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Zofenopril plus Hydrochlorothiazide

Combination Therapy for the Treatment of Mild to Moderate Hypertension

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Abstract

Achieving target blood pressure (BP) levels in clinical practice is one of the main challenges for physicians in the management of patients with hypertension. It is now recognised that the majority of patients will require at least two antihypertensive drugs to achieve optimal BP control; the use of combination therapy as first-line treatment is also increasing as BP goals of antihypertensive therapy become more ambitious.

The fixed combination of zofenopril/hydrochlorothiazide (HCTZ) 30/12.5 mg/day is approved in Italy, France, Switzerland and Greece for the management of mild to moderate hypertension. In clinical trials comparing zofenopril/HCTZ with each agent administered as monotherapy, combination therapy was more effective in normalising BP. This effect was particularly evident in one trial in which patients who were nonresponsive to zofenopril monotherapy were studied. In addition, in clinical trials to date, combination therapy provided sustained and consistent BP control over the entire 24-hour dose interval.

Despite the greater efficacy of zofenopril/HCTZ 30/12.5 mg/day, when directly compared with each agent administered as monotherapy, there were no significant differences in the nature, severity or incidence of treatment-related adverse events; headache, dizziness, cough and polyuria were most frequently reported. Notably, in one study, fewer patients discontinued treatment with combination therapy than with zofenopril monotherapy due to adverse events.

In conclusion, zofenopril/HCTZ 30/12.5 mg/day provides more optimal BP control in a larger proportion of patients than would be achievable with monotherapy, while maintaining the tolerability profile observed with each individual agent, and thereby potentially enhancing patient compliance. The efficacy and safety profiles of this combination shown in clinical trials to date indicate that it will be a useful addition to currently available therapy for patients who have mild to moderate hypertension that is not adequately controlled by monotherapy, as well as for patients who require more rapid, intensive BP control.

Hypertension is expected to affect approximately 1.5 billion people by 2025, and is predicted to increase in prevalence as the world's population ages, unless extensive and effective treatment and prevention strategies are implemented.[1] The prevalence rate varies among differing regions and can be effected by the criteria used for classification, the methodology used to apply these criteria in practice and the population being assessed.[2] Nevertheless, in 2000, it was estimated that approximately 37% of adults in countries with advanced economies had hypertension. The life-long prevalence of developing hypertension after the sixth decade of life is reportedly 90%.[3]

While cardiovascular disease (CVD) is the most common cause of death in the Western world, it is also rapidly emerging as a significant cause of morbidity and mortality in economically developing nations.[4] Hypertension is the single most important independent risk factor for the development of CVD.[4] In particular, a high systolic blood pressure (SBP) is the most potent indicator of level of CVD risk.[5] This excess risk is particularly evident in patients with moderate to severe hypertension, but patients with mild elevation of diastolic blood pressure (DBP) [90–99mm Hg] or SBP (140–159mm Hg) are also at an increased level of risk because of the existence of a continuum of cardiovascular risk across blood pressure (BP) levels.[6] An analysis of the Framingham population has shown that even individuals with BP within the high-to-normal range (i.e. SBP 130–139mm Hg and/or DBP 85–89mm Hg) are at a considerable level of cardiovascular risk.[6] This analysis showed that, compared with individuals with optimal BP (SBP <120mm Hg and DBP <80mm Hg), those with high-normal BP levels had an increased risk of CVD (adjusted hazard ratios of 2.5 for women and 1.6 for men).

Effective treatment of hypertension is associated with a reduction in adverse cardiovascular events.[7,8] A meta-analysis in >47 000 patients determined that a sustained reduction of 5–6mm Hg in DBP resulted in a risk reduction of >50% for heart failure, up to 40% for stroke and 20–25% for coronary heart disease.[6] Data from the HOT (Hypertension Optimal Treatment) trial, evaluating approximately 19 000 patients, reported that the lowest incidence of major cardiovascular events occurred at a mean achieved DBP of 82.6mm Hg. In addition, in a subgroup analysis, a 50% reduction in major cardiovascular events was observed in patients with hypertension and diabetes mellitus randomised to a target DBP of ≤80mm Hg.[8]

1. Blood Pressure Control in Hypertensive Patients

The European Society of Hypertension/European Society of Cardiology (ESH/ESC) 2003 guidelines advocate that the decision to initiate treatment should be based on a patient's total level of cardiovascular risk, as well as their SBP and DBP.[9] Several classes of drugs are recommended in the first-line treatment of mild sustained hypertension,[9] all of which allow a similar average reduction in BP.[10] However, the appropriate choice of a particular class of agent is dependent upon an individual patient's characteristics and risk profile.[9]

The use of long-acting agents or preparations that can be administered on a once-daily basis and provide 24-hour efficacy are recommended by the ESH/ESC guidelines.[9] These therapies offer improved patient compliance while minimising BP variability, and therefore potentially provide greater protection

against major cardiovascular events and the development of target end-organ damage.

Current guidelines for the management of hypertension recommend treating all hypertensive patients to target BP values of ≤140/90mm Hg, and patients with hypertension and comorbidities such as diabetes or renal disease to a target of <130/80mm Hg.[9,11,12] Despite these recommendations, the results of surveys undertaken in the US and Europe indicate that patients are not generally treated to optimal BP levels.[2] An analysis of the NHANES (National Health and Nutrition Examination Survey) data reported that hypertension was controlled in only 31% of patients in the US.[13] These results are mirrored in other studies conducted in Europe and Asia, where it is reported that <20% of patients with hypertension have adequately controlled BP.[2]

1.1 Rationale for Combination Therapy

It is now recognised that the majority of patients will require at least two antihypertensive drugs to achieve optimal BP control.[1,8] The ESH/ESC guidelines recommend the use of either low-dose monotherapy or low-dose combination therapy with two agents (e.g. a β-adrenoceptor antagonist and a diuretic or an ACE inhibitor and a diuretic).[9] The Joint National Committee (JNC)-7 report states that the addition of a second agent from a different class should be initiated when the use of monotherapy fails to achieve adequate control of BP.[11] The HOT trial demonstrated that greater BP reductions and higher response rates are achieved with the use of combination therapy.[8,14] In this trial, a total of 85% of patients achieved a DBP of ≤90mm Hg, but only approximately one-third of patients remained on monotherapy. Interestingly, 27% of patients had well controlled BP when treated according to step 2 treatment, consisting of a low-dose combination of two agents.

A lack of patient compliance is not sufficient to completely account for the poor treatment rates and low target attainment observed in patients with hypertension.[15] As demonstrated by the HOT trial, monotherapy simply does not result in BP lowering to or below target levels in the majority of patients.

Fixed-dose combination therapy is likely to be more effective in achieving BP goals and result in greater patient compliance than titrating individual doses of two single agents.[16] Furthermore, fixed-dose combination therapy offers beneficial BP-lowering effects while minimising the adverse effects that are potentially associated with the titration of each agent administered as monotherapy.[17,18]

1.2 Fixed-Dose Combination Therapy with an ACE Inhibitor and a Diuretic

An effective fixed-dose, two-drug combination should contain agents that have complementary mechanisms of action; an antihypertensive effect that is at least as, if not more, effective than either agent administered as monotherapy or as sequential combination therapy; enhanced ability to offer end-organ protection; and minimal adverse effects (including haemodynamic and humoural effects).[17,18]

There are two distinct advantages associated with the combination of an ACE inhibitor and a diuretic.[17,18] Firstly, this combination, utilising a low-dose diuretic, reduces the probability of adverse metabolic effects often associated with the use of high-dose diuretic therapy. Furthermore, each component in this combination may partially counteract the undesirable effects of the other. ACE inhibitors are known to effectively counteract the tendency of thiazide diuretics to lower serum potassium levels. Secondly, combination therapy may be more effective in the prevention of organ damage associated with hypertension. ACE inhibitor therapy in combination with a diuretic has been shown to be effective in reducing left ventricular hypertrophy.[19] 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 other types of nephropathy.[20-22]

2. Clinical Efficacy of Zofenopril Plus Hydrochlorothiazide

Zofenopril, a highly lipophilic ACE inhibitor, is characterised by long-lasting tissue penetration and sustained cardiac ACE inhibition.[23] The fixed-dose combination of zofenopril/hydrochlorothiazide (HCTZ) 30/12.5 mg/day is approved in Italy,

France, Switzerland and Greece for the management of mild to moderate hypertension. In clinical studies, this combination was more effective in maintaining BP reductions than either agent administered as monotherapy.[24,25] This result was particularly evident in one trial in which patients who were nonresponsive to zofenopril monotherapy were studied.[25]

Three pivotal studies have investigated the clinical efficacy of this combination.[24,25] In all studies, a stable baseline elevated BP was confirmed by repeated measurement of seated or standing SBP/DBP during a single-blind, placebo run-in period of 2–4 weeks' duration. Inclusion criteria for these studies were a seated DBP of 95–110mm Hg for the dose-response study,[24] 95–115mm Hg for the parallel-group comparative study,[25] and 90–110mm Hg for the nonresponder group study.[25] Patients eligible for randomisation to treatment were required to meet the criteria for seated DBP at inclusion and also for intra- and inter-visit variability (<10mm Hg). Randomised, double-blind treatment was to be given as a once-daily regimen at the same time each day. BP was measured approximately 24 hours after the previous dose by cuff sphygmomanometer and, in addition, in the dose-response study by ambulatory BP monitoring (ABPM).

2.1 Dose-Response Study

The results of a 12-week, multicentre, dose-response study in 353 patients with essential hypertension demonstrated that combination therapy with zofenopril plus HCTZ (30/12.5 or 60/12.5 mg/day) was more effective in maintaining continuous 24-

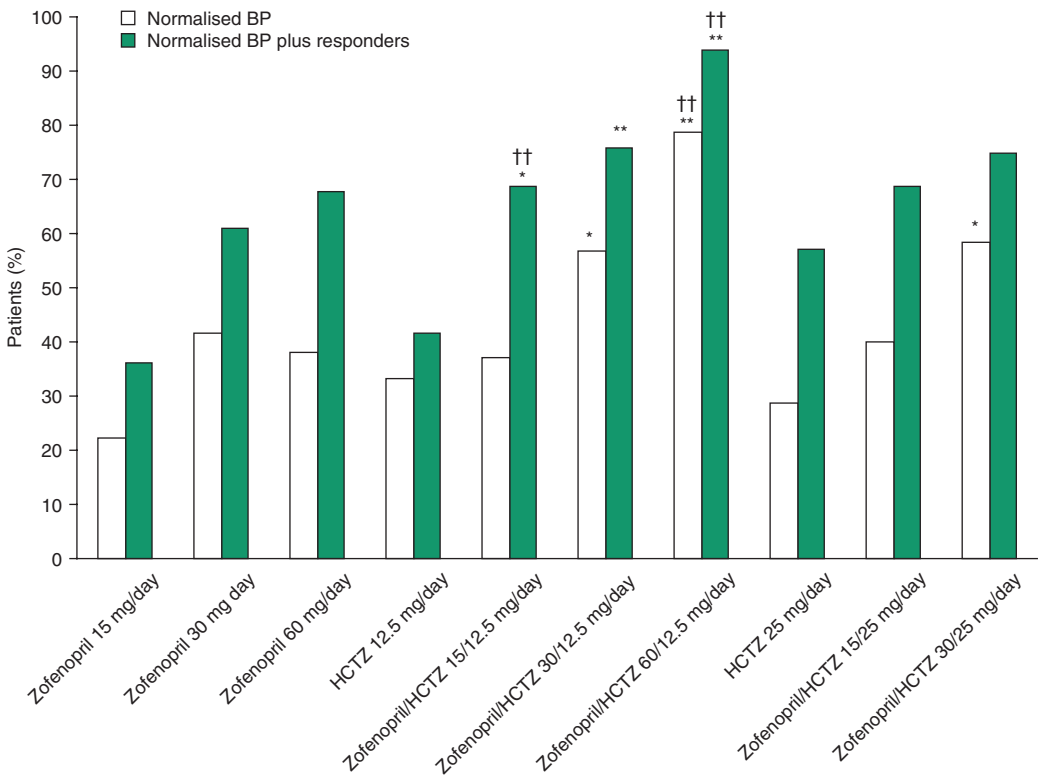

Fig. 1. Normalisation rates and normalisation-plus-response rates for diastolic blood pressure (DBP) in 353 intent-to-treat patients with essential hypertension enrolled in a 12-week randomised, double-blind, dose-response study evaluating zofenopril and hydrochlorothiazide (HCTZ) in combination and as monotherapy (reproduced from Parati et al.,[24] with permission). **BP** = blood pressure; **Normalisation** = seated DBP <90mm Hg; **response** = DBP reduction ≥10mm Hg. * $p < 0.05$, ** $p < 0.01$ vs HCTZ monotherapy; † $p < 0.05$, †† $p < 0.01$ vs zofenopril monotherapy.

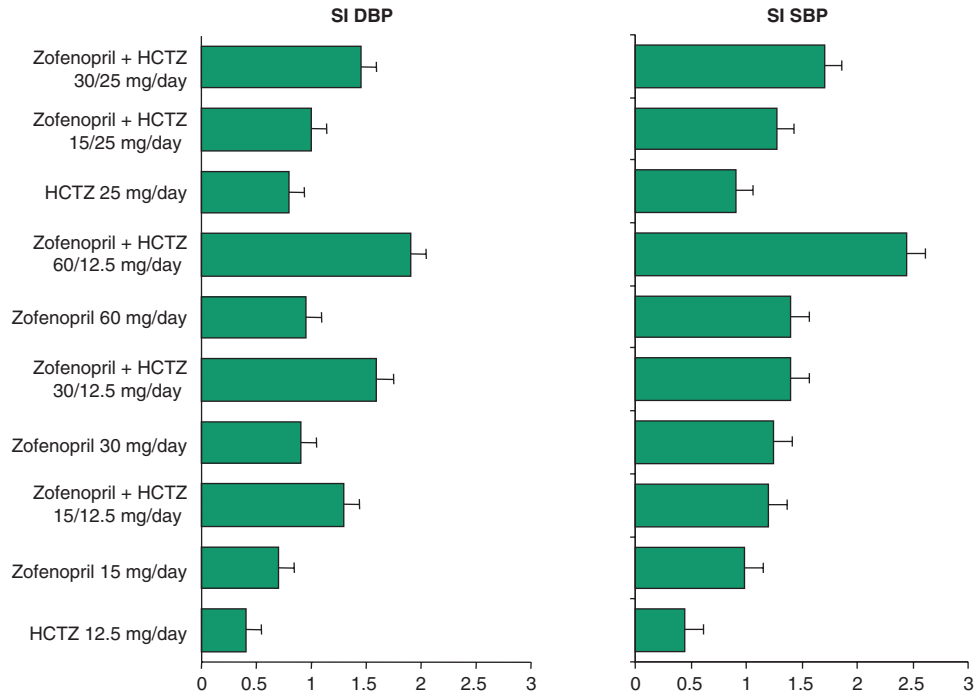

Fig. 2. Smoothness index (SI) of diastolic blood pressure (DBP) and systolic blood pressure (SBP) for the ten treatment groups evaluated in a dose-response study comparing zofenopril, hydrochlorothiazide (HCTZ) or the combination of both drugs. Data are presented as mean ± standard deviation for 353 intent-to-treat patients with essential hypertension (reproduced from Parati et al.,[24] with permission).

hour BP control than either agent administered as monotherapy.[24]

Patients aged 18–75 years were randomised to double-blind treatment with zofenopril 15, 30 or 60mg, HCTZ 12.5 or 25mg, or a combination of zofenopril 15 or 30mg plus HCTZ 12.5 or 25mg, or zofenopril 60mg plus HCTZ 12.5mg, for 12 weeks. The primary efficacy endpoint, proportion of patients achieving office BP normalisation (seated DBP <90mm Hg), was greater for the combination of zofenopril plus HCTZ than either agent administered as monotherapy at the same dose, and reached significance at the 30/12.5, 60/12.5 and 30/25 mg/day dosages ($p < 0.05$; figure 1).

The combination of zofenopril 30 mg/day plus HCTZ 12.5 mg/day normalised BP in 57% of patients, compared with a normalisation rate of 33% for HCTZ 12.5 mg/day ($p < 0.05$). A total of 76% of patients administered the 30/12.5mg combination displayed normalised BP or a DBP reduction ≥10mm Hg (responders), compared with 42% of those receiving HCTZ 12.5 mg/day ($p < 0.01$). A further increase in the proportion of patients achieving BP normalisation was observed with zofenopril 60 mg/day plus HCTZ 12.5 mg/day, but the 25 mg/day HCTZ dosage was not associated with an increased normalisation rate, compared with the 12.5 mg/day HCTZ dose, when given as monotherapy or in combination with zofenopril 15 or 30mg.

Both 24-hour and hourly changes in BP were greater with zofenopril plus HCTZ 30/12.5, 60/12.5 and 30/25 mg/day combination treatment than with either agent administered as monotherapy. Furthermore, higher smoothness indexes, evaluated by ABPM, indicated that combination therapy, in particular 30/12.5, 30/25 and 60/12.5 mg/day, provided superior BP control over the dose administration interval compared with monotherapy (figure 2). The overall benefit **:** risk ratio for zofenopril 30mg plus HCTZ 12.5mg was the most favourable and so was chosen for the comparative studies.

Table I. Primary and secondary endpoints in two randomised, double-blind studies comparing zofenopril/hydrochlorothiazide (HCTZ) 30/12.5 mg/day combination therapy with zofenopril 30 mg/day monotherapy in intent-to-treat patients with mild to moderate hypertension[25]

Study (no. pts)	Drug	BP reductions (mm Hg)		BP response rate (%)	
		DBP	SBP	DBP[a]	SBP[b]
Parallel-group comparative study	Zofenopril/HCTZ	−14***	−20***	70***	57***
(n = 463)	Zofenopril	−10	−12	61	48
Nonresponder study[c]	Zofenopril/HCTZ	−7*	−10**	64*	53*
(n = 369)	Zofenopril	−5	−8	57	44

a Response defined as DBP <90mm Hg or DBP reduction ≥10mm Hg.

b Response defined as SBP <140mm Hg or SBP reduction ≥20mm Hg.

c Patients enrolled in this study were unresponsive to 4-weeks' treatment with zofenopril monotherapy.

BP = blood pressure; **DBP** = diastolic blood pressure; **SBP** = systolic blood pressure; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs monotherapy.

2.2 Comparative Studies

Two international, randomised, double-blind, parallel-group, multicentre studies have evaluated the combination of zofenopril/HCTZ 30/12.5 mg/day compared with monotherapy with zofenopril 30 mg/day. These have been presented at international meetings and published as an abstract.[25]

A 36-week comparison of zofenopril/HCTZ and zofenopril monotherapy demonstrated the superior efficacy of combination therapy in lowering BP in 463 patients aged 18–75 years with mild to moderate hypertension. Following a 4-week washout period, the 12-week efficacy endpoint of reduction in DBP and SBP, and the proportion of responders, were significantly greater with combination therapy than zofenopril monotherapy (table I; $p < 0.001$).

A second study of 369 patients, 18–70 years of age, confirmed the efficacy of combination therapy in treating patients with mild to moderate hypertension who were not responsive to zofenopril monotherapy.[25] Following a 4-week placebo run-in phase, eligible patients were administered 4 weeks' treatment with zofenopril 30 mg/day in a single-blind fashion. Nonresponders (SBP ≥130 and DBP ≥85mm Hg and/or SBP reduction <20mm Hg and/or DBP reduction <10mm Hg) were then randomised to double-blind treatment with zofenopril/HCTZ 30/12.5 mg/day or zofenopril 30 mg/day for a further 8 weeks. Significantly greater and more consistent reductions in BP and higher response rates were reported with combination therapy than with zofenopril monotherapy (table I). BP reached a plateau at week 8 in patients receiving zofenopril monotherapy but continued to decrease in patients receiving combination therapy.

3. Safety and Tolerability of Zofenopril plus Hydrochlorothiazide

In controlled clinical trials involving approximately 600 patients with hypertension, adverse events observed with combination zofenopril/HCTZ were in line with those previously reported with zofenopril or HCTZ monotherapy.[26] The most commonly reported adverse events were dizziness, headache and cough, as would be expected with ACE-inhibitor therapy. These adverse events were generally mild to moderate in severity and were not correlated with age or sex.

In the dose-response study, a total of 9.9% of patients reported an adverse event.[24] The majority (64.3%) of these events were of mild intensity; 61.9% of adverse events were determined to be treatment related but the majority disappeared upon discontinuation of treatment. The incidences of treatment-related adverse events were comparable between the treatment groups, and the most common adverse events were cough and polyuria. The tolerability of 30/12.5 mg/day was better than that of 60/12.5 mg/day in the dose-response study.[24] Treatment withdrawal occurred in only 1.7% of patients. There were no increases from baseline in low-density lipoprotein cholesterol, triglycerides, blood glucose or uric acid levels with combination therapy.

Importantly, in the two comparative studies, zofenopril/HCTZ 30/12.5 mg/day was at least as well tolerated as zofenopril 30 mg/day monotherapy, with the combination therapy having no detrimental effect on heart rate.[25] In parallel-group comparative study, the proportions of patients discontinuing treatment because of adverse events in the

zofenopril/HCTZ and zofenopril monotherapy groups were 6% and 11%, respectively; corresponding values 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 >1% of patients in the combination therapy arms.

4. Role of ACE Inhibitor Therapy in End-Organ Protection

In addition to hypertension and other risk factors (i.e. hyperlipidaemia, diabetes) it has been recognised that activation of the renin-angiotensin-aldosterone system (RAAS) plays a role in the risk of CVD-related morbidity and mortality.[27,28] Angiotensin II, the effector molecule of the RAAS, has been shown to have a direct effect on various tissues including endothelial, vascular and renal tissues.[27]

Agents that actively prevent the formation of angiotensin II, such as ACE inhibitors, may therefore have a beneficial effect in terms of end-organ protection, over and above their effects on BP. Data from clinical trials with an ACE inhibitor, such as the HOPE (Heart Outcomes Prevention Evaluation) and EUROPA (EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) studies, confirm the efficacy of these agents in reducing the risk of cardiovascular death, myocardial infarction (MI) and stroke.[29,30] The SMILE (Survival of Myocardial Infarction Long-Term Evaluation) study specifically demonstrated the efficacy of the ACE inhibitor zofenopril in reducing mortality post-MI.[31] ACE inhibitors have also been shown to reduce morbidity, mortality and/or left ventricular remodelling following MI in a number of major studies, including SAVE (Survival And Ventricular Enlargement),[32] SOLVD (Studies Of Left Ventricular Dysfunction)[33] and PREAMI (Perindopril and Remodeling in Elderly with Acute Myocardial Infarction).[34]

The end-organ protective effects of ACE inhibitors have been clarified in the MICRO-HOPE (Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE) study.[35] Results from this study, which included 3577 patients from the overall HOPE population who had diabetes and either a history of cardiovascular disease or at least one cardiovascular risk factor, demonstrated that ACE inhibition, in this case with ramipril, was associated with significant risk reductions for the composite endpoint of cardiovascular events (stroke, MI or cardiovascular death), and for cardiovascular death, stroke, MI and the development of overt nephropathy.

Preclinical data on combination therapy with zofenopril/HCTZ indicated that, as well as preventing the development of arterial hypertension, it provided more complete organ protection than the combination of enalapril/HCTZ.[36] This was evidenced by a reduction in mortality, and normalisation of renal morphological and functional alterations, including improvements in excretory parameters in hypertensive rats evaluated in an 8-week, placebo-controlled study.

5. Place of Combination Therapy in the Management of Hypertension

One of the primary challenges for physicians in the management of patients with hypertension is achieving target BP levels in clinical practice. Physicians are now more aware than ever before that optimal antihypertensive treatment should be effective, ensuring timely reductions in BP levels, and well tolerated to enhance patient compliance.

The use of combination therapy in the treatment of patients with hypertension is recommended by the ESH/ESC, JNC-7 and the WHO/International Society of Hypertension 2003 guidelines.[9,11,12] ESH/ESC and JNC-7 guidelines acknowledge that the majority of patients will require two or more antihypertensive agents to achieve target BP goals.[9,11] Furthermore, in patients with BP >20/10mm Hg above goal, physicians should consider initiating combination therapy either with two separate agents or as a fixed-dose combination. Combination therapy is also justified in certain patient populations with hypertension and comorbidities (i.e. diabetes, chronic kidney disease) for whom rapid reduction of BP is required.[9,11]

The use of combination therapy as first-line treatment is increasing as BP goals of antihypertensive therapy are becoming more ambitious for all patients and, in particular, for patients at higher risk of cardiovascular complications. While most guide-

lines[9,11] advocate the combinations of two agents from different classes as an alternative to monotherapy, many physicians feel that this does not allow the freedom to vary the dose of the individual components according to patient response. It should be emphasised that for fixed-dose combinations, the individual doses of each component have been selected on the basis of careful investigation to determine the dose that provides the greatest BP reductions with the lowest incidence of adverse events in the largest proportion of patients.[18]

The use of fixed-dose combination therapy with an ACE inhibitor and a diuretic provides physicians with the means to achieve BP control without the need for the prolonged and laborious dose-titrations necessary with initial monotherapy.

The results of a dose-response study comparing zofenopril plus HCTZ with each agent administered as monotherapy clearly demonstrate that a greater antihypertensive effect, in terms of the proportion of patients with normalised DBP, is achieved with combination therapy.[24] In addition, combination therapy provided sustained and consistent BP control over the entire 24-hour dose administration interval. These results suggest that the combination of zofenopril/HCTZ may be indicated in patients who do not achieve target BP with zofenopril 30 mg/day or HCTZ dosages of up to 25 mg/day. A well designed study confirmed the greater BP-lowering efficacy of zofenopril/HCTZ 30/12.5 mg/day versus zofenopril 30 mg/day monotherapy.[25] The advantage of zofenopril/HCTZ 30/12.5 mg/day combination therapy in normalising BP was particularly evident in the study of patients who were nonresponsive to monotherapy.[25]

The overall tolerability profile of zofenopril/HCTZ overlapped with the profile of each individual agent.[24-26] A direct comparison of zofenopril/HCTZ 30/12.5 mg/day with each agent administered as monotherapy did not show any significant differences in the nature, severity or incidence of treatment-related adverse events.[25] Headache, dizziness, cough and polyuria were the most frequently reported treatment-related adverse events. Neither sex nor age had any effect on the safety of the zofenopril/HCTZ combination. Notably, fewer patients receiving combination therapy discontinued treatment because of adverse events compared with those receiving monotherapy.[25]

The fixed combination of zofenopril/HCTZ 30/12.5 mg/day is expected to demonstrate potential additive cardiovascular protective properties as suggested by the efficacy of zofenopril monotherapy in reducing the incidence of death or severe congestive heart failure post-MI in the SMILE study.[31] Preclinical data support its efficacy in providing cardiovascular and renal end-organ protection, although this requires confirmation in well designed clinical trials.[36]

6. Conclusion

In conclusion, data from clinical trials with zofenopril/HCTZ 30/12.5 mg/day show that this combination provides optimal BP control in a larger proportion of patients than would be achievable with monotherapy with zofenopril 30 mg/day, while maintaining the tolerability profile observed with each individual agent, and thereby potentially enhancing patient compliance. The efficacy and safety profiles of zofenopril/HCTZ 30/12.5 mg/day shown in clinical trials to date indicate that this combination will be a useful addition to currently available therapy for patients who have BP that is not adequately controlled by monotherapy, as well as for patients who require more rapid, intensive BP control. Longer-term trials will more definitively confirm the place in therapy of this new combination.

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