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# Atrial Fibrillation and Risk of Clinical Events in Chronic Heart Failure With and Without Left Ventricular Systolic Dysfunction

## Results From the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) Program

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**OBJECTIVES** We assessed the risk of adverse cardiovascular (CV) outcomes associated with atrial fibrillation (AF) in the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program, which enrolled patients with chronic heart failure (CHF) and a broad range of ejection fractions (EFs).

**BACKGROUND** Atrial fibrillation is associated with an increased risk of adverse CV outcomes in patients with CHF and reduced EF. The risk of AF in patients with CHF and preserved left ventricular ejection fraction (PEF) is unknown.

**METHODS** A total of 7,599 patients with symptomatic CHF were randomized to candesartan or placebo. Patients were divided by baseline EF (≤40% or >40%) in low or preserved EF groups. Major outcomes were cardiovascular death or hospitalization for worsening heart failure, and all-cause mortality. Median follow-up was 37.7 months.

**RESULTS** A total of 670 (17%) patients in the low EF group and 478 (19%) in the PEF group had AF at baseline. Atrial fibrillation predicted a high risk of cardiovascular morbidity and mortality regardless of baseline EF. Patients with AF and low EF had the highest absolute risk for adverse CV outcomes. However, AF was associated with greater relative increased risk of the major outcomes in patients with PEF than in patients with low EF: hazard ratio 1.72 (95% confidence interval [CI] 1.45 to 2.06) versus 1.29 (95% CI 1.14 to 1.46), respectively. The same was true for the risk of all-cause mortality. Candesartan was associated with similar treatment effects regardless of baseline rhythm.

**CONCLUSIONS** Atrial fibrillation is associated with an increased risk of CV outcomes in patients with CHF and either reduced EF or PEF. Candesartan improved outcomes similarly regardless of baseline rhythm. (J Am Coll Cardiol 2006;47:1997–2004) © 2006 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common sustained arrhythmia in patients with chronic heart failure (CHF) (1). Its prevalence and incidence increase with age and with severity of heart failure, rising up to 50% in some studies (2). Loss of atrial contraction leads to reduced stroke volume, elevated filling pressures, and atrial dilatation. The rapid ventricular rate and its irregularity further impairs cardiac filling and emptying (3–4). The prognostic importance of AF occurring in CHF has been analyzed in various settings, including clinical trials (5–8), outpatient cohorts (9–12), and within epidemiologic studies (13). These studies have mainly evaluated the risks related to AF in patients with reduced left ventricular systolic function.

A preserved left ventricular ejection fraction (PEF) may be present in up to 50% of patients with heart failure (14). Cohort studies of heart failure patients who were hospitalized (15–17), the Italian Network for Chronic Heart Failure (IN-CHF) registry (18) and the echocardiographic substudy of the Euro-Heart Failure Survey (19) have shown that AF is at least as common in patients with heart failure and PEF as in those with reduced EF. Little is known, however, about the prognostic impact of AF in patients with heart failure and PEF.

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**Abbreviations and Acronyms**

| | |
|---|---|
| ACE-I | = angiotensin-converting enzyme inhibitor |
| AF | = atrial fibrillation |
| CHARM | = Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity |
| CHF | = chronic heart failure |
| COMET | = Carvedilol Or Metoprolol European Trial |
| CV | = cardiovascular |
| DIG | = Digitalis Investigation Group |
| ECG | = electrocardiogram |
| EF | = ejection fraction |
| HR | = hazard ratio |
| IN-CHF | = Italian Network for Chronic Heart Failure |
| LIFE | = Losartan Intervention for End Point Reduction in Hypertension trial |
| LVEF | = left ventricular ejection fraction |
| OR | = odds ratio |
| PEF | = preserved left ventricular ejection fraction |
| PRIME II | = Second Prospective Ibopamine Evaluation trial |
| SOLVD | = Studies Of Left Ventricular Dysfunction |
| Val-HeFT | = Valsartan Heart Failure Trial |

The Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program assessed the effect of candesartan across a broad spectrum of patients with symptomatic heart failure, including those with PEF (20). The objective of the present analysis was to evaluate the risk related to AF according to baseline ejection fraction (EF) using the prespecified clinical outcomes. The risk in patients developing AF during follow-up was also assessed.

## METHODS

The design of the CHARM program has been described in detail earlier (21). In brief, 7,601 patients (7,599 with data) with symptomatic CHF in New York Heart Association functional class II to IV were randomized to candesartan (target dose 32 mg once daily, mean dose 24 mg) or matching placebo. Patients were divided into one of the three component trials based on left ventricular ejection fraction (LVEF) and treatment with an angiotensin-converting enzyme inhibitor (ACE-I). The CHARM-Alternative study included patients with EF $\leq$0.40 not treated with ACE-I because of intolerance. The CHARM-Added study included patients with LVEF $\leq$0.40 already treated with an ACE-I, and the CHARM-Preserved study evaluated patients with LVEF $>$0.40 regardless of ACE-I treatment. Patients in CHARM-Preserved had to have had a hospital admission for a cardiac reason at some time in the past. Major exclusion criteria included serum creatinine $\geq$265 $\mu$mol/l ($\geq$3 mg/dl), serum potassium $\geq$5.5 mmol/l ($\geq$5.5 mEq/l), and symptomatic hypotension. The investigator was asked to complete a structured electrocardiogram (ECG) report at the randomization visit. Follow-up visits were scheduled two, four, and six weeks and six months after randomization and every 4 months thereafter until the end of the study. At the end of follow-up, investigators were asked to report whether or not a new diagnosis of AF had been made during follow-up. In the present analysis, during the median follow-up of 37.7 months, all patients with new development of AF were included regardless of whether the episodes were symptomatic or whether they were paroxysmal or persistent.

**Analysis.** The primary objective of this analysis was to examine the risk of cardiovascular (CV) events related to baseline AF according to baseline EF. We also assessed the frequency of CV events in patients in whom new AF developed during follow-up. These were prespecified analyses, but the data on new development of AF were collected without relationship to the timing of new-onset AF. In secondary analyses, we examined the influence of baseline rhythm (AF or other) on the effect of candesartan on outcomes and on the need for permanent withdrawal from study drug because of serious adverse effects such as hypotension, hyperkalemia, or increased serum creatinine level. Patients were classified as having AF or no AF according to the investigator interpretation of their baseline ECG. Patients in sinus rhythm at baseline but with a history of AF were categorized as no AF. Analyses were carried out for all patients or with patients divided by EF. The CHARM-Added and CHARM-Alternative participants were considered the low EF group and CHARM-Preserved participants were considered the PEF group. The primary outcome of the component trials in the CHARM program was the composite of CV death or unplanned admission to the hospital for the management of worsening CHF, and these events were adjudicated by a blinded committee. Prespecified secondary outcomes included all-cause mortality, CV death, admission to the hospital for CHF, and fatal or nonfatal stroke. We classified all deaths as CV unless an unequivocal non-CV cause was established.

**Statistical analysis.** All outcome variables were defined as the time to an event or censoring and were analyzed with the proportional hazards model. Both simple Cox regression models and multiple Cox regression models were fitted to data. The explanatory variables included in the multiple regression models were the same set of 33 variables that were adjusted for in the CHARM program (20), except for the variable ACE-I at baseline. All subgroups analyzed for the low EF group were stratified by component trial (CHARM-Added or CHARM-Alternative). When an analysis included new-onset AF as an explanatory variable, a logistic regression model was fitted to data because information on timing of occurrence of AF was lacking, and these analyses are therefore presented as odds ratios rather than hazard ratios (HR). In this analysis, the response was considered to be a binary variable, indicating whether or not a patient experienced a CV event. All p values were generated from the Wald test statistics.

**Table 1.** Baseline Demographics

| Variable | Low EF | | Preserved EF | |
|---|---|---|---|---|
| | AF | No AF | AF | No AF |
| n | 670 | 3,906 | 478 | 2,545 |
| Age (yrs) | 68.1 (9.9) | 64.7 (11.1) | 71.4 (9.6) | 66.4 (11.1) |
| DBP (mm Hg) | 76.5 (10.9) | 75.7 (10.7) | 78.4 (11.1) | 77.8 (10.6) |
| SBP (mm Hg) | 127.3 (18.1) | 127.4 (18.9) | 134.3 (18.6) | 136.5 (18.4) |
| HR (beats/min) | 76.5 (15.6) | 73.5 (12.8) | 76.6 (14.5) | 70.3 (11.8) |
| BMI | 27.7 (5.0) | 27.6 (5.1) | 28.9 (5.9) | 29.2 (5.8) |
| Ejection fraction | 0.29 (0.08) | 0.29 (0.08) | 0.55 (0.09) | 0.54 (0.09) |
| Cardiothoracic ratio >0.5 | 231 (34.5%) | 942 (24.1%) | 133 (27.8%) | 361 (14.2%) |
| Male gender | 523 (78.1%) | 2,865 (73.3%) | 277 (57.9%) | 1,534 (60.3%) |
| Current smoker | 81 (12.1%) | 624 (16.0%) | 57 (11.9%) | 352 (13.8%) |
| NYHA functional class | | | | |
| II | 193 (28.8%) | 1,387 (35.5%) | 269 (56.3%) | 1,567 (61.6%) |
| III | 439 (65.5%) | 2,406 (61.6%) | 197 (41.2%) | 943 (37.1%) |
| IV | 38 (5.7%) | 113 (2.9%) | 12 (2.5%) | 35 (1.4%) |
| Creatinine ≥2.0 mg/dl | 16 (9.3%) | 86 (6.1%) | 6 (4.5%) | 46 (4.8%) |
| Medical history | | | | |
| Previous CHF hospitalization | 539 (80.4%) | 2,811 (72.0%) | 390 (81.6%) | 1,686 (66.3%) |
| Previous MI | 294 (43.9%) | 2,370 (60.7%) | 115 (24.1%) | 1,225 (48.1%) |
| Angina pectoris | 293 (43.7%) | 2,242 (57.4%) | 187 (39.1%) | 1,630 (64.0%) |
| Stroke | 73 (10.9%) | 322 (8.2%) | 48 (10.0%) | 220 (8.6%) |
| Hypertension | 346 (51.6%) | 1,897 (48.6%) | 294 (61.5%) | 1,649 (64.8%) |
| Diabetes mellitus | 178 (26.6%) | 1,128 (28.9%) | 108 (22.6%) | 749 (29.4%) |
| CABG | 143 (21.3%) | 994 (25.4%) | 59 (12.3%) | 595 (23.4%) |
| PCI | 57 (8.5%) | 645 (16.5%) | 31 (6.5%) | 495 (19.4%) |
| Implantable cardiac defibrillator | 21 (3.1%) | 147 (3.8%) | 4 (0.8%) | 19 (0.7%) |
| Pacemaker implanted | 82 (12.2%) | 334 (8.6%) | 45 (9.4%) | 176 (6.9%) |
| Etiology | | | | |
| Ischemic heart disease | 341 (50.9%) | 2,634 (67.4%) | 158 (33.1%) | 1,548 (60.8%) |
| Idiopathic dilated cardiomyopathy | 191 (28.5%) | 873 (22.4%) | 52 (10.9%) | 211 (8.3%) |
| Hypertension | 63 (9.4%) | 234 (6.0%) | 133 (27.8%) | 551 (21.7%) |
| Atrial fibrillation | 22 (3.3%) | 10 (0.3%) | 81 (16.9%) | 53 (2.1%) |
| ECG findings at baseline | | | | |
| Bundle branch block | 181 (27.0%) | 1,196 (30.8%) | 78 (16.3%) | 356 (14.1%) |
| Paced rhythm | 64 (9.6%) | 259 (6.7%) | 31 (6.5%) | 125 (4.9%) |
| Left ventricular hypertrophy | 64 (9.6%) | 632 (16.3%) | 86 (18%) | 358 (14%) |
| Concomitant medication | | | | |
| Digitalis glycoside | 533 (79.6%) | 1,879 (48.1%) | 313 (65.5%) | 529 (20.8%) |
| Diuretics | 632 (94.3%) | 3,395 (86.9%) | 430 (90.0%) | 1,829 (71.9%) |
| Spironolactone | 171 (25.5%) | 749 (19.2%) | 87 (18.2%) | 265 (10.4%) |
| Beta-blocker | 332 (49.6%) | 2,187 (56.0%) | 216 (45.2%) | 1,468 (57.7%) |
| Calcium channel blocker | 86 (12.8%) | 512 (13.1%) | 136 (28.5%) | 808 (31.7%) |
| Antiarrhythmic agent | 100 (14.9%) | 493 (12.6%) | 47 (9.8%) | 253 (9.9%) |
| Lipid-lowering drug | 184 (27.5%) | 1,707 (43.7%) | 112 (23.4%) | 1,150 (45.2%) |
| Oral anticoagulant | 513 (76.6%) | 1,077 (27.6%) | 350 (73.2%) | 398 (15.6%) |
| Acetylsalicylic acid | 179 (26.7%) | 2,305 (59.0%) | 107 (22.4%) | 1,655 (65.0%) |
| ACE inhibitors | 397 (59.3%) | 2,152 (55.1%) | 77 (16.1%) | 499 (19.6%) |

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft; CHF = chronic heart failure; DBP = diastolic blood pressure; ECG = echocardiographic; EF = ejection fraction; HR = heart rate; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

## RESULTS

**Baseline characteristics.** A total of 7,601 patients were randomized to candesartan or placebo, 7,599 with available data. Baseline characteristics are summarized in Table 1. In general, patients with AF were older, had a higher baseline heart rate, and more often had a cardiothoracic ratio of >0.5 and a history of hospitalization for heart failure. Patients with AF less frequently had a history of prior myocardial infarction, angina pectoris, or diabetes mellitus. Ischemic heart disease was the most common etiology of heart failure regardless of presence or absence of AF, but it was a less common cause in patients with AF (43.5%) than without AF (64.8%). Hypertension was reported as the etiology of HF more commonly in patients with AF, much more commonly in patients with PEF, and most commonly in those with AF and PEF. Patients with AF had similar EF to those in sinus rhythm but had a worse New York Heart Association functional classification and were more likely to have had a pacemaker implanted. Patients with AF were more often treated with digitalis, diuretic agents, and oral

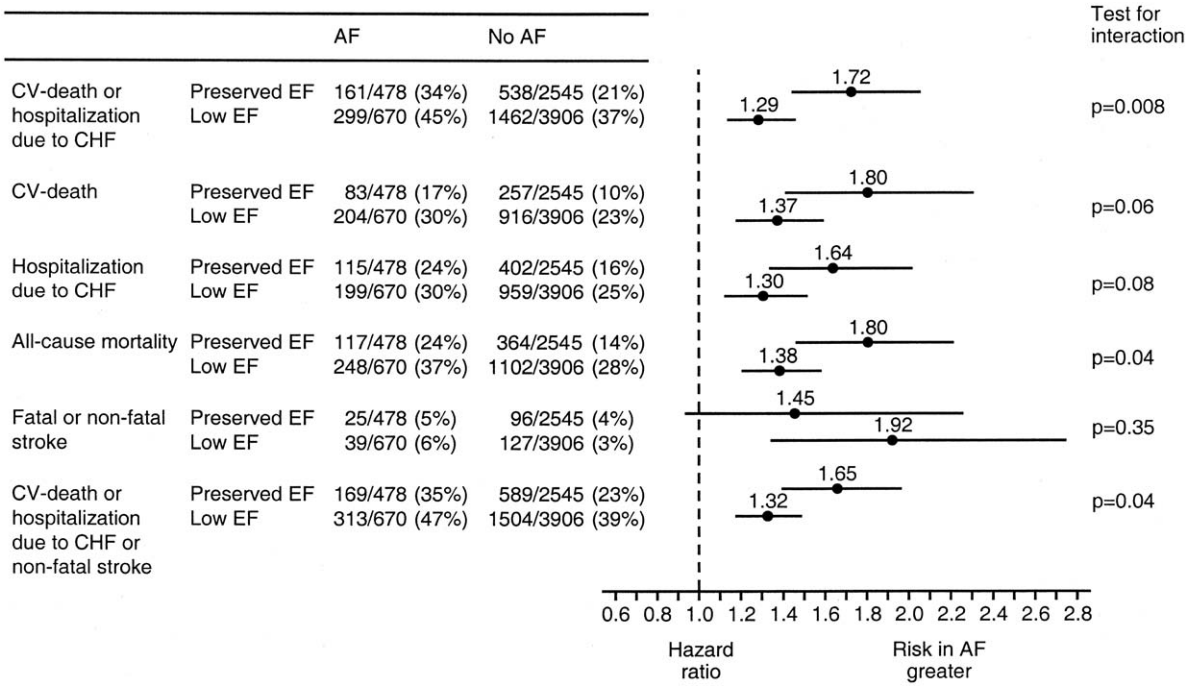



**Figure 1.** Risk of baseline atrial fibrillation (AF) for cardiovascular (CV) events depending on ejection fraction (EF). CHF = chronic heart failure.

anticoagulants and less often with beta-blocker and acetylsalicylic acid. A small number of patients were treated with an antiarrhythmic drug in either group, regardless of AF, with more frequent use in patients with a low EF.

**Outcomes by baseline AF.** Atrial fibrillation recorded on baseline ECG was associated with an increased risk of morbidity and mortality (Figs. 1 to 3). Patients with AF and low EF had the highest absolute risk for adverse CV outcomes (e.g., 45% with CV death or CHF hospitalization) relative to those with low EF and sinus rhythm (37% with an event), PEF and AF (34% with an event), or PEF and sinus rhythm (21% with an event) (Figs. 1 to 3). However, AF was associated with a greater increase in the risk of CV death or hospitalization for worsening heart failure in patients with PEF (HR 1.72, 95% confidence interval [CI] 1.45 to 2.06) than in patients with low EF, (HR 1.29, 95% CI 1.14 to 1.46, p for interaction 0.008). The same was true for all-cause mortality: PEF HR 1.80 (95% CI 1.46 to 2.21) and low EF HR 1.38 (95% CI 1.21 to 1.59, p for interaction 0.041). Similarly, for each of these adverse CV outcomes, with the exception of stroke, patients

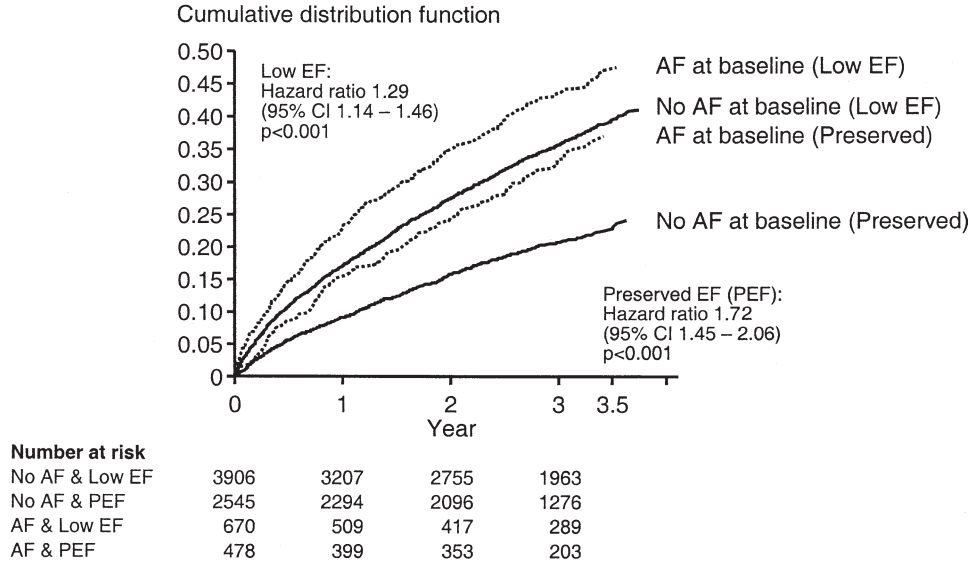
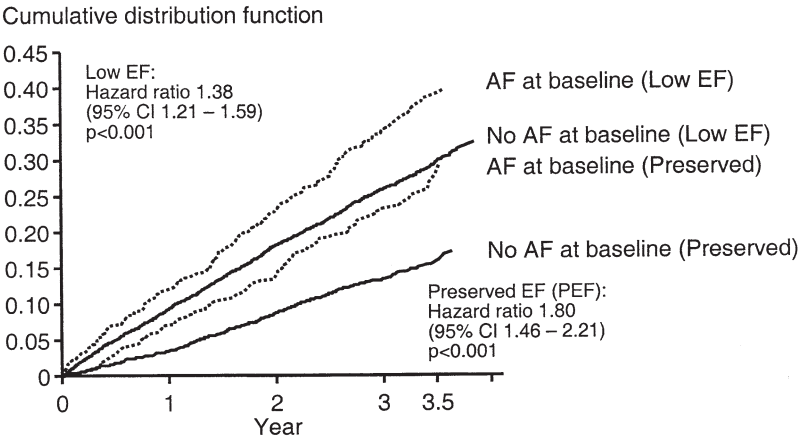



**Figure 2.** Time to cardiovascular (CV) death or hospitalization because of heart failure. AF = atrial fibrillation; EF = ejection fraction; PEF = preserved left ventricular ejection fraction.




| Number at risk | | | | |
|---|---|---|---|---|
| No AF & Low EF | 3906 | 3542 | 3192 | 2359 |
| No AF & PEF | 2545 | 2455 | 2322 | 1418 |
| AF & Low EF | 670 | 589 | 514 | 358 |
| AF & PEF | 478 | 444 | 414 | 243 |

**Figure 3.** Time to all-cause mortality. AF = atrial fibrillation; CI = confidence interval; EF = ejection fraction; PEF = preserved left ventricular ejection fraction.

with low EF and AF at baseline had the highest absolute risk, and patients with PEF and AF at baseline had a greater increase in risk than those with low EF and AF. When adjusted for 32 covariates in multiple regression analysis, baseline AF remained an independent risk factor for CV death or hospitalization for heart failure in patients with PEF (HR 1.32, 95% CI 1.06 to 1.65, p = 0.015) but not in those with low EF (HR 1.12, 95% CI 0.97 to 1.29, p = 0.12). After covariate adjustment, AF at baseline remained an independent predictor of all-cause mortality regardless of baseline EF: PEF HR 1.37 (95% CI 1.06 to 1.79) and low EF HR 1.22 (95% CI 1.04 to 1.43).

**Outcomes in patients with new-onset AF.** In 392 patients, AF developed during follow-up, 263 (7.8%) in the low EF group and 129 (4.9%) in the PEF group. Patients with new-onset AF experienced a higher risk of morbidity and mortality regardless of baseline EF. The odds ratio for CV death or hospitalization for worsening heart failure was 4.22 (95% CI 2.90 to 6.13) in the PEF group and 3.17 (95% CI 2.45 to 4.09) in the low EF group; p = 0.19 for interaction. For all-cause mortality the odds ratio was 2.57 (95% CI 1.70 to 3.90) in the PEF group and 1.85 (95% CI 1.44 to 2.37) in the low EF group; p = 0.18 for interaction. Again, the absolute risk of an adverse CV outcome was highest in the low EF-new AF patient group, but the patients with PEF and new AF had a greater relative increase in risk than those with low EF and new AF (Fig. 4). For example, the absolute risk of CV death or CHF hospitalization was 66% in the low EF-new AF group and was increased from 20% to 47% by the new development of AF in the PEF group (Fig. 4).

**Treatment effects.** In the CHARM-Overall program, candesartan reduced the risk of the composite primary end point in both AF (HR 0.83, 95% CI 0.69 to 0.99) and non-AF groups (HR 0.84, 95% CI 0.77 to 0.92; p for interaction 0.80). There were also trends toward a reduced risk of all-cause mortality in both groups that did not reach statistical significance, HR 0.82 (95% CI 0.67 to 1.01) for AF and HR 0.94 (95% CI 0.85 to 1.04) for no AF, p for interaction 0.22 (Fig. 5). In the PEF group there was no significant effect of candesartan on the primary composite end point in the overall population and no difference in effect according to presence or absence of AF (p for interaction 0.82). In patients with low EF, candesartan reduced CV morbidity and mortality to a similar degree regardless of the presence of AF at baseline (Table 2).

**Adverse effects.** Patients with baseline AF had higher discontinuation rates than those without because of hypotension (3.4% vs. 2.5%), increased creatinine (6.3% vs. 4.3%), and hyperkalemia (1.8% vs. 1.3%), respectively.

## DISCUSSION

This analysis from the CHARM program shows that baseline AF is associated with an increased risk of morbidity and mortality in patients with symptomatic heart failure regardless of baseline EF and that the increase in risk attributable to AF is even higher in patients with PEF. The increased risk of stroke was similar between the two groups. Development of new AF during follow-up was associated with an increased risk of CV mortality or hospitalization for heart failure, all-cause mortality, and fatal or nonfatal stroke. The main difference from previous analyses is that our present analysis involved a broad spectrum of heart failure patients, including those with PEF, treated with contemporary heart failure and other CV medications. This broad perspective affords the opportunity to make an important observation regarding prognosis that previously has not been possible. Specifically, in patients with CHF and PEF, the presence or

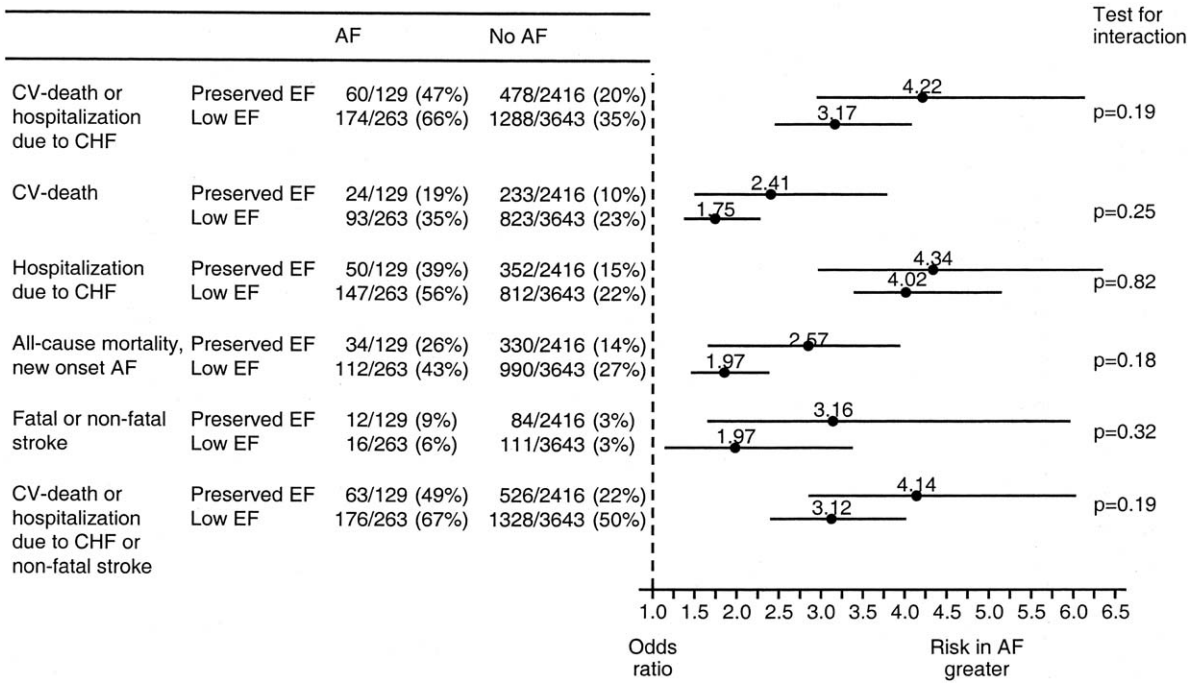



**Figure 4.** Risk of new-onset atrial fibrillation (AF) for cardiovascular (CV) events depending on ejection fraction (EF). CHF = chronic heart failure.

new development of AF is associated with such a substantial increase in risk for adverse CV outcomes that it puts patients at absolute risk levels that are nearly as high as those for patients with CHF and low EF who remain in sinus rhythm.

**Baseline characteristics.** Patients with AF were in general older, had a worse functional class, and had more enlarged hearts despite EF similar to patients with no AF. Several clinical trials, outpatient cohorts, and epidemiologic studies have shown a mutual relationship between the two conditions in which heart failure begets AF (13,22) and AF begets CHF (13,23). In 9,193 patients with hypertension and left ventricular hypertrophy, new-onset AF was associated with a five-fold increase in hospitalizations for CHF (24). Beta-blockers were less often used in patients with AF, which could reflect the higher age and more comorbidity. Treatment with digitalis was more frequent among AF patients, but higher baseline heart rates suggest that single-drug therapy may be insufficient for adequate rate control (25). Around 75% of patients with

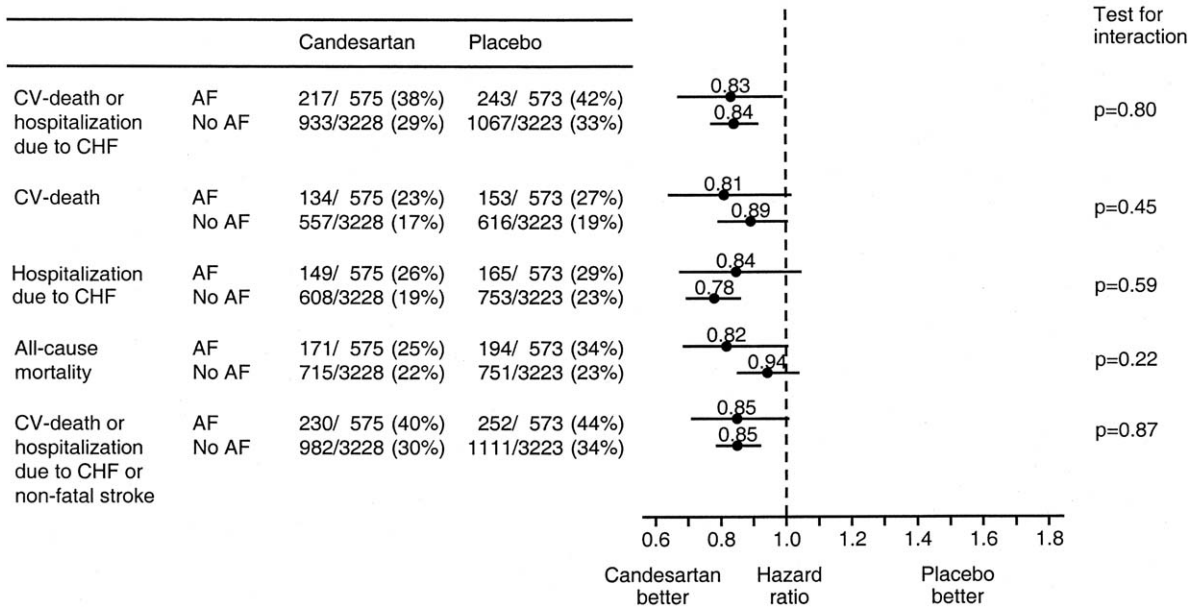



**Figure 5.** Treatment effects depending on baseline heart rhythm in CHARM-Overall. AF = atrial fibrillation; CHF = chronic heart failure; CV = cardiovascular.

**Table 2.** Treatment Effects in Patients With Low EF Depending on Heart Rhythm

| | Candesartan Events | Placebo Events | HR | 95% CI | Interaction |
|---|---|---|---|---|---|
| Cardiovascular death or hospitalization because of heart failure | | | | | |
| AF | 139/336 (41%) | 160/334 (48%) | 0.78 | 0.62–0.98 | 0.62 |
| No AF | 678/1,953 (35%) | 784/1,953 (40%) | 0.82 | 0.74–0.91 | |
| All-cause mortality | | | | | |
| AF | 109/336 (32%) | 139/334 (42%) | 0.70 | 0.55–0.90 | 0.05 |
| No AF | 533/1,953 (28%) | 569/1,953 (29%) | 0.92 | 0.82–1.04 | |
| CV death or CHF hospitalization or nonfatal stroke | | | | | |
| AF | 147/336 (44%) | 166/334 (50%) | 0.80 | 0.64–1.00 | 0.58 |
| No AF | 705/1,953 (36%) | 799/1,953 (41%) | 0.84 | 0.76–0.93 | |

AF = atrial fibrillation; CHF = chronic heart failure; CI = confidence interval; CV = cardiovascular; EF = ejection fraction; HR = hazard ratio.

AF were treated with oral anticoagulants regardless of baseline EF. This is higher than reported from the EuroHeart Failure Survey (26).

**Outcomes.** Our analysis extends previous findings by showing that AF, whether present at baseline or of new onset, is an independent risk factor for adverse CV outcomes in patients with heart failure regardless of baseline EF. After adjustment for baseline factors, there are still differences in risk increase associated with AF between patients with low EF and PEF. The reason for the difference is unclear, but the presence of AF may reflect different stages of CHF between the two patient groups. Although patients with a low EF are at a higher absolute risk for CV events than those with PEF (Figs. 1 to 4) (27), the added risk of AF is particularly important for patients with PEF. Patients with PEF might have a lower tolerability for uncontrolled ventricular rate, thus being more prone to deteriorate (3,4).

**Earlier studies.** To this date, we are aware of only one trial published in full evaluating the prognostic impact of supraventricular tachycardia (including AF) in heart failure patients with evidence of preserved systolic function and clinical evidence of heart failure. The DIG trial included 988 patients with LVEF >0.45 and clinical signs of heart failure in an ancillary study, and these patients were analyzed for incidence of supraventricular tachycardia together with patients in the main trial. The development of supraventricular tachycardia during the study was independently associated with a higher risk of mortality and stroke regardless of baseline EF (28).

In the previous literature there is conflicting evidence about the prognostic importance of AF. Four of five trials with follow-up started before 1990 showed an independent relationship between AF and mortality: one was an epidemiologic study (13); one included patients in the SOLVD trial, in which AF also predicted CV morbidity (6); and two were in severe heart failure (9,10). One (12) of five (7,8,10,11) trials with follow-up starting in 1990 or later showed an independent relationship between AF and mortality. That was an unselected cohort of 944 elderly patients hospitalized for heart failure. AF did not predict 1-month rehospitalization. The other substantial recent analysis was of the 3,029 patients randomized to either carvedilol or metoprolol tartrate and followed up for 5 years within the COMET study (8). The AF did not independently predict all-cause mortality, but did predict all-cause mortality or hospitalization and CV death or hospitalization for heart failure. Of note, in trials with follow-up started in 1990 or later, patients were almost universally treated with ACE-I and the use of class I antiarrhythmic drugs had decreased considerably.

Four of five published analyses of new-onset AF showed a prognostic relationship with mortality, one an analysis from the Framingham study (13). and three analyses from the DIG, COMET, and Val-HeFT clinical studies (8,28,29). The exception was a small group of patients with severe CHF enrolled in the PRIME II study (7).

**Angiotensin II receptor blockers in patients with heart failure and AF.** This is the first trial to evaluate the effect of an angiotensin II receptor blocker on CV outcomes in patients with CHF and concomitant AF, and moreover, over a broad range of EF. In Val-HeFT study, valsartan reduced the incidence of AF in patients with reduced EF (29). In a recent analysis of the CHARM program, we have shown that candesartan reduces the risk of developing AF in patients with both reduced and preserved EF (30). The patients enrolled in the CHARM-Preserved component trial, which had symptomatic CHF and PEF, had some similarities to those in the LIFE trial, in which losartan was superior to atenolol in reducing a composite end point of CV death, stroke, or myocardial infarction in 342 patients with hypertension, left ventricular hypertrophy, and AF despite similar decreases in blood pressure (31).

**Study limitations.** The primary analysis of this study was based on the diagnosis of AF using the baseline ECG. New-onset AF was documented at the end of the study from investigator reports and not by systematic recordings, so episodes of AF may have been missed, particularly paroxysmal AF. Also, patients who died early did not have the opportunity to develop AF, so collectively the relationship reported here probably underestimates the true relationship of new-onset AF and mortality. The relationship in time between an adverse CV outcome and new-onset AF

was not possible to analyze because of lack of information when onset of AF occurred. However, our findings are supported by the fact that three previous randomized trials including >15,000 patients have shown that new-onset supraventricular tachycardia or AF are strong predictors of mortality in time-dependent analyses.

**Conclusions.** Atrial fibrillation is associated with an increased risk of adverse CV outcomes in patients with CHF and either reduced or preserved left ventricular systolic function. Patients with AF and reduced EF have the highest absolute risk, and those with AF and PEF have a greater increase in risk. New-onset AF is also associated with an increased risk with or without left ventricular systolic dysfunction. Candesartan improved clinical outcomes regardless of baseline rhythm.

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