

Comparative Efficacy of Two Angiotensin II Receptor Antagonists, Irbesartan and Losartan, in Mild-to-Moderate Hypertension

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The primary objectives of this double-blind study were to compare the antihypertensive efficacy and tolerability of irbesartan and losartan, two angiotensin II (AT₁ subtype) receptor antagonists with different pharmacokinetic profiles in patients with mild-to-moderate hypertension. Both drugs are approved for once-daily use (although losartan may also be prescribed twice-daily). After a placebo lead-in, 567 patients were randomized (1:1:1:1) to once-daily therapy with placebo, 100 mg losartan, 150 mg irbesartan, or 300 mg irbesartan for 8 weeks. Treatment groups had comparable demographic and baseline characteristics. After 8 weeks of treatment, reductions from baseline in trough seated diastolic blood pressure (SeDBP) and trough seated systolic blood pressure (SeSBP) with 300 mg irbesartan were greater than with 100 mg losartan ($P < .01$ for both comparisons), by 3.0 and 5.1 mm Hg, respectively; larger reductions were also demonstrated at weeks 1 and 4 ($P < .01$ and $P = .017$, respectively, for SeDBP). Throughout the

study, the antihypertensive effect of 150 mg irbesartan did not differ significantly from that of 100 mg losartan. All therapies were well tolerated. The 300 mg dose of irbesartan was associated with the lowest incidence of adverse events (AE) and discontinuations because of AE. This study demonstrates that the maximally effective once-daily doses of two different AT₁ receptor antagonists may result in clinically significant differences in blood pressure reductions, and therefore highlights the potential importance of the pharmacokinetic and pharmacodynamic differences between these two members of this class. Am J Hypertens 1998;11:445-453 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: Irbesartan, losartan, angiotensin II receptor antagonist, mild-to-moderate hypertension, pharmacokinetics, placebo-controlled study.

Angiotensin II (AII) receptor blockers, a new class of antihypertensive agents, inhibit the renin-angiotensin system by selectively blocking the AT₁ subtype of AII receptors.¹ Despite sharing this common mechanism

of action, pharmacologic differences that could result in different efficacy and tolerability profiles do exist among the AT₁ blockers.

Irbesartan (SR 47436, BMS-186295) is a long-acting AT₁ blocker that does not require biotransformation

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The members of the Irbesartan/Losartan Study Group are given in the Appendix.

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for its pharmacologic activity.² In vitro binding studies indicate that irbesartan is a competitive antagonist; however, in isolated rabbit aorta, it behaves as a non-competitive (or insurmountable) antagonist of the AT₁ receptor, ie, it affects both the slope and the maximum response of the concentration/effect relationship.² The oral bioavailability of irbesartan ranges from 60% to 80%³ and its absorption is unaffected by food. Irbesartan is lipophilic and its volume of distribution averages from 53 to 93 L; it displays linear, dose-dependent pharmacokinetics and has a plasma half-life averaging 11 to 15 h.^{4,5}

Losartan, the first orally available AT₁ blocker to be developed for clinical use, is a competitive antagonist^{6,7} with a pharmacokinetic profile very different from irbesartan. Much of the AII-inhibiting effect of losartan can be attributed to its active metabolite, EXP 3174,^{8,9} which is a noncompetitive AT₁ blocker.^{7,8} The oral bioavailability of losartan is approximately 33% with nearly 14% of the administered dose being converted to the active metabolite.^{10,11} Food slightly delays its absorption.¹² Losartan and EXP 3174 have plasma half-lives of 2 h and 6 to 9 h, respectively, and volumes of distribution of approximately 34 L for losartan and 10 L for EXP 3174.⁸⁻¹⁰ Owing to the long duration of activity of EXP 3174, losartan may be administered once daily in the treatment of hypertension.¹³

In healthy subjects, a single dose of 300 mg irbesartan inhibits the AII pressor response by 100% at peak and by 60% at 24 h,¹⁴ whereas in the same setting, 80 and 120 mg losartan produced inhibition of approximately 90% and 40%, respectively.⁹ The specificity and affinity of irbesartan and EXP 3174 for the AT₁ receptors are of the same magnitude, and about 10-fold greater than the affinity of losartan for these receptors.²

The effective dose range of each compound has been defined using once-daily dosing in hypertensive patients. In studies using once-daily doses of irbesartan ranging from 1 mg to 900 mg, doses above 300 mg provided little additional benefit.^{15,16} In a study using once-daily doses of losartan up to 150 mg, maximal reductions in blood pressure were estimated to occur at 50 mg to 100 mg using an E_{max} (maximal efficacy) model.¹⁷ Both drugs exhibited trough-to-peak ratios > 50% at therapeutic doses and dose-limiting side effects did not compromise the evaluation of efficacy dose-response for either drug. Given the same mechanisms of action but different pharmacokinetic and pharmacodynamic profiles, we believed it was important to determine if these established differences could result in clinically significant differences in efficacy. Accordingly, the present study explored the antihypertensive efficacy and tolerability of 150 and 300 mg irbesartan once daily versus 100 mg losartan once daily.

METHODS

Patient Selection Prior to commencement at each study site, the study received Institutional Review Board (IRB) approval as required by local law. All patients provided written informed consent. Men and women were 18 years of age or older and had a well-established history of mild-to-moderate essential hypertension; women were either surgically sterile or postmenopausal. Exclusion criteria included concomitant diseases that would present safety hazards and concomitant medications that might interfere with the assessment of efficacy or safety (eg, drugs known to affect blood pressure). Patients who had previously received irbesartan or losartan as an investigational agent as well as those known to be intolerant of losartan in clinical use were also excluded.

Study Design This study was conducted at 41 sites in the US, Canada, Mexico, Argentina, and Brazil. All antihypertensive agents were withdrawn after consent and prior to a 4- to 5-week, single-blind, placebo lead-in period. During this phase, mean seated diastolic blood pressure (SeDBP) measurements taken on days 22 and 29 (optionally on days 29 and 36) had to be 95 to 110 mm Hg inclusive, and the values for the two visits could not differ by > 8 mm Hg for patients to qualify for randomization. An 8-week, double-blind phase followed in which eligible patients were randomized (1:1:1:1) to one of the following once-daily parallel treatment groups: 150 mg irbesartan, 300 mg irbesartan, 100 mg losartan, or placebo. After the first dose of double-blind therapy, patients remained in the clinic for approximately 6 h for safety observation. Patients also visited the clinic on day 2 (\pm 3 h) and at weeks 1, 2, 4, and 8 (\pm 3 days).

Study Supplies All study drugs were administered in identical gray capsules. In a separate clinical study, the encapsulated losartan product was shown to be equivalent to commercially available losartan (Data on file, Bristol Myers Squibb).

Observation Methods *Efficacy* At all clinic visits, trough (24 ± 3 h after ingestion of study medication) seated and standing blood pressures were measured. Blood pressure was measured using a mercury sphygmomanometer after the patient had rested for 10 min in the seated position. Three measurements were taken at least 1 min apart. If these SeDBP readings were not within 8 mm Hg of each other, an additional two readings were obtained and incorporated into the calculated mean. Three (or five) blood pressure measurements were similarly obtained after 2 min standing. The mean of the three (or five) measurements was used to determine eligibility for the trial and was used in the efficacy analyses.

TABLE 1. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

	Placebo (N = 147)	Losartan, 100 mg (N = 138)	Irbesartan, 150 mg (N = 142)	Irbesartan, 300 mg (N = 140)
Gender, Male/Female, %	61/39	50/50	54/46	57/43
Age				
Mean (SD), years	53.8 (9.6)	55.0 (10.7)	53.1 (10.5)	55.6 (10.4)
< 65/≥ 65 years, %	85/15	80/20	85/15	77/23
Race, white/black/other, %	77/10/13	80/5/14*	77/6/17	78/6/16
Baseline blood pressure				
Mean SeSBP (SD), mm Hg	152.4 (14.7)	153.3 (15.5)	155.3 (16.2)	155.4 (16.0)
Mean SeDBP (SD), mm Hg	100.3 (4.3)	100.6 (4.4)	101.1 (4.6)	100.4 (4.5)

SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure; SD, standard deviation

* Total percentage does not add to 100% because of rounding.

Safety Observed and volunteered adverse events (AE) regardless of cause, including those elicited by general questioning, were recorded at all visits. Blood and urine samples were obtained for standard laboratory tests at the end of the placebo lead-in period and at weeks 4 and 8 of double-blind therapy. A 12-lead electrocardiogram (ECG) and physical examination were performed at the end of the placebo lead-in period and at week 8 of double-blind therapy.

Statistical Methods *Sample Size Determination* A sample size of 115 randomized patients for each treatment group was chosen to give at least 90% power, with a type I error of 5% (two-tailed), of detecting a true difference of 3.5 mm Hg between treatments with regard to the primary variable (change from baseline in trough SeDBP at week 8). The sample size calculation assumed a standard deviation of 8 mm Hg. Dunnett's procedure was used to adjust the sample size to control for multiple comparisons. The planned sample size did not allow for potential dropouts and was not powered to detect differences in normalization rates or responder rates.

Demographic and Baseline Characteristics Quantitative data were analyzed by a one-way analysis of variance and qualitative data were assessed by a χ^2 test. These statistical tests were two-sided with a significance level of $\alpha = 0.05$.

Efficacy and Safety Measurements The primary statistical comparisons were between the two irbesartan groups and the losartan group. Testing of active groups versus placebo was performed to confirm the antihypertensive effects of irbesartan and losartan in this study. Statistical tests were two-sided and carried out at a significance level of $\alpha = 0.05$ (placebo versus each active group) or $\alpha = 0.026$ (adjusted by Dunnett's procedure, for each dose of irbesartan versus losartan).

Efficacy analyses were performed on the data set of

all randomized patients with a baseline and at least one on-therapy evaluation. Treatment groups were compared with regard to changes from baseline in trough blood pressure using an analysis of covariance (ANCOVA) model including terms for randomized group, site, and baseline blood pressure. Treatment groups were compared with regard to the proportions of patients normalized (trough SeDBP < 90 mm Hg) or responding (normalized or a reduction in trough SeDBP ≥ 10 mm Hg) at week 8 only by the Cochran-Mantel-Haenszel procedure, stratified by site.

Safety analyses included all randomized patients who received at least one dose of study medication. Mean changes from baseline to weeks 4 and 8 in serum creatinine, potassium, and uric acid levels were compared among the treatment groups using an ANCOVA model with treatment as a factor and baseline as a covariate. These analytes were selected a priori for statistical testing because of the known effects of losartan or other drugs affecting AII.

Treatment Group Assignments Patients were grouped according to their randomized dose group for analyses of baseline comparability and efficacy. Six patients received a study drug different from their randomized treatment; for safety analyses, these patients were analyzed according to the treatment received.

RESULTS

Patient Disposition A total of 567 patients were randomized (147 to placebo, 138 to 100 mg losartan, 142 to 150 mg irbesartan, and 140 to 300 mg irbesartan). Following randomization, 37 patients (12 placebo, 7 100 mg losartan, 12 150 mg irbesartan, and 6 300 mg irbesartan) withdrew. Thus, 530 patients completed the 8-week, double-blind period.

Demographic and Baseline Characteristics No statistically significant baseline differences were observed among the treatment groups (Table 1). The

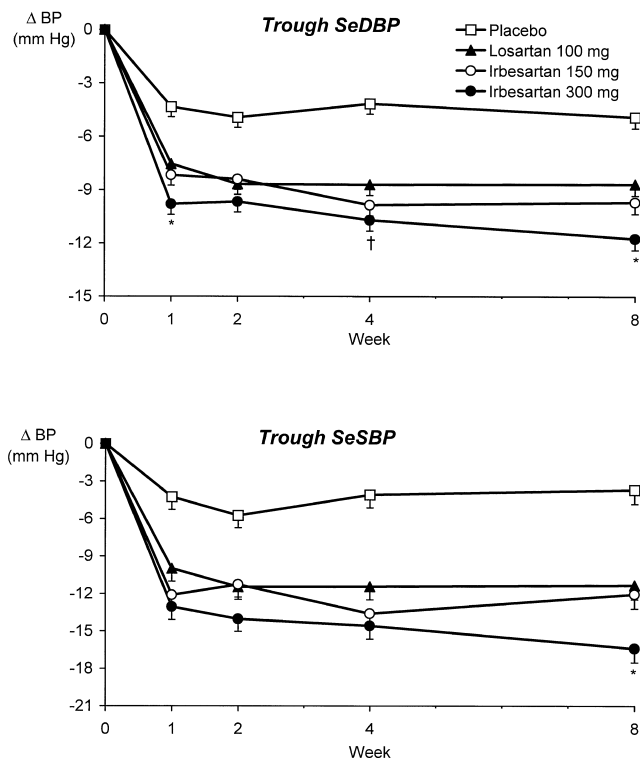


FIGURE 1. Adjusted mean changes from baseline in trough seated diastolic blood pressure (SeDBP) and trough seated systolic blood pressure (SeSBP) during the 8-week study period (bars = SE). * $P < .01$ v losartan; † $P = .017$ v losartan. Note: $P < .001$ v placebo at all times for all active groups.

majority of patients were male (55%) and white (78%). Mean age was 54 years and mean baseline blood pressure was 154/101 mm Hg.

Trough Blood Pressure At week 8, reductions from baseline in trough SeDBP, the primary efficacy variable, and in trough seated systolic blood pressure (SeSBP) were significantly greater with 300 mg irbesartan compared with 100 mg losartan ($P < .01$ for both comparisons; Figure 1 and Table 2). At this time, the mean reductions in the irbesartan group were 5.1/3.0 mm Hg larger than the losartan group. As shown in Figure 1, a greater antihypertensive effect of 300 mg irbesartan compared with 100 mg losartan was present throughout the study and also reached statistical significance at weeks 1 and 4 for SeDBP (at week 1 $P < .01$ and at week 4 $P = .017$). The dose of 150 mg irbesartan produced overall changes in SeDBP and SeSBP comparable to 100 mg losartan (Figure 1 and Table 2). All active groups reduced blood pressure significantly ($P < .001$) versus placebo at all times.

At all times, changes in trough standing diastolic blood pressure and standing systolic blood pressure followed patterns similar to that observed for the seated measurements.

Therapeutic Response Normalization (trough SeDBP < 90 mm Hg) rates were, at week 1, 48% with 300 mg irbesartan and 31% with 100 mg losartan, and at week

TABLE 2. ADJUSTED MEAN CHANGES FROM BASELINE IN TROUGH SEATED BLOOD PRESSURE AT WEEKS 1 AND 8

	Placebo	Losartan, 100 mg	Irbesartan, 150 mg	Irbesartan, 300 mg
Week 1				
N	143	135	139	132
SeDBP (SE), mm Hg	-4.4 (0.56)	-7.5 (0.58)*	-8.2 (0.57)*	-9.8 (0.59)*†
SeSBP (SE), mm Hg	-4.3 (1.00)	-10.0 (1.02)*	-12.1 (1.00)*	-13.1 (1.04)*
Week 2				
N	145	137	137	138
SeDBP (SE), mm Hg	-4.9 (0.56)	-8.7 (0.58)*	-8.4 (0.58)*	-9.7 (0.58)*
SeSBP (SE), mm Hg	-5.8 (0.99)	-11.5 (1.02)*	-11.3 (1.02)*	-14.0 (1.01)*
Week 4				
N	144	135	135	137
SeDBP (SE), mm Hg	-4.2 (0.58)	-8.7 (0.60)*	-9.9 (0.60)*	-10.7 (0.60)*‡
SeSBP (SE), mm Hg	-4.1 (1.03)	-11.4 (1.06)*	-13.6 (1.05)*	-14.6 (1.05)*
Week 8				
N	138	131	129	134
SeDBP (SE), mm Hg	-4.9 (0.63)	-8.7 (0.64)*	-9.7 (0.65)*	-11.7 (0.64)*†
SeSBP (SE), mm Hg	-3.7 (1.12)	-11.3 (1.14)*	-12.1 (1.15)*	-16.4 (1.13)*†

* $P < .001$ v placebo.

† $P < .01$ v 100 mg losartan.

‡ $P = .017$ v 100 mg losartan.

SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure; SE, standard error.

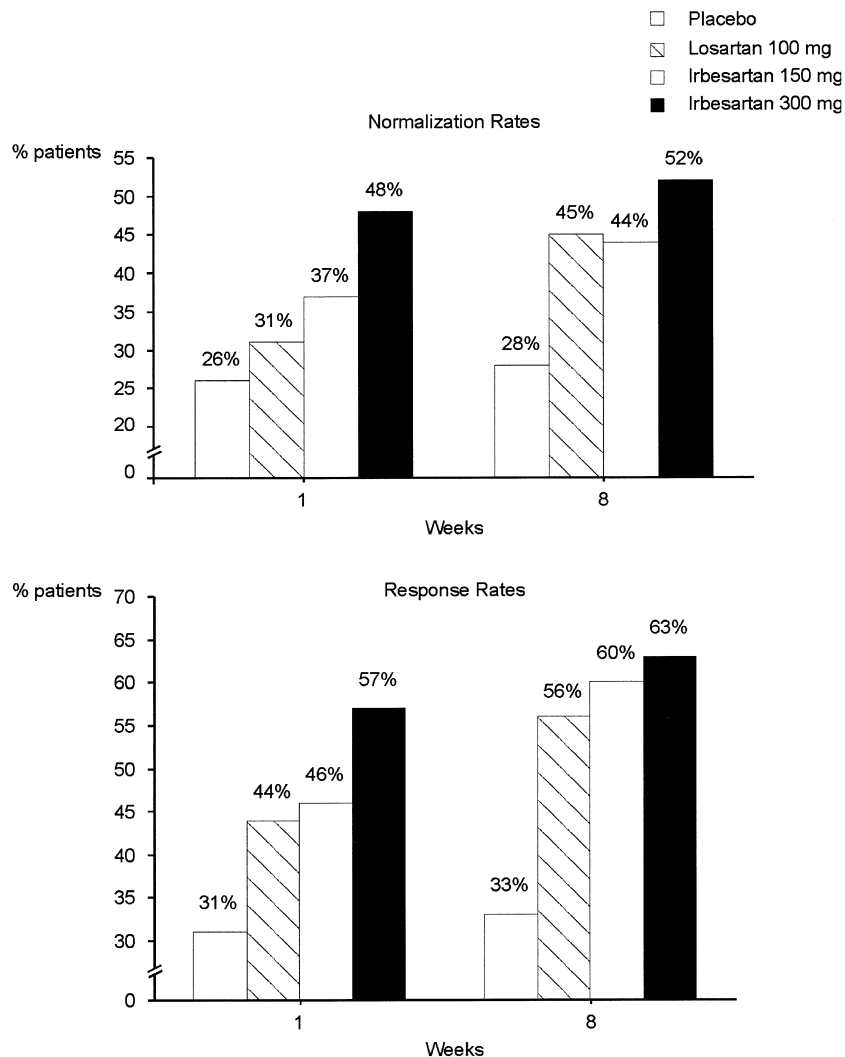


FIGURE 2. Normalization rates (trough seated diastolic blood pressure < 90 mm Hg) and response rates (normalized or a reduction in trough seated diastolic blood pressure 10 mm Hg) at weeks 1 and 8.

8, 52% and 42%, respectively (Figure 2). The corresponding response rates (normalized or a reduction in trough SeDBP \geq 10 mm Hg) were, at week 1, 57% *v* 44% and at week 8, 63% *v* 56%. Although the 300 mg dose irbesartan tended to result in a larger proportion of patients achieving the defined degrees of therapeutic response, none of these differences were statistically significant.

Safety Adverse Events There were no deaths during the study. Early discontinuations because of AE, overall rates of reported AE (ie, all those reported without regard to causality) and adverse drug experiences (ie, adverse events that were related, possibly or probably related, or of unknown relationship to study drug) occurred in the active treatment groups at a rate that was not appreciably different from placebo, with the

TABLE 3. SAFETY AND TOLERABILITY OF IRBESARTAN AND LOSARTAN

	Placebo (N = 146)	Losartan, 100 mg (N = 138)	Irbesartan, 150 mg (N = 141)	Irbesartan, 300 mg (N = 142)
Adverse events, %	52.7	57.2	51.1	43.7
Discontinuations due to adverse events, %*	3.4	3.6	2.1	1.4
Adverse drug experiences, %*	21.2	27.5	21.3	19.7

* Subsets of all patients with adverse events.

300 mg irbesartan group tending to show the lowest rates (Table 3). The most common AE were headache, musculoskeletal pain, dizziness, upper respiratory infection, and fatigue.

Laboratory and Other Assessments Changes in serum creatinine and potassium levels were negligible, and none of the differences between irbesartan and losartan were statistically significant. Serum uric acid levels decreased insignificantly with irbesartan, whereas decreases when compared with baseline were statistically significant with losartan. However, the difference between 100 mg losartan and 300 mg irbesartan did not reach statistical significance. There were no clinically significant changes in ECG or physical examination results.

DISCUSSION

This randomized, double-blind, placebo-controlled, 8-week study compared the antihypertensive efficacy and safety of losartan and irbesartan, two AT₁ receptor antagonists with different pharmacokinetic and pharmacodynamic profiles. Once-daily doses of each compound, including maximum clinical doses, were used to determine their effect on trough blood pressure.¹⁵⁻¹⁷

At the primary endpoint (week 8), the antihypertensive effect of 300 mg irbesartan was significantly greater than that of 100 mg losartan, with irbesartan providing a 3.0 mm Hg and 5.1 mm Hg greater reduction in trough SeDBP and SeSBP, respectively. Significant differences in favor of 300 mg irbesartan were also observed at weeks 1 and 4. The antihypertensive effects of 150 mg irbesartan and 100 mg losartan did not differ statistically; the study was not designed to detect such small (~1 mm Hg) differences. The magnitude of blood pressure lowering observed in this study for the two doses of irbesartan and the once-daily 100 mg dose of losartan is consistent with that reported in previous studies.¹⁷⁻²⁴ These data therefore indicate that the administration of maximally effective doses of two antihypertensive agents with a similar mode of action may produce clinically significant differences in trough blood pressure reduction.

Trends towards differences observed in normalization and responder rates were consistent with the results in SeDBP, but the differences were not statistically significant. This was not unexpected, as the study was not powered according to these secondary outcome measures. Nearly 200 subjects per group would have been required in the analysis to detect a true difference of 45% *v* 30% in normalization rates (similar to what was observed at week 1 for the 300 mg irbesartan and 100 mg losartan groups) with 80% power and an $\alpha = 0.025$ (adjusted for multiple comparisons). The observed difference at week 8 would

require over 900 subjects per group to achieve 80% power for this comparison.

Several factors may contribute to the effectiveness of AT₁ receptor blockade: receptor affinity, pharmacokinetics, and access of the active drug to the sites of action. In vitro, irbesartan had a 10-fold greater affinity for AT₁ receptors compared with losartan,² whereas the affinity of the EXP 3174, the active metabolite of losartan, was comparable to that of irbesartan. These in vitro differences were confirmed with in vivo experiments. In monkeys, irbesartan was roughly 10 times more potent than losartan at inhibiting the pressor response to AII, whereas EXP 3174 and irbesartan were equally potent.² In healthy subjects, as discussed previously, 300 mg irbesartan tended to inhibit the pressor response elicited by AII more than a 100 mg dose of losartan, both at peak and trough.^{9,14,25,26} These pharmacodynamic results suggest that at the dose of 300 mg irbesartan provided more effective and persistent AT₁ blockade than 100 mg losartan, an observation that would appear to be consistent with the difference in antihypertensive efficacy demonstrated in this study.

The pharmacokinetics of irbesartan and losartan also differ, in terms of half-life and biotransformation.^{2,5,6-9} Biotransformation of losartan is dependent on the cytochrome P450 isoform 3A4,²⁷ which is variably present in some individuals.^{28,29} The competition at the receptor site between losartan, a competitive antagonist, and its metabolite, a noncompetitive antagonist, both with different kinetics and affinity might also contribute to the relatively flat dose-response described for this drug; the action of irbesartan at the receptor site appears more straightforward. In addition, the volume of distribution of irbesartan is substantially greater than those of losartan and its metabolite, suggesting that irbesartan could reach AT₁ receptors in compartments that are not accessible to losartan or EXP 3174. For example, the degree of penetration of these agents into the central nervous system might differ. All of these factors may thus contribute to the differences in efficacy observed between the drugs.

The study used seated office BP measures taken by a blinded observer using mercury sphygmomanometry, as recommended by the American Heart Association, the American Society of Hypertension, and the World Health Organization.^{33,34,35} Seated office BP is the standard recommended measure in clinical practice and in the evaluation of efficacy of an antihypertensive agent by regulatory agencies.^{31,32,35-37} Reductions in SeBP have been well documented to correlate with reduced risk of hypertension target end organ damage.³⁸ Therefore, it is an appropriate and relevant measure for comparison of the efficacy of antihypertensive agents. Other measurement techniques, such

as ambulatory blood pressure or home office measurement would have provided additional information regarding blood pressure over 24 h, at times between scheduled visits, and during the patients' normal daily routines. Ambulatory blood pressure might also have improved the precision of the comparisons between the active groups, particularly the 100 mg losartan and the 150 mg irbesartan groups, in which the seated office measurements showed only small differences.

In this study, once-daily dosing regimens were compared. Both drugs have been demonstrated to provide adequate control of BP over 24 h using ambulatory blood pressure and calculation of trough:peak ratio for seated office measurements.^{17,18} As a result, both drugs are recommended for once-daily administration.^{12,16} Comparison of once-daily dosing is also the most clinically relevant, because once-daily dosing regimens are clearly preferred for reasons of patient compliance^{31,32} and will likely represent the vast majority of clinical use.

It is not known if a comparison of dosing regimens more frequent than once-daily would have provided different results. Published data suggest that losartan administered at a dose of 50 mg twice daily may provide somewhat better 24-h mean ambulatory blood pressure control than a dose of 100 mg once daily (24-h mean ambulatory blood pressure 3.3/2.1 mm Hg greater reduction with the twice daily dose), but in the same study, no substantial differences in office blood pressure were noted, and none of the observed differences in blood pressure response reached statistical significance.³⁰ With respect to irbesartan, regimens of 75 mg twice daily and 150 mg once daily have been shown to provide equivalent reductions in mean 24 h ambulatory blood pressure and seated office BP.¹⁷ Although this apparent difference between losartan and irbesartan may suggest that a twice-daily regimen comparison would tend to favor losartan relative to irbesartan, a comparison using a regimen other than once-daily should be based upon the doses of each drug that represent the maximally effective dose when given using the regimen intended for comparison. To our knowledge, the efficacy dose-response relationships for losartan and irbesartan have only been fully defined using once-daily dosing, and thus it is not possible to speculate on the outcome of a different comparison.

Both therapies were well tolerated, consistent with earlier data.^{17–19,21–24} Neither drug caused clinically significant changes from baseline in serum creatinine levels, and only slight increases were observed in serum potassium concentrations. Losartan significantly reduced serum uric acid levels, whereas irbesartan did not, consistent with previous studies demonstrating a uricosuric effect with losartan and only minimal alterations with irbesartan.^{39–41}

CONCLUSIONS

This 8-week, double-blind, placebo-controlled trial in mild-to-moderate hypertension indicates that the maximally effective doses of irbesartan and losartan, two different AT₁ receptor antagonists given once daily, have antihypertensive effects that are significantly different at trough. These findings highlight the potential clinical significance of pharmacokinetic and pharmacodynamic differences between these two members of the AT₁ receptor antagonist class.

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APPENDIX
IRBESARTAN/LOSARTAN STUDY
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