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Antihypertensive Efficacy of Zofenopril Plus Hydrochlorothiazide Fixed Combination for Treatment in Metabolic Syndrome

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ABSTRACT

This study was undertaken to compare the antihypertensive efficacy of zofenopril 30 mg + hydrochlorothiazide 12.5 mg fixed combination versus zofenopril alone in patients with essential hypertension with and without the metabolic syndrome, according to National Cholesterol Education Program–Adult Treatment Panel III criteria. After a 4-wk placebo washout period, 463 patients with mild to moderate essential hypertension (diastolic blood pressure [DBP] 95–115 mm Hg) aged 18 to 75 y were randomly assigned 2:1:1 to treatment with zofenopril+ hydrochlorothiazide, zofenopril, or hydrochlorothiazide for 12 wk in an international, multicenter, double-blind, parallel-group study. DBP and systolic blood pressure changes with treatment were calculated. The first 12 wk of treatment were followed by a 24-wk open-label period during which only safety was assessed. Reported here is a subanalysis of the main study results, performed in patients with and without metabolic syndrome, limited to a zofenopril+hydrochlorothiazide versus zofenopril comparison. The antihypertensive effect of zofenopril+hydrochlorothiazide or zofenopril was similar in patients with (77%) and without metabolic syndrome. In patients with and without metabolic syndrome, however, DBP and systolic blood pressure reductions were significantly greater with zofenopril+hydrochlorothiazide (with metabolic syndrome: 14±8/21±14 mm Hg; without metabolic syndrome: 15±7/23±14 mm Hg) than with zofenopril alone (with metabolic syndrome: 10±9/11±15; without metabolic

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syndrome: 12±10/14±18 mm Hg). The safety of the 2 treatments was similar in patients with and without metabolic syndrome. The fixed combination of zofenopril+hydrochlorothiazide improved the efficacy of zofenopril alone. This effect was particularly evident in patients with metabolic syndrome, in whom blood pressure control is more difficult to achieve and who are at greater risk for cardiovascular events.

Keywords: essential hypertension; metabolic syndrome; zofenopril; hydrochlorothiazide

INTRODUCTION

The metabolic syndrome is characterized by the presence of various cardiovascular risk factors, such as abdominal obesity, atherogenic dyslipidemia, insulin resistance or glucose intolerance, and hypertension.[1] Patients in whom this condition is diagnosed have a 2- to 3-fold higher risk of fatal and nonfatal cardiovascular events compared with healthy people. This risk is increased 5-fold when diabetes mellitus is also present.[2-6] The most common determinant of the metabolic syndrome in nondiabetic subjects is arterial hypertension, followed by dyslipidemia, impaired fasting glycemia, and obesity.[5,7] In these patients, optimal treatment for hypertension should not worsen the patient's metabolic profile and may even improve it.

Zofenopril calcium, a prodrug of the active compound zofenoprilat, is an angiotensin-converting enzyme (ACE) inhibitor that has been successfully and safely used in the treatment of acute myocardial infarction,[8-10] heart failure,[11,12] and essential hypertension.[13-16] In patients with essential hypertension, zofenopril has been shown to be as effective as atenolol,[13] hydrochlorothiazide,[14,17] lisinopril,[15] and candesartan.[16] Its effectiveness and tolerability when used in combination with a diuretic have also been proved[17]; however, no data are available on the efficacy of this drug as monotherapy or when given in combination with a diuretic to high-risk hypertensive subjects with the metabolic syndrome. The present study was designed and conducted to fill this data gap.

SUBJECTS AND METHODS

Study Population

The present study included 463 outpatients of either sex, who had mild to moderate essential hypertension. The main inclusion criteria consisted of age between 18 and 75 y and an office sitting diastolic blood pressure (DBP) between 95 and 115 mm Hg, along with an office sitting systolic blood pressure (SBP) ≤240 mm Hg, after 4 wk of placebo washout from previous antihypertensive treatment. Subjects were excluded if they exhibited (1) a difference >10 mm Hg in office sitting DBP between the screening and randomization visits; (2) secondary or malignant hypertension; (3) clinically significant heart disease (ie, cardiac valvular disease, heart failure, unstable angina, myocardial infarction in the previous 6 mo); (4) cerebrovascular disease; (5) renal insufficiency (serum creatinine >1.8 mg/dL); (6) known or suspected renovascular disease; (7) uncontrolled type 1 or type 2 diabetes mellitus; (8) history of malignancy during the previous 5 y; (9) severe hepatic impairment; (10) history of alcohol or drug

abuse; or (11) known hypersensitivity to ACE inhibitors or thiazide diuretics. Pregnant women and breastfeeding mothers or women with childbearing potential but not practicing an effective method of birth control were also excluded.

Written informed consent was obtained from all subjects prior to their inclusion in the study. The study was approved by the Ethics Committees of the centers involved.

Study Design

This was an international (France, United Kingdom, The Netherlands, Belgium, and Poland), multicenter (58 centers), randomized, double-blind, parallel-group study that consisted of a 4-wk placebo washout period, during which previous antihypertensive treatment had to be withdrawn, followed by 12 wk of 2:1:1 randomized treatment with zofenopril 30 mg plus hydrochlorothiazide 12.5 mg, zofenopril 30 mg, or hydrochlorothiazide 12.5 mg. Treatment was administered once daily between 9 and 11 AM. The initial 12 wk of treatment was considered the efficacy portion of the study and was followed by a 24-wk period during which only safety was assessed.

At the screening visit, the patient's medical history and informed consent were obtained, and a complete physical examination and a 12-lead electrocardiogram (ECG) were performed. The ECG was assessed again at randomization and at 12 and 36 wk of treatment. Hematology, biochemistry, and urinalysis were performed at screening, at randomization, and after 12 and 36 wk of treatment. After 4 wk of treatment, a reduced laboratory assessment that included urea, creatinine, and electrolytes was carried out. Subjects were seen at 4, 8, 12, 24, and 36 wk after randomization. During these visits and at screening and at randomization, BP, heart rate (HR), and adverse events (AEs) were assessed.

BP and HR Measurement

BP was measured in the clinic by a standard sphygmomanometer 24 h after the last drug intake. Three measurements, taken at 2-min intervals after 10 min of rest in a sitting position, were averaged and used as the office BP reference value during the first 12 wk of the study. During the long-term (24 wk) safety part of the study, only a single BP reading was obtained at each visit. Systolic and diastolic values were taken at the reading of the first and fifth Korotkoff sounds, respectively. HR was measured by palpation of the radial artery pulse.

Data Analysis

The present study is a post-hoc analysis of data from an efficacy and safety trial that was conducted in subjects with or without the metabolic syndrome.[18] Subjects were classified as having or not having metabolic syndrome according to modified National Cholesterol Education Program–Adult Treatment Panel (NCEP-ATP) III criteria.[19] The metabolic syndrome was diagnosed if at least 3 of these risk factors were present: (1) body mass index ≥25 kg/m^2 (obesity or overweight); (2) triglycerides ≥150 mg/dL or on drug treatment; (3) high-density lipoprotein (HDL) cholesterol <40 mg/dL in men or <50 mg/dL in women, or on drug treatment; (4) elevated BP (SBP ≥130 mm Hg or DBP ≥85 mm Hg); or (5) fasting glucose ≥100 mg/dL or on drug treatment. For comparison of the effects of monotherapy with zofenopril versus those of the combination treatment, the analysis was limited to 350 subjects who were

randomly assigned to zofenopril 30 mg plus hydrochlorothiazide 12.5 mg or to zofenopril 30 mg alone and was performed on subjects who adhered to the study protocol, that is, all randomly assigned subjects who completed the 12-wk study period without major protocol violations.

At the end of 12 wk of treatment, office sitting SBP and DBP changes were computed. Safety analysis was performed by calculating the incidence of adverse events (AEs) during the study (from randomization to week 36). Comparisons between the 2 treatment groups were made separately for subjects with and without the metabolic syndrome.

BP changes from baseline were compared through analysis of variance. Rates of responders or normalized patients were evaluated with the use of Fisher's exact test. No inferential statistical process was applied to safety data. $P<.05$ was considered to be statistically significant. Data are shown as means±SD.

RESULTS

Demographic and Clinical Data

A total of 350 subjects were randomly assigned to zofenopril 30 mg plus hydrochlorothiazide 12.5 mg (n=235) or zofenopril 30 mg alone (n=115). Of these subjects, 256 completed the 12-wk randomized phase without protocol violation and were thus included in the per-protocol analysis. A total of 198 (77.3%) subjects had metabolic syndrome, with a similar prevalence in the group randomly assigned to zofenopril alone (77.5%) or its combination with the diuretic (77.2%). In addition to hypertension, overweight or obesity was the most common risk factor for metabolic syndrome (91.4% of subjects), followed by low HDL cholesterol (88.3%), elevated fasting glucose (61.6%), and elevated triglycerides (29.4%). No difference in the distribution of these risk factors was found between the 2 randomization groups (Table 1).

Baseline demographics and clinical data were comparable between treatment groups and for subjects with and without the metabolic syndrome, with the exception of components of the metabolic syndrome (Table 2).

Table 1. Absolute and Relative Frequency (%) of Various Components of Metabolic Syndrome in Study Patients

	Zofenopril (n=69) n (%)	Zofenopril + Hydrochlorothiazide (n=129) n (%)
Hypertension	68 (100)	129 (100)
Overweight or obesity	60 (87)	121 (94)
Reduced HDL cholesterol or drug treatment	59 (87)	114 (89)
Elevated fasting glucose or drug treatment	37 (60)	72 (63)
Elevated triglycerides or drug treatment	25 (37)	33 (26)

Table 2. Baseline Demographic and Clinical Characteristics of Study Patients

	Patients With Metabolic Syndrome		Patients Without Metabolic Syndrome	
	Zofenopril (n=69)	Zofenopril + Hydrochloro-thiazide (n=129)	Zofenopril (n=20)	Zofenopril + Hydrochloro-thiazide (n=38)
Age, y, mean±SD	54±10	52±11	53±13	49±15
Males, n (%)	39 (57)	77 (60)	11 (55)	23 (60)
BMI, kg/m^2, mean±SD	28±4	30±4	24±2	24±3
Serum triglycerides, mg/dL, mean±SD	98±84	105±137	61±31	66±51
Serum HDL cholesterol, mg/dL, mean±SD	32±13	30±11	36±16	39±17
Blood glucose, mg/dL, mean±SD	115±38	110±28	91±6	89±8
DBP, mm Hg, mean±SD	101±5	101±4	101±3	100±4
SBP, mm Hg, mean±SD	157±13	161±15	158±13	159±12
HR, bpm, mean±SD	73±10	74±9	73±10	74±10

Office BP Changes

Zofenopril 30 mg plus hydrochlorothiazide 12.5 mg reduced office sitting DBP and SBP in the whole per-protocol population by 14.6±8.1 and 21.1±13.8 mm Hg; zofenopril 30 mg reduced DBP and SBP by 10.4±9.0 and 11.6±15.8 mm Hg, respectively (P<.01 vs combination treatment).

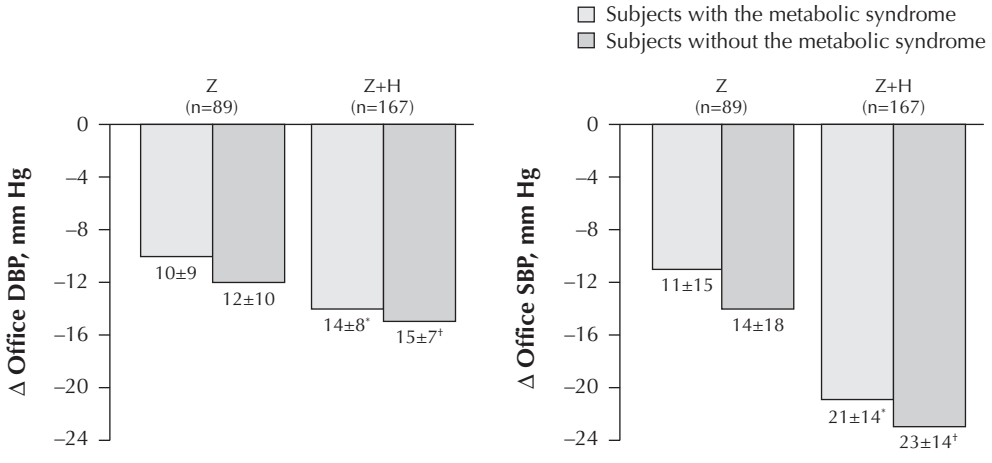
With the zofenopril plus hydrochlorothiazide fixed combination, BP reductions were similar in subjects with or without the metabolic syndrome but were greater than those observed with zofenopril 30 mg alone (Fig 1). The difference between single-drug treatment and combination therapy was statistically significant for subjects with (4.4 mm Hg for DBP and 9.8 mm Hg for SBP; P<.01) or without (3.5 mm Hg for DBP and 8.5 mm Hg for SBP; P<.05) metabolic syndrome.

As shown in Figure 2, the greater efficacy of zofenopril plus hydrochlorothiazide was particularly evident for office SBP and for subjects at greater cardiovascular risk (ie, with a greater number of risk factors for metabolic syndrome).

Safety

A total of 163 (63.7%) patients reported AEs, with similar rates observed in the groups with and without metabolic syndrome (64.1% vs 62.1%). The overall number of AEs was 526, and most (62.2%) were of mild intensity. AEs caused withdrawal from treatment of 9 patients (3.5%). Of these patients, only 2 with metabolic syndrome (1.6%) and only 1 (2.6%) without metabolic syndrome received combination treatment (Table 3).

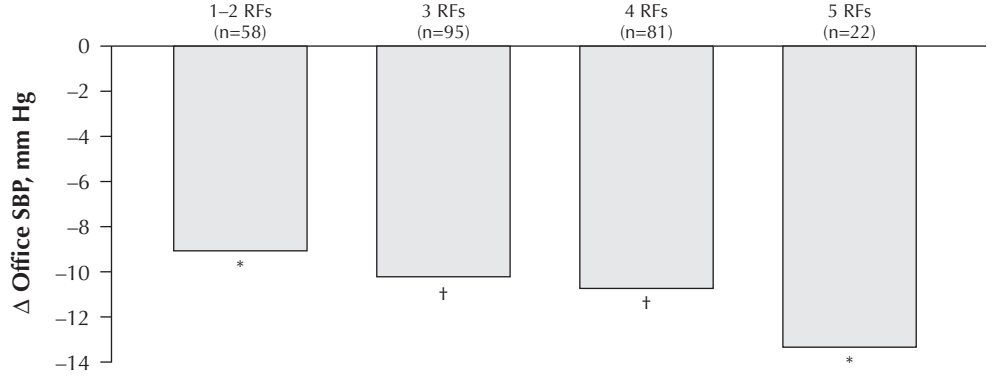
Fig 1. Average office sitting DBP and SBP reductions (Δ) after 12 wk of treatment with zofenopril 30 mg (Z) or zofenopril 30 mg plus hydrochlorothiazide 12.5 mg (Z+H).



Mean values±SD are reported at the bottom of each bar. The *P* values refer to the statistical significance of between-treatment differences.

*$P<.01$; †$P<.05$.

Fig 2. Average office sitting SBP reductions (Δ) after treatment with zofenopril 30 mg plus hydrochlorothiazide 12.5 mg as compared with zofenopril 30 mg, according to the number of risk factors for metabolic syndrome.



The *P* values refer to the statistical significance of between-treatment differences.

*$P<.05$; †$P<.01$.

A total of 87 AEs were attributed to study treatment (16.5% of total events); these occurred in 47 patients (28.8% of patients with AEs), and a similar distribution was noted in patients with (19.2%) and without (15.5%) metabolic syndrome. The number of patients with drug-related AEs was slightly higher with combination treatment (Table 3).

During 36 wk of open-label treatment, cough occurred in only 2 patients on combination therapy—1 with (0.8%) and 1 without (2.6%) metabolic syndrome. With combination treatment, hyperlipidemia occurred in 3 patients (2.3%), hyperglycemia in 2 patients (1.6%), and hyperuricemia in 1 patient (0.8%) with metabolic syndrome; 1 patient (2.6%) without metabolic syndrome reported hyperlipidemia.

Table 3. Number and Frequency (%) of Drug-Related AEs Among Study Patients

	Patients With Metabolic Syndrome		Patients Without Metabolic Syndrome	
	Zofenopril (n=69)	Zofenopril + Hydrochlorothiazide (n=129)	Zofenopril (n=20)	Zofenopril + Hydrochlorothiazide (n=38)
Body as a whole	4 (5.8)	10 (7.8)	1 (5.0)	1 (2.6)
Cardiovascular system	–	3 (2.3)	1 (5.0)	1 (2.6)
Digestive system	–	6 (4.7)	–	2 (5.3)
Metabolic and nutritional system	1 (1.4)	8 (6.2)	1 (5.0)	2 (5.3)
Nervous system	–	6 (4.7)	–	–
Respiratory system	4 (5.8)	1 (0.8)	–	1 (2.6)
Skin and appendages	–	2 (1.6)	–	1 (2.6)
Special senses	–	–	1 (5.0)	–
Urogenital system	2 (2.9)	2 (1.6)	–	–
Patients with AEs	9 (13.0)	29 (22.5)	2 (10.0)	7 (18.4)
Patients withdrawn because of AEs	3 (4)	2 (2)	3 (15)	1 (3)

DISCUSSION

In this study, the BP reduction achieved after 12 wk of treatment with zofenopril alone or as a fixed combination with a low-dose diuretic was consistent not only in patients at relatively low risk, that is, those not responding to the criteria for metabolic syndrome, but also in high-risk patients with this condition. The antihypertensive effect of the drug combination was greater than that of monotherapy in patients with and without metabolic syndrome.

To the knowledge of the investigators, this is one of the first studies to show the antihypertensive efficacy of an ACE inhibitor, given alone or in combination

with a low-dose diuretic, in patients with metabolic syndrome. Such an effect may be expected because metabolic syndrome may be associated with an overexpression of vascular angiotensin II–AT1 receptors and excessive activation of the renin-angiotensin system,[20,21] which may act as a good substrate for optimal ACE inhibition. Efficacy results of the present study confirm the hypothesis that ACE inhibitors may play a key role in patients with hypertension and metabolic syndrome.[22,23]

The use of an ACE inhibitor for controlling BP and for preventing or improving single metabolic abnormalities possibly associated with hypertension has been demonstrated over the past few years in animal models and in humans.[24] For instance, a recent meta-analysis of 12 randomized controlled clinical trials showed a reduction of 27% in the incidence of newly diagnosed diabetes with this therapeutic class.[25] ACE inhibitors have been found to be useful for the treatment of hypertension associated with obesity[26] or dyslipidemia.[27] According to these findings, the metabolic profile of study patients represented an ideal indication for treatment with ACE inhibitors, in that the prevalence of metabolic risk factors was high; 91% of subjects were obese or overweight, 62% had impaired fasting glucose or diabetes, and more than 80% displayed atherogenic dyslipidemia.

The efficacy of treatment with zofenopril alone or combined with a diuretic in study patients with metabolic syndrome but with no overt cardiovascular disease adds to previous evidence in high-risk patients with acute myocardial infarction and diabetes, which showed that early ACE inhibition reduced the incidence of death and severe congestive heart failure.[10]

Another interesting result of the present study is that the fixed combination was more effective than monotherapy even in the treatment of patients at highest risk, that is, those with 4 or more metabolic risk factors in addition to hypertension (40% of the overall sample of subjects). This finding is clinically relevant in that (1) these patients usually show a particular resistance to antihypertensive treatment, often requiring more than 1 drug for adequate BP control,[28] and (2) their chance of cardiovascular disease mortality is 2-fold higher than that of patients with fewer or no metabolic abnormalities.[5]

The safety profile of the study medications was good. A total of 17% of patients experienced drug-related AEs. Although the study size was limited, in most cases, the types of AEs reported were typical of the class of drug employed, with few cases of cough and of increased plasma lipids, glucose, or uric acid. No differences in the prevalence of drug-related AEs and in the frequency of patients who stopped treatment for AEs were observed between patients with and without metabolic syndrome; thus, treatment proved safe in patients with metabolic abnormalities.

Unfortunately, this study had at least 2 limitations. First, the study is based on a post-hoc analysis of a main trial and might be underpowered to demonstrate the study goal; however, when only patients with metabolic syndrome were considered, their rate was high compared with the original per-protocol population (77%). Second, the investigators were unable to evaluate abdominal obesity because no waist circumference measurements were taken, as requested by NCEP-ATP III Guidelines.[19] Thus, the investigators computed body mass index, which is a measure of total adiposity whose increment is strongly associated with cardiovascular outcomes, but which plays a secondary role behind abdominal adiposity.[29,30]

In conclusion, the fixed combination of zofenopril 30 mg plus hydrochlorothiazide 12.5 mg resulted in improved efficacy compared with zofenopril 30 mg alone. This effect was particularly evident in patients with metabolic syndrome, in whom BP control is more difficult to achieve and who are at greater risk for cardiovascular events.

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