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Predictors of Late Development of Heart Failure in Stable Survivors of Myocardial Infarction

The CARE Study

Eldrin F. Lewis, MD, MPH,* Lemuel A. Moye, MD, PHD,† Jean L. Rouleau, MD, FACC,‡ Frank M. Sacks, MD,* J. Malcolm O. Arnold, MD, FACC,§ J. Wayne Warnica, MD, FACC,‖ Greg C. Flaker, MD, FACC,¶ Eugene Braunwald, MD, FACC,* Marc A. Pfeffer, MD, PHD, FACC*

Boston, Massachusetts; Houston, Texas; Toronto and London, Ontario and Calgary, Alberta, Canada; and Columbia, Missouri

OBJECTIVES We sought to determine the predictors of heart failure (HF) development in long-term survivors of myocardial infarction (MI).

BACKGROUND Modern strategies of acute MI care have resulted in an increasing proportion of survivors at heightened risk of future non-fatal events, including HF.

METHODS We assessed the risk of developing HF in 3,860 stable MI patients without a previous history of HF, who were enrolled in the Cholesterol And Recurrent Events (CARE) trial a median of 10 months post MI. Baseline characteristics of patients who did or did not develop HF during the five years of observation were assessed.

RESULTS A total of 243 patients (6.3%) developed HF in a linear pattern at a rate of 1.3%/year. Heart failure development markedly increased the risk of death (hazard ratio 10.2, 95% confidence interval 7.7 to 13.5). Fifty-seven patients (23.5%) who developed HF had a recurrent MI between enrollment and the onset of HF, increasing the risk fivefold. The most important predictors of HF were age and left ventricular ejection fraction. Other predictors included diabetes, history of hypertension, previous MI, and baseline heart rate. Moderate exercise three or more times per week was independently associated with a 30% lower risk of HF.

CONCLUSIONS Heart failure post MI occurs in a time-dependent fashion, which is usually not a direct consequence of a detectable interim MI. Patients who experience late-onset HF have a 10-fold increased risk of death compared with other MI survivors. Baseline characteristics can risk stratify patients at high risk of subsequent HF. (J Am Coll Cardiol 2003;42:1446–53)

Myocardial infarctions (MIs) are associated with increased short- and long-term mortality (1). This risk of death in survivors of MI is not uniform, however. Multiple prognostic factors, including the patient's baseline characteristics, the extent and complications of MI, and the use of medications and procedures, have been shown to impact the risk of death (2,3). Survivors of MI are also at heightened risk of developing major non-fatal cardiovascular events, including recurrent MI, arrhythmia, stroke, and heart failure (HF) (1,4–6). The risk of experiencing these important cardiovascular events also varies considerably across the spectrum of MI survivors. The development of HF post MI is particularly serious because patients manifesting HF have a several-fold increase in the risk of death when compared with other MI survivors (1,7). A better understanding of the factors involved in the eventual development of HF in long-term MI survivors will better identify high-risk patients more likely to benefit from implementation of more intensive preventive measures and generate potential mechanistic information. The objective of this analysis was to provide a quantitative evaluation of the factors that predict the development of HF in stable patients far removed from their MIs.

METHODS

The Cholesterol And Recurrent Events (CARE) trial enrolled 4,159 patients who survived MI within the preceding 3 to 20 months (mean 10), with a total cholesterol level <240 mg/dl, a low-density lipoprotein level between 115 and 174 mg/dl, and a fasting triglyceride level <350 mg/dl. The study organization, recruitment of patients, randomization, and follow-up in the CARE trial have been described in detail elsewhere (8,9). Briefly, patients were randomized to conventional therapy plus either 40 mg/day pravastatin or placebo. Eligible patients were required to have a fasting glucose ≤220 mg/dl. The left ventricular ejection fraction (LVEF) was assessed in all patients, and those with LVEF <25% were excluded. Patients with symptomatic HF at the time of randomization, despite medical therapy, were excluded. Other exclusion criteria included excessive ethanol intake, defined as >3 drinks per day, severe valvular disease, renal disease (creatinine >1.5

From the *Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; †University of Texas School of Public Health, Houston, Texas; ‡University of Toronto, Toronto, Ontario, Canada; §London Health Sciences Center, London, Ontario, Canada; ‖Foothills Hospital, Calgary, Alberta, Canada; and ¶University of Missouri Hospital and Clinics, Columbia, Missouri. Dr. Lewis was supported in part by Grant 1 F32 HL71449-01 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Dr. Pfeffer and Dr. Sacks are consultants and received honoraria from Bristol Myers Squibb. Dr. Arnold received honoraria from Bristol Myers Squibb.

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Abbreviations and Acronyms

CARE = Cholesterol And Recurrent Events trial
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
MI = myocardial infarction
SAVE = Survival And Ventricular Enlargement trial

times the upper limit of normal or urine protein ≥2+), untreated endocrine disorders, significant gastrointestinal disease or surgery that may interfere with drug absorption, hepatobiliary disease, malignancy or a medical condition thought to limit survival, or a history of immune disorders. Recruitment for CARE occurred in 80 centers (67 in the U.S. and 13 in Canada) between December 4, 1989, and December 31, 1991, with a designed follow-up of five years. The institutional review boards at each participating center approved the CARE protocol, and all patients provided informed consent.

The 299 CARE patients with a previous history of HF were excluded from this analysis to create a cohort of 3,860 patients without current or past symptomatic HF. The risk and timing of developing HF in this stable, post-MI population are the subjects of this study.

After randomization, visits to the clinic occurred quarterly. The development of HF was prospectively defined as hospital admission for the management of HF. To confirm the diagnosis of HF, attempts were made to obtain hospital records, consultation notes, discharge summaries, and pertinent laboratory data. A secondary outcome was all-cause mortality or hospitalization for HF. Patients who performed at least moderate physical activity (e.g., brisk walking, riding a stationary bicycle, or moderate gardening or housework) three or more times per week at baseline were grouped into the moderate exercise category. The remaining patients who did not perform this minimum amount of physical activity comprised the reference group.

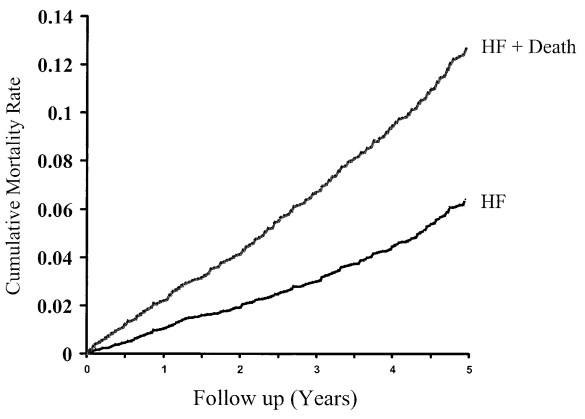

Figure 1. Cumulative incidence of hospitalization for heart failure (HF) and death *or* hospitalization for HF in patients enrolled in the CARE trial without a previous history of HF. The **upper line** represents the cumulative incidence of all-cause mortality or hospitalization for HF, and the **lower line** represents only HF hospitalizations.

Statistical analysis. The comparability of baseline characteristics in the patients who were hospitalized for HF and those without HF was assessed using the chi-square test for categorical variables and the standard *z* test for continuous variables. All hypothesis testing and all risk reductions with confidence intervals were assessed using the Cox proportional hazards model (10). Kaplan-Meier survival curves for the patients who developed HF and those who did not were calculated (11).

The attributable risk of hypertension, diabetes, and exercise was calculated using the difference between the cumulative incidence rate of HF in the exposed group from the cumulative incidence rate of HF in the non-exposed group (12,13). This difference was converted to a percentile, reflecting the absolute effect of the exposure to the putative risk factor on the development of HF. Variables significant on univariate analyses were candidate variables for the multivariate model. Cox proportional hazards modeling was used to determine multivariate baseline predictors of HF development. Predictors in each analysis were tested using the likelihood ratio chi-square test. Hazard ratios (HRs) were calculated with 95% confidence intervals (CIs) for significant variables. The final model included those covariates that remained significant in predicting HF as well as HF and death (using a p value <0.01). Co-linearity was assessed by the evaluation of correlation coefficients, and the presence of effect modification was examined using interaction terms.

Risk profiles were created empirically based on the multivariate predictors of HF post MI. Patients were characterized into low, medium, and high risk of HF based on the presence or absence of baseline predictors. The subsequent development of HF was assessed in these three groups.

RESULTS

Timing of events. Of 3,860 patients without a previous history of HF, a total of 243 (6.3%) were hospitalized for the management of HF during a median follow-up of five years. The cumulative incidence of HF increased in a time-dependent manner at a rate of ~1.3% per year (Fig. 1). The cumulative incidence of death or HF development was also linear, with ~2.2% of patients either dying or developing HF by one year after randomization and 14% of patients dying or developing HF by five years.

Of the 243 patients who developed HF, 57 (23.5%) had a recurrent MI. Among these 57 patients, 34 experienced a recurrent MI at a median of 247 days before the hospitalization for HF, and in the remainder of the patients with recurrent MIs (n = 23), HF occurred simultaneously. Among the 3,617 patients who did not develop HF, recurrent MI occurred significantly less frequently (7.3% vs. 23.5%, $p < 0.0001$).

As a consequence of developing HF, the risk of death was

Table 1. Baseline Characteristics of Patients With and Without the Development of Heart Failure in Long-Term Survivors of MI

Characteristics	No Heart Failure Development (n = 3,617 [93.7%])	Heart Failure Development (n = 243 [6.3%])	p Value
Demographics			
Age (yrs)	58.0 ± 9.3	62.3 ± 7.2	< 0.001
Female (number)	479 (13.2%)	42 (17.3%)	0.081
Race (non-white)	257 (7.1%)	31 (12.8%)	0.002
Body mass index (kg/m^2)	27.6 ± 6.4	28.8 ± 4.9	0.004
Risk factors and behavior			
Diabetes	461 (12.8%)	52 (21.4%)	< 0.001
History of hypertension	1,479 (40.9%)	138 (56.8%)	< 0.001
Current smoker	580 (16.0%)	51 (21.0%)	0.048
Moderate exercise (≥3 times/week)	2,141 (59.2%)	122 (50.2%)	< 0.001
Cardiovascular history			
Previous MI	479 (13.2%)	68 (28.0%)	< 0.001
Previous CABG	881 (24.4%)	87 (35.8%)	< 0.001
Previous angioplasty	1,245 (34.4%)	65 (26.8%)	0.014
Previous CABG or angioplasty	1,950 (53.9%)	135 (55.6%)	0.642
History of atrial fibrillation/flutter	44 (1.2%)	5 (2.1%)	0.233
Presenting characteristics			
Q-wave MI	2,198 (86.3%)	151 (83.4%)	0.684
Thrombolytic treatment	1,540 (42.6%)	94 (38.7%)	0.230
Peak creatinine kinase	1,685 ± 1,586	1,698 ± 1,441	0.901
LVEF (%)	54.1 ± 11.6	48.2 ± 13	< 0.001
Systolic blood pressure (mm Hg)	128.5 ± 18	133.6 ± 20	< 0.001
Diastolic blood pressure (mm Hg)	78.6 ± 10	80.1 ± 12	0.026
Lipid profile			
Total cholesterol (mg/dl)	208.7 ± 17	208 ± 17	0.53
LDL cholesterol (mg/dl)	138.7 ± 15	138.4 ± 14	0.76
HDL cholesterol (mg/dl)	38.9 ± 9	38.4 ± 8	0.40
Triglycerides (mg/dl)	155.7 ± 61	155.5 ± 56	0.96
Medications at presentation			
ACE inhibitors	411 (11.4%)	47 (19.3%)	< 0.001
Beta-blockers	1,474 (40.8%)	89 (36.6%)	0.224
Aspirin	3,054 (84.4%)	189 (77.8%)	0.009
Nitrates	1,108 (30.6%)	120 (49.4%)	< 0.001
Diuretics	278 (7.7%)	56 (23.1%)	< 0.001
Calcium-channel blockers	1,430 (39.5%)	107 (44.0%)	0.176
Digoxin	194 (5.4%)	33 (13.6%)	< 0.001

Data are presented as the mean value ± SD or number (%) of subjects.
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

much greater than in those without HF (HR 10.2, CI 7.7 to 13.5; $p < 0.0001$). Sixty-eight (28%) of 243 patients died at a mean of 43 ± 16 months after HF development. This rate is significantly different from the 252 (7%) of 3,617 patients without HF who died during follow-up ($p < 0.0001$).

Patient characteristics. The baseline characteristics of patients with and without HF development during follow-up are summarized in Table 1. Patients developing HF were older than patients without HF ($p = 0.0001$). The development of HF occurred progressively more commonly with increasing age (Fig. 2). Heart failure occurred in 57 (13%) of 432 patients over 70 years old and in 186 (5.4%) of 3428 patients younger than 70 years old ($p < 0.001$). Only 1.7% of patients under the age of 50 years developed HF during the five-year follow-up. Patients with a lower baseline left ventricular ejection fraction were more likely to develop HF (Fig. 3).

The most common co-morbid illnesses present in patients developing HF were hypertension and diabetes. Among the 243 patients who developed HF, 138 (57%) had a history of hypertension, with an attributable risk of 16%. A total of 52 (21.4%) of the 243 patients had a history of diabetes, with an attributable risk of 9%. Patients who developed HF were also more likely to be current smokers at the time of randomization to the CARE trial. A history of MI before the index MI was more common in patients who developed HF (28.0% vs. 13.2%, $p < 0.001$).

The patients who developed HF had higher systolic and diastolic blood pressures and higher heart rates. Coronary artery bypass grafting was previously performed more commonly in patients who developed HF, whereas previous angioplasty was more prevalent in patients who did not develop HF. Patients who exercised moderately at least three times weekly (n = 2,263) were also less likely to

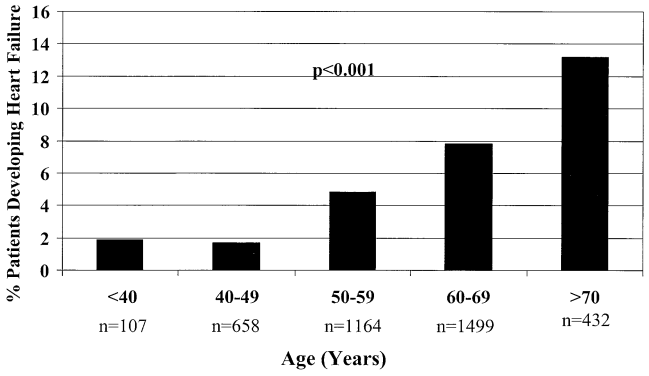

Figure 2. The impact of age on the development of heart failure after an myocardial infarction in the CARE trial.

develop HF than those not exercising regularly at baseline (HR 0.69, 95% CI 0.54 to 0.89; $p < 0.0001$). The characteristics of the index MI were not associated with increased HF development, with no differences in the percentage of patients with Q-wave MI or those who received thrombolytic therapy. The peak cardiac enzyme levels and baseline lipid profile were also not different between the two groups.

At the time of randomization, the patients who developed HF were more often taking angiotensin-converting enzyme inhibitors, nitrates, diuretics, and digoxin and were taking beta-blockers less often.

Multivariate predictors of HF development and outcomes. Multivariate analysis identified seven independent predictors of HF in stable survivors of MI without a previous history of HF (Table 2). Age ($p < 0.001$) was the most powerful predictor of HF development, with a 7% higher risk of HF for every one-year increase in age. Left ventricular ejection fraction was the second most significant predictor of HF development post MI, with a 4% increase in the risk of HF for every 1% decrease in baseline LVEF ($p < 0.001$). Patients <60 years old had a very low HF rate, unless the LVEF was <35% (Fig. 4A).

The only finding on physical examination that was independently associated with the development of HF was a higher baseline heart rate ($p < 0.001$). Hypertension and

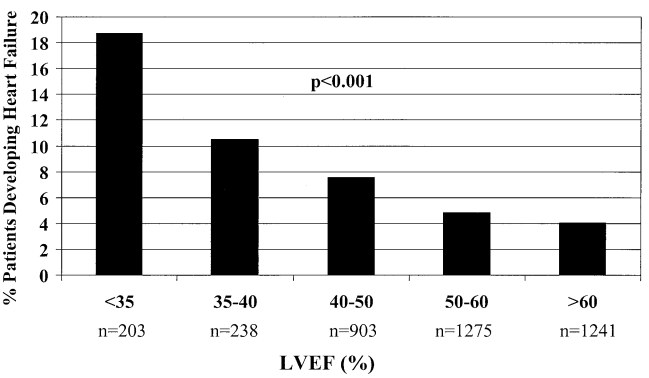

Figure 3. The impact of baseline left ventricular ejection fraction (LVEF) on the development of heart failure after an myocardial infarction in the CARE trial.

MI before the index MI were also important predictors of HF development. Regular exercise at baseline was inversely related to the risk of HF development. Patients who exercised at least three times weekly at baseline exhibited a lower risk of developing HF than patients who did not exercise as frequently. Patients with diabetes had a 42% increase in the risk of HF development, as compared with non-diabetics. After adjusting for confounding factors, the Killip class at the time of the index MI and body mass index (HR 1.01, 95% CI 1.00 to 1.02; $p = 0.07$) no longer remained significant. Assignment to pravastatin, compared with placebo, did not decrease the rate of HF development (6.1% vs. 6.9%, $p = 0.31$).

The risk of developing HF after surviving MI increased with a higher number of risk factors. Based on the final multivariate model, the most important predictors of HF were age and LVEF. Patients can be grouped into high-, intermediate-, and low-risk groups (Table 3) according to the baseline characteristics predictive of HF. The high-risk group was defined as age >60 years, LVEF <50%, a history of hypertension, and diabetes. The intermediate-risk group could have LVEF >50% if they had other predictive risk factors. The patients who did not meet criteria for the high-risk and intermediate-risk groups were considered as the low-risk group. Using the low-risk patients as the reference group, the risk of HF development was fourfold higher in the intermediate group and 15-fold higher in the high-risk group. These two groups were also at a significantly higher risk of HF and death compared with the low-risk group.

A total of 311 patients developed recurrent MI during follow-up. The occurrence of recurrent MI increased the risk of HF development dramatically (HR 4.91, 95% CI 3.45 to 6.97; $p < 0.001$). Recurrent MI significantly increased the risk of HF development, irrespective of the baseline risk profile of the patient.

DISCUSSION

Over the past few decades, with advances in the management of acute MI, there has been a decline of over 40% in all-cause mortality during the acute phase of MI (14). These successes have resulted in a larger pool of infarct survivors who remain at risk of other significant cardiovascular events, such as arrhythmias, recurrent MI, stroke, and the development of HF. Subsequent to increased survival, the risk of HF following MI has not decreased (14). Based on the results of the Multicenter Automatic Defibrillator Implantation Trial (MADIT II) (15), the number of patients with coronary artery disease and LVEF <30% who will receive an implantable defibrillator will likely increase, resulting in an even larger pool of patients surviving MI who will be at risk of subsequent HF development. As such, HF after MI remains a major concern. Patients developing HF during hospitalization for MI have a much greater in-hospital mortality rate. Little is known, however, about the predic-

Table 2. Multivariate Predictors of Heart Failure Development and Heart Failure and Death in Long-Term Survivors of MI

	Heart Failure Development			Heart Failure Development and Death		
Variable	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Age, increase 1 year	1.07	1.05–1.09	< 0.0001	1.06	1.05–1.07	< 0.001
LVEF, decrease by 1%	1.04	1.03–1.05	< 0.0001	1.03	1.02–1.04	< 0.001
Heart rate, increase by 4 beats/min	1.10	1.06–1.15	< 0.0001	1.06	1.03–1.10	< 0.001
History of hypertension	1.70	1.31–2.19	< 0.0001	1.34	1.12–1.62	0.0015
History of previous MI	1.75	1.32–2.33	0.0001	1.42	1.15–1.76	0.0013
Moderate exercise	0.67	0.52–0.86	0.0017	0.67	0.55–0.79	< 0.001
Diabetes	1.42	1.04–1.94	0.028	1.50	1.25–1.93	0.0003
Killip class at index MI (≥II)	1.36	0.97–1.92	0.078	1.36	1.06–1.73	0.0145

CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

tors of late development of HF in patients who survive the initial high-risk months after MI and the impact of this late HF development on mortality. The objective of this analysis was to identify the factors predicting the development of HF after MI among stable patients not previously treated for HF.

The CARE population was a cohort of stable, long-term survivors of acute MI, with 3,860 patients enrolled without a previous history of HF. After a median follow-up of five years, the cumulative incidence of HF was 6.3%, suggesting that these patients remained at continued, albeit low, risk of future adverse events such as HF, even though there was a period of stability after the acute MI. The incidence of HF increased linearly in a time-dependent fashion. This pattern is consistent with the Framingham Heart Study population, which experienced a 2% annual incidence of HF in survivors of acute MI up to 10 years (14).

The cumulative incidence of HF in the CARE popula-

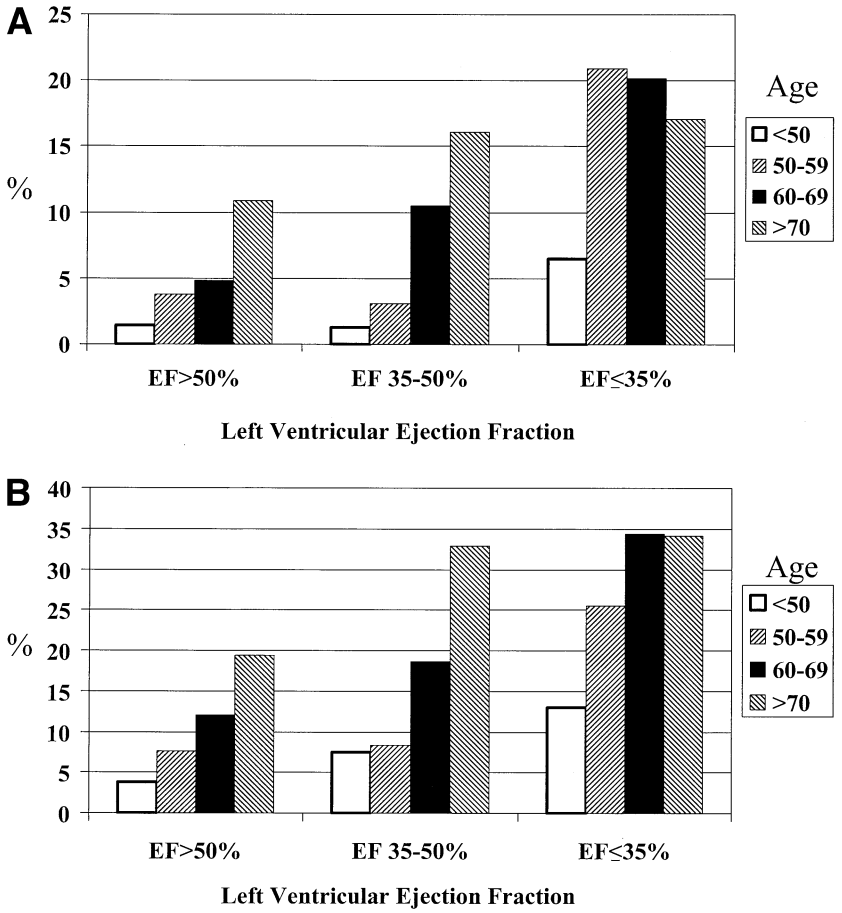

Figure 4. **(A)** The overall effect of the combination of age and left ventricular ejection fraction (LVEF) on the rate of hospitalizations for heart failure (HF) over a mean follow-up of five years in the CARE population. **(B)** The overall effect of the combination of age and LVEF on the rate of hospitalizations for HF and death over a mean follow-up of five years in the CARE population.

Table 3. Description of the Risk Profiles Based on the Final Model

Risk	Description	Heart Failure		Heart Failure and Death	
		5-Year Rate	HR (95% CI)	5-Year Rate	HR (95% CI)
High risk (n = 341)	Age >60 years *and* LVEF <50% *and* diabetes *and* hypertension	64 (18.8%)	15.1 (6.91–32.89)	105 (30.8%)	10.7 (6.34–18.17)
Intermediate risk (n = 3,048)	a) Age 55–60 years *and* LVEF <50% *and* *either* diabetes *or* hypertension b) Age 55–60 years *and* LVEF >50% *and* diabetes *and* hypertension c) Age <60 years *and* LVEF <50% *and* diabetes *and* hypertension d) Age >60 years *and* LVEF <50% *and* no diabetes *or* hypertension e) Age >60 years *and* LVEF >50% *and* diabetes *and* hypertension	172 (5.6%)	4.0 (1.88–8.52)	374 (12.3%)	3.8 (2.30–6.26)
Low risk (n = 471)	Age <55 years *and* LVEF >50% *and* no diabetes *or* hypertension	7 (1.5%)	Reference	16 (3.4%)	Reference

Abbreviations as in Table 2.

tion was much lower than the incidence of acute HF immediately after MI (16,17). The lower incidence of HF in this population could be due to patient selection. Patients with a previous history of HF were excluded and patients had to survive for a minimum of three months after their index MI to be eligible for this study. One reason for the variation in the post-MI incidence of HF could be differing mechanisms for the development of HF. Acute HF that develops as an immediate consequence of acute MI may be related to infarct characteristics such as the location and size of the infarct and time to reperfusion (17–20). However, late development of chronic HF among those without a history of HF is probably related to several mechanisms, including progressive remodeling (21,22), recurrent MI, and subclinical ischemia.

The risk of most cardiac events such as HF is greatest in the first few days post MI. Studies have demonstrated that patients undergoing treatment for an initial MI have a 22% incidence of acute HF before discharge, and the incidence of HF in patients with recurrent MI is 33% (23,24). The percentage of patients developing HF drops dramatically by day 8 after acute MI (25). Because of the high incidence of acute HF early after acute MI, the emphasis of previous studies has been on the predictors and outcomes of HF occurrence immediately following MI. Descriptive risk factors associated with early HF and an increased risk of death post MI include older age, anterior location of MI, and diabetes (25,26).

This study identified several factors that are important predictors of HF development in long-term MI survivors without a history of HF before the index MI. Independent predictors of HF include four historical variables (age, history of hypertension, history of MI before index MI, and diabetes), one physical examination variable (heart rate), one hemodynamic variable (ejection fraction), and one behavioral characteristic (exercise level). Compared with the Killip class at the time of the index MI, these seven factors were more predictive of future HF events, suggesting that clinical signs of HF at the time of the index MI may not be as important in determining patients at high-risk of future HF development. Some of these factors are similar to predictors of acute HF immediately after an MI, such as age and co-morbid illnesses (17,26). A lower LVEF may be a reflection of a larger infarct, more extensive coronary artery disease, less cardiac reserve, and poorer outcomes (18,27,28). Although lower LVEF is a significant predictor, only 14% of patients with LVEF <40% developed HF. This is similar to the rate in the Survival And Ventricular Enlargement (SAVE) trial population, in which only 15% of patients with LVEF <40% required hospitalization for HF (29). Interestingly, most patients who developed HF did not experience another MI between the index event and the development of HF, which supports the concept that a chronic, time-dependent factor such as remodeling plays a major role in this process. The low rate of recurrent MI in this group could also explain the lack of effect of pravastatin in preventing HF, a drug that decreases recurrent MI (9,30). However, the impact of recurrent MI in increasing the risk of HF development was dramatic and was observed in patients at low, intermediate, or high risk of HF development according to baseline predictors.

Patients who developed HF after surviving MI had a markedly increased risk of death compared with patients who did not develop HF, underscoring the importance of HF development in this population. In the SAVE population, the mortality risk was six fold greater over a 3.5-year period in patients developing clinical HF requiring hospitalization than in patients with LVEF ≤40% but no clinical HF (29). In the present study, the impact of HF development on the risk of death in patients surviving a minimum of three months after MI was more than 10-fold higher than in patients not developing HF.

Study limitations. This study has several limitations. Because the development of HF in this study required hospitalization, less severe HF not requiring hospitalization was not considered. Secondly, patients who died before devel-

oping HF were not included in this analysis. However, because the final predictive model was also predictive of HF and death, this limitation should not affect the validity of the final model. Patients enrolled in a clinical trial are often different from populations that are seen in the community, which may be reflected in the relative high adherence rate to regular exercise. Medications other than pravastatin were used at the discretion of the treating physicians and therefore could not be included in the multivariable models. Finally, CARE was not prospectively designed to assess the risk factors for HF development post MI.

However, the results of this analysis have several implications in understanding the complex interaction between MI and HF. Patients at continued risk of HF development can be identified among long-term MI survivors, and in these patients, often secondary prevention efforts should be intensified. The understanding of the association of exercise with HF development should be further studied to determine whether exercise is a marker of patients who are able to exercise due to less severe disease or whether exercise actually prevents HF development. The role of aggressive therapy, such as revascularization, in improving outcomes should be considered in patients with these risk factors for the future development of HF. The efficacy of revascularization in patients with a low ejection fraction and coronary artery disease should partly be answered by the ongoing Surgical Treatment for Ischemic Heart Failure (STICH) trial. Because of the dramatic effect of HF on survival, as well as the associated morbidity and cost after HF development, there is an increasing need to understand potential therapies that may decrease the late development of HF.

Conclusions. Long-term survivors of MI without a previous history of HF remain at risk of the development of HF. A simple model consisting of baseline characteristics and physiologic parameters can predict the late development of HF. Moderate exercise at baseline independently decreases the risk of HF development, even after adjusting for age and co-morbid illnesses. Regardless of the baseline risk, recurrent MI dramatically impacts HF development, although it was not a common occurrence. When HF occurs, the risk of subsequent mortality is very high. The role of potential interventions that may modify the risks of HF development and mortality should be a focus of future investigations.

Reprint requests and correspondence: Dr. Marc A. Pfeffer, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: mpfeffer@rics.bwh.harvard.edu.

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