

# The Changing Prognosis of Myocardial Infarction in the Reperfusion Era: Implications for Evaluation and Management of Ventricular Arrhythmias

Bernard J. Gersh

Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA.

The prognosis of patients with ischemic heart disease has improved markedly with the introduction of reperfusion therapy and with aggressive efforts to modify risk factors. Consequently, the rate of cardiovascular events after myocardial infarction has decreased to approximately 5% over a period of 2 years as compared with the 20% to 30% reported in the prethrombolytic era. In this context, it is unlikely that the results of previous studies in the prereperfusion era can be applied to this group of patients. Others have demonstrated that the identification of subgroups of patients at greater risk and the search for new risk markers can significantly improve survival of patients who are at high risk despite reperfusion therapy. For example, it was found in the GISSI-2 study that unsuitability for exercise stress testing was associated with a mortality of 7% at 6 months. Other factors that determine poor prognosis after myocardial infarction are transitory heart failure, left ventricular dysfunction, and advanced age. The active search for new risk markers has identified other factors such as nonresolution of ST-segment changes, impaired ventricular filling, anomalous baroreflex sensitivity, or T-wave alternans that may be of benefit in assessing risk. Also, the timing of risk stratification can be critical. Often, risk factors have been analyzed weeks or even months after infarction instead of before hospital discharge. Approximately 30% of patients have deterioration of left ventricular function in the next 2 or 3 months, whereas others have improvement, highlighting the difficulties in attempting to risk stratify at one point in time. Although nobody doubts the effect that coronary revascularization has had on the prognosis of ischemic heart disease or the effectiveness of aspirin,  $\beta$ -blockers, lipid-lowering drugs, and angiotensin-converting enzyme inhibitors, the search for cardiac or noncardiac risk markers can contribute notably to increasing the survival of patients who have had myocardial infarction.

**Key words:** *Baroreflex sensitivity. Decreased ventricular filling. Ejection fraction. Mortality. ST segment. T-wave alternans. Ventricular arrhythmias.*

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## El pronóstico cambiante del infarto de miocardio en la era de la reperfusión: implicaciones para la evaluación y el tratamiento de las arritmias ventriculares

El pronóstico de los pacientes con cardiopatía isquémica ha mejorado notablemente con la instauración de la terapia de reperfusión que, además, se ha acompañado de una modificación agresiva de los factores de riesgo. En consecuencia, la tasa de episodios cardiovasculares después de un infarto de miocardio ha descendido aproximadamente a un 5% a los 2 años, comparado con el 20-30% que se registraba en la era pretrombótica. En este contexto, no es probable que los resultados de estudios previos en la era de la reperfusión se puedan aplicar a este grupo de pacientes. Algunos trabajos que abordan esta cuestión han demostrado que la identificación de subgrupos de pacientes con un riesgo mayor y la búsqueda de nuevos marcadores de riesgo pueden aportar mejoras significativas en la supervivencia de los pacientes que se encuentran en una situación de mayor riesgo, a pesar de la terapia de reperfusión. Así, por ejemplo, en el estudio GISSI-2 se observó que la no idoneidad para realizar la prueba de esfuerzo se asociaba a una mortalidad del 7% a los 6 meses. Otros factores que determinan un mal pronóstico tras un infarto de miocardio son la insuficiencia cardíaca transitoria, la disfunción ventricular izquierda y la edad avanzada. La búsqueda activa de nuevos marcadores de riesgo está permitiendo incluir en esta lista otros factores como la no resolución del segmento ST, la presencia de un llenado restrictivo, la sensibilidad barorrefleja anómala o la onda T alternante, que puede ser beneficioso para la valoración del riesgo. Por otra parte, el momento en el que se estratifica el riesgo de un paciente puede ser decisivo. A menudo, los factores de riesgo que se han investigado corresponden a estudios que no analizan la estratificación del riesgo antes del alta hospitalaria sino semanas e incluso meses después de producirse el infarto. Aproximadamente un 30% de pacientes sufre un

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Correspondence: Dr. B.J. Gersh.  
Division of Cardiovascular Diseases and Internal Medicine. Mayo Clinic.  
200 First Street SW, 55905 Rochester, MN, USA.

deterioro de la función ventricular izquierda durante los siguientes 2-3 meses, mientras que otros presentan una mejoría, lo que destaca la dificultad en intentar estratificar el riesgo en un período determinado. Aunque nadie duda del impacto que ha supuesto la revascularización coronaria en el pronóstico de la cardiopatía isquémica, unido a la eficacia de la aspirina, bloqueadores beta, liporredutores e inhibidores de la ECA, la búsqueda de marcadores de riesgo cardíacos o no cardíacos puede contribuir notablemente a aumentar la supervivencia de los pacientes con infarto de miocardio.

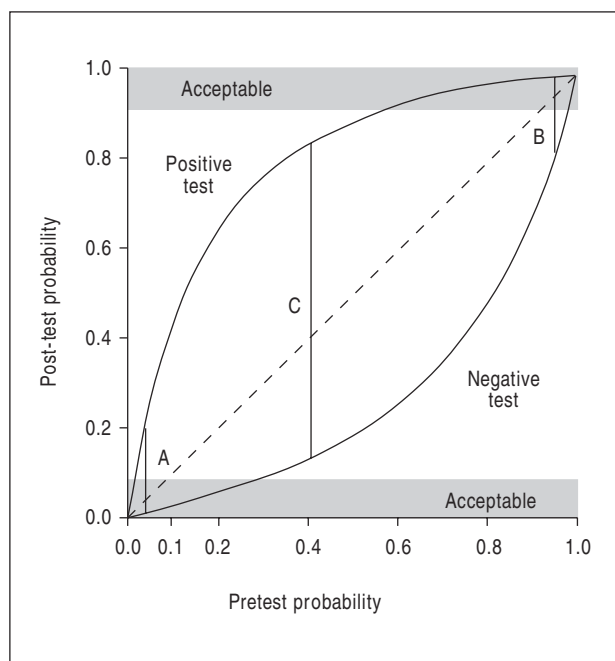
**Palabras clave:** Sensibilidad barorrefleja. Llenado restrictivo. Fracción de eyección. Mortalidad. Segmento ST. Onda T alternante. Arritmias ventriculares.

## INTRODUCTION

The era of reperfusion has changed clinical practices and the prognosis of patients who have acute myocardial infarction. Although there is little doubt that reperfusion therapy has improved the prognosis of the disease, it should not be forgotten that patients who benefit from reperfusion tend to accept aggressive modification of risk factors. The reperfusion era is also the era of aspirin, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors. Aggressive revascularization often is part of acute reperfusion therapy. Therefore, many reasons explain why patients who undergo thrombolysis or primary angioplasty have a good prognosis. The challenge for the twenty-first century is to determine if risk stratification before hospital discharge can significantly improve the prognosis of these patients.

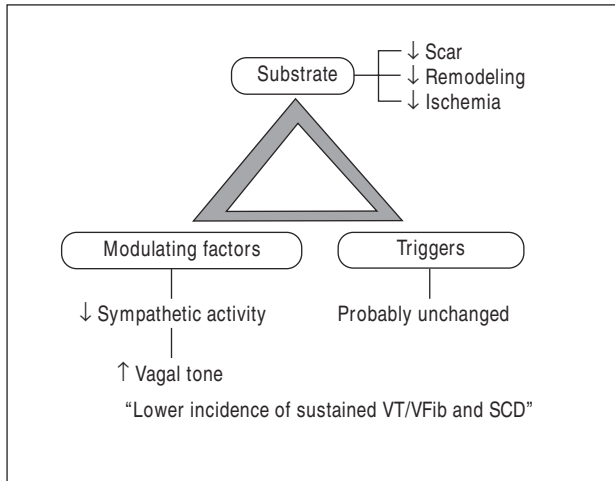
## BAYESIAN APPROACH TO RISK STRATIFICATION

To meet this twenty-first century challenge, we have to apply the so-called Bayesian principles, which relate the probability of an event or disease before the diagnostic test is performed (pretest probability) to the probability of the event actually being negative or positive after the diagnostic test has been performed. The distribution of negative and positive tests in relation to their respective predictive values and accuracy is shown in Figure 1. This distribution is particularly useful in the assessment of patients who have an



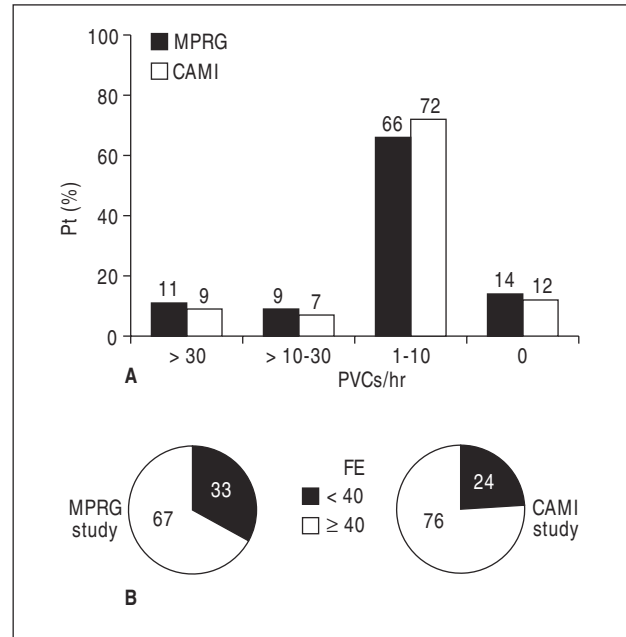
**Fig. 1.** Application of Bayesian principles. The distribution of negative and positive tests in relation to their predictive values and accuracy. A, low probability; B, high probability; C, intermediate probability. (From Berman DS, Garcia EV, Maddahi J. Thallium-201 myocardial scintigraphy in the detection and evaluation of coronary artery disease. In: Berman DS, Mason DT, editors. Clinical nuclear cardiology. New York: Grune & Stratton, 1981; p. 49-106. By permission of WB Saunders Company.)

intermediate probability of having a disease. For example, the theoretical probability that a 60-year-old woman with some risk factors and chest pain during exercise and occasionally at rest has obstructive coronary artery disease is 30% to 40%. If a diagnostic test is performed and the result is positive, the probability of her having coronary artery disease increases to 80% to 90%, but if the test is negative the probability decreases to about 10%. In contrast, for patients who have a very high or very low theoretical probability (the two extremes of the graph), the usefulness of Bayesian distribution in predicting an episode decreases markedly. Consequently, for the same patient at age 75 who has chest pain with effort that improves with nitroglycerin, the theoretical probability of obstructive coronary artery disease is 90%. If the diagnostic test is positive, her probability of disease increases to 98%, but if the test result is negative, it only decreases to 75% to 80%. In other words, a positive diagnostic test confirms what we already know, and a negative diagnostic test may be a false-positive result.



**Fig. 2.** The arrhythmia triangle (center) illustrating the effect of reperfusion on ventricular arrhythmias. Vfib indicates ventricular fibrillation; VT, ventricular tachycardia; SCD, sudden cardiac death.

Bayesian principles can be applied to risk stratification after myocardial infarction. Most of the studies performed 20 to 30 years ago approached risk in patients who had an event rate of about 30% at 2 years. With this event rate, positive or negative test results contribute very useful information. However, cardiologists now care for highly selected patients who have received reperfusion therapy and may have a cardiovascular event rate of 5% at 2 years. Three independent studies conducted in the 1980s in patients who had a 1-year mortality rate of 5% to 8.5% demonstrated that ST-segment depression after an exercise stress test was associated with a significant increase in mortality (19%), whereas the absence of ST-segment depression was associated with a lower mortality (2.5%).<sup>1-3</sup> These studies confirmed that the exercise stress test is extremely useful for stratifying risk in patients who previously had a myocardial infarction. More recently, the 6-month mortality rate was studied in the GISSI-2 trial, and the following results were obtained: if the exercise stress test was negative, the mortality rate was 0.9%, but if the test was positive at a maximal workload, the rate was 1.5%. If the exercise stress test was positive at a submaximal workload, the mortality rate was 1.9%, and if the test failed to yield a diagnosis, the mortality rate was 1.3% (if exercise testing was contraindicated, the rate increased to 7.1%).<sup>4</sup> Although the results were

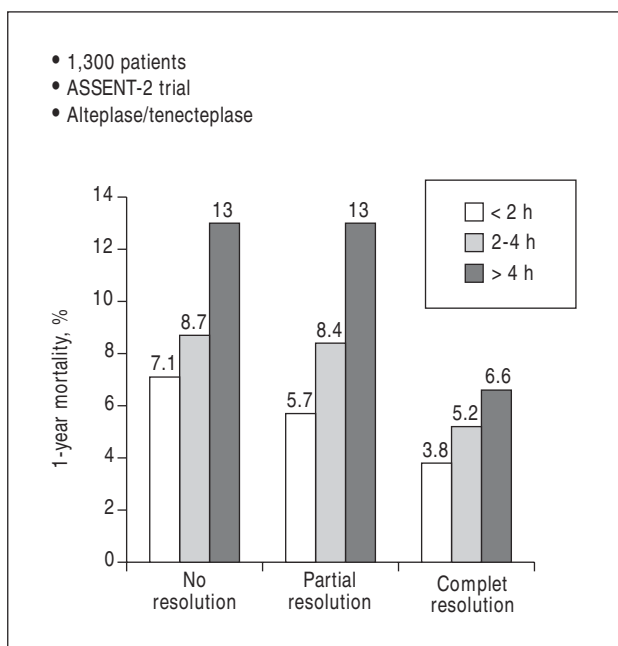


**Fig. 3.** A, Frequency of premature ventricular contractions (PVCs) in myocardial infarction survivors changes over time. B, Distribution of left ventricular function in the MPRG and CAMI studies. EF indicates ejection fraction. (From Hohnloser SH, Gersh BJ. Changing late prognosis of acute myocardial infarction: impact on management of ventricular arrhythmias in the era of reperfusion and the ICD. *Circulation* [in press]. By permission of the American Heart Association.)

statistically significant, the conclusion is that the exercise stress test has no clinical value for patients with a low mortality rate. If the test results were negative, the probability of being alive at 6 months would be 99.1%, and if they were positive, the probability would be 98.5%.

In a Canadian study that included more than 3000 patients younger than 75 years, the 1 to 2-year rate of sudden cardiac death was 2.7% for patients, the majority of whom had received reperfusion therapy.<sup>5</sup> How can these patients be identified? The Brugada brothers defined the «arrhythmia triangle», which determines, on the one hand, the interaction between triggers (fundamentally, premature ventricular contractions) and a substrate and, on the other hand, the interaction of triggers with certain modulating factors such as the autonomic nervous system (Figure 2). For sustained ventricular arrhythmia or sudden cardiac death to occur, these three factors must interact. The substrate can be either permanent (e.g., a scar caused by myocardial infarction) or dynamic (the presence of ischemia).

Reperfusion therapy alters this relation and



**Fig. 4.** Time to treatment and resolution of ST-segment changes and 1-year mortality rate. (From Fu et al.<sup>8</sup> By permission of the American Heart Association.)

markedly decreases the incidence of ventricular tachycardia, ventricular fibrillation, and sudden death (Figure 2). Reperfusion can salvage part of the myocardium from necrotic death, thus reducing scar tissue and remodeling (and changing the substrate). It also decreases sympathetic activity and increases vagal tone (modulators), which are beneficial effects. Nevertheless, it is likely that reperfusion therapy will not change the triggers and premature ventricular contractions will continue to occur. It is important to emphasize that what is modified is the relation of the trigger, substrate, and modulating factors, and the result of this modification is a significantly decreased incidence of sudden cardiac death.

To illustrate the importance of this concept, compare the results of two studies that investigated the relation between ejection fraction or the frequency of premature ventricular contractions and mortality: the MPRG and CAMI studies (Figure 3). The MPRG study corresponds to the prethrombolytic era<sup>6</sup> and the CAMI study, to the reperfusion era.<sup>5</sup> The two studies reported an increase in mortality when the ejection fraction was lower, but what has changed recently is the distribution of abnormal left

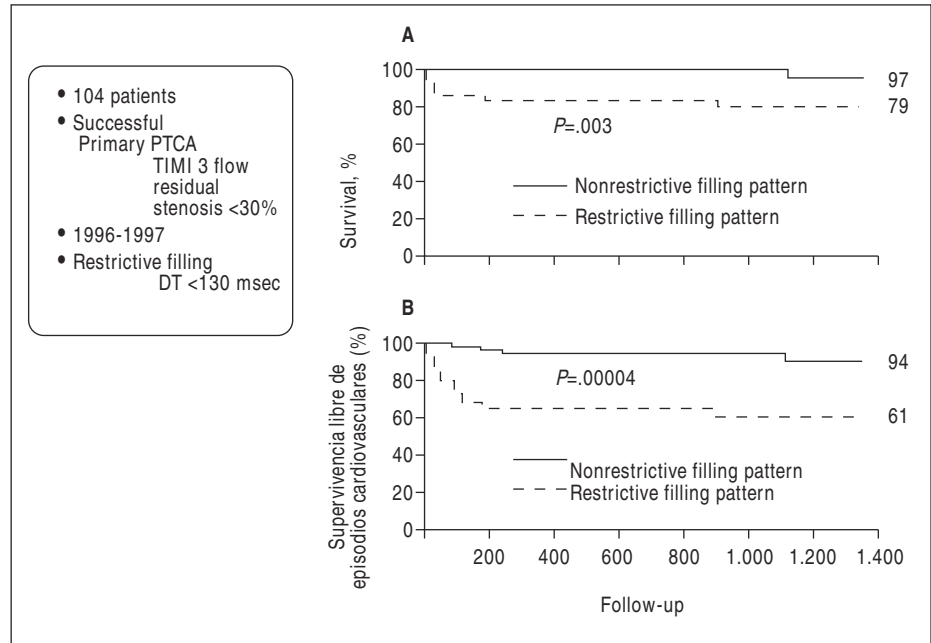
ventricular function in the population. Whereas one-third of the patients in the MPRG study had an ejection fraction less than 40%, only 24% of the patients in the CAMI study had such a low ejection fraction. As a result, although the frequency of premature ventricular contraction in the two studies is the same, the effect of premature ventricular contractions on mortality is now significantly lower than it was two decades ago. Thus, although there is still a relation between ejection fraction and mortality and between premature ventricular contractions and mortality, reperfusion therapy has changed the substrate by reducing the degree of left ventricular dysfunction.

## THE SEARCH FOR NEW RISK MARKERS

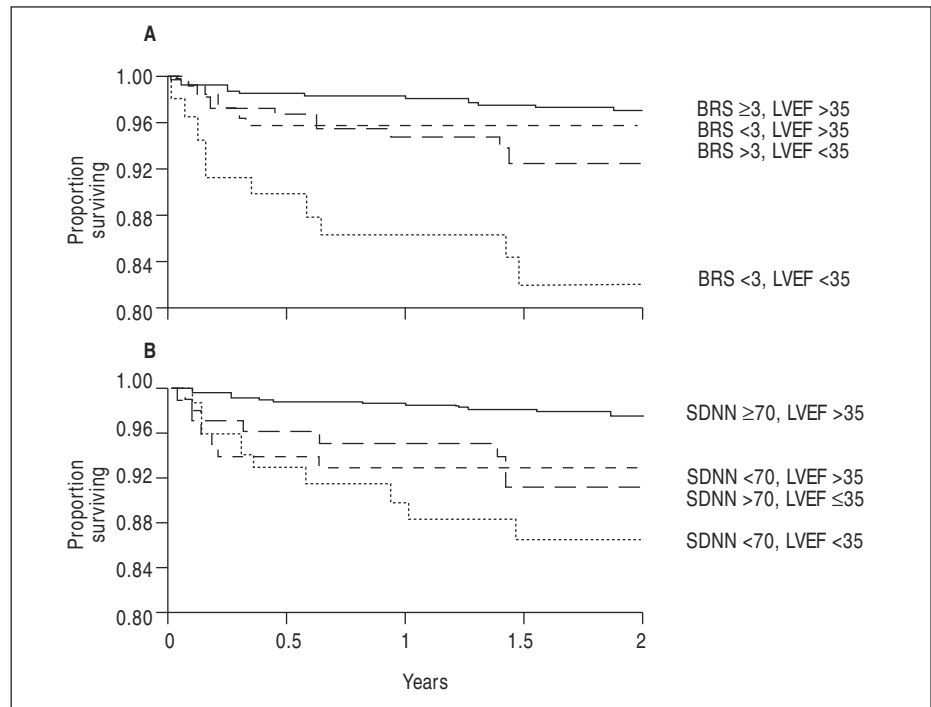
Currently, the annual rate of cardiovascular events after myocardial infarction is only 3% to 5%; however, not all patients who undergo reperfusion therapy are at low risk. The challenge that must be considered is how to identify the subgroup of patients at greater risk. By analyzing the various subgroups of patients in the GISSI-2 trial, it is evident that certain risk factors can notably increase mortality. For example, the mortality rate for patients for whom exercise stress testing is unsuitable, whether for cardiac or noncardiac reasons, is 7% at 6 months. The mortality rate at 1 year for patients with transitory heart failure, left ventricular dysfunction, or age older than 70 years is 18% to 20%. Other factors that increase cardiovascular risk after infarction are electrical instability, late heart failure, a history of previous infarction, or a history of hypertension.<sup>7</sup>

Other observations that support the conclusion that risk should be stratified in patients receiving reperfusion therapy are from the ASSENT-2 study, which analyzed the effect of alteplase or tenecteplase treatment on the resolution of ST-segment changes in the electrocardiogram (Figure 4). The results of this study demonstrated that the mortality rate for patients who had complete resolution of the ST-segment changes and received early treatment (within 2 hours) was 3.8%. If treatment was delayed (more than 4 hours), the mortality rate increased to 6.6% even if the ST-segment

**Fig. 5.** Prognosis after primary percutaneous transluminal coronary angioplasty (PTCA). A, Survival free of cardiac death. B, Survival free of cardiac death, myocardial infarction, and hospitalization for congestive heart failure. DT, deceleration time. (From Cerisano et al.<sup>9</sup> By permission of the American College of Cardiology.)



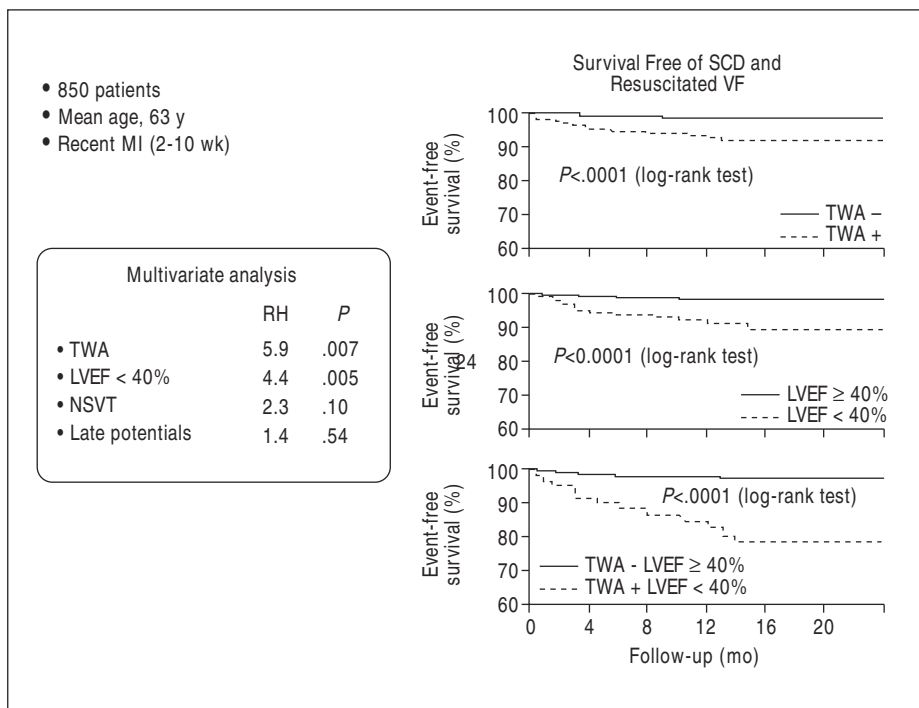
**Fig. 6.** Cardiac mortality in the ATRAMI study. A, Baroreflex sensitivity (BRS). B, Heart rate variability. LVEF indicates left ventricular ejection fraction; SDNN, standard deviation of normal to normal RR intervals. (From La Rovere et al.<sup>10</sup> By permission of the Lancet Publishing Group.)



changes resolved completely. The interesting point is that even when patients received early reperfusion therapy, the mortality rate was 7.1% if the ST-segment changes did not resolve. For the subgroup of patients who were treated later and had no resolution of the ST-segment changes, the mortality rate was 13%.<sup>8</sup>

Overall, these findings demonstrate that only with risk stratification of all patients can we identify subgroups of patients who have a high risk of mortality despite reperfusion therapy.

An Italian study of 104 patients with satisfactory primary angioplasty results and no residual stenosis has introduced a novel



**Fig. 7.** T-wave alternans (TWA) as a predictor for sudden cardiac death (SCD). LVEF indicates left ventricular ejection fraction; MI, myocardial infarction; NSVT, nonsustained ventricular tachycardia; RH, relative hazard; VF, ventricular fibrillation. (From Ikeda et al.<sup>11</sup> By permission of Excerpta Medica.)

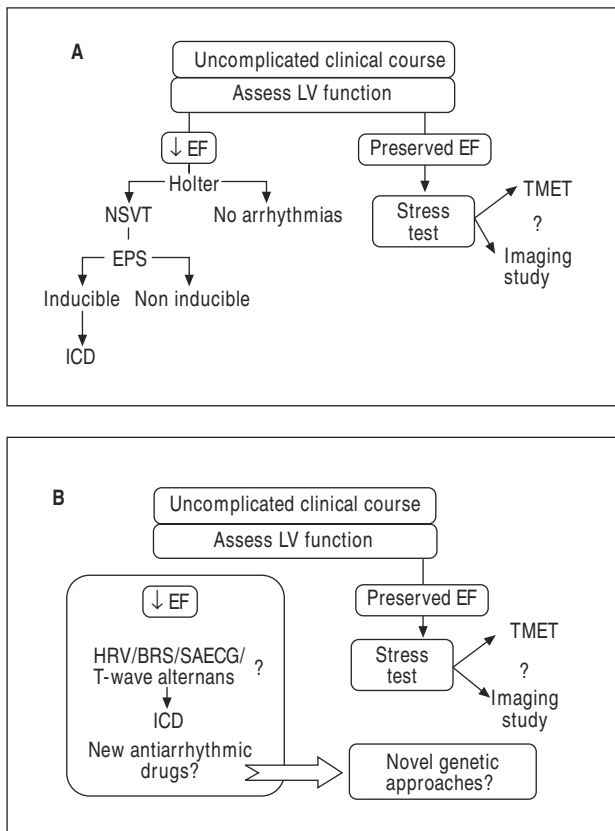
approach to stratify risk after reperfusion therapy.<sup>9</sup> This study defined diastolic dysfunction as decreased ventricular filling with a deceleration time of 130 seconds.

At 6 to 7 years, the survival rate of patients with normal diastolic function (i.e., no reduction in ventricular filling after primary angioplasty) was 97%. However, impaired ventricular filling, which indicates that filling pressures are high, was associated with a mortality rate of 21% at 5 years. If survival free of cardiovascular events (recurrent myocardial infarction or hospitalization for heart failure) is considered, decreased ventricular filling was a significant prognostic factor for these patients: 38% of patients with high ventricular filling pressures were hospitalized within 1 year for one of the end points (Figure 5).

Another method of risk stratification, reported by the European ATRAMI study, assessed baroreflex sensitivity as an indicator of vagal tone and ejection fraction (Figure 6).<sup>10</sup> Patients with normal baroreflex sensitivity (which implies strong vagal tone) and an ejection fraction greater than 35% had a very good survival rate. In contrast, anomalous baroreflex sensitivity and a poor ejection fraction were associated with a mortality rate of 20% at 4 years.

T-wave alternans is an interesting variable that is beginning to be considered. A recent Japanese study of 850 patients who had had an acute myocardial infarction in the previous weeks analyzed the influence of the presence or absence of T-wave alternans on survival free of ventricular fibrillation events.<sup>11</sup> The combination of T-wave alternans and an ejection fraction less than 40% was accompanied by a mortality rate of 25% at 3 years; in comparison, the absence of T-wave alternans and an ejection fraction greater than 40% were associated with a mortality rate of 2%. According to the results of an analysis of combined end points in this study, T-wave alternans and an ejection fraction less than 40% were the most powerful predictive factors of mortality due to arrhythmias (Figure 7). Of note, late potentials and unsustained ventricular tachycardia were not significant predictors.

An algorithm summarizing the protocol followed at Mayo Clinic for the evaluation of ventricular arrhythmias after reperfusion therapy in 2001 is shown in Figure 8 A. This approach was based on the results of the MADIT and MUSTT trials. Although neither of these studies examined risk stratification before hospital discharge, both of them stratified risk in patients who had had a



**Fig. 8.** Algorithm used at Mayo Clinic to evaluate ventricular arrhythmias after reperfusion therapy. A, Algorithm used in 2001 (pre-MADIT 2 study). B, Algorithm used after the MADIT 2 study. BRS indicates baroreceptor sensitivity; EF, ejection fraction; EPS, electrophysiologic study; HRV, heart rate variability; ICD, implantable cardiac defibrillator; LV, left ventricular; NSVT, nonsustained ventricular tachycardia; SAECG, signal-averaged electrocardiogram; TMET, treadmill exercise test.

myocardial infarction weeks or months earlier.

Nevertheless, the moment at which risk stratification is performed is extremely important. If the change in ejection fraction from day 1 to day 90 is considered, only a very small change occurs in most patients. Still, a significant number of patients (about 30%) experience deterioration in left ventricular function of 20% to 39% in the next 3 months.<sup>12</sup> Therefore, the problem of basing risk stratification on the ejection fraction at the time of discharge is that it can vary in the following months. However, it has a relative interest for stratifying risk after the first 3 months because high-risk patients have already died. The greatest risk of sudden death is in the first 3 days after infarction, and this is a problem that we cannot escape.

The results of the MADIT 2 study, involving

1200 patients who had had a myocardial infarction more than 30 days earlier, have just been published<sup>13</sup>. In 57% of the patients, bypass surgery had been performed previously. Although the results of this study do not answer the question of how risk stratification should be carried out before hospital discharge, they are the most solid findings available. The cutoff value for the ejection fraction was 30%. According to this study, patients who received an implantable cardiac defibrillator (ICD) had a 32% lower risk. Figure 8 B shows how the Mayo Clinic algorithm for risk stratification changed after the publication of the results of the MADIT 2 trial. Patients with an uncomplicated clinical course follow the same procedure used previously in clinical practice (Figure 8 A) because the MADIT 2 trial does not apply to patients with an ejection fraction greater than 30%. Patients with an ejection fraction less than 30% receive an ICD. An important question is what should be the role of T-wave alternans, heart rate variability, or anomalous baroreflex sensitivity, because the preliminary findings of the MADIT 2 study for these variables are discouraging. We do not know if the development of new antiarrhythmic drugs can help eliminate the uncertainty about how to stratify risk in this subgroup of patients. However, there is no doubt that because of the inadequacy of the results now available, we must seek out and evaluate new methods for risk stratification.

Certain noncardiac factors modify the prognosis of patients after myocardial infarction. In the CAST trial of encainide and flecainide, investigators studied how keeping pets influenced the 1-year survival rate.<sup>14</sup> Thirty percent of the patients included in the study had pets (mainly dogs, but also cats, horses, fish, snakes, rabbits, and ducks). The results demonstrated a 3.9% mortality rate for patients who kept pets compared with a 6.5% rate for those who did not. This difference increased still more if the pet was a dog; dog owners had a mortality rate of 1.2% versus 7.2% for those who were not dog owners. Unexpectedly, cat owners had a greater mortality rate than those who did not have cats, although the difference was small (7.3% vs 5.5%).

To summarize, the management of patients who have survived myocardial infarction must

include the administration of aspirin, beta-blockers, ACE inhibitors, and lipid-lowering drugs. The role of amiodarone remains to be seen, although it seems clear that ICD implantation produces a significant benefit in many patients. There is no doubt that coronary revascularization has an important effect on survival after myocardial infarction. Also, we should not forget that having a dog is a highly cost-effective alternative for preventing sudden death, given the effect of this noncardiac risk factor on prognosis.

## REFERENCES

1. Theroux P, Waters DD, Moise A, Bouchard A, Bosch X. Exercise testing in the early period after myocardial infarction in the evaluation of prognosis. *Cardiol Clin* 1984;2:71-7.
2. Sami M, Kraemer H, DeBusk RF. The prognostic significance of serial exercise testing after myocardial infarction. *Circulation* 1979;60:1238-46.
3. Starling MR, Crawford MH, Henry RL, Lembo NJ, Kennedy GT, O'Rourke RA. Prognostic value of electrocardiographic exercise testing and noninvasive assessment of left ventricular ejection fraction soon after acute myocardial infarction. *Am J Cardiol* 1986; 57:532-7.
4. Vilella A, Maggioni AP, Vilella M, Giordano A, Turazza FM, Santoro E, et al. Prognostic significance of maximal exercise testing after myocardial infarction treated with thrombolytic agents: the GISSI-2 data-base. Gruppo Italiano per lo Studio della Sopravvivenza Nell'Infarto. *Lancet* 1995;346:523-9.
5. Rouleau JL, Talajic M, Sussex B, Potvin L, Warnica W, Davies RF, et al. Myocardial infarction patients in the 1990s-their risk factors, stratification and survival in Canada: the Canadian Assessment of Myocardial Infarction (CAMI) study. *J Am Coll Cardiol* 1996;27:1119-27.
6. Swerdlow CD, Winkle RA, Mason JW. Determinants of survival in patients with ventricular tachyarrhythmias. *N Engl J Med* 1983; 308:1436-42.
7. Tavazzi L, Volpi A. Remarks about postinfarction prognosis in light of the experience with the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) trials. *Circulation* 1997;95:1341-5.
8. Fu Y, Goodman S, Chang WC, van De Werf F, Granger CB, Armstrong PW. Time to treatment influences the impact of ST-segment resolution on one-year prognosis: insights from the assessment of the safety and efficacy of a new thrombolytic (ASSENT-2) trial. *Circulation* 2001;104:2653-9.
9. Cerisano G, Bolognese L, Buonamici P, Valenti R, Carrabba N, Dovellini EV, et al. Prognostic implications of restrictive left ventricular filling in reperfused anterior acute myocardial infarction. *J Am Coll Cardiol* 2001;37:793-9.
10. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ, ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1998;351:478-84.
11. Ikeda T, Saito H, Tanno K, Shimizu H, Watanabe J, Ohnishi Y, et al. T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. *Am J Cardiol* 2002;89:79-82.
12. Solomon SD, Glynn RJ, Greaves S, Ajani U, Rouleau JL, Menapace F, et al. Recovery of ventricular function after myocardial infarction in the reperfusion era: the Healing and Early Afterload Reducing Therapy study. *Ann Intern Med* 2001;134:451-8.
13. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al., and the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-83.
14. Friedmann E, Thomas SA. Pet ownership, social support, and one-year survival after acute myocardial infarction in the Cardiac Arrhythmia Suppression Trial (CAST). *Am J Cardiol* 1995;76: 1213-7.