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 *v* 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 mg) or irbesartan/HCTZ (150/12.5 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 (SBP: −13.0 *v* −10.6 mm Hg, $P = .0094$; DBP: −9.5 *v* −7.4 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 <135 mm Hg and DBP <85 mm Hg) were significantly greater with irbesartan/HCTZ than with valsartan/HCTZ (50.2 *v* 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 mg) over valsartan/HCTZ (80/12.5 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[1] comparing three AIIRA versus placebo in normotensive subjects demonstrated that a single administration of the recommended starting dose of irbesartan (150 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[2] 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.[3] The choice of HBPM is supported by recent recommendations[4–6] 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.[7] A prospective study even suggests that HBPM has a better prognostic accuracy than office BP measurement in treated elderly hypertensive patients.[8]
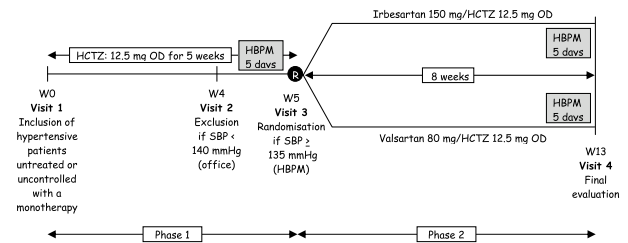
Methods
Study Objective

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

FIG. 1. Study design. HBPM = home blood pressure monitoring; HCTZ = hydrochlorothiazide; OD = once daily; SBP = systolic blood pressure; W = week.

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[9] (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 treatment 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 χ^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 α 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
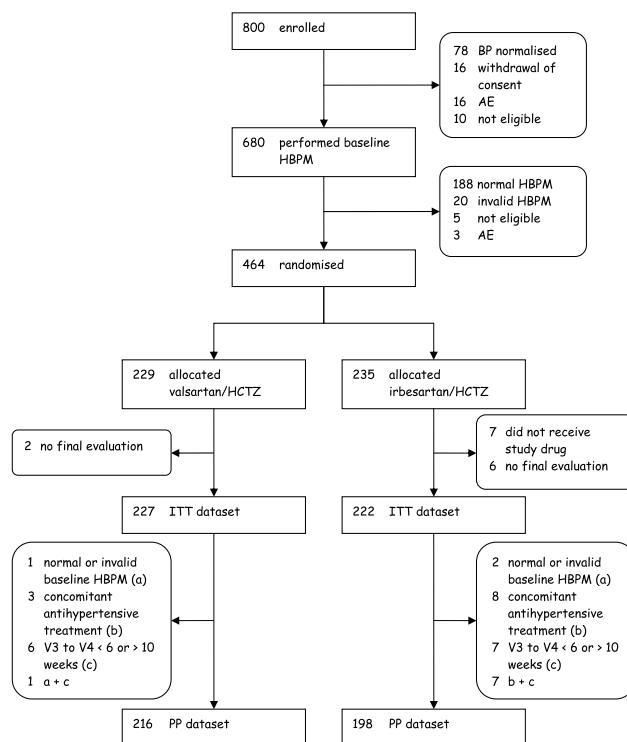

FIG. 2. Trial profile. AE = adverse events; ITT = intent to treat; other abbreviations as in Fig. 1.

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 χ^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.

Table 1. Baseline characteristics of study subjects

Characteristics	Valsartan/HCTZ (80/12.5 mg)	Irbesartan/HCTZ (150/12.5 mg)
Number of patients	227	222
Age (y)	60 ± 10	59 ± 11
Sex (male/female, %)	60/40	53/47
Body weight (kg)	79 ± 14	77 ± 14
Height (cm)	168 ± 9	167 ± 9
Current smoker (%)	19	19
Treated/untreated (%)	61/39	64/36
Office BP values		
SBP (mm Hg)	153 ± 11	153 ± 11
DBP (mm Hg)	90 ± 9	91 ± 9
Heart rate (beats/min)	75 ± 10	75 ± 9
HBPM values		
SBP (mm Hg)	149 ± 11	149 ± 11
DBP (mm Hg)	89 ± 10	90 ± 10

BP = blood pressure; DBP = diastolic blood pressure; HBPM = home blood pressure monitoring; SBP = systolic blood pressure.

All values are expressed as mean ± SD; there were no significant differences between groups for any baseline characteristics. Intent-to-treat analysis.

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 v 153.0 ± 11.1) and 1.1 mm Hg (DBP: 89.5 ± 10.0 v 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: The ITT and PP analyses yielded comparable results. Compared with baseline, irbesartan/HCTZ produced a significantly greater reduction in SBP measured by HBPM than valsartan/HCTZ after 8 weeks (primary endpoint, ITT analysis): −13.0 ± 9.5 v −10.6 ± 9.5 mm Hg (Δ = −2.4 mm Hg, P = .0094). The reduction in DBP was also greater in the irbesartan/HCTZ group: −9.5 ± 6.2 v −7.4 ± 6.2 mm Hg (Δ = −2.0 mm Hg, P = .0007). These differences were more pronounced in the morning than in the evening (Fig. 3): the differences between the valsartan/HCTZ and irbesartan/HCTZ groups were respectively −2.9/−2.3 mm Hg for the morning SBP/DBP values v −2.1/−1.9 mm Hg for the evening values in the ITT population. All of these differences were significant (P < .05), except for the evening SBP comparison, in which a nonsignificant trend was observed (P = .065).

The percentage of patients with normalized BP at the final visit (defined as average SBP <135 and DBP <85 mm Hg) was higher in the irbesartan/HCTZ group than in

the valsartan/HCTZ group: respectively 50.2% v 33.2% (P = .0003) in the ITT population (Fig. 4).

Efficacy of Office Measurements

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 v −11.8 ± 11.2 mm Hg (Δ = −3.2 mm Hg, P = .0027) and −8.6 ± 7.1 v −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 51.4 v 41.9% (P = .0436) 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

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

	HBPM				Office BP			
	BP at final visit, mean (SD)	Δ from baseline, mean (SD)*	Difference between groups*	P	BP at final visit, mean (SD)	Δ from baseline, mean (SD)*	Difference between groups*	P
ITT dataset (n = 449)								
SBP								
Valsartan/HCTZ	138.3 (11.7)	−10.6 (9.5)	−2.4	.0094	141.3 (12.9)	−11.8 (11.2)	−3.2	.0027
Irbesartan/HCTZ	135.3 (12.4)	−13.0 (9.5)			137.8 (12.4)	−15.0 (11.2)		
DBP								
Valsartan/HCTZ	81.8 (9.1)	−7.4 (6.2)	−2.0	.0007	83.3 (8.4)	−6.9 (7.1)	−1.7	.0113
Irbesartan/HCTZ	80.1 (9.9)	−9.5 (6.2)			82.2 (8.3)	−8.6 (7.1)		
PP dataset (n = 414)								
SBP								
Valsartan/HCTZ	138.4 (11.8)	−10.6 (9.2)	−2.8	.0024	141.4 (12.9)	−11.6 (11.4)	−3.2	.0047
Irbesartan/HCTZ	135.0 (12.4)	−13.4 (9.2)			137.9 (12.8)	−14.8 (11.4)		
DBP								
Valsartan/HCTZ	81.7 (9.2)	−7.4 (6.0)	−2.2	.0003	83.2 (8.3)	−6.8 (7.0)	−1.4	.0374
Irbesartan/HCTZ	79.8 (9.7)	−9.6 (6.0)			82.4 (8.3)	−8.2 (7.0)		

ITT = intent-to-treat; PP = per-protocol; HCTZ = hydrochlorothiazide; Valsartan/HCTZ =valsartan 80 mg/HCTZ 12.5 mg. Irbesartan/HCTZ = irbesartan 150 mg/HCTZ 12.5 mg.
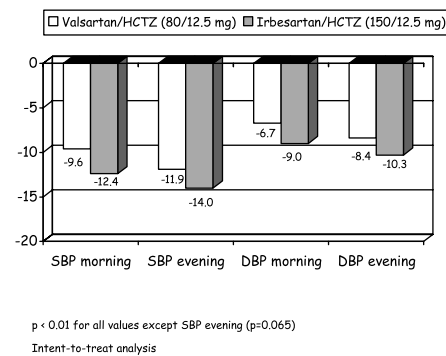* Adjusted.

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.

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
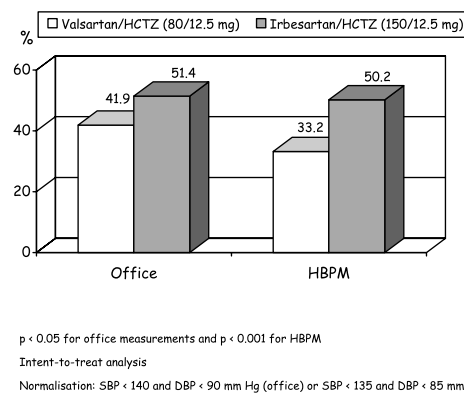

FIG. 4. Percentage of patients whose blood pressure had normalized by the final visit. $P < .05$ for office measurements and $P < .001$ for HBPM, intent-to-treat analysis. Normalization based on SBP <140 mm Hg and DBP <90 mm Hg (office) or SBP <135 mm Hg and DBP <85 mm Hg (HBPM). Abbreviations as in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

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[11] showed a positive, continuous, and independent association between DBP levels and the incidence of stroke or coronary heart disease, whereas a more recent one[12] 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[13]: 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,[14] which compared valsartan and amlodipine in hypertensive patients at high CV risk, amlodipine achieved greater BP reductions, especially in the early phase of the trial. Odds ratios in favor of amlodipine 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,[15,16] 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[17] (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,[2] five other trials have been reported: one trial comparing a calcium-channel antagonist versus a β-blocker,[18] two trials comparing a calcium-channel antagonist versus an angiotensin-converting enzyme (ACE) inhibitor in moderate-to-severe hypertension[19] and in isolated systolic hypertension,[20] one trial comparing two ACE inhibitors,[21,22] and one trial comparing an ACE inhibitor versus an AIIRA.[23] 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[24–27] 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.[3,28] Although no data are available for HBPM, a recent report[29] indicates that PROBE designed trials yield the same results as double-blind, placebo-controlled, trials with respect to ABPM. Another recent meta-analysis[8] 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[2] 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.

Acknowledgment

References

1. Mazzolai L, Maillard M, Rossat J, Nussberger J, Brunner HR, Burnier M: Angiotensin II receptor blockade in normotensive subjects. A direct comparison of three AT$_1$ receptor antagonists. Hypertension 1999;33:850–855.
2. Mancia G, Korlipara K, Van Rossum P, Villa G, Silvert B: An ambulatory blood pressure monitoring study of the comparative efficacy of two angiotensin II receptor antagonists, irbesartan and valsartan. Blood Press Monit 2002;7:135–142.

3. Hansson L, Hedner T, Dahlöf B: Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Blood Press 1992;1:113–119.

4. Asmar R, Zanchetti A, on behalf of Organizing Committee and participants: Guidelines for the use of self-blood pressure monitoring: a summary report of the First International Consensus Conference. J Hypertens 2000;18:493–508.

5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, and the National High Blood Pressure Education Program Coordinating Committee: The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. JAMA 2003;289:2560–2572.

6. Guidelines Committee: 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011–1053.

7. Committee for Proprietary Medicinal Products (CPMP): Note for guidance on clinical investigation of medicinal products in the treatment of hypertension. CPMP/EWP/238/95 Rev. 1.

8. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, Mallion JM: Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA 2004;291:1342–1349.

9. Nemeth Z, Moczar K, Deak G: Evaluation of the Tensioday ambulatory blood pressure monitor according to the protocols of the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. Blood Press Monit 2002;7:191–197.

10. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P, European Society of Hypertension Working Group on Blood Pressure Monitoring: European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 2003;21:821–848.

11. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J: Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765–774.

12. Prospective Studies Collaboration: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360:1903–1913.

13. Blood Pressure Lowering Treatment Trialists' Collaboration: Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003;362:1527–1535.

14. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A, for the VALUE trial group: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363:2022–2031.

15. Muller JE, Tofler GH, Stone PH: Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989;79:733–743.

16. Kiowski W, Osswald S: Circadian variation of ischemic cardiac events. J Cardiovasc Pharmacol 1993;21(Suppl 2):S45–S48.

17. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, Poulter N, Stegmayr B, Thamm M: Hypertension treatment and control in five European countries, Canada, and the United States. Hypertension 2004;43:10–17.

18. Mengden T, Binswanger B, Weisser B, Wetter W: An evaluation of self-measured blood pressure in a study with a calcium-channel antagonist versus a beta-blocker. Am J Hypertens 1992;5:154–160.

19. Fowler G, Webster J, Lyons D, Witte K, Crichton WA, Jeffers TA, Wickham EA, Sanghera SS, Cornish R, Petrie JC: A comparison of amlodipine with enalapril in the treatment of moderate/severe hypertension. Br J Clin Pharmacol 1993;35:491–498.

20. Webster J, Fowler G, Jeffers TA, Lyons D, Witte K, Crichton WA, Wickham EA, Sanghera SS, Cornish R, Petrie JC: A comparison of amlodipine with enalapril in the treatment of isolated systolic hypertension. Br J Clin Pharmacol 1993;35:499–505.

21. Bobrie G, Dutrey-Dupagne C, Vaur L, Dubroca I, Elkik F, Chatellier G, Menard J: Demonstration of differences in the effect of 2 antihypertensive agents by self blood pressure measurement: comparison of trandolapril and perindopril. Therapie 1997;52:187–193.

22. Vaur L, Bobrie G, Dutrey-Dupagne C, Dubroca I, Vaisse B, d'Yvoire MB, Elkik F, Chatellier G, Menard J: Short-term effects of withdrawing angiotensin converting enzyme inhibitor therapy on home self-measured blood pressure in hypertensive patients. Am J Hypertens 1998;11:165–173.

23. Ragot S, Ezzaher A, Meunier A, Poterre M, Bourkaib R, Herpin D: Comparison of trough effect of telmisartan vs perindopril using self blood pressure measurement: EVERESTE study. J Hum Hypertens 2002;16:865–873.

24. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Menard J, Rhan KH, Wedel H, Westerling S, for the HOT Study Group: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755–1762.

25. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmäki K, Dahlöf B, de Faire U, Mörlin C, Karlberg BE, Wester PO, Björck JE, for the Captopril Prevention Project (CAPPP) study group: Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611–616.

26. Lindholm LH, Hansson L, Ekbom T, Dahlöf B, Lanke J, Linjer E, Schersten B, Wester PO, Hedner T, de Faire U: Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP-Hypertension-2 Study Group. J Hypertens 2000;18:1671–1675.

27. Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Marley JE, Morgan TO, West MJ, Second Australian National Blood Pressure Study Group: A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med 2003;348:583–592.

28. Soghikian K, Casper SM, Fireman BH, Hunkeler EM, Hurley LB, Tekawa IS, Vogt TM: Home blood pressure monitoring. Effect on use of medical services and medical care costs. Med Care 1992;30:855–865.

29. Smith DH, Neutel JM, Lacourciere Y, Kempthorne-Rawson J: Prospective, randomized, open-label, blinded-endpoint (PROBE) designed trials yield the same results as double-blind, placebo-controlled trials with respect to ABPM measurements. J Hypertens 2003;21:1291–1298.