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Comparison of the Antihypertensive Efficacy of Irbesartan/HCTZ and Valsartan/HCTZ Combination Therapy: Impact of Age and Gender

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Abstract

This analysis aimed to explore whether low-dose irbesartan/hydrochlorothiazide (HCTZ) has superior blood pressure (BP)-lowering efficacy over low-dose valsartan/HCTZ in the elderly and across both genders. This is a post-hoc analysis of data from a multicenter, parallel group, open-label, blinded-endpoint study in patients with hypertension uncontrolled with HCTZ monotherapy. The reduction in systolic BP (SBP)/diastolic BP (DBP) and rate of BP control achieved following 8 weeks of treatment with irbesartan/HCTZ 150/12.5 mg or valsartan/HCTZ 80/12.5 mg were analyzed for older (≥65 years) vs. younger (<65 years) patients and for men vs. women. Blood pressure measurements were by home BP monitoring (HBPM). In the age and gender subgroups, both treatments significantly decreased home SBP and DBP ($p < 0.0001$). The reduction in home SBP and DBP was numerically greater with irbesartan/HCTZ compared to valsartan/HCTZ for all subgroups: the difference in DBP was significant for all except the elderly ($p < 0.05$), and the difference in SBP was significant in the elderly and in men ($p < 0.03$). In all subgroups, more patients achieved BP control (HBPM ≤135/85 mmHg) in the irbesartan/HCTZ arm (range 45%–58%) than in the valsartan/HCTZ arm (range, 23%–39%; $p < 0.02$). Both combination therapies were well tolerated and safety parameters were similar in both age and gender subgroups. More patients with mild or moderate hypertension, uncontrolled in HCTZ monotherapy alone, had their BP controlled with irbesartan/HCTZ 150/12.5 mg than with valsartan/HCTZ 80/12.5 mg, irrespective of age or gender.

Keywords: irbesartanHCTZ, valsartanHCTZ, fixed-dose combination anti-hypertensive therapy, age, gender

INTRODUCTION

It is well recognized that achieving blood pressure (BP) control is important for reducing cardiovascular (CV) morbidity and mortality. Recent guidelines recommend that hypertensive patients should be treated to reduce BP to <140/90 mmHg or <130/80 mmHg in diabetic and high-risk patients, in order to effectively reduce the risk of CV events (1,2). This is supported by data indicating that the risk of death from ischemic heart disease and stroke increases linearly with BP for systolic BP/diastolic BP (SBP/DBP) of 115/75 to 185/115 mmHg in individuals over 40 years old (3). The relationship between BP and CV disease is continuous, consistent, and independent of other risk factors (2). A reduction of 5 mmHg DBP is associated with 34% less stroke and 21% less coronary heart disease (4).

In order to achieve the recommended BP targets, many patients require at least two antihypertensive agents (1,2), as studies suggest that only 40% to 50% of patients achieve BP targets with monotherapy (5–7). Thus, recently published guidelines recommend that for patients with severe hypertension, physicians should consider initiating treatment with combination therapy since it increases the likelihood of achieving the BP goal in a more timely manner (1,2). There are also accumulating data supporting the efficacy and safety of regimens involving various combinations of antihypertensive agents. Early effective antihypertensive therapy is important as patients inadequately treated from the outset never catch up in terms of BP goal attainment (8–11).

The combination of an angiotensin II receptor blocker (ARB) with a thiazide diuretic has been shown to be effective and well tolerated, and is a recommended option for achieving BP control in patients who are insufficiently controlled with monotherapy (1). Fixed-dose combinations are now available for various anti-hypertensive therapies and offer the important advantage of reducing the number of tablets to be taken by a patient, which in turn can be expected to improve patient compliance (8,12,13). Two available fixed-dose ARB/thiazide combinations are irbesartan/hydrochlorothiazide (HCTZ) and valsartan/HCTZ.

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Irbesartan (150 mg) has previously been shown to be more effective than valsartan (80 mg) in reducing SBP and DBP (14). In an 8-week randomized study in patients with mild-to-moderate hypertension, irbesartan produced significantly greater reductions from baseline in mean ambulatory SBP at trough (−11.62 vs. −7.5 mmHg; $p < 0.01$), mean ambulatory DBP at trough (−6.73 vs. −4.84; $p = 0.035$), mean 24-h ambulatory SBP (−10.24 vs. −7.76 mmHg; $p < 0.01$), and mean 24-h ambulatory DBP (−6.38 vs. −4.82; $p = 0.023$), as well as significantly greater reductions in office-measured SBP and DBP (14).

In a further study, the fixed-dose combination, irbesartan/HCTZ (150/12.5 mg) has been shown to achieve significantly superior BP-lowering compared with valsartan/HCTZ (80/12.5 mg), as assessed by office BP measurements and home BP monitoring (HBPM) (15). Known as 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, this open-label, parallel group trial directly compared irbesartan/HCTZ and valsartan/HCTZ in patients with uncontrolled or untreated mild-to-moderate hypertension. It showed significantly greater reductions in average SBP and DBP, as assessed by HBPM, for irbesartan/HCTZ compared to valsartan/HCTZ (SBP: −13.0 vs. −10.6 mmHg, $p = 0.0094$; DBP: −9.5 vs. 7.4 mmHg, $p = 0.0007$).

The COSIMA study involved 449 patients, approximately 55% of whom were men, and a third of whom were ≥65 years old. Given the high prevalence of hypertension in the elderly (66% in individuals ≥60 years vs. 33% in individuals 40–60 years old) (16), and the requirement for at least two drugs to control BP in approximately 50% of elderly patients (6,7), it is particularly relevant to assess the efficacy and safety of ARB/diuretic combinations in this patient group.

This article reports the results of a post-hoc analysis of the COSIMA study aimed at exploring whether the superior BP-lowering efficacy of irbesartan/HCTZ (150/12.5 mg) over valsartan/HCTZ (80/12.5 mg) obtained in the total trial population was also observed in the elderly and across both genders.

METHODS

Patients

COSIMA was a multicenter, parallel group Prospective Randomized Open-label Blinded-End point (PROBE) study, which enrolled adult patients aged 18 to 79 years old with untreated (office SBP >160 mmHg) or uncontrolled (office SBP >140 mmHg on anti-hypertensive monotherapy) mild-to-moderate essential hypertension and was carried out by 139 primary care physicians in France (15). The protocol and informed consent were approved by a National Ethics Committee and all patients gave written consent.

The study consisted of two phases. Following the first enrollment visit when patients with uncontrolled hypertension discontinued prior anti-hypertensive therapy, all patients received HCTZ 12.5 mg once daily for 5 weeks (phase I). At the second study visit, at the end of week 4, patients with controlled BP (office SBP <140 mmHg) were excluded from the study. The remaining patients then performed a baseline HBPM over a 5-day period (during week 5) and returned for a further assessment at the end of week 5 (visit 3). Those in whom the average SBP (HSBP) was >135 mmHg were eligible for the second phase of the study, in which patients were randomized 1:1 to receive irbesartan/HCTZ 150/12.5 mg once daily, or valsartan/HCTZ 80/12.5 mg once daily, for 8 weeks. During the last week of this phase (week 13) patients performed a second HBPM over 5 days.

Efficacy Assessment

Home BP monitoring was performed twice a day for 5 days in the last week of phase I and phase II, using a validated electronic device (TensioDay monitor, TensioMed, Budapest, Hungary). Patients were trained to use the device according to a standard procedure. The morning measurements were taken between 6 am and 10 am, immediately before taking the study drug. After a 5-min rest period, three seated measurements were obtained at 1-minute intervals. The evening measurements were taken in the same manner between 6 pm and 10 pm. Data were transferred automatically every night by telephone to an independent center blinded to the treatment allocation. All measurements performed on the first day of each study period were considered as part of the patient's training period and were excluded from the analysis. Quality criteria used for an acceptable HBPM were at least 12 valid measurements obtained during at least 3 days. The following values were considered incompatible: SBP <60 or >250 mmHg, DBP <40 or >150 mmHg, and SBP-DBP <10 mmHg (15).

Change in home SBP (HSBP) and home DBP (HDBP) from baseline (arithmetic mean of all morning and evening values), and the percentage of patients achieving BP control (average HSBP/HDBP ≤135/85 mmHg), were determined.

Safety Assessments

All randomized patients who received at least one dose of study medication were included in the safety assessment. The incidence of adverse events was determined according to the treatment group and was analyzed for the age and gender subgroups.

Statistics

This post-hoc analysis was based on the intention-to-treat (ITT) population from the COSIMA study, defined as all patients in the randomized population who received at least one treatment dose with at least one

evaluation after the study treatment was administered. Changes in HSBP and HDBP from baseline after 8 weeks of treatment in each of the age and gender subgroups were analyzed using a signed rank test. Differences in HSBP and HDBP reductions were analyzed using a one-way analysis of covariance (ANCOVA) model (adjusted means on baseline HSBP), including treatment as fixed effect and baseline averaged HSBP as covariate. Differences in the percentage of patients achieving BP control with the two treatments in the age and gender subgroups were analyzed using chi-squared or Fisher exact tests. A Breslow-Day test for homogeneity of the odds ratio of BP control was used to analyze the interactions between age and gender. Differences in safety parameters between treatment groups were analyzed by chi-squared and Fisher exact tests.

RESULTS

Demographics and Baseline Characteristics

As described previously (15), among the 800 patients enrolled in phase I, 464 patients were randomized to receive irbesartan/HCTZ or valsartan/HCTZ in phase II, and 449 were included in the ITT analysis. Among the 222 patients assigned to irbesartan/HCTZ, 73 were ≥65 years old, 149 were <65 years old, 104 were women, and 118 were men. Among the 227 patients assigned to valsartan/HCTZ, 77 were ≥65 years old, 150 were <65 years old, 93 were women, and 134 were men (Table 1).

The baseline characteristics for the total study population, age, and gender subgroups are summarized in Table 1; there were no significant differences between the two treatment groups among these. Cardiovascular risk factors (i.e., history of myocardial infarction, coronary disease, transient ischemic attack, cerebrovascular accident, and lower limb artheriopathy) and associated comorbidities were also similar between treatment groups and among subgroups.

Table 1. Baseline characteristics for the total study population and age and gender subgroups

	Irbesartan/HCTZ	Valsartan/HCTZ
Total study population	n = 222	n = 227
Gender, male (%)	53	59
Age, y, mean (SD)	58 ± 11	59 ± 10
Weight, kg, mean (SD)	77 ± 14	78 ± 14
Elderly ≥65 y	n = 73	n = 77
Gender, male (%)	45	52
Weight, kg, mean (SD)	74 ± 14	74 ± 13
Younger <65 y	n = 149	n = 150
Gender, male (%)	57	63
Weight, kg, mean (SD)	79 ± 14	81 ± 14
Women	n = 104	n = 93
Age, y, mean (SD)	59 ± 12	61 ± 11
Weight, kg, mean (SD)	71 ± 14	71 ± 2
Men	n = 18	n = 134
Age, y, mean (SD)	58 ± 11	58 ± 10
Weight, kg, mean (SD)	82 ± 12	84 ± 13

Abbreviations: HCTZ - hydrochlorothiazide.

Table 2. Home BP measurements at week 5, prior to treatment with combination therapy

	Irbesartan/HCTZ	Valsartan/HCTZ
Elderly ≥65 y	n = 73	n = 77
SBP mmHg	150 ± 13	151 ± 11
DBP mmHg	86 ± 10	86 ± 9
Younger <65 y	n = 149	n = 150
SBP mmHg	148 ± 10	148 ± 11
DBP mmHg	92 ± 10	91 ± 10
Women	n = 104	n = 93
SBP mmHg	147 ± 10	147 ± 10
DBP mmHg	86 ± 9	84 ± 10
Men	n = 118	n = 134
SBP mmHg	150 ± 11	151 ± 12
DBP mmHg	94 ± 9	93 ± 8

All values mean ± SD.
Abbreviations: HCTZ - hydrochlorothiazide; SBP - systolic blood pressure; DBP - diastolic blood pressure.

The baseline home BP measurements in each subgroup are shown in Table 2. Both HSBP and HDBP values were similar in the two treatment groups and among subgroups.

Changes From Baseline

Both treatment regimens yielded significant reductions in HSBP and HDBP from baseline (week 5) to week 13 ($p < 0.0001$). Table 3 shows the mean changes in HSBP and HDBP measurements during the combination therapy period (week 5 to week 13). The reduction in HBPM was numerically greater with irbesartan/HCTZ 150/12.5 mg than with valsartan/HCTZ 80/12.5 mg in all subgroups, and this difference was statistically significant in patients ≥65 years (HSBP only; $p < 0.02$), patients <65 years (HDBP only; $p < 0.01$), in women (HDBP only; $p < 0.04$), and in men (HSBP and HDBP; $p < 0.03$ and 0.007, respectively).

Table 3. Mean changes in home BP measurements from baseline (week 5) to end of therapy

Mean Changes in Home BP, mmHg	Irbesartan/HCTZ	Valsartan/HCTZ	p Value*
≥65 y	n = 70	n = 74	
SBP	−12 ± 9	−9 ± 9	<0.02
DBP	−8 ± 6	−6 ± 5	NS
<65 y	n = 141	n = 143	
SBP	−13 ± 12	−12 ± 9	NS
DBP	−10 ± 8	−8 ± 6	<0.01
Women	n = 99	n = 88	
SBP	−12 ± 9	−11 ± 10	NS
DBP	−8 ± 6	−7 ± 6	<0.04
Men	n = 112	n = 129	
SBP	−14 ± 12	−11 ± 9	<0.03
DBP	−10 ± 8	−8 ± 6	<0.007

*p value for comparison irbesartan/HCTZ vs. valsartan/HCTZ.
Abbreviations: HCTZ - hydrochlorothiazide; SBP - systolic blood pressure; DBP - diastolic blood pressure.

Table 4. Percentage of patients with home BP controlled (≤135/85 mmHg) with irbesartan/HCTZ 150/12.5 mg or valsartan/HCTZ 80/12.5 mg at week 13

	Irbesartan/HCTZ	Valsartan/HCTZ	*p* Value
Elderly ≥65 y	49% (n = 70)	23% (n = 74)	0.001
Younger <65 y	52% (n = 141)	38% (n = 143)	0.017
Women	58% (n = 99)	39% (n = 88)	0.009
Men	45% (n = 112)	29% (n = 129)	0.010

Abbreviations: HCTZ - hydrochlorothiazide.

Rate of Achieving BP Control

Table 4 shows rates of BP control (HBPM ≤135/85 mmHg) from baseline to week 13 by age and gender subgroups. In all subgroups, significantly more patients achieved BP control in the irbesartan/HCTZ 150/12.5 mg treatment arm than in the valsartan/HCTZ 80/12.5 mg treatment arm (elderly, $p < 0.001$; younger patients, $p < 0.017$; women $p < 0.009$; men, $p < 0.01$). Controlling for age and gender, the Breslow-Day test for homogeneity of the odds ratio showed no difference, making the individual comparisons legitimate (chi-squared = 0.267, $p = 0.9661$ for age group and gender).

Adverse Events

Combination therapy was well tolerated and the overall safety profile was similar in the two treatment arms and in the age and gender subgroups. Nonserious treatment-emergent adverse events occurred in the irbesartan/HCTZ arm and valsartan/HCTZ arms, respectively, in 15% and 16% of the elderly subgroup, 18% and 15% of younger patients, 16% and 18% of women, and 18% and 13% of men. The most common adverse events in all groups were musculoskeletal and connective tissue disorders, gastrointestinal disorders, and infections.

DISCUSSION

The results of this post-hoc age and gender subgroup analysis of the COSIMA study showed that significantly more patients achieved BP control with irbesartan/HCTZ 150/12.5 mg than with valsartan/HCTZ 80/12.5 mg, and this was achieved in older and younger patients, and in men and women. Within these subgroups, BP control ranged from 45% to 58% of patients with irbesartan combination therapy compared to only 23% to 39% with valsartan combination therapy. The difference in BP control was particularly marked in the elderly, where the BP control rate with irbesartan/HCTZ 150/12.5 mg was two-fold greater than with valsartan/HCTZ 80/12.5 mg (49% vs. 23%; $p = 0.001$). Blood pressure control rates with irbesartan/HCTZ treatment were similar for elderly and younger patients (49% vs. 52%), and slightly better for women compared to men (58% vs. 45%). Given the importance of achieving BP control to reduce CV risk, these data suggest that irbesartan/HCTZ 150/12.5 mg may offer significant advantages over valsartan/HCTZ 80/12.5 mg in patients with hypertension, particularly in the elderly. The importance of controlling BP in the elderly was recently demonstrated in the HYpertension in the Very Elderly Trial (HYVET), in which BP reduction in hypertensive patients of 80 years of age and over significantly reduced total mortality by 21% and stroke mortality by 39% over a median 1.8-year follow-up period (17).

The current COSIMA analysis showed that absolute decreases in HSBP and HDBP achieved with irbesartan/HCTZ 150/12.5 mg were numerically greater than for valsartan/HCTZ 80/12.5 mg in the age and gender subgroups, and the differences between the two treatment groups in HDBP reached statistical significance for most subgroups. The decrease in HDBP achieved with irbesartan/HCTZ 150/12.5 mg was from 1.7 to 2.2 mmHg greater than with valsartan/HCTZ 80/12.5 mg, with the difference being more pronounced in younger patients and men. The greater decrease in HSBP achieved with irbesartan/HCTZ 150/12.5 mg compared to valsartan/HCTZ 80/12.5 mg ranged from 1.4 mmHg in women to 3.4 mmHg for elderly patients: the difference in HSBP reductions between treatment groups was only statistically significant for the elderly and men.

The present analysis of the COSIMA study was based on HBPM rather than office BP measurements. Home BP measurement is a recommended method for assessing BP (2,19,20), but has not been used widely in clinical studies. In the COSIMA study, both office measurements and HBPM were performed and yielded similar results with treatment, although HBPM readings were generally lower (15). Home BP measurements are often lower than office measurements as a result of the white-coat effect, and are closer to the average BP recorded by 24-h ambulatory monitors (19,20). The white-coat effect has been attributed to anxiety, a hyperactive alerting response, or a conditioned response to attending clinic, and tends to be greater in older rather than younger patients, and in women rather than men (21). Home BP measurement is recommended for evaluating the response to anti-hypertensive treatment and may improve adherence to therapy (19,20,22).

Given the low BP control rates recently reported for patients treated for hypertension (approximately 50% in the US and Canada and 20% to 40% in Europe) (23–25), strategies that improve hypertension control are urgently needed. Fixed-dose combination therapy is clearly an important strategy to help achieve this. Use of the most effective ARB/diuretic combination could be an important means to improve BP control in hypertensive patients, particularly those in whom hypertension is difficult to control, such as in the elderly.

CONCLUSIONS

The results of this analysis indicate that irbesartan/HCTZ 150/12.5 mg achieves significantly better BP control rates (HBPM ≤ 135/85 mmHg) compared to valsartan/HCTZ 80/12.5 mg in both men and women and in older and

younger patients inadequately controlled with HCTZ monotherapy alone. Treatment was well tolerated and safety parameters were similar in all subgroups. These data suggest that irbesartan/HCTZ is an appropriate therapy for patients with hypertension uncontrolled on monotherapy, irrespective of age or gender.

DISCLOSURES

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