Prognosis After Acute Myocardial Infarction: A Multivariate Analysis of Mortality and Survival

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SUMMARY. We examined early mortality (within 30 days) and survival (beyond 30 days) after acute myocardial infarction in 221 patients by screening 158 variables measured soon after the patient's admission to the hospital. Nineteen of these measurements had predictive value, but each variable alone was relatively insensitive. Therefore, we subjected groups of variables to stepwise discriminant function analysis and classification rates were estimated by calculating 95% confidence intervals using a jackknife procedure. When factors from the history, physical examination, and noninvasive assessment were combined, we identified 70% of deaths (confidence interval 48-80%) and 94% (90-98%) of survivors; when 11 selected variables including hemodynamic data were combined, we identified 86% (66-98%) of deaths and 96% (92-100%) of survivors (93% overall accuracy). We further tested the validity of this method in a subsequent series of 150 patients. Using the original discriminant functions, classification rates based on noninvasive and hemodynamic data fell within predicted limits, although the number of patients studied hemodynamically was unrepresentative and too small to allow overall predictive accuracy. Therefore, we randomly divided the entire population (371 patients) into a base sample from which we constructed new discriminant functions, with which we classified the remaining patients. The classification rates for the validation sample fell within the predicted confidence intervals. Thus, our method provides a reliable approach for predicting the risk of early death or the likelihood of survival in patients soon after acute myocardial infarction.

IF STUDIES EARLY after hospital admission were reliably predictive of survival and mortality in patients with acute myocardial infarction, individual therapy and design of therapeutic trials might be improved. In previous studies, the usual approach has been to place subjects into prognostic categories, rather than to predict survival or non survival in the individual patient. Single prognostic factors have been used, and prognostic indices have been constructed from multiple indicators, including data from the bedside examination, historical, clinical and laboratory information, and precisely measured or defined data; but large classification errors have been reported using predominantly clinical information. Multivariate statistical approaches have also been used to group patients with similar prognoses or obtain overall classification rates, rather than to identify patients predicted to die; these have used historical and clinical, or hemodynamic data or both.

The present investigation, directed toward predicting death or survival in the individual patient, is a retrospective study of patients with acute myocardial infarction who were carefully characterized by clinical and objective noninvasive measurements and in many instances by hemodynamic data as well. Risk factors were identified and used multivariately to predict early and late mortality by means of stepwise linear discriminant analysis. The approach could identify soon after hospital admission patients who would die within 1 month and those who would survive. We validated the methodology by determining confidence limits for the classification rates in the original population, applying the initial functions to a subsequent population, and testing the reliability of the general approach in the combined population using two randomized samples.

Methods

The initial population of 224 patients with acute myocardial infarction (77% males and 23% females, mean age 59.6 years) was studied between July 1969...
and October 1973; in Appendix A we describe in detail the procedures used to collect data. We compiled 158 variables for computer storage from the history and physical findings obtained upon admission, the 12-lead ECG, ECG monitoring, radiographic study of the left heart, and laboratory and hemodynamic measurements. The electrocardiographic analysis of arrhythmias included all arrhythmias that appeared on any 12-lead ECG, or a recorded ECG during monitoring, beginning in the emergency room and including the first 24 hours after hospital admission. The radiographic results were obtained within 24 hours in all but three patients and hemodynamic studies were within 24 hours in all but six patients (maximum on third day). The maximum creatine kinase (CK) was the highest value reached within 24 hours of admission. From the original population of 224 patients, three with noncardiac early death were omitted. Of the remaining 221 patients, 206 had complete data for both historical and clinical variables, 177 had complete noninvasive data, and 92 had hemodynamic studies. In this initial phase of the investigation, patients with acute myocardial infarction studied hemodynamically were representative of the total population in regard to the incidence of patients with shock and those without complications. During data retrieval we used search routines to extract specified data for two exclusive populations: patients with acute myocardial infarction who died from a cardiac cause within 30 days after the onset of acute symptoms (early mortality) and patients who survived the 30-day period.

Identification of Risk Indicators

We examined selected data for differences between the early death and survival groups. We identified 10 quantitative or measurable variables by t test, and nine nominal findings by chi-square analysis applied to the proportions of early deaths and survivors with and without a given finding. For the measured variables, we established breakpoints by determining the value that maximized the chi-square statistic and thereby yielded the minimum overall classification error rate. In some instances, because of a rather high number of patients not in the risk group who died within 30 days, we selected a breakpoint value to reduce this error rate even though the overall rate was slightly increased. We rounded off the variables, e.g., the optimum breakpoint for heart rate was 92 beats/min, but we used 90 beats/min without increasing the error rate appreciably. The breakpoint for clinical class (for definition, see Appendix A and figure 1) was between class II and class III; class III and IV patients were considered at risk.

The data in table 1 are mean (± SD) and prevalences (%) for all 19 significant factors are identified; we used 16 variables for multivariate analyses. We omitted clinical class because it was a composite of several significant clinical findings, and used stroke volume index and arteriovenous oxygen difference instead of the cardiac index; we used the maximum CK value instead of CK area estimate of infarct size because ideal, complete curves were available in only 86 patients (see Appendix A).

Multivariate Data Analysis and Validation

Historical and electrocardiographic variables were categorized as present or absent, while measured variables were analyzed both as absolute values (analysis I) and dichotomized variables (analysis II), in which we developed breakpoints for optimal partition of cardiac deaths and survivors. We then obtained a

Figure 1. Distribution of patients in clinical classes, together with associated mortality and survival rates. Class I: no or minimal left ventricular (LV) failure; class II: mild to moderate LV failure; class III: pulmonary edema; and class IV: cardiogenic shock (for complete definitions see Appendix A). With increasing severity of heart failure (class II-IV) there are significant increases in early mortality and decreases in late survival. EM = early mortality (within 30 days); LM = late mortality. Asterisks indicate p values of the differences in mortality or survival between the two adjacent clinical classes of that portion of the bar next to the asterisk (*** p < 0.01; ** p < 0.02; * p < 0.05).
weighted combination of variables derived from stepwise linear discriminant analysis (Appendix B). First, we determined the best set of predictors from the historical variables and then determined the improvement in classification by sequentially including variables from the physical examination and noninvasive data, while the final analysis added hemodynamic data—all 16 factors were available. In each analysis, we could use only patients for whom we had complete data for the variables included.

We used three approaches to validation (Appendix B). In the initial population, we classified patients by the functions derived from that population to determine the "resubstitution" classification rates; we then obtained theoretical expected correct classification rates and 95% confidence intervals by the jackknife procedure, which itself provides a nearly unbiased initial approach for validation (Appendix B).

In addition to this procedure, 150 additional patients with acute myocardial infarction admitted to the research unit between November 1973 and October 1976 were classified by the discriminant functions derived from the initial group. Since the use of the continuous (raw) data and the breakpoint analysis gave similar results in the initial population, we used only analysis I in this and the additional validation technique using randomization described below. When we used noninvasive data, the classification rates for the second series of patients fell within the computed confidence intervals, but when we used hemodynamic data, they were barely within the limits, and the overall classification was outside the confidence limits (see Results). However, because of changes in research protocols and in the clinical indications for pulmonary artery balloon catheterization, we did not consider it necessary or ethically sound to perform hemodynamic studies in all classes of patients in the second series. As a result, we obtained fewer hemodynamic measurements only in severely ill patients, and the mean values for left ven-
tricular filling pressure, stroke volume index and arteriovenous oxygen difference were significantly different from those in the initial group. Thus, the second group did not have sufficient representative data with which we could completely validate the discriminant functions derived from the first series of patient.

Therefore, we used a third approach to validate the discriminant function methodology. We randomly divided the total population of 371 patients into two samples, and constructed new discriminant functions using the base random sample (186 patients). Then, using the new functions, we classified the patients in the validation sample (185 patients) as early deaths or survivors. In the base population, 138 patients (30 early deaths, 108 survivors) had complete noninvasive data and 56 (18 early deaths, 38 survivors) had hemodynamic data; in the validation population of 185 patients, 150 patients (29 early deaths, 121 survivors) had complete noninvasive data and 64 (20 early deaths, 44 survivors) had hemodynamic data. We then examined the classification rates for the validation sample to determine whether they fell within the 95% confidence limits computed for the base sample by the jackknife procedure (Appendix B).

### Results

#### Usefulness of Single Prognostic Variables

Table 1 shows the absolute data and table 2 summarizes the predictive value of the individual factors identified in the initial population (221 patients) as indicative of increased early mortality. We analyzed each factor using all patients for whom the information was available. Twenty-one percent of the population died within 30 days. Historical factors which predicted increased early mortality were previous myocardial infarction, congestive heart failure, chronic obstructive lung disease and age over 60 years (the latter established by breakpoint analysis). The physical examination and other noninvasive indicators associated with more than a twofold increase in early mortality were heart rate, systolic blood pressure, radiographic left heart dimension, CK integrated curve area, maximum CK, electrocardiographic evidence of anterior infarct location, certain arrhythmias, and clinical class (fig. 1). The initial hemodynamic measurements indicating a greater than fourfold increase in early mortality were left ventricular

### Table 2. Prediction of Early Death (Within 30 Days) and Survival Using Single Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Early Mortality (%)</th>
<th>Early Classification (%)</th>
<th>Incorrect Classification (%)</th>
<th>Survivors</th>
<th>Correct Classification (%)</th>
<th>Incorrect Classification (%)</th>
<th>Overall Classification Error Rate (%)</th>
<th>Overall Correct Classification Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Historical factors</strong></td>
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<td></td>
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<tr>
<td>Age (&gt; 60 years)</td>
<td>30</td>
<td>29 (64)</td>
<td>16 (36)</td>
<td>109 (62)</td>
<td>67 (38)</td>
<td>38</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>27</td>
<td>15 (55)</td>
<td>27 (65)</td>
<td>120 (76)</td>
<td>41 (24)</td>
<td>33</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Previous CHF</td>
<td>27</td>
<td>10 (22)</td>
<td>34 (78)</td>
<td>145 (84)</td>
<td>27 (16)</td>
<td>28</td>
<td>72</td>
<td></td>
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<tr>
<td>COPD</td>
<td>50</td>
<td>12 (27)</td>
<td>31 (73)</td>
<td>163 (93)</td>
<td>12 (7)</td>
<td>20</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td><strong>Physical examination and noninvasive factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HR (&gt; 90/min)</td>
<td>40</td>
<td>27 (60)</td>
<td>18 (40)</td>
<td>136 (77)</td>
<td>40 (23)</td>
<td>26</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>SBP (&lt; 100 mm Hg)</td>
<td>65</td>
<td>17 (38)</td>
<td>28 (62)</td>
<td>167 (95)</td>
<td>9 (5)</td>
<td>17</td>
<td>83</td>
<td></td>
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<tr>
<td>Rales above scapulae</td>
<td>49</td>
<td>11 (24)</td>
<td>34 (76)</td>
<td>164 (93)</td>
<td>12 (7)</td>
<td>21</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Clinical class (III + IV)</td>
<td>66</td>
<td>25 (36)</td>
<td>20 (44)</td>
<td>163 (93)</td>
<td>13 (7)</td>
<td>15</td>
<td>85</td>
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<tr>
<td>LHD (&gt; 50 mm/m²)</td>
<td>28</td>
<td>31 (78)</td>
<td>8 (22)</td>
<td>96 (54)</td>
<td>80 (46)</td>
<td>41</td>
<td>59</td>
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<tr>
<td>CK area (&gt; 40 IU/Ih)</td>
<td>29</td>
<td>4 (33)</td>
<td>8 (67)</td>
<td>64 (86)</td>
<td>10 (14)</td>
<td>21</td>
<td>79</td>
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<td>Max CK (&gt; 1100 IU/I)</td>
<td>33</td>
<td>27 (60)</td>
<td>18 (40)</td>
<td>121 (69)</td>
<td>54 (31)</td>
<td>33</td>
<td>67</td>
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<td>MI location (anterior)</td>
<td>24</td>
<td>24 (65)</td>
<td>13 (35)</td>
<td>82 (52)</td>
<td>75 (48)</td>
<td>45</td>
<td>55</td>
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<td>Sinus tachycardia</td>
<td>35</td>
<td>26 (58)</td>
<td>19 (42)</td>
<td>128 (73)</td>
<td>48 (27)</td>
<td>30</td>
<td>70</td>
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<tr>
<td>VF</td>
<td>46</td>
<td>6 (13)</td>
<td>39 (87)</td>
<td>169 (96)</td>
<td>7 (4)</td>
<td>21</td>
<td>79</td>
<td></td>
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<tr>
<td>3º AV block</td>
<td>31</td>
<td>11 (24)</td>
<td>34 (76)</td>
<td>171 (97)</td>
<td>5 (3)</td>
<td>18</td>
<td>82</td>
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</table>

**Invasive factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Early Mortality (%)</th>
<th>Early Classification (%)</th>
<th>Incorrect Classification (%)</th>
<th>Survivors</th>
<th>Correct Classification (%)</th>
<th>Incorrect Classification (%)</th>
<th>Overall Classification Error Rate (%)</th>
<th>Overall Correct Classification Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVFP (&gt; 20 mm Hg)</td>
<td>53</td>
<td>19 (58)</td>
<td>14 (42)</td>
<td>91 (84)</td>
<td>17 (16)</td>
<td>22</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>CI (&lt; 2 l/min/m²)</td>
<td>58</td>
<td>19 (66)</td>
<td>10 (34)</td>
<td>77 (85)</td>
<td>14 (15)</td>
<td>20</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>SVI (&lt; 25 ml/beat/m²)</td>
<td>53</td>
<td>25 (56)</td>
<td>4 (14)</td>
<td>67 (75)</td>
<td>22 (25)</td>
<td>22</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>AVO₂D (&gt; 5.6 ml/100 ml)</td>
<td>50</td>
<td>22 (73)</td>
<td>8 (27)</td>
<td>72 (77)</td>
<td>22 (23)</td>
<td>24</td>
<td>76</td>
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**Abbreviations:** see table 1.
filling pressure, cardiac index, stroke volume index, and arteriovenous oxygen difference.

Early deaths were classified with an accuracy of up to 80% by certain single variables, and the presence or absence of other single variables allowed correct classification of survivors with an accuracy up to 95% (table 2). However, the error rates for overall classification (early deaths plus survivors) were all relatively high (15–45%) (table 2).

Late mortality (death after 30 days) was 16% in the entire population during an average follow-up of 26 months. Only three indicators showed statistically significant differences between the late deaths and the late survivors. Late mortality was increased about twofold in patients with previous myocardial infarction; a left heart dimension > 50 mm/m² in the hospital carried a threefold higher late mortality than in patients whose left heart dimension was < 50 mm/m², and a left ventricular filling pressure > 20 mm Hg during the acute myocardial infarction was associated with a twofold higher late mortality than in patients with pressures < 20 mm Hg.

Classification by Discriminant Function Analysis

Figures 2–4 show the results of classification of early deaths and survivors by the functions obtained from the stepwise linear discriminant function analysis. The adjacent bars give the resubstitution classification rates for analysis I and analysis II, using the absolute values for abnormality of the variables as determined by breakpoint analysis shown in table 2 (e.g., heart rate > 90 beats/min, systolic blood pressure < 100 mm Hg). The dashed lines (figs. 2–4) give the theoretical correct classification rates and their 95% confidence limits (Appendix B).

When we examined historical factors by discriminant function analysis (fig. 2), 23% (11 of 43) of the early deaths were classified correctly, as shown in the left-hand bar for analysis II, while 98% (159 of 163) of the survivors were correctly identified. As a result, as shown on the right, we correctly classified 82% (170 of 206) of the entire population.

Next, we included factors from the history, physical examination and noninvasive assessment in the discriminant function (fig. 3). Classification of early deaths was improved, for we classified 73% (24 of 33) correctly (analysis II). We correctly classified 97% (140 of 144) of the survivors (middle bar), as well as 93% (164 of 177) of the total population.

Figure 4 shows the classification results allowing the analysis to select from all 16 variables, including hemodynamic data. We selected 11 variables and classification was further improved, with 91% (20 of 22) of early deaths and 97% (68 of 70) of the survivors correctly identified. Thus, 96% (88 of 92) of all patients with complete information regarding these variables were classified correctly.

The resubstitution classification rates were in some instances slightly higher than the upper limits of the theoretical confidence intervals, demonstrating that bias is inherent in classification rates estimated in this manner, but the confidence limits obtained by the jackknife procedure indicated the good predictive ability of this approach (fig. 4).

Table 3 gives the standardized weights (Appendix B) that signify the relative contribution of each variable to the value of the discriminant function. These weights were significantly greater than zero by t test and each contributed significantly to the prognostication; for example, heart rate (−0.508) was weighted approximately three times as much as the left heart dimension (−0.186). The relative importance of all variables was similar whether or not we used measurable variables in raw or breakpoint (dichotomized) form, whether shock patients (class IV) were included.

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**Figure 2.** Classification of early deaths, survivors and the total initial group (%) by discriminant function analysis using historical factors alone. Numbers adjacent to bars give exact resubstitution classification values. The adjacent bars give results for analysis I (raw data) and analysis II (dichotomized data). For analysis I the variables selected were: age, history of previous myocardial infarction, (MI) and history of chronic obstructive pulmonary disease (COPD). For analysis II the variables selected were: age > 60 years, history of previous MI, and history of COPD. Theoretical rates and confidence limits were not computed since this set of variables by itself had little practical use.
or excluded, and when we added invasive parameters to the discriminant function analysis (table 3); for example, the heart rate always had a larger weight than the left heart dimension.

Further Validation in an Additional Population

We applied the functions developed in the initial 221 patients to the second series of 150 patients. The results are summarized in table 4. In the second group, the classification rates for the noninvasive data fell within the error rates determined by the jackknife procedure in the original group — 88% of the patients were classified correctly. Using all variables including hemodynamic data, the prediction of early death and survival barely fell within the confidence limits (69% and 92% classified correctly, respectively), but the overall correct classification rate (79%) for both early deaths and survivors was outside the confidence interval.

Table 4 also shows the results obtained by randomizing all 371 patients from both groups into base and validation samples. The classification rates achieved in the validation sample fell within the 95% confidence limits established for the base sample by the jackknife procedure.

Discussion

If it is possible to identify patients early in their course who are at high risk of dying within 30 days after acute myocardial infarction, there are important
therapeutic implications. Thus, selecting patients for special medical treatment, early operative intervention, or controlled therapeutic trials might be made on the basis of an accurately predicted outcome without such therapy. Our study shows that death within 30 days or survival beyond 30 days can be predicted accurately in a group of patients with acute myocardial infarction based on information obtained soon after hospital admission.

Estimating correct classification rates for discrimi-

<table>
<thead>
<tr>
<th>Table 3. Candidate Variables Used in Discriminant Function Analyses</th>
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<tr>
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<tr>
<td>Age</td>
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<tr>
<td>Previous MI</td>
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<tr>
<td>History of CHF</td>
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<tr>
<td>History of COPD</td>
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<tr>
<td>Heart rate</td>
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<td>Systolic blood pressure</td>
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<td>Rales above scapulae</td>
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<td>LHD</td>
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<tr>
<td>Peak CK</td>
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<td>Location of MI</td>
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<td>Sinus tachycardia</td>
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<td>Ventricular fibrillation</td>
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<td>3(^\circ) AV block</td>
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<tr>
<td>LVFP</td>
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<tr>
<td>AVO(_2) difference</td>
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<tr>
<td>Stroke volume index</td>
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</table>

The importance of the indicators is shown by the standardized weights of the discriminant function. Analysis I refers to variables used in their measured form and analysis II in their dichotomized form. Blank entries indicate that a variable was not selected by the stepwise procedure for inclusion in the discriminant function. These coefficients are in standardized form and are shown to indicate the relative importance of variables in the discriminant analysis; they are not the ones used to classify individual patients (see Appendix B). Details for use of scheme are available from the authors.

Abbreviations: see table 1.

<table>
<thead>
<tr>
<th>Table 4. Validation</th>
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<tbody>
<tr>
<td>Initial patient group</td>
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<tr>
<td>Noninvasive data alone</td>
</tr>
<tr>
<td>Early death</td>
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<tr>
<td>Survival</td>
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<tr>
<td>Total</td>
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<tr>
<td>Hemodynamic data added</td>
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<tr>
<td>Early death</td>
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<tr>
<td>Survival</td>
</tr>
<tr>
<td>Total</td>
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</table>

The three columns to the left pertain to the analysis of the initial patient group and the application of the derived functions to a second patient group. The three columns to the right show the results of randomizing all available patients into base and validation samples. In both sections, the resubstitution classification rate is shown first, followed by the jackknifed classification rate (with 95% confidence limits in parentheses), and by the results of the derived functions applied to the second group (validation sample).
rant function analyses is difficult. There is bias in the simple resubstitution classification rates obtained in many previous studies by reclassifying a population using the predictive function developed from that same population group. The error rates and confidence limits we obtained by the nearly unbiased jackknife procedure could also be unreliable if the data did not conform ideally to the assumptions underlying linear discriminant function analysis (Appendix B). Accordingly, we validated our discriminant function methodology in other ways. First, in the original population of 221 patients (hemodynamic data being available in a representative sample of this group) we determined the 95% confidence limits by the jackknife procedure. Second, we analyzed the second population (150 patients) using the discriminant functions developed in the initial population, and compared the classification rates in this new population with the confidence limits developed for the original population. The noninvasive data base worked well, but hemodynamic data in the second population were sparse and not representative; the predictions using hemodynamic data barely fell within the confidence limits, while overall classification fell outside them. Third, we randomly divided the entire population (371 patients) into two subsamples, classified the members of one subgroup by functions derived from the other, and compared the classification rates for the validation sample with the 95% confidence limits predicted in the base sample by the jackknife procedure. Rates for the validation group fell within predicted confidence limits and we are therefore confident that the methodology and the results derived from it are reliable.

We used a wider spectrum of objectively determined, quantitative variables in this study than has been used in previous studies.5,6,12,14 Our data were always rechecked for accuracy by at least two observers, and the criteria for accepting a positive historical finding were strict (Appendix A). In some studies, only clinical parameters determined at the bedside were used to establish prognostic indices by empirical groupings,8 but these clinical variables were probably insufficiently reliable to allow accurate prognostication. For example, although the increased mortality in class III and IV patients (fig. 1) was undoubtedly related mainly to left ventricular failure, the bedside clinical examination of class I and II patients often failed to establish the presence of left ventricular failure later documented by hemodynamic studies. Thus, among the 93 patients in clinical classes I and II who had admission hemodynamic studies, 26% had a reduced cardiac index (< 2 L/min/m²), 33% had a stroke volume index < 25 ml/m², 37% had an arteriovenous oxygen difference > 5.2 ml/100 ml, and 28% had a pulmonary artery wedge pressure > 18 mm Hg. Moreover, class I and II patients with these hemodynamic abnormalities had a significantly higher early mortality (twice that of all class I and II patients who had hemodynamic assessment), and 70% of the early deaths among class I and II patients occurred in this subset of patients. For this reason, a prognostic index based on the clinical examination alone probably cannot predict mortality with high accuracy. The relative importance of some factors previously used for prognosis has changed with improvements in therapy and with careful serial measurements. For example, in one study in 1953, ventricular tachycardia and shock carried an equal prognostic score.9 In our study, ventricular tachycardia within the first 24 hours was not associated with increased early mortality, but moderate lowering of blood pressure even in the absence of shock was an important variable for predicting increased early mortality. Therefore, prognostic systems should be readily amenable to ongoing revision.

Prognostic indices have been devised by assigning weights to historical data, clinical findings, and routine laboratory measurements (all of which have the advantage of being uniformly available), the assigned weightings being based on clinical impressions of their relative importance in prognosis.6,7 In Peel's prognostic index, such numerical values were assigned to six variables (age, sex, previous history of myocardial infarction, shock, heart failure, and conduction or rhythm abnormalities on the ECG) which yielded a prognostic score that could be related to mortality rate in each of four patient groups, a higher score indicating a more unfavorable prognosis.8 An accurate prediction of early death after myocardial infarction was obtained only in patients who had high scores, but this method did not allow precise prediction of death and survival in patients with lower scores. Individual factors were evaluated only as present or absent and a wide scoring scale was used for the relative importance of any single factor; some variables, such as shock, were poorly defined. Such a prognostic system is imprecise, as demonstrated by later studies.7,8

More recently, there have been efforts to develop quantitative indicators and to devise prognostic indices using multivariate statistical techniques.10 Norris and associates7 presented a method using discriminant function analysis which had six selected indicators: age, electrocardiographic changes, systolic blood pressure, heart size, radiographic signs of congestive heart failure, and a history of previous ischemic heart disease. They used the index to divide patients into six groups, each with increasing mortality; hospital mortality was about 80% in the group with the highest scores and about 5% in the group with the lowest scores. This approach allowed grouping of patients with similar mortality, but accurate classification of both deaths and survivors was not possible.

Other investigations have used linear regression10,12 or discriminant analysis15,14 with varied results. McHugh and Swan9 predicted outcome with an overall accuracy of 85% (using resubstitution) based on a weighted combination of mixed venous oxygen saturation, x-ray determination of left ventricular failure, and the Peel Index calculated and included as an individual variable, but no mention was made of the prediction accuracy for death only, and the study was based on only 42 patients. Shubin et al.14 used dis-
criminant function analysis on 20 patients with shock to successfully predict outcome (94% accuracy using resubstitution) based on the stroke volume index and diastolic arterial pressure. Lemlich et al. used regression and factor analysis on 368 patients to determine the relative importance of multiple historical, clinical and physical findings for determining survival and death, but prognosis was not predicted, as the emphasis was on evaluating the relative importance of the factors examined. Hughes et al. predicted hospital mortality in a retrospective study of 445 patients from three hospitals. The correct overall prediction rate was 91.7% (again, by resubstitution) for a discriminant function based only on historical, clinical and physical findings (in agreement with our resubstitution values of 90% and 93% for the noninvasive set of variables using analyses I and II, respectively). However, the validation compared the discriminant function's prognostic ability with that of several physicians on a randomly chosen subset of 38 patients. The physicians' classification rates averaged 68%, while that of the discriminant function was 92%.

A precise prognostic index should include multiple objective and quantitative indicators, and the analytical technique must consider the relative importance and interdependency of variables to the final prognostic function. With the present approach, clinical, historical, and routine laboratory features including the ECG were verified and rechecked by knowledgeable observers, and objective, noninvasive studies and hemodynamic data were included. We used linear discriminant analysis because it takes into account the relative significance of each variable when considering multiple variables and approximates clinical judgments. In analysis II we used breakpoints for the measured indicators, which were set to differentiate between early deaths and survivors, and allowed us to convert these indicators into dichotomized variables. This approach makes the underlying multivariate distributions more homogeneous and improves discriminating power. However, comparison of the results of analysis I (raw data) and analysis II (dichotomized data) reveals no clear advantage of one approach over the other; classification rates differed at most by 5% for the two methods (figs. 2-4).

Complications during the course of myocardial infarction could unfavorably alter a prognosis based only on findings obtained soon after admission. It would be useful to reassess a patient's prognosis several times during hospitalization to account for evolving conditions or new arrhythmias, although this approach would necessitate a special prognostic function for each point of application. In this connection, we considered the course of 13 patients misclassified by the discriminant function. Of the nine patients who were predicted to survive but died, three died from sudden arrhythmias, two died suddenly from an undocumented cause, one died from recurrent myocardial infarction, two died from late development of shock and one died from progressive congestive heart failure; all of these deaths might not have been predicted or could have occurred relatively independently of early findings. We identified 50% of the patients who died 8-30 days after myocardial infarction. This high-risk group comprised 54% of all cardiac deaths in the first 30 days, and most were judged to have a relatively good prognosis on clinical grounds when discharged from the coronary care unit.

Only three of the single variables obtained after admission signified increased late mortality after hospital discharge: a history of previous myocardial infarction, increased left heart size, and elevated pulmonary artery wedge pressure. Prognosis after discharge from the hospital may not correlate well with admission data and better methods for predicting later complications after hospital discharge obviously would be desirable. Moss et al. recently devised and validated a simple scheme which identified a high risk group with a 4-month post-hospital mortality of 14% (five of 37) compared with a 3% (six of 197) mortality for the low-risk group. The high-risk group was characterized by the presence of two or more of the following characteristics: 1) prior history of angina pectoris, 2) hospital hypotension or congestive heart failure, and 3) more than 20 ventricular premature depolarizations per hour on a 4-hour recording. Item 3 does not relate to admission findings, while item 2 may or may not be present early after admission. To examine this question further, we used discriminant function analysis to predict mortality between 30 days and 6 months in the late survivors who had complete data for noninvasive variables soon after admission. The mortality in the group predicted to die within 6 months was 62.5% (five of eight) compared with a 7.2% mortality (16 of 223) for the group predicted to survive longer than 6 months. The variables we selected were systolic blood pressure < 100 mm Hg, chronic obstructive lung disease, anterior location of infarct, and history of congestive heart failure. When hemodynamic variables were added, 60% (three of five) of the group predicted to die did so within 6 months, while the mortality in the group predicted to survive was 10.3% (eight of 78). The variables selected were rates above the scapulae, stroke volume index < 5.6 ml/beat/m², and left ventricular filling pressure > 20 mm Hg. Although a left heart dimension > 50 mm/m² was significant as a single variable, it was not selected by the discriminant analysis. These results are based on a rather small population and have not been validated. However, admission variables seem to have prognostic value, and perhaps when used in a discriminant function analysis together with data obtained later during the hospital stay and at discharge they may prove valuable in identifying a high risk group. Beyond the first 6-7 months after myocardial infarction (see Appendix A, fig. A1) coronary artery lesions, the state of the coronary collateral circulation, and the status of left ventricular function are probably the dominant factors influencing mortality.

Let us now illustrate one strategy for applying our classification method. If a patient admitted soon after acute myocardial infarction and carefully evaluated during the first few hours by clinical, historical and
noninvasive measurements as reported herein exhibits a good chance of survival, we would undertake no further diagnostic measurements and might recommend ordinary therapy. If, however, the chance of survival is less than 40%, we would recommend hemodynamic studies and a second computation, including hemodynamic measurements, to define the likely outcome more precisely. This prospective approach is being used at this institution and several collaborating hospitals. Patients established to be at high risk by such complete studies might receive special treatment depending upon the level of risk and the clinical features (e.g., degree of left ventricular failure, presence of dysrhythmias). For example, in patients who survive the first few days, monitoring might be continued, or early angiographic studies might be considered. If myocardial infarct size can be limited in man after acute myocardial infarction, specific therapy might be recommended. Alternately, clinical trials might be undertaken using randomization after patient stratification has been accomplished by the approach we describe. Finally, a prognostic index might be used at discharge to identify patients who should receive special follow-up.

Some factors in this discriminant analysis may require revision if it is to be applied to a population whose characteristics differ significantly from those of the population examined here. These results also should be further validated in a prospective manner in patients from other institutions who resemble our population with respect to the incidence of prognostic variables, early mortality rate, and time of admission relative to onset of symptoms. Within these constraints, the discriminant analysis we describe should provide accurate prognostication of early deaths and survival after acute myocardial infarction.

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Appendix A

Study Population and Protocols

Between July 1969 and October 1973, we analyzed 224 consecutive patients with acute myocardial infarction who had been followed after undergoing serial studies in the Myocardial Infarction Research Unit (MIRU) of the University of California, San Diego. There were 173 males and 51 females, ages 30–79 years (mean 59.6 years); the average age of males was 58.8 years and of females 61.8 years. The diagnosis of myocardial infarction was established by at least two of the following criteria: 1) a history of characteristic chest pain, 2) electrocardiographic changes indicative of acute myocardial injury with subsequent evolution of a transmural infarction pattern, and 3) characteristic elevations of the serum enzymes (CK, GOT or LDH). Subendocardial infarction was diagnosed by typical ST- and T-wave changes accompanied by criteria 1 and 3. We included in the study all patients admitted consecutively to the emergency room or coronary care unit (CCU) with a diagnosis of acute myocardial infarction who gave written consent for participation. In patients admitted for recurrent myocardial infarction, only the record of the first infarction was included. The time from onset of symptoms to hospital admission ranged from 0.5 hours to 5 days (mean 8.3 hours), and most patients had received routine emergency treatment before admission to the research unit, including morphine sulfate and antiarrhythmic drugs when indicated. Standard therapies were applied to all patients during their hospital course, and no lives were temporarily prolonged beyond 30 days by unusual medical therapy. Included were 12 patients referred from other hospitals, of whom nine had persistent cardiogenic shock and three refractory congestive heart failure; these patients were admitted at a mean of 3.1 days after the onset of symptoms of acute myocardial infarction. Three patients who died early from noncardiac causes were excluded from the discriminant analysis.

The patients were studied in the MIRU for 36 hours to 9 days (mean 2.8 days). In the patients who died within the first 30 days after the onset of symptoms, the duration of study was 5 hours to 28 days (mean 2.7 days). Patients were subsequently transferred to the CCU and observed for 1–22 days (mean 4.5 days). After transfer to the ward, the patients remained in 1–25 days (mean 12.7 days) before discharge.

On admission, a detailed history and physical examination were recorded by a research cardiologist for storage in an XDS Sigma 3 computer. Based on the admission physical findings, the patients were divided into four clinical classes: class I — no or minimal evidence of left ventricular failure (no more than one of the findings listed for class II); class II — mild-to-moderate left ventricular failure based on two or more of the following findings: third heart sound, persistent basilar rales, and pulmonary venous congestion on chest x-ray; class III — pulmonary edema defined as bilateral rales above the lower tips of the scapulae; class IV — cardiogenic shock defined by a systemic arterial pressure < 90 mm Hg systolic (or 80 mm Hg below the previous basal level) and reduced tissue perfusion evidenced by two of the following: 1) urine output < 20 ml/hr, 2) impaired mental function and 3) peripheral underperfusion with cyanotic, cool extremities. A patient was not considered to be in shock if hypotension was secondary to hypovolemia, pain, or vasovagal reaction. We used radiographic findings to define class II patients to provide more sensitivity and objectivity than the auscultatory detection of pulmonary rales alone. This approach was supported by the fact that 20% of patients with shock had a heart sound but no rales had pulmonary venous congestion on the chest x-ray, allowing them to be placed in class II. Various other individual physical findings on admission consistent with cardiac dysfunction also were examined (e.g., hepatomegaly, displacement of the cardiac apex, atrial gallop, pulsus alternans, palpable systolic bulge). All findings were verified by a second physician within 24 hours of admission.

A standard 12-lead ECG was recorded on admission and at least once daily during the subsequent period in the MIRU and CCU. When available, we reviewed electrocardiographic tracings anatanging the myocardial infarction to verify the location of the acute event and to search for evidence of previous infarction. Also, cardiac rhythm disturbances and conduction abnormalities were defined by 12-lead ECGs and visual monitoring in the emergency room, and then by continuous visual electrocardiographic monitoring, with rhythm strips recorded from continuous tape loops on demand or when tachycardia or bradycardia exceeded preset limits. Twelve-lead ECGs were also recorded at least twice during the first 24 hours. Since most patients had more than one type of arrhythmia, patients were categorized according to the most serious ventricular arrhythmia or the highest degree of atrioventricular (AV) block. Eighteen patients had only isolated premature ventricular or atrial depolarizations, and these patients served as a control group for analyzing the effect on mortality and survival of the various other arrhythmias; early mortality in these 18 patients was 11.1%, and 77.8% survived the follow-up period.

A history of angina pectoris was diagnosed when substernal distress of short duration (often associated with discomfort radiating to the arms or neck) was related to exertion or excitement and relieved by rest or nitroglycerin. Eighty-eight patients (39.3%) gave a past history of angina pectoris; in 25 patients the history was equivocal and they were excluded from the analysis of this factor. A history of congestive heart failure was considered positive when shortness of breath on exertion was associated with either orthopnea or paroxysmal nocturnal dyspnea. A history of hypertension was considered positive when the patient had a prior diagnosis of hypertension or a treatment of systolic blood pressure ≥ 160 mm Hg or a diastolic pressure ≥ 100 mm Hg. Sixty patients (26.8%) had hypertension by these criteria; 10 patients gave a positive history which was not supported by review of previously obtained blood pressure measurements, and in 29 patients no objective information was available. These 39 patients were excluded from the analysis of this factor. Peripheral ischemic vascular disease (10.7%), a positive history of chronic obstructive pulmonary disease24 was obtained, but in 22 patients no definite objective information was available. If definite information about any of the above historical factors was not available, the
history was considered equivocal and the patient was excluded from the analysis of that factor.

The left heart dimension (LHD), measured radiographically from midline markers using a calibrated frontal plane supine chest X-ray exposed at end-diastole by ECG trigger, at a standard inspiratory volume of 1000 ml above functional residual capacity, has been shown to correlate well with cineangiographic measurements of left ventricular size; the upper limit of normal is 52 mm/m² BSA. In 86 patients, we estimated the ejection fraction of myocardial infarction using CK curves. We collected serum samples at 2-hour intervals during 24 hours from the time of admission and subsequently at 4-hour intervals until values were normal. The curve was integrated and the curve area expressed as international units of CK per liter of serum times hours (IU/1-h). CK curves in patients who had intramuscular injections, electrical defibrillation, or cardiogenic shock were excluded. CK curves were studied only for 86 patients, the maximum CK value was examined as an index of the extent of infarct. Recently, we examined the CK activity for these patients as well as others who had complete curves and found a good correlation between peak CK and CK curve area (r = 0.93); furthermore, CK remained at 90% of peak for an average of 7.6 hours. Based on these findings, and in order to include some estimate of infarct size in the prognostic function, the maximum CK value as determined within 24 hours of admission was used in all patients. We measured CK activity in all studies by Rosalki's method.*

We obtained hemodynamic measurements in 141 of the patients (63%). Early in the investigation nearly all patients had hemodynamic studies, and we found that the group having hemodynamic measurements was representative of the total patient population. For the purpose of present analysis, in class I, 63% and in class II and 68% in class III were studied hemodynamically; these proportions were not statistically different. All patients in class IV were studied throughout the series. Pulmonary artery or mean pulmonary arterial wedge pressures or both were measured in most patients by a Swan-Ganz flow-directed catheter. In some early studies we studied a small polyethylene catheter, and in 16 patients we used the pulmonary arterial end-diastolic pressure to estimate the mean left ventricular filling pressure. In 75 patients we measured the systemic arterial pressure using a Teflon catheter placed in the radial or brachial artery. Pressures were measured with Ailetech MS/10 or MS/5 transducers and recorded using a Honeywell system and a direct writing recorder (Clevite Brush Mark 260). The zero reference point for all pressures was 5 cm below the sternal angle. Cardiac output was determined by indocyanine green dye dilution techniques. We used an on-line computer program to calculate cardiac output and stroke volume in most studies.

In the 176 patients surviving hospitalization, we obtained follow-up data by visits to the research outpatient clinic or, in a few instances, by verbal or written contact with the patient's physician or the patient. We collected data 3, 6, and 12 months after the myocardial infarction, and at 6-month intervals thereafter. At each clinic visit, a detailed history and physical examination were recorded and entered into the computer. In patients who died, the time and cause of death were obtained from the physician, death certificates or autopsy reports. The follow-up periods ranged from 8–62 months (mean 26.1 months), and 13 patients (7%) were lost to follow-up 1–14 months after discharge.

Twenty-one percent of the population (48 patients) died early (within 10 days) of admission. Table 1A shows the causes of death related to the stage of treatment. Seventy-five percent of the early deaths took place in the MIRU or CCU within 12 days of admission. Of the 20 patients who died of cardiogenic shock, 13 were admitted as class IV patients. Of the 25% of patients who died outside the MIRU or CCU, eight died in the hospital and four died after discharge. The noncardiac deaths excluded from the discriminant analysis included two from cerebrovascular incidents (one outside the hospital) and one from pneumonia. Of the 176 patients surviving beyond 30 days, 28 (15.9%) died during the average follow-up period of 26.1 months; the mortality was 12% in the first year and 3.9% in the subsequent 14 months. The survival curve (actuarial method) for all patients and curves for a normal population (age- and sex-matched) and a population with ischemic heart disease and angina pectoris are shown in figure 1A. As expected, there was increased mortality in the patients with myocardial infarction for 6–7 months, but the survival rates in the population with angina pectoris and our population are not significantly different when compared at 1, 2, and 3 years. Both survival curves beyond 7 months were significantly different from the curve of a normal population.*

Appendix B

Multivariate Discriminant Analysis

We performed stepwise discriminant analysis using the Statistical Package for the Social Sciences (SPSS) available at University of California, Santa Barbara, by remote job entry on an IBM 370 Model 95 Computer. The description of the stepwise linear discriminant function analysis which follows is intended to show how the procedure operated before the analysis all of the patient data for the candidate variables were scaled to standardized values by subtracting the population mean and dividing by its standard deviation. The first step in the stepwise analysis was to select the single variable for which the early death and survivor groups differed most and for which overlap was such that a point could be chosen that optimally separated the two groups (that is, the point at which a minimum number of classification errors resulted when a patient with a value for this variable less than the separation point was placed in one group, and a patient with a value greater than this point was placed in the other group). Second, we considered two-dimensional plots of the first variable versus all other variables. The second variable chosen was the one which maximized the distance between group means in two-dimensional space, and for which a line could be drawn which optimally separated the class of points representing the two groups of patients. Patients falling on one side of the line were one group and those falling on the other side were the other group. At each step, the procedure chose the variable from the candidate set which contributed most to the discriminating power by increasing the distance in hyperspace between the points representing the group means and determined the hyperplane which optimally separated the two groups. This procedure continued until we determined that the remaining variables did not contribute to the function's discriminating ability.

When correlations exist among variables, the variable selected first may preclude its correlates from being accepted into the discriminant function. The final set of variables includes those factors which best account for group differences. The program outputs the resulting discriminant function with coefficients (weights) in both standardized and nonstandardized units. The standardized weights indicate the relative importance of the selected variable and would
be used with the standardized patient data. In practice, the nonstandardized weights can be applied to each patient's raw measurements and the products added to compute the final discriminant score. This score would be compared with the point that best separates the early death and survivor groups in order to classify individual patients as likely to die within 30 days or to survive.

The program also computes additional coefficients for the early death and survival groups which can be used to estimate the relative probability that an individual patient belongs to either group. For example, when a probability of survival > 50% is used to classify a patient as a survivor, this procedure is equivalent to comparing the discriminant score to the appropriate separation point. Thus, a predictive function was obtained which allowed us to determine the prognosis in an individual patient. Information about each patient's actual classification could then be compared with the results of the above procedure to determine the classification error rate for the function for a group of patients.

The resubstitution classification error rates obtained by applying a discriminant function to the same patients used in its development are inherently biased. However, we used the BMDP7M computer program based on the method of Lachenbruch to obtain theoretical correct classification rates and their 95% confidence intervals. This method, known as "jackknifing," sequentially omits each patient in the population and recomputes the discriminant function coefficients, which are then used to classify the omitted patient. Thus, an almost unbiased estimated classification rate for the discriminant function can be obtained.

The entire linear discriminant analysis methodology is based on certain assumptions regarding the nature of the multivariate statistical distributions for the data. It is assumed that the distributions for each group are multivariate normal and have equal covariance matrices, and that the groups of interest can best be separated by linear functions. Although these criteria may not be strictly met, using Monte Carlo simulation techniques investigators have shown that linear discriminant function methodology performs well. Another potential problem with this technique as applied to our initial population is that the functions derived from a sample might not generalize to an entire population of interest if the sample were not representative enough to yield appropriate estimates of population parameters. For example, when using this methodology prospectively, it is necessary to develop criteria which characterize the study population and then restrict the sample to subjects who conform to these criteria. It is always advisable to validate a classification function prospectively by testing it on a second sample from the study population. Assuming that the classification rates achieved for this validation sample fall within the confidence limits determined from the original sample by the jackknife method, it is then appropriate to use the function in a real clinical setting. Because of these considerations, we attempted to further validate our method by applying it to a subsequent series of 150 patients using the discriminant functions developed in the initial population. In addition, we randomized the entire population of 371 patients (for reasons discussed in the methods section) into two groups, constructed new discriminate function for one group together with error rates determined by the jackknife method, and then compared classification rates in the second group with these error rates.

**Figure A1. Actuarial survival curve for patients with myocardial infarction in the present study (solid line). The survival rates of an age- and sex-matched normal population (dashed line) computed from mortality rates published by the U.S. Public Health Service and in patients with angina pectoris (dashed and dotted line, data from Richards et al. are shown for comparison). The survival rates in the normal population and the population with angina were significantly higher (p < 0.01) at 1, 2 and 3 years compared with the population with myocardial infarction, but the mortality rates at several points on the lower two curves were not significantly different after the first 6 months after myocardial infarction (see text).**
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