REVIEW

Cardiovascular Therapeutics

Zofenopril Plus Hydrochlorothiazide Fixed Combination in the Treatment of Hypertension and Associated Clinical Conditions

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Zofenopril, is a highly lipophilic ACE inhibitor, characterized by long-lasting tissue penetration and sustained cardiac ACE inhibition, indicated for the treatment of hypertension and myocardial infarction. Comparative studies with different antihypertensive drug classes have demonstrated the good efficacy and tolerability of this compound in the management of the patient with mild–moderate hypertension. Zofenopril may also be combined with hydrochlorothiazide, a combination which has proved to be effective and safe as compared with monotherapy with either agent in three studies, including more than 600 patients. In addition, recent *post hoc* analyses in high-risk patients, such as those with the metabolic syndrome, impaired fasting glucose or diabetes, atherogenic dyslipidemia, and impaired renal function, have confirmed the superiority of zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily combination as compared with zofenopril monotherapy also in these high-risk populations of patients with hypertension. These data suggest the usefulness of this fixed combination in the treatment of patients with hypertension requiring more prompt, intensive, and sustained blood pressure reduction, according to guidelines recommendation.

Introduction

Several observational prospective studies have shown that blood pressure levels are strongly and directly related to the relative risks of stroke and heart disease. A meta-analysis of nine major prospective observational studies, involving a total of 420,000 individuals, performed in the 1990 showed that prolonged differences in usual diastolic blood pressure of 5, 7.5, and 10 mmHg are associated with at least 34%, 46%, and 56% reduction in stroke and at least 21%, 29%, and 37% reduction in coronary heart disease, respectively [1]. In another meta-analysis of 14 randomized trials, including 37,000 individuals treated mainly with diuretics or beta-blockers, risk of stroke was reduced by 42%, that of coronary heart disease by 14%, and that of cardiovascular mortality by 21% over a follow-up period of 5 years [2]. More recently, the importance of an effective and sustained blood pressure reduction for the prevention of cardiovascular events has been demonstrated also for new drugs, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, and calcium antagonists, this being the case for young or older subjects and for subjects at higher risk for cardiovascular disease [3,4].

However, large intervention trials have also shown that, on average, 60% of patients with hypertension may need a combination treatment to achieve a satisfactory blood pressure control and an effective cardiovascular prevention. This is particularly true for patients at high risk for cardiovascular events, such as older subjects, patients with metabolic syndrome or atherogenic dyslipidemia, diabetes, cardiovascular diseases, or other associated clinical conditions (Table 1) [5–15]. In the Hypertension Optimal Treatment (HOT) study a total of 85% of patients achieved a diastolic blood pressure $\leq$90 mmHg, but only approximately one-third of patients remained

Table 1 Frequency of use of combination therapy (two or more drugs concurrently) in major hypertension trials

Study	Year	n	Characteristics of the hypertensive population	Active treatment	Proportion undergoing combination therapy (%)
SYSTEUR [5]	1997	4695	Isolated systolic hypertension and age ≥60 years old	Nitrendipine (+enalapril, hydrochlorothiazide)	59
HOT [6]	1998	18,790	Age 50–80 years old	Felodipine (+ACE inhibitor, beta-blocker, diuretic)	68
UKPDS [7]	1998	1148	Type 2 diabetes and age 25–65 years old	Captopril or atenolol	70
INSIGHT [8]	2000	6321	Age 55–80 years old and one additional risk factor	Nifedipine or diuretic	30
NORDIL [9]	2000	10,881	Age 50–69 years old	Diltiazem or diuretic and beta-blocker	85
ALLHAT [10]	2002	33,357	Age ≥55 years old and at least one other cardiovascular risk factor	Chlortalidone, amlodipine or lisinopril	41
LIFE [11]	2002	9193	Age 55–80 years old and left ventricular hypertrophy	Losartan or atenolol	64
ANBP-2 [12]	2003	6083	Age 65–84 years old	Enalapril or diuretic	34
CONVINCE [13]	2003	16,476	Age ≥55 years old and at least one other cardiovascular risk factor	Verapamil, atenolol or hydrochlorothiazide	80
VALUE [14]	2004	15,245	Age ≥50 years old with a combination of cardiovascular risk factors and cardiovascular disease	Valsartan or amlodipine	59
HYVET [15]	2008	3845	Isolated systolic hypertension and age ≥80 years old	Indapamide (+perindopril)	73

on monotherapy; of interest, approximately 30% of patients had well-controlled blood pressure when treated with a low-dose combination of two agents [6]. The risk of fatal and nonfatal macrovascular and microvascular complications in the 1148 patients with type 2 diabetes mellitus and high blood pressure of the UK Prospective Diabetes Study (UKPDS) was significantly reduced after 8.4 years of follow-up, with two-thirds of patients being under combination treatment [7]. In the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) study, 33,357 patients with hypertension and at least one other cardiovascular risk factor were treated for 4.9 years with chlorthalidone, amlodipine, or lisinopril, and approximately 40% were under combination treatment at the end of the study [10]. In the Controlled ONset Verapamil INvestigation of Cardiovascular End points (CONVINCE) trial, enrolling 16,602 patients with hypertension and one or more additional risk factor for cardiovascular disease, randomized to verapamil, atenolol, or hydrochlorothiazide, after a median follow-up of 3 years, 80% of patients were taking combination treatment [13]. Almost all patients with hypertension at high risk of cardiovascular events enrolled in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study were under treatment with two or more antihypertensive drugs at study end (including randomized treatment with valsartan or amlodipine) [14]. Finally, in the more recent HYpertension in the Very Elderly Trial (HYVET), which assessed treatment efficacy in very old subjects (age ≥ 80 years old) with isolated systolic hypertension, combination treatment in the group randomized to indapamide was taken by 73% of patients at the end of the 1.8 years of follow-up [15].

Thus, in major intervention trials, combination treatment with two or more agents from different antihypertensive drug classes, selected on a rational basis, typically resulted in a high response rate and may represent an appropriate alternative to increasing dosage of drugs given as monotherapy, an approach which is often associated with a disproportionate increase in the risk of adverse events. On the basis of this evidence, guidelines for the management of hypertension now acknowledge and recommend combination treatment, particularly when blood pressure control with initial monotherapy treatment is inadequate. Beginning pharmacologic management of high blood pressure with combination treatment is often advised for patients with Grade 2 or moderate hypertension (systolic blood pressure 160–179 mmHg and/or diastolic blood pressure 100–109 mmHg) or in patients with Grade 1 or mild hypertension (systolic blood

pressure 140–149 mmHg and/or diastolic blood pressure 90–99 mmHg) with diabetes mellitus, coronary disease, or other associated clinical conditions, increasing their cardiovascular risk [16,17].

Fixed Combination Treatment of an ACE Inhibitor and a Diuretic

Various combination therapies, for example those between a beta-blocker and a diuretic, a calcium antagonist and a beta-blocker, a calcium antagonist and an angiotensin II antagonist, or an ACE inhibitor [18,19] have proved to be effective and safe. However, that between an ACE inhibitor and a diuretic offers several advantages as respect to others, with response rates >80% being observed in patients with mild–moderate hypertension treated with such combination [20]. The two drugs have a synergistic, contrasting effect on the renin–angiotensin–aldosterone system. Stimulation of this system, as a result of diuretic-induced low sodium levels, increases the antihypertensive activity of ACE inhibitors, and ACE inhibitors block the production of angiotensin II, which may reduce the antihypertensive activity of diuretics [20]. Furthermore, the ACE inhibitor counteracts the diuretic-induced reactive hyper-reninemia, which would increase blood pressure, allowing maximum benefit from sodium depletion. Conditions are therefore created for the ACE inhibitor to function with its maximum antihypertensive effect, and the efficacy of the diuretic does not diminish over time. Because of this synergy, the dosages of each agent needed to achieve adequate blood pressure control with such a combination are less than those required in monotherapy. This may improve tolerability of single drug components. In particular, the use of a low dose diuretic (e.g., hydrochlorothiazide 12.5 or 25 mg) reduces the probability of adverse metabolic effects often associated with the use of high-dose diuretic (e.g., hydrochlorothiazide 50 mg) treatment. The loss of potassium and bicarbonate induced by the diuretic is effectively reversed by the ACE inhibitor, due to its activity on the renin–angiotensin system [20].

Several studies have demonstrated that the combination of an ACE inhibitor and a diuretic is effective not only for lowering blood pressure [21] but also for preventing target organ damage, in particular in the heart and kidney [22]. Additionally, in clinical trials of patients with hypertension and diabetes, an ACE inhibitor in combination with a diuretic plays a role in retarding the progression of renal failure in diabetic and in other types of nephropathy [23,24].

Zofenopril Plus Hydrochlorothiazide Combination in Patients with Essential Hypertension

Zofenopril calcium, a prodrug of the active compound zofenoprilat, is a highly lipophilic ACE inhibitor, characterized by long-lasting tissue penetration and sustained cardiac ACE inhibition [25]. This characteristic confers this drug ancillary antioxidant and cardioprotective properties, including the ability to improve endothelial function in animals and humans, making it a potentially useful tool for the treatment of both hypertension and myocardial infarction [26–28]. Zofenopril has been successfully and safely used in the treatment of acute myocardial infarction [29–31], heart failure [32,33], and essential hypertension [34–40]. In six double blind, placebo-controlled, dose-ranging studies carried out in approximately 1600 patients with mild–moderate essential hypertension, 6–8 weeks of double blind treatment with zofenopril at doses of 30 or 60 mg once-daily were associated with a significantly greater blood pressure reduction than that observed under placebo [41].

In 12 randomized, double blind, active controlled, comparative studies carried out in approximately 3200 patients with mild–moderate essential hypertension (diastolic blood pressure ranging between 90 and 114 mmHg), zofenopril showed an antihypertensive efficacy similar to that of atenolol [34], amlodipine [35], hydrochlorothiazide [36], enalapril [37], lisinopril [38], losartan [39], and candesartan [40]. Pooled blood pressure reduction results of these comparative studies are summarized in Figure 1 [34–40].

The lipophilicity of zofenopril may confer favorable pharmacokinetic characteristics when the agent is administered in conjunction with hydrochlorothiazide, as shown in animal models. In a study carried out in rats with myocardial infarction, co-administration of zofenopril and hydrochlorothiazide produced a significant increase ($P < 0.05$) in zofenopril concentrations in tissue (kidney and heart) but not in plasma, while hydrochlorothiazide increased the concentration of the hydrophilic lisinopril in plasma but not tissue [42]. Furthermore, as shown in rats with induced renal injury, zofenopril in combination with hydrochlorothiazide maintains its peculiar organ-protective properties [43]. Studies are needed to demonstrate organ protection of zofenopril in humans, though partial evidence on its cardioprotective and antioxidant activity is available [26–28].

The fixed dose combination of zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily is approved in several European countries for the management of mild–moderate hypertension, for patients whose blood pressure is not adequately controlled on zofenopril or

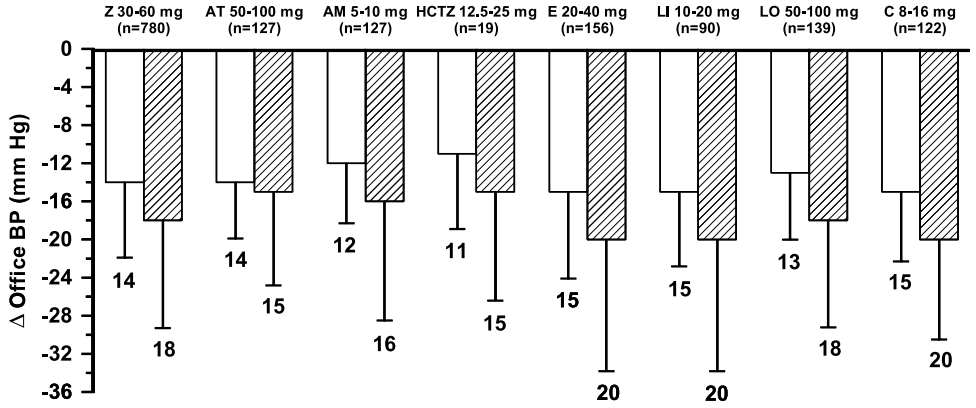

Figure 1 Pooled diastolic (open bars) and systolic (striped bars) blood pressure (BP) reduction (Δ) ±SD after 12 weeks of treatment with zofenopril (Z) 30–60 mg versus atenolol (AT), amlodipine (AM), hydrochlorothiazide (HCTZ), enalapril (E), lisinopril (LI), losartan (LO), and candesartan (C). The mean changes are reported at the bottom of each SD bar. Please note that data are derived from seven zofenopril versus active comparator trial [34–40].

hydrochlorothiazide alone. Studies are currently ongoing in order to show efficacy and safety of high-dose fixed combination of zofenopril (60 mg) plus hydrochlorothiazide (12.5 mg) once-daily in patients with hypertension and at least three additional risk factors (hyperglycemia, hyperlipemia, obesity, smoking, familiar history for premature cardiovascular disease).

The combination of zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily has been shown to be effective for the treatment of hypertension in clinical studies and has also been shown to be superior to monotherapy with either agent. Overall efficacy data from a total of approximately 600 patients with mild–moderate hypertension treated with the combination zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily have been collected and compared. The greater efficacy of the combination versus that of either zofenopril 30 mg or hydrochlorothiazide 12.5 mg once-daily administered alone was first demonstrated in a dose-finding multifactorial study [44] and was confirmed in two parallel group studies [45], a first one carried out in patients with mild–moderate essential hypertension and a second one in patients with hypertension not responding to previous zofenopril 30 mg monotherapy. In all studies, double blind treatments, given as combination or single components, were administered in a once-daily regimen to be taken approximately at the same time on each day (regardless of the concomitant food intake).

Post hoc analyses of the first double-blind, randomized, parallel group study have also been carried out to demonstrate superiority of combination treatment of zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily in subgroups of high-risk patients with hypertension such as those with the metabolic syndrome, diabetes, atherogenic dyslipidemia, high cardiovascular risk level, and kidney disease [46,47].

Dose-Finding Study

Regimens including hydrochlorothiazide 12.5 mg appeared to have a greater effect as compared with the other combinations tested in the study, with statistical significant differences ($P < 0.05$) attained more often versus single drug treatment (zofenopril or hydrochlorothiazide alone): the highest proportion of normalization of office diastolic blood pressure (diastolic blood pressure <90 mmHg) after 12 weeks (primary study endpoint) was obtained with the association of zofenopril 30 plus hydrochlorothiazide 12.5 mg once-daily (57%) and zofenopril 60 plus hydrochlorothiazide 12.5 mg once-daily (79%). Also the proportion of normalized plus responder patients (reduction in diastolic blood pressure >10 mmHg with office diastolic blood pressure ≥90 mmHg) was greatest with these two combinations (80% and 93%, respectively).

A dose-finding study was carried out in 353 patients with mild–moderate essential hypertension (diastolic blood pressure at baseline between 95 and 110 mmHg), treated for 12 weeks with zofenopril 15, 30, or 60 mg plus hydrochlorothiazide 12.5 or 25 mg, or each of their possible combinations [44]. In a subgroup of 245 patients with valid ambulatory blood pressure recordings (i.e., full 24 h recordings at baseline and at the end of the study), the antihypertensive efficacy was assessed also over the 24 h, with particular attention to evaluation of the distribution of the blood pressure control over the 24 h.

The study demonstrated that the antihypertensive drug efficacy in terms of 24-h blood pressure reduction was greater with the combination of zofenopril plus diuretic than with the individual treatments with best results achieved with the combination of zofenopril 30 or 60 mg plus hydrochlorothiazide 12.5 mg once-daily. Under zofenopril 30 mg plus hydrochlorothiazide 12.5 mg, 24-h systolic and diastolic blood pressures were reduced by 9 and 11 mmHg, respectively ($P < 0.05$ vs. hydrochlorothiazide for both pressures and $P < 0.01$ vs. zofenopril for diastolic blood pressure) and under zofenopril 60 mg plus hydrochlorothiazide 12.5 mg by 9 and 13 mmHg ($P < 0.01$ vs. hydrochlorothiazide for both pressures and $P < 0.05$ vs. zofenopril for diastolic blood pressure).

This study also demonstrated the ability of such drug combination to induce a smooth and homogenous blood pressure control, as reflected by the high smoothness indices (systolic blood pressure 1.6 and diastolic blood pressure 1.8 for zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily and 1.9 and 2.5 for zofenopril 60 mg plus hydrochlorothiazide 12.5 mg once-daily). The smoothness index is calculated by averaging the 24 hourly blood pressure reductions with treatment and by computing the ratio of this average value with the corresponding standard deviation. This index is much more suitable than the trough-to-peak ratio for quantification of duration of antihypertensive drug effect, since it is more reproducible over time, it is not affected by the placebo effect, and has a close correlation with the reduction of target organ damage (the greater the value of the smoothness index, the greater the improvement of target organ damage) [48–50]. The smoothness index obtained under zofenopril 30 or 60 mg plus hydrochlorothiazide 12.5 mg once-daily in the dose finding study is similar to that of other well-known two-drug combinations of an ACE inhibitor or an angiotensin II antagonist plus a diuretic, thus confirming the optimal blood pressure control exerted by this fixed drug combination over the 24 h (Table 2) [44,49,51–54].

Since zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily had the most favorable benefit–risk ratio among the possible combinations, it was chosen for the subsequent comparative studies.

Table 2 Smoothness indices for systolic and diastolic blood pressure in open label or double blind studies based on two drugs combinations of and ACE inhibitor or an angiotensin II antagonist with a diuretic. Data are separately shown for low- and high-dose combinations. Please note that the efficacy of the various combinations was not evaluated in head-to-head clinical trials

Treatment	Study design	Patients' characteristics	Treatment duration (weeks)	n	Smoothness index	
					SBP	DBP
"Low-dose" combinations						
Zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily [44]	Double blind	Age range 18–75 years old DBP 95–110 mmHg	12	26	1.66	1.77
Lisinopril 20 mg plus hydrochlorothiazide 12.5 mg once-daily [51]	Open label	Age range 18–70 years old DBP 105–115 mmHg	8	58	1.60	1.50
Telmisartan 80 mg plus hydrochlorothiazide 12.5 mg once-daily [54]	Open label	Mean age 59 years old DBP 95–109 mmHg	12	62	1.77	1.89
"High-dose" combinations						
Zofenopril 60 mg plus hydrochlorothiazide 25 mg once-daily [44]	Double blind	Age range 18–75 years old DBP 95–110 mmHg	12	27	1.88	2.45
Lisinopril 20 mg plus hydrochlorothiazide 12.5–25 mg once-daily [49]	Open label	Age range 20–65 years old DBP 95–115 mmHg LVH	12	174	1.36	1.32
Perindopril 2–4 mg plus indapamide 0.625–1.250 mg once-daily [52]	Double blind	Age range 25–77 years old SBP 160–209 mmHg or DBP 95–109 mmHg	48	107	1.45	1.07
Irbesartan 300 mg plus hydrochlorothiazide 25 mg once-daily [53]	Open label	Age range 45–78 years old SBP $\geq$140 mmHg and DBP $\geq$90 mmHg	12	57	1.70	1.30

SBP, systolic blood pressure; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy.

Comparative Studies

Two comparative, multicenter, double-blind (phase III) randomized studies evaluated the efficacy and safety of the zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily combination versus each component given as monotherapy [45].

In the first comparative study [45], 463 patients with mild–moderate hypertension (diastolic blood pressure between 95 and 115 mmHg) were treated for 12 weeks with combination treatment or single agents. Those patients with a good antihypertensive response at the end of this phase entered the long-term 24-week safety period of the study. At the end of the first 12 weeks, efficacy endpoint of reduction in blood pressure and the proportion of responders were significantly greater with combination treatment than with zofenopril monotherapy (Table 3).

In the second comparative study [45], 369 patients with mild–moderate essential hypertension not responding to 4 weeks of single-blind treatment with zofenopril 30 mg (systolic blood pressure $\geq$130 mmHg and diastolic blood pressure $\geq$85 mmHg, and/or systolic blood pressure reduction <20 mmHg and/or diastolic blood pressure reduction <10 mmHg) were randomized to double-blind treatment with combination treatment or zofenopril alone for a further 8 weeks. Significantly ($P < 0.05$), greater reductions in blood pressure and higher response rates were observed with the combination treatment than with the monotherapy (Table 3). Furthermore, the reduction in blood pressure plateaued at 6 weeks with zofenopril monotherapy but continued to decrease over the entire study period with combination treatment.

Efficacy of Zofenopril Plus Hydrochlorothiazide Combination in Patients with Metabolic Disorders

The metabolic syndrome is characterized by the association of different cardiovascular risk factors such as abdominal obesity, atherogenic dyslipidemia, insulin resistance or glucose intolerance, and blood pressure elevation [55]. Subjects suffering from this condition have a 2- to 3-fold higher risk of cardiovascular fatal and nonfatal events than healthy people: the risk is increased by 5-fold when diabetes mellitus is also present [56–60]. The most common determinant of the metabolic syndrome in subjects without diabetes mellitus is arterial hypertension, followed by dyslipidemia, impaired fasting glycemia, and obesity [58,61]. In these patients, optimal treatment for hypertension should not worsen the patient's metabolic profile and should even improve it.

The efficacy of treatment with an ACE inhibitor not only for controlling blood pressure but also for preventing or improving single metabolic abnormalities possibly associated with hypertension has been demonstrated in the past few years in animal models and humans [62]. For instance, a recent meta-analysis of 12 randomized controlled clinical trials has shown a reduction in the incidence of newly diagnosed diabetes by 27% with this therapeutic class [63]. ACE inhibitors have been found useful also for the treatment of hypertension associated with obesity [64] or dyslipidemia [65].

Given these premises, and the beneficial effects shown by zofenopril in patients with diabetes and myocardial infarction [66], *post hoc* analyses were carried out on

Table 3 Overall efficacy results obtained in the three pivotal studies in which the zofenopril 30 mg plus hydrochlorothiazide 12.5 mg combination was tested versus zofenopril 30 mg monotherapy.

	Treatment			BP reduction (mmHg)		BP response rate (%)	
Study description	Reference	Treatment duration (weeks)	n	DBP	SBP	DBP[a]	SBP[b]
Dose finding study [44]	Zofenopril plus hydrochlorothiazide	12	36	12	18	80	62
	Zofenopril		37	11	16	71	50
Parallel-group comparative study [45]	Zofenopril plus hydrochlorothiazide	12	235	11**	16**	73**	67**
	Zofenopril		115	7	8	51	44
Nonresponder study [45]	Zofenopril plus hydrochlorothiazide	8	185	7*	10**	64*	53*
	Zofenopril		184	5	8	57	44

[a]Blood pressure (BP) response defined as diastolic blood pressure (DBP) $\leq$90 mmHg ($\leq$85 mmHg in the nonresponder study) or reduction $\geq$10 mmHg.
[b]Blood pressure response defined as systolic blood pressure (SBP) $\leq$140 mmHg ($\leq$130 mmHg in the nonresponder study) or reduction $\geq$20 mmHg. *$P <$ 0.05 and **$P < 0.01$ versus monotherapy.

subgroups of patients of the parallel group study, with metabolic syndrome, diabetes, or atherogenic dyslipidemia but with no overt cardiovascular disease.

Data of patients with metabolic syndrome have been previously published [46], while other analyses have been performed for this review. In this *post hoc* analysis the 198 out of the 256 patients of a double-blind, parallel group study, matching the Adult Treatment Panel (ATP)-III criteria for metabolic syndrome, were selected [67]. Under the zofenopril plus hydrochlorothiazide fixed combination, blood pressure reductions were similar in subjects with or without the metabolic syndrome, but were greater than those observed with zofenopril 30 mg alone. In particular, in subjects with the metabolic syndrome, the difference in blood pressure reduction between monotherapy and combination treatment (4.4 mmHg for diastolic and 9.8 mmHg for systolic blood pressure; $P < 0.01$ in favor of combination treatment) was greater than that observed in subjects without the metabolic syndrome (3.5 mmHg for diastolic and 8.5 mmHg for systolic blood pressure; $P < 0.05$) (Fig. 2).

A further interesting result of this study is that the fixed combination was more effective than the monotherapy even in the patients at highest risk and particularly for systolic blood pressure (Fig. 3). This finding is clinically relevant, since patients with the metabolic syndrome usually show a particular resistance to antihypertensive treatment, often requiring more than one drug for adequate blood pressure control [68], and they display a chance of cardiovascular disease mortality 2-fold higher than that of patients with fewer or no metabolic abnormalities [59].

Post hoc analyses have also been performed in patients with elevated fasting glucose and in patients with atherogenic dyslipidemia. Patients with elevated fasting glucose (≥100 mg/dL) include patients with impaired glucose tolerance or type 2 diabetes mellitus, conditions often coexisting with the metabolic syndrome [67]. As shown in Figure 2, also in these patients, the blood pressure reduction obtained after 12 weeks of treatment with zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily was significantly greater than that observed under zofenopril 30 mg once-daily alone, particularly for systolic blood pressure.

Strong evidence indicates that high low density lipoprotein cholesterol (LDL-C) concentrations initiate atherogenesis and promote atherosclerosis [69,70]. However, despite their apparent independence, small LDL particles often coexist with other lipoprotein abnormalities, notably slightly raised triglycerides and low high-density lipoprotein cholesterol (HDL-C). As a matter of fact, these three abnormalities are metabolically intertwined. Each one may be atherogenic, but separation

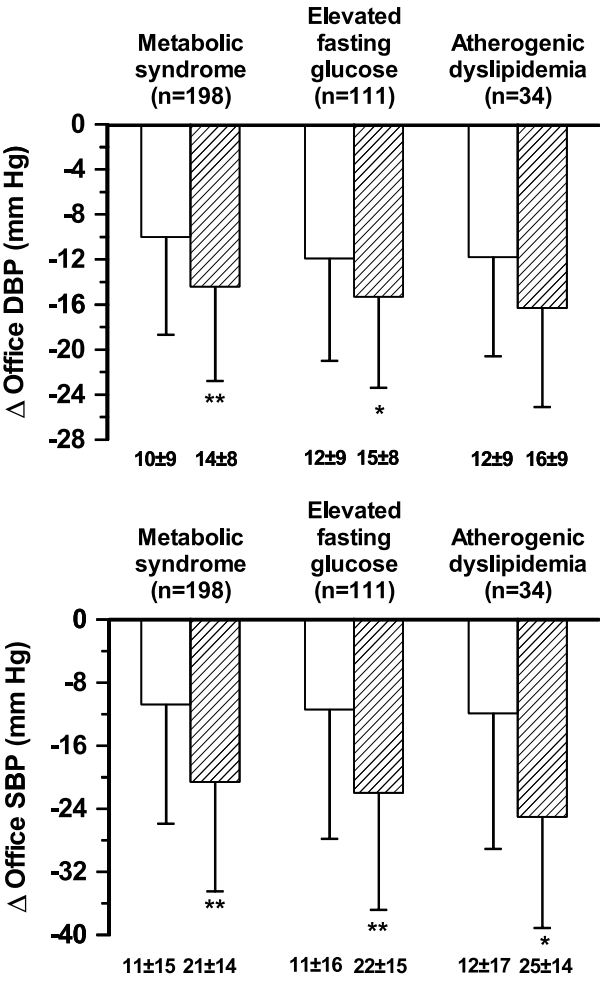

Figure 2 Mean changes (Δ) ±SD in office diastolic (DBP) and systolic blood pressure (SBP) in the subgroups of patients of the parallel group study with metabolic syndrome, elevated fasting glucose, or atherogenic dyslipidemia. Open bars refer to the zofenopril 30 mg once-daily group and striped bars to the zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily group. Mean values ±SD are reported at the bottom of each SD bar ([46], reproduced with permission). *$P < 0.05$ and **$P < 0.01$ versus monotherapy.

of their relative contributions to atherogenesis is difficult. Because of this, the coexistence of slightly raised triglycerides, small LDL, and low HDL-C has called forth the umbrella term "atherogenic lipoprotein phenotype." In this context, atherogenic dyslipidemia, also known as the "lipid triad," is defined as the concomitant finding of low HDL-C (<40 mg/dL in men or <50 mg/dL in women), elevated LDL-C (≥100 mg/dL), and elevated triglycerides (≥150 mg/dL) [68]. In the group of patients of the *post hoc* analysis with atherogenic dyslipidemia, the blood pressure reduction observed with zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily was greater than that observed with monotherapy, the difference

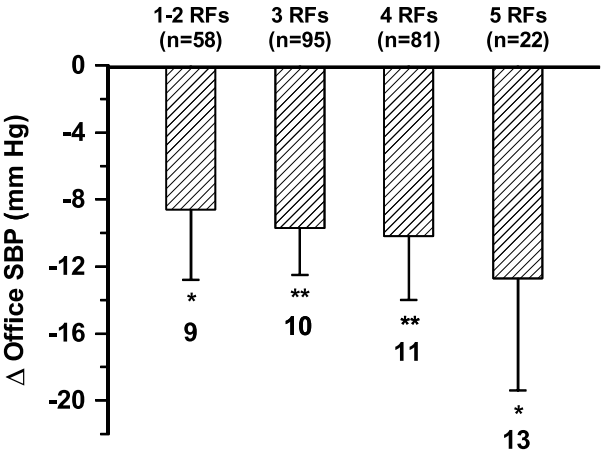

Figure 3 Difference (Δ) ±SD in average office sitting systolic blood pressure (SBP) reductions after treatment between zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily and zofenopril 30 mg once-daily, according to the number of risk factors (RFs) for metabolic syndrome ([46], reproduced with permission). Mean changes are reported at the bottom of each SD bar. $^{*}P < 0.05$; $^{**}P < 0.01$ versus monotherapy.

achieving statistical significance for systolic blood pressure (Fig. 2).

Thus, the fixed combination of zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily is capable of improving the efficacy of zofenopril alone also in subgroups of patients with metabolic disorders, in whom blood pressure control is more difficult to achieve and who are at higher risk for cardiovascular events. As discussed below, this result is reached with tolerability similar to that observed for patients under monotherapy or without metabolic disorders.

Efficacy of Zofenopril Plus Hydrochlorothiazide Combination in Patients with Reduced Renal Function

An impaired renal function is a frequent finding in patients with hypertension and constitutes a very potent predictor of future cardiovascular events [71–73]. According to recent meta-analyses ACE inhibitors and angiotensin II antagonists are the ideal drugs to slow progression of chronic kidney disease, due to their specific renoprotective effects [74,75]. According to these evidences, European Guidelines [16] now recommend estimation of creatinine clearance as a routine laboratory test in the evaluation of organ damage of hypertension and specify that ACE inhibitors and angiotensin II antagonists, also combined with other drugs such as loop diuretics, are the drugs of choice for the treatment of hypertension in patients with renal disease.

Creatinine clearance may now be easily estimated via the Cockroft–Gault formula [76], using serum creatinine, age, gender, and body weight. We evaluated the blood pressure-lowering effect of zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily in patients of the parallel group study according to the stage of renal disease as follows: (a) Stage 1 or normal function (creatinine clearance ≥ 90 mL/min); (b) Stage 2 or slightly impaired renal function (creatinine clearance 60–89 mL/min); (c) Stage 3 or moderately impaired renal function (creatinine clearance 30–59 mL/min); (d) Stage 4 or severely impaired renal function (creatinine clearance 15–29 mL/min); and (e) Stage 5 or end-stage renal failure (creatinine clearance < 15 mL/min or on dialysis) [77]. The majority of patients in our *post hoc* analysis had a slightly impaired renal function, with equal distribution of patients with normal renal function or moderately impaired renal function. No patients had severely impaired renal function or end-stage renal failure. In all patients, the blood pressure reduction was similar at various stages of kidney disease, but greater under combination treatment than under monotherapy, particularly in patients with slightly impaired or moderately impaired renal function (Fig. 4).

This post-hoc analysis confirms that treatment with ACE inhibitor alone or in combination with a thiazide diuretic is effective also in patients with hypertension and renal impairment.

Efficacy of Zofenopril Plus Hydrochlorothiazide Combination According to Individual Cardiovascular Risk Level

As previously mentioned, patients with hypertension at highest risk of cardiovascular disease have a greater chance of being resistant to monotherapy [18]. Therefore, they require combination drug treatment to achieve adequate blood pressure control and protection from cardiovascular events. To assess whether the zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily treatment is effective also in patients at high risk of cardiovascular events, data of the parallel group study were analyzed according to cardiovascular risk level using the Heart Score algorithm, which determines the risk for developing cardiovascular disease in the next 10 years, taking into account age, gender, total cholesterol levels, systolic blood pressure, and patient's smoking status [78].

Analysis was carried out by subdividing the sample into four groups according to quartiles of cardiovascular risk (0.5% first quartile; 2.2% second quartile; 7.1% third quartile; 19.9% fourth quartile). Office sitting diastolic and systolic blood pressure reductions after 12 weeks of

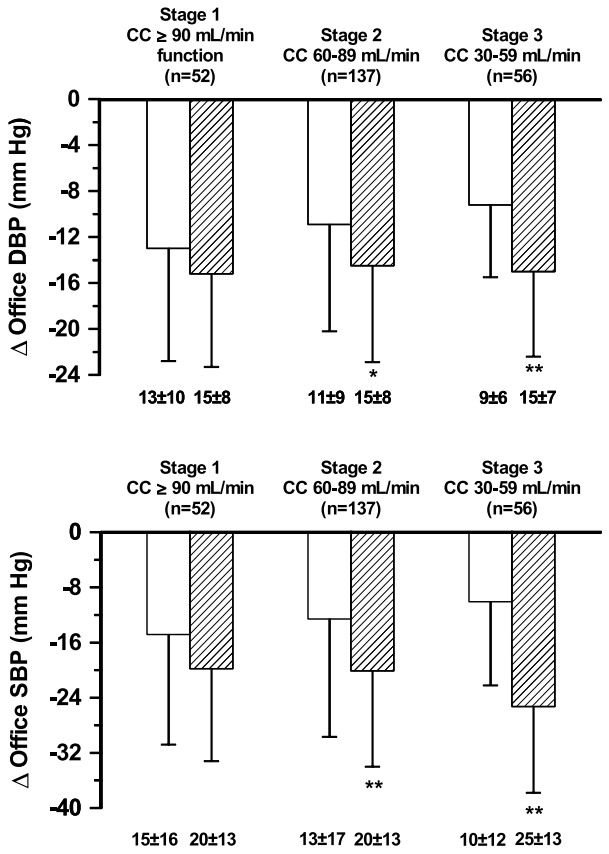

Figure 4 Mean changes (Δ) ±SD in office diastolic (DBP) and systolic blood pressure (SBP) according to the level of creatinine clearance (CC). Open bars refer to the zofenopril 30 mg once-daily group and striped bars to the zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily group. Mean values ±SD are reported at the bottom of each SD bar. $^{*}P < 0.05$ and $^{**}P < 0.01$ versus monotherapy.

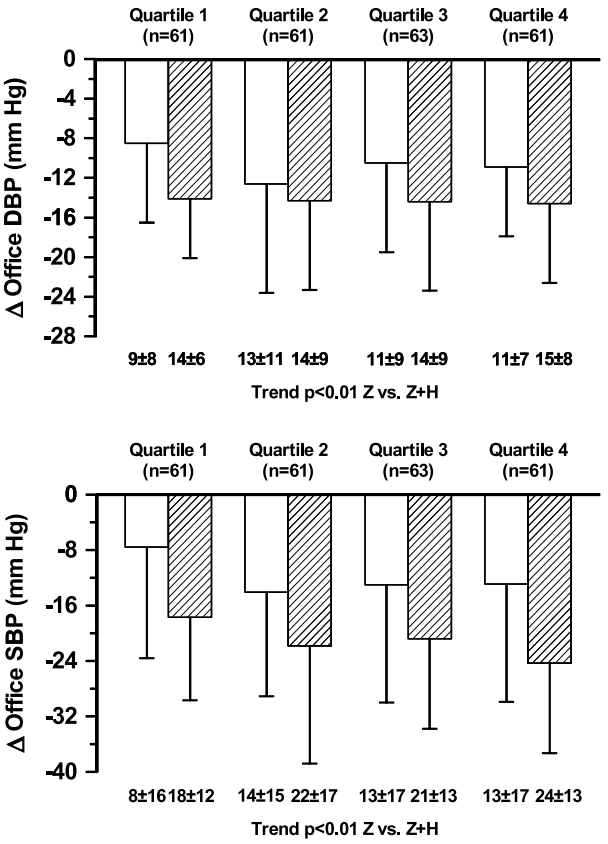

Figure 5 Average office sitting diastolic (DBP) and systolic (SBP) blood pressure reductions (Δ) ±SD after 12 weeks of treatment according to quartiles of increasing cardiovascular risk level in patients treated with zofenopril 30 mg once-daily ($n = 89$, open bars) or zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily ($n = 157$, striped bars). Mean values ±SD are reported at the bottom of each SD bar. The *P* value refers to the statistical significance of the trend of the difference between zofenopril (Z) and combination treatment (Z+H) over the four quartiles ([47], reproduced with permission).

double-blind treatment, according to quartiles of baseline cardiovascular risk, were significantly greater (both $P < 0.01$) in the group receiving zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once daily than in the zofenopril 30 mg once-daily monotherapy group (Fig. 5).

The mean baseline cardiovascular risk was similar (P = not significant) in the zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily group and the zofenopril once-daily monotherapy group (7% vs. 9%). However, cardiovascular risk reduction at the end of the 12 weeks of double-blind treatment was significantly ($P < 0.01$) greater in the zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily group than in the zofenopril 30 mg once-daily monotherapy group (1.9% vs. 0.2%), particularly in the group of patients in the fourth or highest quartile of cardiovascular risk at baseline (5.2% vs. 2.0%). At the end of the 24-week open-label treatment period, the mean reduction in cardiovascular risk was also significantly ($P < 0.01$) greater in the combination treatment group than that in the monotherapy group (1.4% vs. 0.5%).

In patients treated with zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily, a significantly ($P < 0.01$) greater reduction in 10-year risk of cardiovascular disease was observed in patients in the higher risk quartiles (Fig. 6). Of the 44 patients at high cardiovascular risk (>5%) at baseline, 22 (50%) had their risk reduced to a low level (≤5%) after 12 weeks of treatment.

Tolerability of Zofenopril Plus Hydrochlorothiazide Combination in Patients with Hypertension

In more than 600 patients with hypertension involved in controlled clinical trials, the most common adverse

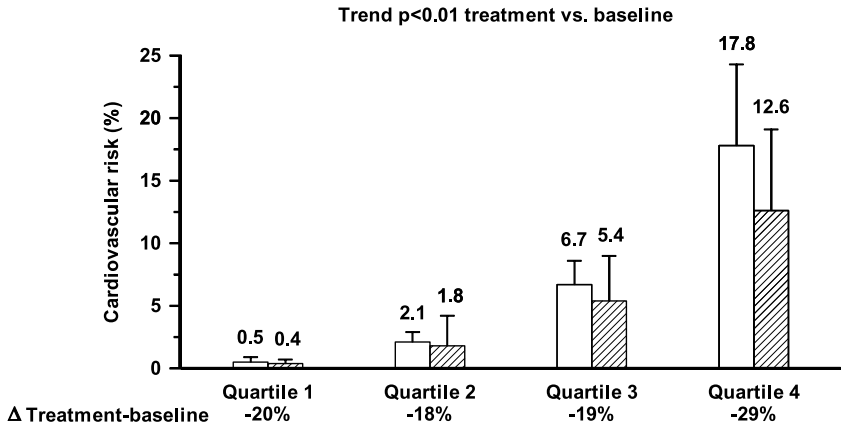

Figure 6 Mean cardiovascular risk at baseline (open bars) and after 12 weeks of treatment (striped bars), by quartiles of the cardiovascular risk level, in patients treated with zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily (n = 157). The treatment-baseline reduction (Δ) is shown below each quartile. *P* refers to the statistical significance of the trend of the difference between baseline and treatment over the four quartiles ([47], reproduced with permission).

events observed under zofenopril plus hydrochlorothiazide combination were those expected during treatment with an ACE inhibitor, namely dizziness, headache, and cough. These adverse events were generally of mild to moderate severity and were not correlated with age or sex.

In the dose-finding study [44], a total of 9.9% of patients reported an adverse event. The majority (64.3%) of these events were of mild intensity and 61.9% of them were classified as treatment-emergent adverse reactions. The incidence of these events was comparable among the different treatment groups, the most common being cough for the ACE inhibitor and polyuria for the diuretic. The proportion of adverse events was better under zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily (no patients with adverse events) as compared with the zofenopril 30 mg once-daily monotherapy (3% of patients displaying adverse events) and zofenopril 60 mg plus hydrochlorothiazide 12.5 mg once-daily combination (12% of patients). Treatment withdrawal occurred in only 1.7% of patients.

In the two comparative studies zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily was at least as well tolerated as zofenopril 30 mg once-daily monotherapy, the greater efficacy of combination treatment being not associated with reflex tachycardia, as often observed in the case of a consistent antihypertensive effect [45]. In the first parallel-group comparative study, the proportions of patients discontinuing treatment because of adverse events in the combination treatment and monotherapy group were 6% and 11% respectively, while in the nonresponder study were 2% and 2%. Adverse events leading to treatment discontinuation in both studies included headache, cough, and dizziness, but no single adverse event resulted in discontinuation for more than 1% of patients in the combination treatment arms.

In the *post hoc* analysis performed in patients with the metabolic syndrome, the number of patients experiencing drug-related adverse events was similar (P = not significant) in the presence (19.2%) or absence (15.5%) of the metabolic syndrome. The proportion of patients with drug-related adverse events was slightly but not significantly higher under combination treatment both in patients with (22.5% vs. 13% monotherapy) and without the metabolic syndrome (18.4% vs. 10.0%). The number of patients withdrawn for adverse events in the group with the metabolic syndrome was similar under monotherapy (4%) and combination treatment (2%). During the 36 weeks of open label treatment, cough occurred only in two patients under combination treatment, one with (0.8%) and one without the metabolic syndrome (2.6%). Under combination treatment, new cases of hyperlipidemia were reported in three (2.3%) patients, new cases of hyperglycemia in two (1.6%), and of hyperuricemia in one (0.8%) patient with the metabolic syndrome, while one patient (2.6%) without the metabolic syndrome reported new onset of hyperlipidemia.

Thus, in all the studies, overall tolerability of zofenopril plus hydrochlorothiazide was similar to that of monotherapy, even in patients with metabolic abnormalities.

Conclusions

Results of the clinical trials based on zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily show that this combination provides a good blood pressure control in a larger proportion of patients than would be achievable with monotherapy with zofenopril 30 mg, while maintaining the tolerability profile observed with each

individual agent. The good efficacy of the combination treatment is evident also in high-risk patients, i.e. those with the greatest indication to first-line combination treatment [16]; in these subjects, the safety profile of zofenopril 30 mg plus hydrochlorothiazide 12.5 mg once-daily is maintained. All these data suggest that this combination may be a useful addition to currently available treatment for patients who have blood pressure that is not adequately controlled by monotherapy, as well for patients with high cardiovascular risk, requiring a more prompt and intensive blood pressure reduction. Ongoing trials assessing efficacy of zofenopril plus hydrochlorothiazide on cardiac (left ventricular mass and function), renal (microalbuminuria), and vascular (carotid intima-media thickness and plaques) damage of hypertensive patients not responding to monotherapy will add new information on the possible organ-protective role of zofenopril in humans.

Conflict of Interest

Both authors have occasionally served as scientific consultants for Menarini Industrie Farmaceutiche Riunite and Istituto Lusofarmaco d'Italia S.p.A. manufacturers of zofenopril.

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