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# Post Myocardial Infarction Risk Stratification: 1991 Perspective

Michael Lesch, MD\*

The prospective identification of subsets of post myocardial infarction (MI) patients at risk for increased cardiac mortality or morbidity has been termed "post-MI risk stratification." By virtue of the research effort devoted to this topic, a number of risk stratification variables have been identified and utilized to develop management strategies for post-MI patients. Definition of these techniques and strategies represents significant accomplishment, yet algorithms capable of defining specific risk categories in individual patients have yet to be developed. This goal remains the objective of much research because the need to develop improved risk stratification strategies is pressing and apparent from a number of perspectives.

Achievement of accurate stratification methodologies would allow for: 1) improved post-MI care with resultant decreased mortality and morbidity; 2) cost-efficient care (targeting expensive therapies and/or diagnostic techniques to populations likely to benefit from them); 3) rapid identification of different pathophysiologic mechanisms that could guide specific therapy; 4) cost-efficient treatment trials since smaller numbers of patients would need to be enrolled in cooperative protocols if endpoint incidence could be predicted more accurately; and 5) the development of post-MI care guidelines for different patient subsets based upon hard data, thus alleviating arbitrary regulatory mechanisms presently utilized by third-party bodies to control costs.

The impetus to develop post-MI risk stratification strategies developed soon after research in the coronary care unit (CCU) identified strategies capable of defining in-hospital morbidity and mortality for the MI patient (1,2). Most studies of in-hospital mortality and morbidity also observed increased mortality in post-MI patients in the period following discharge from the hospital regardless of apparent patient status (3-7). When controlling for all known predictors of mortality and morbidity in coronary disease (ventricular function, symptomatic state, presence of congestive heart failure, and arrhythmia status), a comparison of patients with chronic stable coronary disease to matched controls who were 0 to 18 months post MI revealed that the latter group experienced significantly increased mortality and morbidity. This single factor—the inordinately high morbidity and mortality of the immediate post-MI period—stands as the epidemiologic imperative defining the necessity to develop improved post-MI risk stratification strategies. The early post-MI period is a perilous interval for the patient with coronary disease and offers a window of opportunity in which finite benefit can be provided to this patient population. Thus, while risk stratifi-

cation has been a continuous theme of research in coronary artery disease for many years, the realization that the post-MI state carries added risk for the coronary patient has served to focus attention on this particular time period.

The importance of defining quantifiable variables capable of predicting risk not only in defined populations but also in individual patients was widely recognized by the mid 1970s, receiving particular impetus from the work of Arthur Moss (8) at the University of Rochester, NY, and J. Thomas Bigger (9) of Columbia University. The current post-MI risk stratification literature is too large to be reviewed comprehensively in a single article. Therefore, this article will focus on the following aspects of the risk stratification literature: 1) current concepts of post-MI risk stratification, 2) methodologies used to stratify risk with particular emphasis on problems inherent to such methodologies, and 3) specific problems regarding the application of post-MI risk stratification studies to clinical practice.

## Post-MI Risk Stratification: Current State of the Art

In 1987, Moss et al (7) observed in their review that six major pathophysiologic considerations formed the conceptual framework for post-MI risk stratification: 1) infarct size, 2) ventricular function, 3) ventricular arrhythmias, 4) anginal status, 5) stress testing, and 6) coronary angiography. While new techniques relevant to these six parameters have been introduced since 1987, they can be analyzed within the format of the 1987 article with a few notable exceptions. Thus, dipyridamole perfusion imaging with thallium can be considered a variant of stress testing while the signal-averaged ECG and analysis of heart rate variability can be considered new methods for assessing the potential for serious ventricular arrhythmia. Conversely, the potential role of silent ischemia, thrombolytic therapy, and the concept of patent infarct-related arteries as determinants of post-MI risk are not so easily accommodated within the conceptual context of the 1987 article. The original Moss-Bigger-Odoroff format will thus be utilized herein to present currently available data with additional headings added as necessary to accommodate post-1987 concepts.

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## Infarct size

The importance of infarct size in determining MI prognosis was initially established from autopsy studies of patients with cardiogenic shock or pump failure. These quantitative pathologic studies correlated pump failure to the total amount of necrotic myocardium, demonstrating that pump failure occurred when more than 40% of the left ventricle had become infarcted. Moreover, the timing of such necrosis was found not to be of importance (e.g., a single recent episode causing infarction of 40% of the left ventricle was equivalent to an old 20% infarct and a recent 20% infarct) (10-12). Recognition of the importance of infarct size as a determinant of survivorship prompted investigation of techniques for measuring infarct size *in vivo* in acute MI patients. The original goal of measuring infarct size precisely and accurately in units of mass of infarcted myocardium was not fully realized as the complexity of measuring infarct size became apparent (13). However, while precise measurement of infarct size might not be possible, semi-quantitative estimation of relative infarct size was feasible (14). When these techniques for semi-quantitative estimation of infarct size were used to stratify risk in surviving MI patients, an unequivocal relationship between infarct size and mortality (both early and late) was established (7,14,15). This relation remains the keystone of risk stratification to this day. Issues concerning infarct size that have not been definitively dealt with to date despite significant discussion in the literature relate to the equivalency of equally sized infarcts in determining post-MI risk, when infarcts are subcategorized as to type (Q wave versus non-Q wave infarcts) (16,17), location (anterior versus inferior) (18), or specific electrophysiologic effect (heart block, conduction disturbance, etc.) (19,20).

## Ventricular function

Post-MI ventricular function, ostensibly a surrogate measurement of infarct size, has been directly measured both invasively (21) and noninvasively (22) as well as indirectly estimated by a variety of techniques ranging from clinical examination (23) to chest x-ray analysis (24) to an ECG scoring system (25). The pathologic data referenced above (10-12) have been evaluated relative to ventricular function in survivors of acute MI and summarized by Petch (26) as follows:

"There is a good relationship between the amount of left ventricular damage and the resulting physiology; less than 10% loss and there is merely some reduction in left ventricular ejection fraction, 15% loss is associated with elevation of filling pressure, 25% loss results in clinical cardiac failure, and 40-50% results in cardiogenic shock."

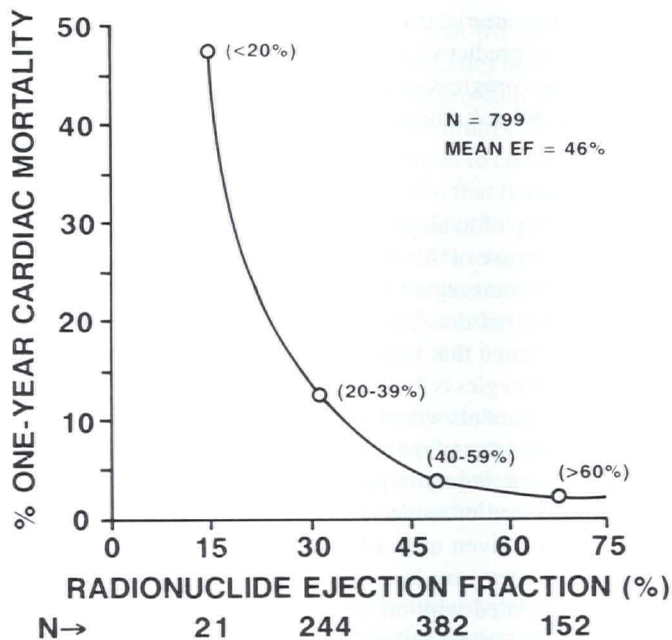
Despite the multiplicity of techniques available for the post-MI estimation of left ventricular (LV) function and the numerous time points during and after hospitalization at which such determinations could be made, multiple-gated image acquisition (MUGA) measurement of ejection fraction predischARGE has achieved *de facto* "gold standard" status as the technique of choice. This status presumably derives from two factors: the landmark data obtained from MUGA ejection fractions as re-

ported by the Multicenter Postinfarction Research Group (22) in 1983, and the combined widespread availability and ease of reproducibility of this technique.

The landmark 1983 study (22) demonstrated a curvilinear relationship between one-year post-MI cardiac mortality and pre-discharge MUGA ejection fractions (Figure). While mortality was minimally increased at decreasing levels of ejection fraction down to the 40% range, a dramatic increase in mortality was noted at ejection fraction levels below 35%. All studies published on this topic, regardless of methodology utilized to measure LV function, confirm this general conclusion (7,21). Although discrepancies may exist as to what specific numerical value for risk should be attributed to any given degree of ventricular dysfunction, the general curvilinear relationship between decreased ventricular function and increased post-MI mortality is accepted as fact.

## Arrhythmia analysis

Attempts to predict the risk for subsequent ventricular arrhythmia (ventricular tachycardia/ventricular fibrillation [VT/VF]) and sudden cardiac death in post-MI subsets based upon analysis of ambulatory ECG recordings were derived from early CCU experience. The latter demonstrated ventricular ectopic activity (VEA) to be a harbinger of more advanced forms of ventricular arrhythmia (VT/VF) in the setting of acute infarction and that pharmacologic suppression of this VEA significantly reduced the occurrence rate of VT/VF (17). To hypothesize that VEA occurring in the post-hospital phase of coronary artery disease might have similar significance and that chronic antiarrhythmic therapy might have similar beneficial effect seemed reasonable and a logical extension of known fact at the time (27). Consequently, numerous centers tested the first half of this hypothesis by obtaining pre or post discharge ambulatory ECGs of various duration in MI patients and correlating the ECG data *vis-à-vis* VEA to post-MI endpoints (usually sudden cardiac death) (28). Although it appeared evident that the presence of VEA was statistically associated with increased risk for subsequent cardiovascular morbidity, consensus could not be reached regarding the precise quantitative implication of VEA. The inability to define with great precision the implications of VEA in the post-MI period was to a significant degree related to two specific issues. First, there was no quantitative grading system for VEA which accounted for both arrhythmia frequency and severity (29). No techniques existed then or now which would allow for assessment of a single run of 3 beat VT on a 24-hour tape as compared to one demonstrating five unifocal premature ventricular contractions per minute in each minute of the day. One is more "severe," the other is more "frequent." The question of which, if either, carries greater prognostic significance remains unanswered. Second, data accumulated indicating that VEA was not an independent marker of adverse prognosis, but rather a dependent variable related primarily to compromised ventricular function (30-34). Numerous studies of the correlation between LV dysfunction and VEA supported the concept that VEA was a surrogate marker of myocardial scar and thus ventricular dysfunction. Moss et al (7) addressed this issue and examined the data base from two large MI studies wherein both



Figure—Cardiac mortality rate in four categories of radionuclide ejection fraction determined before hospital discharge after myocardial infarction. (From the Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *New Engl J Med* 1983;309:331-6. Reprinted with permission.)

LV function and VEA had been tabulated as a function of post-MI mortality. They concluded that repetitive VEA (> 10 premature ventricular beats/hour) was strongly correlated to mortality even after adjusting for LV dysfunction. VEA and LV dysfunction were shown in this analysis to be independent contributors to post-MI mortality, with the predicted mortality for a patient with both VEA and LV dysfunction being greater than the arithmetic sum of each individual risk factor. In other words, the two risk factors positively interacted.

Attempts to use "stress testing" as a modality to expose latent risk for arrhythmic death in post-MI populations have been disappointing. Treadmill testing to induce arrhythmia in the exercise state (7,35) (also see section entitled Exercise Testing) has not provided improved prognostic indices in the post-MI patient. Initial experiences with electrophysiologic testing to induce arrhythmia with different stimulation protocols indicated this technique was of marginal value in predicting the likelihood of subsequent arrhythmia in the post-MI population (7,36). Recent experiences have demonstrated greater predictive value for the technique (37,38), although the failure of this methodology to gain wider clinical acceptance within the cardiology community at large represents indirect support for the skepticism expressed in an editorial review (39) of one of these latter (38) publications.

Two new methodologies not based upon the presence, absence, or inducibility of VEA have recently drawn attention as techniques potentially capable of predicting risk of VT/VF in post-MI populations. The "signal-averaged ECG" takes advan-

tage of the observation that direct intraoperative epicardial electrograms, obtained at or near foci of spontaneous VT/VF generation in patients undergoing mapping studies, reveal fractionation of the terminal portion of the QRS, implying some form of disordered impulse conduction at those sites. This fractionation is not discernible with routine surface ECGs due to the very low signal-to-noise ratio inherent to ECG signals in this portion of the QRS complex. These observations stimulated development of a technology to evaluate dispersion of terminal QRS forces from surface ECGs by subjecting surface ECG data to "signal averaging" so as to amplify the low voltage signals of interest. While some initial reports suggest that an abnormal signal-averaged ECG in the post-MI period may be predictive of subsequent risk for VT/VF, many details with this approach need to be worked out before it can be considered clinically useful (40-45).

Analysis of heart rate variability is a second, ambulatory monitor-based, non-VEA-dependent methodology presently being evaluated as a post-MI risk stratification variable (46-48). This technique takes advantage of the observation that normal cardiovascular function is characterized by a rather large variation in heart rate throughout the day. Conversely, progressive degrees of impaired cardiovascular function, and thus presumably increased risk for sudden cardiac death, is characterized by decreased heart rate variability. This technique, like the signal-averaged ECG, may hold significant promise as a risk stratification variable. However, the two techniques share the common drawback of not yet having been studied adequately for this purpose to be of proven clinical utility.

### Postinfarction angina

The long-term prognostic implication of anginal syndromes in the immediate post-MI phase is not likely to be investigated further given recent conceptual changes regarding our understanding of the mechanisms operative in the pathophysiology of postinfarction angina and infarction (49,50), the introduction of thrombolytic and anticoagulant therapy (51), the widespread availability of percutaneous transluminal coronary angioplasty, and the commonly held precept that postinfarction angina implies the need for revascularization therapy (52,53). In the current therapeutic climate, the pressure to treat post-MI ischemia manifesting as anginal pain is so overwhelming that a controlled study designed to analyze the prognostic implication of angina in the immediate post-MI period is not feasible. The consensus that MI patients who manifest early post-MI ischemia are at greater risk than those without such manifestations is based upon considerable experience and probably should be accepted.

### Exercise stress testing

The specificity and sensitivity of exercise stress testing using the ECG, LV function analysis, or perfusion scanning either singly or in combination for the detection of coronary artery disease have been well delineated (54-58). Although the sensitivity and specificity of these techniques are far from perfect and the precision and accuracy with which they can predict future morbid events are even less perfect, data derived from these tests have been developed into meaningful algorithms for evaluation

of the patient with stable ischemic heart disease. In patients with stable documented or suspected coronary disease, the utility of stress testing is largely due to the use of standardized protocols for test performance and interpretation. A similar degree of "standardization" is not available in post-MI stress testing. Different centers utilize different exercise protocols and endpoints and perform the test at different times post-MI, thus making it impossible to develop any general statement about this procedure. As exemplified by a number of recent publications, not much consensus exists as to what specific endpoints in what specific protocols have what specific implication in the post-MI population at large (59-64). While there appears to be some agreement that ST segment depression is not as important an endpoint and that evidence of LV dysfunction (maximum metabolic equivalents achieved, blood pressure response) is more important as compared to similar testing in chronic stable populations, post-MI stress testing remains a commonly used procedure in clinical practice which remains incompletely defined and characterized.

### Coronary angiography

The pattern of the progression of coronary atherosclerosis was initially defined from serial angiographic analysis. The major conclusion derived from these studies which analyzed retrospectively populations of patients who had undergone angiography on at least two occasions for diverse reasons was that progression of coronary atherosclerosis is unpredictable (65-67). In these studies high-grade lesions frequently were found to be stable over many years while total occlusions developed within a short term at sites which had been normal or minimally diseased at the time of initial study. This observation was confirmed prospectively in a post-MI population by Little et al (68). These investigators performed angiography on a MI population at or around the time of the index MI. Those patients not subjected to revascularization procedures who sustained a subsequent MI were submitted to repeat angiography at the time of the second event to define the culprit lesion and/or infarct-related artery of the second event. The data indicated that the vascular site responsible for the second MI could not be predicted on the basis of lesion anatomy defined by the angiogram performed immediately after the first MI.

These puzzling data went unexplained until Davies and others (49-51) demonstrated, using pathologic technique and analysis, that the rapid deterioration (development of infarction or an unstable anginal syndrome) of a patient with previously stable coronary atherosclerosis was due not to progression of the atherosclerotic process but to the rupture of the fibrous cap overlying atherosclerotic lesions and the subsequent formation of total or subtotal occlusive thrombotic plugs at the rupture site as blood was exposed to the thrombogenic influence of the lipid and collagen which comprise the bulk of an atherosclerotic lesion. It was further demonstrated that the likelihood of fibrous cap rupture was not related to the initial degree of lesion severity, thus explaining the previously enigmatic "random" progression of coronary atherosclerosis.

In view of these considerations, coronary angiography is best conceptualized as a technique for evaluating the anatomic status

of the coronary arterial tree at a given point in time. It offers little in the way of predictive capability regarding either the site or rate of disease progression and is thus of limited value as a predictive post-MI risk stratification variable.

### New concepts

The majority of available post-MI stratification data predate the widespread use of thrombolytic therapy. It is unclear if presently held concepts regarding stratification need to be modified in the thrombolytic era. One concept emanating from the thrombolytic experience that may significantly impact stratification studies and strategies is that of the "patent infarct-related artery" (69). In some patients where thrombolysis is achieved, it occurs too late to salvage any myocardium. Patients left with such an infarct and a patent infarct-related artery experience fewer episodes of death and/or sudden cardiac death following infarction. Patients with a given mass of infarcted tissue and a patent infarct-related artery are less likely to have electrophysiologic findings associated with an increased risk for sudden cardiac death (70-76) compared to patients with an occluded infarct artery. If these findings are substantiated, the implication for the routine management of post-MI patients will be profound. Such substantiation would justify attempts to open infarct-related arteries, even after infarction has occurred, with thrombolytic or mechanical approaches.

A second emerging concept relative to post-MI stratification relates to the general topic of silent ischemia (77,78). The significance and relevance of silent ischemia is presently being evaluated in numerous subsets of coronary disease patients, and a firm statement relative to post-MI stratification would be premature. What is apparent at this juncture, however, is that ischemia, be it painful or painless, is of definite significance in patients with coronary disease. Whether these two syndromes are of "equal" significance and prognostic importance remains to be determined.

### Methodologic Problems Inherent to Post-MI Risk Stratification Studies

All risk stratification studies test the general hypothesis that a particular study parameter (e.g., LV function, arrhythmia status, heart rate variability, exercise tolerance), when measured at some defined time point (e.g., on admission to CCU, before CCU discharge or at hospital discharge), defines subset groups within a large MI patient population with different risks for certain predetermined endpoints (e.g., death, sudden cardiac death, reinfarction, unstable angina, or need for revascularization surgery). Patient populations used for these studies have been obtained retrospectively (79), prospectively (80), or by a combination approach with retrospective analysis of a data base obtained from MI patients studied for some other protocol (7).

In recent years clinical investigators have become sensitive to (and more sophisticated with) statistical issues in clinical research. Accordingly, most post-MI risk stratification studies demonstrate considerable expertise regarding both the statistical definition of the MI population(s) studied, the data to be analyzed, and the techniques utilized for analysis. Despite the vig-

orous statistical techniques applied to post-MI risk stratification studies, conclusions drawn from such studies remain potentially inaccurate due to the very nature of the problem being studied.

All attempts to study post-MI risk stratification, no matter what inclusion/exclusion criteria are used to construct the study group(s), perforce make the assumption that the study group(s) is(are) statistically identical. This assumption requires that the MI population be homogeneous or, if heterogeneous, that the statistical variation raised by such heterogeneity can be overcome by studying increased numbers and thus "averaging out" any differences. The probability that these requirements can be achieved is questionable.

The inherent, complex heterogeneity of the MI patient population and the potential fallacy behind the strategy of averaging out hidden differences between such populations by studying large numbers of patients have been previously discussed by Kelly (81) who states:

"A further caveat is that, while management and treatment in our contemporary medical times is determined by the response of a large series of patients in controlled trials, physicians treat individuals, and it is he or she who must have risk determined, investigated, and treated appropriately. Although most series, and particularly those evaluating treatment following myocardial infarction, contain large numbers of patients, it is important and cannot be emphasized strongly enough that these patients represent the pooled data base of patients of diverse ages, disease states, and thus prognosis. While such information from these studies is valuable, myocardial infarction is not a homogeneous entity. It is complex and heterogeneous and this again emphasizes that the physician must evaluate each individual patient."

Issues such as differences in age, sex, number of previous infarcts, infarct location, and infarct type (Q wave versus non-Q wave) are further discussed by Kelly (81). Topics which are more complex and are not discussed, thus posing greater statistical methodologic challenges, include the following:

1. In studies of patients with first MIs, the historical presence/absence of angina is frequently tabulated, but the clinical and temporal pattern of the angina is usually not. Two patients with a first MI and a history of angina will be inappropriately considered statistically identical even if in one the anginal pattern was of a chronic stable type of five years' duration while in the second there was a five-day history of acute onset unstable angina.

2. In patients with second MIs, how should the duration between the historical MI and the index MI be dealt with? Should one consider patients with a second MI to be statistically identical if the duration between MIs is two weeks versus two months versus two years versus two decades?

Many more examples of true infarct population heterogeneity, despite apparent statistical homogeneity, could be provided. The issue to recognize is that just as there exists no American family with 2.3 children and 1.7 parents living at home, there exists no average infarct patient. The concept of an average infarct population, while scientifically valid in the statistical sense for analysis of population subsets, suffers from an inability to mod-

el adequately the multiple complexities of the infarct population so as to make comparisons between a given individual patient and the average population valid. Alternatively stated, our inability to define all pertinent patient variables when attempting to study post-MI risk stratification results in our statistical approach being inadequately "robust."

A second methodologic problem inherent to all post-MI risk stratification studies is best described as "endpoint ambiguity." The term ambiguity is used because death, reinfarction and/or the development of angina, or the need for revascularization are commonly used as endpoints in post-MI risk stratification studies. The use of such endpoints mandates the assumption that the particular endpoint under consideration either results from, is directly caused by, or is an immediate complication of the index MI, i.e., the MI which caused the patient to be entered into the study in the first place. Because coronary atherosclerosis tends to be a progressive disease, such progression is not necessarily limited to the infarct-related artery of the index MI, and progression in non-infarct-related arteries can also result in death, reinfarction and/or the development of angina, or the need for revascularization, and thus ambiguity results. If a subject in a post-MI risk stratification study experiences sudden death six to 12 months post-MI, how can it be determined whether that episode of sudden cardiac death was mediated by the scar and/or resultant ischemia related to the index infarct as opposed to progression of atherosclerosis and/or acute thrombotic occlusion of a remote non-infarct-related artery? The death, while considered a hard endpoint for the study, is nonetheless an ambiguous endpoint since it cannot definitely be considered as a complication of the original infarct.

### Future Challenges: Statistical Significance Versus Clinical Importance

This review has attempted to analyze for the clinician the present status of post-MI risk stratification. The obvious conclusions from the material presented are that, statistically speaking, the worse the LV function, the greater the degree of arrhythmia or potential for arrhythmia, and the greater the degree of residual ischemic myocardium at risk, the worse the prognosis. While different mortality/morbidity rates can be defined for population subsets, and statistical significance of these differences calculated, the accurate calculation of a precise risk for a given patient is not yet possible.

There is yet another caveat about post-MI risk stratification. Using the data in the Figure as a prototype, the issue raised is that while specific factors which carry exceedingly high risk for mortality or morbidity can be identified (e.g., LV ejection fraction < 20%), the fraction of MI patients that fall into these high-risk categories is so small that the total number of morbid events accounted for by the "high-risk group" represents the minority of events that occur in the total MI population. The data from the Figure are presented in tabular form in the Table which includes a data set for absolute number of deaths accounted for in each LV ejection fraction subgroup. From the Table, the following is obvious: 1) of 64 total deaths, only 10 (16%) occurred in the highest risk group; 2) the two lowest risk subgroups accounted

**Table**  
**Mortality Rate and Absolute Numbers of**  
**Deaths as a Function of LVEF\***

LVEF	Number of Patients	Mortality Rate	Calculated Number of Deaths
< 20%	21	47%	10
20%-39%	244	12%	29
40%-59%	382	5%	19
> 60%	152	4%	6

\*Data from the Figure presented in tabular form.  
 LVEF = left ventricular ejection fraction.

for a total of 25 deaths (39%); and 3) depending upon the value chosen to represent the true inflection point of the curve depicted in the Figure, since the group defined as having LV ejection fractions in the 20% to 39% range clearly straddles this point, it is highly probable that more than 50% of the total deaths occurred in patients with a LV ejection fraction > 35%, i.e., a subgroup defined as being at low relative risk. When a similar analysis is applied to any other stratifying variable in any of a number of studies, a similar pattern emerges. Thus, one must conclude that presently recognized risk stratification strategies do not identify the majority of patients who will experience morbidity or mortality in the dangerous interlude that follows acute MI. Alternatively stated, while it takes no great cardiologic wisdom in 1991 to recognize that a post-MI patient with an LV ejection fraction of < 20%, high-grade VEA, and poor exercise tolerance is at high risk for cardiac mortality and morbidity, it remains frustrating that the majority of patients experiencing early post-MI morbidity are relatively healthy in a cardiac sense, insofar as our major stratifying variables are concerned. The challenge of the future is not only to prolong the life of the patient with poor LV function and arrhythmia but also to identify why and who of the ostensibly healthy post-MI patients will experience early morbidity or mortality.

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