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Bholasingh, R.; de Winter, R.J.; Fischer, J.C.; Koster, R.W.; Peters, R.J.G.; Sanders, G.T.B.

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Safe discharge from the cardiac emergency room with a rapid rule-out myocardial infarction protocol using serial CK-MB_{mass}

R Bholasingh, R J de Winter, J C Fischer, R W Koster, R J G Peters, G T Sanders

Abstract

Objective—To determine whether a new protocol, using a rapid and sensitive CK-MB_{mass} assay and serial sampling, can rule out myocardial infarction in patients with chest pain and decrease their length of stay in the cardiac emergency room without increasing risk.

Design—The combined incidence of cardiac death and acute myocardial infarction at 30 days, six months, and 24 months of follow up were compared between patients discharged home from the cardiac emergency room after ruling out myocardial infarction with a CK-MB_{activity} assay in 1994 and those discharged home after a rapid CK-MB_{mass} assay in 1996.

Setting—Cardiac emergency room of a large university hospital.

Patients—In 1994 and 1996, 230 and 423 chest pain patients, respectively, were discharged home from the cardiac emergency room with a normal CK-MB and an uneventful observation period.

Results—The median length of stay in the cardiac emergency room was significantly reduced, from 16.0 hours in 1994 to 9.0 hours in 1996 (p < 0.0001). Mean event rates in patients from the 1994 and 1996 cohorts, respectively, were 0.9% (95% confidence interval (CI) −0.3% to 2.1%) v 0.7% (95% CI −0.1% to 1.5%) at 30 days, 3.0% (95% CI 0.8% to 5.2%) v 2.8% (95% CI 1.2% to 4.4%) at six months, and 7.0% (95% CI 3.7% to 10.3%) v 5.7% (95% CI 3.5% to 7.9%) at 24 months. Kaplan–Meier survival analysis showed no difference in mean event-free survival at 30 days, six months, and 24 months of follow up.

Conclusions—Using a rule-out myocardial infarction protocol with a rapid and sensitive CK-MB_{mass} assay and serial sampling, the length of stay of patients with chest pain in the cardiac emergency room can be reduced without compromising safety.

(Heart 2001;85:143–148)

Keywords: length of stay; cardiac emergency room; creatine kinase-MB; myocardial infarction

It is important to rule out acute myocardial infarction early in the triage of patients presenting with chest pain. Patients at low risk of a cardiac event can then be discharged home safely, while those at intermediate or high risk should be admitted for further management.

Several biochemical markers can be used to rule out myocardial infarction in the early stages. These are cardiac troponins, and the creatine kinase MB isoenzyme (CK-MB). In a recent study by Zimmerman and colleagues, the most sensitive early marker of myocardial infarction was the analysis of CK-MB subforms (91% at six hours after the onset of symptoms), CK-MB_{mass} was used as the diagnostic standard “because it has been the diagnostic standard worldwide for more than two decades and because extensive clinical and experimental evidence indicates increased plasma CK-MB reflects infarction.” Hamm and colleagues recently reported that cardiac troponins may also be effective for early triage, and they showed that patients with chest pain in the emergency room are at low risk of subsequent cardiac events after negative (serial) troponin T or I test results.

It has been found that the sensitivity and specificity of cardiac markers for the early diagnosis of myocardial infarction change rapidly in the first six hours after the onset of symptoms, so serial measurements may increase the sensitivity of these tests for detecting myocardial infarction. Rule-out protocols have most often relied on serial CK-MB measurements. With the development of a new, rapid, and sensitive CK-MB_{mass} assay, early triage of patients presenting with chest pain is feasible and may result in a reduction in the length of stay in the cardiac emergency room.

In the present study, we evaluated prospectively a new rule-out myocardial infarction protocol which was introduced into our cardiac emergency room in 1995. This replaced the CK-MB_{activity} assay with a rapid and sensitive CK-MB_{mass} assay and serial sampling. Our aim in this study was to determine whether this protocol decreased the length of stay in the cardiac emergency room while preserving the overall risk assessment.

Methods

To assess the efficacy and safety of the new rule-out myocardial infarction protocol, we performed a prospective study of all patients who were discharged home from our cardiac emergency room during 1994 and 1996.
Patients presenting with chest pain to our cardiac emergency room usually stay for observation to exclude severe instability and to rule out myocardial infarction before they are discharged home. Our cardiac emergency room is a five bed department equipped with ECG monitoring, where patients can remain under observation for a maximum of 24 hours. In 1995, a new rule-out myocardial infarction protocol using serial CK-MBmass was introduced.

In 1994, blood samples were routinely drawn at admission and at 6, 12, 18, and 24 hours after the onset of symptoms to measure CK-MBmass. The results were made available twice daily: at 11.00 and 16.00 hours.

In 1996, blood samples were drawn on admission and at 5, 7, and 10 hours after the onset of symptoms to measure CK-MBmass. The results were made available within one hour from blood sampling, the last result being available 11 hours after the onset of symptoms.

Patients with chest pain were included in the present study when they were discharged home from the cardiac emergency room after normal CK-MB measurements and an uneventful observation period. These patients were followed up. Patients with abnormal or nondiagnostic ECGs were included in both cohorts. Patients were excluded if they were transferred to the coronary care unit. Patients were transferred to the coronary care unit for the following reasons: if there was evidence of minor myocardial damage or myocardial infarction; if there was unstable angina defined as recurrent symptoms together with concomitant dynamic ECG changes; or on the basis of the clinical judgement of the attending physician.

For patients who presented more than once to the cardiac emergency room, only the first admission was included.

An exercise tolerance test was not routinely performed in all patients before discharge home from the cardiac emergency room but was available at the request of the attending physician. In addition, on discharge the patients usually received drug treatment and an appointment for the outpatient clinic, at the discretion of the attending physician.

The study was approved by the locally appointed ethics committee and informed consent was obtained.

Assays

**1994 Cohort**

CK-MBmass was determined using an ion exchange column chromatography method, the CK-MM and CK-MB fractions being separated on a Sephadex A-50 column. After separation, the activities were measured with a commercial kit (CPK, acetylcysteine activated, product 124184, Boehringer Mannheim, Germany). The reaction was started by the addition of creatine phosphate and the activities were measured at 340 nm in a spectrophotometer. The upper limit for myocardial infarction was 8.0 U/l. Precision, as expressed by the coefficient of variation, was 13.5% at the level of 6.31 U/l. Assay temperature was 37°C.

**1996 Cohort**

CK-MBmass was measured with the Immuno-1 analyser (Bayer, Leverkusen, Germany). The upper limit for myocardial infarction was 7.0 µg/l. Precision (coefficient of variation) was 2.5% at the level of 5.0 µg/l. Assay temperature was 37°C. An increase in serial CK-MBmass values larger than the reference change value (2.0 µg/l) was considered abnormal.

Myocardial infarction was defined according to the World Health Organization criteria. Minor myocardial damage was defined either as a typical rise and fall of CK-MBmass with a peak above the upper limit of normal but less than or equal to twice the upper limit of normal, or as a significant increase in serial CK-MBmass values of more than the reference change value.

**Follow up**

The 30 days, six months, and 24 months follow up assessments were made by telephone interview with either the patient, the patient's relatives, the cardiologist, or the patient's general practitioner. In case of a cardiac event, either the medical records were reviewed or the patient's general practitioner or cardiologist was consulted to confirm the diagnosis. A cardiac event was defined as non-fatal myocardial infarction or as death from cardiac causes (fatal myocardial infarction, sudden cardiac death, or death from other cardiac causes), which occurred after discharge from the cardiac emergency room.

**Statistical analysis**

Comparisons of frequency distribution between groups were performed with the χ² test. To assess event-free survival, Kaplan–Meier curves were constructed for the cardiac events, and differences in mean survival were compared using the log-rank test. Difference between median lengths of stay was assessed by the Mann–Whitney U test.

**Results**

In 1994, 1892 patients presented at the cardiac emergency room. Of these, 1109 (59%) had chest pain and 393 (35%) were admitted to the coronary care unit. The other patients with chest pain were either discharged from the car-
diac emergency room without CK-MB measurements because of the diagnosis of atypical or non-cardiac chest pain (486 of 1109 (44%)), or they were included in the rule-out myocardial infarction protocol and remained under observation at the cardiac emergency room (230 of 1109 (21%)).

In 1996, 2266 patients presented at the cardiac emergency room. Of these, 1162 (51%) had chest pain and 398 (34%) were admitted to the coronary care unit. The other patients with chest pain were either discharged from the cardiac emergency room without CK-MB measurements because of the diagnosis atypical or non-cardiac chest pain (341 of 1162 (29%)), or they were included in the rule-out myocardial infarction protocol and remained under observation at the cardiac emergency room (423 of 1162 (36%)).

Thus, according to the inclusion criteria, the 1994 cohort comprised 230 patients and the 1996 cohort comprised 423 patients. The baseline characteristics are shown in table 1: diabetes mellitus and hypertension were more prevalent in the 1996 cohort (15% v 7%, respectively (p = 0.004), and 30% v 21% (p = 0.02)), whereas a history of myocardial infarction was more prevalent in the 1994 cohort (36% v 24% (p = 0.001)). Other characteristics were not different between the two cohorts.

In 1994, using the CK-MB activity assay to rule out myocardial infarction, the median length of stay in the cardiac emergency room was 16.0 hours (range 1.25–47.2 hours). In 1996, using the new, rapid, and sensitive CK-MB mass assay, the median length of stay in the cardiac emergency room was significantly reduced by 44% to a median of 9.0 hours (range 1.0–52.0 hours) (p < 0.0001).

Follow up of the 1994 and the 1996 cohorts was, respectively, 95% and 99% complete. The cardiac events in both cohorts which occurred

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Cardiac events (cardiac death and non-fatal acute myocardial infarction) in the 1994 and 1996 cohorts during 30 days, 6 months, and 24 months of follow up</th>
</tr>
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<tbody>
<tr>
<td>Cohort</td>
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<td>MI</td>
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<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>1996 (n=423)</td>
<td>CD</td>
</tr>
<tr>
<td></td>
<td>MI</td>
</tr>
<tr>
<td></td>
<td>Total</td>
</tr>
</tbody>
</table>

CD, cardiac death; MI, acute myocardial infarction.

Table 3 | Cardiac events in the 1994 cohort (n=16): patient characteristics and days of follow up |
<table>
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<tbody>
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<td>M</td>
<td>80</td>
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</tbody>
</table>

CABG, coronary artery bypass grafting; CD, cardiac death; CE, cardiac event; DM, diabetes mellitus; MI, acute myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; +, present; –, absent.

Table 4 | Cardiac events in the 1996 cohort (n=24): patient characteristics and days of follow up |
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<tbody>
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</table>
Discussion

Our data show that the application of a rule-out myocardial infarction protocol with a rapid and sensitive CK-MB assay and serial sampling can significantly reduce the length of stay of patients with chest pain in the cardiac emergency room without compromising safety. The incidence of events in patients discharged home from the cardiac emergency room was low during the 30 days, six months, and 24 months follow up.

Several triage protocols have been evaluated to identify low risk patients with chest pain. To identify low risk patients, it is as important to rule out myocardial infarction using cardiac markers as it is to exclude severe instability by means of an observation period in the cardiac emergency room. Early identification of low risk patients may result in a reduction in the length of stay in hospital (or in the cardiac emergency room). Different cardiac marker test policies may affect the length of stay. The length of stay may be reduced significantly either when the results of serial measurements are made available in the morning as opposed to the end of the day, when an assay with a shorter turn around time is used, or when the testing policy is changed from batch to random access. Apple and colleagues compared a CK-MB mass assay with a rapid and sensitive CK-MB mass assay (Stratus, Dade Behring, USA) in a small study group (65 patients) admitted to a coronary care unit. Results of CK-MB mass were made available once daily, whereas those of CK-MB mass were made available twice daily, and it was possible to obtain the result from a single specimen within 10 minutes. These investigators showed that the rapid and sensitive CK-MB mass assay improved triage and management of these patients, resulting in a reduction of between 3 and 23 hours in the length of stay in the coronary care unit and a reduction in costs compared with the CK-MB mass assay. Their general conclusions that a frequent and rapid testing policy, using a sensitive assay, is associated with a shorter length of stay in the hospital are in accordance with our results in the present study, which involved larger study cohorts.

Serial CK-MB measurements have been used for several years as the gold standard for the diagnosis of myocardial infarction. In addition, serial CK-MB measurements may be used effectively in early triage of patients with chest pain by ruling out myocardial infarction. Other cardiac markers that may be used as well for early triage are, for example, myoglobin and cardiac troponin I. Myoglobin is an early marker but it is not heart specific. On the other hand, the troponins are heart specific and have the ability to detect minor myocardial damage, although the biological and analytic variation of the cardiac troponin I assays has not yet been established and cardiac troponins are relatively late markers of myocardial infarction. However, for routine diagnosis of myocardial infarction an earlier marker has been recommended, such as CK-MB, which has additional advantages of established biological and analytic characteristics and the ability to diagnose minor myocardial damage.

Polanczyk and colleagues evaluated a strategy for using CK-MB mass and troponin I in patients presenting with chest pain. According to this strategy, patients were divided into four different risk groups for cardiac events occurring within 72 hours after admission. Positive troponin I values did not have additional value in low risk patients presenting with chest pain without evidence of acute ischaemia on an admission ECG and with normal CK-MB mass values (event rate 6% in the presence of positive troponin I vs 4% in presence of negative troponin I values). In addition, normal tro-
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Critical difference: serial CK-MB_max values were considered abnormal when the difference between two serial samples exceeded the reference change value. Moreover, patients stayed for observation for a maximum of 12 hours after the onset of symptoms (in 1994 the maximum was 24 hours) and they were discharged after an uneventful observation period and after ruling out myocardial infarction. The observation period of 12 hours was chosen when it was shown by Lee and colleagues that a 12 hour strategy was safe for patients at low risk.

Using our carefully defined sampling protocol, the event rate after discharge was very low, and was comparable with the event rate reported by Hamm and colleagues. In addition, we have extended our observation to a six month and a 24 month follow up, which showed a low incidence of adverse events over a two year period.

Although the troponins (T and I) are increasingly used for risk stratification in patients with acute coronary syndromes, there is not much evidence at present that they will make a major contribution to present clinical practice with respect to ruling out myocardial infarction. In contrast, a recent paper by Pope and colleagues on missed diagnosis of acute myocardial infarction in the emergency department showed a very low percentage of patients inadvertently discharged (2.1–2.3%) using a rule-out myocardial infarction protocol that included serial CK-MB measurements but no troponin measurements. Whether a troponin T or I measurement added to such a protocol would substantially improve clinical outcome in these patients remains to be demonstrated.

LIMITATIONS OF THE STUDY

This study has some limitations. The 1996 cohort was nearly twice as large as the 1994 cohort, whereas the total number of patients presenting with chest pain at the cardiac emergency room in both cohorts was similar (1162 in 1996 and 1109 in 1994), and the number of patients with chest pain who were admitted to the coronary care unit was also similar (398 vs 393). This may reflect a more aggressive discharge policy combined with the utilisation of serial CK-MB sampling in a larger proportion of patients in 1996.

Some baseline characteristics differed between the two cohorts. These data were obtained from the database, from medical records, and from the patients or the patients’ relatives. The differences may reflect a change in the patient population over the years, or a different admission policy, with more beds being available in 1996 because of a reduction in the length of stay. However, although the proportion of patients with a previous myocardial infarct was lower in the 1996 cohort than in the 1994 cohort, the incidence of a history of diabetes mellitus and hypertension was higher, indicating that the 1996 cohort was not a lower risk group than the 1994 cohort. Our study was of course not randomised, and there could have been changes in the use of diagnostic tests and refinements of treatment between 1994 and 1996 (applied in the outpatient department,
not in the cardiac emergency room), which remained undetected but which might have influenced our results.

CONCLUSIONS
Our data show that, using a rule-out protocol for myocardial infarction with a rapid and sensitive CK-MB assay and serial sampling, the length of stay of patients with chest pain in the cardiac emergency room was significantly reduced by 44%—that is, from a median of 16.0 hours to a median of 9.0 hours, compared with the protocol used up to 1994. These patients were discharged home from the cardiac emergency room without compromising safety—the incidence of adverse events was low during the subsequent 30 days, six months, and 24 months.


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