Relations Between Heart Failure, Ejection Fraction, Arrhythmia Suppression and Mortality: Analysis of the Cardiac Arrhythmia Suppression Trial

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Objectives. We studied the relations between heart failure, ejection fraction, arrhythmia suppression and mortality.

Background. Both left ventricular ejection fraction and functional class of heart failure are strongly associated with mortality after acute myocardial infarction. Both are also related to the presence of ventricular arrhythmias and have been identified as factors related to the ability to suppress ventricular arrhythmias. Little has been reported about the relations between these two factors and arrhythmia suppression or mortality.

Methods. Baseline data from the Cardiac Arrhythmia Suppression Trial were used to define several categories of heart failure and to relate both the resulting categories and ejection fraction to arrhythmia suppression and mortality using logistic and survival regression analytic methodologies.

Results. Regardless of the prospective baseline definition of heart failure used, the data consistently showed that heart failure was a more powerful predictor of subsequent congestive heart

failure events and arrhythmia suppression and was equally powerful in predicting death. However, each variable provided incremental information when included in the prediction model. Heart failure and ejection fraction appeared to be independent predictors of death. Interactions were observed: A low ejection fraction was more predictive of failure of arrhythmia suppression in patients with than without evidence of heart failure before or at baseline; a low ejection fraction was more predictive of subsequent congestive heart failure events in patients without than with evidence of heart failure before or at baseline.

Conclusions. Although heart failure as a prognostic feature appears to be somewhat superior to ejection fraction, both are powerful predictors of arrhythmia suppression and cardiac events in patients with ventricular arrhythmia after myocardial infarction. Each provides incremental prediction.

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Mortality after acute myocardial infarction is strongly associated with extent of left ventricular dysfunction, judged either by quantitative means (left ventricular ejection fraction) or clinical assessment by functional class of heart failure (1-5). Previous studies (1,3) have identified ventricular arrhythmias as an independent predictor of sudden death and total cardiovascular mortality after myocardial infarction. However, many relations exist between left ventricular function and spontaneous ventricular arrhythmias. For example, the proportion of patients with nonsustained ventricular tachycardia increases as

left ventricular ejection fraction decreases or as heart failure status worsens (6,7). In the Cardiac Arrhythmia Suppression Trial (CAST) low arrhythmic death and total cardiac mortality rates were noted in patients with relatively preserved ejection fraction who were randomized to receive placebo (8).

The CAST data base offers a rare opportunity to explore the relations between the clinical syndrome of congestive heart failure and ejection fraction. Both prognostic variables can be compared with subsequent clinical outcome and with the observed extent of arrhythmia suppression by CAST antiarrhythmic drugs. Selected aspects of the open-label CAST experience, as well as the randomized placebo-controlled trial (main trial), have been reported that provide insights into these relations (8,9). The major goal of the present study was to analyze the relation between ejection fraction measured at baseline and baseline heart failure syndromes, defined by historic and baseline descriptors, with subsequent clinical outcomes in the patients enrolled in CAST. A second goal of this study was to evaluate the influence of baseline ejection fraction and heart failure syndromes on arrhythmia suppression achieved during the open-label phase.

Methods

CAST study design. Details of the CAST study design have been described previously (8). Briefly, CAST included patients surviving acute myocardial infarction who had an average of ≥6 ventricular premature beats/h with at least 18 h of interpretable ambulatory electrocardiographic (ECG) recording, identified 6 days to 2 years after an acute myocardial infarction. If the qualifying ambulatory ECG recording was obtained within 90 days of the myocardial infarction, an ejection fraction ≤55% was required; >90 days after the index myocardial infarction, an EF of ≤40% was required. Left ventricular ejection fraction was obtained from either routine angiographic, radionuclide or echocardiographic techniques. Written informed consent was obtained before enrollment.

There was a mandatory open-label phase in CAST that consisted of the unblinded administration of encainide, flecainide or moricizine in specified sequences until a therapy was identified that achieved the CAST arrhythmia suppression goals (see definitions described later). The antiarrhythmic drug sequence was different for patients with ejection fraction <30% and those with ejection fraction ≥30%; the former had an equal likelihood of the sequence encainide–moricizine or moricizine–encainide, whereas the latter had equal likelihood of either the sequence encainide–moricizine–flecainide or flecainide–moricizine–encainide.

Patient population. A total of 3,549 patients were enrolled in CAST (81% male, mean age 61.8 years, mean of 130 ventricular premature beats/h). The mean duration of the open-label phase was 22 ± 17 days. Over three fourths (76%) of enrollees achieved adequate arrhythmia suppression and were randomized to the successful antiarrhythmic therapy or matching placebo. Because the titration sequence was limited by the ejection fraction, the analysis relating ejection fraction and heart failure syndromes to suppression was restricted to patients randomized to encainide as the first drug in the titration sequence. This restriction provided an essentially random subset of 1,159 of the 3,549 patients enrolled, which did not confound the ejection fraction with the titration sequence but did restrict the analyses of suppression to the results with encainide.

Description of ejection fraction measurement. Ejection fraction was measured in all patients in CAST, 42% by standard radionuclide techniques and the remainder by echocardiography or contrast ventriculography. Preliminary exploratory analysis indicated that the relation of ejection fraction to survival was quadratic rather than linear and was well described by dichotomizing ejection fraction at 30%.

Definitions of congestive heart failure syndrome on the basis of baseline descriptors. Because it is not established which definition of heart failure is prognostically most useful, this study explored a range of three prospective definitions of a congestive heart failure syndrome. *Definition 1* = a history of symptomatic congestive heart failure. There were 582 patients who met this definition enrolled in the open-label phase of CAST, of whom 187 were randomized to the encainide or

flecainide limbs and 149 to the moricizine limb. *Definition 2* = history of congestive heart failure as mentioned in definition 1 or physical examination evidence of congestive heart failure (rales, third heart sound [S3] gallop or jugular venous distention) at the baseline examination. This definition was met by 783 patients enrolled in the open-label phase, of whom 240 were randomized to the encainide or flecainide limbs and 214 to the moricizine limb. *Definition 3* = the broadest category, referred to as any congestive heart failure. It included the criteria of definition 2 or the use of digitalis, diuretic agents or afterload reduction agents at the time of study entry. Decisions regarding these therapies were made solely by the individual physician, not mandated by protocol. Patients taking digitalis or diuretic agents for a supraventricular tachycardia, atrial fibrillation or hypertension were not included. This third classification was met by 1,767 patients enrolled in the open-label phase of CAST, of whom 1,148 were randomized in the main trial (593 in the encainide/flecainide limbs and 555 in the moricizine limb).

The purpose of investigating a spectrum of prospective definitions of congestive heart failure was to determine the relative prognostic values of each.

Definitions of end points in the main study. An events committee classified the following occurrences based on standard prospective definitions developed in the Cardiac Arrhythmia Pilot Study (10) using all available historic and clinical evidence, with blinding to the specific therapy.

Death/cardiac arrest. Death or cardiac arrest was defined as spontaneous cessation of respiration and blood circulation (pulse) with loss of consciousness, whether or not resuscitation attempts were successful. This event occurred in 721 patients.

Arrhythmic death/cardiac arrest. This event was defined prospectively as the primary end point in the CAST study. It refers to witnessed, instantaneous death in the absence of severe congestive heart failure or cardiogenic shock; unwitnessed death with no preceding change in symptoms and for which no other cause could easily be ascribed, or cardiac arrest (without a nonarrhythmic cause) that resulted in resuscitation. This event occurred in 412 patients.

Definite congestive heart failure. This event was defined as any death ascribed to congestive heart failure or hospitalization specifically for new or worsened congestive heart failure. It occurred in 328 patients (142 heart failure deaths, 186 admitted to hospital). Note that this event was not recorded for patients after the open-label titration was completed if they were not randomized.

Any evidence of congestive heart failure. This event included all patients with definite congestive heart failure or with development of new congestive heart failure, or worsening of congestive heart failure symptoms causing changes in heart failure therapy but not requiring hospital admission. It occurred in 690 patients.

Definitions of arrhythmia suppression. In CAST, suppression of ventricular premature beats required ≥80% reduction compared with baseline; partial suppression referred to a degree of arrhythmia reduction (1% to 79%) falling short of

the study goal. For patients with ≥10 runs of ventricular tachycardia, 90% suppression was required; for those with 1 to 9 runs, total abolition of runs of ventricular tachycardia was required.

Statistical methods. Baseline comparisons were by chi-square or t statistics where appropriate. Time to occurrence of death, cardiac arrest or development of heart failure was estimated by the method of Kaplan and Meier (11) and comparisons between groups were based on the log-rank statistic. Investigation of the relation of ejection fraction (<30% vs. ≥30%), congestive heart failure syndrome and outcome was based on the proportional hazards regression model of Cox and was adjusted for the possible confounders of age, previous myocardial infarction and diabetes (time from the index myocardial infarction to enrollment was not predictive, even univariately, in any of our models) (12). Because the outcome of definite congestive heart failure was not determined for nonrandomized patients after completion of titration, follow-up of these patients for this outcome was censored at completion of titration. Because of the design of CAST with an open-label titration before randomization, we could not adjust for assignment to active or placebo therapy. However, the adverse effect of active therapy on death or on arrhythmic death was independent of ejection fraction and of a history of heart failure (13), so that active versus placebo therapy was not a confounder for the relative effects or interactions of these prognostic factors. The test of homogeneity of common odds or relative risks was based on the method of Cornfield (14).

Analysis of the relation of baseline ejection fraction and heart failure status to arrhythmia suppression during the open-label titration was performed using multivariate logistic regression (15), conditioning for age and history of myocardial infarction. Other factors such as gender, time from the myocardial infarction to titration and a history of diabetes had not been associated univariately with suppression.

Results

Relation of heart failure, ejection fraction and arrhythmia suppression. The overall results of titration and the risk profiles of those not receiving suppression and not randomized to long-term therapy are reported elsewhere (16). Patients whose arrhythmias were not suppressed had lower ejection fractions, more frequently had a history of congestive heart failure and a greater use of digitalis and diuretic agents and had a lower mean frequency of ventricular premature beats (16).

To examine the relation of baseline heart failure status and ejection fraction to the extent of ventricular arrhythmia suppression achieved, we evaluated an unbiased sample of 1,159 patients first tested for ventricular arrhythmia suppression on encainide (patients who started titration on encainide were a randomly selected subsample of all the enrolled patients). These 1,159 patients included 16% with a history of heart failure (definition 1). The comparative frequency of ventricular premature beats in patients with and without a history of heart

failure was 141 ± 243/h versus 126 ± 250/h (p = NS). Patients with a history of heart failure had more frequent runs of nonsustained ventricular tachycardia (30% vs. 21%; p < 0.01). Patients with a history of heart failure were less likely to achieve the arrhythmia suppression criteria required by CAST than were those without heart failure (58% vs. 75%; p < 0.001). The results were similar for heart failure definitions 2 and 3. Left ventricular ejection fraction obtained at baseline also was significantly related to suppressibility; 75% of patients with ejection fraction ≥30% at baseline had their arrhythmias suppressed, compared with 64% of patients whose ejection fraction was <30% (p < 0.001).

We performed an analysis to determine the relative contribution of baseline heart failure status and ejection fraction (<30% vs. ≥30%) to the degree of observed arrhythmia suppression. By univariate stepwise logistic regression, both a history of congestive heart failure (p < 0.0007 for any of the three definitions) and a lower ejection fraction (p = 0.0015) were associated with the failure to achieve arrhythmia suppression. A history of heart failure remained strongly predictive after adjusting for ejection fraction, age and history of myocardial infarction (p < 0.009). Left ventricular ejection fraction was marginally predictive after adjusting for any of the three definitions of heart failure, age and history of myocardial infarction (p < 0.03). A marginally significant interaction was observed between ejection fraction and heart failure (definition 1, p = 0.06; definition 2, p = 0.08; definition 3, p = 0.47): In patients without evidence of heart failure before or at baseline, the risk of failure to achieve arrhythmia suppression associated with lower versus higher ejection fraction was about half that for patients with a heart failure syndrome. Figure 1 illustrates the proportion of patients achieving arrhythmia suppression in this sample of the 1,159 patients first treated for suppression with encainide. The figures characterize the response by the three definitions of heart failure and subcategorized by high versus low ejection fraction.

Influence of ejection fraction on clinical outcome. Left ventricular ejection fraction was strongly related to each of the four major prospectively defined clinical outcome variables of CAST, as shown in Table 1. Patients with ejection fraction <20% had a 75% major clinical event rate (death, cardiac arrest, congestive heart failure) during the 23-month mean follow-up period in the CAST; in contrast, only 22% of the 416 patients with ejection fraction ≥50% had major clinical events (p < 0.0001).

Clinical value of baseline heart failure status. Patients meeting any of the three definitions of congestive heart failure syndrome at baseline generally had a twofold higher mortality rate and a threefold increase in congestive heart failure events (Table 2) compared with those not meeting the definition.

The incidence of clinical congestive heart failure requiring hospital admission or leading to death in the active and placebo treatment groups was recorded, stratified for baseline ejection fraction (Table 1, brackets) and baseline heart failure classifications (Table 2, brackets). The results demonstrate the underreporting expected because hospital admission for heart
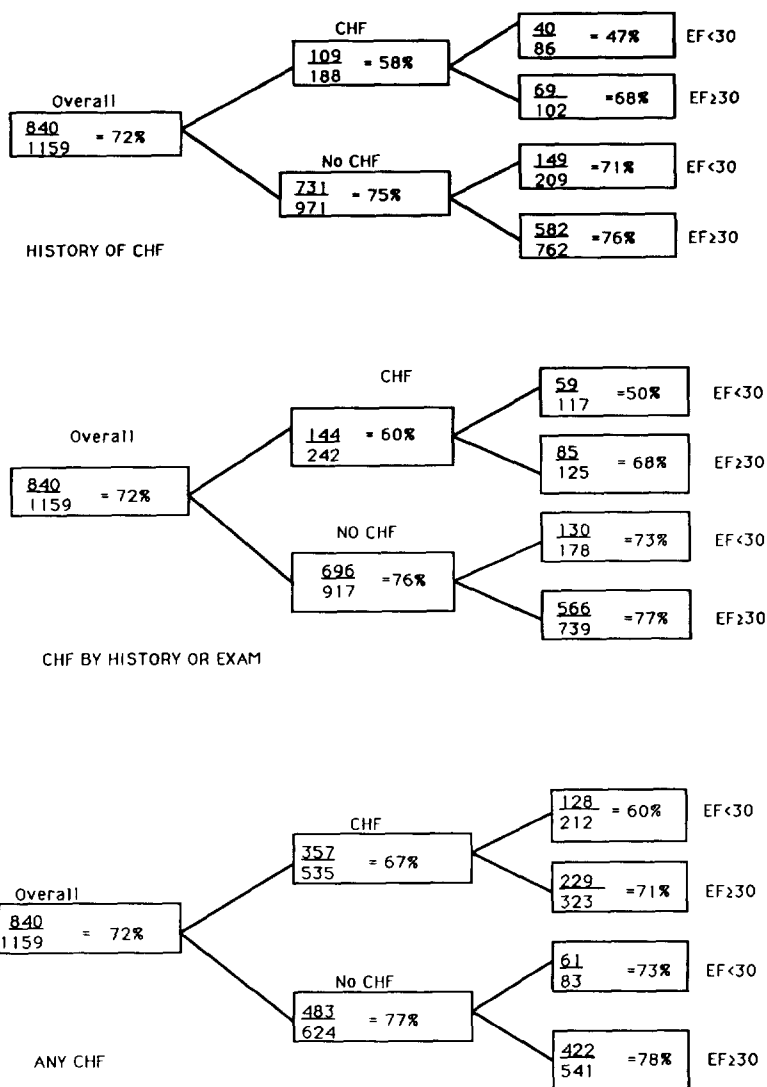
Figure 1. Top, Relation of left ventricular ejection fraction (EF) to **(top)** history of congestive heart failure (CHF); **(middle)** congestive heart failure by history or examination; and **(bottom)** any indicator of congestive heart failure in predicting arrhythmia suppression. Percents refer to patients achieving CAST arrhythmia suppression criteria. See Methods for definitions of congestive heart failure.

failure after completion of titration was not recorded for those patients not randomized. For reference the incidence of any heart failure event is also shown in brackets for the randomized patients. For all congestive heart failure events the randomized patients had an incidence of 14.5% compared with 19% for all enrolled patients. For definite (requiring hospital admission or leading to death) heart failure events the corresponding incidences were 9.5% and 9%, respectively. This suggests underreporting of 2% to 3%. Although there was a greater incidence of definite heart failure events occurring in the stratum with ejection fraction <20%, this finding did not reach statistical significance.

Table 1. Clinical Outcome Stratified by Left Ventricular Ejection Fraction at Baseline in the Cardiac Arrhythmia Suppression Trial

LVEF (%)	No. of Pts	Death/Cardiac Arrest	Arrhythmic Death/ Cardiac Arrest	Definite CHF Events	All CHF Events
<20	190	48%	27%	22% [44%:13%]*	40% [52%:19%]*
20-29	797	30%	18%	15% [17%:20%]	30% [24%:26%]
30-39	1,318	17%	10%	8% [9%:8%]	19% [15%:15%]
40-49	828	14%	7%	5% [5%:6%]	12% [9%:9%]
≥50	416	13%	6%	3% [3%:1%]	7% [7%:3%]
Total	3,549	20%	12%	9% [10%:9%]	19% [16%:13%]

*Restricted to the 1,257 patients (Pts) randomized to receive active therapy and the 1,234 patients randomized to receive placebo therapy [active:placebo]. CHF = congestive heart failure; LVEF = left ventricular ejection fraction.

Table 2. Clinical Outcome Stratified by Heart Failure Status at Baseline in the Cardiac Arrhythmia Suppression Trial

	No. of Pts	Death/Cardiac Arrest	Arrhythmic Death/ Cardiac Arrest	Definite CHF Events	All CHF Events
History of CHF					
Yes	582	40%	24%	21% [25%:26%]*	39% [35%:35%]*
No	2,967	17%	9%	7% [8%:7%]	16% [12%:8%]
History of CHF + physical exam evidence of CHF					
Yes	783	38%	22%	20% [24%:24%]	38% [33%:35%]
No	2,766	15%	9%	6% [7%:6%]	14% [13%:9%]
History of CHF + physical exam evidence of CHF + medications for CHF					
Yes	1,767	28%	16%	15% [18%:17%]	30% [26%:22%]
No	1,782	13%	7%	4% [3%:4%]	9% [6%:6%]

*Restricted to the 1,257 patients randomized to receive active therapy and the 1,234 patients randomized to receive placebo therapy [active:placebo]. Abbreviations as in Table 1.

Do baseline ejection fraction and heart failure assessments provide complementary prognostic information? The contributions of the baseline ejection fraction and baseline congestive heart failure syndromes in predicting survival were investigated using regression analysis and are depicted in Figure 2. Ejection fraction and congestive heart failure status were equally and independently predictive of survival (for each factor, $p < 0.001$ after adjustment for age, history of myocardial infarction, history of diabetes and the other factor). The survival data presented in Figure 2 are for total mortality/cardiac arrest, and the relation for the end point of arrhythmic death were identical.

Figure 3 presents the relation of heart failure syndromes obtained at entry and baseline ejection fraction assessments in predicting subsequent heart failure hospital admissions or death due to heart failure for each of the three prospective definitions of heart failure syndrome. Consistent with the observations from the analyses in Figures 1 and 2, each of the three syndromes of congestive heart failure at baseline and lower ejection fraction significantly ($p < 0.0001$ after adjustment for age, history, diabetes and gender) identified patients who were likely to require readmission to hospital for new or worsened congestive heart failure. No single definition appeared superior. Ejection fraction provided significant additional discrimination after adjustment for any of the three heart failure indexes, and each of the three heart failure indexes provided significant additional discrimination after adjusting for ejection fraction (all comparisons $p < 0.0004$). There was a significant interaction of ejection fraction and heart failure status per definitions 1 and 2 but not definition 3 (definition 1, $p = 0.001$; definition 2, $p = 0.005$; definition 3, $p = 0.54$): the relative risk associated with heart failure per definition 1 was 1.9 in patients with low ejection fraction and 4.0 in patients with high ejection fraction; per definition 2 it was 1.9 and 3.8, respectively.

Discussion

The CAST study provides a large data base to explore the relation between clinical congestive heart failure, ejection fraction and arrhythmia suppression. Of the 3,549 patients with ventricular arrhythmias surviving acute myocardial infarction and tested with antiarrhythmic therapy, ~76% achieved arrhythmia suppression by CAST criteria. The presence or absence of congestive heart failure before or at baseline was prognostically important; only 58% of patients with a history of heart failure achieved arrhythmia suppression compared with 75% of patients without such a history. Regardless of which prospective definition of heart failure was used, ejection fraction made an important contribution in predicting arrhythmia suppression, particularly in patients with no history of and no heart failure at baseline. In the highest risk CAST population (with both congestive heart failure syndrome and ejection fraction <30%), nearly 50% did not achieve arrhythmia suppression. Thus, there is a significant loss of drug effect in the subset of the CAST population known to be at higher risk for arrhythmic death.

Both heart failure status and ejection fraction provided incremental prediction of ventricular arrhythmia suppression. Our data suggest that baseline heart failure status is a more significant predictor than ejection fraction as measured in CAST.

The information on the relation of heart failure status to arrhythmia suppression in a population with mild to moderate left ventricular dysfunction is complementary to previous published observations on the relation of ejection fraction to arrhythmia suppression. In a report of 201 patients with lethal ventricular arrhythmias, antiarrhythmic drugs more commonly failed to prevent inducible sustained ventricular tachycardia when the ejection fraction was <40% (17). Likewise, a Holter analysis of arrhythmia suppression in 246 patients with frequent ventricular premature beats revealed a significantly poorer arrhythmia suppression rate in patients with ejection
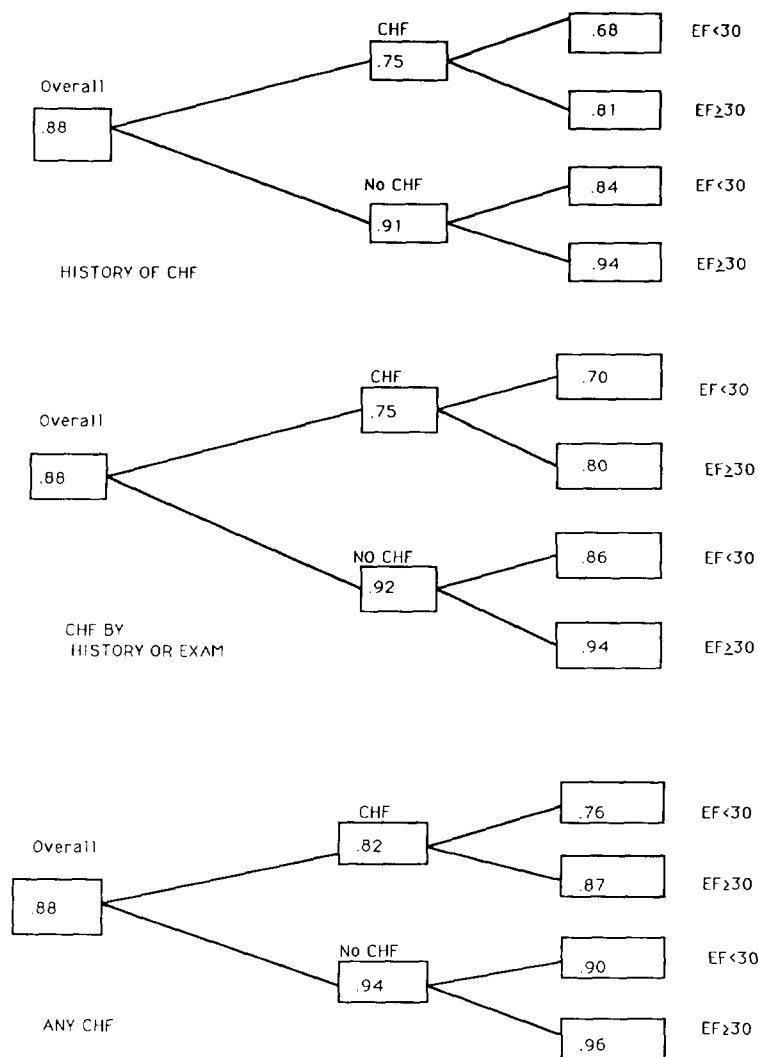
Figure 2. Relative contribution of left ventricular ejection fraction (EF) to **(top)** history of congestive heart failure (CHF); **(middle)** congestive heart failure by history or physical examination; and **(bottom)** any indicator of congestive heart failure in predicting survival to death/cardiac arrest. Each **number** in **box** refers to the 1-year survival rate.

fraction <40% (18). In addition, a sevenfold increase in life-threatening complications due to antiarrhythmic drugs occurred in the 61 patients with a baseline ejection fraction <30% (18).

During the open-label titration in this study, we observed event rates (death, cardiac arrest and all heart failure events) as high as 13% to as low as 3% for ejection fraction strata of <20% and >50%, respectively. This consistent relation between ejection fraction and antiarrhythmic drug efficacy or toxicity highlights the serious limitations of currently available antiarrhythmic drugs (17–19). These results also emphasize the difficulty in testing the hypothesis that suppressing these arrhythmias would improve prognosis: unfortunately, the patients most likely to benefit from antiarrhythmic therapy (by showing a reduction in mortality) have the least likelihood of achieving arrhythmia suppression, but a higher potential for toxicity.

The evaluation of the relation between heart failure status, ejection fraction and arrhythmia suppression was performed on patients randomly selected to receive encainide as the first drug, sometimes followed by moricizine. For this particular

analysis, flecainide patients were not used because they would have biased our goal of exploring relations between ejection fraction and suppression. Patients with baseline ejection fractions <30% could not receive flecainide based on observations of new or worsened heart failure in patients treated with flecainide in the Cardiac Arrhythmia Pilot Study (CAPS) (20). However, we performed an identical analysis of all open-label patients, the results of which are totally consistent with the analyses presented.

Assessment of heart failure status at baseline: a simple, important prognostic variable. The CAST data base allowed testing of the prognostic contributions of a number of prospective definitions of congestive heart failure in a postinfarction population not selected for significant left ventricular dysfunction, thus consisting primarily of patients with minimal or modest left ventricular dysfunction. A history of heart failure alone or combined with physical examination evidence of heart failure at the time of randomization was equally powerful, identifying a patient population with a twofold increased risk of death.
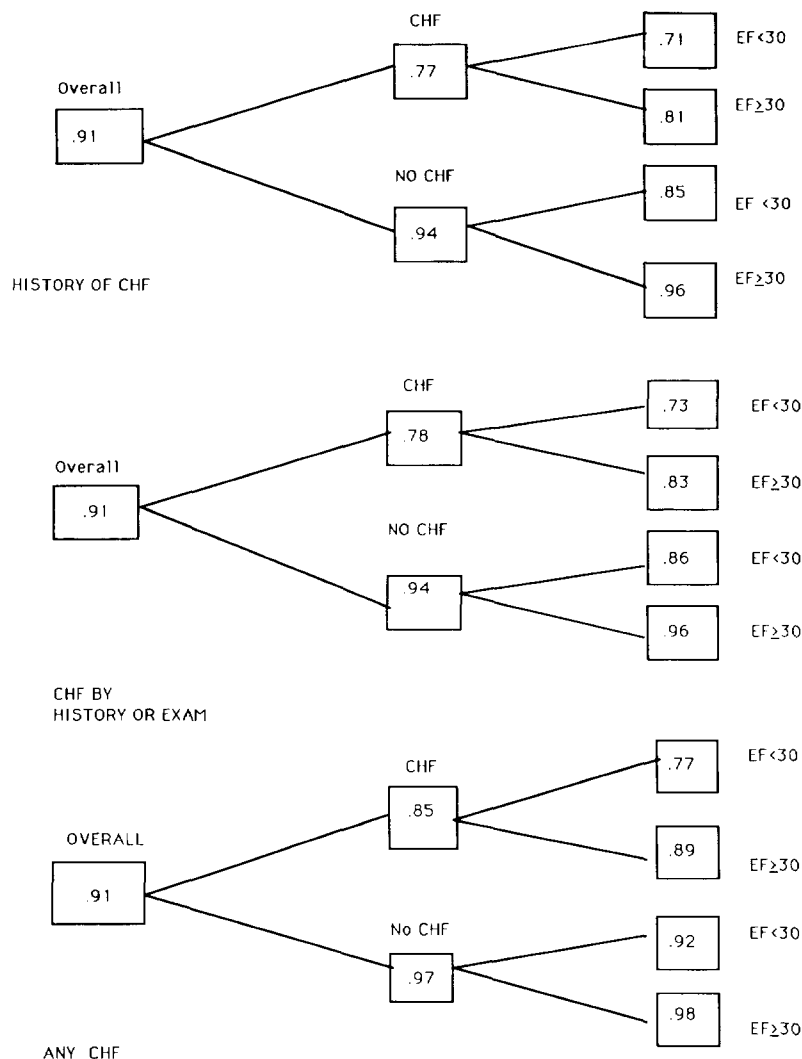
Figure 3. Relative contribution of left ventricular ejection fraction (EF) to (top) history of congestive heart failure (CHF); (middle) congestive heart failure by history or physical examination; and (bottom) any indicator of congestive heart failure in predicting definite congestive heart failure events. Each number in box refers to survival free of heart failure events.

Previous reports have focused on patients with overt congestive heart failure. For example, Wilson et al. (21) studied 77 patients and noted a 6.8-fold increase in deaths at 1 year in patients with class IV rather than class III symptoms at baseline. This and other studies are small in comparison to the present report and focused on symptomatic or hospitalized patients with heart failure. What is striking in the present study is the prognostic benefit of assessing baseline congestive heart failure status in a large, predominantly asymptomatic population.

Relative importance of heart failure status and ejection fraction in predicting cardiac events after myocardial infarction. Previous studies have established that ejection fraction is a powerful predictor of clinical outcome (1–5). Our results are in complete agreement.

Because both heart failure status and measurement of left ventricular ejection fraction were analyzed prospectively in all CAST patients at baseline, we were interested in the relative contributions of both expressions of left ventricular dysfunction in assessing prognosis. Regardless of the prospective baseline definition of heart failure used, the data consistently

show that heart failure as a determinant of subsequent death is as important as ejection fraction. Moreover, they appear to be independent predictors of death. However, heart failure status appears to be more predictive of subsequent congestive heart failure events with the relative risk dependent on ejection fraction. A history of heart failure identified a population at four times increased risk for significant congestive heart failure requiring hospitalization or causing death among those with preserved left ventricular function. The increased risk was twofold among those with ejection fraction ≤30%. The broadest definition of congestive heart failure appeared less useful in discriminating the high-risk population.

Previous studies addressing this issue focused on patients with symptomatic heart failure. In assessing the relative contributions of heart failure and ejection fraction, Glover and Littler (22) reported on 50 patients with heart failure secondary to ischemic cardiomyopathy. In that study, ejection fraction, S3 gallop, class IV heart failure symptoms and severe ventricular arrhythmia predicted outcome. However, class IV heart failure status predicted early mortality whereas ejection fraction was more useful in predicting long-term prognosis.

Measurements of left ventricular systolic performance such as ejection fraction do not necessarily correlate with the symptomatic status of patients with heart failure (23). In a report of 236 patients with a history of congestive heart failure, Califf et al. (24) found the following to be independent predictors of survival: class IV heart failure, left main coronary artery stenosis, decreased ejection fraction and widened arteriovenous oxygen difference. Cohn et al. (25) believed that exercise tolerance and left ventricular function contributed independently to prognosis. The present report extends these previous observations to an ambulatory patient population with more subtle or frequently asymptomatic left ventricular dysfunction.

Conclusions. The CAST study provides a substantial data base from which to make observations on the degree to which heart failure status and ejection fraction contribute to predicting clinical outcome and arrhythmia suppression. Although both variables are predictive, heart failure status appears somewhat superior in predicting heart failure events and arrythmia suppression and equally predictive of death. The predictive effects of ejection fraction and baseline heart failure status were largely independent of each other although there was some interaction. The absence of heart failure at baseline had a strong relation to arrhythmia suppression and predicted a lower mortality.

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