Irbesartan/HCTZ Fixed Combinations in Patients of Different Racial/Ethnic Groups with Uncontrolled Systolic Blood Pressure on Monotherapy

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The IrbesartaN/hydroChlorothiazide (HCTZ) bLood pressUre reductionS In diVErse patient populations (INCLUSIVE) trial was a multicenter, prospective, open-label, single-arm study evaluating the efficacy and safety of irbesartan/HCTZ fixed combinations in patients ≥18 years old with uncontrolled systolic blood pressure (SBP, 140–159 mmHg; 130–159 mmHg for type-2 diabetes mellitus patients) after ≥4 weeks of antihypertensive monotherapy. This analysis focused on different racial/ethnic subgroups. Treatment was sequential: placebo (4–5 weeks), HCTZ 12.5 mg (two weeks), irbesartan/HCTZ 150/12.5 mg (eight weeks) and irbesartan/HCTZ 300/25 mg (eight weeks). Overall, 515 Caucasians, 191 African Americans and 119 Hispanics/Latinos completing placebo treatment were enrolled. Mean SBP changes from baseline (placebo treatment end) to week 18 were -21.5 ± 13.8 mmHg for Caucasians, -20.7 ± 16.5 mmHg for African Americans and -22.9 ± 13.2 mmHg for Hispanics/Latinos, respectively ($p<0.001$ for each). Mean diastolic BP (DBP) changes were statistically significant ($p<0.001$) and similar among racial/ethnic subgroups. By week 18, 70% (95% CI, 66%, 74%) of Caucasian, 66% (95% CI, 59%, 74%) of African-American and 65% (95% CI, 57%, 74%) of Hispanic/Latino patients achieved dual SBP/DBP goal. Treatments appeared to be well tolerated. In conclusion, irbesartan/HCTZ treatment provided SBP/DBP goal attainment in approximately two-thirds of Caucasian, African-American and Hispanic/Latino patients with SBP uncontrolled on antihypertensive monotherapy.

Key words: hypertension ■ fixed-dose combination therapy ■ irbesartan/hydrochlorothiazide ■ ethnicity/race

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INTRODUCTION

Hypertension prevalence varies across racial/ethnic subgroups in the United States. Data from the 1999–2000 U.S. National Health and Nutrition Examination Survey (NHANES) showed that approximately 48 million non-Hispanic white adults, 9 million non-Hispanic black adults, 3 million Mexican-American adults and 5 million adults of other race/ethnicity had hypertension.[1] Other NHANES 1999–2000 data analyses reveal racial/ethnic variations in the awareness and control of hypertension: 69.0% of non-Hispanic whites, 75.5% of non-Hispanic blacks and 57.7% of Mexican Americans were aware of their hypertension; and rates of blood pressure (BP) control to <140/90 mmHg were poor, at 33.3% in non-Hispanic whites, 28.2% in non-Hispanic blacks and 17.6% in Mexican Americans.[2] Variations in socioeconomic factors (e.g., level of education, employment status, cultural bias, income, Internet access, time available for the pursuit of health-related activities and access to healthcare services) may contribute to these racial/ethnic differences.[3,4]

Treatment recommendations for minority populations in the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) are mostly consistent with those for the general population.[2,5] The BP target is <140/90 mmHg for patients with uncomplicated hypertension; <130/80 mmHg if diabetes or chronic kidney disease is present. Weight reduction and sodium reduction are proposed as being particularly effective in lowering BP in minority populations. Monotherapy with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) is considered less efficacious in African Americans than Caucasians when used at the usual doses.[6-8] In the African-American population, this lesser response may be attributed to factors such as a greater prevalence of obesity, salt-sensitive hypertension and low plasma renin activity.[9,10] Nevertheless, combining a beta-blocker, ACE inhibitor or ARB with a diuretic abolishes any racial or ethnic differences in the therapeutic response to these agents.[5,7,8,11] Racial differences also exist in the incidence of antihypertensive drug side-effects. For example, African Americans have a higher risk of angioedema and, possibly, cough attributed to ACE inhibitors than Caucasians.[12,13]

To date, insufficient numbers of Hispanics have been included in large, well-powered clinical trials to allow conclusions to be drawn regarding their response to specific antihypertensive drugs. No hypertension management guidelines have been developed for Hispanic patients due to this lack of trial data. Findings from NHANES indicate that greater efforts are needed to improve BP management among Hispanics, especially with regard to the provision of antihypertensive medications and the adoption of lifestyle modifications.[2]

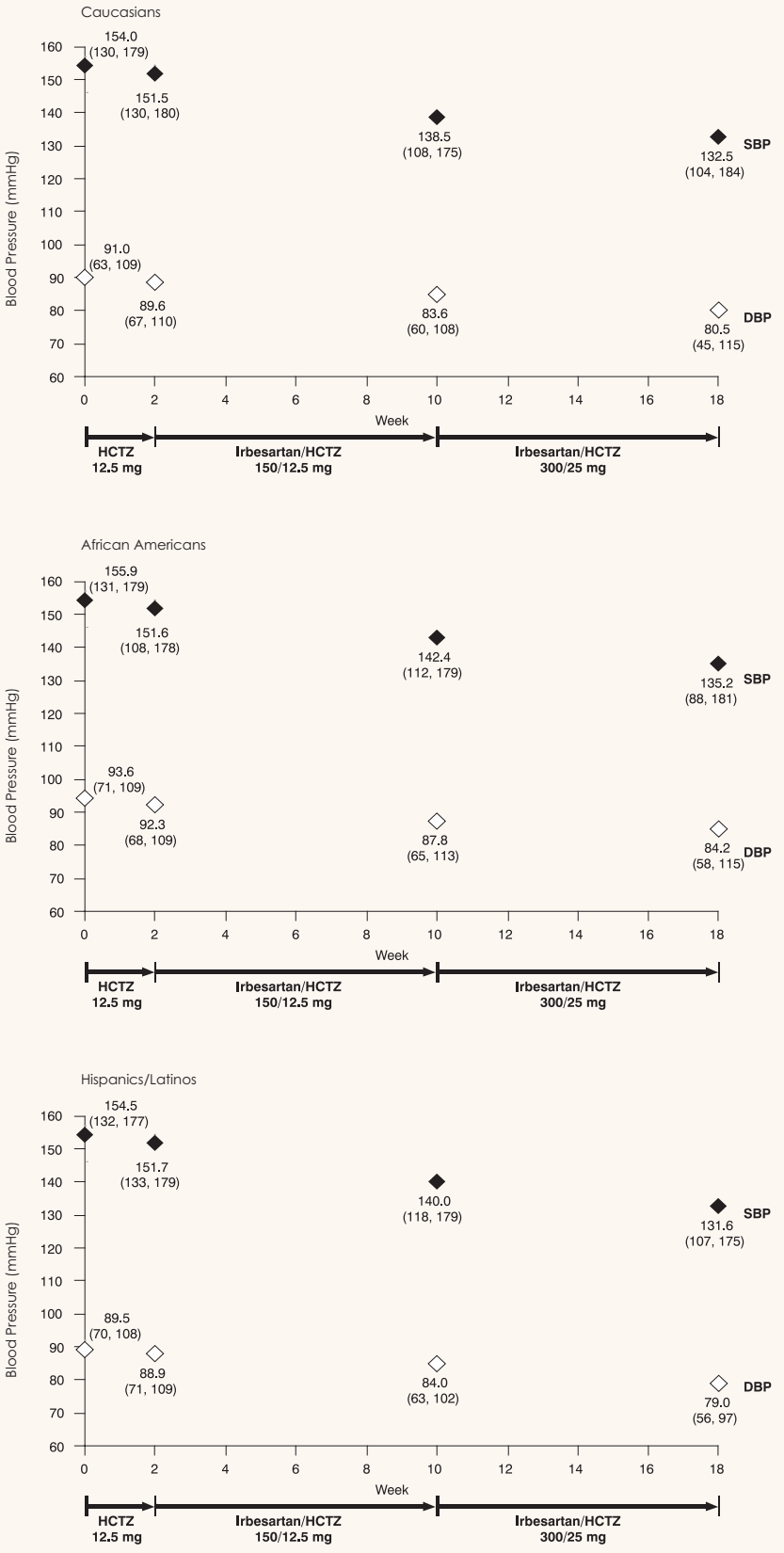
Many patients will need multiple antihypertensive

Table 1. Demographic characteristics of the enrolled study population, by self-identified race/ethnicity

	Caucasians (n=515)	African Americans (n=191)	Hispanics/Latinos (n=119)
Age, mean, years	58.8	53.5	56.7
Women, n (%)	242 (47)	115 (60)	72 (61)
Previous Antihypertensive Monotherapy, n (%)			
ACE inhibitor	175 (34)	50 (26)	54 (45)
ARB	109 (21)	37 (19)	17 (14)
Calcium channel blocker	85 (17)	67 (35)	12 (10)
Beta-blocker	69 (13)	10 (5)	15 (13)
Diuretic	69 (13)	27 (14)	16 (13)
Alpha-blocker	7 (1)	0	3 (3)
Other	4 (<1)	1 (<1)	3 (3)
Type-2 diabetes mellitus, n (%)	153 (30)*	48 (25)†	50 (42)‡
Metabolic syndrome, n (%)	246 (48)*	72 (38)†	64 (54)‡

ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; * Includes 112 patients with both type-2 diabetes mellitus and metabolic syndrome; † Includes 31 patients with both type-2 diabetes mellitus and metabolic syndrome; ‡ Includes 33 patients with both type-2 diabetes mellitus and metabolic syndrome

Figure 1. Systolic blood pressure and diastolic blood pressure levels during the study according to race/ethnicity (intent-to-treat population)



Values are mean (95% confidence intervals); last observation carried forward for week 18 data

agents to achieve target BP. JNC 7 recommends first-line use of two drugs, as separate prescriptions or in fixed combination, for patients whose BP is >20 mmHg above the systolic BP (SBP) goal or >10 mmHg above the diastolic BP (DBP) goal.[5] The Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks (ISHIB) guidelines recommend the initial use of combination therapy for patients whose BP is ≥15/10 mmHg above goal.[11] Several different ARB/hydrochlorothiazide (HCTZ) combinations have been shown to exhibit good antihypertensive efficacy in African Americans.[14-18]

The efficacy and safety of irbesartan/HCTZ combinations have not been evaluated systematically in minority populations.[19-23] Analysis of the results of placebo-controlled trials by racial subgroup showed that irbesartan was effective in reducing BP regardless of race. Although the effect was somewhat less in African Americans, these patients typically showed an improved response with the addition of a low-dose diuretic.[24] The current prespecified subgroup analysis of the IrbesartaN/HCTZ bLood pressUre reductionS In diVErse patient populations (INCLUSIVE)[25] trial evaluated, as a secondary end point, the efficacy and safety of low- and high-dose irbesartan/HCTZ fixed combinations in patients from different racial/ethnic groups, including those of African-American and Hispanic/Latino origin with SBP uncontrolled on monotherapy.

METHODS

Study Design

The INCLUSIVE trial was a multicenter, prospective, open-label, single-arm, four-phase study with titration to SBP response, conducted at 119 sites in the United States between July 2003 and August 2004.[25] The study protocol was approved by the institutional review board/ ethics committee of each participating site. Written informed consent was obtained from each patient before enrollment.

Following screening, patients discontinued previous antihypertensive monotherapy and started sequential treatment with placebo (4–5 weeks), HCTZ 12.5 mg (two weeks, one tablet once daily), irbesartan/HCTZ 150/12.5 mg (eight weeks, one fixed-dose combination tablet once daily) and irbesartan/HCTZ 300/25 mg (eight weeks, two irbesartan/HCTZ 150/12.5 mg fixed-dose combination tablets once daily). The respective daily regimen was administered to the assigned patient at 8 AM (±2 hours), except on the day of a clinic visit, when it was taken after BP measurement.

Entry into each treatment period was dependent upon BP qualification criteria. To enter the placebo, HCTZ 12.5 mg, and irbesartan/HCTZ 150/12.5 mg treatment periods, SBP had to be 140–179 mmHg, or 130–179 mmHg for patients with type-2 diabetes mellitus. Per protocol, patients whose SBP was 120–179 mmHg at week 10 were titrated to irbesartan/HCTZ 300/25 mg; patients whose SBP was below 120 mmHg were discontinued from the study because of preset criteria. A lower SBP limit for this treatment period was set as a safety measure for this titration step. Furthermore, the JNC 7 report suggests that SBP risk starts at 115 mmHg.[5] Patients were seen at weeks 4 and 12 to ensure safety of the change in dose. Diastolic BP had to be 70–109 mmHg for entry into each period. Patients not meeting these criteria at the start of each phase, either because they had achieved their BP goal, or their BP was higher than allowed by the protocol, were withdrawn.

Study Population

The study included men and women ≥18 years of age with hypertension and uncontrolled SBP (140–159 mmHg; 130–159 mmHg for patients with type-2 diabetes mellitus) at screening, i.e., following ≥4 weeks of antihypertensive monotherapy and prior to placebo administration. Fixed-dose HCTZ/triamterene combinations were considered monotherapy. Patients self-identified their racial/ethnic group as Caucasian, African-American, Hispanic or Latino, Asian, American Indian or Native Alaskan, Native Hawaiian or other Pacific Islander, or other. Patients could select more than one category. Efforts were made to recruit ≥100 patients of African-American and of Hispanic/Latino origin. This was achieved by recruitment of some investigators in areas with large African-American and/or Hispanic/Latino populations and by tracking enrollment of these racial/ethnic subgroups.

Patients with severe (SBP ≥180 mmHg or DBP ≥110 mmHg) or secondary hypertension; hypertensive encephalopathy, stroke or transient ischemic attack in the previous year; myocardial infarction,

Table 2. SBP and DBP goal attainment rates at weeks 2, 10 and 18

Intent-to-Treat Population	Caucasians (n=454)	African Americans (n=157)	Hispanics/Latinos (n=110)
*SBP Goal, n (%)**			
Baseline to week 2	10 (2)	11 (7)	0 (0)
Baseline to week 10	265 (58)	82 (52)	54 (49)
Baseline to week 18	360 (79)	113 (72)	83 (75)
95% CI for baseline to week 18	76, 83	65, 79	67, 83
DBP Goal, n (%)†			
Baseline to week 2	174 (38)	47 (30)	41 (37)
Baseline to week 10	331 (73)	103 (66)	75 (68)
Baseline to week 18	382 (84)	122 (78)	91 (83)
95% CI for baseline to week 18	81, 88	71, 84	76, 90
SBP and DBP Goal, n (%)†*			
Baseline to week 2	9 (2)	6 (4)	0 (0)
Baseline to week 10	225 (50)	72 (46)	48 (44)
Baseline to week 18	319 (70)	104 (66)	72 (65)
95% CI for baseline to week 18	66, 74	59, 74	57, 74

CI: confidence interval; DBP: diastolic blood pressure; SBP: systolic blood pressure; * SBP goal: <140 mmHg (<130 mmHg for patients with type-2 diabetes mellitus); † DBP goal: <90 mmHg (<80 mmHg for patients with type-2 diabetes mellitus)

percutaneous coronary intervention, coronary artery bypass graft or unstable angina pectoris in the previous six months; symptomatic resting bradycardia; other significant cardiac, hepatic, renal or gastrointestinal disease; systemic lupus erythematosus; malignancy in the previous five years (except localized skin carcinoma); drug or alcohol abuse in the preceding five years; hypersensitivity to irbesartan, other ARBs, HCTZ or other thiazide diuretics, or with an arm circumference >17 inches were excluded from participation. Also excluded were patients receiving insulin or drugs that might interfere with efficacy or safety evaluations, and women who were pregnant, lactating or of childbearing potential and not using contraception.

Blood Pressure Determination

BP readings were taken at trough (8 AM ±2 hours) with the patient in a seated position following a five-minute period of rest, using a validated (Association for the Advancement of Medical Instrumentation),[26] automatic Omron measurement device (model: HEM 705CP; Omron Healthcare Inc., Illinois). This device had a variance of ±4 mmHg. Blood pressure was determined from the mean of three readings obtained 2 minutes apart and was recorded on the case report form.

Efficacy Evaluations

The primary efficacy parameter was the mean change in SBP from the end of placebo treatment (baseline; week 0) to the end of irbesartan/HCTZ 300/25 mg treatment (week 18). The mean change in DBP from baseline to week 18, and the mean changes in SBP and DBP from baseline to irbesartan/HCTZ 150/12.5 mg treatment end (week 10) were evaluated as secondary efficacy parameters. Mean changes in SBP and DBP from baseline to HCTZ 12.5 mg treatment end (week 2) were also assessed, although these were not predefined end points. Individual SBP and DBP and dual SBP/DBP goal attainment rates were calculated at weeks 2, 10 and 18 using the following definitions:

- SBP goal: <140 mmHg (<130 mmHg for patients with type-2 diabetes mellitus)
- DBP goal: <90 mmHg (<80 mmHg for patients with type-2 diabetes mellitus).

Safety Evaluations

Patients were monitored and questioned from administration of the first dose of placebo until the end of the study regarding signs and symptoms of adverse events, the degree of severity, the date and time of onset, action taken, relationship to study medication, and outcome. Clinical laboratory safety evaluations were conducted on blood and urine samples [chemistry panel (sodium, potassium, glucose, blood urea nitrogen and creatinine), liver function tests (aspartate aminotransferase, alanine aminotransferase and total bilirubin), fasting plasma glucose, hemoglobin A1c serum pregnancy (for women of childbearing potential only), hematology (hemoglobin, hematocrit and complete blood count) and

Table 3. Total adverse events and those occurring in ≥2% of patients during treatment with irbesartan/HCTZ 150/12.5 mg or irbesartan/HCTZ 300/25 mg

	Treatment Period				
Safety Population	**Placebo**	**HCTZ 12.5 mg**	**Irbesartan/HCTZ 150/12.5 mg**	**Irbesartan/HCTZ 300/25 mg**	**Total**
Caucasians					
Safety population, n	605	515	482	424	605
Total with an adverse event, n (%)	153 (25)	90 (17)	139 (29)	109 (26)	343 (57)
Dizziness, n (%)	6 (<1)	5 (1)	11 (2)	13 (3)	35 (6)
African Americans					
Safety population, n	237	191	172	151	237
Total with an adverse event, n (%)	60 (25)	36 (19)	44 (26)	43 (28)	133 (56)
Headache, n (%)	20 (8)	0	2 (1)	5 (3)	26 (11)
Constipation, n (%)	3 (1)	2 (1)	3 (2)	4 (3)	12 (5)
Upper respiratory tract infection, n (%)	3 (1)	1 (<1)	5 (3)	1 (<1)	10 (4)
Pain in extremity, n (%)	0	1 (<1)	4 (2)	0	6 (3)
Hispanics/Latinos					
Safety population, n	138	119	113	103	138
Total with an adverse event, n (%)	24 (17)	14 (12)	25 (22)	22 (21)	66 (48)
Nasopharyngitis, n (%)	3 (2)	1 (<1)	1 (<1)	4 (4)	8 (6)
Dizziness, n (%)	0	0	1 (<1)	3 (3)	3 (2)

routine urinalysis)]. Clinically significant changes in physical examination or laboratory findings were determined by the investigators and recorded on the case report form.

Statistical Analyses

This prespecified subgroup analysis evaluated efficacy and safety parameters in patients enrolled in the INCLUSIVE trial according to racial/ethnic subgroup (self-reported as Caucasian, African-American or Hispanic/Latino). To achieve a 95% confidence interval of width 2.5 mmHg on the primary endpoint for each racial/ethnic subgroup, it was determined that ≥100 patients in each group needed to be enrolled. The estimate of the standard deviation for the change in mean SBP was 12 mmHg. No prespecified statistical power was used to determine the sample size for this study.

Efficacy data were analyzed for the intent-to-treat (ITT) populations, which included patients with one or more recorded SBP measurements after taking at least one dose of irbesartan/HCTZ 150/12.5 mg. The last observation carried forward (i.e., the last BP measurement before discontinuation) was used to calculate efficacy parameters for ITT patients who were controlled or withdrawn from the study before week 18. Safety evaluations were conducted on all patients taking at least one dose of placebo.

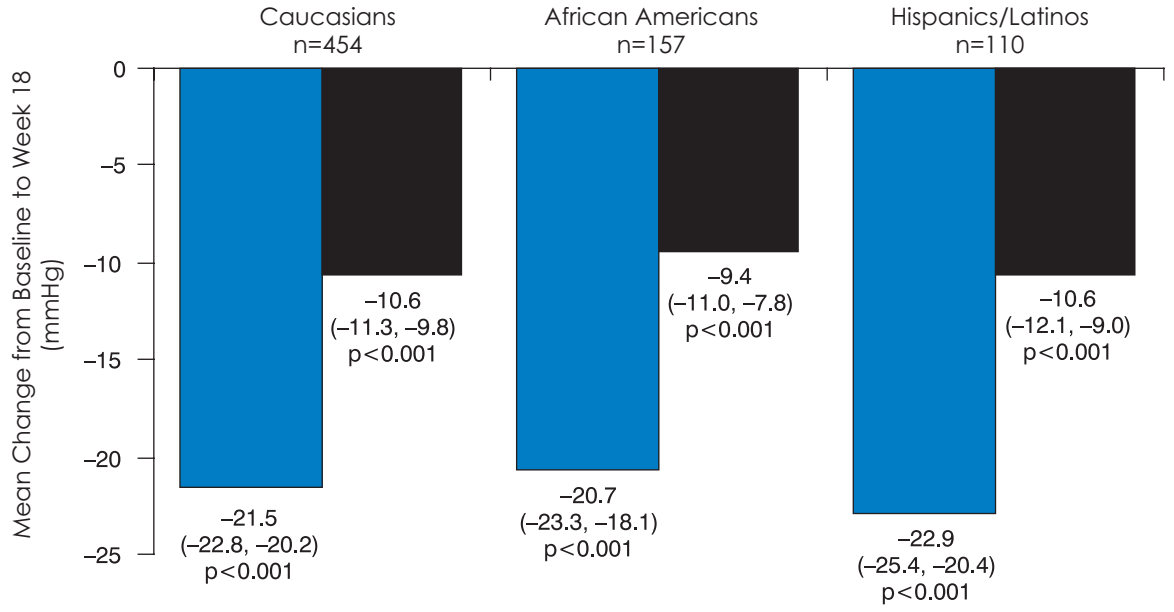
Mean, standard deviation, median, minimum and maximum values were calculated for continuous variables. Approximate 95% confidence (CIs) were calculated for point estimates of mean change scores in continuous variables. Mean changes in BP from baseline were tested using a paired t test for a normally distributed population. If sample data appeared to be selected from a population that was not normally distributed, the Wilcoxon signed rank test was used. Goal attainment rates were expressed as frequency counts and percentages with 95% CIs. Alternative formulae from Fleiss[27] were used to calculate the upper and lower limits of the interval for point estimates <0.1 or >0.9.

RESULTS

Patient Characteristics

Of 1,568 patients initially screened, 1,005 started placebo treatment, and 844 were enrolled into the HCTZ 12.5-mg treatment period. The safety population comprised 605 Caucasians, 237 African Americans and 138 Hispanics/Latinos. The enrolled population included 515 (61.0%) Caucasians, 191 (22.6%) African Americans, 119 (14.1%) Hispanics/Latinos and 21 (2.5%) patients of other race/ethnicity. Two patients self-identified into more than one group. Overall, 374 Caucasian, 135 African-American and 91 Hispanic/Latino patients completed the study. Patients were discontinued from the study if they did not meet BP qualification criteria at the start of the next treatment period; in most cases,

Figure 2. Change from baseline in systolic blood pressure and diastolic blood pressure at the end of irbesartan/HCTZ 300/25 mg treatment according to race/ethnicity (intent-to-treat population)



Values are mean (95% confidence intervals); last observation carried forward for week 18 data

SBP or DBP was below the BP qualification limits. Six percent (39/605) of Caucasian, 4% (9/237) of African-American and 7% (9/138) of Hispanic/Latino patients in the safety population discontinued due to adverse events.

Table 1 shows the baseline demographic characteristics of enrolled patients by racial/ethnic subgroup. Compared with Caucasians, African Americans were younger, with a greater proportion being women, and a greater percentage having received a calcium channel blocker as monotherapy. The Hispanic/Latino subgroup included a higher percentage of women, more had type-2 diabetes mellitus and metabolic syndrome, and a greater percentage had been on ACE inhibitor monotherapy when compared with the Caucasian subgroup. Median baseline SBP was 153.0 mmHg among Caucasians, 156.0 mmHg among African Americans and 154.5 mmHg among Hispanics/Latinos (ITT population). Median baseline DBP was 92.0 mmHg among Caucasians, 95.0 mmHg among African Americans and 90.0 mmHg among Hispanics/Latinos (ITT population).

Mean Changes in SBP and DBP from Baseline

Mean changes in SBP and DBP from baseline to week 2, week 10 and week 18 were calculated separately for the 454 Caucasian patients, 157 African-American patients and 110 Hispanic/Latino patients in the ITT population (Figure 1). Statistically significant ($p<0.001$) and similar mean changes in SBP and DBP from baseline to week 18 were observed in each of the racial/ethnic subgroups (Figure 2). The mean change in SBP from baseline to week 18 was -21.5 ± 13.8 mmHg for Caucasians, -20.7 ± 16.5 mmHg for African Americans and -22.9 ± 13.2 mmHg for Hispanics/Latinos ($p<0.001$ for each subgroup). The mean change in DBP from baseline to week 18 was -10.6 ± 8.2 mmHg for Caucasians, -9.4 ± 10.2 mmHg for African Americans and -10.6 ± 8.1 mmHg for Hispanics/Latinos ($p<0.001$ for each subgroup).

Blood Pressure Goal Attainment

By week 18, 79% (95% CI, 76%, 83%) of Caucasian, 72% (95% CI, 65%, 79%) of African-American and 75% (95% CI, 67%, 83%) of Hispanic/Latino patients attained the SBP goal; 84% (95% CI, 81%, 88%) of Caucasian, 78% (95% CI, 71%, 84%) of African-American and 83% (95% CI, 76%, 90%) of Hispanic/Latino patients attained the DBP goal; and 70% (95% CI, 66%, 74%) of Caucasian, 66% (95% CI, 59%, 74%) of African-American and 65% (95% CI, 57%, 74%) of Hispanic/Latino patients achieved the dual SBP/DBP goal (Table 2).

Safety and Tolerability

All patients taking at least one dose of placebo underwent safety evaluation. Throughout the entire study period, adverse events were experienced by 57% Caucasian, 56% African-American and 48% Hispanic/Latino patients. Table 3 shows the most common adverse events during treatment with irbesartan/HCTZ combination therapy. Most adverse events were of mild or moderate intensity, and of transient duration. One serious adverse event of hypotension was considered "probably" related to therapy.

DISCUSSION

This subgroup analysis of the INCLUSIVE trial demonstrated that a treatment regimen with irbesartan/HCTZ can lead to substantial reductions in BP that allows dual SBP/DBP goal attainment in the majority of Caucasian, African-American and Hispanic/Latino patients with SBP previously uncontrolled by antihypertensive monotherapy. The SBP and DBP reductions observed over the 18-week active treatment period were of a similar magnitude in Caucasians, African Americans and Hispanics/Latinos, and to the overall patient population,[25] suggesting that BP control can be achieved in challenging groups of patients when appropriate therapy is provided. The INCLUSIVE trial adds to the growing evidence base supporting the efficacy and safety of irbesartan/HCTZ combination therapy in a heterogeneous patient population, including those of different races or ethnicities. The findings should give physicians confidence that this drug combination will enable most of their patients with previously uncontrolled SBP to reach goal, irrespective of their race or ethnicity.

Baseline SBP in Hispanic/Latino patients was similar to that of Caucasians and lower than that of African Americans; baseline DBP in Hispanic/Latinos was lower than both Caucasians and African Americans; and Hispanic/Latinos had the greatest reductions in BP. Despite this, the dual SBP/DBP goal attainment rate for Hispanics/Latinos was lower than for Caucasians and African Americans. One explanation for this observation is the higher prevalence of type-2 diabetes mellitus (which required lower BP goals) among the Hispanic/Latino subgroup (42%) compared with the Caucasian (30%) and African-American (25%) subgroups.

All treatments appeared to be well tolerated. Adverse events were in line with the proven tolerability profile of irbesartan when administered in combination with HCTZ and with current drug labeling.[19,20,24] Although a greater proportion of patients in each racial/ethnic group reported an adverse event during treatment with irbesartan/HCTZ 150/12.5 mg than HCTZ 12.5 mg, this may be explained by the longer irbesartan/HCTZ 150/12.5-mg treatment peri-

od (eight weeks) versus HCTZ 12.5 mg (two weeks). There was no increase in adverse events as patients were titrated from low- to high-dose irbesartan/HCTZ, and the percentage of patients reporting an adverse event during treatment with either irbesartan/HCTZ combination was similar to that during treatment with placebo.

The JNC 7 guidelines recommend thiazide diuretics as first-line therapy for all patients with uncomplicated hypertension of all races and ethnicities.[5,8] Clinical trials and practice suggest slightly diminished antihypertensive responses to monotherapy with ACE inhibitors, ARBs and beta-blockers in African Americans compared with Caucasians. However, the efficacy of these agents is similar across all ethnic/racial groups if combined with a diuretic.[5,7,8,11] The filter design of the current study allowed selection of patients with uncontrolled SBP after ≥4 weeks of antihypertensive monotherapy and after two weeks of treatment with HCTZ 12.5 mg, enabling direct evaluation of the add-on effect of irbesartan 150 mg and uptitration to irbesartan/HCTZ 300/25 mg. This study design is consistent with current hypertension management recommendations, including JNC 7, which advocates the initial use of a thiazide diuretic in most patients with hypertension and wider use of combination therapy;[5] it is also consistent with current labeling for the drug.[24]

Combination therapy comprising an ACE inhibitor or ARB will allow patients to benefit from their vasculoprotective properties beyond BP lowering.[28,29] The recent ISHIB consensus document recommends the initial use of antihypertensive combination therapy in African Americans with SBP ≥15 mmHg above goal and/or DBP ≥10 mmHg above goal.[11] Fixed-dose combination therapy providing simplified and effective approaches to BP control should particularly benefit patients at a socioeconomic disadvantage, regardless of ethnicity. Selection of efficacious, well-tolerated, once-daily, fixed-dose combinations, such as irbesartan/HCTZ, expedites BP goal attainment in a broad range of patients in just one or two steps. Use of combination therapy should thus result in fewer office visits for dose titration, treatment-related side effects or laboratory tests, which complicate treatment and increase the cost of therapy.

Angiotensin-receptor blockers are the newest class of antihypertensive agent, and clinical trials have demonstrated their efficacy in African Americans, especially when combined with a diuretic.[14-18] The specific ARB used in the INCLUSIVE trial, irbesartan, has been shown to delay the development and progression of diabetic nephropathy.[30-32] This is particularly pertinent given the relatively high prevalence of type-2 diabetes mellitus among African Americans and Hispanics compared with Caucasians.[33]

The patients enrolled in the INCLUSIVE trial were typical of those seen in usual clinical practice, including substantial numbers of patients from different racial/ethnic minorities. Hispanics/Latinos encompass a heterogeneous mix of people, with origins in Europe, Africa and the American continents. As the fastest growing minority in the United States, they now surpass African Americans as the largest minority in terms of percentage of the U.S. population.[34,35] Consequently, physicians (such as general practitioners, cardiologists, nephrologists and diabetologists), nurse practitioners and physician assistants—who see a wide range of patients with hypertension from various backgrounds—need data demonstrating the efficacy and safety of antihypertensive medications across all races or ethnicities. The subgroup of Hispanic/Latino patients enrolled in the INCLUSIVE trial represents, perhaps, the largest dataset indicating the efficacy and safety of antihypertensive therapy, specifically with irbesartan/HCTZ, in this important and growing population.

Limitations of the INCLUSIVE trial include the short active treatment period (18 weeks in total; eight weeks for each irbesartan/HCTZ dose combination), allowing only short-term efficacy and tolerability evaluation; the lack of a control group; the open study design; and the lack of randomization. Nevertheless, the inclusion of placebo and HCTZ run-in treatment periods, and the use of a validated automatic manometer to measure BP should have minimized potential sources of bias and regression to the mean.

In conclusion, the INCLUSIVE trial demonstrated that clinically compelling BP lowering, as well as BP goal attainment, was achievable in African Americans and Hispanics/Latinos whose SBP was otherwise uncontrolled on monotherapy when following a simple treatment algorithm founded on irbesartan/HCTZ.

APPENDIX

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REFERENCES

1. Fields LE, Burt VL, Cutler JA, et al. The burden of adult hypertension in the United States 1999 to 2000: a rising tide. *Hypertension.* 2004;44:398–404.

2. Wang Y, Wang QJ. The prevalence of prehypertension and hypertension among US adults according to the new Joint National Committee guidelines: new challenges of the old problem. *Arch Intern Med.* 2004;164: 2126–2134.

3. Glover MJ, Greenlund KJ, Ayala C, et al. Racial/ethnic disparities in prevalence, treatment, and control of hypertension–United States, 1999–2002. *MMWR Morb Mortal Wkly Rep.* 2005;54:7–9.

4. He J, Muntner P, Chen J, et al. Factors associated with hypertension control in the general population of the United States. *Arch Intern Med.* 2002;162:1051–1058.

5. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206–1252.

6. Jamerson K, DeQuattro V. The impact of ethnicity on response to antihypertensive therapy. *Am J Med.* 1996;101(3A):22S–32S.

7. Cushman WC, Reda DJ, Perry HM, et al. Regional and racial differences in response to antihypertensive medication use in a randomized controlled trial of men with hypertension in the United States. *Arch Intern Med.* 2000; 160:825–831.

8. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA.* 2002;288:2981–2997.

9. Cooper R, Rotimi C. Hypertension in blacks. *Am J Hypertens.* 1997;10: 804–812.

10. Richardson AD, Piepho RW. Effect of race on hypertension and antihypertensive therapy. *Int J Clin Pharmacol Ther.* 2000;38:75–79.

11. Douglas JG, Bakris GL, Epstein M, et al. Management of high blood pressure in African Americans: consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. *Arch Intern Med.* 2003;163:525–541.

12. Elliott WJ. Higher incidence of discontinuation of angiotensin converting enzyme inhibitors due to cough in black subjects. *Clin Pharmacol Ther.* 1996;60:582–588.

13. Brown NJ, Ray WA, Snowden M, et al. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. *Clin Pharmacol Ther.* 1996;60:8–13.

14. McGill JB, Reilly PA. Combination treatment with telmisartan and hydrochlorothiazide in black patients with mild to moderate hypertension. *Clin Cardiol.* 2001;24:66–72.

15. Flack JM, Saunders E, Gradman A, et al. Antihypertensive efficacy and safety of losartan alone and in combination with hydrochlorothiazide in adult African Americans with mild to moderate hypertension. *Clin Ther.* 2001;23:1193–1208.

16. Association of Black Cardiologists (ABC) Candesartan Study Group. Evaluation of candesartan cilexetil in black patients with systemic hypertension: the ABC Trial. *Heart Dis.* 2000;2:392–399.

17. Levine B. Effect of eprosartan and enalapril in the treatment of black hypertensive patients: subgroup analysis of a 26-week, double-blind, multicentre study. Eprosartan Multinational Study Group. *Curr Med Res Opin.* 1999;15:25–32.

18. Weir MR, Smith DH, Neutel JM, et al. Valsartan alone or with a diuretic or ACE inhibitor as treatment for African American hypertensives: relation to salt intake. *Am J Hypertens.* 2001;14:665–671.

19. Rosenstock J, Rossi L, Lin CS, et al. The effects of irbesartan added to hydrochlorothiazide for the treatment of hypertension in patients nonresponsive to hydrochlorothiazide alone. *J Clin Pharm Ther.* 1998;23: 433–440.

20. Kochar M, Guthrie R, Triscari J, et al. Matrix study of irbesartan with hydrochlorothiazide in mild-to-moderate hypertension. *Am J Hypertens.* 1999;12:797–805.

21. Howe P, Phillips P, Saini R, et al. The antihypertensive efficacy of the combination of irbesartan and hydrochlorothiazide assessed by 24-hour ambulatory blood pressure monitoring. *Clin Exp Hypertens.* 1999;21: 1373–1396.

22. Coca A, Calvo C, Sobrino J, et al. Once-daily fixed-combination irbesartan 300 mg/hydrochlorothiazide 25 mg and circadian blood pressure profile in patients with essential hypertension. *Clin Ther.* 2003;25:2849–2864.

23. Raskin P, Guthrie R, Flack J, et al. The long-term antihypertensive activity and tolerability of irbesartan with hydrochlorothiazide. *J Hum Hypertens.* 1999;13:683–687.

24. Bristol-Myers Squibb Co., Sanofi~Synthelabo. Avalide U.S. prescribing information. www.avalide.com/. Accessed April 2005.

25. Neutel JM, Saunders E, Bakris GL, et al. The efficacy and safety of low- and high-dose fixed combinations of irbesartan/HCTZ in patients with uncontrolled systolic blood pressure on monotherapy: the INCLUSIVE trial. *J Clin Hypertens (Greenwich).* 2005;7:578–586.

26. O'Brien E, Mee F, Atkins N, et al. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP5332, and Nissei DS-175. *Blood Press Monit.* 1996;1:55–61.

27. Fleiss JL. *Statistical Methods for Rates and Proportions*. 2nd ed. New York: John Wiley & Sons; 1981.

28. Toto RD, Rinner S, Ram CV. ACE inhibitors and target organ protection. An expanded role for these antihypertensive agents? *Postgrad Med.* 2004;116:11–16, 19–22, 48.

29. Silverstein RL, Fenves AZ, Ram CVS. ARBs and target organ protection. Exploring benefits beyond their antihypertensive effects. *Postgrad Med.* 2004;116:31–41.

30. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345:851–860.

31. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med.* 2001;345:870–878.

32. Sasso FC, Carbonara O, Persico M, et al. Irbesartan reduces the albumin excretion rate in microalbuminuric type 2 diabetic patients independently of hypertension: a randomized double-blind placebo-controlled crossover study. *Diabetes Care.* 2002;25:1909–1913.

33. American Heart Association. *Heart Disease and Stroke Statistics—2005 Update*. Dallas, TX: American Heart Association; 2005.

34. Population Division U.S Census Bureau. Table 6: Annual Estimates of the Components of Population Change by Race and Hispanic or Latino Origin for the United States: July 1, 2002 to July 1, 2003 (NC-EST2003-06). Release Date: June 14, 2004.

35. Population Division U.S Census Bureau. Table 3: Annual Estimates of the Population by Sex, Race and Hispanic or Latino Origin for the United States: April 1, 2000 to July 1, 2003 (NC-EST2003-03). Release Date: June 14, 2004. ■