

# Baroreflex Sensitivity and Heart Rate Variability in the Identification of Patients at Risk for Life-Threatening Arrhythmias

## Implications for Clinical Trials

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**Background**—The need for accurate risk stratification is heightened by the expanding indications for the implantable cardioverter defibrillator. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) focused interest on patients with both depressed left ventricular ejection fraction (LVEF) and the presence of nonsustained ventricular tachycardia (NSVT). Meanwhile, the prospective study Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) demonstrated that markers of reduced vagal activity, such as depressed baroreflex sensitivity (BRS) and heart rate variability (HRV), are strong predictors of cardiac mortality after myocardial infarction.

**Methods and Results**—We analyzed 1071 ATRAMI patients after myocardial infarction who had data on LVEF, 24-hour ECG recording, and BRS. During follow-up ( $21 \pm 8$  months), 43 patients experienced cardiac death, 5 patients had episodes of sustained VT, and 30 patients experienced sudden death and/or sustained VT. NSVT, depressed BRS, or HRV were all significantly and independently associated with increased mortality. The combination of all 3 risk factors increased the risk of death by  $22 \times$ . Among patients with  $LVEF < 35\%$ , despite the absence of NSVT, depressed BRS predicted higher mortality (18% versus 4.6%,  $P=0.01$ ). This is a clinically important finding because this group constitutes 25% of all patients with depressed LVEF. For both cardiac and arrhythmic mortality, the sensitivity of low BRS was higher than that of NSVT and HRV.

**Conclusions**—BRS and HRV contribute importantly and additionally to risk stratification. Particularly when LVEF is depressed, the analysis of BRS identifies a large number of patients at high risk for cardiac and arrhythmic mortality who might benefit from implantable cardioverter defibrillator therapy without disproportionately increasing the number of false-positives. (*Circulation*. 2001;103:2072-2077.)

**Key Words:** nervous system, autonomic ■ baroreceptors ■ heart rate ■ myocardial infarction ■ arrhythmia

The prospective study Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI),<sup>1</sup> in which 55% of deaths were sudden, showed that within the group of patients who had a myocardial infarction and who had a depressed left ventricular ejection fraction (LVEF), an increased risk of death was associated with the presence of autonomic imbalance. This was particularly evident when the autonomic marker was depressed baroreflex sensitivity (BRS). Within the entire study population with a mortality

rate  $< 5\%$ , the combination of reduced LVEF ( $< 35\%$ ) and depressed BRS ( $< 3$  ms/mm Hg) identified a subgroup of patients with a 2-year mortality rate of 18%. As a marker of electrical instability, the initial analysis examined the role of frequent premature ventricular complexes rather than nonsustained ventricular tachycardia (NSVT); the latter has gained renewed interest after the results of implantable cardioverter defibrillator (ICD) trials such as the Multicenter Automatic Defibrillator Implantation Trial (MADIT).<sup>2</sup>

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Ongoing primary prevention trials such as MADIT II<sup>3</sup> and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT),<sup>4</sup> which randomize patients solely on the basis of decreased LVEF and clinical symptoms of heart failure, are likely to enlarge the indications for ICD therapy should they be positive. Compared with MADIT-I, implanting ICDs in these patients will lead not only to the improved survival of a larger number of patients, but also to an increase in the number of unnecessary ICDs, given the size of the population and the lower mortality rate. This consideration heightens the need for a more accurate risk stratification, which is equally important for a better selection of patients to be studied with antiarrhythmic drugs, with the aim of identifying the subgroups at higher and lower risk. The use of autonomic markers, such as BRS<sup>5</sup> or heart rate variability (HRV),<sup>6</sup> may help achieve these goals.

Thus, the objectives of the present analysis were to examine the role of both BRS and HRV in modifying the risk for cardiac and arrhythmic mortality associated with runs of NSVT in the entire population of ATRAMI who had a myocardial infarction and in the subgroup with depressed LVEF.

**Methods**

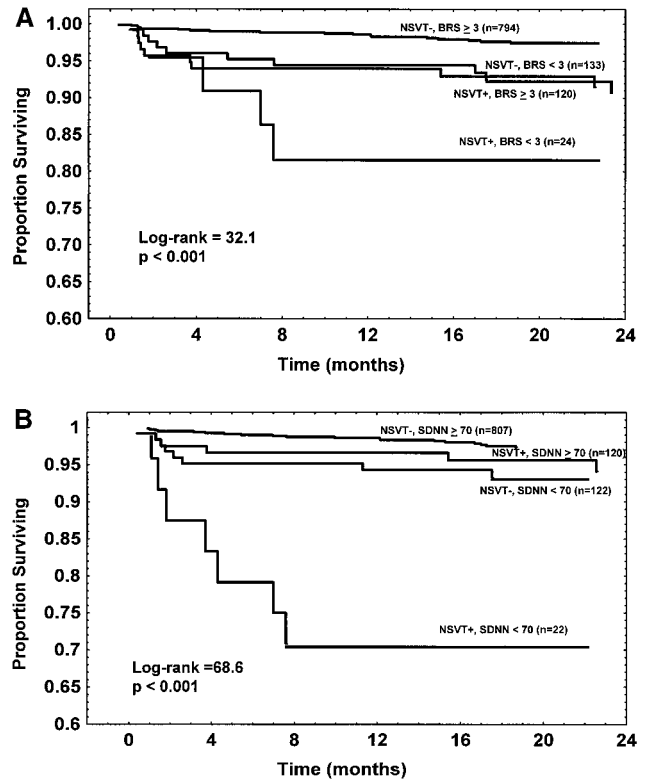
The protocol of the study has been described previously.<sup>1</sup> Briefly, 1284 patients (aged <80 years) with a recent (<1 month) myocardial infarction were enrolled if they were in sinus rhythm and (1) had no contraindications to exercise, (2) did not have unstable angina or ischemia requiring coronary bypass surgery in the 3 months after enrollment and (3) had no signs or symptoms of congestive heart failure at the time of evaluation. LVEF was assessed by echocardiography, Tc-99 scintigraphy, or left ventriculography; NSVT and HRV (standard deviation of normal-to-normal RR intervals [SDNN]) were assessed by 24-hour ECG recording; and BRS was evaluated by the phenylephrine method.<sup>5</sup> NSVT was defined as ≥3 consecutive ventricular premature contractions at a rate >100 bpm. LVEF, 24-hour ECG recording, and BRS data were available in 1071 patients in ATRAMI; 157 (14.6%) had a LVEF<35%.

**Statistical Analysis**

Clinical characteristics were summarized in terms of frequencies and percentages for categorical variables and as mean±1SD for continuous variables. The statistical analysis included the χ<sup>2</sup> test for categorical variables and ANOVA for continuous variables. BRS and SDNN were log-transformed because of their skewed distribution. NSVT was dichotomized as present or absent. LVEF, BRS, and SDNN were also dichotomized according to the ATRAMI cut off values of 35%, 3 ms/mm Hg, and 70 ms, respectively. End points of survival analysis were total cardiac mortality and combined sudden death or sustained ventricular tachycardia.

Kaplan-Meier curves were used to describe the event-free survival of patients stratified according to the levels of the categorical variables, and the log-rank test was used for statistical comparisons. Data on surviving patients were censored on the last day they were known to be alive. Data on deaths from causes other than cardiac mortality were censored on the last day the patients were known to be alive.

The association of NSVT, BRS, and HRV with cardiac mortality was assessed with univariate and multivariate Cox regression analysis, and relative risks (RR) with 95% confidence intervals (CI) were also computed. In the analysis of arrhythmic mortality, which was not presented in the previous article,<sup>1</sup> we considered the association of autonomic markers with LVEF and NSVT. The sensitivity and



**Figure 1.** Kaplan-Meier survival curves for total cardiac mortality according to combination of NSVT and BRS (a) and NSVT and SDNN (b). Total population was divided into 4 groups after dichotomization of BRS and SDNN, according to ATRAMI cutoff values of <3 and ≥3 ms/mm Hg and <70 and ≥70 ms, respectively. Probability value refers to differences in event rates between subgroups.

specificity of event-free prediction were also evaluated. A 2-tailed P<0.05 was accepted as significant.

**Results**

**All Patients**

Clinical characteristics of the patients evaluated in this article did not differ from those of the entire ATRAMI population. Specifically, mean age and LVEF were 59±10 years and 49±11%, respectively. The site of infarction was anterior in 49%, and NSVT was observed in 13.4% of patients. Over 21±8 months of follow-up, there were 48 end point events, including 43 cardiac deaths or nonfatal cardiac arrests and 5 episodes of sustained ventricular tachycardia. The combined end point of sudden death or sustained ventricular tachycardia included 30 events. The only significant, albeit small, differences between patients with and without NSVT were that the former were older (59 versus 57 years) and had a lower LVEF (47±12% versus 50±11%). Interestingly, the percentage of patients with depressed BRS or SDNN was not greater within this group. Mortality was higher among patients with NSVT (9.7% versus 3.1%, P=0.0001).

Figure 1 examines the contribution to mortality of combining NSVT and BRS and NSVT and SDNN. Mortality was higher among patients with both NSVT and depressed BRS (21%), and it differed significantly from that of patients without NSVT and preserved BRS (2.4%) and from that of

**TABLE 1. Multivariate Cox Analysis for Cardiac Mortality and Cumulative RRs for Different Combinations of Risk Predictors**

	Wald $\chi^2$	RR (95% CI)	P
NSVT+	12.20	3.1 (1.6–5.9)	<0.001
SDNN<70 ms	11.65	3.2 (1.6–6.3)	<0.001
BRS<3 ms/mm Hg	4.77	2.1 (1.1–4.2)	0.03
NSVT+ and BRS<3 ms/mm Hg		9.6 (3.6–25.7)	<0.001
NSVT+ and SDNN<70 ms		17.0 (7.2–40.5)	<0.001
BRS<3 ms/mm Hg and SDNN<70 ms		7.0 (3.5–15.4)	<0.001
NSVT+, SDNN<70 ms, and BRS<3 ms/mm Hg		22.2 (7.3–66.8)	<0.001

patients with either NSVT or depressed BRS (7.5%,  $P=0.0001$ ). Mortality was even greater for patients with NSVT who also had reduced SDNN (29%), and it was significantly higher than that of all the other combinations (NSVT–, SDNN $\geq$ 70; NSVT+, SDNN $\geq$ 70; NSVT–, SDNN<70; 2.5%, 6%, and 7.2%, respectively,  $P=0.0001$ ).

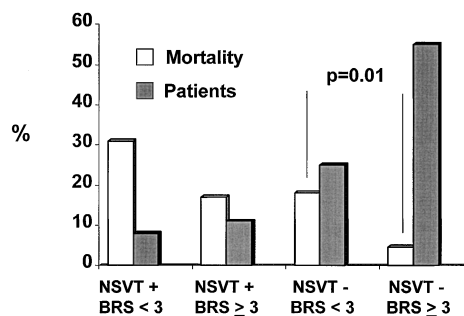
Univariate Cox analysis identified the presence of NSVT (RR, 3.1; 95% CI, 1.7 to 6.0), depressed BRS (RR, 3.2; 95% CI, 1.7 to 5.9), and reduced SDNN (RR, 4.1; 95% CI, 2.2 to 7.5) as significantly associated with cardiac mortality. In multivariate analysis, NSVT, SDNN, and BRS were independently predictive of worse prognosis (Table 1). Cumulative RRs indicate that when NSVT was combined with depressed BRS, it increased the risk by  $\approx 10\times$ , and when it was combined with depressed SDNN, it increased the risk by  $17\times$ , albeit with a larger confidence interval. The combination of all 3 risk factors further increased risk by  $\approx 22\times$  (Table 1).

### Patients with LVEF<35%

Table 2 shows the effect of the interaction between autonomic markers and NSVT in predicting cardiac mortality in the subset of patients with LVEF<35%. Using multivariate Cox analysis, both NSVT and depressed BRS maintained an independent prognostic association with cardiac mortality, but this was not the case for reduced SDNN. When NSVT and BRS were used as single predictors of mortality, the sensitivity and specificity were, respectively, 39% and 83% for NSVT and 61% and 70% for BRS, with positive predictive values of 23% and 21%, respectively. When the presence of either NSVT or depressed BRS was considered, this produced a sensitivity of 78% and specificity of 60%, with

**TABLE 2. Multivariate Cox Analysis for Cardiac Mortality in Patients With LVEF<35%**

	Wald $\chi^2$	RR (95% CI)	P
NSVT+	4.01	2.7 (1.02–7.06)	0.04
BRS<3 ms/mm Hg	3.97	2.8 (1.01–7.72)	0.04
SDNN<70 ms	0.29	1.3 (0.49–3.53)	0.58
NSVT– and BRS<3 ms/mm Hg		4.1 (1.18–13.88)	0.02
NSVT+ and BRS $\geq$ 3 ms/mm Hg		4.0 (0.90–18.07)	0.067
NSVT+ and BRS<3 ms/mm Hg		7.9 (1.97–32.01)	0.003



**Figure 2.** Bar graph illustrating relation among different combinations of NSVT and BRS in patients with LVEF<35% and their relation to size of the subgroups under evaluation. Note that for patients without NSVT, presence of depressed (<3 ms/mm Hg) BRS identifies a subset of patients accounting for >20% of patients with reduced LVEF (greater than entire group of patients with NSVT) with a 2-year mortality rate similar to that of patients with NSVT as a whole. A subgroup with a very low mortality rate, which accounts for >50% of patients with reduced LVEF, is identified by absence of NSVT (NSVT–) and a preserved autonomic balance.

positive and negative predictive values of 20% and 95%, respectively. In patients with NSVT, a depressed BRS yielded a sensitivity of 57%, a specificity of 63%, and a positive predictive value of 31%.

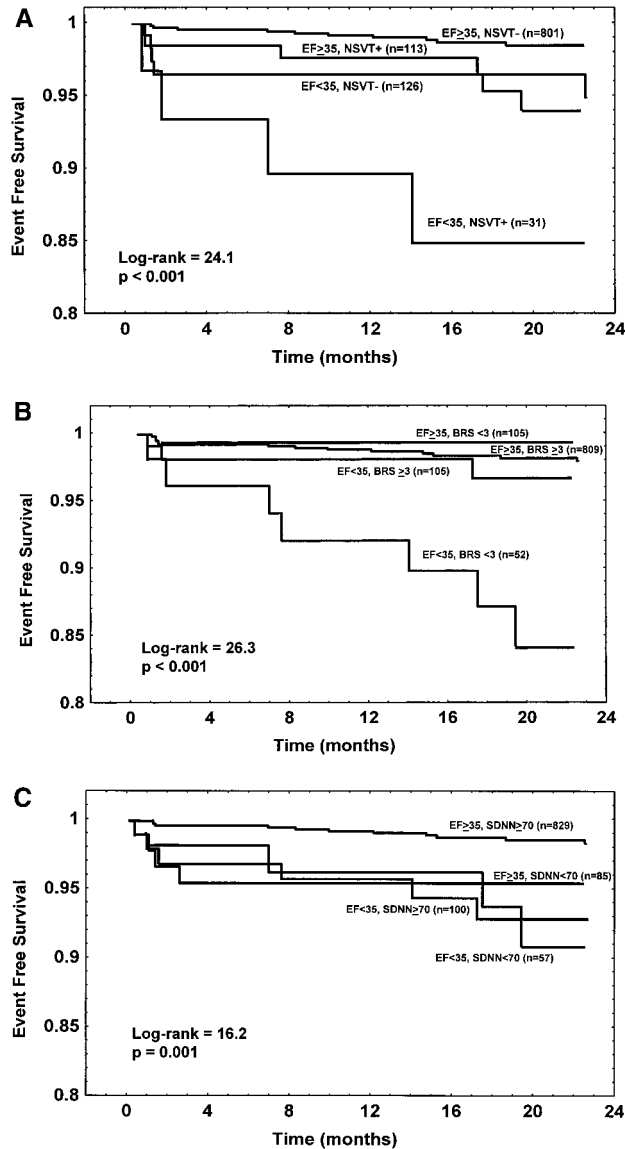
In patients without NSVT, who were generally regarded as at relatively low risk, the presence of depressed BRS increased the mortality risk 4-fold (from 4.6% to 18%,  $P=0.01$ ). Of practical significance, this is not a small subgroup: it constitutes 25% of all patients with depressed LVEF (Figure 2). In this subset of patients, a depressed BRS carried a sensitivity of 64% and a specificity of 72%, with positive and negative predictive values of 18% and 95%, respectively.

### Prediction of Arrhythmic Events

The association between LVEF and BRS or SDNN was evaluated against the combined end point of arrhythmic death or sustained VT. Because NSVT is an independent predictor of mortality, the effects of combinations including NSVT were also tested. Although the survival curves stratified according to the combinations of LVEF with NSVT, BRS, or SDNN were all statistically significant (Figure 3), within patients with LVEF<35% the contribution of depressed SDNN seemed less important.

The cumulative RRs for arrhythmic events for the multiple combinations of these different risk predictors are shown in Table 3. The RR provided by LVEF<35% and NSVT is slightly higher than that provided by the combination of LVEF<35% and BRS, but it involves only about half of the patients (Figures 3a and 3b). With an even smaller group of patients ( $n=22$ ), the combination of NSVT and SDNN was associated with the greatest RR (Table 3).

Given the relatively small incidence of arrhythmic events in patients with LVEF<35%, the positive predictive value is obviously low (15% for BRS, 16% for NSVT, and 7% for SDNN); however, the sensitivity of depressed BRS is markedly greater than that of NSVT and SDNN (73% versus 45% and 36%, respectively), at the expense of a modest loss in



**Figure 3.** Kaplan-Meier event-free survival curves for arrhythmic events according to combination of EF with NSVT and autonomic markers. Total population was divided into 4 groups after dichotomization of EF according to  $<35\%$  and  $\geq 35\%$ . BRS and SDNN were dichotomized as indicated in Figure 1. Probability value refers to differences in event rates among subgroups.

specificity versus NSVT but not SDNN (70% versus 82% and 64%, respectively).

**Discussion**

The complexities and costs of mortality trials for arrhythmic death increase the need for better risk stratification of patients at high and low risk. The results of MADIT have focused interest on patients with both depressed LVEF and the presence of NSVT for the design of trials with antifibrillatory drugs or ICDs. The major limitation of this approach is that those with NSVT represent only a small minority of post-myocardial infarction patients.<sup>7</sup> The present study improves risk stratification by demonstrating that within patients with

**TABLE 3.** Cumulative RRs for Arrhythmic Events for Different Combinations of Risk Predictors

	Wald $\chi^2$	RR (95% CI)	P
EF<35% and BRS<3 ms/mm Hg	19.6	6.7 (2.9–15.5)	<0.001
EF<35% and NSVT+	16.5	9.0 (3.0–26.0)	<0.001
BRS<3 ms/mm Hg and NSVT+	10.1	6.6 (2.0–21.4)	0.001
EF<35% and SDNN<70 ms	6.2	4.1 (1.3–12.2)	0.013
BRS<3 ms/mm Hg and SDNN<70 ms	9.1	4.6 (1.7–12.4)	0.03
SDNN<70 ms and NSVT+	20.9	13.3 (4.4–40.2)	0.001

NSVT depressed HRV increases risk, and that within the much larger group of patients without NSVT it is possible, particularly in the presence of depressed LVEF, to identify patients at high and low risk based on the presence or absence of depressed BRS. Because this finding applies to both cardiac and arrhythmic mortality, our data have implications for the design of mortality clinical trials and for the choice of candidates for ICD implant.

**BRS and HRV**

The evidence linking the autonomic nervous system to life-threatening arrhythmias and to cardiovascular mortality is well established.<sup>8</sup> There is a clear association between increased sympathetic activity and/or reduced vagal activity and a greater propensity for ventricular fibrillation during myocardial ischemia.<sup>9,10</sup> These experimental observations have been translated to the clinic; several studies using various markers of impaired vagal activity<sup>11–14</sup> have consistently confirmed the concept<sup>15</sup> that this type of autonomic imbalance increases cardiovascular risk. However, measures of autonomic control are only slowly entering the process of risk stratification on a routine basis. This would probably accelerate with the development and better evaluation of methods that use spontaneous fluctuations in blood pressure and heart rate.<sup>16</sup>

The value of autonomic imbalance in predicting susceptibility to cardiac death and life-threatening arrhythmic events is independent of markers of electrical instability, be they frequent premature ventricular complexes (as in the original ATRAMI analysis) or NSVT (as in the present one). Indeed, our data show not only that BRS and HRV are independent of NSVT in their predictive value, but also that BRS is associated with increased sensitivity. Furthermore, the combination of BRS and NSVT provides an acceptable balance between sensitivity and specificity in the identification of high-risk patients in a population at a relatively low risk, such as the one studied in ATRAMI.

Among patients surviving myocardial infarction, the analysis of autonomic markers, especially BRS, constitutes an improved strategy that more accurately identifies patients at high risk for total and arrhythmic mortality. Importantly, the assessment of BRS provides useful information among those patients who, according to the presently accepted noninvasive MADIT criteria, are not included in the high-risk population

because they do not have NSVT in a 24-hour Holter recording.

### A Reassessment of Risk Stratification

After the results of MADIT, some suggested that the indication for ICDs should be expanded to include prophylactic treatment of patients at high risk for life-threatening arrhythmias. This made the correct identification of patients at truly high risk a most critical issue. However, this goal has been made more complex by the fact that the therapeutic progress has modified the profile of patients with acute myocardial infarction by improving the post-hospital discharge survival rate and reducing the ability to identify high-risk patients by traditional means. For instance, in the thrombolytic era, ventricular late potentials are less helpful in predicting arrhythmic complications.<sup>17</sup>

The same occurred for arrhythmias detected by pre-discharge 24-hour Holter recordings. Indeed, although the presence of frequent ventricular complexes or NSVT have long been known to contribute to prognosis as independent variables that augment the risk related to low LVEF,<sup>18</sup> recently their predictive value has become controversial. In the Multicenter Postinfarction Research Program,<sup>18</sup> NSVT was present in 12% of patients and was associated with a 2-fold increase in total and arrhythmic deaths, independent of LVEF. In contrast, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico 2 (GISSI-2) Investigators failed to demonstrate that NSVT was an independent predictor of cardiac mortality in postinfarction patients who underwent thrombolysis.<sup>19</sup> Importantly, in the GISSI-2 trial, NSVT was less frequent (6.8%). In another study<sup>7</sup> in which most patients (78%) had a successful revascularization of the infarct-related artery, NSVT (9%) carried a significant but small multivariate RR for the composite end point of cardiac death, sustained VT, or resuscitated ventricular fibrillation, but not for arrhythmic events considered alone.

In the present study, we show that NSVT adversely influences prognosis, independent of reduced LVEF and depressed BRS or HRV. Its prevalence in the ATRAMI population (13.4%) was higher than in the GISSI-2 trial (6.8%) and in the study by Hohnloser et al<sup>7</sup> (9%), despite frequent thrombolysis (63%). The predictive value of NSVT does not represent the main finding of our study; it is actually within the group without NSVT that we made the most interesting and clinically important observation, ie, that depressed BRS identifies a subgroup with the same mortality risk as patients with depressed LVEF and NSVT.

In the entire population, the predictive value of HRV is strong and adds prognostic power to the combination of NSVT and BRS (RR from 9.6 to 22.2; at the expense, however, of a very large confidence interval). Nonetheless, in the present population, HRV did not significantly increase the risk for patients with LVEF<35%.

In the modified situation created by thrombolysis and advanced therapeutic regimens, depressed left ventricular function is the only risk stratifier that has not lost its predictive value. Ongoing primary prevention trials with ICDs<sup>3,4</sup> and mortality trials with antiarrhythmic drugs randomize mainly on the basis of ejection fraction, and there is

growing evidence for accentuated benefit of ICDs among patients with greater impairment of systolic function.<sup>20</sup> However, because the 1-year mortality rate in postinfarction patients with reduced LVEF does not exceed 15%, a large number of unnecessary ICDs will be implanted.

The present analysis shows that a reasonable compromise between sensitivity and specificity is provided by considering autonomic markers and especially by combining reduced LVEF with the presence of NSVT or depressed BRS (sensitivity and specificity 78% and 60%, respectively). Indeed, in the subset of 157 patients with LVEF<35%, the 2-year mortality rate was only 11.4%. By selecting patients on the basis of BRS or NSVT, the mortality rate, and hence the positive predictive value, increased to 20%, and the negative predictive value was reduced to 95%. This would imply a reduction of 55% in the number of implanted ICDs.

### Clinical Implications

The integration of traditional risk stratifiers, such as LVEF and NSVT, with autonomic markers, such as BRS and HRV, provides a more powerful approach to the ever-daunting problem of the early identification of post-myocardial infarction patients at a risk for cardiac and arrhythmic mortality that is high enough to justify aggressive and expensive preventive strategies. In addition, this information will contribute to a more accurate design of mortality clinical trials.

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