Utility of cardiac troponin I, creatine kinase-MB_{mass}, myosin light chain 1, and myoglobin in the early in-hospital triage of "high risk" patients with chest pain

G S Hillis, N Zhao, P Taggart, W C Dalsey, A Mangione

Abstract

***Objective*—To evaluate the use of cardiac troponin I (cTnI), creatine kinase-MB_{mass} (CK-MB_{mass}), myosin light chain 1 (MLC 1), and myoglobin in identifying "high risk" patients with chest pain who will experience serious cardiac events (SCEs) in hospital.**

***Design*—Prospective study.**

***Setting*—University affiliated medical centre in Philadelphia, USA.**

***Patients*—208 patients with chest pain, at > 7% risk of acute myocardial infarction (MI), but without new ST segment elevation on their presenting ECG.**

***Interventions*—cTnI, CK-MB_{mass}, MLC 1, and myoglobin concentrations were obtained on admission (0 hour) and at 4, 8, 16, and 24 hours.**

***Main outcome measures*—The sensitivity, specificity, positive and negative predictive value, and pre- and post-test probabilities of patients suffering an SCE in hospital were determined. SCEs included cardiac death, acute MI, cardiac arrest, life threatening cardiac arrhythmia, cardiogenic shock, and urgent coronary revascularisation.**

***Results*—Admission concentrations of all markers were poor predictors of SCEs in hospital but improved substantially at subsequent timepoints. cTnI and CK-MB_{mass} were consistently the most useful prognostic indicators. If both were negative at 0, 4, and 8 hours, then 99% (95% confidence interval 96% to 100%) of patients remained free from SCEs. The only SCEs not thus predicted were revascularisation procedures and associated complications. Additional tests after 8 hours, or the inclusion of additional markers, did not improve predictive accuracy further.**

***Conclusions*—Patients with high risk clinical features on admission who have negative cTnI and CK-MB_{mass} concentrations at 0, 4, and 8 hours later have a favourable in-hospital prognosis and could be considered for early triage out of coronary care units.**

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Keywords: cardiac markers; triage; chest pain; risk stratification

Department of Emergency Medicine, Albert Einstein Medical Center, Philadelphia, Pennsylvania, USA
G S Hillis
N Zhao
P Taggart
W C Dalsey
A Mangione

Correspondence to:
Dr G Hillis, Department of Cardiology, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK.

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Patients with acute chest pain are often difficult to assess. They represent a heterogeneous population ranging from those with trivial pathology to those with life threatening illness. Determining the optimal disposition of such patients is, therefore, often difficult.

In practice, the main concern is whether or not the patient is suffering from an acute myocardial infarction (MI). In some cases, this will be obvious from the clinical presentation and ECG. More commonly, however, the picture is less clear. For this reason a variety of clinical algorithms,[1] biochemical tests,[2–5] and myocardial imaging studies[6–9] have been used to help clarify the origin of patients' symptoms and assist in the early diagnosis of acute MI.

Over recent years, however, it has become increasingly recognised that MI merely represents one end of the spectrum of acute coronary syndromes.[10] Thus, while patients with overt myocardial damage have the highest short term risk of death and other adverse outcomes, there are others, not categorised as having acute MI, who are also at high risk.[10 11] Ideally, clinicians also wish to be able to identify these patients as early as possible in order to target therapeutic interventions and assist in the early triage of those at low risk out of coronary care units to less intensively monitored environments.

Clinical features such as the duration, timing, and frequency of ischaemic pain assist in determining the long term prognosis of patients with acute coronary syndromes[12 13] but fail to predict accurately adverse events in hospital.[14] The advent of newer, more sensitive and specific markers, capable of detecting minor degrees of cardiac damage, may enable clinicians to risk stratify patients earlier and make decisions regarding their disposition sooner.

Several studies have shown that increased concentrations of cardiac troponins predict an adverse medium to long term prognosis in patients with acute coronary syndromes.[15–18] Other cardiac markers have also been shown to predict prognosis over the subsequent months.[19–21] No previous studies have, however, compared the relative value of simple, widely available, rapid biochemical tests in the early in-hospital triage of patients who would otherwise be considered to be at high risk for adverse events. Such information could be used to influence decisions as to which of these patients might be suitable for early transfer from coronary care units to less stringently monitored

environments and, possibly, to help determine which patients merit early coronary angiography.

Our study aimed to assess whether widely available cardiac markers, at different timepoints, could predict serious cardiac events (SCEs) in hospital among patients at high risk of acute MI.

Methods

PATIENTS

The study group comprised a convenience sample of 208 patients presenting to the emergency department of the Albert Einstein Medical Center, Philadelphia, between 1 February 1995 and 31 January 1997. To be eligible patients had to have had ⩾ 15 minutes of chest pain within the previous 24 hours which was thought clinically to represent myocardial ischaemia and required hospital admission. In addition, eligible subjects had to be designated as "high risk" (> 7%) of having an acute MI by a well validated clinical algorithm,[1 22] but without new ST elevation (⩾ 1 mm in two contiguous leads) on their presenting ECG. All patients who were approached, met eligibility criteria, and were willing to provide informed written consent were included in the data analysis.

STUDY PROTOCOL

The study protocol was approved by the institutional review board of the Albert Einstein Medical Center. Blood samples were taken at presentation (0 hour) and 4, 8, 16 and 24 hours later. Each patient also underwent a standard 12 lead ECG at presentation. Blood samples were allowed to clot and then were centrifuged at 2000 rpm for 15 minutes after which serum was aliquoted and stored at −20°C. Samples, identified only by study code numbers, were subsequently transported to the laboratories of Spectral Diagnostics, Toronto, Ontario. Concentrations of myoglobin, cardiac troponin I (cTnI), creatine kinase-MB_{mass} (CK-MB_{mass}), and myosin light chain 1 (MLC 1) were measured quantitatively. CK-MB_{mass} and myoglobin concentrations were determined using the respective Stratus fluorometric enzyme immunoassay (Dade Behring, Newark, Delaware, USA). MLC 1 concentrations were measured quantitatively using an enzyme linked immunosorbent assay (ELISA). Briefly, serum samples were added to ELISA plates coated with chicken anti-MLC 1 capture antibody. Mouse anti-MLC 1 monoclonal antibody was added and, after an hour long incubation at room temperature, this was conjugated with donkey anti-mouse antibody. Following a further 30 minute incubation substrate was added and the resultant reaction stopped after 10 minutes. Plates were read on an absorbance reader at 490 nm and the amount of MLC 1 antigen present was calculated by comparison with a standard curve. Concentrations of cTnI were assayed using a similar ELISA. Samples were added to plates coated with goat anti-TnI polyclonal antibody enabling bound cTnI to be measured using anti-human cTnI monoclonal antibodies and a standard horseradish peroxidase detection system. Positive cTnI was defined prospectively as ⩾ 0.2 ng/ml, CK-MB_{mass} as ⩾ 5 ng/ml, myoglobin as ⩾ 100 ng/ml, and MLC 1 as ⩾ 1 ng/ml; these cut off points are comparable to available bedside tests and reflect our own previous experience.[23]

Table 1 Samples available for data analysis

	Myoglobin	*CK-MB_{mass}*	*MLC 1*	*cTnI*
Admission	177 (85)	177 (85)	184 (88)	185 (89)
4 hours	186 (89)	184 (88)	188 (90)	189 (91)
8 hours	191 (92)	197 (95)	198 (95)	199 (96)
16 hours	182 (88)	183 (88)	188 (90)	189 (91)
24 hours	152 (73)	151 (73)	161 (77)	161 (77)

Values are n (%).

The assays were performed by technicians who were blinded to all clinical data and the study results were not available to the clinicians treating the patients. Outcome measures (SCEs) were: cardiac death; acute MI; cardiac arrest; life threatening cardiac arrhythmias (ventricular tachycardia, Mobitz type II second degree atrioventricular (AV) block or third degree AV block); cardiogenic shock; and urgent (within 24 hours of admission) coronary revascularisation during the course of the index hospitalisation. The diagnosis of acute MI was confirmed by an observer blinded to study cardiac marker results, using World Health Organisation criteria.[24] The creatine kinase and CK-MB_{mass} measurements used for this purpose were those performed locally in our institution.

STATISTICAL ANALYSES

Sensitivity and specificity, pretest probability (the overall probability of a patient suffering an SCE before applying any marker data) and post-test probability (the probability of a patient suffering an SCE even after a negative test result) were determined at 0, 4, 8, 16, and 24 hours following presentation. In addition, the probability of a patient experiencing an SCE after a positive test result (positive predictive value (PPV)) and the probability of a patient avoiding an SCE after a negative result (negative predictive value (NPV)) were calculated. Cumulative results were also determined, taking into account the results of all assays for each individual marker to that particular timepoint.

Blood samples were missing in 13% of the available timepoints (538 out of a total of 4160). Table 1 shows the number of samples available for each marker at each timepoint. Where data are missing for a particular time the patient has been excluded from specific and cumulative analyses at and to this point. When assessing the cumulative results to subsequent timepoints, however, missing values were assumed to be negative. For example, if a patient had a missing 4 hour cTnI result they would be excluded from assessments of the sensitivity, specificity, pre- and post-test probability, PPV, and NPV of cTnI at or to 4 hours. Assuming, however, that an 8 hour result was available they would be included in the assessment of the utility of cumulative cTnI values up to 8 hours, with the 4 hour value assumed to

Table 2 Sociodemographic and clinical characteristics of study cohort (n = 208)

Mean (SD) age	65 (14) years
Male/female	113/95 (54/46)
Race	
Black	113 (54)
White	81 (40)
Hispanic	11 (5)
American Indian	2 (1)
Asian	1 (0.5)
History	
Angina	129 (62)
Myocardial infarction	78 (38)
Revascularisation (PTCA or CABG)	55 (26)
Risk factors	
Hypertension	145 (70)
Diabetes mellitus	60 (29)
Current smoker	51 (25)
Time to presentation (hours)	
⩽ 6	121 (58)
> 6 ⩽ 12	47 (23)
> 12 ⩽ 24	28 (13)
> 24	8 (4)
Uncertain	4 (2)
Predominant ECG feature on presentation	
Normal	29 (14)
ST segment elevation* (pre-existing)	4 (2)
Bundle branch block/paced rhythm with abnormal repolarisation	25 (12)
ST segment depression*	22 (11)
T wave inversion*	72 (35)
Other non-specific T wave or ST segment abnormalities	56 (27)
Ongoing pain at presentation	147 (71)

Values are n (%) unless stated.
*⩾1 mm in two contiguous leads.
PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

be negative. This may have had the effect of reducing slightly the sensitivity and NPV of markers for predicting SCEs while possibly increasing their specificity, PPV, and the post-test probability of disease. In clinical terms, however, the most important deficiency would be a failure to identify patients at risk of SCEs.

Data were entered into a Microsoft Access 97 (Microsoft Inc, Redmond, Washington, USA) database and imported into SPSS for Windows (SPSS Inc, Chicago, Illinois, USA) for statistical analysis. Continuous data are expressed as mean (SD). Categorical data are expressed as absolute values and percentages. Time related sensitivity, specificity, positive and negative predictive values (with 95% confidence interval (CI)) for SCEs were calculated for each marker at each time using the Epi Info statistics program (Epi Info 6, Centers for Disease Control and Prevention, Atlanta, Georgia, USA). Post-test probability of disease after a negative test result with 95% CI was determined using the method of Monsour and colleagues.[25] Differences between the sensitivity and specificity of markers were calculated using a two tailed, exact McNemar's test with significance defined as $p < 0.05$.

Results

BASELINE SOCIODEMOGRAPHIC AND CLINICAL VARIABLES

All eligible patients who were screened and were willing to provide informed written consent were enrolled (n = 208). Their ages ranged from 31–95 years, with a mean age of 65.3 (13.8) years, and included a high percentage of women and racial minorities (table 2). As expected they had a high prevalence of previous cardiac problems, ECG abnormalities, and risk factors for coronary artery disease.

The time between the onset of pain and presentation to the emergency department could be accurately determined in 176 cases (85%); in these patients the mean time to arrival was 6.4 (8.3) hours. The majority of patients presented within 6 hours of the onset of symptoms and most had ongoing pain on arrival (table 2).

TREATMENT AND INVESTIGATIONS IN HOSPITAL

One hundred and ninety six (94%) subjects received aspirin within the emergency department or were already taking it on a daily basis, 143 (69%) were treated with intravenous

Table 3 Sensitivity, specificity, pre- and post-test probabilities, positive and negative predictive values (NPV and PPV) of individual cardiac markers for SCEs at 0, 4, 8, 16, and 24 hours after admission to hospital

Time (hours)	*Marker*	*False negatives (n)**	*Sensitivity (95% CI)*	*Specificity (95% CI)*	*NPV† (95% CI)*	*PPV‡ (95% CI)*	*Pretest probability§*
0	Myoglobin	16	33.3 (26.6 to 40.9)	79.7 (72.9 to 85.2)	88.4 (81.6 to 93.0)	20.5 (10.6 to 36.0)	13.6
4	Myoglobin	11	50.0 (42.6 to 57.4)	76.8 (70.0 to 82.6)	92.0 (85.8 to 95.7)	22.5 (12.9 to 36.2)	11.8
8	Myoglobin	10	58.3 (51.0 to 65.3)	77.8 (71.2 to 83.4)	92.9 (86.9 to 96.3)	27.4 (17.0 to 41.2)	12.6
16	Myoglobin	13	48.0 (40.6 to 55.5)	81.5 (75.0 to 86.7)	90.8 (84.4 to 94.8)	29.3 (17.4 to 44.8)	13.7
24	Myoglobin	14	39.1 (31.4 to 47.4)	81.4 (74.1 to 87.1)	88.2 (80.7 to 93.2)	27.3 (14.8 to 44.7)	15.1
0	CK-MB_{mass}	15	37.5 (30.4 to 45.1)	94.8 (90.1 to 97.4)	90.6 (84.7 to 94.5)	52.9 (30.3 to 74.5)	13.6
4	CK-MB_{mass}	4	78.9 (72.2 to 84.4)	93.9 (89.2 to 96.8)	97.5 (93.3 to 99.2)	60.0 (40.3 to 77.0)	10.3
8	CK-MB_{mass}	4	84.0 (78.0 to 88.7)	95.3 (91.1 to 97.7)	97.6 (93.6 to 99.2)	72.4 (53.8 to 85.6)	12.7
16	CK-MB_{mass}	4	84.0 (77.7 to 88.8)	94.3 (89.6 to 97.0)	97.4 (93.0 to 99.2)	70.0 (51.7 to 83.6)	13.7
24	CK-MB_{mass}	8	65.2 (57.0 to 72.7)	95.3 (90.2 to 97.9)	93.8 (87.8 to 97.1)	71.4 (49.2 to 86.6)	15.2
0	MLC 1	14	44.0 (36.8 to 51.5)	68.6 (61.2 to 75.1)	88.6 (81.3 to 93.4)	18.0 (10.3 to 29.7)	13.6
4	MLC 1	6	75.0 (68.1 to 80.9)	65.9 (58.5 to 72.5)	94.7 (88.4 to 97.8)	24.3 (15.9 to 35.3)	12.8
8	MLC 1	6	78.6 (72.1 to 83.9)	63.5 (56.4 to 70.2)	94.7 (88.4 to 97.8)	26.2 (17.9 to 36.6)	14.1
16	MLC 1	5	81.5 (75.0 to 86.6)	63.4 (56.0 to 70.2)	95.3 (88.9 to 98.3)	27.2 (18.6 to 37.8)	14.4
24	MLC 1	5	80.0 (72.8 to 85.7)	66.2 (58.3 to 73.3)	94.7 (87.6 to 98.0)	30.3 (20.5 to 42.4)	15.5
0	cTnI	14	44.0 (36.8 to 51.5)	93.8 (89.0 to 96.6)	91.5 (85.8 to 95.1)	52.4 (31.8 to 72.2)	13.5
4	cTnI	3	87.0 (81.1 to 91.2)	91.0 (85.7 to 94.5)	98.1 (94.0 to 99.5)	57.1 (40.6 to 72.3)	12.2
8	cTnI	3	88.9 (83.4 to 92.7)	91.3 (86.2 to 94.7)	98.1 (94.2 to 99.5)	61.5 (45.6 to 75.3)	13.6
16	cTnI	3	88.9 (83.3 to 92.8)	90.7 (85.4 to 94.3)	98.0 (93.8 to 99.5)	61.5 (45.6 to 75.3)	14.3
24	cTnI	3	88.0 (81.7 to 92.4)	90.4 (84.6 to 94.3)	97.6 (92.7 to 99.4)	62.9 (46.0 to 77.1)	15.5

*Patients sustaining an SCE despite negative marker at this timepoint.
†Probability of a patient avoiding any SCEs in hospital after a negative test result.
‡Probability of a patient experiencing an SCE in hospital after a positive test result.
§Probability of a patient experiencing an SCE in hospital before applying the results of tests.
Post-test probability (%) of a patient suffering an SCE after a negative test = 100 − NPV.

Table 4 Cumulative sensitivity, specificity, pre- and post-test probabilities, positive and negative predictive values (NPV and PPV) of cardiac markers for SCEs at 4, 8, 16, and 24 hours after admission (using all values for each marker to this timepoint)

Time (hours)	*Marker*	*False negatives (n)**	*Sensitivity (95% CI)*	*Specificity (95% CI)*	*NPV† (95% CI)*	*PPV‡ (95% CI)*	*Pretest probability§*
4	Myoglobin	10	54.6 (47.1 to 61.8)	74.4 (67.4 to 80.4)	92.4 (86.2 to 96.1)	22.2 (13.1 to 35.2)	11.8
8	Myoglobin	9	65.4 (58.2 to 71.9)	71.2 (64.2 to 77.3)	93.1 (86.9 to 96.6)	25.8 (16.7 to 37.6)	13.3
16	Myoglobin	8	70.4 (63.3 to 76.6)	69.5 (62.4 to 75.8)	93.4 (87.1 to 96.9)	27.5 (18.3 to 39.2)	14.1
24	Myoglobin	8	70.4 (62.8 to 77.0)	65.3 (57.6 to 72.3)	92.2 (84.7 to 96.3)	27.5 (18.3 to 39.2)	15.8
4	CK-MB_{mass}	4	80.0 (73.4 to 85.4)	92.1 (87.0 to 95.4)	97.4 (93.2 to 99.2)	55.2 (37.2 to 71.9)	10.8
8	CK-MB_{mass}	3	88.0 (82.4 to 92.0)	91.9 (86.9 to 95.1)	98.1 (94.2 to 99.5)	61.1 (44.6 to 75.4)	12.7
16	CK-MB_{mass}	3	88.9 (83.3 to 92.8)	90.6 (85.3 to 94.2)	98.0 (93.7 to 99.5)	61.5 (45.6 to 75.3)	14.4
24	CK-MB_{mass}	3	89.3 (83.2 to 93.4)	87.9 (81.6 to 92.3)	97.5 (92.3 to 99.3)	61.0 (45.5 to 74.5)	17.5
4	MLC 1	6	75.0 (68.1 to 80.9)	64.2 (56.9 to 71.0)	94.6 (88.2 to 97.8)	23.4 (15.2 to 34.1)	12.7
8	MLC 1	6	78.6 (72.1 to 83.9)	61.1 (53.9 to 67.8)	94.6 (88.1 to 97.8)	24.7 (16.9 to 34.7)	14.0
16	MLC1	5	81.5 (75.0 to 86.5)	56.5 (49.2 to 63.5)	95.0 (88.3 to 98.2)	22.9 (15.6 to 32.4)	13.7
24	MLC 1	5	81.5 (75.0 to 86.6)	52.5 (45.1 to 59.9)	94.3 (86.6 to 97.9)	22.7 (15.4 to 32.1)	14.6
4	cTnI	3	87.0 (81.1 to 91.2)	90.1 (85.0 to 94.0)	98.0 (93.9 to 99.5)	55.6 (39.3 to 70.7)	12.2
8	cTnI	3	88.9 (83.5 to 92.7)	90.1 (84.8 to 93.7)	98.1 (94.1 to 99.5)	58.5 (43.1 to 72.4)	13.6
16	cTnI	3	89.3 (83.8 to 93.1)	88.3 (82.7 to 92.4)	98.0 (93.7 to 99.5)	56.8 (42.0 to 70.5)	14.7
24	cTnI	3	89.3 (83.4 to 93.3)	85.7 (79.3 to 90.5)	97.6 (92.5 to 99.4)	55.6 (41.0 to 69.2)	16.7
4	Any marker	3	88.0 (82.4 to 92.1)	57.7 (50.4 to 64.7)	97.0 (90.8 to 99.2)	23.7 (16.1 to 33.3)	13.0
8	Any marker	2	92.9 (88.2 to 95.8)	54.0 (46.9 to 61.0)	97.9 (92.0 to 99.6)	24.5 (17.3 to 33.6)	13.9
16	Any marker	2	92.9 (88.1 to 95.9)	51.5 (44.3 to 58.5)	97.8 (91.5 to 99.6)	23.6 (16.6 to 32.5)	13.9
24	Any marker	2	92.9 (88.0 to 95.9)	46.6 (39.4 to 54.0)	97.4 (90.9 to 99.5)	23.2 (16.3 to 31.9)	14.8

*Patients sustaining an SCE despite negative marker concentrations up to and including this timepoint.
†Probability of a patient avoiding any SCEs in hospital after a negative test result.
‡Probability of a patient experiencing an SCE in hospital after a positive test result.
§Probability of a patient experiencing an SCE in hospital before applying the results of tests.
Post-test probability (%) of a patient suffering an SCE after a negative test = 100 − NPV.

heparin, and 146 (70%) were treated with intravenous nitrates. No patient received thrombolysis. Eighty three patients (40%) underwent coronary angiography, 103 (50%) had an echocardiogram, and 72 (35%) a stress test during the course of their admission.

CLINICAL DIAGNOSES AND SERIOUS CARDIAC EVENTS

Twenty seven (13%) patients sustained an acute MI during their index admission, one of which was in the setting of cocaine use (with positive urinary drug screen). Four of these 27 infarcts occurred > 24 hours after hospitalisation. One hundred and twelve (54%) patients had a discharge diagnosis of unstable angina, five (2%) had cocaine induced chest pain, and the remaining 64 (31%) subjects were ultimately diagnosed as having non-ischaemic chest pain or chest pain of uncertain aetiology. Five patients (2%) died during the index admission (all of whom sustained acute MI). The two cases of cardiogenic shock and three cardiac arrests all occurred in these subjects. No patient developed Mobitz type II or third degree AV block during the course of their admission. Only two subjects underwent urgent revascularisation (within 24 hours of admission), though 36 subsequently did so during their stay in hospital.

CARDIAC MARKER RESULTS AND THE RISK OF SERIOUS CARDIAC EVENTS

The positive and negative predictive values, pre- and post-test probability, sensitivity and specificity for each marker, and timepoint are shown in table 3; the cumulative results for individual markers up until each timepoint are shown in table 4.

Predictive value of individual markers at specific timepoints

At the time of presentation, all four markers were poor predictors of SCEs in hospital. In all cases, however, the sensitivity and NPV improved considerably thereafter. The sensitivities and NPVs of cTnI and CK-MB_{mass} were only marginally higher than those of MLC 1 but the former markers were more specific ($p < 0.001$ at all timepoints). Myoglobin was of intermediate specificity and PPV but had the lowest sensitivity and NPV.

The sensitivity and NPV of both cTnI and CK-MB_{mass} peaked at 8 hours, such that if either of these markers was negative at this time patients had a < 2% chance of suffering an SCE. The specificity and PPV of cTnI and CK-MB_{mass} were also maximal at 8 hours.

Cumulative predictive value of all values for markers before and including specific timepoints

When comparing cumulative results CK-MB_{mass} and cTnI were superior to MLC 1 and myoglobin and similar to each other in all parameters. Maximal prognostic information could, once again, be obtained by 8 hours. Although cumulative data marginally improved the sensitivity and NPV of CK-MB_{mass} at 8 hours it did not improve the performance of cTnI.

The assessment of all four markers did identify one additional patient when compared to either cTnI or CK-MB_{mass} alone. This advantage, however, was at the expense of greatly reduced PPV and specificity ($p < 0.001$ any marker versus cTnI or CK-MB_{mass} at all timepoints). Assaying both cTnI and CK-MB_{mass} at 8 hours also identified one additional patient compared to using either alone. This resulted in an equivalent sensitivity (92.6%; 95% CI 82.8% to 100%) and NPV (98.7%; 95% CI 96.2% to 99.6%) to using all four markers (table 4) but considerably improved specificity (86.7%; 95% CI 81.0% to 90.9%) and PPV (52.1%; 95% CI 38.2% to 65.7%).

Serious cardiac events not predicted by positive cardiac markers

cTnI—Three patients suffered an SCE, which was not predicted by a positive cTnI during the initial 24 hours. One underwent percutaneous transluminal coronary angioplasty (PTCA) and stenting of the left anterior descending coronary artery within 24 hours of admission (though this was not performed immediately or for ongoing symptoms). The other two were individuals who had perioperative infarctions several days after admission. One had an acute MI during coronary artery bypass grafting (which was performed for severe three vessel coronary artery disease with reversible ischaemia on previous stress testing), and the other had an infarction approximately 6 hours after a femoral haematoma evacuation and pseudoaneurysm repair (following complicated angioplasty and stenting of the right coronary artery).

CK-MB$_{mass}$—CK-MB$_{mass}$ also remained negative throughout the initial 24 hours in three patients who suffered SCEs. In two cases this was associated with negative cTnI (in the patient who had a PTCA within the initial 24 hours and the patient who suffered an intraoperative acute MI during bypass surgery). The patient whose infarction followed the complicated PTCA and subsequent haematoma repair (and was not predicted by cTnI) had a marginally positive CK-MB$_{mass}$ on admission (5.4 ng/ml). Conversely, CK-MB$_{mass}$ failed to identify a patient who suffered a late non-Q wave MI that was predicted by positive cTnI (and MLC 1).

MLC 1 and myoglobin—Five patients with SCEs had negative MLC 1 concentrations during the first 24 hours of hospitalisation and eight had negative myoglobin throughout this period. No patient who suffered an SCE had raised MLC 1 and/or myoglobin concentrations in the absence of raised CK-MB$_{mass}$ or cTnI.

Discussion

The principal finding from our study was that patients with normal concentrations of CK-MB$_{mass}$ or cTnI at 0, 4, and 8 hours are at very low risk of adverse events in hospital. If both these markers were negative at this timepoint then the only events that occurred were a perioperative MI and an early PTCA. The small numbers involved preclude any definitive statement as to whether cTnI or CK-MB$_{mass}$ is superior in predicting risk. Both, however, have advantages over MLC 1 and myoglobin, even at the time of presentation, where the early rise in the latter might have been predicted to confer some superiority.

In a smaller study of 109 patients with unstable angina, cTnT was found to be significantly better than CK-MB$_{activity}$ in predicting death or acute MI in hospital (though not revascularisation).[26] Measurements of CK-MB$_{activity}$ are, however, less sensitive than newer mass assays[27] and this may, in part, explain the improved predictive accuracy in the current study. Certainly others have found that cTnT and CK-MB$_{mass}$ (but not CK-MB$_{activity}$) convey equivalent long term prognostic information,[28] and are of similar efficacy in predicting a wide range of short term adverse events in patients presenting with chest pain.[29] It has recently been reported that cTnI is a more sensitive predictor of major cardiac events within the first 72 hours of hospitalisation than CK-MB$_{mass}$.[30] Both, however, were considerably less accurate than we found in the current study. This is primarily because of the decision by Polanczyk and colleagues to include all revascularisation procedures as end points (of which they constituted 85%).[30 31] Certainly, their results contrast considerably with other large studies assessing the utility of cTnI in predicting major adverse events and establishing the diagnosis of acute MI.[31–33]

In the one other study directly comparing the prognostic value of myoglobin, CK-MB$_{mass}$, and cTnT in patients presenting with chest pain but without infarction, only a raised cTnT concentration was found to be predictive of adverse events over the subsequent six months.[34] Once again, however, all but three of the end points were revascularisation procedures. Of the three patients who suffered an MI or died, cTnT was only positive in one (as were both other markers).

It has been suggested that MLC 1 concentrations are particularly sensitive indicators of minor myocardial damage,[35] and can be used to identify patients with severe coronary disease and determine prognosis.[36] We found no evidence, however, that this marker was any better at predicting adverse events in hospital than the more widely available cTnI and CK-MB$_{mass}$ assays. In addition, MLC 1 concentrations are particularly non-specific for the detection of SCEs.

TIMING OF SAMPLES

Our data suggest that maximal prognostic information can be obtained within 8 hours of arrival in the emergency department. With the advent of rapid and accurate bedside tests, these results would be available to the treating physician within 20 minutes and could, therefore, be used to assist in clinical decisions at this time.

Admission samples may be helpful in assessing the long term prognosis of populations but they are too insensitive to assist in decisions regarding the disposition of individual patients. This is in accordance with the findings of Hamm and colleagues who found that a delay of at least 6 hours from the onset of pain was necessary to maximise the predictive value of negative troponin concentrations.[32] As in the current study, they reported that, if cTnI remained negative, the risk of an adverse outcome (in this case death or non-fatal MI within 30 days) was extremely low.

SENSITIVITY OF cTnI AND CK-MB$_{mass}$ FOR SCEs UNRELATED TO REVASCULARISATION

Although our analysis included perioperative complications as SCEs, it may be unrealistic to expect that early cardiac markers could predict such events. Indeed, patients undergoing these procedures would require careful early

monitoring, regardless of their marker status. Similarly, the single "urgent" PTCA not predicted by positive cTnI and CK-MB_{mass} does not appear to have been a truly emergent procedure, and would also necessitate ongoing monitoring. If revascularisation procedures and associated complications are excluded, the sensitivity of both cTnI and CK-MB_{mass} remaining negative at 0, 4, and 8 hours rises to 100% (95% CI 83.4% to 100%), with an NPV of 100% (95% CI 96.9% to 100%). Post hoc analyses are open to criticism. It is clear, however, that if these markers remain negative 8 hours after arrival in the emergency department the risk of "spontaneous" SCEs is extremely low.

STUDY LIMITATIONS

The use of a convenience sample has some drawbacks. All eligible patients who were approached and gave consent have, however, been included in our analysis. There is, therefore, no reason to believe that our sample differs from the general population of similar patients presenting with chest pain. While the missing data points may have had a minor effect it is highly unlikely that they have significantly affected the overall results. This is particularly true in the case of the cTnI, CK-MB_{mass}, and MLC 1 data as increases of these serum markers persist for over 24 hours. It is possible that the missing data points have slightly reduced the sensitivity and increased the specificity of myoglobin, which usually remains detectable within the bloodstream for only a few hours following release. It is unlikely, however, that these effects would be substantial and it remains clear that myoglobin has little to offer as a prognostic indicator in such patients.

The main limitation to the current study is the relatively small sample size and low incidence of adverse events, which may have masked subtle differences in the predictive accuracy of markers. For this reason our results require validation in a larger study. Further study is also necessary to determine whether the combination of cTnI and CK-MB_{mass} is preferable to using either alone for early triage, to assess how much additional information is conveyed by the use of multiple sampling timepoints, and to explore further the optimal sampling times.

CONCLUSIONS

Our data suggest that if CK-MB_{mass}, cTnI, or both, remain negative during the initial 8 hours of hospitalisation, even those patients who initially appear to be at highest risk have a favourable early prognosis and may be safely transferred out of the coronary care unit.

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