Survivorship Patterns in the Posthospital Phase of Myocardial Infarction

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SUMMARY A prospective postinfarction follow-up study was used to identify subsets of patients with different survival patterns. Nine hundred forty patients who survived the hospital phase of an acute myocardial infarction were followed for 12-60 months. During the 5-year follow-up, 115 patients died of cardiac causes. Univariate analysis showed that prior myocardial infarction (PMI), left ventricular dysfunction (LVD) in the CCU, one or more ventricular premature depolarizations (VPDs) on a 6-hour Holter recording, and anterior myocardial infarction were significantly ($p < 0.01$) more frequent in patients who died of cardiac causes than in survivors. Survivorship analyses revealed a variety of survival patterns, depending on the presence or absence of the risk factors PMI, LVD, VPD and anterior infarction, as well as their interactive combinations. A combination of anterior infarction with LVD and VPDs identified a high-risk subset that made up 15% of the myocardial infarction population, and this group had 6-month and 3-year survival rates of 85% and 70%, respectively. After we excluded the high-risk subset, PMI, LVD and VPD each had significant yet independent influence on survival, with PMI having a greater effect on mortality than either LVD or VPDs. A low-risk subset that made up 24% of the population was identified by the absence of PMI, LVD and VPDs, and this group had a 3-year survival of 94%.

PATIENTS WHO SURVIVE an acute myocardial infarction (MI) are at an increased risk of cardiac death and recurrent MI during the subsequent posthospital years. Poor posthospital prognosis has been associated with older age, ST-segment depression and ventricular conduction defects on the resting ECG, cardiomegaly, advanced New York Heart Association functional class, left ventricular dysfunction (LVD) and frequent and complex ventricular premature depolarizations (VPDs).

Although these factors have been used to classify patients in terms of their risk of cardiac death, very little is known about variable interactions as they pertain to the mechanisms influencing mortality. Techniques using multiple variables for modeling survivorship of postinfarction populations are useful in this regard because they utilize the entire experience of all patients, i.e., take into account the length of follow-up. However, only limited use has been made of the full power of these techniques.

In 1973, a prospective, longitudinal, posthospital follow-up program was initiated in Rochester, New York for patients discharged alive after recovering from acute MI. The purposes of the present study are twofold: 1) to determine in this population whether clinical univariate risk factors act independently or in combination with each other to influence posthospital mortality; and 2) to use survivorship modeling to identify and describe subsets of patients with different survival patterns.

Methods

Population

Between January 1, 1973 and December 31, 1976, 1299 Monroe County residents younger than 66 years of age entered coronary care units in two Rochester community hospitals with a definite or probable acute MI and survived hospitalization. From this population, 978 patients (798 men and 180 women) were enrolled with physician and patient consent; 321 patients were not enrolled; there were 116 patient refusals and 53 physician refusals; 30 patients had psychological or behavioral problems; 15 patients were missed; 92 patients had a short hospital stay; and 15 patients anticipated a change in residence. The demographic characteristics of the 321 nonenrolled and the 978 enrolled patients were similar, and the 1-year mortality of the nonenrolled and enrolled groups was 7.1% and 7.2%, respectively. Definite MIs were substantiated by the presence of any two of the following: typical coronary-type chest pain, serial acute myocardial enzyme changes, or ECG documentation (an evolving Q-wave abnormality with acute ST-segment and T-wave changes). Probable MIs had typical coronary-type chest pain with minor enzyme changes and/or acute ST-segment and T-wave changes on the ECG.

Data Acquisition

Nurse investigators interviewed the patients and reviewed their hospital charts during the last week of hospitalization. The patients' medical history before entry and their clinical course while in the coronary care unit and during subsequent hospitalization were

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recorded on prospectively designed forms as previously described. Clinical variables used in this study included: 1) demographic data; 2) historical comorbidity, such as prior myocardial infarction (PMI) (history of a hospital admission for documented myocardial infarction or Q-wave abnormality on the ECG of old MI), hypertension (history of elevated blood pressure necessitating treatment with specific antihypertensive medication), angina pectoris (history of recurrent precordial chest discomfort relieved by sublingual nitrates), diabetes mellitus (documented hyperglycemia necessitating treatment with antidiabetic diet, oral hypoglycemic agents, or insulin); 3) the severity of the acute coronary event in terms of LVD as manifested by pulmonary congestion and/or congestive heart failure (roentgenographic evidence of interstitial or alveolar edema, significant pulmonary rales, and/or pitting edema) in the coronary care unit; 4) ventricular irritability as determined by the presence of one or more VPDs on a predischARGE 6-hour Holter recording; and 5) myocardial infarct location (MIL) as determined by the Minnesota classification of a 12-lead ECG taken before discharge and categorized into anterior (Q/QS 1.11-1.12), posterior (Q/QS 1.14), and other (non-Q/QS abnormality) locations.

Missing Values

The population used in the analyses consisted of 940 of the 978 patients in the study population. Thirty-eight patients were excluded because they lacked complete baseline information: 28 had a technically unsatisfactory predischARGE Holter recording, nine had missing data regarding the variable LVD, and one had missing data for the PMI variable. The 940 patients with complete data make up the analysis population.

Population Mortality

All patients who died before January 1, 1978 were identified. The 940 patients in the analysis population were followed from 12 months (those who entered in December 1976) to 60 months (those who entered in January 1973). When a nonsurvivor was identified, information was gathered from immediate family members, the personal physician and witnesses of the death and evaluated by a mortality review committee, and a cause of death was assigned to each nonsurvivor as previously reported.

From January 1, 1973 through December 31, 1977, 134 of the 940 patients in the analysis population died; 115 of these deaths were from cardiac causes. In addition, two of the 38 excluded patients died, both from cardiac causes.

In the analyses reported in this paper, cardiac death was used as the nonsurvival end point. This was done because we were searching for mechanisms influencing cardiac mortality. However, all the analyses reported in the Results section were also carried out using death from all causes as the nonsurvival end point, and the findings were substantially the same.

Statistical Methods

Two major statistical techniques were used. A Mantel-Haenszel modification of the Wilcoxon-Gehan statistic was used to evaluate the effect of MIL on survival. This test is similar to the Peto-Peto test and yields a summary chi-square statistic that tests the null hypothesis that there is no difference in the survival patterns of the groups being compared.

Survivorship analysis was carried out using the Kaplan-Meier technique and the Cox regression model for censored survival data. The basic principle behind the latter analysis is model comparison. To determine whether a group of variables influence survival, a comparison is made between a model that contains the variables as covariates and the same model with one or more variables deleted. A log-likelihood ratio chi-square statistic is used to compare the two models. If a model without a particular covariate fits the data as well as the same model with the covariate, then the covariate does not affect survival.

Results

Preliminary Analyses

We compared the pertinent clinical characteristics of patients who died with those of the survivors (table 1). There was no association between sex and mortality. The mean age of the two groups was similar, a reflection of the population age limit of ≤65 years. However, a significantly (p < 0.05) greater percentage of patients in the 61-65-year age range died than survived. The three dichotomous variables that showed the most significant (p < 0.01) association with cardiac death were PMI, LVD and VPDs. For the three-level variable MIL, the preponderance (p < 0.01) of anterior infarctions in the mortality group is evident. The survival of the entire population and subdivisions of the population by MIL are presented in figure 1 using a Kaplan-Meier analysis.

Risk Factor Interactions

A Mantel-Haenszel modification of the Wilcoxon-Gehan statistic was used to evaluate influence of MIL on survival. In this analysis, the patients were separated into eight strata according to the presence or absence of the individual variables PMI, LVD and VPD and all the possible combinations of these variables. For each strata, four chi-square test statistics (Wilcoxon-Gehan) were computed to evaluate the importance of infarct location on survival; anterior with posterior, anterior with other, posterior with other, and an overall comparison of the three groups. Summary chi-square statistics were obtained and the results are summarized in table 2.

The most striking feature of table 2 is stratum 4, which contains both LVD and VPD. In this stratum, the anterior infarcts were significantly different from the posterior and other infarcts (p < 0.001), and the overall statistic was also significant (p < 0.01). These findings suggest that patients with anterior infarcts and LVD and VPDs have a significantly reduced sur-
survival pattern compared with the remainder of the population.

Basic Survivorship Analyses

On the basis of the risk factor interaction findings, Kaplan-Meier survivorship analysis was carried out on three groups of patients: group 1 — anterior infarcts with both LVD and VPD; group 2 — anterior infarcts without the LVD and VPD combination; and group 3 — all patients not in group 1. The survival curves for these three groups are presented in figure 2. The survival patterns of groups 2 and 3 are similar, and both curves have a nearly exponential decline over 40 months. The survival pattern of group 1 shows a large initial decline in the first 6 months (15% mortality) and a more gradual decline thereafter. However, although the group 1 survival pattern is nearly exponential after the first 6 months, its slope is more negative than that of groups 2 and 3, indicating a greater hazard rate, i.e., a greater instantaneous probability of death. The survival curves of groups 1 and 3 were compared by a Wilcoxon-Gehan analysis and found to be significantly different ($\chi^2 = 33.87$, one degree of freedom) ($p < 0.001$). Group 1 makes up 15% (137 of 940) of the MI patients and is a high-risk subset that is significantly different from the remainder of the population.

Cox Survivorship Analyses

After exclusion of group 1, Cox survivorship analysis was carried out on the remainder of the patients (group 3, n = 803), including anterior infarcts without the LVD-VPDs combination. Five models were applied to the group 3 data using the risk factors PMI, LVD and VPDs: 1) the “full model” included seven covariates — one for each of the dichotomous risk factors PMI, LVD and VPDs plus their two- and

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**TABLE 1. Population Characteristics**

<table>
<thead>
<tr>
<th>Total population</th>
<th>Deaths</th>
<th>Chi-square (cardiac death vs survivors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>940</td>
<td>134</td>
</tr>
<tr>
<td>Age (years)</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>PMI (%)</td>
<td>806</td>
<td></td>
</tr>
<tr>
<td>LVD (%)</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>VPD (%)</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Ant MI (%)</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Post MI (%)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Other MI (%)</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>940</th>
<th>134</th>
<th>115</th>
<th>806</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% male)</td>
<td>81</td>
<td>79</td>
<td>83</td>
<td>82</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;50 (%)</td>
<td>31</td>
<td>27</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>51 - 55 (%)</td>
<td>21</td>
<td>19</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>56 - 60 (%)</td>
<td>28</td>
<td>28</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>61 - 65 (%)</td>
<td>20</td>
<td>26</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>53.7 ± 0.3</td>
<td>54.5 ± 0.7</td>
<td>54.5 ± 0.7</td>
<td>53.6 ± 0.3</td>
<td>NS §</td>
</tr>
<tr>
<td>PMI (%)</td>
<td>19</td>
<td>39</td>
<td>37</td>
<td>16</td>
<td>25.88 ‡</td>
</tr>
<tr>
<td>LVD (%)</td>
<td>49</td>
<td>63</td>
<td>63</td>
<td>46</td>
<td>10.43 †</td>
</tr>
<tr>
<td>VPD (%)</td>
<td>50</td>
<td>67</td>
<td>67</td>
<td>47</td>
<td>15.21 ‡</td>
</tr>
<tr>
<td>Ant MI (%)</td>
<td>46</td>
<td>57</td>
<td>60</td>
<td>44</td>
<td>9.68 †</td>
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<tr>
<td>Post MI (%)</td>
<td>22</td>
<td>14</td>
<td>15</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Other MI (%)</td>
<td>32</td>
<td>28</td>
<td>24</td>
<td>33</td>
<td>NS</td>
</tr>
</tbody>
</table>

*p < 0.05. †p < 0.01. ‡p < 0.001. §t test used to determine the significance of the difference between the cardiac death and survivor groups.

Abbreviations: PMI = prior myocardial infarction; LVD = left ventricular dysfunction; VPD = ventricular premature depolarization; MI = myocardial infarction; Post = posterior; Ant = anterior.

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**FIGURE 1. Kaplan-Meier survival curves of the total population and subdivisions of the population by infarct location (anterior, posterior and others).**
three-factor interactions; 2) the "main-effects-only" model included three covariates — risk factors PMI, LVD and VPDs without their interactions; 3) the PMI and LVD combination; 4) the PMI and VPDs combination; and 5) the LVD and VPDs combination.

Four model comparisons were made and the results are presented in Table 3. Each of the three risk factors PMI, LVD and VPDs has a pronounced influence on survival, and each factor acts independently of the other two in influencing survival; that is, the "main-effects-only" model is the most appropriate model for the data, and the subsequent results will be based on this model. Within the "main-effects-only" model, the factors LVD and VPDs have equivalent effects on survival, while PMI has a greater effect on mortality than either LVD or VPDs (Table 4).

Table 5 details the number of patients in each sub-
The table below shows the ratio of instantaneous probability of death for various combinations of risk factors. The ratios are derived from the survival functions of the Cox regression analysis.

### Table 4: Contribution of Factors PMI, LVD and VPDs to the Cox Survivorship Main-Effects-Only Model of Group III

<table>
<thead>
<tr>
<th>Factor</th>
<th>Ratio of instantaneous probability of death* (present:absent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMI</td>
<td>2.48:1</td>
</tr>
<tr>
<td>LVD</td>
<td>1.46:1</td>
</tr>
<tr>
<td>VPDs</td>
<td>1.46:1</td>
</tr>
</tbody>
</table>

*Derived from the survival functions of the Cox regression analysis.17, 38

Abbreviations: PMI = prior myocardial infarction; LVD = left ventricular dysfunction; VPDs = ventricular premature depolarizations.

A group of group 3 that was used in the computation of the survival curves for the risk factors PMI, LVD and VPDs using the “main-effects-only model.” Figure 3 shows the survival curves for patients without PMI: patients having no risk factors (neither LVD nor VPD), patients having an additional risk factor (either LVD or VPD), and patients having two risk factors (LVD and VPD). The survival outcome for each of these three groups is good, with the best survival evident in the patients with no risk factors. Figure 4 shows the survival curves for patients in the higher risk groups with PMI: patients having no other risk factors (neither LVD or VPDs), patients having one other risk factor (either LVD or VPDs), and patients having two other risk factors (LVD and VPDs). The survival patterns for these last three groups (fig. 4) are considerably worse than for the preceding three groups (fig. 3). The curves in figures 3 and 4 apply only to group 3 patients because anterior infarct patients with these combinations of risk factors are categorized in group 1.

A Cox regression model was applied to the group 1 data using PMI as a covariate. Ninety-nine patients without and 38 patients with PMI were used in the computation of the survival curves. The survival pattern of these two subsets is poor, particularly with respect to early mortality. The presence of PMI is associated with a considerable increment in mortality, even in this high-risk group.

### Table 5: Number of Patients with Various Risk Factor Combinations in Group III

<table>
<thead>
<tr>
<th>Risk factor combinations</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors</td>
<td>224</td>
</tr>
<tr>
<td>One risk factor (LVD or VPDs)</td>
<td>364</td>
</tr>
<tr>
<td>LVD and VPDs only</td>
<td>74</td>
</tr>
<tr>
<td>PMI only</td>
<td>31</td>
</tr>
<tr>
<td>PMI and LVD or VPDs</td>
<td>77</td>
</tr>
<tr>
<td>PMI, LVD and VPDs</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>803</td>
</tr>
</tbody>
</table>

Abbreviations: LVD = left ventricular dysfunction; VPDs = ventricular premature depolarizations; PMI = prior myocardial infarction.

**Figure 3.** Cox survival curves for group 3 patients without prior myocardial infarction. The group 3 patients are subdivided according to the presence or absence of left ventricular dysfunction (LVD) and/or ventricular premature depolarizations (VPDs).

**Figure 4.** Cox survival curves for group 3 patients with prior myocardial infarction. The group is subdivided according to the presence or absence of left ventricular dysfunction (LVD) and/or ventricular premature depolarizations (VPDs).
Age correction was performed on all the Cox survivorship analyses. After correction for the risk factors PMI, LVD, VPDs and anterior infarct location, age correction provided insignificant change in survival (<1% at 3 years) for all subgroups.

Discussion

The major findings of this study are: 1) patients with anterior MI do not do as well as patients with MIs at other sites; 2) the combination of anterior infarction with LVD and VPDs identifies a high-risk subset that makes up 15% of the MI population and has a 6-month mortality of 15%; 3) after exclusion of the aforementioned high-risk subset, each of the three factors PMI, LVD and VPDs has a significant yet independent influence on survival, with PMI having a greater effect on mortality than either LVD or VPDs; 4) a low-risk subset can be identified by the absence of PMI, LVD and VPDs (3-year survival 94%); and 5) the first 6-month posthospital interval is the period of greatest mortality risk, with a considerable reduction in the mortality rate thereafter.

The method of analysis applied in this study warrants some comment. Survivorship modeling uses the entire mortality experience of a sample from a population. In nonparametric modeling, the population survivorship function is derived from the sample survivorship experience. Parameter estimates of the survivorship function are not required. The Kaplan-Meier graphs presented in figures 1 and 2 are examples of this type of analysis. Parametric modeling assumes a mathematical form for the survivorship function that involves several parameters whose values are unknown. The data from a sample are used to estimate the parameters, and hence the survivorship function. The estimation of survivorship curves in both nonparametric and parametric modeling uses censored observations, i.e., follow-up observation of individuals who survived for a known yet variable period of time and did not die. The Cox life-table regression analysis is a semiparametric method that assumes that the hazard rate (the instantaneous probability of death) has the form

$$\lambda(t) \exp \left[ \sum_{i=1}^{m} \theta_i x_i \right]$$

where $\lambda(t)$ is an arbitrary function of time, and $\theta_1, \ldots, \theta_m$ are unknown parameters for concomitant factors $x_1, \ldots, x_m$. The Cox regression analysis estimates the parameters $\theta_1, \ldots, \theta_m$, i.e., coefficients for each factor in the model. Thus, the relative magnitude of each covariate factor to survival can be evaluated. This Cox survivorship analysis is quite different from the many multivariate linear and logistic regression techniques reported in epidemiologic cardiovascular studies. These techniques determine the importance of specific factors to outcome of a cohort over a fixed time period. Censored observations are not permitted, and all patients must be followed for the same period of time. Patients whose status during the study time interval is not known are deleted from analysis.

The four factors PMI, LVD, VPD and MIL used in the present study were selected on the basis of a screening univariate analysis. These factors have pathophysiologic meaning, and their association with increased postinfarction mortality is well documented. The current study extends previous observations by showing that the patients who have anterior infarcts with LVD and VPDs have a significantly reduced survival pattern compared with the remainder of the population, and that PMI has a greater effect on mortality than either LVD or VPDs. The historical covariate PMI reflects in some qualitative way coronary disease chronicity and a reduction in myocardial reserve function. It is not surprising that this variable has been identified as an important risk indicator in many postcoronary studies. LVD as evaluated clinically in the coronary care unit has been used in the Killip prognostic classification scheme and more recently, radionuclide ejection fraction determinations have substantiated more precisely the association between low ejection fraction and posthospital mortality. Using a Cox survivorship analysis, Ruberman et al. have shown the importance of complex VPDs as an independent risk indicator of postinfarction mortality. They used a sedentary 1-hour ECG recording obtained weeks to months after infarction, whereas a 6-hour ambulatory recording obtained before discharge was used in the present study. These procedural differences may explain why the more simplistic arrhythmia variable “any VPD” was an effective prognostic indicator in the Rochester study, but “complex VPDs” were required in the Ruberman study.
With regard to infarct location, the findings support the conventional view that anterior infarcts are associated with an increased mortality when compared with posterior and other locations. Miller et al. have suggested on the basis of biplane left ventricular angiography that anterior as opposed to inferior infarction is associated with greater reduction in left ventricular function as a result of the more extensive area of necrosis. However, a recent abstract that evaluated the relationship between site of infarction, infarct size and mortality revealed that creatine kinase infarct size was similar in anterior and posterior infarctions. This group concluded that the higher mortality associated with anterior infarction related to damage occurring solely in the left ventricle rather than being distributed in both ventricles, as with inferior infarction.

The clinical implications of the findings of the present study are multifold. First, a low-risk group can be identified. Patients without PMI, LVD or VPDs (n = 224) have a 97% 1-year and a 94% 3-year survival, regardless of infarct location. This low-risk group comprises about 24% of the total population, and obviously very little benefit would be gained by preventive intervention in these patients. In contrast, the highest risk group (n = 137), which involves patients with anterior infarction plus LVD and VPDs, makes up 15% of the population and has an 81% 1-year and a 70% 3-year survival. An intermediate-risk group, those not included in the low- and high-risk subsets, makes up 62% (579 of 940) of the population and has a 94% 1-year and an 89% 3-year survival. These intermediate- and high-risk groups would seem to have the greatest potential for mortality reduction by appropriate interventions after infarction. Furthermore, because mechanical (LVD) and electrical (VPDs) factors dominate the higher risk groups, it seems reasonable that combined therapeutic regimens involving afterload reduction and antiarrhythmic therapy would be necessary to improve survival.

The survivorship curve of the high-risk group (group 1 — anterior MI with LVD and VPDs), with its rapid and significant decline during the first 6-month posthospital interval, raises important considerations about future analyses and interventions. For example, a conditional survivorship analysis involving only the patients alive 6 months after MI and using follow-up information in combination with baseline data may optimize late posthospital risk stratification. This type of analysis may indicate the need for different intervention regimens at different chronologic intervals in the convalescent phase after MI.

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