Changing Late Prognosis of Acute Myocardial Infarction

Impact on Management of Ventricular Arrhythmias in the Era of Reperfusion and the Implantable Cardioverter-Defibrillator

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In science, generally to solve one set of problems may be to create or discover a whole new set, and of no science is this more true than in medicine.

George P. Elliott, The American Scholar, 1975

Sudden cardiac death (SCD) causes approximately 3 million fatalities in the United States annually.1 With the advent of the implantable cardioverter-defibrillator (ICD), an intervention that reduces the risk of arrhythmogenic death is available.2-4 The challenge is to identify risk factors for SCD among most patients at relatively low risk, specifically including survivors of acute myocardial infarction (MI), in an era when the prognosis is substantially better than before the widespread use of reperfusion therapy. As in the description of medicine in the epigraph above, reperfusion therapy has solved one set of problems, but the improved prognosis has generated a whole new set of questions about risk stratification. This review discusses risk stratification in contemporary cardiology for patients after acute MI.

Case Illustration

A 54-year-old man was admitted to the hospital after he experienced severe chest pain for approximately 8 hours. He had an acute anterior Q-wave infarction, and he underwent coronary angiography with subsequent recanalization of a totally occluded left anterior descending coronary artery. In addition, the right coronary artery showed a 50% narrowing. At the time of discharge, echocardiography demonstrated a left ventricular ejection fraction of 33%. Exercise stress testing revealed no evidence of ongoing myocardial ischemia. The patient requested advice concerning his risk for subsequent arrhythmias and SCD.

Epidemiological Impact of Risk Stratification

To be epidemiologically meaningful, prognostic tests must have a high positive predictive accuracy with a reasonable degree of sensitivity to ensure that the findings are not restricted to a small minority of patients. The first step toward this goal requires knowledge of the total number of sudden deaths within a specific patient population expressed as a fraction of total mortality within this group. Thus, for an intervention specific for SCD, one must not only identify survivors of acute MI who are at high risk for death but also predict whether arrhythmic or...
nonarrrhythmic death is more likely. Patients for whom arrhythmic death is more likely may benefit from preventative antiarrhythmic interventions (such as ICD implantation), whereas such treatment may provide no advantage for patients for whom nonarrrhythmic death is more likely.

For risk stratification to be clinically useful, the methods must be applicable not only to specialized referral centers but also to community hospitals in which the majority of patients with acute MI receive care. For this reason, invasive procedures are unlikely to gain widespread acceptance; consequently, current research focuses on the development of noninvasive methods of risk stratification. Because the highest risk of SCD is within the first 12 months after the index MI and the majority of events occurs within the first few months, another prerequisite for risk stratification for arrhythmic death is that it be initiated in the predischarge period.

Bayesian Approach to the Impact of the Changing Prognosis on Tests for Risk Stratification
Bayesian principles are commonly used to evaluate the incremental value of a new test for the diagnosis of coronary artery disease, but these basic concepts can be extended to various tests for prognosis. Bayesian principles can facilitate an understanding of the effect of a lower event rate on the utility of tests for risk stratification, such as for survivors of acute MI in the contemporary era. This approach indicates that the post-test probability of disease or an event can be calculated from the sensitivity and specificity of the test and the pretest probability, and that the post-test probability can be plotted graphically (Figure 2).

For death or arrhythmic events after an MI, line B in Figure 2 represents an intermediate probability of an event occurring; line A, a low probability; and line C, a high probability. Irrespective of whether the test results are positive or negative, the event rate for a high probability (for example, SCD or late ventricular arrhythmias) is high and the event rate for a low probability is low. Accordingly, for patients with a high or low probability of an event, the test does not provide substantial incremental value beyond the pretest knowledge of the likelihood of an event. However, among patients with an intermediate probability of an event occurring, the difference in outcomes between a positive and negative test result is substantial.

Implications of Reperfusion Therapy on the Mechanisms of Ventricular Arrhythmias
The genesis of sustained ventricular arrhythmias is based on complex interactions among an arrhythmic substrate, triggering factors, the modulating influence of the autonomic nervous system, the electrolyte milieu, and other undefined variables.

Substrate
Clearly, reperfusion reduces infarct size, improves left ventricular function and ventricular remodeling, and, in many patients, reduces recurrent ischemia. Further evidence that the arrhythmic substrate is altered in patients with a patent infarct-related artery or in those receiving thrombolytic therapy is provided by a series of other studies that demonstrate a lower frequency of late potentials in such patients.

Triggers
Reperfusion has little effect on the frequency of potential arrhythmic triggers, such as ventricular extrasystoles and nonsustained ventricular tachycardia (VT). Differences are modest in the frequency of premature ventricular complexes (PVCs) between patients studied in the pre-reperfusion era and those in the more contemporary series. Similarly, the
frequency of nonsustained VT among a series of patients (60% of whom received thrombolytic therapy) does not seem to be substantially different from that of earlier studies.

**Modifying Factors**

The autonomic nervous system is a pivotal modifier of arrhythmic risk according to both experimental and clinical data. Studies of patients after infarction have demonstrated that baroreflex sensitivity as a marker of sympathetic-parasympathetic balance is substantially and unfavorably increased in patients with an occluded infarct-related artery compared with survivors of MI who have a patent infarct vessel. Similarly, studies using heart rate variability for assessment of cardiac autonomic tone have conclusively demonstrated that reperfusion therapy is associated with preservation of vagal tone.

**Interactions**

What is far more striking, however, is the reduction in the positive predictive value of known triggering factors such as PVCs and nonsustained VT in contemporary studies. Moreover, even markers of an arrhythmic substrate have lost much of their prognostic significance in patients who have received reperfusion therapy. A lower incidence of sustained VT or ventricular fibrillation in patients with risk factors previously demonstrated to have high predictive value reflects the altered arrhythmogenic milieu after successful reperfusion and contemporary adjunctive therapy.

**Current Approaches to Risk Stratification in the Overall Population of Survivors of MI**

**General**

The overall reduction in late cardiac mortality and ventricular arrhythmias poses a formidable challenge in the identification of the relatively few individuals who have a major arrhythmic event. Nonetheless, the increasingly favorable prognosis, both early and late after MI, does not negate the value of a search for new methods of risk stratification, which remain a pivotal component of the assessment of the survivor of MI. According to Bayesian principles, the goal of risk stratification is to identify which patients in a group with a low pretest likelihood of an event occurring are, in fact, at intermediate risk and are most likely to receive the greatest incremental benefit from diagnostic testing (Figure 2).

**Clinical and Demographic Data**

The GISSI-2 (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico II) trial of 10,219 hospital survivors who received thrombolytic therapy identified the following clinical variables (listed in order of importance) that were independently predictive of 6-month mortality: 1) ineligibility for an exercise test (for cardiac or noncardiac reasons); 2) early left ventricular failure; 3) left ventricular dysfunction in the recovery phase; 4) age older than 70 years; 5) electrical instability; 6) late left ventricular failure; 7) prior MI; and 8) history of hypertension. For example, in a study of 103,164 patients with MI who were 65 years or older, a single-risk model (including older age, comorbidity, heart failure, reduced left ventricular ejection fraction [LVEF], and peripheral vascular disease) effectively stratified patients according to their risk of death 1 year after discharge.

**Stress Testing**

Several studies examining the role of treadmill exercise testing for survivors of MI demonstrated that patients without ST-segment depression had a lower mortality (2% to 3%) than patients with ST-segment depression (approximately 19%). In contrast, the GISSI-2 trial, which compared 2 thrombolytic regimens, demonstrated that 6-month mortality was similar between patients with positive stress test results and patients with negative results, and the main determinant of prognosis was whether the patient had an exercise test.

**Ventricular Function**

Although the proportion of patients with impaired left ventricular function has declined after reperfusion therapy, the correlation between impaired LVEF and late mortality persists. Nonetheless, compared with earlier studies, recent series suggest that the curve relating mortality to ejection fraction has shifted to the left, implying that for a given degree of left ventricular dysfunction, the increase in mortality is somewhat less than previously reported (Figure 3). Another study emphasized the importance of impaired diastolic function, the predictive power of which was independent of LVEF.

**Ambulatory Monitoring**

The Beta-blocker Heart Attack Trial (BHAT) and other studies confirmed a strong association between the frequency of PVCs and mortality. However, the futility of using only PVCs as markers for SCD in a contemporary patient population is demonstrated by 6-month survival data from the GISSI-2 trial. An increasing frequency of PVCs was associated with a statistically significant increase in total mortality: 2% for patients with no PVCs, 2.7% for patients with 1 to 10 PVCs/h, and 5.5% for patients with 10 PVCs/h (SCD rates were 0.6%, 0.8%, and 2.1%, respectively). Similarly, in the Canadian Assessment of Myocardial Infarction study, the frequency of PVCs was similar to that described in the prethrombolytic era (Multicenter Postinfarction Research Group study), as was the relationship to mortality. What is striking, however, is the reduction in the proportion of patients with left ventricular dysfunction in the more recent group. These data were statistically significant but not clinically relevant because the rate of events was so low.

Another example relates to the presence of nonsustained VT on electrocardiographic monitoring. In studies conducted before the widespread use of reperfusion therapy in acute MI, nonsustained VT was a marker for increased risk of subsequent death from any cause or from arrhythmia. In the thrombolytic era, the prognostic
The significance of nonsustained VT is more controversial. Signal-Averaged Electrocardiography

For the prediction of late ventricular arrhythmias and SCD, several studies attested to the value of signal-averaged electrocardiography and programmed ventricular stimulation. Subsequent studies, however, drew attention to the markedly lower positive predictive value of both tests in patients with a patent infarct-related artery and in those who received thrombolytic therapy. In these studies, the tests were not altered, but the patient population undergoing testing changed, resulting in the same tests being applied to patients who had a lower risk of recurrent ischemic or arrhythmic events.

Measures of Cardiac Autonomic Control

Cardiac autonomic control is important in the genesis of life-threatening ventricular arrhythmias. There is evidence that markers of impaired autonomic tone such as heart rate variability (HRV) and baroreflex sensitivity (BRS), which are considered to be indicators of cardiac autonomic control, are useful prognostic indicators of the risk of arrhythmic death. After extensive evaluation of these 2 risk stratifiers in several retrospective studies, investigators in the Autonomic Tonus and Reflexes After Myocardial Infarction (ATRAMI) study performed a definitive prospective study of HRV and BRS determination for risk stratification after acute MI. In the ATRAMI study, prospectively defined cutoff values were used for both BRS and HRV, markers of autonomic nervous system activity. The trial enrolled 1284 survivors of MI (63% receiving thrombolytic therapy), and risk stratification including determination of HRV and BRS was performed for all participants at the time of hospital discharge. Both markers of autonomic tone were found to yield high predictive power for subsequent cardiovascular mortality.

Invasive Electrophysiological Testing

An analysis of 11 studies of programmed electrical stimulation in 1314 patients after an MI demonstrated a 23% arrhythmic event rate among patients with inducible VT or ventricular fibrillation and an event rate of only 5% among patients without inducible arrhythmias. In patients with nonsustained VT, the corresponding rates were 14% and 6%, respectively. Nonetheless, the lack of specificity and a growing disenchantment with antiarrhythmic drugs led to less use of this invasive approach to pre-discharge risk stratification. This perception is further supported by the Multicenter UnSustained Tachycardia Trial (MUSTT), in which patients had a worse prognosis even if arrhythmias were not inducible in the electrophysiology laboratory.

Noncardiac Risk Factors

Risk stratification of survivors of MI is primarily based on the use of traditional measurements that reflect the presence of left ventricular dysfunction, electrical stability, ischemia, and comorbidity. What should not be overlooked, however, is an assessment of the whole patient, including the patient’s age and psychosocial and socioeconomic status. Although the nontraditional psychosocial risk factors are difficult to quantify, abundant evidence links psychosocial influences such as education, income, isolation, stress, and depression with increased mortality, probably mediated by altered cardiac autonomic tone, which is manifested by either increased sympathetic or decreased parasympathetic nervous system activity.

Recommendations for a Stepwise Approach to Risk Stratification for Ventricular Arrhythmias in Asymptomatic Patients After Reperfusion Therapy

For survivors of MI complicated by congestive heart failure, recurrent ischemia, or arrhythmias, there is little controversy about the role of an aggressive therapeutic strategy, including the implantation of an ICD. There is, however, a lack of consensus about the optimal and most cost-effective ap-
proach to the predischarge assessment of the asymptomatic patient who had reperfusion therapy within 6 hours, or at the most 12 hours, after the onset of symptoms and who had an uncomplicated clinical course. Available data integrated into a Bayesian approach suggest the following stepwise approach to arrhythmic risk stratification in survivors of predischarge MI.

First, measurement of the ejection fraction is logical, particularly because in trials comparing ICD use with antiarrhythmic therapy, the benefit from ICD therapy was greatest in patients with ejection fractions of 35% or less. However, these randomized controlled trials do not directly apply to survivors of predischarge MI because such patients were excluded from the trials. Also, the measurement of ejection fraction before discharge is made at only 1 point in time. In a trial of placebo versus ramipril, 58% of patients with anterior acute MI and left ventricular dysfunction on day 1 improved within 90 days, and 22% had full recovery. Still, it seems that the most practical time to assess ejection fraction as a starting point for risk stratification is before discharge, particularly because a substantial proportion of fatal events occurs during the early postdischarge period.

Second, among patients with a preserved LVEF (ie, ≥45%), no further testing is indicated other than a stress test before discharge, primarily to define pulse and blood pressure guidelines for the cardiac rehabilitation period and to detect recurrent myocardial ischemia. In this patient group, the yield of arrhythmia risk stratification is too low to be cost-effective.

Third, in the event that left ventricular function is depressed, a reasonable strategy may be to extrapolate from the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and MUSTT and perform ambulatory monitoring. For patients with nonsustained VT, invasive electrophysiologic testing may be pursued, and in patients with inducible sustained arrhythmias, this would be followed by the implantation of an ICD. In the MADIT II study, patients were assigned randomly to receive either ICD therapy or no ICD therapy solely on the basis of the finding of an LVEF less than 31% after MI. After enrollment of 1232 patients, the trial was stopped because of a significant reduction in all-cause mortality in patients with an ICD. However, neither of these trials applied directly to survivors of predischarge MI because in all 3 trials, patients were enrolled late after their index MI. Moreover, MADIT II applies only to patients with an LVEF less than 31%. At present, it is reasonable to extrapolate the MADIT II results to survivors of early postinfarction with ejection fractions of 30% or less but with the caveat that in some patients, a subsequent improvement in ventricular function may occur; such patients were not included in MADIT II. For patients with an ejection fraction of 30% to 45%, MADIT II again does not answer the question, and perhaps the strategy used before MADIT II, based on the MUSTT and MADIT I trials, still applies. Regardless, there is a burning need to identify additional noninvasive methods of risk stratification (ie, baroreflex sensitivity, heart rate variability, or T-wave alternans assessment) within the population of patients with ejection fractions less than 30%.

**Ongoing Studies Evaluating the Value of Risk Stratification Early After MI**

Two trials, the Defibrillator IN Acute Myocardial Infarction Trial (DINAMIT) and the BEta-blocker STRategy plus Implantable Cardioverter Defibrillator (BEST-ICD) trial, will help to define the role of new antiarrhythmic agents, particularly prophylactic ICD therapy, in high-risk patients surviving acute MI. In contrast to MADIT and MUSTT, these trials will more closely approximate the early peri-infarction period because patients will be randomly assigned at an earlier stage before discharge. The period immediately after this event, which is the time of highest risk for arrhythmic events, will be investigated by these studies. Besides allowing evaluation of the effectiveness of the respective treatments, results of these trials will help to establish the future role of methods of risk stratification.

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