Dose-related Beneficial Long-term Hemodynamic and Clinical Efficacy of Irbesartan in Heart Failure

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OBJECTIVES
The primary purpose of this study was to determine the acute and long-term hemodynamic and clinical effects of irbesartan in patients with heart failure.

BACKGROUND
Inhibition of angiotensin II production by angiotensin-converting enzyme (ACE) inhibitors reduces morbidity and mortality in patients with heart failure. Irbesartan is an orally active antagonist of the angiotensin II AT₁ receptor subtype with potential efficacy in heart failure.

METHODS
Two hundred eighteen patients with symptomatic heart failure (New York Heart Association [NYHA] class II–IV) and left ventricular ejection fraction ≤40% participated in the study. Serial hemodynamic measurements were made over 24 h following randomization to irbesartan 12.5 mg, 37.5 mg, 75 mg, 150 mg or placebo. After the first dose of study medication, patients receiving placebo were reallocated to one of the four irbesartan doses, treatment was continued for 12 weeks and hemodynamic measurements were repeated.

RESULTS
Irbesartan induced significant dose-related decreases in pulmonary capillary wedge pressure (average change \(-5.9 \pm 0.9 \text{ mm Hg}\) and \(-5.3 \pm 0.9 \text{ mm Hg}\) for irbesartan 75 mg and 150 mg, respectively) after 12 weeks of therapy without causing reflex tachycardia and without increasing plasma norepinephrine. The neurohormonal effects of irbesartan were highly variable and none of the changes was statistically significant. There was a significant dose-related decrease in the percentage of patients discontinuing study medication because of worsening heart failure. Irbesartan was well tolerated without evidence of dose-related cough or azotemia.

CONCLUSIONS
Irbesartan, at once-daily doses of 75 mg and 150 mg, induced sustained hemodynamic improvement and prevented worsening heart failure. (J Am Coll Cardiol 1999;33:1174–81)

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Study design and methodology. This multicenter, randomized, double-blind study consisted of three study periods. A 2- to 14-day, single-blind, placebo lead-in period was followed by a 2-day acute, placebo-controlled, double-blind period and a 12-week long-term, double-blind period.

During the placebo lead-in period and prior to baseline hemodynamic measurements, dosages of required (diuretics) and permitted (digoxin and nitrates) medications were stabilized (diuretics for ≥2 days, digoxin for ≥14 days and nitrates for ≥4 days). Angiotensin-converting enzyme inhibitor therapy was discontinued ≥4 days prior to baseline hemodynamic measurements. The type and dose of ACE inhibitor is given in Table 1. Other prohibited medications, including vasodilators, calcium channel blockers and beta-blockers, were discontinued ≥3 days prior to baseline hemodynamic measurements. Initial hemodynamic measurements, determined 2 h after placement of a Swan-Ganz catheter, had to demonstrate that PCWP was ≥14 mm Hg and cardiac index (CI) was ≥3.0 L/min-m² in order for the patient to be eligible for determination of baseline hemodynamic measurements.

Baseline hemodynamic measurements were assessed ≥12 h after placement of the Swan-Ganz catheter and were required to be reproducible (i.e., PCWP, measured at 15 min intervals, differing by ≤10% and ≤2 mm Hg and CI differing by ≤10%). The average of two sets of baseline measurements of PCWP and CI had to be ≥14 mm Hg and ≥3.0 L/min-m², respectively, for the patient to be eligible for randomization. Each randomized patient received a single dose of placebo or irbesartan 12.5 mg, 37.5 mg, 75 mg, or 150 mg. Following 24 h of acute hemodynamic assessments, patients randomized to irbesartan continued to receive the same dose of irbesartan once-daily for 12 weeks. Patients initially randomized to placebo were reassigned to one of the four doses of irbesartan for the 12-week study period. The protocol required that the maintenance dose of concomitant medication for the treatment of heart failure remain stable, although up to three supplemental doses of diuretic were permitted after randomization. Patients who required additional medications for the treatment of worsening heart failure were required to be discontinued from study medication.

Hemodynamic assessments. Hemodynamic measurements were made at baseline (prior to study medication administration) and at 0.5, 1, 2, 3, 4, 6, 9, 12 and 24 h following the administration of study medication. Baseline measurements were made at least 10 h after each patient’s most recent meal. Patients were restricted to no more than 500 ml of oral intake following catheter insertion prior to baseline measurements and 1600 ml oral intake during the 24-h
measurement period. All measurements were the average of three readings and were recorded at end expiration with the patient in a semisupine (30°) position. For 24 h prior to baseline hemodynamic measurements and during the 24-h interval of hemodynamic measurements, the maintenance doses of diuretic, digoxin and nitrate were withheld. After 12 weeks of study medication, 24-h hemodynamic readings were repeated in the same manner as at study entry.

Neurohormonal substudy. Blood samples to assess plasma renin activity and concentrations of aldosterone and norepinephrine were collected from a subset of 48 patients at baseline and at 2, 6, 12 and 24 h after the first and last doses of study medication.

Safety assessments. Safety was evaluated through physical examinations, clinical laboratory assessments and electrocardiograms. Spontaneously reported adverse events and adverse events elicited by general questioning were recorded.

STATISTICAL ANALYSIS
The primary efficacy measure was the change from baseline in PCWP determined at Week 12. Secondary efficacy measures were changes from baseline in mean pulmonary arterial pressure (MPAP); mean systemic arterial pressure (MSAP) and heart rate at 12 weeks; acute change from baseline in PCWP, MPAP, MSAP and heart rate after the first dose of study medication; and change in clinical status after 12 weeks of study medication. The protocol also required that LVEF be assessed at baseline and again at 12 weeks after randomization either by a radionuclide technique or by two-dimensional echocardiography, using the same technique for each determination in a given patient. The protocol required that additional hemodynamic data, including CI and mean right atrial pressure (MRAP) be recorded during periods of hemodynamic monitoring.

With a sample size of 50 patients per group, there was a 90% ability to detect a 4.7 mm Hg difference in PCWP between groups. Assuming a dropout rate of 20% (40 patients per group), the power to detect this difference in PCWP was 81%. All tests were two-sided tests with \( \alpha = 0.05 \). This analysis was performed using SAS, version 6.07.

Hemodynamic effects of irbesartan were assessed by calculating a time-weighted average change from baseline value for each hemodynamic parameter averaged over the first 12 h after the dose of study medication. The time-weighted average changes in hemodynamic parameters were compared by analysis of covariance (ANCOVA). In addition, dose-related trends in average change in hemodynamic parameters were assessed utilizing a linear model. The effect of irbesartan on neurohormones was assessed by calculating the time-weighted average change from baseline value over the first 24 h after administration of study medication.

There were fewer patients in the placebo group than in other groups due to a delay in the entry of placebo kit numbers into the central randomization system. This did not affect analysis of the primary end point because placebo patients were reallocated to active drug following the acute hemodynamic measurements.

RESULTS

Baseline characteristics and patient disposition. Baseline demographic, clinical and hemodynamic characteristics for each treatment group are presented in Table 2. Baseline demographic variables were similar among treatment groups, although nonischemic etiologies of heart failure were slightly more prevalent in the group randomized to initially receive 37.5 mg of irbesartan. The disposition of patients in the trial is presented in Figure 1. The mean duration of the lead-in period during which patients were not treated with ACE inhibitors was 9.1 days. No patient...
decompensated as a result of ACE inhibitor discontinuation. The adverse events requiring discontinuation of study medication during the acute phase consisted of complete heart block, atrial fibrillation, hypotension, nonsustained ventricular tachycardia and a severe vasovagal reaction during removal of the right heart catheter. During long-term administration, adverse events requiring discontinuation consisted of: worsening heart failure (n = 10), hypotension (n = 5), laboratory abnormalities (n = 5), acute myocardial infarction (n = 4), nonsustained ventricular tachycardia (n = 2), atrial fibrillation (n = 1), dizziness (n = 1), heart transplant (n = 1), hypertension (n = 1), angina pectoris (n = 1) and respiratory infection (n = 1).

Hemodynamic effects of irbesartan. Pulmonary capillary wedge pressure (PCWP). The time course of change from baseline PCWP after the first dose of study medication is shown in Figure 2A. The largest decrease in PCWP was seen 3 h after the administration of 150 mg of irbesartan, at which time PCWP had decreased by 4.4 mm Hg. Decrease from baseline PCWP was generally dose-related during the first 12 h after administration of the first dose of study medication. The time course of change from baseline PCWP after administration of the Week-12 dose of study medication is shown in Figure 3. At trough (24 h after administration of the previous dose) PCWP had decreased 4.0 to 4.5 mm Hg in patients treated with 37.5 mg, 75 mg or 150 mg of irbesartan and by 1.6 mm Hg in patients treated with 12.5 mg irbesartan. Administration of a new dose of irbesartan produced further reductions in PCWP as shown in Table 3. Patients receiving 75 mg or 150 mg of irbesartan had a significantly greater average decrease in PCWP (5.3 to 5.9 mm Hg) than did patients receiving 12.5 mg of irbesartan (2.3 mm Hg), and the average decrease in PCWP was significantly related to dose of irbesartan (p = 0.013). Taken together, these data indicate that irbesartan induces significant, dose-related decreases in PCWP that are sustained for up to 24 h after administration of irbesartan for 12 weeks.

Mean pulmonary arterial pressure (MPAP). As shown in Figure 2B, irbesartan induced acute, dose-related decreases in MPAP. As shown in Table 3, the dose-related-decreases in MPAP were sustained after 12 weeks of treatment.

Mean systemic arterial pressure (MSAP). As shown in Figure 2C, administration of irbesartan resulted in acute, dose-related decreases in MSAP. As shown in Table 3, long-term administration of 75 mg of irbesartan reduced MSAP on average by 8.7 mm Hg compared with 4.0 mm Hg for 12.5 mg irbesartan, but changes in MSAP were not clearly related to dose after 12 weeks of administration (p = 0.243).

Heart rate. As shown in Figure 2D and in Table 3, there were no significant dose-related effects of irbesartan on heart rate during either acute or long-term administration.

Cardiac index (CI). There were no significant acute changes in CI seen with the administration of the first dose of study medication. After administration of 12 weeks of irbesartan, there was a small increase in average CI in the 37.5 mg dose group (0.3 L/min-m²) compared with the 12.5 mg group (0.1 L/min-m², p < 0.05), but increases in CI were not generally dose-related at Week 12 (p = 0.56) (Table 3).

Left ventricular ejection fraction (LVEF). There was a tendency for LVEF to increase as a function of dose of irbesartan (p = 0.088). Irbesartan 75 mg and 150 mg produced greater average changes in LVEF when compared with irbesartan 12.5 mg; however, these changes did not achieve statistical significance (Table 3).

Clinical effects of irbesartan. The number of patients discontinuing study medication and the number of patients hospitalized for heart failure are shown in Table 4. Discontinuation of study medication as a consequence of worsening heart failure decreased as a function of dose of irbesartan (p = 0.045). Death, discontinuation of study medication for worsening heart failure or hospitalization for worsening heart failure occurred in 13.9% of patients receiving either 12.5 mg or 37.5 mg of irbesartan as compared with 5.5% of patients receiving either 75 mg or 150 mg of irbesartan (p = 0.04). Discontinuation of study medication and hospitalization for worsening heart failure were at the discretion of the individual investigator.

Neurohormonal effects of irbesartan. As shown in Table 5, plasma renin activity tended to increase as a function of dose of irbesartan while serum aldosterone and plasma

Figure 1. Patient disposition. Reasons for discontinuation of study medication are shown.
norepinephrine tended to decrease in the 150 mg group after the first dose of study medication. In general, the variability of the data was too large to detect statistically significant changes in neurohormone levels following 12 weeks of therapy, perhaps in part because of variability in baseline disease severity.

Safety and tolerability of irbesartan. Three deaths (two deaths in the 37.5 mg group, one death in the 150 mg group) occurred during the 12-week treatment period. Each death was either sudden or unwitnessed.

One patient in the placebo group, two patients in the 75 mg group and two patients in the 150 mg group discontinued study medication due to adverse events during the acute phase of the study. During the long-term phase of the study, adverse events lead to the discontinuation of study medication in 6 (11%) patients in the 12.5 mg group, 14 (26%) patients in the 37.5 mg group, 4 (8%) patients in the 75 mg group and 8 (15%) patients in the 150 mg group. Hypotension was reported as an adverse event in three patients (1.6%) during the acute phase of the study (one patient receiving 37.5 mg irbesartan and two patients receiving 150 mg irbesartan). During the long-term phase of the study, hypotension or orthostatic hypotension was reported as an adverse event in an additional 12 (5.7%) patients, including 1 patient (1.9%) receiving 12.5 mg irbesartan, 4 patients (7.4%) receiving 37.5 mg irbesartan, 1 patient (1.9%) receiving 75 mg irbesartan and 6 patients (11.3%) receiving 150 mg irbesartan. There was no evidence for dose-related increases in the frequency of adverse events related to either cough or azotemia. There were no statistically significant changes in blood urea nitrogen (BUN), creatinine, potassium or uric acid at Week 12 compared with baseline.

DISCUSSION

Hemodynamic effects of irbesartan. Patients who have marked elevation of resting PCWP in the setting of heart failure are at increased risk for adverse clinical outcome (15,16). Irbesartan induced significant, dose-related reductions in PCWP that were sustained after 12 weeks of treatment. The magnitude of this effect, 5–6 mm Hg with 75-mg or 150-mg doses, is clinically important. Irbesartan
produced reductions in PCWP 24 h after dosing, indicating that once-per-day dosing with irbesartan provides sustained reductions in left ventricular filling pressure during long-term treatment. Irbesartan also induced dose-related, sustained reductions in MPAP. The decrease in blood pressure was not dose-related as shown by the range of doses characterized in the study, in contrast to the dose-related reduction in systemic arterial pressure that is seen in mild-to-moderate hypertension (17,18). Attenuation of blood pressure lowering at higher doses of AT1 receptor antagonists has been reported previously in patients with heart failure (2). Although irbesartan lowered left ventricular filling pressures, CI was maintained during long-term treatment. These hemodynamic effects of irbesartan were not accompanied by reflex tachycardia.

Clinical effects of irbesartan. Discontinuation of study medication due to worsening heart failure was significantly reduced in a dose-related manner by irbesartan. Since the protocol required discontinuation of study medication in patients who needed new medications or an increase in the maintenance dose of concomitant medications for heart failure, these data indicate that irbesartan prevented worsening of heart failure in a dose-related manner and provide a clinical correlate to the dose-related improvement in PCWP.

Neurohormonal effects of irbesartan. There was a tendency for irbesartan to induce an acute increase in plasma renin activity. This is likely to be due to blockade of AT1 receptors located in the juxtaglomerular apparatus of the kidney and has been reported previously during the acute administration of AT1 receptor antagonists in patients with heart failure (2,3). In the 150 mg irbesartan group, serum aldosterone and plasma norepinephrine levels tended to decrease acutely and during long-term administration.

Safety and tolerability of irbesartan. Irbesartan was generally well-tolerated in this 12-week study of patients with mild-to-severe heart failure. Discontinuation of study medication and adverse events were not related to dose of irbesartan.

Comparison with previous studies. The results of this study are consistent with and confirm the results of a previous study in which 96 patients with heart failure received either placebo or single doses of irbesartan ranging from 1 mg to 200 mg. In the previous study, irbesartan acutely decreased PCWP, mean systemic arterial pressure and heart rate while maintaining CI (19).

Previous studies with the AT1 receptor antagonist losartan demonstrated reductions in PCWP, MSAP, systemic vascular resistance and heart rate associated with an increase in CI in patients with heart failure (2,3). There is a preliminary report that administration of the AT1 receptor antagonist valsartan, at a dose of 160 mg twice daily to patients already being treated with ACE inhibitors, results in acute and long-term reduction of PCWP (20). Irbesartan was well tolerated in two additional studies of patients with heart failure (21,22).

Whether AT1 receptor antagonism provides survival that is comparable with or superior to inhibition of ACE needs to be addressed in a prospectively designed mortality trial of sufficient size and duration.

Study limitations. Ethical considerations preclude assessment of the effects of irbesartan or other AT1 receptor antagonists in a long-term, placebo-controlled trial in patients not receiving ACE inhibitors.

Thus, the long-term phase of this study was not placebo-controlled. The 12.5 mg irbesartan group served as a control during the long-term phase of the study, and the analysis of data was based upon comparison of the 12.5 mg group with groups receiving higher doses and by assessment of dose-related trends in the data. This design is likely to provide a conservative estimate of what the treatment effect would have been in a placebo-controlled trial. Given the small number of NYHA class IV patients included in the trial, the

| Table 3. Average Changes from Baseline in Hemodynamic Variables at Week 12 |
|------------------|------------------|------------------|------------------|------------------|
|                  | PCWP* mm Hg      | MPAP† mm Hg      | MSAP mm Hg       | HR beats/min     |
| Irbesartan 12.5 mg | –2.3 ± 0.9       | 0.2 ± 1.1        | –4.0 ± 1.2       | 0.3 ± 1.4       |
| Irbesartan 37.5 mg | –4.8 ± 1.0       | –4.2 ± 1.1       | –5.9 ± 1.3       | 3.2 ± 1.5       |
| Irbesartan 75 mg  | –5.9 ± 0.9       | –5.4 ± 1.1       | –8.7 ± 1.2       | –3.3 ± 1.4      |
| Irbesartan 150 mg | –5.3 ± 0.9       | –3.0 ± 1.1       | –5.3 ± 1.2       | –0.6 ± 1.4      |

*p = 0.013 for dose-related trend; †p = 0.021 for dose-related trend; ‡p = 0.088 for dose-related trend.

PCWP = pulmonary capillary wedge pressure; MPAP = mean pulmonary arterial pressure; MSAP = mean systemic arterial pressure; HR = heart rate; CI = cardiac index; LVEF = left ventricular ejection fraction.

| Table 4. Drug Discontinuation or Hospitalization for Worsening Heart Failure |
|------------------|------------------|------------------|------------------|
|                  | 12.5 mg | 37.5 mg | 75 mg  | 150 mg |
| Discontinued due to worsening heart failure | 5       | 6       | 2      | 1      |
| Hospitalized due to worsening heart failure  | 3       | 3       | 2      | 2      |
Table 5. Average Changes from Baseline in Neurohormones*

<table>
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<tr>
<th>Dose Level</th>
<th>Plasma Renin Activity ng angiotensin I/mL/hr</th>
<th>Serum Aldosterone ng/dL</th>
<th>Plasma Norepinephrine ng/dL</th>
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<tbody>
<tr>
<td></td>
<td>First Dose</td>
<td>Week 12</td>
<td>First Dose</td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.1 ± 0.1</td>
<td>—</td>
<td>-1.4 ± 0.7</td>
</tr>
<tr>
<td>Irbesartan 12.5 mg</td>
<td>1.7 ± 0.9</td>
<td>2.6 ± 2.0</td>
<td>-1.9 ± 1.2</td>
</tr>
<tr>
<td>Irbesartan 37.5 mg</td>
<td>3.2 ± 1.2</td>
<td>3.9 ± 1.7</td>
<td>-1.3 ± 0.5</td>
</tr>
<tr>
<td>Irbesartan 75 mg</td>
<td>5.7 ± 2.4</td>
<td>9.0 ± 3.9</td>
<td>-3.2 ± 2.1</td>
</tr>
<tr>
<td>Irbesartan 150 mg</td>
<td>11.7 ± 4.6</td>
<td>4.5 ± 1.7</td>
<td>-9.6 ± 7.0</td>
</tr>
</tbody>
</table>

*The mean ± standard error of the mean are shown.

results are most applicable to patients with mild-to-moderate heart failure.

Conclusions. In conclusion, the once-daily administration of irbesartan 75 mg or 150 mg to patients with symptomatic heart failure (NYHA functional class II, III or IV) and LVEF ≤40% was well-tolerated, resulted in sustained hemodynamic improvement and prevented worsening heart failure. Irbesartan appears to be a promising new therapy for patients with chronic heart failure.

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APPENDIX

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