Optimal Diagnosis in Acute Myocardial Infarction

A Cost-effectiveness Study

PEER GRANDE, M.D., CLAUS CHRISTIANSEN, M.D., ASGER PEDERSEN, M.D., AND MERETE SANVIG CHRISTENSEN, M.D.

SUMMARY The predictive value of a diagnostic test estimates the likelihood for presence or absence of disease in a patient with a positive or negative test result (PV_{pos} or PV_{neg}). We evaluated the predictive values of serum activities of the heart-specific creatine kinase isoenzyme MB (CK-MB), aspartate aminotransferase, lactate dehydrogenase, CK, and ECG in 401 consecutively admitted patients suspected of acute myocardial infarction (AMI). The study showed that CK-MB (PV_{pos} = 0.98, PV_{neg} = 1.00) was better than the other enzymes (single as well as serial) and ECG, evaluated both separately and in combinations. In all cases of AMI CK-MB was positive within 17 hours from admission. Replacement of the standard enzymes with CK-MB provides a faster and safer diagnosis of AMI and reduces hospitalization time considerably for patients without AMI.

THE BALANCE between increased health care costs vs mortality and morbidity makes cost-effectiveness studies necessary. As laboratory services increase the costs in this field must be spent wisely. Although the technical reliability of a laboratory test is important, only the diagnostic validity and consequences for patients can justify its use.

Acute myocardial infarction (AMI) is one of the most common causes of death and one of the most frequent causes of hospitalization in the Western world, so many attempts have been made to improve its diagnosis. Detection of myocardial damage by increasing serum concentrations of enzymes as creatine kinase (CK), aspartate aminotransferase (ASAT), and lactate dehydrogenase (LDH) are now widely used to diagnose AMI. Recent studies indicate that measurements of the CK isoenzyme MB (CK-MB) in serum are more sensitive and specific in diagnosis of AMI. However, several of these reports do not meet the criteria for establishing the true diagnostic efficacy of CK-MB. The comparative patient group should consist of patients suspected of AMI and the establishment of the true diagnosis should be done independently of the results of CK-MB measurements. Furthermore, only a few of these studies answer the clinically important problem of the likelihood of AMI if a positive or negative CK-MB
result is found in a patient suspected of AMI.\textsuperscript{15, 18, 19}

In the present study we compared the diagnostic value of CK-MB with that of ECG and the three standard enzymes (ASAT, CK and LDH) used as single or serial values and in different combinations. The study was done with regard to economical cost-effectiveness and to patient care.

**Patients and Methods**

**Patients**

In a period of 6 months during 1977, 486 patients suspected of AMI were admitted to the coronary care unit (CCU) at Glostrup Hospital. Excluded from the study were patients with symptoms older than 24 hours ($n = 26$) and patients who died or were discharged before enough blood samples were obtained ($n = 39$). Twenty patients were also excluded because no definite diagnosis could be established. This left 401 patients, and 373 of these were admitted less than 15 hours from the onset of symptoms. The 401 patients were classified into two groups according to the diagnosis: 192 patients (146 men and 46 women, ages 36–88 years, mean age 62.2 years) fulfilled the World Health Organization (WHO) criteria for the diagnosis of AMI, and 209 patients (140 men and 69 women, age 36–90 years, mean age 59.8 years) did not meet the same criteria. Thus, the prevalence of AMI was 0.48.

**Methods**

AMI was defined strictly according to the WHO criteria,\textsuperscript{22} which include clinical symptoms, ECG findings, and the results of serum ASAT, CK, and LDH. The results of CK-MB were blinded and did not affect the AMI diagnosis. ECGs were recorded daily. ECG changes indicating transmural or subendocardial infarction were both considered ECG-positive. Transmural AMI was defined by the characteristic pattern of both QRS complex and ST-T-segment changes and subendocardial AMI was defined by changes exclusively in the ST-T segment.

Blood samples were drawn immediately after admission and at 8 a.m. and 8 p.m. for the next 2 days and thereafter at 8 a.m. for the next 4 days. Analysis of ASAT, LDH, and CK were made according to the Scandinavian recommended methods with reaction temperature of 37°C.\textsuperscript{23, 24} CK-MB determinations were performed by electrophoresis on agarose gel and quantitated by fluorescence scanning.\textsuperscript{25} The detection limit of CK-MB was 5 U/l and the coefficient of variation was below 10%. CK-MB was undetectable in serum from normal subjects. The discriminatory level used was the upper reference values of our laboratory: ASAT 40 U/1, CK 200 U/1, and LDH 400 U/1. The discriminatory level of CK-MB was 30 U/l (corresponding to about 10 U/l with reaction temperature of 25°C) found in a preliminary study to distinguish between patients with and without AMI.\textsuperscript{25}

Two criteria for a positive enzyme test were used: a **single enzyme test** was positive if one of the blood samples had an enzyme activity above the discriminatory level; a **serial enzyme test** was positive if a significant rise and fall in serum enzyme activities were seen. The significance level of enzyme changes was expressed as a rise and fall of more than $\sqrt{2} \sigma \Delta$ of the analysis interassay variation.

**Presentation of Results**

The results of the enzyme tests and of ECG were classified as follows: true positive if the test was positive in an AMI patient; false negative if the test was negative in an AMI patient; true negative when a negative test was found in a patient without AMI; and false positive when a positive result occurred in a patient without AMI (fig. 1).

The predictive value\textsuperscript{20} of test results were defined as follows:

\[
PK_{\text{pos}} = \frac{\text{true positives}}{\text{true positives} + \text{false positives}}
\]

and

\[
PK_{\text{neg}} = \frac{\text{true negatives}}{\text{true negatives} + \text{false negatives}}
\]

and the effectiveness\textsuperscript{20} as

\[
\frac{\text{true positives} + \text{true negatives}}{\text{all positives} + \text{all negatives}}
\]

Thus, $PK_{\text{pos}}$ gives the likelihood for presence of disease in a patient with a positive test result. $PK_{\text{neg}}$ estimates the likelihood for freedom of disease in a patient with a negative test.

Although ASAT, LDH, CK and ECG were used in the WHO diagnosis of AMI, the predictive values of these measurements were estimated so we could compare them with the predictive values of CK-MB. This will necessarily induce some overestimation of the predictabilities of ASAT, LDH, CK and ECG.

**Results**

Figure 2 shows the mean activities of the four enzymes in the 192 patients with AMI in relation to time

![Figure 1. Frequency distribution of a test result for the diagnosis of a disease. The dotted line indicates an arbitrary discriminatory level.](http://circ.ahajournals.org/)}
after onset of symptoms. The mean rise in CK-MB activity was about three times higher than for the other three enzymes. The duration of the enzyme elevations was 2 days for CK-MB, 3 days for ASAT and CK, and about 5 days for LDH.

The frequency of true positive/negative or false positive/negative test results is given in Table 1.

The predictive values of single enzyme test and ECG are given in Table 2. The predictability of CK-MB is not significantly different from 1.00. The effectiveness of all the other tests is significantly lower than that of CK-MB.

Among the 20 patients without definite diagnosis, i.e., classified as possible AMI, 17 had a positive CK-MB single test. If these patients were included the predictive values of CK-MB were: PV\textsubscript{pos} 0.98, PV\textsubscript{neg} 0.99 and the effectiveness 0.98.

Table 3 gives the predictive values for the serial enzyme tests. Compared with the single test in Table 2, serial tests increased the effectiveness of the standard enzyme tests, especially with regard to LDH, but were still significantly different from CK-MB single enzyme test. For CK-MB the effectiveness declined significantly. The increased effectiveness for the standard enzymes resulted from a reduction of false-positive en-

![Figure 2. Relation between mean enzyme activity in serum and time from onset of symptoms in 192 patients suffering from acute myocardial infarction. ASAT = aspartate aminotransferase; CK = creatine kinase; CK-MB = creatine kinase isoenzyme MB; LD = lactate dehydrogenase. Upper reference values for ASAT were 40 U/l; for CK, 200 U/l; for CK/MB, 30 U/l; and for LDH, 400 U/l.]
zyme tests, whereas the lower effectiveness of CK-MB was caused by an increase in false-negative tests.

Table 4 shows that the predictability of two combinations of single standard enzyme tests is better than ASAT, LDH or CK alone (table 2). The diagnostic effectiveness is lower when three rather than two enzymes are used, owing to an increased number of false-positive results. The combination of three enzymes with the ECG gives the same effectiveness as two enzymes.

Table 5 reveals that the diagnostic effectiveness of the combinations of serial analyses was not significantly better than that obtained with either ASAT or LDH alone (table 3). There was not complete agreement between the combination of the standard enzymes with ECG and the WHO criteria.

Cost-effectiveness Calculations

In a population of 5 million persons in Denmark, where hospital admission is free of charge for the patient, approximately 22,000 are admitted each year for suspected AMI, and the diagnosis is confirmed in 11,000. In the present series of patients with suspected AMI, we estimated that 30% did not require hospitalization as soon as AMI was excluded, corresponding to 1320 patients per 1 million inhabitants per year. Table 6 gives the mean time to discharge using the WHO criteria or the CK-MB single test for diagnosis. For the 30% of the patients whose condition allowed discharge if AMI was disproved, the actual mean time in-hospital was 2.4 days, whereas the calculated maximal hospitalization was 1.5 days for diagnosis by CK-MB. With blood sampling at admission at 8 a.m. and 8 p.m. all cases of AMI had a positive CK-MB value within 17 hours from admission (fig. 2). An average of 18 hours elapsed from blood sampling until the CK-MB results were available to the clinician, allowing for patient discharge for those in whom AMI was excluded. Table 6 shows that replacement of the older enzymes with CK-

<table>
<thead>
<tr>
<th>Predictive value of</th>
<th>CK-MB</th>
<th>ASAT</th>
<th>CK</th>
<th>LDH</th>
<th>ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive test</td>
<td>0.98</td>
<td>0.87</td>
<td>0.74</td>
<td>0.77</td>
<td>1.00</td>
</tr>
<tr>
<td>Negative test</td>
<td>1.00</td>
<td>0.97</td>
<td>0.98</td>
<td>0.98</td>
<td>0.77</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>0.99</td>
<td>0.92</td>
<td>0.82</td>
<td>0.85</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Numbers in parenthesis are 95% confidence limits.

Abbreviations: ASAT = aspartate aminotransferase; CK = creatine kinase; CK-MB = creatine kinase isoenzyme MB; LDH = lactate dehydrogenase.

<table>
<thead>
<tr>
<th>Predictive value of</th>
<th>CK-MB</th>
<th>ASAT</th>
<th>CK</th>
<th>LDH</th>
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</thead>
<tbody>
<tr>
<td>Positive test</td>
<td>0.94</td>
<td>0.96</td>
<td>0.95</td>
<td>0.96</td>
</tr>
<tr>
<td>Negative test</td>
<td>0.96</td>
<td>0.93</td>
<td>0.86</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Numbers in parenthesis are 95% confidence limits.

Abbreviations: ASAT = aspartate aminotransferase; CK = creatine kinase; CK-MB = creatine kinase isoenzyme MB; LDH = lactate dehydrogenase.

<table>
<thead>
<tr>
<th>Predictive value of</th>
<th>ASAT</th>
<th>ASAT</th>
<th>CK</th>
<th>CK</th>
<th>ASAT</th>
<th>ASAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive test*</td>
<td>0.91</td>
<td>0.87</td>
<td>0.85</td>
<td>0.82</td>
<td>0.91</td>
<td>0.91</td>
</tr>
<tr>
<td>Negative test</td>
<td>0.97</td>
<td>0.97</td>
<td>0.98</td>
<td>0.98</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>0.94</td>
<td>0.92</td>
<td>0.91</td>
<td>0.89</td>
<td>0.94</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*Defined as: both of two tests positive, at least two of three or three of four tests positive.

Numbers in parenthesis are 95% confidence limits.

Abbreviations: ASAT = aspartate aminotransferase; CK = creatine kinase; CK-MB = creatine kinase isoenzyme MB; LDH = lactate dehydrogenase.
TABLE 5. Predictive Value of Combinations of Serial Enzymes Analyses and ECG in Diagnosis of Acute Myocardial Infarction (n = 373)

<table>
<thead>
<tr>
<th>Predictive value of</th>
<th>ASAT CK</th>
<th>ASAT LDH</th>
<th>CK LDH</th>
<th>ASAT CK</th>
<th>ASAT LDH</th>
<th>ECG CK</th>
<th>ECG LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive test*</td>
<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
<td>0.94</td>
<td>0.98</td>
<td>0.94</td>
<td>0.98</td>
</tr>
<tr>
<td>Negative test</td>
<td>0.94</td>
<td>0.95</td>
<td>0.93</td>
<td>0.97</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effectiveness</td>
<td>0.95</td>
<td>0.95</td>
<td>0.94</td>
<td>0.96</td>
<td>0.97</td>
<td>(0.93-0.97)</td>
<td>(0.93-0.97)</td>
</tr>
</tbody>
</table>

*Defined as: both two tests positive or at least two of three or three of four tests positive. Numbers in parenthesis are 95% confidence limits. Abbreviations: ASAT = aspartate aminotransferase; CK = creatine kinase; CK-MB = creatine kinase isoenzyme MB; LDH = lactate dehydrogenase.

MB would reduce the hospitalization by about 40% in 30% of all the admissions who are referred with a suspected AMI.

Discussion

The aim of any diagnostic procedure is to show the presence or absence of a disease. The diagnostic accuracy of tests may be expressed in terms of specificity and sensitivity. These indicate the likelihood of a positive or negative test in patients with established diagnosis, and are therefore of minor interest to the clinician. The main concern is the probability of disease if the patient has a given test result. The final answer is given by establishing the predictive value for a positive or negative test result\(^{20,21}\) as done in the present study for CK-MB in the diagnosis of AMI.

The present study evaluates the diagnostic effectiveness of a laboratory test.\(^{20,21}\) The efficacy of the test for confirming or disproving the diagnosis of AMI is studied in a large and representative population of patients clinically suspected of AMI. Associating bias between the test results and the disease is avoided by blinding the test (CK-MB) and establishing the diagnosis independently. A major problem in evaluating diagnostic procedures for AMI is the lack of an unequivocal diagnostic standard. In this study the WHO criteria of AMI were used because of their generally accepted validity. The shortcomings of the criteria are evident: About 5% of patients suspected of AMI could not be definitely classified according to these criteria.

The present results demonstrate that CK-MB is the most reliable single diagnostic test for AMI in the patients admitted within 24 hours from the onset of symptoms. Furthermore, the data demonstrate that a single test of CK-MB is superior to both static (table 4) and dynamic (table 5) combinations of the older enzymes and ECG. The slightly higher predictive values of CK-MB as a single test compared with serial analyses are due to the short duration of CK-MB elevation; the sampling procedure did not catch both the rise and the fall in CK-MB necessary for a positive serial test. The effectiveness of the combination of ASAT, CK, LDH and ECG was not 1.00, but 0.97. This difference probably reflects the combined effect of mainly two factors: The false-positive enzyme tests in the presence of liver failure, and the fact that the WHO criteria allow for the diagnosis of AMI by positive ECG changes without rise in enzymes as opposed to the criteria utilized in this study (tables 4 and 5). The blinding of CK-MB in making the diagnosis must enhance the relative predictive value of the other enzyme tests.

The only diagnostic test of comparable quality to the enzyme and ECG tests seems to be the infarct scintigraphic techniques. These techniques demand expensive equipment and a highly specialized and skilled staff, so the cost of an infarct scanning is very high. Furthermore, the predictive value is hampered by a considerable number of both false-negative results primarily due to small infarcts and false-positive results caused by prior infarcts.\(^\) In this study we used a quantitative determination of CK-MB and a discriminatory level of 30 U/l.\(^{25}\) This level is much higher than that of healthy controls, in whom CK-MB is hardly detectable (< 5 U/l). In the present study we found a temporary detectable rise in serum levels of CK-MB not greater than 30 U/l in 46 of the 209 patients considered not to have AMI. A similar observation was made by Marmor et al.\(^{28}\) A gradual transition may exist between myocardial ischemia without necrosis, myocardial ischemia with all degrees of microscopic cellular damage, and necrosis up to the unequivocal macroscopic necrosis. In fact, a borderline between clinical infarction (AMI) and less extensive cellular damage is a question of definition. The possibility that some of this increase in serum levels of CK-MB could originate from skeletal

Table 6. Benefit Calculations for a Period of 1 Year Per Million Inhabitants (see text)

<table>
<thead>
<tr>
<th>Diagnosis of AMI</th>
<th>Mean time to discharge per patient</th>
<th>Mean time to discharge per 1320*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO criteria</td>
<td>2.4 days</td>
<td>3168 days</td>
</tr>
<tr>
<td>CK-MB positive</td>
<td>1.5/1980 days</td>
<td>1980 days</td>
</tr>
<tr>
<td>Difference</td>
<td>0.9/1188 days</td>
<td>1188 days</td>
</tr>
</tbody>
</table>

*AMI negative patients, medically ready for discharge. Abbreviations: AMI = acute myocardial infarction; CK-MB = creatine kinase isoenzyme MB; WHO = World Health Organization.
muscle is unlikely: We have evidence that no CK-MB was detected in serum from patients with severe skeletal muscle damage.6

The prognosis of the patients with CK-MB values between 5–30 U/l is unknown. It should be noted that these patients were not ready for discharge. In fact, of the 46 patients in this CK-MB range, 25 had prolonged and severe attacks of angina during admission and 21 had severe heart failure (with pulmonary edema in 12). An important question is whether the mortality of the patients with CK-MB values between 5–30 U/l is the same as in the patients with CK-MB lower than 5 U/l. This is being investigated.

The rapid rise and short duration of the CK-MB elevation and the very low rate of false-positive results establish an earlier diagnosis of AMI than that obtained by serial analysis of the other enzymes. Another practical advantage of CK-MB measurements is that the interpretation of one CK-MB result is simple compared with serial analysis of two or three enzymes.9 Moreover, CK-MB analysis probably reduces the number of patients in whom the presence or absence of AMI cannot be established by present methods.

The ability to establish an early and reliable diagnosis of AMI has marked benefits. A shorter time needed for correct diagnosis is very desirable, since the observation period is a considerable strain for most patients. Furthermore, the monitored beds in the CCU will be more appropriately used. We estimate that about 1400 hospital days can be saved per million inhabitants per year if CK-MB is used for diagnosis of AMI instead of the present methods. The savings will, of course, vary between populations, because they depend on the tradition for admission of patients with suspicious symptoms, the prevalence of AMI in the population and the cost of hospitalization.

Acknowledgment

Our thanks are due to Dr. Henrik R. Wulf, chief physician at the Gastroenterological Department at Copenhagen County Hospital in Hellerup, for much valuable advice about methodologic and statistical problems; Hanne Kjøhn and Rigmor Jensen for technical assistance; and Jytte Jensen for secretarial help.

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