Influence of Ejection Fraction on Cardiovascular Outcomes in a Broad Spectrum of Heart Failure Patients

Scott D. Solomon, MD; Nagesh Anavekar, MD; Hicham Skali, MD; John J.V. McMurray, MD; Karl Swedberg, MD, PhD; Salim Yusuf, DPhil, FRCP; Christopher B. Granger, MD; Eric L. Michelson, MD; Duolao Wang, PhD; Stuart Pocock, PhD; Marc A. Pfeffer, MD, PhD; for the Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators

Background—Left ventricular function is a principal determinant of cardiovascular risk in patients with heart failure. The growing number of patients with preserved systolic function heart failure underscores the importance of understanding the relationship between ejection fraction and risk.

Methods and Results—We studied 7599 patients with a broad spectrum of symptomatic heart failure enrolled in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program. All patients were randomized to candesartan at a target dose of 32 mg once daily or matching placebo and followed up for a median of 38 months. We related left ventricular ejection fraction (LVEF), measured before randomization at the sites, to cardiovascular outcomes and causes of death. Mean LVEF in patients enrolled in CHARM was 38.8±14.9% (median LVEF 36%). Patients with lower LVEF tended to have higher baseline New York Heart Association class. The hazard ratio for all-cause mortality increased by 39% for every 10% reduction in ejection fraction below 45% (hazard ratio 1.39, 95% CI 1.32 to 1.46), with adjustment for baseline covariates. All-cause mortality, cardiovascular death, and all components of cardiovascular death declined with increasing ejection fraction until an ejection fraction of 45%, after which the risk of these outcomes remained relatively stable with increasing LVEF. The absolute change in rate per 100 patient-years for each 10% reduction in LVEF was greatest for sudden death and heart failure–related death. The effect of candesartan in reducing cardiovascular outcomes was consistent across LVEF categories.

Conclusions—LVEF is a powerful predictor of cardiovascular outcome in heart failure patients across a broad spectrum of ventricular function. Nevertheless, once elevated to a range above 45%, ejection fraction does not further contribute to assessment of cardiovascular risk in heart failure patients.

Key Words: heart failure ■ mortality ■ trials ■ cardiac function ■ ejection fraction

Left ventricular ejection fraction (LVEF) is the most commonly used clinical measure of left ventricular systolic function and is established as a powerful predictor of death in patients with low LVEF heart failure.1,2 The relationship between LVEF and nonfatal outcomes in low LVEF heart failure is less well documented. Furthermore, it is now recognized that many patients with signs and symptoms of heart failure have preserved left ventricular systolic function. The relationship between LVEF and both fatal and nonfatal outcomes has not been described in patients with heart failure across the full spectrum of ejection fraction.

The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program was designed to assess the effect of the angiotensin receptor blocker candesartan on cardiovascular morbidity and mortality in a broad spectrum of patients with heart failure, irrespective of LVEF.3 The CHARM Program was designed and powered with the intention of pooling the overall results. In this report, we assess the influence of ejection fraction on fatal and nonfatal cardiovascular and noncardiovascular outcomes in the CHARM Program.4–6

Methods

Patients: The CHARM Program

The design, baseline findings, and primary results of the CHARM Program have been reported in detail.3 Briefly, the CHARM Program consisted of 3 independent but related trials performed concurrently in which 7599 patients with New York Heart Association (NYHA) class II to IV chronic heart failure of ≥4 weeks’ duration were randomized to placebo or candesartan (target dose 32 mg once
Assessment of Ejection Fraction and End Points

LVEF was assessed clinically at the individual enrolling sites by quantitative echocardiography (79%), radionuclide ventriculography (16%), or x-ray contrast ventriculography (5%) and recorded on a case report form. Sites were instructed that ejection fraction needed to be calculated by an accepted formula. When several measures of ejection fraction were available, sites were instructed to use the most recent. For the 2 low systolic function studies (CHARM-Alternative and CHARM-Added), ejection fraction had to have been measured within the previous 6 months. For the preserved systolic function study (CHARM-Preserved), ejection fraction had to have been measured within the previous 6 months. For the preserved systolic function study (CHARM-Preserved), ejection fraction had to have been measured within the previous 6 months. The primary outcome of the individual component trials of the CHARM Program was the composite of cardiovascular death or hospital admission with worsening heart failure, analyzed by time to first event. The primary outcome of the overall CHARM Program was all-cause mortality (time to first event).

Statistical Analysis

We divided the range of ejection fractions across the entire CHARM Program into 11 separate 5-point bins: <17%, 18% to 22%, 23% to 27%, 28% to 32%, 33% to 37%, 38% to 42%, 43% to 47%, 48% to 52%, 53% to 57%, 58% to 62%, and ≥63%. Each of these bins was centered around a multiple of 5, because we observed a substantial “digit preference” for ejection fraction values in multiples of 5. On the basis of these categories represented by 11 values, we characterized the LVEF effect on the primary end points utilizing various models (including linear, quadratic, and logarithmic models) and found a linear effect with a threshold at the category 43% to 47% that fit the effect of ejection fraction best. For reporting purposes, we further compressed adjacent 5-point categories into single 10-point categories to achieve the following LVEF categories: ≥22%, 23% to 32%, 33% to 42%, 43% to 52%, and >52%.

Differences across ejection fraction categories were assessed with a test for trend by means of linear regression for continuous variables and logistic regression for categorical variables. Incidence rates were calculated per 100 person-years. Hazard ratios were calculated with a Cox proportional hazards model, and we reported the hazard associated with each 10-point change in ejection fraction (representing a change of 2 ejection fraction categories). Comparisons between treatment groups were made for the overall program. The influence of LVEF on cardiovascular outcome was assessed in a multivariable model, which adjusted for all important predictors of mortality and morbidity identified in the CHARM Program, including age, sex, diabetes mellitus, NYHA class, rest dyspnea, current cigarette smoking, previous hospitalization for heart failure (none, within 6 months, or ≥6 months), first diagnosis of heart failure >2 years ago, previous MI, atrial fibrillation, heart rate, diastolic blood pressure, dependent edema, pulmonary crackles, cardiomegaly, bundle-branch block, pulmonary edema, mitral regurgitation, and candesartan treatment. We tested for interaction between ejection fraction and gender.

Results

The mean LVEF in the patients enrolled in CHARM was 38.8±14.9% (median LVEF 36%). The distribution of LVEF is shown in Figure 1. Patients with higher ejection fractions were older and more often female (Table 1). Patients with higher LVEF were more likely to have a history of hypertension and had higher baseline diastolic blood pressure. The incidence of diabetes did not differ across LVEF categories. The majority of patients enrolled in the lower LVEF categories were in NYHA class III, whereas the majority of patients enrolled in the higher LVEF categories were in NYHA class II. The proportion of patients treated with a diuretic, an ACE inhibitor, spironolactone, and especially digitalis decreased as
LVEF increased. Conversely, the use of calcium channel blockers increased with increasing LVEF. There was no difference in the use of β-blockers and lipid-lowering agents across LVEF categories.

The relationship between LVEF and the risk of cardiovascular death, the individual components of cardiovascular death, and selected nonfatal outcomes is shown in Table 2 and Figure 2. The risk of death declined with increasing ejection fraction until an ejection fraction of \(\approx 45\%\). This trend was also observed for cardiovascular death and the components of cardiovascular death, with the exception of fatal stroke. The rate of noncardiovascular death did not vary by ejection fraction.

The rate of heart failure hospitalization declined significantly with increasing LVEF up to an ejection fraction of \(\approx 45\%\). This trend was also observed with fatal and nonfatal

### TABLE 1. Baseline Characteristics by LVEF

| LVEF | Age, y | Heart rate, bpm | Systolic BP, mm Hg | Diastolic BP, mm Hg | Male gender | Current smoker | NYHA class II | NYHA class III | NYHA class IV | History of hypertension | Ischemic heart disease | Prior CABG or PTCA | Diabetes mellitus | Digitalis glycoside | Diuretics | β-Blocker | Calcium channel blocker | Other vasodilators | Lipid-lowering drug | ACE inhibitors | Spironolactone |
|------|--------|-----------------|-------------------|-------------------|--------------|----------------|---------------|---------------|----------------|----------------|----------------------|------------------|----------------|----------------|----------------|----------|----------------|------------------|----------------|----------------|----------------|--------------|---------|
| 22%  | 64.1±11.3 | 75.8±13.0 | 121.5±18.7 | 73.7±10.8 | 79 | 17 | 28 | 65 | 7 | 43 | 67 | 32 | 30 | 64 | 70 | 54 | 10 | 38 | 39 | 63 | 25 |
| 23%–32% | 64.7±10.8 | 73.4±13.0 | 127.0±18.3 | 75.6±10.6 | 75 | 17 | 32 | 66 | 3 | 48 | 72 | 34 | 29 | 54 | 68 | 55 | 11 | 41 | 43 | 59 | 22 |
| 33%–42% | 64.9±11.0 | 73.1±13.7 | 131.5±18.2 | 77.5±10.6 | 70 | 13 | 43 | 55 | 2 | 54 | 75 | 36 | 29 | 43 | 66 | 56 | 18 | 43 | 45 | 64 | 15 |
| 43%–52% | 66.3±10.8 | 71.4±12.4 | 135.2±18.9 | 78.2±10.8 | 68 | 15 | 64 | 36 | 0.8 | 60 | 72 | 38 | 27 | 43 | 64 | 57 | 26 | 43 | 21 | 63 | 11 |
| >52%  | 67.4±11.1 | 71.2±12.4 | 137.6±18.2 | 77.4±10.6 | 51 | 12 | 59 | 38 | 2 | 70 | 62 | 31 | 28 | 63 | 63 | 54 | 37 | 40 | 17 | 12 |

BP indicates blood pressure.
Values are mean±SD or percent.
MI, although the absolute rate of these outcomes was considerably lower than the rates of heart failure hospitalization or cardiovascular death. The rate of fatal or nonfatal stroke did not vary significantly across LVEF categories.

The relationship between LVEF and cardiovascular outcomes, taking account of other predictors of outcome, is shown in Table 3 and Figure 3. In a multivariable model that adjusted for all known important covariates, the hazard ratio for all-cause mortality increased by 39% for every 10% reduction in ejection fraction below 45%. Each 10% reduction in ejection fraction (below an LVEF of 45%) was independently associated with a significant increased risk of death due to any cause, cardiovascular death, sudden death, death due to heart failure, death due to MI, and other/procedure-related cardiovascular death but not death due to stroke or death due to noncardiovascular causes. The greatest increases in relative risk were seen for cardiovascular death (47% increase per 10% decrease in LVEF) and sudden death (48%), as well as death due to heart failure (58%) and MI (57%). Among the causes of death, the absolute change in rate per 100 patient-years for each 10% reduction in ejection fraction was greatest for sudden death and heart failure-related death and was considerably lower for fatal MI. Although the incidence of both fatal and nonfatal MI increased with decreasing ejection fraction below 45%, the absolute rate of increase in heart failure hospitalization for every 10% reduction in LVEF was more than 10-fold higher than that for fatal or nonfatal MI. Ejection fraction was not related to fatal and nonfatal stroke in the multivariable analysis. We observed no interaction between gender and ejection fraction. The effect of candesartan in reducing cardiovascular outcomes was consistent across LVEF categories.

Discussion

The results of the present analysis from the CHARM Program show that LVEF was an important predictor of fatal and nonfatal cardiovascular outcomes, including heart failure death and hospitalization, sudden death, and fatal and nonfatal MI, in a broad spectrum of patients with symptomatic heart failure, but only in those with moderate to severe reductions in left ventricular systolic function. Ejection fraction was a poorer predictor of cardiovascular outcomes in those with an LVEF above 45%. LVEF was not predictive of fatal or nonfatal stroke (although the number of events was small) or of death due to noncardiovascular causes.

### Table 3. Univariate and Adjusted Hazard Ratio and Absolute Change in Rate per 100 Patient-Years for Each 10% Reduction in Ejection Fraction

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio per 10% Reduction in LVEF Below 45% (95% CI)</th>
<th>Change in Rate per 100 Patient-Years for Each 10% Reduction in LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1.47 (1.40 to 1.54)</td>
<td>4.27 (3.80 to 4.74)</td>
</tr>
<tr>
<td>CV death</td>
<td>1.57 (1.49 to 1.65)</td>
<td>3.95 (3.48 to 4.42)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1.59 (1.47 to 1.71)</td>
<td>1.23 (0.94 to 1.53)</td>
</tr>
<tr>
<td>CHF death</td>
<td>1.73 (1.58 to 1.90)</td>
<td>1.77 (1.58 to 1.97)</td>
</tr>
<tr>
<td>Fatal MI</td>
<td>1.61 (1.34 to 1.94)</td>
<td>0.32 (0.16 to 0.49)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>1.05 (0.85 to 1.31)</td>
<td>0.02 (−0.06 to 0.10)</td>
</tr>
<tr>
<td>Other CV and procedure-related death</td>
<td>1.37 (1.17 to 1.62)</td>
<td>0.62 (0.30 to 0.94)</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>1.12 (1.01 to 1.24)</td>
<td>0.33 (0.19 to 0.47)</td>
</tr>
<tr>
<td>Fatal or nonfatal MI (1st episode)</td>
<td>1.19 (1.07 to 1.32)</td>
<td>0.26 (0.02 to 0.51)</td>
</tr>
<tr>
<td>CHF hospitalization</td>
<td>1.37 (1.31 to 1.44)</td>
<td>3.02 (1.63 to 4.40)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>0.96 (0.85 to 1.09)</td>
<td>0.04 (−0.10 to 0.18)</td>
</tr>
<tr>
<td>CV death or CHF hospitalization</td>
<td>1.45 (1.39 to 1.50)</td>
<td>5.62 (4.27 to 6.98)</td>
</tr>
</tbody>
</table>

CV indicates cardiovascular; CHF, chronic heart failure.

Adjusted for age, sex, diabetes mellitus, NYHA class, rest dyspnea, current cigarette smoking, previous hospitalization for heart failure (none, within 6 months, ≥6 months), first diagnosis of heart failure ≥2 years ago, previous MI, atrial fibrillation, heart rate, diastolic blood pressure, dependent edema, pulmonary crackles, cardiomegaly, bundle-branch block, LVEF, pulmonary edema, mitral regurgitation, and candesartan treatment.

![Figure 2. Annualized incidence of death, with components of death by LVEF. CV indicates cardiovascular; HF, heart failure; and EF, ejection fraction.](image-url)
The well-known inverse relationship between LVEF and mortality has been described mainly in patients with systolic dysfunction. These prior analyses, generally performed in clinical trial cohorts, were biased by the exclusion of patients with preserved systolic dysfunction, who constitute up to half of all patients with heart failure. Furthermore, because patients with heart failure and preserved systolic function are more often elderly, the prior analyses are further biased by exclusion of older patients, who are intrinsically at higher risk for adverse outcomes. A similar bias applied to women with heart failure, who also are more likely to have preserved systolic function. Moreover, the relationship between LVEF and nonfatal outcomes, such as hospitalization for worsening heart failure, has not been well defined, yet these are common and important events for patients and healthcare systems. The CHARM Program, by including large numbers of patients with preserved systolic function, older patients, and women, overcomes some of these limitations. That we found that LVEF was related to death due to heart failure only up to a value of \( \approx 45\% \) is not unexpected. The same conclusion is true for sudden death, although the relationship with low LVEF might have been expected to be weaker given that older age and hypertension are associated with ventricular hypertrophy and increased myocardial fibrosis, both of which are linked to increased electrical instability and predisposition to sudden death. The relationship between LVEF and MI, however, is more surprising. Although based on small numbers of events, we observed that lower LVEF was associated with a greater risk of both fatal and nonfatal MI. It is conceivable that in this population, low LVEF may simply be a marker for coronary artery disease. Lower LVEF has previously been shown to be a risk factor for stroke, at least after acute MI. That stroke was not related to LVEF in the present cohort likely reflects the small number of strokes in CHARM.

The present data show that patients with an LVEF over 45% have a much lower risk of adverse cardiovascular outcomes than those with reduced systolic function. In the subgroup with an LVEF above 45%, LVEF was not useful in further risk-stratifying patients. In other words, individuals with preserved systolic function appeared to experience the same rate of events, regardless of their LVEF, above 45%. Although we had fewer events in this subset of patients, the absolute numbers were still large, and it is not clear why LVEF failed to continue to discriminate above 45%, especially in relation to the risk of death or hospitalization for heart failure. One explanation for this finding is that ejection fraction is an incomplete measure of ventricular function. Because LVEF is so load-dependent, this measure can dramatically underestimate or overestimate true myocardial function in a variety of pathological conditions. In addition, although a reasonable measure of systolic function, LVEF is a poor measure of diastolic function and many of these patients will have

Figure 3. Hazard ratio based on LVEF for all-cause mortality (top left), cardiovascular death (top middle), heart failure–related death (top right), sudden death (bottom left), fatal and nonfatal MI (bottom middle), and cardiovascular death or hospitalization for heart failure (bottom right). CHF indicates chronic heart failure.
diastolic dysfunction.\textsuperscript{15,16} Measures of diastolic function are thus likely to provide incremental prognostic information in this patient population.

The present findings add to the emerging knowledge base on heart failure and preserved systolic function. Some investigators have reported similar survival irrespective of systolic function,\textsuperscript{17–20} whereas others have reported better survival for patients with preserved LVEF than for those with reduced systolic function.\textsuperscript{21,22} The reason for such wide differences in outcomes from various analyses is not clear, although possible explanations have included age-dependent bias and lack of information concerning ejection fraction.\textsuperscript{7} The present analysis is strengthened by the availability of LVEF in all patients, spanning a wide spectrum of age groups, and the fact that detailed and consistent adjudication of end points was performed across the broad LVEF spectrum. Finally, these data may have important implications for trial design in patients with both low and preserved systolic function heart failure and in determining appropriate end points for future clinical trials.

Some limitations of the present analysis should be noted. First, ejection fractions were measured at the sites and not in a core laboratory, and site ejection fractions were measured with a variety of techniques. Although we recognize this limitation, ejection fraction measures based on various technologies and techniques are commonly used to make clinical decisions. Moreover, the noise in the ejection fraction measure as a result of this limitation should be offset by the very large number of patients in CHARM. An analysis of decentralized echocardiography readings in theValsartan in Heart Failure Trial (Val-HeFT), another large heart failure trial, supports the idea that site readings of ejection fraction in a large clinical trial correlate with core values and can be reliably related to outcomes.\textsuperscript{23} Second, we did not obtain sophisticated measures of myocardial function in this population. A measure that accounted for both systolic and diastolic function, such as the myocardial performance index, might relate better to cardiovascular risk at the higher end of the ejection fraction spectrum. Finally, we report only on adjudicated first events of each type. It is possible that the relationship between LVEF and total number of recurrent events (such as recurrent hospitalizations for heart failure) may be different in patients with widely different ejection fractions.

Conclusions

Across a broad spectrum of patients with symptomatic heart failure, declining LVEF is an important and powerful predictor of cardiovascular outcomes, including all-cause mortality, cardiovascular mortality, sudden death, heart failure–related death, fatal or nonfatal MI, and heart failure hospitalization. Every 10% reduction in ejection fraction below 45% was independently associated with a 39% increased risk for all-cause mortality, with the most common events experienced being sudden death and heart failure–related death. The discriminatory effect of ejection fraction for prediction of adverse outcomes, however, was limited above an LVEF of 45%, which suggests that in these patients, factors other than systolic function contribute to the adverse risk.

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Disclosures

Drs Solomon, Pfeffer, Swedberg, Granger, McMurray, and Yusuf have served as consultants to or received research grants and honoraria from AstraZeneca. Drs Pocock, Wang, Skali, and Anavekar have received research support form AstraZeneca. Dr Michelson is an employee of AstraZeneca.

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