Efficacy and Safety of Fixed Combinations of Irbesartan/Hydrochlorothiazide in Hypertensive Women: The Inclusive Trial

Elizabeth O. Ofili, M.D., M.P.H.,¹ Greg Cable, Ph.D., M.P.A.,² Joel M. Neutel, M.D.,³
and Elijah Saunders, M.D., FACC, FACP⁴

Abstract

Objective: This *post hoc* analysis of the Irbesartan/Hydrochlorothiazide Blood Pressure Reductions in Diverse Patient Populations (INCLUSIVE) trial evaluated the efficacy and safety of irbesartan/hydrochlorothiazide (HCTZ) in a diverse population of hypertensive women.

Methods: INCLUSIVE was a multicenter, prospective, open-label, single-arm trial. Adult subjects had uncontrolled systolic blood pressure (SBP 140–159 mm Hg; 130–159 mm Hg for those with type 2 diabetes mellitus [T2DM]) after ≥ 4 weeks of antihypertensive monotherapy. Treatment was sequential: placebo (4–5 weeks), HCTZ 12.5 mg (2 weeks), irbesartan/HCTZ 150/12.5 mg (8 weeks), and irbesartan/HCTZ 300/25 mg (8 weeks). Mean changes from baseline to treatment end in SBP and diastolic blood pressure (DBP), BP goal attainment, and safety were assessed.

Results: Treatment with irbesartan/HCTZ was associated with significant mean reductions in BP (intent-to-treat population, $n = 370$; SBP/DBP: $-22.9/-10.3 \pm 14.7/8.8$ mm Hg). Improvements in SBP were observed in all subgroups ($p < 0.001$): Caucasian ($n = 207$) -23.5 ± 13.5 mm Hg; African American ($n = 93$) -21.0 ± 17.2 mm Hg; Hispanics/Latino ($n = 66$) -23.6 ± 14.3 mm Hg; age < 65 years ($n = 281$) -22.5 ± 14.7 mm Hg; age ≥ 65 years ($n = 89$) -24.3 ± 14.5 mm Hg; T2DM ($n = 97$) -19.0 ± 15.1 mm Hg; and metabolic syndrome ($n = 187$) -22.1 ± 14.6 mm Hg. Overall, 82% (95% confidence interval [CI] 78%–86%) of women achieved their SBP goal, 86% (95% CI 83%–90%) achieved their DBP goal, and 76% (95% CI 71%–80%) achieved their dual SBP/DBP goal. Treatments were well tolerated in all groups.

Conclusions: Irbesartan/HCTZ treatment was effective and well tolerated in a diverse population of women whose BP was previously uncontrolled on monotherapy.

Introduction

HYPERTENSION AFFECTS APPROXIMATELY one third of the adult population.¹ It is the most prevalent modifiable risk factor for cardiovascular (CV) disease and the most common risk factor for death from any cause worldwide in both men and women.² However, hypertension is associated with a greater increased risk of both CV events^{3–5} and CV mortality⁶ in women than in men. Furthermore, CV disease (CVD) mortality rates have decreased in men during the past

20 years but have steadily increased in women.⁷ Compared to age-matched men, blood pressure (BP) levels tend to increase in postmenopausal women, suggesting a role for ovarian hormones in BP regulation.⁸ Therefore, men and women may require different antihypertensive treatment strategies as a result of differences in the progression and presentation of hypertension.

Hypertension treatment guidelines recommend lowering BP levels to $< 140/90$ mm Hg in the general population and to $< 130/80$ mm Hg in those with diabetes or chronic kid-

¹Morehouse School of Medicine, Atlanta, Georgia.

²Biostatistics, Sanofi-Aventis, Bridgewater, New Jersey.

³Orange County Research Center, Tustin, California.

⁴University of Maryland School of Medicine, Baltimore, Maryland.

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ney disease.^{9–11} Although effective BP control is associated with a reduced risk of CVD mortality and morbidity,^{12–14} the majority of people with hypertension remain untreated, and only around one third achieve their BP goal.¹ This is partly due to poor treatment compliance and physician inertia. As the majority of patients will require more than one antihypertensive agent to achieve their BP goal,^{9,10,12} the increased use of aggressive first-line combination therapy may help improve hypertension management in the community.

Clinical studies show that a combination of the angiotensin receptor blocker (ARB), irbesartan, with the thiazide diuretic, hydrochlorothiazide (HCTZ), safely and effectively lowers BP levels in subjects irrespective of baseline BP level, age, race, diabetic status, and metabolic syndrome^{15–24} and has a significantly greater dose-dependent BP-lowering effect than either agent alone.^{15,16,23,24} For example, in the Irbesartan/Hydrochlorothiazide Blood Pressure Reductions in Diverse Patient Populations (INCLUSIVE) trial, fixed-dose irbesartan/HCTZ was associated with systolic BP (SBP) control in 77% of subjects with previously uncontrolled hypertension.²⁰ The present subgroup analysis of the INCLUSIVE trial evaluated the efficacy and safety of irbesartan/HCTZ fixed combinations in women with SBP previously uncontrolled on antihypertensive monotherapy.

Materials and Methods

Subjects

The INCLUSIVE trial methods have been published previously.²⁰ Briefly, subjects were aged ≥ 18 years with uncontrolled SBP at screening (140–159 mm Hg; 130–159 mm Hg for those with type 2 diabetes mellitus [T2DM]) after ≥ 4 weeks of antihypertensive monotherapy. Major exclusion criteria included SBP ≥ 180 mm Hg, diastolic BP (DBP) ≥ 110 mm Hg, and secondary hypertension. At least 100 subjects were recruited into each of the following subpopulations: elderly (age ≥ 65 years), African American, Hispanic/Latino, T2DM (fasting plasma glucose ≥ 126 mg/dL [6.993 mmol/L] and/or taking antidiabetic medication), and metabolic syndrome (according to the criteria of the National Cholesterol Education Program [NCEP]²⁵). All subjects provided written informed consent prior to study enrollment.

Study design

INCLUSIVE was a multicenter, prospective, open-label, single-arm study conducted between July 2003 and August 2004 at 119 sites in the United States. Eligible subjects discontinued their previous antihypertensive therapy prior to entering the trial. The four sequential phases of the study were as follows: (1) placebo for 4–5 weeks, (2) HCTZ 12.5 mg for 2 weeks (one tablet once daily), (3) irbesartan/HCTZ 150/12.5 mg for 8 weeks (one fixed-combination tablet once daily), (4) irbesartan/HCTZ 300/25 mg for 8 weeks (two fixed-combination tablets once daily). Entry requirements for each phase of the trial included SBP 140–179 mm Hg (130–179 mm Hg for those with T2DM) for the first three phases and SBP 120–179 mm Hg (all subjects) for the final phase. DBP was 70–109 mm Hg throughout the study. Subjects who did not meet the BP criteria at each stage of the trial were withdrawn from the study. In the study, 436 pa-

tients were assigned to receive HCTZ 12.5 mg, 393 patients were assigned to receive irbesartan/HCTZ 150/12.5 mg, and 338 patients were assigned to receive irbesartan/HCTZ 300/25 mg (Fig. 1).

Medication was taken at 8 A.M. (± 2 hours) except on the morning of a clinic visit, when it was taken after BP had been measured. Seated trough BP (8 AM ± 2 hours) was measured using an automated oscillometric device (HEM705CP, Omron Healthcare, Inc., Bannockburn, IL) (error rate ± 4 mm Hg),²⁶ and BP was considered to be the mean of three readings obtained at 2-minute intervals. The study design was approved by the institutional review board/ethics committee of each participating site.

Efficacy end points

The primary efficacy end point was the mean SBP change from the end of the placebo phase (baseline) to the end of the irbesartan/HCTZ 300/25 mg treatment period (week 18). Secondary end points were the mean DBP change from baseline to week 18, mean SBP and DBP changes from baseline to the end of the irbesartan/HCTZ 150/12.5 mg treatment period (week 10), and SBP (< 140 mm Hg or < 130 mm Hg for those with T2DM) and DBP goal (< 90 mm Hg or < 80 mm Hg) attainment rates.

Safety evaluations

All adverse events, including clinically significant changes in physical examinations and abnormal laboratory test findings, were documented.

Statistical analyses

Efficacy data were analyzed for the intent-to-treat (ITT) population (subjects with at least one valid SBP measurement following at least one dose of irbesartan/HCTZ 150/12.5 mg). Efficacy end points were calculated from the last observation carried forward for ITT subjects who were controlled or withdrew from the study before week 18. The safety population comprised all patients taking at least one dose of study medication, including placebo.

Mean, standard deviation (SD), median, minimum, and maximum values were calculated for continuous variables, and 95% confidence intervals (CIs) were calculated for point estimates of mean change scores in continuous variables. Mean changes in BP from baseline were analyzed using a paired *t* test for a normally distributed population or a Wilcoxon signed rank test for data not normally distributed. Goal attainment rates were calculated as frequency counts and percentages with 95% CIs. If a point estimate was < 0.1 or > 0.9 , the upper and lower limits of the interval were calculated using alternative formulas.²⁷

Results

Patient characteristics

Of the 832 women screened, 529 formed the safety population, 436 commenced HCTZ 12.5 mg treatment, and 298 completed the study (Fig. 1). The mean baseline SBP/DBP was 153.9/90.3 mm Hg ((9.8/8.7 mm Hg), and the mean age at enrollment was 57.6 ± 11.3 years. The majority of subjects

FIG. 1. Flow diagram of female participants through each phase of the INCLUSIVE study. HCTZ, hydrochlorothiazide; BP, blood pressure.

were Caucasian (56%), but there were significant proportions of African Americans (26%) and Hispanics/Latinos (17%). Patient demographics, including previous antihypertensive monotherapy class, are shown in Table 1.

Mean changes in SBP and DBP from baseline

For the female ITT population ($n = 370$), there was a significant mean reduction from baseline to week 18 in both

TABLE 1. PATIENT DEMOGRAPHICS OF ENROLLED FEMALE INCLUSIVE STUDY POPULATION

Parameter	Enrolled population (n = 436)
Age, years, mean	57.6
Baseline SBP/DBP, mm Hg ($\pm$ SD)	153.9/90.3 ($\pm$ 9.8/8.7)
Race/ethnic group, n (%) ^a	
Caucasian	242 (56)
African American	115 (26)
Hispanic/Latino	72 (17)
Other	9 (2)
Type 2 diabetes mellitus, n (%)	112 (26)
Metabolic syndrome, n (%)	213 (49)
Previous antihypertensive monotherapy, n (%) ^a	
ACE inhibitors ^b	142 (33)
Calcium channel blockers	84 (19)
ARBs	82 (19)
Diuretics	66 (15)
Beta-blocker	58 (13)
Other	6 (1)
Alpha-blocker	1 (<1)

^aPatients may have been categorized into more than one group.

^bARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme.

SBP (-22.9 ± 14.7 mm Hg; 95% CI -24.4 to -21.4 ; $p < 0.001$) and DBP (-10.3 ± 8.8 mm Hg; 95% CI -11.2 to -9.5 ; $p < 0.001$) (Fig. 2). The mean final SBP/DBP at week 18 was 131.0/79.9 mm Hg (Fig. 3). Similar improvements from base-

line to week 18 in SBP and DBP were observed in women from all ethnic subgroups, in those aged <65 years and ≥ 65 years, and in those with T2DM or metabolic syndrome ($p < 0.001$ for every subgroup) (Fig. 2).

FIG. 2. Mean change from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the end of irbesartan/HCTZ 300/25 mg treatment (intent-to-treat population). Values are mean $\pm$ SD; last observation carried forward for week 18 data.

FIG. 3. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels during the study for women (intent-to-treat population). Values are mean (minimum, maximum, 95% CIs); last observation carried forward for week 18 data. HCTZ, hydrochlorothiazide.

BP goal attainment rates

Overall, at week 18, 82% (95% CI 78%–86%) and 86% (95% CI 83%–90%) of women achieved their SBP and DBP goals, respectively, and 76% (95% CI 71%–80%) achieved their dual SBP/DBP goal (Table 2). Similar dual SBP/DBP goal attainment rates ($\geq 67\%$) were achieved in most subgroups, with slightly lower rates in the T2DM population (46%) (Table 2).

Goal SBP, DBP, and dual SBP/DBP attainment rates increased steadily from baseline to weeks 2, 10, and 18, with little difference between groups (Table 2).

Safety and tolerability

Study medications were generally well tolerated. The majority of adverse events in women were mild, moderate, and

TABLE 2. SBP AND DBP GOAL ATTAINMENT RATES AT WEEKS 2, 10, AND 18 AMONG SUBGROUPS OF WOMEN (INTENT-TO-TREAT POPULATION)

Intent-to-treat population	All women n = 370	Caucasian n = 207	African American n = 93	Hispanic/Latino n = 66	Age < 65 years n = 281	Age > 65 years n = 89	With T2DM ^a n = 97	With metabolic syndrome n = 187	All men n = 366
SBP goal, n (%)									
Baseline to week 2	14 (4)	7 (3)	7 (8)	0	9 (3)	5 (6)	1 (1)	2 (1)	7 (2)
Baseline to week 10	224 (61)	134 (65)	52 (56)	35 (53)	172 (61)	52 (58)	29 (30)	105 (56)	187 (51)
Baseline to week 18	302 (82)	178 (86)	67 (72)	53 (80)	233 (83)	69 (78)	58 (60)	146 (78)	267 (73)
DBP goal, n (%)									
Baseline to week 2	155 (42)	100 (48)	28 (30)	25 (38)	96 (34)	59 (66)	21 (22)	56 (30)	111 (30)
Baseline to week 10	271 (73)	161 (78)	59 (63)	48 (73)	194 (69)	77 (87)	44 (45)	124 (66)	248 (68)
Baseline to week 18	319 (86)	184 (89)	72 (77)	59 (89)	233 (83)	86 (97)	66 (68)	155 (83)	291 (80)
SBP and DBP goal, n (%)									
Baseline to week 2	11 (3)	6 (3)	5 (5)	0 (0)	7 (2)	4 (4)	1 (1)	2 (1)	4 (1)
Baseline to week 10	195 (53)	114 (55)	44 (47)	33 (50)	148 (53)	47 (53)	20 (21)	87 (47)	159 (43)
Baseline to week 18	280 (76)	165 (80)	62 (67)	49 (74)	212 (75)	68 (76)	45 (46)	130 (70)	227 (62)

^aSBP, systolic blood pressure; DBP, diastolic blood pressure; T2DM, type-2 diabetes mellitus.

^bSBP goal, < 140 mm Hg (< 130 mm Hg for patients with T2DM); DBP goal, < 90 mm Hg (< 80 mm Hg for patients with T2DM).

transient and considered unrelated to study medications. Overall, the most common adverse events in women were headache (9%), dizziness (5%), urinary tract infection (5%), sinusitis (4%), and nasopharyngitis (4%). The percentage of women who experienced an adverse event was similar between subgroups but was highest in African Americans (60%), those with T2DM (66%), and those with metabolic syndrome (68%). Headache was the most common adverse event in all female subgroups except Hispanics/Latinos and patients with T2DM.

Discussion

ARB/HCTZ combination therapy has been shown to be safe and effective in a diverse range of hypertensive subgroups.^{15–18,23,24,28–33} In this *post hoc* analysis of the INCLUSIVE study,²⁰ treatment with irbesartan/HCTZ combination therapy was associated with significant reductions from baseline to week 18 in both SBP and DBP in women, including “difficult-to-treat” female subgroups, such as the elderly,¹⁰ African Americans, and those with T2DM.³⁴ Overall, the mean SBP and DBP reductions in women (-22.9 ± 14.7 mm Hg and -10.3 ± 8.8 mm Hg, respectively) were similar to those obtained in the male INCLUSIVE population (-20.1 ± 13.88 mm Hg and -10.4 ± 8.56 mm Hg, respectively [data not shown]; $p < 0.001$ vs. baseline for SBP and DBP reductions in both men and women). However, a slightly higher proportion of women than men achieved their SBP, DBP, and dual SBP/DBP goals at every time point in the study (Table 2). These data are consistent with those from a population-based longitudinal study of 9,328 men and 10,062 women in which 38.3% of treated men with hypertension achieved BP control compared with 52.7% of treated women.⁶

The proportion of women who achieved their BP goals increased as the study progressed (Table 2). Previous studies have demonstrated that SBP is the single best predictor of mortality in women treated for hypertension⁶ and should be the primary focus for antihypertensive therapy.⁹ In this study, irbesartan/HCTZ combination therapy was especially effective at reducing SBP compared with HCTZ monotherapy, although the dosage and duration of HCTZ monotherapy used may not have been sufficient to attain optimal therapeutic benefits. Overall, 76% of women achieved their dual SBP/DBP goal by week 18. In comparison, the U.S. National Health and Nutrition Examination Survey (NHANES) 1999–2004 revealed that only around one third of the hypertensive population in the United States achieve their BP goal.¹ These findings suggest an opportunity for improved hypertension management using fixed-dose combination therapy in clinical practice.

The current treatment guidelines recommend initiating combination therapy in all subjects with BP levels $>20/10$ mm Hg above goal,^{9,10} in those with T2DM,^{9–11} and in African American women with BP levels $\geq 15/10$ mm Hg above goal.³⁵ Although ARB, angiotensin-converting enzyme (ACE) inhibitor, and beta-blocker monotherapies have been shown to be less effective than other antihypertensive drug classes for the reduction of BP levels in African Americans,¹² the efficacy of these agents is similar across all racial groups when combined with a diuretic.^{9,12,22,35} This obser-

vation is supported by the current subanalysis, in which BP goal attainment rates were similar across all ethnic groups (Table 2).

The highest dual SBP/DBP rates were seen in Caucasian women (80%), African American women (67%), Hispanic/Latino women (74%), women aged <65 years (75%) or ≥ 65 years (76%), and those with metabolic syndrome (70%). Slightly fewer women with T2DM (46%) achieved their dual SBP/DBP goal at week 18. However, the rate was comparable to that obtained in the overall INCLUSIVE T2DM subgroup (40%),²¹ suggesting that female gender had little or no impact on the BP-lowering efficacy of irbesartan/HCTZ combination therapy in patients with T2DM. The results from this subanalysis are consistent with those from previous studies, which suggest that BP control is more difficult to achieve in subjects with T2DM.^{12,21,34} However, dual SBP/DBP goal attainment rates were considerably better in the current subanalysis than for diabetic patients in other trials^{2,12,13,36–38} in which monotherapy frequently was used.

These data support the current hypertension treatment guidelines^{9–11} that recommend initiating combination antihypertensive therapy using either an ACE inhibitor or an ARB together with a thiazide diuretic in patients with diabetes. This recommendation takes into account the proven BP-lowering efficacy and tolerability of ACE inhibitors and ARBs, both as monotherapy and in combination with a thiazide diuretic,^{15–18,23,24,28–33} their BP-independent renoprotective benefits,^{39–44} and their potential to mitigate some of the adverse cardiometabolic effects of thiazide diuretics that lead to the development or progression of diabetes.^{28,45–47}

Limitations of this study include the relatively short treatment duration (18 weeks) and the fact that it was a *post hoc* analysis of a nonrandomized, nonplacebo-controlled trial. In addition, statistical tests were not adjusted for potential multiple comparison artifacts. Further prospective, randomized, placebo-controlled trials are, therefore, necessary to confirm the results of this study. However, our subanalysis indicates that fixed-dose irbesartan/HCTZ combination therapy effectively reduces BP in a diverse range of female patients, including difficult-to-treat subgroups, such as the elderly, African Americans, and those with T2DM.^{10,12,34} In line with previous studies that have established the tolerability of irbesartan and other ARBs either alone or in combination with HCTZ,^{15–20,44,48–51} both the low-dose and high-dose irbesartan/HCTZ combinations were well tolerated in this heterogeneous female population. All adverse events were either mild or moderate in nature and transient in duration, with no obvious gender-specific side effects. In conclusion, irbesartan/HCTZ fixed combination therapy provided well-tolerated BP lowering and SBP goal attainment in $>80\%$ of a diverse population of women whose BP was previously uncontrolled using monotherapy.

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Address reprint requests to:
 Elizabeth O. Ofili, M.D., M.P.H.
 Professor and Chief of Cardiology
 Director, Clinical Research Center
 Morehouse School of Medicine
 720 Westview Drive SW
 Atlanta, GA 30310

E-mail: eofili@msm.edu