A Home Blood Pressure Monitoring Study Comparing the Antihypertensive Efficacy of Two Angiotensin II Receptor Antagonist Fixed Combinations

Guillaume Bobrie, Jean Delonca, Cyril Moulin, Alain Giacomino, Nicolas Postel-Vinay, and Roland Asmar, for the COmparative Study of Efficacy of Irbesartan/HCTZ with Valsartan/HCTZ Using Home Blood Pressure Monitoring in the TreAtment of Mild-to-Moderate Hypertension (COSIMA) Investigators

**Background:** The objective of this prospective, randomized, open-label, blinded-endpoint study was to compare the antihypertensive efficacy of valsartan 80 mg versus irbesartan 150 mg when combined with hydrochlorothiazide (HCTZ) 12.5 mg.

**Methods:** Untreated or uncontrolled hypertensive adults \((n = 800)\) were enrolled by primary care physicians. After a 5-week open-label lead-in phase in which all patients received 12.5 mg HCTZ once daily, subjects whose blood pressure (BP) remained uncontrolled were randomized \((n = 464)\) to valsartan/HCTZ \((80/12.5 \text{ mg})\) or irbesartan/HCTZ \((150/12.5 \text{ mg})\) for 8 weeks. Home BP monitoring (HBPM) was performed in the morning and in the evening for 5 days, at baseline, and after 8 weeks. Office BP measurements were obtained at baseline and after 8 weeks.

**Results:** Irbesartan/HCTZ produced greater reductions in average systolic BP (SBP) and diastolic BP (DBP) measured by HBPM than valsartan/HCTZ \((-13.0 \text{ mm Hg}, P = .0094; -9.5 \text{ mm Hg}, P = .0007)\). These differences were more pronounced in the morning (trough) than in the evening. Office BP measurements also showed greater reductions in trough seated SBP and DBP with irbesartan/HCTZ compared with valsartan/HCTZ. Normalization rates observed with HBPM \((SBP \leq 135 \text{ mm Hg} \text{ and } DBP \leq 85 \text{ mm Hg})\) were significantly greater with irbesartan/HCTZ than with valsartan/HCTZ \((50.2\% \text{ vs } 33.2\%; P = .0003)\). The overall safety was similar in the two groups.

**Conclusions:** The superior BP-lowering potency of the fixed combination irbesartan/HCTZ \((150/12.5 \text{ mg})\) over valsartan/HCTZ \((80/12.5 \text{ mg})\), evidenced independently from the investigators by HBPM, supports the use of this technique in trials with prospective, randomized, open-label, blinded-endpoint designs. Am J Hypertens 2005;18:1482–1488 © 2005 American Journal of Hypertension, Ltd.

**Key Words:** Home blood pressure monitoring, self blood pressure measurement, angiotensin II receptor antagonists, irbesartan/hydrochlorothiazide, valsartan/hydrochlorothiazide.

Angiotensin II receptor antagonists (AIIRA) have become an established class for the treatment of hypertension. Their widespread use is related to their recognized antihypertensive efficacy combined with a placebo-like tolerability profile. Differences between agents in pharmacodynamic and pharmacokinetic properties could translate into significant differences in their relative antihypertensive potency. A clinical pharmacology study comparing three AIIRA versus placebo in normotensive subjects demonstrated that a single administration of the recommended starting dose of irbesartan \((150 \text{ mg})\) induced a greater and more sustained angioten-
sin II receptor blockade than a comparable single dose of losartan (50 mg) or valsartan (80 mg). More recently a clinical study compared irbesartan 150 mg and valsartan 80 mg in hypertensive subjects using different methods: ambulatory blood pressure monitoring (ABPM), home blood pressure monitoring (HBPM), and office measurements. The results indicate that irrespective of the method chosen, irbesartan is more effective than valsartan, at the once-per-day doses used, in reducing systolic blood pressure (SBP) and diastolic blood pressure (DBP) at trough and in providing greater overall 24-h blood pressure (BP) lowering efficacy, with a similar tolerability. Despite the increasing use of the fixed combination of an AIIRA and a diuretic to improve response rates, limited information is available on their comparative antihypertensive efficacy. The COMparative Study of Efficacy of Irbesartan/HCTZ with Valsartan/HCTZ Using Home Blood Pressure Monitoring in the TreAtment of Mild-to-Moderate Hypertension (COSIMA) study was designed to establish whether the fixed combination with hydrochlorothiazide (HCTZ) would blunt the differences in BP-lowering efficacy observed between irbesartan and valsartan monotherapy.

An important limitation of clinical randomized trials is their applicability to real-life practice. Therefore we decided to use a prospective, randomized, open-label, blinded-endpoint evaluation (PROBE) design which was developed as an attractive alternative to the double-blind placebo-controlled design. The choice of HBPM is supported by recent recommendations that outline the benefits of HBPM in providing response to antihypertensive medication, improving patient adherence to therapy, and evaluating white-coat hypertension. This methodology is now cited as an alternative approach to characterize BP levels and to estimate the effect of antihypertensive treatment in clinical trials, provided the device used has been validated. A prospective study even suggests that HBPM has a better prognostic accuracy than office BP measurement in treated elderly hypertensive patients.

Methods

Study Objective

The objective of COSIMA was to assess whether the fixed combination irbesartan/HCTZ (150/12.5 mg, once daily) was superior to the fixed combination valsartan/HCTZ (80/12.5 mg, once daily) in terms of BP lowering as assessed by HBPM after 8 weeks of treatment.

Patient Population

Patients >18 years and <80 years of age with untreated (office SBP >160 mm Hg) or uncontrolled (office SBP >140 mm Hg despite antihypertensive monotherapy) mild-to-moderate essential hypertension were enrolled in the study. The protocol and informed consent were approved by a National Ethics Committee and all patients gave their written informed consent before any study-related procedure was undertaken.

Study Design

COSIMA was a multicenter, randomized, open-label, parallel-group study designed according to the PROBE methodology. It was carried out in France by 139 primary care physicians and consisted of two phases (Fig. 1). After an enrollment visit (visit 1 [V1]) in which uncontrolled patients discontinued prior antihypertensive therapy, all patients received HCTZ 12.5 mg once daily during 5 weeks (Phase 1). At the end of week 4 (visit 2 [V2]), patients with office SBP <140 mm Hg were excluded; the others performed a baseline HBPM over a 5-day period during week 5. At the end of week 5 (visit 3 [V3]), patients whose BP remained uncontrolled (average home SBP >135 mm Hg) with HCTZ 12.5 mg were eligible to enter the second phase of the study and received either irbesartan/HCTZ or valsartan/HCTZ for 8 weeks according to a 1:1 central randomization procedure. The final visit (V4) was performed at the end of week 13, after a second HBPM period over 5 days during week 13. Although each center had a randomization target of four patients, the enrollment was competitive with no limitation.

Office BP Measurements and HBPM

The week before randomization (V3) and the final visit (V4), patients performed HBPM twice a day for 5 days using a validated electronic device (TensioDay Monitor, TensioMed, Budapest, Hungary), according to a standard procedure for which they were trained: after 5 min of rest, three seated measurements in the morning (between 6 and 10 AM) at 1-min intervals, just before taking the study drug; and three seated measurements in the evening (between 6 and 10 PM) at 1-min intervals. Data were transferred automatically every night (11 PM to 6 AM) by means of a telephone line to an independent center blinded to allocation. All measurements performed on the first day of each study period (morning and evening) were considered as part of the patient’s training and excluded from the analysis. Quality criteria used for an acceptable HBPM were at least 12 valid measurements (incompatible
values defined as follows: SBP <60 or >250 mm Hg, DBP <40 or >150 mm Hg, and SBP − DBP <10 mm Hg, whereas SBP values >110 mm Hg were considered invalid) obtained during at least 3 days.

Office BP was measured three times at 1-min intervals in a sitting position after 5 min of rest, either manually with a mercury sphygmomanometer or with a validated electronic device; each physician used the same method throughout the study.10

Statistical Analyses
The comparability of patients in the two treatment groups was determined from the demographic data and baseline BP values. The intent-to-treat (ITT) population consisted of all randomized patients who received at least one dose of study drug with at least one valid final evaluation and was analyzed according to the treatment allocated by the randomization. The per-protocol (PP) population consisted of the above population from which patients with a major protocol deviation were withdrawn (baseline HBPM invalid or yielding SBP values <135 mm Hg, concomitant antihypertensive treatment, time between V3 and V4 <6 or >10 weeks) and was analyzed according to the actual treatment received. The primary efficacy endpoint was the difference from baseline in average SBP (arithmetic mean of all morning and evening values) measured by HBPM after 8 weeks of treatment. Treatment effects were analysed using a one-way analysis of covariance model including treatment as fixed effect and baseline average SBP as covariate. Two-sided 95% confidence intervals were calculated using the least square mean and root mean square of error of the analysis of covariance model. Secondary efficacy endpoints included the following: 1) differences from baseline in DBP and in morning (trough) SBP and DBP measured by HBPM as well as differences from baseline in office SBP and DBP, treated as quantitative data; and 2) percentage of patients normalized after 8 weeks of treatment based on both HBPM (defined as average SBP <135 and DBP <85 mm Hg) and office measurements (defined as SBP <140 and DBP <90 mm Hg), treated as binary data. The same methodology as that used for the primary endpoint was applied for quantitative data, and the \( \chi^2\) test was used for comparing binary data.

Sample size calculations were based on the ability to detect a 3–mm Hg difference in average SBP assessed by HBPM between the two treatment groups after 8 weeks. A sample size of 176 patients in each group would yield 80% power to detect such a difference, assuming a standard deviation of 10 mm Hg and a two-tailed \( \alpha \) of 0.05. Considering that around 10% of patients randomized would have unacceptable HBPM data, a total of 400 patients (200 in each treatment group) were required for randomization.

Safety Evaluation
All reported adverse events were categorized by body system and preferred term using the Medical Dictionary for Regulatory Activities. All randomized patients who received at least one dose of study drug were included in the analyses which were performed according to the actual treatment received. The incidence of adverse events was tabulated by treatment group, according to severity and to relationship to study drug. To compare treatment groups \( \chi^2\) and Fischer exact tests were performed.

Results

Patient Participation
Of 800 patients enrolled at V1, 680 patients successfully completed V2 to perform baseline HBPM and 464 patients were randomized in Phase 2 (Fig. 2). The high expected drop-out rate between Phase 1 and Phase 2 was mostly related to the number of patients normalized with HCTZ 12.5 mg (78 patients normalized at V2 based on office BP measurements and 188 normalized at V3 based on HBPM). The ITT dataset included 449 patients: 227 in the valsartan/HCTZ group and 222 in the irbesartan/HCTZ group. Two patients randomized to valsartan/HCTZ and six patients randomized to irbesartan/HCTZ did not have a final evaluation, and seven additional patients randomized to irbesartan/HCTZ were randomized inappropriately and did not receive study drug or undergo follow-up. The PP dataset included 414 patients: 216 in the valsartan/HCTZ group and 198 in the irbesartan/HCTZ group. Reasons for exclusion are described in Fig. 2.
Baseline Characteristics

There were no significant differences in terms of baseline characteristics between the two groups, either in the ITT (Table 1) or in the PP population (data not shown). The ITT population was also strictly comparable to the population randomized within each group. The mean age of the population was 59.3 years, with slightly more male subjects (56%) and a mean weight of 77.9 kg. As could be expected, HBPM values were on average 4.2 mm Hg (SBP: 148.8 ± 11.0 vs 153.0 ± 11.1) and 1.1 mm Hg (DBP: 89.5 ± 10.0 vs 90.6 ± 8.9) lower than office values.

Efficacy of HBPM

Mean BP values at the final visit and changes from baseline are shown in Table 2. Irbesartan/HCTZ also produced a significantly greater reduction in office SBP and DBP than valsartan/HCTZ: respectively -15.0 ± 11.2 vs -11.8 ± 11.2 mm Hg (Δ = -3.2 mm Hg, P = .0027) and -8.6 ± 7.1 vs -6.9 ± 7.1 mm Hg (Δ = -1.7 mm Hg, P = .0113). The percentage of patients with normalized BP at the final visit (defined as SBP <140 and DBP <90 mm Hg) was also higher in the irbesartan/HCTZ group than in the valsartan/HCTZ group: respectively 50.2% vs 33.2% (P = .0003) in the ITT population (Fig. 4).

Adverse Events

The overall safety was similar in the two groups: 42 of 226 patients who received irbesartan/HCTZ (18.6%) and 36 of 227 patients who received valsartan/HCTZ (15.9%) experienced at least one adverse event (P = .44). The most common adverse events, which were mild to moderate in intensity and unlikely related or unrelated to study drug in most cases, were infections, gastrointestinal disorders, and musculoskeletal disorders.

Discussion

The COSIMA study demonstrates that in hypertensive patients who remain uncontrolled with HCTZ 12.5 mg monotherapy, a fixed regimen combining irbesartan/HCTZ (150/12.5 mg) for 8 weeks is more effective in reducing BP than a fixed regimen combining valsartan/HCTZ (80/12.5 mg).

It is worth noting that our study was very close to the
real clinical practice setting, both because of its PROBE design and treatment strategy, strictly in line with the latest guidelines on hypertension management: initiation of treatment with a low dose diuretic, followed by a fixed combination including a diuretic if BP control was not achieved.\(^5\),\(^6\)

Our findings are consistent with previously reported results\(^2\) which showed that irbesartan 150 mg was superior to valsartan 80 mg in monotherapy. Indeed, self-measured SBP/DBP differences were respectively 3.2/2.5 mm Hg in the morning (\(v\) 2.9/2.3 mm Hg in our study) and 2.6/1.6 mm Hg in the evening (\(v\) 2.1/1.9 mm Hg in our study). In both instances, these differences were more pronounced in the morning (trough) than in the evening. Although some comparisons were borderline in terms of statistical significance (evening SBP and DBP values in the former study and evening SBP values in COSIMA), this was probably caused by the lack of power of both studies to detect smaller differences in the evening. These greater BP differences consistently observed in the morning could partly be explained by a longer duration of action,\(^1\) which might amplify the superior potency at trough of irbesartan 150

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**FIG. 3.** Mean morning and evening blood pressure (BP) decrease (in mm Hg), measured by home BP monitoring (HBPM). DBP = diastolic BP; SBP = systolic BP. \(P < .01\) for all values except SBP evening (\(P = .065\)), intent-to-treat analysis.

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**FIG. 4.** Percentage of patients whose blood pressure had normalized by the final visit. \(P < .05\) for office measurements and \(P < .001\) for HBPM, intent-to-treat analysis. Normalization based on SBP < 140 mm Hg and DBP < 90 mm Hg (office) or SBP < 135 mm Hg and DBP < 85 mm Hg (HBPM). Abbreviations as in Fig. 3.

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**Table 2.** Blood pressure (BP) values (mm Hg) at final visit and changes from baseline

<table>
<thead>
<tr>
<th></th>
<th>Office BP</th>
<th>HBPM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP at final visit, mean (SD)</strong></td>
<td><strong>A from baseline, mean (SD)</strong></td>
<td><strong>Difference between groups</strong></td>
</tr>
<tr>
<td>SBP</td>
<td>Valsartan/HCTZ</td>
<td>135.3 (12.4)</td>
</tr>
<tr>
<td>DBP</td>
<td>Valsartan/HCTZ</td>
<td>80.1 (9.9)</td>
</tr>
<tr>
<td>SBP</td>
<td>Irbesartan/HCTZ</td>
<td>135.0 (12.4)</td>
</tr>
<tr>
<td>DBP</td>
<td>Irbesartan/HCTZ</td>
<td>79.8 (9.7)</td>
</tr>
</tbody>
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* Adjusted.
mg over valsartan 80 mg. Another important finding of this study is that combination with HCTZ, which also has a well-established prolonged duration of action, did not blunt the BP differences detected between these two compounds in monotherapy.

Evidence from numerous prospective observational studies supports the existence of a strong linear correlation between clinic BP and the incidence of major cardiovascular events: an initial meta-analysis showed a positive, continuous, and independent association between DBP levels and the incidence of stroke or coronary heart disease, whereas a more recent one demonstrated that BP was strongly and directly related to vascular and overall mortality throughout middle and old age. These observational results are corroborated by the findings of prospective randomized trials comparing different BP lowering regimens based on different drug classes: for every outcome other than heart failure, the difference between randomized groups in achieved BP reduction is directly related to the observed difference in risk. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, which compared valsartan and amiodipine in hypertensive patients at high CV risk, amiodipine achieved greater BP reductions, especially in the early phase of the trial. Odds ratios in favor of amiodipine were noted for all endpoints during the first 6 months, when differences in BP levels were greatest (Δ SBP: −3.8 mm Hg from 0 to 3 months and −2.3 mm Hg from 3 to 6 months). Therefore, achieving a sustained difference in SBP of around 2 to 3 mm Hg, which is even more pronounced in the morning when the incidence of CV events is at its peak, could be clinically meaningful and should be an element of choice when selecting an antihypertensive agent.

Irbesartan 150 mg and valsartan 80 mg combined with HCTZ 12.5 mg are usually the first available doses of the fixed combinations indicated in patients with essential hypertension that is uncontrolled despite AIIRA or HCTZ monotherapy. Higher dosages are also available for patients who require more intensive therapy, with a doubling of either one or both of the agents; our study does not provide any information regarding the comparative efficacy of these other fixed combinations. However given the poor control rates in treated hypertensive patients still reported recently in the literature (approximately 50% in the United States and Canada, between 20% and 40% in five European countries based on a 140/90-mm Hg threshold), it would seem that most physicians are probably reluctant to go beyond one or two titration steps. Consequently our findings provide important information on the relative potency of two widely used fixed combinations.

Although HBPM has become an established method to measure BP in the daily management of hypertensive patients as well as in the more formal setting of clinical trials, very few data directly comparing antihypertensive agents are available. Apart from the results discussed previously, five other trials have been reported: one trial comparing a calcium-channel antagonist versus a β-blocker, two trials comparing a calcium-channel antagonist versus an angiotensin-converting enzyme (ACE) inhibitor in moderate-to-severe hypertension and in isolated systolic hypertension, one trial comparing two ACE inhibitors, and one trial comparing an ACE inhibitor versus an AIIRA. Our study is the largest so far to compare directly the effects of two antihypertensive agents by means of HBPM; our results indicate that this method is more accurate than casual office measurement to detect small differences in terms of BP reduction, especially with regard to DBP.

A number of landmark hypertension trials have used the PROBE design. Although the benefits of a strict randomization are maintained, the clear definition of blinded endpoints helps to eliminate bias by allowing an independent evaluation of the study results, which was the case in COSIMA, where all HBPM data were transferred automatically to an independent center blinded to treatment allocation. Moreover, studies using this design are much closer to standard clinical practice and tend to be more cost-effective. Although no data are available for HBPM, a recent report indicates that PROBE designed trials yield the same results as double-blind, placebo-controlled, trials with respect to ABPM. Another recent meta-analysis also indicates that PROBE designed trials are equivalent to double-blind placebo-controlled trial to rule out a difference of >3 mm Hg in SBP and >2 mm Hg in DBP measured by ABPM, which further supports the use of a PROBE design in our HBPM trial. The validity of our results are further reinforced by the findings from an earlier randomized, double-blind study in which differences in BP reduction between valsartan 80 mg and irbesartan 150 mg were very similar to our own findings. In addition, despite the fact that both physicians and patients were aware of the treatment allocated, the differences observed with office BP measurement were very consistent with those detected by HBPM. This could simply be caused by the fact that we were comparing two agents of the same class that were perceived as equivalent and therefore that awareness of treatment allocation did not influence the gathering of data.

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References


