ORIGINAL ARTICLE

Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction

Barry M. Massie, M.D., Peter E. Carson, M.D., John J. McMurray, M.D., Michel Komajda, M.D., Robert McKelvie, M.D., Michael R. Zile, M.D., Susan Anderson, M.S., Mark Donovan, Ph.D., Erik Iverson, M.S., Christoph Staiger, M.D., and Agata Ptaszynska, M.D., for the I-PRESERVE Investigators*

ABSTRACT

BACKGROUND

Approximately 50% of patients with heart failure have a left ventricular ejection fraction of at least 45%, but no therapies have been shown to improve the outcome of these patients. Therefore, we studied the effects of irbesartan in patients with this syndrome.

METHODS

We enrolled 4128 patients who were at least 60 years of age and had New York Heart Association class II, III, or IV heart failure and an ejection fraction of at least 45% and randomly assigned them to receive 300 mg of irbesartan or placebo per day. The primary composite outcome was death from any cause or hospitalization for a cardiovascular cause (heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke). Secondary outcomes included death from heart failure or hospitalization for heart failure, death from any cause and from cardiovascular causes, and quality of life.

RESULTS

During a mean follow-up of 49.5 months, the primary outcome occurred in 742 patients in the irbesartan group and 763 in the placebo group. Primary event rates in the irbesartan and placebo groups were 100.4 and 105.4 per 1000 patient-years, respectively (hazard ratio, 0.95; 95% confidence interval [CI], 0.86 to 1.05; P=0.35). Overall rates of death were 52.6 and 52.3 per 1000 patient-years, respectively (hazard ratio, 1.00; 95% CI, 0.88 to 1.14; P=0.98). Rates of hospitalization for cardiovascular causes that contributed to the primary outcome were 70.6 and 74.3 per 1000 patient-years, respectively (hazard ratio, 0.95; 95% CI, 0.85 to 1.08; P=0.44). There were no significant differences in the other prespecified outcomes.

CONCLUSIONS

Irbesartan did not improve the outcomes of patients with heart failure and a preserved left ventricular ejection fraction. (ClinicalTrials.gov number, NCT00095238.)

From the University of California, San Francisco, and San Francisco Veterans Affairs Medical Center, San Francisco (B.M.M.); Georgetown University and Washington DC Veterans Affairs Medical Center, Washington, DC (P.E.C.); British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.M.); Université Paris 6 and Hospital Pitié–Salpêtrière, Paris (M.K.); Hamilton Health Sciences, McMaster University, Hamilton, ON, Canada (R.M.); Ralph H. Johnson Veterans Affairs Medical Center and Medical University of South Carolina, Charleston (M.R.Z.); University of Wisconsin, Madison (S.A., E.I.); Bristol-Myers Squibb, Princeton, NJ (M.D., A.P.); and Sanofi-Aventis, Bridgewater, NJ (C.S.). Address reprint requests to Dr. Massie at the Veterans Affairs Medical Center, 111C, 4150 Clement St., San Francisco, CA 94121, or at barry.massie@va.gov.

*Committee members and investigators in the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

This article (10.1056/NEJMoa0805450) was published at www.nejm.org on November 11, 2008.

N Engl J Med 2008;359:2456-67.

Approximately half of patients with a diagnosis of heart failure have a normal or near-normal left ventricular ejection fraction.[1-5] Such patients differ from those with heart failure and a low left ventricular ejection fraction in a number of important ways: they tend to be older and female, and their condition is more likely to be associated with hypertension than with ischemia. The rates of death and illness among these patients are high and have not declined, as they have in patients with heart failure and a low left ventricular ejection fraction.[6]

Unfortunately, no pharmacologic therapy has been shown to be effective in improving outcomes in patients with heart failure with a preserved left ventricular ejection fraction. However, because the renin–angiotensin–aldosterone system is involved in many of the processes associated with this syndrome (including hypertension, left ventricular hypertrophy, myocardial fibrosis, and vascular dysfunction),[7,8] inhibitors of this system have been of particular interest as a therapeutic intervention for these patients.[9,10] Although information about neurohormone levels in this syndrome is limited, available data indicate that plasma renin activity is increased in patients with heart failure and a preserved left ventricular ejection fraction, as compared with control subjects, although levels are lower than in patients who have heart failure with a low left ventricular ejection fraction.[7] Furthermore, blockade of the renin–angiotensin system has had favorable effects in patients with a low left ventricular ejection fraction. It has also improved outcomes in patients after myocardial infarction, in those with hypertension, and in those with other high-risk vascular disease — populations that are thought to be at risk for heart failure with a preserved left ventricular ejection fraction.

Accordingly, we conducted the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) to evaluate the effect of the angiotensin-receptor blocker irbesartan on mortality and cardiovascular morbidity in patients with heart failure and a preserved left ventricular ejection fraction.

METHODS

PATIENTS

We enrolled patients from centers in 25 countries. All patients were at least 60 years of age and had heart failure symptoms and a left ventricular ejection fraction of at least 45%.[11,12] In addition, we required patients to have been hospitalized for heart failure during the previous 6 months and have current New York Heart Association (NYHA) class II, III, or IV symptoms with corroborative evidence; if they had not been hospitalized, they were required to have ongoing class III or IV symptoms with corroborative evidence. Such evidence could include findings of pulmonary congestion on radiography, left ventricular hypertrophy or left atrial enlargement on echocardiography, or left ventricular hypertrophy or left bundle-branch block on electrocardiography. Treatment with an angiotensin-converting–enzyme (ACE) inhibitor was permitted only when such therapy was considered essential for an indication other than uncomplicated hypertension.

Exclusion criteria included previous intolerance to an angiotensin-receptor blocker; an alternative probable cause of the patient's symptoms (e.g., significant pulmonary disease); any previous left ventricular ejection fraction below 40%; a history of acute coronary syndrome, coronary revascularization, or stroke within the previous 3 months; substantial valvular abnormalities; hypertrophic or restrictive cardiomyopathy; pericardial disease; cor pulmonale or other cause of isolated right heart failure; a systolic blood pressure of less than 100 mm Hg or more than 160 mm Hg or a diastolic blood pressure of more than 95 mm Hg despite antihypertensive therapy; other systemic disease limiting life expectancy to less than 3 years; substantial laboratory abnormalities (such as a hemoglobin level of less than 11 g per deciliter, a creatinine level of more than 2.5 mg per deciliter [221 μmol per liter], or liver-function abnormalities); or characteristics that might interfere with compliance with the study protocol.

STUDY PROCEDURES

The trial was approved by the ethics committee at each participating center; all patients provided written informed consent. Eligible patients were treated with single-blind placebo for 1 to 2 weeks before randomization; those who successfully completed this run-in phase and whose condition remained clinically stable were randomly assigned in a 1:1 ratio to receive irbesartan or matching placebo. The randomization schedule was implemented with the use of an interactive voice-response system. The randomization block size was two and was stratified according to site. Patients were

also stratified according to their use of an ACE inhibitor at randomization. Therefore, for each site, separate blocks of two were designated for patients who were taking an ACE inhibitor and for those who were not taking an ACE inhibitor. Randomization of patients who were taking an ACE inhibitor at baseline was capped at 33% at each site.

Patients were started on 75 mg of irbesartan or placebo once daily. The dose was doubled to 150 mg after 1 to 2 weeks and was doubled again to 300 mg after an additional 1 to 2 weeks, according to a forced-titration protocol as tolerated. In addition to the titration visits, patients were seen 8 weeks, 14 weeks, and 6 months after randomization and every 4 months thereafter. The score on the Minnesota Living with Heart Failure scale[13] and the plasma level of N-terminal pro-B–type natriuretic peptide (NT-proBNP) were recorded at randomization, at 6 and 14 months, and at the final study visit. Serum creatinine and potassium were measured before randomization and at weeks 2 and 8, at month 6, and annually thereafter and, along with NT-proBNP, were analyzed in a central laboratory (Esoterix Belgium).

The executive committee designed and oversaw the trial in collaboration with representatives of the study sponsors (Bristol-Myers Squibb and Sanofi-Aventis), with assistance from an international steering committee. The sponsors or a contract research organization collected the trial data, which were then analyzed at the Statistical Data Analysis Center at the University of Wisconsin, Madison, independently of the sponsors and according to a predefined statistical analysis plan. All investigators and committee members who were involved in the conduct of the study (except for members of the data and safety monitoring board) were unaware of study-group assignments. The manuscript was prepared and submitted for publication by members of the executive committee, who had unrestricted access to the study data and who vouch for the accuracy and completeness of the reported analyses.

STUDY OUTCOMES AND DEFINITIONS

The primary outcome, which was analyzed as the time from randomization to the first event, was a composite of death from any cause or hospitalization for a protocol-specified cardiovascular cause. Reasons for such hospitalizations included worsening heart failure, myocardial infarction, stroke, unstable angina, ventricular or atrial dysrhythmia, or myocardial infarction or stroke that occurred during any hospitalization. The secondary outcomes were the components of the primary outcome (death from any cause and hospitalization for cardiovascular causes), a composite heart failure outcome (death due to worsening heart failure or sudden death or hospitalization due to worsening heart failure), a change in the total score on the Minnesota Living with Heart Failure scale at 6 months, a change in the plasma level of NT-proBNP at 6 months, a composite vascular-event outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), and death from cardiovascular causes. Deaths and hospitalizations were adjudicated by members of an independent end-point committee who were unaware of study-group assignments and used prespecified criteria.

STATISTICAL ANALYSIS

We originally anticipated an annual event rate of 18% for the primary outcome in the placebo group. A sample size of 3600 patients was planned to provide 1440 primary events, yielding a statistical power of 90% to detect a 14.5% reduction in risk with irbesartan, corresponding to a reduction in hazard of 15.75%, with a two-sided alpha of 0.05, assuming a recruitment period of 2 years and a minimum follow-up period of 2 years. A blinded review of event rates in 2004 indicated that outcomes had accumulated at a slower-than-anticipated rate. Consequently, to achieve the target number of events for the same decrease in the hazard in a reasonable time period, the sample size was increased to 4100 patients.

Data from all patients who underwent randomization were analyzed according to the intention-to-treat principle. The analyses of the primary outcome and other composites of death or hospitalization were performed with the use of Kaplan–Meier estimates, with the log-rank test for the comparison of the study groups, and a supportive Cox proportional-hazards model to calculate hazard ratios and 95% confidence intervals. Consistency of effects was assessed for eight prespecified subgroups, according to age (<65, 65 to 75, and >75 years), sex, ejection fraction (≤59% or >59%), the use or nonuse of ACE inhibitors and beta-blockers, the presence or ab-

sence of diabetes, hospitalization for heart failure within the previous 6 months, and geographic region (Europe, North America, or all other countries). Interactions were evaluated by fitting an interaction term between treatment and each of the eight covariates and then assessing significance with the use of a Wald test. The score on the Minnesota Living with Heart Failure scale and the log-transformed plasma level of NT-proBNP were studied by analysis of covariance, with the baseline value as a covariate. All analyses included the use of ACE inhibitors as a term in the model. To control for the global type I error, the study outcomes were examined in a prespecified sequence as described previously. If at any step superiority was not demonstrated at the 0.05 level, no conclusion would be drawn for subsequent outcomes. All P values are two-sided and were not adjusted for multiple testing.

The protocol specified that the data and safety monitoring board should conduct a single interim efficacy analysis for mortality from any cause after 50% of the total expected deaths had occurred. For this analysis, the Pocock approach was applied for harm and the O'Brien–Fleming approach was applied for benefit.

RESULTS

PATIENTS

From June 2002 through April 2005, a total of 4563 patients were formally screened and 4128 underwent randomization at 293 sites in 25 countries in Western Europe, Eastern Europe, North America, South America, South Africa, and Australia. Of those patients, 2067 were assigned to receive irbesartan and 2061 to receive placebo. The common study termination date was set for April 17, 2008, when it was estimated that at least 1440 events of the primary outcome would have occurred. The mean follow-up time was 49.5 months, and the trial included 16,798 patient-years of follow-up.

The study groups did not differ significantly in baseline characteristics (Table 1). The mean age was 72 years, and 60% of the patients were women. The primary cause of heart failure was hypertension in 64% of the patients and ischemic heart disease in 25%, and hypertension was present in 88% overall. Atrial fibrillation was present in 29% and diabetes mellitus in 27%. Forty-one percent of the patients were obese, which was defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 30. At baseline, the median level of NT-ProBNP was 339 pg per milliliter (interquartile range, 133 to 964). Baseline medications included diuretics (83%, including 52% who were taking a loop diuretic), beta-blockers (59%), calcium-channel blockers (40%), spironolactone (15%), and ACE inhibitors (25%).

STUDY-DRUG ADMINISTRATION AND FOLLOW-UP

At the end of the titration phase, 84% of the patients in the irbesartan group and 88% of those in the placebo group had reached the 300-mg dose (mean doses, 275 mg and 284 mg, respectively). The proportion of patients reaching the target dose did not differ according to the use of an ACE inhibitor. During the study, the proportion of patients receiving an ACE inhibitor rose from 25% in the two groups at baseline to 39% in the irbesartan group and 40% in the placebo group, the use of spironolactone rose from 15% in the two groups at baseline to 28% in the irbesartan group and 29% in the placebo group, and the use of beta-blockers rose from 59% in the irbesartan group and 58% in the placebo group to 73% in the two groups.

Between baseline and 6 months, blood pressure declined by a mean (±SD) of 3.8±18.0 mm Hg systolic and 2.1±10.5 mm Hg diastolic in the irbesartan group and by a mean of 0.2±17.6 mm Hg systolic and 0.2±10.4 mm Hg diastolic in the placebo group; the decreases in the two groups persisted for the duration of the trial. Among the surviving patients, the discontinuation rates in the irbesartan group and in the placebo group, respectively, were 13% and 12% at 1 year, 21% and 20% at 2 years, and 34% and 33% at the end of the trial.

At the end of the study, vital-status data were not available for 29 patients (1%) in the irbesartan group and 44 patients (2%) in the placebo group. If contact could not be made at end of study, data for these patients were censored from the analysis at the date they were last known to be alive.

PRIMARY OUTCOME

The primary composite outcome occurred in 742 patients (36%) in the irbesartan group and in 763 patients (37%) in the placebo group. There were 100.4 end-point events per 1000 patient-years in

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=2061)	Irbesartan (N=2067)
Demographic		
Age		
Mean — yr	72±7	72±7
≥75 yr — no. (%)	716 (35)	697 (34)
Female sex — no. (%)	1264 (61)	1227 (59)
Race — no. (%)†		
White	1925 (93)	1934 (94)
Black	43 (2)	39 (2)
Asian	15 (1)	19 (1)
Other	78 (4)	75 (4)
Clinical		
NYHA class — no. (%)‡		
II	445 (22)	426 (21)
III	1562 (76)	1582 (77)
IV	53 (3)	59 (3)
Heart rate — beats/min	71±10	72±11
Blood pressure — mm Hg		
Systolic	136±15	137±15
Diastolic	79±9	79±9
Body-mass index	29.6±5.3	29.7±5.3
Electrocardiographic findings — no. (%)		
Left ventricular hypertrophy	624 (30)	636 (31)
Left bundle-branch block	169 (8)	167 (8)
Atrial fibrillation or flutter	344 (17)	353 (17)
Ejection fraction	0.60±0.09	0.59±0.09
Cause of heart failure — no. (%)		
Ischemia	500 (24)	536 (26)
Hypertension	1304 (63)	1318 (64)
Hospitalization for heart failure within previous 6 mo — no. (%)	906 (44)	910 (44)
Medical history — no. (%)		
Hypertension	1816 (88)	1834 (89)
Angina symptoms§	824 (40)	828 (40)
Unstable angina	149 (7)	166 (8)
Myocardial infarction	482 (23)	487 (24)
PCI or CABG	267 (13)	281 (14)
Atrial fibrillation	603 (29)	606 (29)
Diabetes mellitus	564 (27)	570 (28)
Stroke or transient ischemic attack	201 (10)	198 (10)

Table 1. (Continued.)

Characteristic	Placebo (N=2061)	Irbesartan (N=2067)
Quality of life		
Score on the Minnesota Living with Heart Failure scale¶		
Median	42	42
Interquartile range	28–58	27–58
Laboratory measurements		
Hemoglobin		
Mean — g/dl	14±2	14±2
Anemia — no. (%)‖	258 (13)	256 (12)
Creatinine — mg/dl	1.0±0.34	1.0±0.32
Estimated glomerular filtration rate		
Mean — ml/min/1.73 m^2 of body-surface area	72±22	73±23
<60 ml/min/1.73 m^2 — no. (%)	613 (30)	632 (31)
Potassium — mmol/liter	4.5±0.5	4.4±0.5
NT-proBNP — pg/ml**		
Median	320	360
Interquartile range	131–946	139–987
Medication — no. (%)		
Diuretic††	1721 (84)	1696 (82)
Loop	1072 (52)	1078 (52)
Thiazide	779 (38)	776 (38)
Spironolactone	313 (15)	320 (15)
ACE inhibitor	510 (25)	538 (26)
Digoxin	269 (13)	291 (14)
Beta-blocker	1202 (58)	1225 (59)
Antiarrhythmic drug	175 (8)	184 (9)
Calcium-channel blocker	811 (39)	825 (40)
Nitrate	550 (27)	558 (27)
Oral anticoagulant	398 (19)	392 (19)
Antiplatelet	1193 (58)	1222 (59)
Lipid-lowering agent	623 (30)	656 (32)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, CABG coronary-artery bypass grafting, NT-proBNP N-terminal pro-B–type natriuretic peptide, NYHA New York Heart Association, and PCI percutaneous coronary intervention.

† Race was reported by the investigators.

‡ One patient in NYHA class I was mistakenly included in the placebo group.

§ This category includes any angina-like symptoms at any time in the past, with no confirmation of diagnosis of coronary heart disease required.

¶ Possible scores range from 0 to 105, with lower scores indicating a better quality of life.

‖ Anemia was defined by World Health Organization criteria as a hemoglobin level of less than 13 g per deciliter in men and less than 12 g per deciliter in women.

** NT-proBNP levels are influenced by a variety of factors, including age, sex, body-mass index, and renal function. No clinically useful normal range has been established.

†† Some patients were taking both loop and thiazide diuretics.

Figure 1. Kaplan–Meier Curves for the Primary Outcome.

The primary outcome of death from any cause or hospitalization for prespecified cardiovascular causes (worsening heart failure, myocardial infarction, stroke, atrial or ventricular arrhythmia, and myocardial infarction or stroke occurring during hospitalization for any cause) is shown for patients receiving irbesartan and those receiving placebo. The Kaplan–Meier curves illustrate the time to the first event (hazard ratio in the irbesartan group, 0.95; 95% confidence interval [CI], 0.86 to 1.05; P=0.35 by the log-rank test). The vertical lines represent 95% confidence intervals.

the irbesartan group and 105.4 events per 1000 patient-years in the placebo group. The hazard ratio for the primary outcome in the irbesartan group, as compared with the placebo group, was 0.95 (95% confidence interval [CI], 0.86 to 1.05; P=0.35) (Fig. 1 and Table 2). The neutral effect of treatment was consistent across all prespecified subgroups (Fig. 2).

SECONDARY OUTCOMES

Rates of death from any cause were 52.6 and 52.3 per 1000 patient-years in the irbesartan group and the placebo group, respectively (hazard ratio, 1.00; 95% CI, 0.88 to 1.14; P=0.98) (Table 3). The rates for protocol-specified hospitalization were 70.6 and 74.3, respectively (hazard ratio, 0.95; 95% CI, 0.85 to 1.08; P=0.44). There were also no significant differences between the study groups for any of the other prespecified secondary outcomes or for hospital admissions for specific cardiovascular indications or for any cause (Table 3). After 6 months, scores on the Minnesota Living with Heart Failure scale improved in both groups, but the difference in the magnitude of change between the two groups was not significant. There was also no significant difference between the groups in the change in the level of NT-proBNP after 6 months.

ADVERSE EVENTS

During the course of the study, 16% of patients in the irbesartan group and 14% of patients in the placebo group discontinued a study drug because of an adverse event (P=0.07) (Table 4). At baseline, the mean levels of serum creatinine were 1.00±0.34 mg per deciliter (88.4±30.1 μmol per liter) in the irbesartan group and 1.00±0.32 mg per deciliter (88.4±28.3 μmol per liter) in the placebo group. At the final visit, the mean levels of serum creatinine were 1.02±0.46 mg per deciliter (90.2±40.7 μmol per liter) in the irbesartan group and 0.98±0.34 mg per deciliter (86.6±30.1 μmol per liter) in the placebo group (P=0.11). During the course of the study, a doubling of the serum creatinine level occurred in at least one measurement in 6% of patients in the irbesartan group and in 4% of patients in the placebo group (P<0.001). A serum potassium level of more than 6.0 mmol per liter occurred at least once in 3% of patients in the irbesartan group and in 2% of patients in the placebo group (P=0.01). However, the differences in the rates of serious adverse events due to hypotension, renal dysfunction, and hyperkalemia between the two groups were not significant (Table 4).

DISCUSSION

Treatment with irbesartan did not reduce the risk of death or hospitalization for cardiovascular causes among patients who had heart failure with a preserved left ventricular ejection fraction, nor did it improve any of the secondary clinical outcomes, including disease-specific quality of life. These findings are in contrast to the benefits seen with inhibitors of the renin–angiotensin–aldosterone system, including angiotensin-receptor blockers, in patients with heart failure with a low left ventricular ejection fraction.[14-17] However, these findings are concordant with the results of two other studies involving patients who had heart failure with a preserved left ventricular ejection fraction, the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Mor-

Table 2. Primary Outcome with Component Events.*

Outcome	Placebo (N=2061)		Irbesartan (N=2067)		Hazard Ratio (95% CI)	P Value
	No. of Patients with Event	Event Rate per 1000 Patient-Yr	No. of Patients with Event	Event Rate per 1000 Patient-Yr		
Primary outcome	763	105.4	742	100.4	0.95 (0.86–1.05)	0.35
Death	226		221			
Hospitalization for protocol-specified cardiovascular cause	537		521			
Worsening heart failure	314		291			
Myocardial infarction	54		60			
Unstable angina	19		20			
Stroke	79		68			
Atrial arrhythmia	68		77			
Ventricular arrhythmia	3		5			

* Event rates were normalized for the duration of follow-up before the event occurrence.

bidity (CHARM)–Preserved trial (ClinicalTrials.gov number, NCT00634712)[17,18] and the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial.[19]

The reasons for the lack of benefit are uncertain, but several explanations warrant consideration. One possibility is that many of the patients may not have had heart failure, since the diagnosis of heart failure with a preserved left ventricular ejection fraction is often not straightforward and can be mimicked by other conditions.[20] We believe that this is unlikely, since 44% of the patients had been hospitalized for heart failure within 6 months, and the remainder had at least NYHA class III symptoms and evidence of structural heart disease. The baseline NT-proBNP values in our trial were generally consistent with values used to diagnose heart failure with a preserved left ventricular ejection fraction in the outpatient setting.[21-24] However, the most compelling evidence that we enrolled a population with heart failure is the high rate at which patients had subsequent hospitalizations for heart failure. These hospitalizations occurred at rates approximately 4 to 8 times the rates observed in trials involving patients with hypertension and diabetes and those at high vascular risk.[25-28]

A second consideration is whether the 300-mg target dose of irbesartan, although the highest approved dose, was suboptimal for efficacy in this disease. However, this dose reduced systolic and diastolic blood pressure by a mean of 3.8/2.1 mm Hg. Furthermore, the same dose of irbesartan reduced the onset of heart failure by 28% in the Irbesartan in Diabetic Nephropathy Trial.[29] On the basis of our study, we cannot assess whether a higher dose would have been beneficial.

Several other factors may have adversely affected the power of the trial. One factor was the high rate of study-drug discontinuation, which reached 34% by the end of the study, a proportion that was similar to that of other heart-failure trials of this duration. A second factor was the high rate of concomitant use of ACE inhibitors, which were taken at some time during the trial by 39% of patients in the irbesartan group and 40% of those in the placebo group, and spironolactone, which was taken by 28% of patients in the irbesartan group and 29% of those in the placebo group. In addition, 73% of patients in the two groups received a beta-blocker during the study. The treatment of a large proportion of patients with multiple inhibitors of the renin–angiotensin–aldosterone system might have left little room for further benefit from the addition of an angiotensin-receptor blocker.

The patients in our study closely resembled those with this syndrome in the community, and as expected their characteristics differed from

Subgroup	Irbesartan	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/no. of events (%)			
All patients	742/2067 (36)	763/2061 (37)	0.95 (0.86–1.05)	
Age				0.60
<65 yr	86/376 (23)	86/364 (24)	0.96 (0.71–1.30)	
65–74 yr	331/994 (33)	322/981 (33)	1.01 (0.87–1.18)	
≥75 yr	325/697 (47)	355/716 (50)	0.90 (0.78–1.05)	
Sex				0.78
Female	392/1227 (32)	420/1264 (33)	0.94 (0.82–1.08)	
Male	350/840 (42)	343/797 (43)	0.96 (0.83–1.12)	
Ejection fraction				0.28
≤59%	433/1054 (41)	423/1027 (41)	0.98 (0.85–1.12)	
>59%	309/1011 (31)	339/1033 (33)	0.92 (0.79–1.07)	
Use of ACE inhibitor				0.36
No	529/1529 (35)	566/1551 (36)	0.93 (0.82–1.04)	
Yes	213/538 (40)	197/510 (39)	1.03 (0.85–1.25)	
Use of beta-blocker				0.14
No	299/842 (36)	336/859 (39)	0.87 (0.75–1.02)	
Yes	443/1225 (36)	427/1202 (36)	1.02 (0.89–1.16)	
Diabetes				0.28
No	491/1495 (33)	494/1496 (33)	0.99 (0.87–1.12)	
Yes	251/570 (44)	269/564 (48)	0.88 (0.74–1.04)	
Hospitalization for heart failure within 6 mo				0.81
No	323/1157 (28)	334/1155 (29)	0.96 (0.82–1.12)	
Yes	419/910 (46)	429/906 (47)	0.94 (0.82–1.08)	
Geographic region				0.50
Europe	518/1475 (35)	534/1464 (36)	0.95 (0.84–1.07)	
North America	87/190 (46)	99/195 (51)	0.85 (0.64–1.14)	
Other	137/402 (34)	130/402 (32)	1.07 (0.84–1.35)	

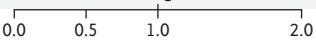

Figure 2. Primary Outcome According to Prespecified Subgroups.

The plot shows hazard ratios and 95% confidence intervals for the primary outcome, with patients stratified according to eight subgroups prespecified in the statistical analysis plan. No heterogeneity was observed for these subgroups.

those of patients who had heart failure with a low left ventricular ejection fraction.[12] In patients with a preserved ejection fraction, the pathophysiologic substrate of a dilated remodeled heart and clinically manifested atherosclerotic disease are either less evident or absent. Furthermore, in spite of the preponderance of patients with a history of hypertension, only a minority of patients had electrocardiographic evidence of left ventricular hypertrophy. Thus, important targets for renin–angiotensin blockade may have been absent in this population. Two previous large trials, PEP-CHF and CHARM-Preserved,[18,19] have also evaluated inhibitors of the renin–angiotensin system in patients with heart failure and a preserved left ventricular ejection fraction (predominantly in patients with a left ventricular ejection fraction of 50% or more), and neither showed an overall beneficial effect of such drugs.

In these patients, heart failure may be related to a variety of factors, including impairment of left ventricular diastolic dysfunction from myocardial hypertrophy and fibrosis or altered myocyte calcium handling,[30-32] abnormal ventricular–vascular coupling related to decreased vascular compliance,[33] impaired renal handling of salt and fluid, and other as-yet-poorly-characterized abnormalities. Although data from experimental models suggest that inhibitors of the renin–angiotensin–aldosterone system may affect these abnormalities,[34] it is unclear which of these potential mechanisms are primarily responsible for the clinical syndrome of heart failure with a preserved left ventricular ejection fraction. Although

Table 3. Secondary Outcomes.*

Outcome	Placebo (N=2061)		Irbesartan (N=2067)		Hazard Ratio (95% CI)	P Value
	No. of Patients with Event	Event Rate per 1000 Patient-Yr	No. of Patients with Event	Event Rate per 1000 Patient-Yr		
Death from any cause	436	52.3	445	52.6	1.00 (0.88–1.14)	0.98
Death from heart failure or hospitalization for heart failure†	438	57.4	428	54.8	0.96 (0.84–1.09)	0.51
Death from a cardiovascular cause or nonfatal myocardial infarction or stroke	400	49.4	402	48.9	0.99 (0.86–1.13)	0.84
Death from a cardiovascular cause	302	36.3	311	36.7	1.01 (0.86–1.18)	0.92
Hospitalization for a protocol-specified cardiovascular cause	537	74.3	521	70.6	0.95 (0.85–1.08)	0.44
Hospitalization for worsening heart failure	336	44.0	325	41.6	0.95 (0.81–1.10)	0.50
Hospitalization for any cause	1126	199.8	1152	203.6	1.02 (0.94–1.11)	0.64
Change in score on the Minnesota Living with Heart Failure scale at 6 mo‡						0.85
Median	−7		−8			
Interquartile range	−19 to 0		−19 to 1			
Change in NT pro-BNP at 6 mo (pg/ml)						0.14
Median	−2		−13			
Interquartile range	−125 to 119		−149 to 100			

* Event rates were normalized for the duration of follow-up before the event occurrence.
† Death from heart failure includes death due to pump failure and sudden death. NT pro-BNP denotes plasma N-terminal pro B–type natriuretic peptide.
‡ Possible scores range from 0 to 105, with lower scores indicating a better quality of life.

ACE inhibitors and angiotensin-receptor blockers have not proved to be beneficial in heart failure with a preserved left ventricular ejection fraction, aldosterone antagonists may have more success, since aldosterone plays a major role in stimulating myocardial collagen formation and in inhibiting the turnover of extracellular matrix.[35,36] This possibility is being tested in the ongoing Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial (NCT00094302) being conducted by the National Heart, Lung, and Blood Institute.

In conclusion, we evaluated the effect of irbesartan versus placebo in patients who had heart failure with a preserved ejection fraction. No significant benefit of irbesartan was shown for a variety of cardiovascular outcomes, including death

Table 4. Drug Discontinuations and Adverse Events.

Variable	Placebo (N=2061)	Irbesartan (N=2067)	P Value
	no. (%)		
Discontinuation of the study drug*			
Any reason	684 (33)	702 (34)	0.60
Adverse event	288 (14)	331 (16)	0.07
Patient's choice	223 (11)	208 (10)	0.43
Serious adverse event			
Hypotension	62 (3)	60 (3)	0.84
Renal failure	57 (3)	69 (3)	0.29
Hyperkalemia	9 (<1)	12 (<1)	0.34

* Reasons for discontinuation did not include death.

from any cause and hospitalization for cardiovascular causes.

Supported by Bristol-Myers Squibb and Sanofi-Aventis.

Dr. Massie reports receiving grant support from Bristol-Myers Squibb, Sanofi-Aventis, and Merck, consulting fees from Bristol-Myers Squibb, Sanofi-Aventis, Merck, Duke Clinical Research Institute, Momentum Research, Novartis, GlaxoSmithKline, Scios–Johnson & Johnson, Corthera, and Niles Therapeutics, and lecture fees from Merck; Dr. Carson, receiving consulting fees from Bristol-Myers Squibb, Sanofi-Aventis, and Merck and lecture fees from AstraZeneca and Novartis; Dr. McMurray, receiving support from Bristol-Myers Squibb (to Glasgow University) for his work on this trial; Dr. Komajda, receiving consulting fees from Bristol-Myers Squibb and Servier and lecture fees from Servier, Sanofi-Aventis, and AstraZeneca; Dr. McKelvie, receiving consulting fees from Bristol-Myers Squibb and Sanofi-Aventis and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, Pfizer, Merck, and AstraZeneca; Dr. Zile, receiving consulting fees from Bristol-Myers Squibb and Sanofi-Aventis; Ms. Anderson, being employed by the Statistical Data Analysis Center at the University of Wisconsin–Madison, which conducted statistical analysis for this trial, supported by Bristol-Myers Squibb and Sanofi-Aventis; Drs. Donovan and Ptaszynska, being employees of and having an equity interest in Bristol-Myers Squibb; and Dr. Staiger, being an employee of and having an equity interest in Sanofi-Aventis. No other potential conflict of interest relevant to this article was reported.

We thank clinical scientists Jean-Michel Bocquet and Magalie Thuault for their care in handling the logistics of the trial.

REFERENCES

1. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004;43:317-27.
2. Lenzen MJ, Scholte op Reimer WJ, Boersma E, et al. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J 2004;25:1214-20.
3. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995;26:1565-74.
4. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. Prog Cardiovasc Dis 2005;47:320-32.
5. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251-9.
6. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260-9.
7. Hogg K, McMurray J. Neurohumoral pathways in heart failure with preserved systolic function. Prog Cardiovasc Dis 2005;47:357-66.
8. Wright JW, Mizutani S, Harding JW. Pathways involved in the transition from hypertension to hypertrophy to heart failure: treatment strategies. Heart Fail Rev 2008;13:367-75.
9. Little WC, Brucks S. Therapy for diastolic heart failure. Prog Cardiovasc Dis 2005;47:380-8.
10. Desai A. Current understanding of heart failure with preserved ejection fraction. Curr Opin Cardiol 2007;22:578-85.
11. Carson P, Massie BM, McKelvie R, et al. The Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial: rationale and design. J Card Fail 2005;11:576-85.
12. McMurray JJ, Carson PE, Komajda M, et al. Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. Eur J Heart Fail 2008;10:149-56.
13. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. Am J Cardiol 1993;71:1106-7.
14. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
15. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.
16. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.
17. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759-66.
18. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.
19. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study. Eur Heart J 2006;27:2338-45.
20. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. BMJ 2000;321:215-8.
21. Paulus WJ, Tschöpe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539-50.
22. Grewal J, McKelvie RS, Persson H, et al. Usefulness of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide to predict cardiovascular outcomes in patients with heart failure and preserved left ventricular ejection fraction. Am J Cardiol 2008;102:733-7.
23. Galasko GI, Lahiri A, Barnes SC, Collinson P, Senior R. What is the normal range for N-terminal pro-brain natriuretic peptide? How well does this normal range screen for cardiovascular disease? Eur Heart J 2005;26:2269-76.
24. Abhayaratna WP, Marwick TH, Becker NG, Jeffery IM, McGill DA, Smith WT. Population-based detection of systolic and diastolic dysfunction with amino-terminal pro-B-type natriuretic peptide. Am Heart J 2006;152:941-8.
25. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003.
26. Einhorn PT, Davis BR, Massie BM, et al. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Heart Failure Validation Study: diagnosis and prognosis. Am Heart J 2007;153:42-53.
27. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 2008;359:1225-37.
28. Arnold JM, Yusuf S, Young J, et al. Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (HOPE) Study. Circulation 2003;107:1284-90.
29. Berl T, Hunsicker LG, Lewis JB, et al. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients

with type 2 diabetes and overt nephropathy. Ann Intern Med 2003;138:542-9.
30. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002;105:1387-93.
31. *Idem.* New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. Circulation 2002;105:1503-8.
32. Borlaug BA, Kass DA. Mechanisms of diastolic dysfunction in heart failure. Trends Cardiovasc Med 2006;16:273-9.
33. Kass DA, Bronzwaer JG, Paulus WJ. What mechanisms underlie diastolic dysfunction in heart failure? Circ Res 2004;94:1533-42.
34. Berk BC, Fujiwara K, Lehoux S. ECM remodeling in hypertensive heart disease. J Clin Invest 2007:568-75.
35. Weber KT. Aldosterone in congestive heart failure. N Engl J Med 2001;345:1689-97.
36. Mottram PM, Haluska B, Leano R, Cowley D, Stowasser M, Marwick TH. Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. Circulation 2004;110:558-65.