were positive by both LL and MMS-1 or MMS-2, time to positivity was significantly shorter for MMS ($P=0.023$ for LL versus MMS-1; $P=0.026$ versus MMS-2). Patients who were myoglobin-positive at baseline had shorter symptom duration than those positive by either CK-MB or cTnI (Table 1).

For all testing strategies, patients who were positive were older, more often men, and were more likely to have diabetes, hypertension, prior anginal symptoms or MI, congestive heart failure, and chronic renal insufficiency (Table 2). Patients who were marker-positive also had ST-segment depression, ECG confounders, or T-wave inversion more often.

There was a strong relation between baseline MMS status and the rate of death or MI at 30 days (Table 3). For MMS-1, the rate was 18.8% among positive patients versus 3.0% among negative patients ($P=0.001$). Although slightly fewer patients were positive by MMS-2, the relation of its status to 30-day death or MI was similar (positive, 21.9% versus negative, 3.2%; $P=0.001$). MMS status also predicted the individual end points of death and MI and the composite of death, MI, and revascularization. MMS-1 was a better dis-

TABLE 3. 30-Day Outcomes

	MMS-1			MMS-2			LL Single Marker		
	Positive (n=149)	Negative (n=641)	*P*	Positive (n=114)	Negative (n=684)	*P*	Positive (n=44)	Negative (n=807)	*P*
Baseline testing									
Death, n (%)	3 (2.0)	0	0.007	2 (1.8)	1 (0.2)	0.055	0	4 (0.5)	1.000
MI, %	17.5	3.0	0.001	21.1	3.1	0.001	13.6	5.1	0.029
Revascularization, %	14.8	5.7	0.001	18.4	5.5	0.001	25.0	7.3	<0.001
Death or MI, %	18.8	3.0	0.001	21.9	3.2	0.001	13.6	5.5	0.038
Death, MI, or revascularization, %	27.5	7.3	0.001	33.3	7.3	0.001	36.4	10.3	0.001
Serial testing	(n=228)	(n=725)		(n=180)	(n=775)		(n=85)	(n=883)	
Death, n (%)	3 (1.3)	1 (0.1)	0.045	2 (1.1)	2 (0.3)	0.163	1 (1.2)	3 (0.3)	0.308
MI, %	18.0	1.7	0.001	20.0	2.2	0.001	55.3	0.9	0.001
Revascularization, %	14.5	4.9	0.001	17.8	4.7	0.001	32.1	5.1	0.001
Death or MI, %	18.9	1.8	0.001	20.6	2.5	0.001	55.3	1.3	0.001
Death, MI, or revascularization, %	27.6	5.8	0.001	31.1	6.3	0.001	67.1	5.9	0.001

criminator for 30-day mortality (2.0% among positive versus 0.0% among negative patients; $P=0.007$) than either MMS-2 (positive, 1.8% versus negative, 0.2%; $P=0.055$) or LL (positive, 0.0% versus negative, 0.5%; $P=1.000$) results. Results were similar with serial testing.

At baseline, MMS status (MMS-1 or MMS-2) was the strongest independent predictor of death or MI at 30 days in multivariable analyses (Table 4). Prior MI, female sex, and abnormal ECG changes also were significant independent baseline predictors in both models. The overall C-index values of both models (0.804 for MMS-1 and 0.823 for MMS-2) were >0.8, indicating good ability to predict the outcomes of interest. Variables entering the models were similar when MMS status on serial testing was considered, and the models were somewhat stronger (C-index 0.848 for MMS-1 and 0.839 for MMS-2) than those developed with baseline MMS results.

TABLE 4. Predictors of Death or Myocardial Infarction at 30 Days

	Wald χ^2	*P*	Odds Ratio (95% CI)	Model χ^{2*}	C-Index
Baseline testing models					
MMS-1				62.2	0.804
MMS-1 status	25.1	0.0001	5.4 (2.8–10.40)		
Prior infarction	7.6	0.0060	2.7 (1.3–5.5)		
Female sex	6.6	0.0104	0.38 (0.18–0.80)		
Abnormal ECG	4.2	0.0396	2.0 (1.0–4.0)		
MMS-2				69.9	0.823
MMS-2 status	27.6	0.0001	5.9 (3.0–11.4)		
Prior infarction	8.6	0.0033	2.9 (1.4–6.0)		
Female sex	8.7	0.0032	0.31 (0.14–0.68)		
Diabetes	5.0	0.0247	2.3 (1.1–4.9)		
Abnormal ECG	4.0	0.0446	2.0 (1.0–4.0)		
Serial testing models					
MMS-1				87.4	0.848
MMS-1 status	42.3	0.0001	9.6 (4.9–19.0)		
Female sex	5.6	0.0177	0.45 (0.23–0.87)		
Prior anginal pain	5.0	0.0257	2.0 (1.1–3.7)		
Abnormal ECG	4.5	0.0345	2.0 (1.1–3.7)		
MMS-2				80.5	0.839
MMS-2 status	42.6	0.0001	7.8 (4.2–14.4)		
Female sex	6.8	0.0090	0.41 (0.21–0.80)		
Prior anginal pain	6.5	0.0110	2.2 (1.2–4.0)		
Abnormal ECG	5.9	0.0152	2.2 (1.2–4.1)		

*Log-likelihood.

Discussion

The use of bedside quantitative multimarker strategies for cardiac marker testing in CPUs identified significantly more marker-positive patients (and earlier) than did laboratory-based single-marker testing. All testing strategies discriminated risk for a composite 30-day end point of death or MI, but only MMS identified cohorts with increased mortality risk at 30 days. Significantly more patients were identified as high risk when myoglobin was incorporated into the MMS versus a strategy including only CK-MB and cTnI or single-marker LL testing. At baseline, only this multimarker strategy identified all patients at risk for 30-day mortality. Time to detection of positive patients also was significantly shorter with bedside MMS strategies than with LL single-marker strategies and shortest when myoglobin was included in the strategy.

Cardiac troponins have been shown to be useful for identifying patients at short-term risk for death and nonfatal cardiac complications in acute MI, acute coronary syndromes, and general ED chest pain populations.[9,13–15] Further, troponin status has correlated with the severity of coronary disease in lower-risk CPU populations and with long-term mortality in these patients.[10,11] In these studies, troponin testing has been additive to ECG data and superior to CK-MB results. Myoglobin has excellent sensitivity and negative predictive value in acute chest pain evaluation,[4,5,16] but its use in risk stratification has been limited somewhat by its lack of cardiac specificity.

In addition to differences in sensitivity, specificity, and risk prediction, the interplay between symptom duration before ED presentation, timing of testing, and unique release and clearance kinetics of each marker affects whether a marker will be positive at a given time.[12,17] Serial testing of cardiac markers has been shown to be important for "rule-out" strategies for myocardial necrosis (with myoglobin, CK-MB, or troponins) and for risk stratification (with troponins).[5,9,18,19] A strategy combining markers with different times to positivity and sensitivity/specificity profiles therefore may be advantageous for evaluating patients with chest pain, allowing us to extend the concept of and rationale for serial testing to testing at a single point in time. In small studies, serial testing of combinations of myoglobin with CK-MB or TnT has shown improved diagnostic sensitivity and specificity for MI.[9,20,21]

This study tested prospectively whether measuring combinations of markers at baseline or serially could improve short-term risk stratification in low- to moderate-risk patients evaluated in CPUs. We have made the first observation that bedside quantitative testing for a combination of markers at 1 time point can risk-stratify such patients for short-term adverse cardiac events, including death. MMS strategies provided advantages in diagnosis and risk stratification over single-marker LL testing both at baseline and with serial testing, and high-risk patients were identified earlier. In addition to allowing earlier triage decisions, the MMS may provide an immediate advantage for treatment decisions in this diverse population.

Either MMS identified significantly more patients as positive than did the LL strategies. Importantly, this also translated into more effective discrimination of patients at high risk for short-term adverse cardiac outcomes, including death. In multivariable modeling that included baseline clinical characteristics and ECG patterns, MMS status was the most important predictor of death or MI at 30 days.

Consistent with the rationale for MMS, the use of serial MMS testing increased the number of positive patients detected by this strategy only modestly and had only a small effect on the strength of the predictive models compared with baseline testing. As expected, serial testing nearly doubled the number of positive patients detected by single-marker LL testing. Despite this increase in yield of positive patients, however, single-marker LL testing remained unable to discriminate patients at risk for 30-day mortality.

The MMS of cTnI with CK-MB provided a substantial advantage over single-marker LL testing in identifying positive patients and in determining 30-day cardiac risk. Adding myoglobin to MMS identified 35 additional patients as positive and 1 additional patient at risk for 30-day death. It did not significantly improve risk stratification for other adverse cardiac outcomes. Two observations support consideration of a 3-marker strategy that includes myoglobin. First, positive patients were identified slightly earlier with 3 rather than 2 markers (2.5 versus 2.8 hours). Second, as expected, patients who were myoglobin-positive at baseline were seen earlier after symptom onset (median, 4.4 hours) than were patients who were cTnI- or CK-MB-positive (median, 6.4 and 5.6 hours, respectively). These findings could translate into earlier triage or treatment. Either MMS strategy detected positive results significantly earlier than LL strategies (median, 3.4 hours).

This study has several strengths. First, it was conducted at the bedside, in real time, at multiple CPUs. It was designed to compare the ability of standardized, near-patient strategies versus usual local practices for marker testing to predict adverse outcomes. It therefore did not depend on or mandate which markers were tested or specific LL assay parameters. This design probably enhances the generalizability of our findings to clinical practice. Second, all testing strategies were carried out concurrently in all study patients, eliminating any potential imbalances in patient characteristics or outcome determinations. Third, management decisions were at the discretion of the treating physicians and were based on routine LL testing, so that knowledge of MMS results themselves would not influence treatment use or outcome.

Our study had a maximum of 5% of patients lost to follow-up or with incomplete marker data. This cohort had higher-risk clinical features, which may have reduced our ability to predict risk, particularly for death. Further, our definition of MI relied on LL CK-MB results. Therefore, particularly in the analysis of serial testing, some confounding of outcome MI with LL positivity is possible. To minimize this for the baseline testing analysis, we required a negative baseline CK-MB for an event to be considered an end point MI. Death and revascularization are not likely to be so affected. For revascularization, however, one should take into account that results of LL testing were available to treating physicians, whereas multimarker testing results were not. Finally, because investigators were instructed to base all

treatment decisions on their usual testing protocols and results, we cannot directly assess the impact that MMS could have on treatment decisions, clinical outcomes, and costs. On the basis of data showing earlier detection of positive patients and greater ability to discriminate high-risk patients, however, one might expect improvements with the use of MMS.

The use of quantitative, near-patient strategies incorporating ≥2 cardiac markers with different times to positivity and sensitivity and specificity profiles is clinically feasible, maximizes the strengths of each marker, improves 30-day risk stratification, and identifies high-risk patients earlier among those examined in CPUs. Routine incorporation of such strategies could improve the process of care, minimize costs, and improve outcomes in these patients.

Appendix

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