

# Heart Rate Recovery Immediately After Treadmill Exercise and Left Ventricular Systolic Dysfunction as Predictors of Mortality

## The Case of Stress Echocardiography

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**Background**—An attenuated heart rate recovery after exercise has been shown to be predictive of mortality. In prior studies, recovery heart rates were measured while patients were exercising lightly, that is, during a cool-down period. It is not known whether heart rate recovery predicts mortality when measured in the absence of a cool-down period or after accounting for left ventricular systolic function.

**Methods and Results**—We followed 5438 consecutive patients without a history of heart failure or valvular disease referred for exercise echocardiography for 3 years. Heart rate recovery was defined as the difference in heart rate between peak exercise and 1 minute later; a value  $\leq 18$  beats per minute was considered abnormal. Patients assumed the left lateral decubitus position after exercise. An abnormal heart rate recovery was present in 805 patients (15%); during follow-up, 190 died. An abnormal heart rate recovery was predictive of death (9% versus 2%, hazard ratio [HR] 3.9, 95% CI 2.9 to 5.3,  $P < 0.0001$ ) and predicted death whether or not left ventricular systolic dysfunction (ejection fraction  $\leq 40\%$ ) was present. After adjusting for age, sex, exercise capacity, left ventricular systolic function, presence or absence of myocardial ischemia, and other confounders, an abnormal heart rate recovery remained predictive of death (adjusted HR 2.09, 95% CI 1.49 to 2.82,  $P < 0.001$ ).

**Conclusions**—Even in the absence of a cool-down period and even after accounting for left ventricular systolic function, heart rate recovery is a powerful and independent predictor of death. (*Circulation*. 2001;104:1911-1916.)

An attenuated heart rate recovery after exercise, thought to be a marker of reduced parasympathetic activity,<sup>1,2</sup> is an independent predictor of all-cause mortality among patients undergoing exercise electrocardiography and exercise SPECT.<sup>3,4</sup> Previous studies of heart rate recovery have incorporated recovery heart rate measurements while patients were still walking slowly; this is known as a cool-down period.

Stress echocardiography mandates assumption of a supine position after exercise<sup>5,6</sup>; this increases venous return, leading to a bradycardic response. Furthermore, left ventricular systolic function is routinely assessed. The primary purpose of this study was to determine whether heart rate recovery predicts mortality among patients undergoing stress echocardiography. Because previous studies of heart rate recovery did not account for left ventricular systolic function, we sought to determine whether the predictive value of heart rate recovery persisted even after considering estimated left ventricular ejection fraction.

### Methods

#### Patient Population Sample

The study population consisted of consecutive patients referred for exercise stress echocardiography at the Cleveland Clinic between

October 1990 and April 1999. Patients were excluded if they were  $< 30$  years of age, had a history of heart failure, valvular or congenital heart disease, had an implanted pacemaker or atrial fibrillation, or used digoxin. Patients were also excluded if a valid Social Security number was not available. The local Institutional Review Board approved the performance of systematic research based on the Foundation's exercise and echocardiography databases.

#### Clinical Data

Before exercise testing, all patients underwent a structured interview and chart review, described in detail elsewhere.<sup>3-5,7</sup> Data were recorded systematically, prospectively and online regarding demographics, testing indications, symptoms, risk factors, previous cardiac procedures and diagnoses, and medications.

#### Exercise Testing

After a supine rest ECG was obtained, symptom-limited exercise testing was conducted according to standard protocols (usually Bruce, modified Bruce, or Cornell).<sup>8</sup> Treadmill exercise was used in 93% of patients. An ischemic ST-segment response was defined as horizontal or downsloping ST-segment depression of  $\geq 1$  mm below baseline taken 80 ms after the J-point if there was  $< 1$  mm of ST-segment depression at baseline. Chronotropic response was assessed on the basis of the proportion of heart rate reserve used as peak exercise, or (peak heart rate—resting heart rate)/

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**TABLE 1. Baseline Characteristics According to Heart Rate Recovery**

Baseline Characteristics	Normal Heart Rate Recovery (HRR>18 bpm)	Abnormal Heart Rate Recovery (HRR≤18 bpm)	P
No. of patients	4633	805	
Age, y	56±11	65±10	<0.0001
Male sex, n (%)	2929 (63)	518 (64)	0.54
Body mass index, kg/m <sup>2</sup>	29±6	30±6	0.007
Hypertension, n (%)	1966 (42)	497 (62)	0.001
Present or recent smoker, n (%)	715 (15)	147 (18)	0.04
Diabetes, n (%)	489 (11)	188 (23)	0.001
COPD, n (%)	81 (2)	49 (6)	<0.0001
PVD, n (%)	75 (2)	44 (5)	<0.0001
Prior coronary artery disease, n (%)	1596 (34)	410 (51)	0.001
Prior coronary angioplasty, n (%)	585 (13)	130 (16)	0.006
Prior coronary artery bypass, n (%)	581 (13)	187 (23)	0.001
Prior myocardial infarction, n (%)	421 (9)	113 (14)	0.001
β-Blocker use, n (%)	925 (20)	251 (31)	0.001
Nondihydropyridine Ca blocker use, n (%)	591 (13)	151 (19)	0.001
Dihydropyridine Ca blocker use, n (%)	365 (8)	107 (13)	0.001
Lipid-lowering agent use, n (%)	885 (19)	168 (21)	0.24
ACE-I use, n (%)	494 (11)	134 (17)	0.001
Resting heart rate, bpm	77±14	79±16	0.0001
Resting systolic BP, mm Hg	138±20	146±22	<0.0001
Resting diastolic BP, mm Hg	86±11	86±11	0.44
LV ejection fraction <40%, n (%)	252 (5)	85 (11)	0.001
LV ejection fraction, %	53±6	51±8	<0.0001
Diabetes and LV ejection fraction <40%, n (%)	51 (1)	24 (3)	<0.0001

Continuous variables are shown as mean±SD, whereas categorical variables are shown as number (percent). COPD indicates chronic obstructive pulmonary disease; PVD, peripheral vascular disease; Ca, calcium; ACE-I, angiotensin I-converting enzyme inhibitor; BP, blood pressure; LV, left ventricular; and bpm, beats per minute.

(220-age-resting heart rate)<sup>9</sup>; a value of ≤0.80 was considered chronotropic incompetence. Functional capacity was measured in metabolic equivalents (or METs, where one MET is 3.5 mL/kg per min of oxygen consumption) on the basis of a previously published nomogram<sup>8</sup>; impaired physical fitness was defined as a fair or poor functional capacity for age and sex on the basis of a previously validated scheme. Impaired functional capacity was considered present when fair or poor for age and sex on the basis of a previously validated scheme from our laboratory.<sup>7</sup> Specific values for impaired functional capacity were <10, <9, <8, <7, and <6 METs for ages ≤29, 30 to 39, 40 to 49, 50 to 59, and ≥60 years, respectively, for women, and <11, <10, <8.5, <8, and <7 METs for ages ≤29, 30 to 39, 40 to 49, 50 to 59, and ≥60 years, respectively, for men.<sup>7</sup>

Immediately after exercise, patients lay down in a supine position to allow for immediate poststress echocardiography. Heart rates were continuously monitored on the basis of the computerized R-R interval on the ECG.

### Stress Echocardiography

Two-dimensional echocardiography was performed before and immediately after exercise using methods described previously.<sup>5,6</sup> Images were obtained in the left lateral decubitus position in parasternal long- and short-axis and apical four- and two-chamber views using standard commercially available equipment. Patients who underwent bicycle stress testing also had pretest and posttest images obtained in the left lateral decubitus position. Interpretation was based on one attending physician reading. The readers had no

knowledge of clinical, exercise electrocardiographic, and, if applicable, previous coronary arteriographic data and were not aware of the study hypothesis. Left ventricular ejection fraction was estimated visually, a technique commonly used in routine clinical practice that has been shown to have a reasonable degree of accuracy.<sup>10-13</sup> Qualitative analysis was done in a standard 16-segment model of the left ventricle to identify ischemia and infarction.<sup>6,14</sup> There were no missing values for left ventricular ejection fraction or for exercise hemodynamic or stress echocardiographic variables.

### End Points

The primary end point was all-cause mortality, as determined by query of the Social Security Death Index,<sup>15,16</sup> which had mortality data through May 1999 at the time the query was run. For 1990s mortality data, the Social Security Death Index has been shown to be highly specific.<sup>17</sup> We have demonstrated that the sensitivity of this death index is ≈97% among patients in our exercise laboratory.<sup>4</sup> All-cause mortality was chosen as the end point of interest, because it is clinically relevant and not subject to inherent biases and inaccuracies of an end point like cardiac mortality.<sup>18</sup> Median follow-up time was 3 years (range for survivors, 1 month to 9 years).

### Statistical Analyses

Heart rate recovery was defined as the difference between heart rate at peak exercise and 1, 2, or 3 minutes later. We performed unadjusted Cox regression analyses relating the difference in heart rate at peak exercise with heart rate at these different points in

**TABLE 2. Exercise Characteristics According to Heart Rate Recovery**

Characteristic	Normal Heart Rate Recovery (HRR>18 bpm)	Abnormal Heart Rate Recovery (HRR≤18 bpm)	P
Total No. of patients	4633	805	
Peak heart rate, bpm	154±20	133±22	0.0001
Proportion of heart rate reserve used	0.9±0.20	0.7±0.25	0.0001
Peak systolic blood pressure, mm Hg	194±27	190±29	0.0002
Fair or poor fitness, n (%)	1223 (26)	411 (51)	0.001
Chronotropic incompetence, n (%)	1353 (29)	516 (64)	0.001
Heart rate recovery, bpm	33±9	12±7	0.0001
Peak MET in men	9.4±2.4	7.0±2.0	0.0001
Peak MET in women	7.5±2.0	5.5±1.7	0.0001
Angina during exercise, n (%)	560 (12)	131 (16)	0.001
Abnormal ST-segment changes, n (%)	706 (17)	111 (18)	0.88
Echocardiographic ischemia, n (%)	598 (13)	160 (20)	0.001
Increase in LV size after exercise, n (%)	249 (5)	85 (11)	0.001

Continuous variables are shown as mean±SD, whereas categorical variables are shown as number (percent). bpm indicates beats per minute; LV, left ventricle.

recovery to all-cause mortality. The Wald  $\chi^2$  values for 1-, 2-, and 3-minute heart rate recoveries were 87, 60, and 58, respectively. Therefore, we chose to use 1-minute heart rate recovery as the primary variable for analyses.

To determine an optimal cutoff value for 1-minute heart rate recovery, a series of Kaplan-Meier curves was constructed describing mortality rates above and below all heart rate recovery values between the 10th and 90th percentiles of the entire cohort.<sup>19</sup> A cutoff value of ≤18 beats per minute was considered abnormal, because this value yielded the highest log-rank  $\chi^2$  statistic.

The association of heart rate recovery with all-cause mortality was formally tested by construction of Kaplan-Meier plots<sup>20</sup> and Cox proportional hazards analyses.<sup>21</sup> The proportional hazards assumption was confirmed by analysis of time-dependent covariates. Stratified analyses according to prespecified variables were used to explore potential interactions. For descriptive purposes, heart rate recovery values were sorted according to deciles, and 5-year Kaplan-Meier survival rates were plotted along with 95% Greenwood confidence limits.

Multivariable Cox analyses were performed in two stages.<sup>22</sup> First, stepwise modeling was done on 500 bootstrap samples for purposes of variable selection<sup>23–25</sup>; those variables, including interaction

terms, that entered at least 50% of models were considered viable. In the second stage, parameter estimates and standard errors were calculated on the basis of a separate set of 500 additional bootstrap resamplings.

Because left ventricular ejection fraction was visually estimated rather than quantitatively measured, a supplementary analysis was done to validate prognostically this approach. Patients were divided into the following 4 groups: (1) ejection fraction >50%; (2) ejection fraction 41% to 50%; (3) ejection fraction 31% to 40%; and (4) ejection fraction ≤30%. Kaplan Meier survival curves were drawn for each of these groups with the log-rank  $\chi^2$  test used to test for differences. A test for trend was used to determine if decreasing visually assessed ejection fraction was associated with higher mortality risk. All analyses were performed using the SAS statistical package, version 6.12 (SAS Institute, Inc).

## Results

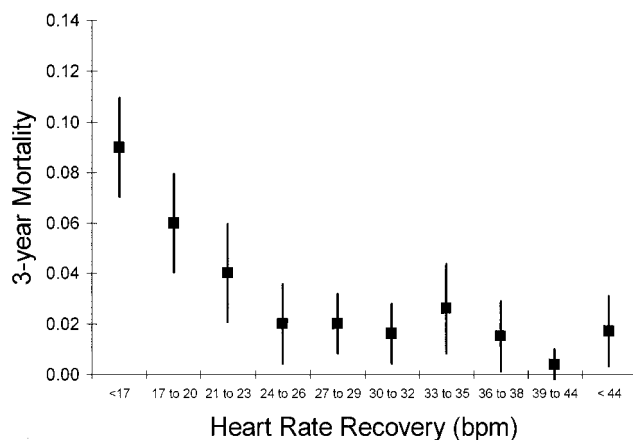
### Patient Characteristics

The study sample consisted of 5438 patients; of those, 15% (n=805) had an abnormal heart rate recovery (≤18 beat/min). The median value of heart rate recovery was 30 bpm, with 25th and 75th percentile values of 22 and 37 bpm.

Baseline characteristics according to heart rate recovery are shown in Table 1. Patients with an abnormal heart rate recovery were older and had a more adverse risk profile. They were more likely to take cardioactive medications. Exercise characteristics according to heart rate recovery are summarized in Table 2. Patients with an abnormal heart rate recovery were more likely to manifest impaired functional capacity, chronotropic incompetence, angina, and evidence of myocardial ischemia.

### Heart Rate Recovery and Mortality

During 16,446 person-years, there were 190 deaths. Figure 1 shows Kaplan-Meier 3-year death rates, along with 95% confidence intervals, according to deciles of heart rate recovery. Once heart rate recovery values fell below 21 to 23 beats per minute, the mortality rate increased substantially. When considered as a dichotomous variable, an abnormal heart rate



**Figure 1.** Unadjusted Kaplan-Meier 3-year mortality rates and 95% Greenwood confidence intervals according to decile of heart rate recovery.

**TABLE 3. Risk of Death According to Univariate Analysis**

Variable	Deaths/N With Predictor (%)		Hazard Ratio (95% CI)	Wald $\chi^2$	P
	Present	Absent			
Abnormal heart rate recovery	75/805 (9)	115/4633 (2)	3.92 (2.93–5.25)	85	<0.0001
Older age ( $\geq 65$ years)	120/1725 (7)	70/3713 (2)	3.78 (2.82–5.08)	78	<0.0001
LV ejection fraction $\leq 40\%$	40/337 (12)	150/5101 (3)	3.76 (2.66–5.34)	55	<0.0001
Fair or poor fitness	98/1634 (6)	92/3804 (2)	2.76 (2.07–3.66)	49	<0.0001
Prior coronary artery disease	115/2006 (6)	75/3432 (2)	2.56 (1.91–3.43)	40	<0.0001
Diabetes	49/677 (7)	141/4761 (3)	2.68 (1.94–3.71)	35	<0.0001
Echocardiographic ischemia	49/758 (6)	141/4680 (3)	2.18 (1.57–3.01)	21	<0.0001
Hypertension	107/2463 (4)	83/2975 (3)	1.65 (1.24–2.20)	12	0.0006
Female sex	49/1991 (2)	141/3447 (4)	0.63 (0.46–0.88)	8	0.006
Present or recent smoker	39/862 (5)	151/4576 (3)	1.38 (0.97–1.96)	3	0.08

recovery, defined as  $\leq 18$  bpm, was associated with an increased risk of death (9% versus 2%, hazard ratio [HR] 3.9, 95% CI 2.9 to 5.3,  $P < 0.0001$ ). Heart rate recovery was also predictive of death when considered as a continuous variable. Other predictors of death in univariable analyses are shown in Table 3.

When we tested for interactions, we found a weak interaction whereby the increase in mortality risk associated with an abnormal heart rate recovery was lower among patients taking  $\beta$ -blockers (taking  $\beta$ -blockers, 6% versus 3%, HR 2.2, 95% CI 1.2 to 4.1,  $P = 0.015$ ; not taking  $\beta$ -blockers, 11% versus 2%, HR 4.6, 95% CI 3.3 to 6.5,  $P < 0.0001$ ). Heart rate recovery and left ventricular systolic dysfunction provided additive predictive information (Figure 2).

### Multivariable Analyses

An abnormal heart rate recovery remained independently predictive of death (adjusted HR 2.1, 95% CI 1.5 to 2.8,  $P < 0.0001$ ) even after adjusting for age, sex, resting blood pressure, resting heart rate, present or recent smoking, diabetes, use of antihypertensive medications, history of known coronary disease and previous myocardial revascularization, use of aspirin, nitrates, lipid lowering drugs,  $\beta$ -blockers, calcium channel blockers, and angiotensin-converting en-

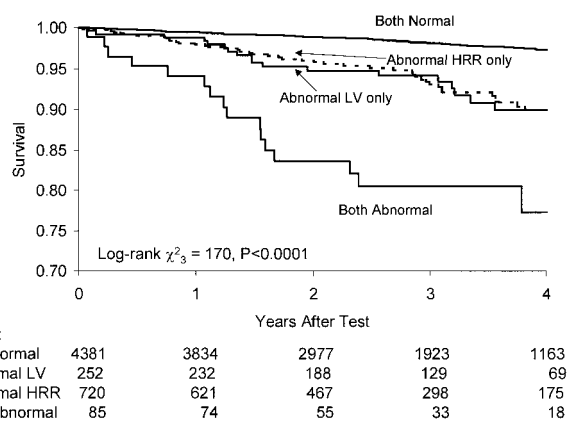
zyme inhibitors, history of peripheral vascular disease and chronic lung disease, exercise capacity, exercise-induced angina, chronotropic response, left ventricular ejection fraction, change in left ventricular cavity size with stress, and echocardiographic evidence of myocardial ischemia (Table 4). No interaction terms were found to be significant.

### Validity of Visually Assessed Left Ventricular Ejection Fraction

A visually estimated ejection fraction of 41% to 50% was present in 466 patients (9%), whereas values of 31% to 40% and  $\leq 30\%$  were noted in 229 (4%) and 108 (2%) patients, respectively. Visually estimated ejection fraction was strongly correlated with risk of death, as shown in Figure 3.

### Sensitivity Analyses

To test the robustness of our findings, we examined the association of heart rate recovery with mortality in several sensitivity analyses. First, we took into account posttest revascularization, which occurred in 221 patients within the first 2 months of follow-up. Incorporating performance of early revascularization into the multivariable analysis had no impact on the overall results. We also limited analyses to

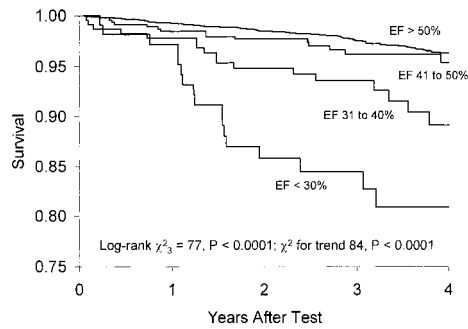


**Figure 2.** Unadjusted Kaplan-Meier curves of survival according to heart rate recovery (HRR) and left ventricular (LV) systolic dysfunction. Left ventricular dysfunction was defined as an estimated left ventricular ejection fraction  $\leq 40\%$ .

**TABLE 4. Results of Multivariable Analyses**

Predictor	Bootstrap Models, %	Hazard Ratio (95% CI)
Older age ( $\geq 65$ years)	100	1.9 (1.6–2.3)
Fair or poor fitness	98	2.1 (1.5–2.8)
Abnormal heart rate recovery	94	1.9 (1.3–2.5)
LV ejection fraction $\leq 40\%$	82	1.9 (1.3–2.7)
Male sex	72	1.5 (1.0–2.0)
Present or recent smoker	72	1.6 (1.1–2.3)
Diabetes	62	1.6 (1.1–2.1)
Prior coronary artery disease	50	1.3 (0.9–1.8)

Second column refers to the proportion of 500 bootstrap samples in which the predictor entered at least 50% of models at a  $P$  value  $\leq 0.05$ . Third column refers to the hazard ratio and confidence intervals of these intervals based on a second set of 500 bootstrap analyses in which the variables for each model were fixed.



**Figure 3.** Unadjusted Kaplan-Meier curves of survival according to visually estimated left ventricular ejection fraction (EF).

those people who had at least 6 months of follow-up and again found no difference in the overall results.

Second, we excluded the 28 patients who had undergone coronary artery bypass graft within 90 days before the stress test; this also had no effects on the overall results. Third, as the population was quite obese, we examined whether a body mass index of  $\geq 30$  kg/m<sup>2</sup> was predictive of mortality; after adjusting for age, sex, ejection fraction, heart rate recovery, and fitness, it was not (adjusted HR 0.9, 95% CI 0.7 to 1.2).

Fourth, we found no material difference in the distribution of heart rate recovery among patient exercised by bicycle or by treadmill. Follow-up for bicycle testing was very brief (only 1.3 years) given its limited and relatively recent use in our laboratory. There was no interaction between type of exercise used and heart rate recovery for prediction of death ( $P > 0.5$ ).

Fifth, when we excluded the patients taking  $\beta$ -blockers, heart rate recovery was again strongly predictive of death (Table 4); after adjusting for potential confounders it remained independently predictive (adjusted HR 2.0, 95% CI 1.4 to 2.3,  $P = 0.0002$ ). Finally, we examined the 527 patients who had a resting heart rate of  $< 60$  beats per minute; 81 had an abnormal heart rate recovery. Only 18 of these patients died. Heart rate recovery tended to be associated with an increased mortality rate in this small subgroup (HR 2.4, 95% CI 0.8 to 6.6,  $P = 0.10$ ).

## Discussion

### Principal Findings

Among consecutive patients referred for exercise stress echocardiography for evaluation of known or suspected coronary disease, an abnormal heart rate recovery was a strong and independent predictor of mortality. This association was independent of and additive to left ventricular systolic dysfunction as well as impaired functional capacity and echocardiographic evidence of myocardial ischemia.

### Previous Reports

We have previously reported on heart rate recovery as an independent predictor of death among patients undergoing exercise electrocardiography<sup>4</sup> and stress nuclear testing<sup>3</sup> as well as among healthy adults undergoing submaximal exercise testing.<sup>26</sup> In our two studies that were based on patients,<sup>3,4</sup> exercise was followed by a cool-down period. It has

been suggested that routine incorporation of heart rate recovery into exercise test interpretation may be problematic because a cool-down period decreases diagnostic sensitivity.<sup>27</sup>

Because we specifically analyzed patients undergoing stress echocardiography, we were able to analyze systematically the prognostic power of heart rate recovery alongside left ventricular systolic function. Patients with an abnormal heart rate recovery were more likely to have left ventricular systolic dysfunction. Nonetheless, heart rate recovery was predictive of death independent of and in addition to left ventricular systolic dysfunction (Figure 3). These data should be interpreted with caution, however, given that we deliberately excluded patients with a clinical history of heart failure and that left ventricular function was measured by a semi-quantitative visual estimation.

### Mechanisms

Heart rate recovery is correlated with vagal reactivation, which is thought to be primarily important during the first minute after exercise.<sup>1,2</sup> Because increased vagal tone is associated with reduced risks of death among people with and without cardiovascular disease,<sup>28,29</sup> we had previously hypothesized that decreased heart rate recovery would be predictive of death risk. The present analysis demonstrates that this measure is not merely a reflection of decreased left ventricular systolic function or stress-induced ischemia. As we had noted before in a different population,<sup>3</sup> heart rate recovery was correlated with impaired functional capacity; nonetheless, it was predictive of risk even after taking functional capacity into account.

### Limitations

Data on frequency of physical activity or dosages of medications were not available. Because abnormal heart rate recovery was defined on the basis of maximization of the log-rank  $\chi^2$  statistic, the strength of association may well have been overstated. We tried to minimize this by using sequential bootstrapping in our multivariable analyses and also by analyzing heart rate recovery as a continuous variable. Left ventricular ejection fraction was measured on the basis of visual estimation. Although we did prognostically validate this measure and others have supported its use,<sup>10,12,13</sup> it is possible that the strength of association between heart rate recovery and mortality may have been additionally attenuated had a more quantitative measure of left ventricular function been used.

Patients referred for stress echocardiography represent a select group in that their physicians feel that they are capable of exercise and also are likely to have reasonable echocardiographic windows. Indeed, we noted that comorbidities such as chronic lung disease, peripheral vascular disease, and the combination of diabetes and left ventricular dysfunction were quite uncommon in this population (Table 1). We did not record data on history of cancer.

### Conclusions

Despite these limitations, we found that an attenuated heart rate recovery was a powerful and independent predictor of

risk of death, even when measured in the absence of a cool-down period and even when taking into account a systematic measure of left ventricular systolic dysfunction. These data provide additional support for routine incorporation of heart rate recovery into standard risk stratification assessments among patients with known or suspected coronary artery disease. Future research is needed to determine how best to manage patients with abnormal heart rate recovery.

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