Risk Stratification of Patients With Non-Q Wave Myocardial Infarction

The Critical Role of ST Segment Depression

Kenneth B. Schechtman, PhD, Robert J. Capone, MD, FACC, Robert E. Kleiger, MD, FACC, Robert S. Gibson, MD, FACC, David J. Schwartz, MD, FACC, Robert Roberts, MD, FACC, Phillip M. Young, PharmD, William E. Boden, MD, FACC, and the Diltiazem Reinfarction Study Research Group

One-year follow-up data on 515 patients who survived hospitalization with MB-creatine kinase–confirmed, acute non–Q wave myocardial infarction were analyzed for factors related to mortality (n=57) and late reinfarction (n=64). Twelve of 24 analyzed variables were significantly associated with mortality. Those factors, which were independently predictive of mortality by Cox regression analysis, were persistent ST depression (p=0.0009), a history of congestive heart failure (CHF) (p=0.0069), older age (p=0.0128), and ST elevation at hospital discharge (p=0.0173). In-hospital reinfarction achieved borderline significance (p=0.0512).

Mortality during the follow-up period was 5.5% in patients with no ST depression, 10.1% in those with ST depression at baseline or discharge, and 22.2% in patients with ST depression at baseline and discharge (i.e., “persistent” ST depression). The age-adjusted risk of mortality for patients with persistent ST depression, discharge-ST elevation, and CHF was 13.99 times as high as was the risk for patients with no ST depression, no discharge-ST elevation, and no CHF.

Of the 483 patients with complete electrocardiographic data at both baseline and discharge, 203 (42%) could be stratified into a high risk population with a risk ratio for 1-year mortality more than sevenfold that of patients with no risk factors. Although persistent ST depression was significantly associated with several measures of structural left ventricular damage, the independent significance of ST depression persisted even after adjusting for these factors. The independent predictors of late reinfarction (persistent ST depression, p=0.0058; Killip class II or III, p=0.0106; and left ventricular hypertrophy, p=0.0470) permitted a similar risk stratification. We conclude that 1) easily identified clinical and electrocardiographic factors permit stratification of patients with non–Q wave infarction into high-risk subsets who may benefit from aggressive therapy; 2) ST depression is a highly significant and independent predictor of poor prognosis; and 3) the powerful predictive value of persistent ST depression suggests that non–Q wave myocardial infarction patients with this depression should be viewed as potentially high-risk patients who may be candidates for additional noninvasive testing or early coronary angiography. (Circulation 1989;80:1148–1158)

Stratification of postmyocardial infarction (MI) patients into low- and high-risk subgroups is vitally important in the overall investigation and management of patients, both acute and long term. Risk stratification is particularly important during the first year after acute MI, the period during which the risk of recurrent infarction and sudden death is greatest. Previous studies that have identified high-risk subsets of patients with acute MI have included both Q wave and non–Q wave infarction.1–4 However, recent reports have delineated a distinctly different natural history for patients

From the Divisions of Biostatistics and Cardiology, Washington University School of Medicine, St. Louis (K.B.S., R.E.K.); the Division of Cardiology, Brown University, Providence (R.J.C.); Rhode Island; the Division of Cardiology, University of Virginia, Charlottesville (R.S.G.); the Division of Cardiology, Baylor College, Houston, Texas (R.R.); Marion Laboratories, Kansas City, Missouri, (P.M.Y.); the Division of Cardiology, Wayne State University, Detroit, Michigan (W.E.B.); Internal Medicine Group, Cheyenne, Wyoming (D.J.S.).

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Address for correspondence and reprints: Kenneth B. Schechtman, PhD, Washington University School of Medicine, Division of Biostatistics, 660 S. Euclid, Box 8067, St. Louis, MO 63110.

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with non-Q wave MI. Non-Q wave infarction is associated with less myocardial necrosis and with a lower in-hospital mortality than Q-wave MI. Nevertheless, despite this favorable early prognosis, long-term survival of patients with non-Q wave MI is similar to that of patients with Q wave infarction. The high-risk period after Q wave infarction lasts for perhaps 8–12 weeks, whereas, after non-Q wave infarction, there is a vulnerable period that is characterized by reinfarction and sudden death, and it persists for at least 1 year.

Several studies have noted that early postinfarction angina associated with transient electrocardiographic changes defines a high-risk subset of patients with non-Q wave MI. Others have hypothesized that many patients recovering from non-Q wave MI have extensive areas of jeopardized ischemic myocardium that results from an initial subtotal coronary occlusion. This incomplete infarction, together with insufficient or threatened collaterals, may create a vulnerability to repetitive ischemic events. If this hypothesis is correct, it may account, in some patients, for the comparatively poor long-term prognosis associated with this type of infarction. Despite the recognition that patients with non-Q wave MI have heterogeneous risk profiles, a prevalent belief has been that the only way to identify the high-risk population is to perform cardiac catheterization, exercise thallium scintigraphy, or, both, on all patients with non-Q wave MI. Nevertheless, no previous study conducted in an explicitly defined population of MB-creatine kinase (CK)–confirmed non-Q wave infarctions has examined, through multivariate analysis, which of several easily measured clinical and electrocardiographic parameters may have independent prognostic significance.

The purpose of the present study was to report the results of the 1-year follow-up on patients enrolled into the Diltiazem Reinfarction Study. The Diltiazem Reinfarction Study was a multicenter, double-blind, placebo-controlled, randomized clinical trial designed to determine whether prophylactic diltiazem would reduce the rate of in-hospital reinfarction in patients with MB-CK–confirmed non-Q wave MI. This report defines a set of routinely available parameters that permit the delineation of differential risk strata for 1-year mortality and late reinfarction in patients with non-Q wave MI. The analysis indicates that ST segment depression that is present at both hospital admission and discharge is a powerful independent predictor of adverse long-term outcome and that a small and easily identified set of predictor variables permits stratification of patients with non-Q wave MI into high- and low-risk subsets that warrant differential diagnosis and therapy.

Methods

The data base produced by the Diltiazem Reinfarction Study contains information on 576 patients with MB-CK–confirmed non-Q wave acute MI. To minimize the number of enrolled patients who would later develop Q waves, randomization did not occur until at least 24 hours after admission. The latest allowable randomization time was 72 hours after admission. Complete details of the organization and conduct of the Diltiazem Reinfarction Study have been reported elsewhere.

Follow-up Procedures

Although the primary focus of the Diltiazem Reinfarction Study involved blinded therapy only during the acute hospitalization, the follow-up protocol was prospectively designed and implemented. Follow-up telephone interviews were conducted by institutional study coordinators both 6 months and 1 year after the index infarction. Information about mortality, recurrent MI, rehospitalization, and the frequency of coronary artery bypass surgery or angioplasty was collected from patients and physicians and, in the case of deceased subjects, from family members, friends, physicians, and hospital records. Death was defined as sudden if it occurred within 1 hour of the onset of symptoms. However, because of the inherent uncertainty involved in establishing the precise cause of death, data analysis focused on all-cause mortality.

Clinical and Laboratory Evaluation

After randomization, the following evaluations were performed: 1) daily clinical evaluation by the investigator; 2) 12-lead electrocardiogram on enrollment and daily for the first 5 days, followed by every other day, thereafter, for 14 days or until hospital discharge; 3) electrocardiogram at the time of recurrent pain and for a minimum of 3 consecutive days if reinfarction was suspected; and 4) serial blood samples for analysis of total CK and MB-CK activity. Sampling times consisted of an initial sample at the time of randomization. This was followed by samples drawn every 12 hours, thereafter, throughout the study. Additional samples were obtained at least every 8 hours for the subsequent 72 hours in patients in whom reinfarction was suspected. All protocol samples were forwarded to the CK core laboratory for quantitative analysis of plasma MB-CK activity by the batch-adsorption glass-bead method.

Electrocardiographic Analyses

Four sequential electrocardiograms from each of the 576 randomized patients were analyzed by five investigators blinded to treatment assignment and the clinical outcome of patients. One fourth of the ECGs were interpreted randomly and independently by all investigators to ensure the reproducibility of their results. The remainder were divided evenly among the five readers. Any ECG that was considered ambiguous in any way by one of the assigned readers was evaluated by all five investigators until a consensus was reached. Serial trac-
ings at baseline (i.e., the most representative ECG obtained on admission before entry into the trial), on study day 2, study day 3, and predischarge were analyzed. For the purposes of this study, we decided prospectively to consider only the baseline and predischarge electrocardiograms. Thus, we cannot be certain that these are the most informative electrocardiograms and have no data regarding changes in ECG parameters that occurred between baseline and discharge. The mean time of randomization was 50±10 hours after onset of myocardial infarction, and the predischarge electrocardiogram was obtained at 11.0±3.5 days. The baseline (admission) tracing was available on all patients, whereas a predischarge tracing was available in 93% (533 of 576) of the sample.

Patients included in the Diltiazem Reinfarction Study were defined electrocardiographically by the absence of new abnormal Q waves (i.e., <0.03 seconds in duration in two leads within a given lead group or the absence of R waves>0.04 seconds in lead V1, and an R-to-S ratio >1 in lead V5). In the absence of new Q waves, patient enrollment required the diagnosis of infarction as defined by elevated MB-CK activity in plasma in 2 or more samples taken at least 4 hours apart and either 1) ischemic chest pain of at least 30 minutes duration or 2) new ST segment elevation or depression of at least 0.1 mV or new T-wave inversion in 2 or more of the inferior, anterior, or lateral leads. Acute ST-T-wave abnormalities were not absolute prerequisites for trial entry.

Definition of Predictor Variables

The variables that were investigated as potential predictors of 1-year mortality and late reinfarction included the following:

First, significant ST-segment shifts were defined as the presence of at least 1 mm of ST segment elevation or depression (or in the presence of left ventricular hypertrophy, at least 2 mm of ST segment depression) in at least two leads within a given non-Q wave MI location: anterior, leads V1–V4; lateral, leads I, aVL, V5, and V6; inferior, leads II, III, and aVF. ST segments shifts were identified at 80 m/sec after the J point. When electrocardiograms acquired before the index infarction were available and showed ST segment shifts, corresponding deviations were defined as being present for the purpose of this study only if the magnitude of shift on the study electrocardiogram was greater than the magnitude on the old electrocardiogram. Old electrocardiograms were available for about half of the total sample and about three fourths of those with previous symptomatic ischemia. Thus, there may be a small number of patients who are defined in this report as having ST segment shifts when, in fact, those shifts are of remote origin.

Second, an acute non-Q wave MI was characterized as localizable if ST segment elevation, ST segment depression, or T wave inversion was present in accordance with the above definition in at least one of the three infarct locations (anterior, lateral, or inferior).

Third, in-hospital reinfarction during the first 14 days after the onset of acute MI was defined as an increase of 50% or more in plasma MB-CK activity above baseline (mean of two preceding samples) in at least two samples, separated by a minimum of 6 hours within a 24-hour interval, with an absolute value of 14 or more IU/l in at least one sample.

Fourth, post-infarction angina associated with electrocardiographic changes was characterized by a new occurrence of typical ischemic chest pain during the 2-week study that was not associated with abnormal reelevation in plasma MB-CK activity and that was accompanied by concurrent transient ST segment or T wave changes.

Fifth, left ventricular hypertrophy was defined electrocardiographically by the presence of one or more of the following voltage criteria: R in I plus S in III greater than 25 mm; R in aVL greater than 11 mm; S in V1–V3 greater than 25 mm; R in V1 or V6 greater than 25 mm; S in V1 plus R in V5 or V6 greater than 35 mm; or S in V2 plus R in V6 greater than 35 mm. Because the trial design did not include two-dimensional echocardiography, radionuclide ventrigulography, or coronary angiography on all patients, the diagnosis of left ventricular hypertrophy was made on electrocardiographic grounds only.

Sixth, other predictor variables. A total of 24 variables were used as potential univariate predictors of 1-year mortality and reinfarction in this report. These included the above factors with ST segment elevation and depression analyzed at both study entry and hospital discharge. Additional predictor variables include male gender; smoking; obesity; age; assignment to the diltiazem-treatment group; T wave inversion; anterior infarct location; peak CK on the index infarction; Killip class II or III; postinfarction angina with or without electrocardiographic changes; progression to Q wave MI during hospitalization; and a history that predates the index non-Q wave MI of coronary artery bypass surgery, previous MI, hypertension, congestive heart failure, or diabetes. All predictor variables except for age and peak CK were dichotomous. Peak CK values were adjusted to account for different definitions of a “normal range” at the sites participating in the Diltiazem Reinfarction Study. The use of Killip class II or III as a predictor variable reflected the exclusion of patients in Killip class IV from the Diltiazem Reinfarction Study. For use in multivariate analysis, a single three-category measure of ST segment depression was defined. These categories were defined by 1) ST depression at neither baseline nor discharge; 2) ST depression at baseline or discharge, but not at both time points; and 3) ST depression at both baseline and discharge.
Statistical Analysis

Data were analyzed using the STATISTICAL ANALYSIS SYSTEM,22,23 as implemented on the Washington University IBM mainframe computer system. Continuous data are expressed as mean±SD. Gehan’s generalized Wilcoxon test was used to compare Kaplan-Meier survival curves.24 The ratio of the risk of late mortality and late reinfarction (defined as mortality or reinfarction between hospital discharge and 1 year) among different groups of patients was estimated using the hazard-function ratios computed by Cox regression.25 The Cox model was also used to determine which variables had independent significance as predictors of mortality and late reinfarction. When the end point of the analysis was mortality or reinfarction, a Cox model that considered time to the first event in patients who reinfarcted and died at a later time was used. All reported p values reflect two-sided hypothesis tests. Because of its skewed lognormal distribution, adjusted peak CK was analyzed after logarithmic transformation. Comparison of time to death among the three groups of patients characterized by the persistence of ST depression was done by analysis of variance. Because a data transformation of time to death that produced normal distributions with equal variance in all three groups could not be found, this analysis was performed on the ranks of the data.26 Confidence bounds on risk ratios are based on the Mantel-Haenszel estimate.27

Results

Of the 576 patients randomized to the Diltiazem Reinfarction Study between July 1982 and April 1985, 32 were excluded from this report because of the subsequent determination that pathologic Q or R waves were present at baseline. Additional exclusions include 16 patients with confirmed non-Q wave myocardial infarction who died in hospital. Of the remaining 528 patients, follow-up data was obtained on 515 (98%). Baseline electrocardiographic data were available on all 515 patients, whereas discharge electrocardiograms were available on 484 patients. Of the 484 patients with discharge electrocardiograms, there was one patient on whom ST elevation data were not recorded.

One-Year Mortality

Univariate analysis. The 1-year postdischarge actuarial mortality in this cohort of non-Q wave MIs was 11%. This represents a total of 57 deaths, 19 of which were sudden (33.3%), and 10 of which were noncardiac or of unknown cause, during the follow-up period. The univariate relation between 22 dichotomous predictor variables and mortality is summarized in Table 1. Eleven of these variables were significantly associated with mortality (p<0.05 for a two-sided generalized Wilcoxon test). Among these 11 variables, the unadjusted risk of 1-year mortality of those with the risk factor compared with those without the risk factor ranged from a low of 1.74 for left ventricular hypertrophy to a high of 2.95 for discharge ST depression and 3.35 for a history of congestive heart failure. In addition, the relations between mortality and age and between mortality and peak CK on the index infarction were considered. Peak CK values of 629±681 IU among those who survived did not differ from the CK values of 615±618 IU among those who died. However, patients who died were significantly older than those who survived (66.5±10.8 versus 60.6±7.7 years, p<0.0001). The unadjusted risk ratio for a 70-year-old compared with a 50-year-old patient was 3.21. Variables with highly significant univariate p values of less than 0.01 included baseline ST depression (p=0.004; 1-year mortality, 15.4% with and 6.2% without baseline-ST depression); discharge-ST depression (p<0.0001; mortality, 19.9% versus 7.4%); Killip class II or III (p=0.0002; mortality, 21.1% versus 8.4% for Killip class I); a history of diabetes (p=0.0010; mortality, 20.2% versus 8.9%); a history of congestive heart failure (p<0.0001; mortality, 23.4% versus 7.7%); and age (p<0.0001).

The low p value attached to both baseline and discharge ST depression, coupled with the much greater prevalence of baseline ST depression (52.8% versus 30.2%), suggested that those variables be combined into a single three-category predictor that measures the persistence of that factor. Among the 484 patients on whom ST depression data were available at both baseline and discharge, 1-year mortality was 5.5% (11 of 199; 95% confidence bounds, 2.3–8.7%) in patients with ST depression at neither time point (group 1); 10.1% (17 of 168; confidence bounds, 5.6–14.7%) in patients with ST depression at exactly one time point (group 2); and 22.2% (26 of 117; confidence bounds, 14.7–29.8%) when ST depression was present at both time points (group 3).

Figure 1 compares the survival pattern of these three groups of patients. Survival in group 3 differed significantly from survival in each of the other two groups (p<0.0001 when compared with group 1 and p=0.0031 when compared with group 2). Groups 1 and 2 were not quite significantly different (p=0.0834). Unadjusted relative risks for mortality were 4.02 (group 3 versus group 1), 2.20 (group 3 versus group 2), and 1.83 (group 2 versus group 1). These data demonstrate that the persistence of ST depression is an important univariate predictor of 1-year mortality.

Multivariate analysis. Cox regression analysis was performed to determine which factors had independent significance as predictors of mortality. Variables included in the model were those with significance (p<0.05) summarized in Table 1, except that the single three-group measure of the persistence of ST depression was substituted for the two dichotomous measures of ST depression at baseline and at discharge. Table 2 indicates that the independent predictors were persistent ST depression...
(p=0.0009), a history of congestive heart failure (p=0.0069), age (p=0.0128), and discharge ST elevation (p=0.0173). In-hospital reinfarction, the primary end point of the Diltiazem Reinfarction Study achieved borderline independent significance (p=0.0512). Because reinfarction had marginal significance and a low prevalence in this population (6.4%), its use in such a model would yield risk strata with very few patients. Thus, this variable is omitted from the ensuing discussion of age-adjusted mortality-risk ratios. Patients with discharge ST elevation were characterized by a strong tendency to progress to Q wave MI during the index hospitalization (rate of progression is 26.2% among those

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<th>TABLE 1. Univariate Associations With Late Mortality and Late Reinfarction</th>
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<td>Male gender</td>
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<td>T wave inversion</td>
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<td>Localizability</td>
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<td>Left ventricular hypertrophy</td>
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<td>Hypertension</td>
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<td>Congestive heart failure</td>
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**Figure 1.** Kaplan-Meier survival curves for patients with no ST depression (group 1), ST depression at baseline or discharge (group 2), and ST depression at baseline and discharge (group 3). Mortality was 5.5% in group 1 (n=199), 10.1% in group 2 (n=168), and 22.2% in group 3 (n=117).
with versus 10.4% among those without discharge ST elevation, \( p < 0.0001 \). Although it was not significant \( (p = 0.119) \), there was a trend suggesting that patients with discharge ST elevation \( (n = 145) \) may have had a better prognosis if they did progress to Q wave MI in hospital \( (1\text{-year mortality, } 7.9\%) \) than if they did not progress \( (\text{mortality, } 18.7\%) \).

**Risk stratification.** Figures 2A and 2B summarize the age-adjusted risk of 1-year mortality for patients with various combinations of independent risk factors compared with patients with no ST depression \( (\text{group 1}) \), no congestive heart failure, and no discharge-ST elevation. Compared with this group without risk factors, the risk of mortality in group 2 patients with no other risk factor was 1.82. Persistent ST depression by itself yielded an age-adjusted risk ratio of 3.32. The risk ratio of a history of congestive heart failure by itself was 2.18, whereas patients with both persistent ST depression \( (\text{group 3}) \) and congestive heart failure had more than sevenfold the age-adjusted mortality risk of patients with none of these three risk factors. Figure 2B indicates that these risk ratios were approximately doubled in patients whose profile also included discharge-ST elevation in leads other than those that showed ST depression. Thus, a group 3 patient with both discharge ST elevation and CHF had an age-adjusted risk of 1-year mortality that was 13.99-fold the risk of a patient with none of the three risk factors.

The independent significance of ST depression, a history of CHF, and discharge ST elevation permitted stratification of patients into low-, medium-, and high-risk categories according to the number of these risk factors that were present. Accordingly, we defined a low-risk stratum as one consisting of patients with none of these risk factors; a medium-risk stratum as one containing patients with precisely one risk factor but without persistent ST depression; and a high-risk stratum as one with patients who have at least two risk factors or have

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**Table 2. Independent Predictors of Mortality**

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<th>Predictor</th>
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<td>Persistent ST depression</td>
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<td>Congestive heart failure</td>
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<td>Age</td>
<td>0.0128</td>
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<tr>
<td>Discharge ST elevation</td>
<td>0.0173</td>
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**Figure 2.** Bar graphs of age-adjusted risk ratios for one-year mortality among patients with \( (\text{Panel A}) \) and without \( (\text{Panel B}) \) discharge ST elevation. Each histogram represents patients with some combination of ST depression and CHF. All risk ratios are compared with patients having no ST depression, no CHF, and no discharge ST elevation.
related to ST depression in patients with and in patients without angina associated with electrocardiographic changes.

In addition to a strong relation between ST depression and mortality, there was a clear association between the time from onset of MI to death and the category of ST depression. Among the 57 deaths, there were 54 who had electrocardiographic data at both baseline and discharge. Among these deaths, those without ST depression lived a mean of 249 ± 103 days; those with ST depression at a single time point lived 158 ± 115 days; and those with persistent ST depression lived 111 ± 102 days. The difference in time to death between groups 1 and 3 was highly significant \((p = 0.0011)\), whereas the other pairwise differences were not quite significant (group 1 versus group 2, \(p = 0.0886\); and group 2 versus group 3, \(p = 0.0741\)).

### Late Reinfarction

**Univariate analyses.** Data relating to late reinfarction were analyzed with procedures that corresponded precisely to those used for mortality. The 1-year posthospital actuarial reinfarction rate was 13% and represented a total of 64 events. Variables with significant univariate associations with late reinfarction (Table 1) included baseline ST depression \((p = 0.0125, 15.9\% \text{ reinfarction rate with, compared with } 9.4\% \text{ without baseline ST depression})\); discharge ST depression \((p = 0.0002, 21.0\% \text{ reinfarction rate with, versus } 9.1\% \text{ without})\); Killip class II or III \((p < 0.0001, 23.8\% \text{ versus } 9.9\%); left ventricular hypertrophy \((p = 0.0050, 20.7\% \text{ versus } 10.5\%); a history of congestive heart failure \((p = 0.0232, 19.0\% \text{ versus } 11.2\%); diabetes \((p = 0.0465, 18.9\% \text{ versus } 11.4\%); and age \((p = 0.0047)\), with those who reinfarcted being 3.7 years older \((64.5 \pm 10.1 \text{ versus } 60.8 \pm 9.8 \text{ years})\) than those who did not reinfarct. Reinfarction rates were 7.8% \((15 \text{ of } 192); 95\% \text{ confidence bounds, } 4.0–11.2\%\) among patients without ST depression, 12.3% \((20 \text{ of } 163); \text{ confidence bounds, } 7.2–17.3\%\) in patients with ST depression at exactly one time point; and 21.4% \((24 \text{ of } 112); \text{ confidence bounds, } 13.8–29.0\%\) in those with ST depression at both time points. This total population of 467 excludes 17 patients with follow-up mortality data in whom information about reinfarction was unavailable. Figure 3 contains the Kaplan-Meier reinfarction curves for group 1 (no ST depression), group 2 (ST depression at exactly one time point), and group 3 (ST depression at both time points). The reinfarction rate in group 3 differed significantly from the corresponding rates in the other two groups \((p = 0.0003 \text{ versus group } 1; \text{ and } p = 0.0165 \text{ versus group } 2)\). The difference between groups 1 and 2 was not significant.

**Risk stratification.** Independent predictors of reinfarction were determined by a Cox model that included the three-group measure of persistent ST depression and the five other significant univariate predictors. Persistent ST depression \((p = 0.0058), \text{ Killip class II or III } (p = 0.0106), \text{ and left ventricular hypertrophy } (p = 0.003)\).
LATE REINFARCTION BY CATEGORY OF ST DEPRESSION

FIGURE 3. Kaplan-Meier curves for cumulative incidence of late reinfarction for patients with no ST depression (group 1), ST depression at baseline or discharge (group 2), and ST depression at baseline and discharge (group 3). Late reinfarction rates were 7.8% in group 1, 12.3% in group 2, and 21.4% in group 3.

Hypertrophy (p=0.0470) were the only independent predictors of reinfarction (Table 4). The independent significance of these variables permitted stratification into low- and high-risk strata. The high-risk stratum contained all patients with persistent ST depression or with at least two other risk factors, with ST depression at a single time point being defined as a risk factor in this definition. Low-risk patients had, at most one risk factor and did not have persistent ST depression. The reinfarction rate was 20.2% (36 of 178; 95% confidence bounds, 14.3–26.1%) in the high-risk group and 8.0% (23 of 289; confidence bounds, 4.8–11.1%) in the low-risk group. The relative risk of reinfarction in the high-compared with the low-risk stratum was 2.54 (p<0.0001, confidence bounds, 1.56–4.14).

Predictors of Death or Reinfarction

There were 94 patients who either reinfarcted or died during the 1-year follow-up period. The same 24 variables that were used to predict mortality and reinfarction separately were analyzed to assess their relation with the occurrence of either of these events. A Cox model, which analyzed time to first event, found four variables that were independently predictive of the combined event. These were persistent ST depression (p=0.0004), age (p=0.0104), discharge ST elevation (p=0.0135), and Killip class (p=0.0335). Analysis of risk ratios yielded conclusions similar to those described separately for mortality and reinfarction.

Twenty-seven of the 64 patients who had reinfarctions died subsequent to that event. Thus, we compared the fatal with the nonfatal reinfarctions with respect to the identified risk factors. Although the statistical power for these comparisons was low due to the small number of reinfarctions, there were trends (p<0.1) suggesting that mortality was higher after reinfarction among patients with persistent ST depression (mortality was 58.3% in group 3 versus 34.3% in groups 1 or 2, p=0.068), angina with ECG changes (66.7% versus 36.5%, p=0.057); Killip class II or III (56.0% versus 33.3%, p=0.073), congestive heart failure (60.0% versus 34.1%, p=0.052), and previous MI (59.3% versus 40.7%, p=0.090).

**Discussion**

Several reports have documented the favorable early prognosis of patients with non–Q wave myocardial infarction. Non–Q wave infarction is typically associated with less myocardial damage than Q wave infarction. Such events are smaller by enzymatic, radionuclide, and echocardiographic estimates of infarct size and generally are associated with less myocardial dysfunction. Non–Q wave MI is also characterized by a decreased frequency of total occlusion of the infarct-related coronary artery, possibly because of early reperfusion resulting from spontaneous thrombolysis, a cessation of vaso-spasm, or both. However, despite their favorable early outcome, non–Q wave MI patients 1) are more likely to demonstrate residual ischemia as detected by exercise thallium scintigraphy; 2) have a higher reinfarction rate than Q wave infarction; and 3) have a long-term prognosis that is essentially the same as that of Q wave infarction, although some studies have shown a better 1- or 2-year survival rate. Because it appears that the prevalence of non–Q wave MI is increasing, with the increased availability of therapeutic interventions such as calcium antagonists, $\beta$-blockers, coronary bypass surgery, and angioplasty, the desirability of characterizing risk strata in non–Q wave MI patients has increased.

**One-Year Mortality**

The data from several studies indicate that patients recovering from acute non–Q wave MI, who have
residual ischemia, are at high risk of developing more ischemically mediated events including reinfarction, sudden death, and progressive myocardial necrosis leading to congestive heart failure. Although the present study does not include direct measure of residual ischemia, our data appear to be concordant with this hypothesis. We previously reported, in preliminary form, that ST depression on both the baseline and the discharge electrocardiogram are associated through univariate analysis with increased long-term mortality. Based on observations from the MILIS study, Willich et al.22 have also emphasized the poor prognosis in non-Q wave MI patients who present with ST depression. They reported that ST depression is a more important risk factor in non-Q wave MI patients than ST elevation, despite the fact that the latter group have larger infarcts. The results of our study confirm and extend Willich’s observations and demonstrate also that the persistence of ST depression during hospitalization for acute non-Q wave MI defines an important and independent risk categorization for adverse long-term outcome. Thus, 1-year mortality in patients without ST depression was 5.5%, approximately 10% with either entry- or discharge-ST depression, and 22% with both. Of all the independent clinical and electrocardiographic predictors of mortality, persistent ST depression was the strongest. The other independent predictors included age, congestive heart failure before admission, and ST segment elevation at discharge. Any of these risk factors plus persistent ST depression markedly increased the mortality risk. For example, the age-adjusted risk ratio of CHF by itself was 2.18, but the age-adjusted mortality risk among patients with CHF and persistent ST depression was more than seven-fold the corresponding risk in patients with none of the identified risk factors. Discharge ST elevation had a similar but less marked effect.

The data summarized in Figures 2A and 2B are striking in the degree to which they demonstrate a gradation in ascending risk with each added risk factor. However, many of the individual subsets summarized in those figures represent a few patients yielding wide confidence bounds on risk ratios and a corresponding uncertainty that the precise pattern observed within these small categories would be repeated in a second data set. Nevertheless, the independent significance of each variable was clear from the Cox models we have presented. Moreover, the risk strata we have defined provide confidence bounds that demonstrate the usefulness of these variables, and in particular of ST depression, in stratifying the risk of patients with non-Q wave infarction. The low-risk stratum consisted of 25.3% of the total sample and had an observed 2.5% mortality rate. The 32.7% of the sample in the medium-risk stratum (mortality 7.6%) had an unadjusted relative risk of 3.09 compared with the low-risk group. Moreover, of particular importance, the unadjusted relative risk of the high-risk stratum, a group that contained 42% of the total sample and had a mortality of 19.2% was 7.81-fold as great as the risk of the low-risk stratum. Associated confidence bounds on risk ratios were 3.10–19.72 (high versus low-risk groups), 1.42–4.51 (high versus medium), and .96–10.0 (medium versus low).

Late Reinfarction

Late reinfarction occurred in 13% of patients and, as with mortality, showed a strong relation to persistent ST depression. Other independent predictors were LVH and Killip class of more than I. In combination, these 3 factors permitted stratification into easily defined groups of low and high risk for reinfarction. Thus, an apparently homogeneous group of non-Q wave MI patients could be stratified into subgroups with markedly different risks of either death or reinfarction. The prospective application of such risk stratification techniques may form the basis of a useful triage system to determine the advisability of both diagnostic and therapeutic interventions such as coronary angiography, percutaneous transluminal coronary angioplasty, coronary bypass surgery, and intensive medical therapy.

Limitations of the Study

The results of this report emphasize that easily obtained clinical and electrocardiographic parameters can identify subsets of patients with non-Q wave MI that have adverse long-term outcome. However, several considerations suggest the need for more comprehensive, prospective investigation. The follow-up used in our study yielded precise information about mortality but not about cause of death. Thus, we did not assess the association between the risk factors we have defined and cause-specific mortality. By trial design, noninvasive and invasive studies were not uniformly performed on all study participants, a circumstance that made it difficult to determine whether additional noninvasive diagnostic procedures such as ambulatory ECG recordings, stress thallium scintigraphy, two-dimensional echocardiography, or radionuclide ventriculography could further aid in the process of risk stratification. In particular, we do not have data on left ventricular ejection fraction, which can influence outcome importantly. In addition, we did not collect follow-up data on the use of diltiazem. The principal significance of this report was the identification of factors that can delineate differential risk strata early in the course of non-Q wave MI. These observations should provide the basis for performing a more comprehensive prospective analysis of other variables that might refine our ability to stratify risk in these patients.

Potential Implications

This study was not intended to be an investigation into the mechanism of persistent ST depression. However, these findings are consistent with the hypotheses10,14,32,33 that 1) non-Q wave MI
patients have large residual areas of hypoperfused and ischemic myocardium subtended by a critically stenosed or subtotally occluded infarct-related coronary artery, 2) ST segment depression in non-Q wave MI may represent a clinical model of “hibernating myocardium” due to inadequate or threatened collaterals, or 3) that persistent ST depression may be a manifestation of “silent myocardial ischemia,” which predisposes this subgroup to a higher incidence of subsequent cardiac events. Alternatively, it is possible that structural changes (i.e., cumulative post-MI left ventricular damage) may play an important role in the high-risk profile associated with non-Q wave MI patients who exhibit persistent ST depression.

Because we do not have data on ejection fraction, we cannot address the degree to which ST depression reflects “hibernating” or “stunned” myocardium and the degree to which this has contributed to the left ventricular dysfunction associated with congestive heart failure. Moreover, we believe that the presence of ST depression does not represent a reciprocal change in these patients because, by design, patients were enrolled 24–72 hours after admission. This ensured the elimination of all patients with high-magnitude ST segment elevation and attendant reciprocal ST depression indicative of evolving Q wave MI. Moreover, when ST depression was accompanied by ST elevation, they were usually found in the same lead group, mostly anterior, and with ST elevation being of small magnitude and in leads V1 and V2.

Although a significant role for structural changes in explaining the genesis of persistent ST depression is consistent with our data, this depression retained its independent importance after statistical adjustment for variables reflecting left ventricular injury. In particular, this was true of all the markers of structural damage summarized in Table 3, despite their strong relations with ST depression. Furthermore, the risk ratio for those with persistent ST depression compared with those without ST depression was substantial, regardless of patient status on such variables as congestive heart failure, ST elevation, Killip class, and left ventricular hypertrophy. Peak CK was not included in this formulation because this variable was not associated with either mortality or reinfarction and because it did not differ according to category of ST depression. This was not surprising because any potential role for peak CK was obscured by its low magnitude and narrow range in these non-Q wave MI patients.

The therapeutic implications of managing the non-Q wave MI patient with persistent ST depression are presently unclear. This is particularly true of the asymptomatic patient. However, our data demonstrate that these patients can be stratified into high- and low-risk subsets. Furthermore, these data indicate that persistent ST depression, whether in the presence or absence of angina, is a powerful predictor of adverse long-term outcome. On the basis of these findings, non-Q wave MI patients with persistent ST segment depression should be viewed as potentially high-risk patients who may be candidates for additional noninvasive diagnostic testing or early coronary angiography.

References


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