ORIGINAL ARTICLE

Effectiveness of initiating treatment with valsartan/hydrochlorothiazide in patients with stage-1 or stage-2 hypertension

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This prospective, 6-week, multicenter, double-blind study examined the benefits of initiating treatment with combination valsartan/hydrochlorothiazide (HCTZ) compared with initial valsartan monotherapy for 648 patients with stage-1 or stage-2 hypertension (age = 52.6 ± 10 years; 54% male; baseline blood pressure (BP) = 161/98 mm Hg, 32% stage 1). Patients were randomized to valsartan 80 mg (V-low), valsartan 160 mg (V-high) or valsartan/HCTZ 160/12.5 mg (V/HCTZ), and electively titrated after weeks 2 and 4 to the next dosage level (maximum dose valsartan/HCTZ 160/25 mg) if BP remained >140/90 mm Hg. At end of the study, patients initiated with V/HCTZ required less titration steps compared with the initial valsartan monotherapy groups (63 vs 86% required titration by study end, respectively) and reached the target BP goal of <140/90 mm Hg in a shorter period of time (2.8 weeks) (P<0.0001) vs V-low (4.3 weeks) and V-high (3.9 weeks). Initial combination therapy was also associated with higher BP control rates and greater reductions in both systolic and diastolic BP from baseline (46%, –27.7 ± 13/–15.1 ± 8 mm Hg) compared with V-low (46%, –21.2 ± 13/–11.4 ± 8 mm Hg, P<0.0001) or V-high (51%, –24.0 ± 13/–12.0 ± 10 mm Hg, P<0.01). Overall and drug-related AEs were mild to moderate and were similar between V/HCTZ (53.1 and 14.1%, respectively) and the two monotherapy groups, V-low (50.5 and 13.8%) and V-high (50.7 and 11.8%). In conclusion, initiating therapy with a combination of valsartan and low-dose HCTZ results in early, improved BP efficacy with similar tolerability as compared with starting treatment with a low or higher dose of valsartan for patients with stage-1 and stage-2 hypertension.

Keywords: valsartan; valsartan/hydrochlorothiazide; initial combination therapy

Introduction

Based on recent national surveys, blood pressure (BP) control rates for patients with hypertension continue to be low and improvements in therapeutic management strategies are required in order for more patients to reach target BP goals.¹ It is well recognized that most patients with hypertension will require two or more antihypertensive agents for effective BP control.² Rational combinations of antihypertensive agents as single-pill formulations are readily available, but their use remains low primarily due to health care providers who are reluctant to intensify therapy.³ Earlier and more frequent use of combination therapy in the management of hypertension would greatly improve BP control rates. The FDA recently approved single-pill combinations of an angiotensin-receptor blocker (ARB) and hydrochlorothiazide (HCTZ)⁴,⁵ and combinations of ARB with amlodipine for initial treatment of hypertension in patients whose BP would not be controlled on monotherapy alone. The initial therapy indication did not stipulate the BP level at which combination therapy should be initiated, but current treatment guidelines suggest that use of combination therapy should be guided by baseline BP and the cardiovascular (CV) risk status of the patient.⁶,⁷

For patients unresponsive to valsartan or low-dose HCTZ monotherapy, addition of the other agent has resulted in further reductions of BP, without increase in adverse events (AEs).⁶–¹¹ The excellent tolerability and complementary BP-lowering effects of this combination makes it an ideal agent for initial use in patients with stage-1 and stage-2 hypertension. The primary arguments against initiating

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treatment with combination therapy for hypertension are based on clinical need and safety concerns. Initial combination therapy for patients whose BP could be controlled by monotherapy, may lead to excessive drops in BP and thus increase the risk for hypotension-related AEs. Common practice is to initiate treatment with low-dose monotherapy and up-titrate to higher dose every 4 weeks. There has been no prospective study that has evaluated initial combination therapy using valsartan and HCTZ as compared with monotherapy when evaluating BP control rates and time to BP control in patients with primary essential hypertension without additional CV risk factors. Based on the need for improved BP control strategies, we conducted a study to determine the efficacy of initial combination therapy with valsartan and HCTZ for patients with stage-1 or stage-2, uncomplicated hypertension as compared with initiating therapy with low (80 mg) or higher dose (160 mg) valsartan monotherapy.

**Patients and methods**

**Patients**
The study enrolled patients ≥18 years of age with a documented diagnosis of hypertension defined as mean sitting systolic BP (MSSBP) ≥150 and <180 mm Hg and mean sitting diastolic BP (MSDBP) ≥90 and <110 mm Hg. Patients were excluded if they had severe hypertension, known or suspected secondary hypertension, previous myocardial infarction, stroke or other CV complications, severe hepatic disease, history of malignancy, or allergy/hypersensitivity to valsartan or HCTZ. Women of childbearing potential were eligible if pregnancy testing was negative. The protocol was approved by all relevant ethics committees and all patients provided written informed consent.

**Study design**
This was a 6-week, multicenter, randomized, double-blind, parallel-group study conducted across 78 US centres. Following a 14- to 28-day washout period, during which all pre-study antihypertensive medications, if used, were discontinued; eligible patients entered a 6-week, double-blind period during which they received valsartan (80 mg), valsartan (160 mg) or valsartan (160 mg)/HCTZ (12.5 mg) for 2 weeks according to the randomization scheme (Figure 1). The three groups were referred to as valsartan-low (V-low), valsartan-high (V-high) and the combination group, valsartan + HCTZ, (V/HCTZ), respectively. At the end of this period, patients whose BP was uncontrolled (MSSBP ≥140 mm Hg or MSDBP ≥90 mm Hg) at week 4, were titrated to the next dosage level (valsartan + HCTZ 160/12.5 mg or valsartan + HCTZ 160/25 mg) in the V-low and V-high groups while V/HCTZ was maintained at the dose of 160/25 mg (Figure 1). Patients achieving a target BP goal of <140/90 mm Hg were maintained at the dose level to which they responded during the double-blind treatment phase. Patients were instructed to take their medication in the morning at the same time each day. To maintain the blinded nature of the study, patients on monotherapy received one placebo pill along with a pill of active therapy.

Concomitant therapy with the following medications was prohibited: other ARBs, angiotensin-converting enzyme (ACE) inhibitors, β-adrenergic antagonists, calcium-channel blockers, any other anti-hypertensive(s), and potassium-sparing diuretics (for example, spironolactone, triamterene or amiloride), anti-arrhythmic drugs, nitrates, α-adrenergic antagonists and digitalis glycosides. Drugs to treat erectile dysfunction were permitted, except within 24 h (sildenafl, vardenafil) and 48 h (tadalafil) of study visits.

**Outcomes**
The objectives of this trial were to compare the proportion of patients achieving BP control and the change in MSSBP and MSDBP from baseline between antihypertensive treatment regimens, initiated with valsartan (80 mg), valsartan (160 mg) or valsartan + HCTZ (160/12.5 mg). The primary efficacy variable was change in MSSBP from baseline to week 4. Secondary outcomes included time to achieve BP goal (defined as the first achievement of the target BP goal of <140 mm Hg systolic BP and <90 mm Hg diastolic BP during the 6-week period), in all patients and in patients with stage-1 (SBP 140–159 mm Hg or DBP 90–99 mm Hg) and stage-2 hypertension (SBP ≥160 mm Hg or DBP ≥100 mm Hg).

During study visits, BP and heart rate measurements were obtained and AEs that occurred since the last study visit were recorded. Any unfavourable medical occurrence, regardless of its suspected cause, was considered an AE. The frequency and severity of AEs, as well as their relationship to study medication, were summarized.

**Statistical methods**
The sample size was based on the comparison of treatment effects between patients initiated with valsartan (80 mg) and those initiated with valsartan (160 mg) with respect to the primary efficacy variable, change in MSSBP from baseline to week 4. Assuming a between-group difference in change in mean MSSBP from baseline to week 4 of the double-blind treatment period of 4.0 (s.d. = 14 mm Hg), it was projected that 216 patients per treatment group (a total sample size of 648 randomized patients) would provide an 80% power to detect a
statistically significant difference at the 0.05 level (two-sided). To control for overall type-I error, a stepwise testing procedure for the primary analyses was adopted. The primary efficacy comparison between the V-low group and the V-high group was tested first. Primary efficacy comparison between V-low and V/HCTZ was performed only if test result from V-low group vs V-high group was statistically significant.

The safety population consisted of all randomized subjects who received at least one dose of the study medication. All efficacy analyses were performed using the intent-to-treat population (all randomized patients who received at least one dose of the study drug and had a valid baseline and at least one valid post-baseline assessment of the primary efficacy variable). For analysis of efficacy data, a last-observation carried forward (LOCF) method was used. An analysis of covariance model was used with baseline measurement as a covariate and treatment as a factor in the model for analyses of all continuous primary and secondary efficacy variables. The primary time point for the analyses was week 4. χ²-Tests were used for categorical variables (the number and percentage of patients achieving BP goal). The time to achieving BP control was analysed by Kaplan-Meier estimates and was presented for each treatment arm. Wilcoxon tests were used to test the differences between treatments.

Results

Patient disposition
From a total of 1413 patients screened for the study, 652 patients were enrolled in the double-blind phase and randomly assigned to one of the three treatment groups: V-low (n = 218), V-high (n = 221) and V/HCTZ (n = 213). Most patients who participated in the double-blind treatment phase were Caucasian (67%), with a mean age of 53 years and almost 88% of the patients <65 years of age. Most of the patients were not diabetic (87%), but a majority had the metabolic syndrome (57%). At least half of all patients enrolled were on previous antihypertensive therapy. Overall, demographic characteristics were similar between the treatment groups (Table 1).

Of the 652 patients randomized into the study, 51 withdrew prior to completing their participation: V-low, n = 17; V-high, n = 17 and V/HCTZ, n = 17. The most common reasons for patient withdrawal were AEs, unsatisfactory therapeutic effect and patient withdrawal of consent. A total of four patients (1 patient in the V-high group and 3 patients in the V/HCTZ group) were excluded from the intent-to-treat population due to missing baseline or post-baseline assessments. Patient disposition throughout the study is illustrated in Figure 2. Most of the patients followed the treatment regimen as prescribed, with the exception of 37 patients (10 patients in the V-low group, 15 patients in the V-high group and 12 patients in the V/HCTZ group) with reported missed doses, titration errors or intake of prohibited medications. During the study 87% of patients in the V-low group and 86% of patients in the V-high group required titration to the next dose level (level 2 or level 3) as compared with 63% of patients for V/HCTZ.

Efficacy outcomes
The proportion of patients achieving a BP control rate <140/90 mm Hg was higher (P < 0.05) for the V/HCTZ group as compared with the V-low and V-high group at weeks 2, 4 and 6 (Figure 3). Significant differences between the V-high group and V-low group regarding the percentage of patients achieving the target BP goal of <140/90 mm Hg at week 4 (46 vs 26%, respectively; P < 0.0001), and numerically higher number of patients achieving the BP goal in the V-high group at week 6 (51 vs 45%, respectively; P = NS) was observed. This was primarily attributed to the addition of HCTZ. Within each treatment group,
Table 1 Patient characteristics at baseline during the double-blind treatment period

| Treatment groups | V-low | V-high | V/HCTZ |
|------------------|-------|--------|--------|
| n                | 218   | 221    | 213    |
| Age (years)      | 52.2±10.7 | 53.1±9 | 52.6±10.4 |
| ≥65 years, n (%) | 21 (9.6) | 25 (11.3) | 30 (14.1) |
| Female, n (%)    | 99 (45.4) | 98 (44.3) | 101 (47.4) |
| Race, n (%)      |       |        |        |
| Caucasian        | 152 (69.7) | 150 (67.9) | 137 (64.3) |
| Black            | 37 (17.0) | 38 (17.2) | 39 (18.3) |
| Hispanic         | 21 (9.6) | 22 (10.0) | 23 (10.8) |
| Previous antihypertensive medication (last 30 days), n (%) |       |        |        |
| BW (kg)          | 92.7±21 | 94.2±21 | 93.2±20 |
| BMI (kg.m⁻²)     | 32.0±6.8 | 32.7±6.4 | 32.5±6.9 |
| Potassium (mmol.l⁻¹) | 4.36±0.5 | 4.27±0.4 | 4.29±0.4 |
| Serum creatinine (mg.dl⁻¹) | 0.87±0.2 | 0.89±0.2 | 0.86±0.2 |
| Glucose (mg.dl⁻¹) | 107±38  | 107±38  | 107±34  |
| Total cholesterol (mg.dl⁻¹) | 205±41  | 200±44  | 204±39  |
| LDL-C (mg.dl⁻¹)  | 121.5±33 | 119.3±35 | 122.3±32 |
| Triglycerides (mg.dl⁻¹) | 51.5±14  | 50.4±13  | 52.6±14  |
| Metabolic syndrome, n (%) | 125 (57.3) | 126 (57.0) | 121 (56.8) |
| Diabetes*, n (%)  | 23 (10.6) | 30 (13.6) | 30 (14.1) |

Abbreviations: BMI, body mass index; BP, blood pressure; BW, body weight; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; V/HCTZ, valsartan/hydrochlorothiazide; V-high, valsartan 160 mg; V-low, valsartan 80 mg.

*Diabetes defined as fasting plasma glucose ≥126 mg dl⁻¹ (7.0 mmol l⁻¹). Data represented as mean ± s.d. unless otherwise noted.

Figure 2 Patient disposition. V-low refers to patients initiated therapy with valsartan (80 mg); V-high refers to patients initiated therapy with valsartan (160 mg) and V/HCTZ refers to patients initiated with combination therapy. V/HCTZ, valsartan/hydrochlorothiazide.

Figure 3 Percentage of patients achieving the BP goal (<140/90 mmHg). The primary efficacy time point was at week 4. At all weeks, 2, 4 and 6, the difference in the percentage of patients achieving BP control between the V/HCTZ and V-low (P<0.001) and between the V/HCTZ and V-high (P<0.05) groups was statistically significant. The difference between V-low and V-high was significant (P<0.001) only at week 4 but not at weeks 2 and 6. BP, blood pressure; V/HCTZ, valsartan/hydrochlorothiazide; V-high, valsartan 160 mg; V-low, valsartan 80 mg.

the changes in MSSBP and MSDBP from baseline were statistically significant at weeks 2, 4 and 6 (Figures 4a and b). At weeks 2, 4 and 6, the reduction in the MSSBP and MSDBP were greater (P<0.01) in the V/HCTZ group as compared with reductions observed in both V-low and V-high groups. Change in MSSBP from baseline at week 4 (primary efficacy) was: −15.3±12 mmHg for the V-low group; −22.0±13 mmHg for the V-high group and −26.0±14 mmHg for V/HCTZ. At week 6 maximal reduction in SBP from baseline was observed in the V/HCTZ group (−27.7±13 mmHg) and was greater (P<0.01) when compared with that in the V-low (−21.2±13 mmHg, difference =
were higher (stage-2 hypertension group. BP control rates after 4 weeks of therapy for patients with stage-1 and stage-2 hypertension were higher (P < 0.05) for V/HCTZ (70 and 52%, respectively) as compared with that for V-low (38 and 20%, respectively). Reductions in SBP and DBP were greater in stage-2 as compared with stage-1 hypertension among the treatment groups; however, the BP lowering advantage with V/HCTZ remained (P < 0.05) when compared with V-low and V-high for patients with either stage-1 or stage-2 hypertension. The systolic and diastolic BP difference between V/HCTZ and V-low at week 4 was −9.2/−6.1 mm Hg in stage-1 and −11.7/−5.9 mm Hg in stage-2.

**Time to BP goal**

The mean time to achieve BP goal, defined as first achievement of the target BP goal of <140/90 mm Hg, was significantly improved (P < 0.0001) with V/HCTZ (2.8 ± 0.13 weeks) as compared with that in the V-high (3.9 ± 0.15 weeks) and V-low groups (4.3 ± 0.14 weeks) in both stage-1 and stage-2 hypertension (Figure 5). The median time to first treatment success (that is, the time point at which 50% of patients reached their goal) was 2.0 weeks (95% confidence interval 2.0, 3.0) in the V/HCTZ group, compared with 6.0 weeks (95% confidence interval 4.0, 6.0) in the V-low and 3.0 weeks (95% confidence interval 3.0, 4.0) in the V-high group.

**Adverse events**

The three treatment regimens, valsartan (80 mg), valsartan (160 mg) and valsartan/HCTZ (160/12.5 mg), were well-tolerated. There were no clinically or statistically significant differences in the AE rates among the three groups. Overall, AEs were experienced by 50.5% (110/218) of patients in the V-low group, 50.7% (112/221) of patients in the V-high group and 53.1% (113/213) of patients in the V/HCTZ group. Drug-related AEs were similar across the three treatment groups for V-low.
The most frequent AEs experienced by at least 3% of patients in any treatment group were headache, dizziness, fatigue, nausea, diarrhea, upper respiratory tract infection, back pain, and myalgia (Table 2). Most AEs were considered by the investigator to be of mild or moderate severity and were not suspected to be treatment-related. AEs associated with low BP, such as dizziness (including postural dizziness), vertigo and hypotension (including orthostatic hypotension), were observed in 5% of patients with V-low, 9% of patients with V-high and 8% of patients with V/HCTZ. The incidence of AEs associated with low BP appeared to be higher for V/HCTZ and V-high as compared with V-low, but only three patients in V/HCTZ and V-high reported symptoms of moderate severity, compared with four in the V-low group; all else were mild.

Analysis of the most frequent AEs experienced by at least 5% of patients (headache and dizziness) showed an overall increased incidence in the first two weeks of the study compared with 4 and 6 weeks after therapy was initiated. At week 2, the incidence of dizziness (overall 2.9%; V-low 2.3%; V-high 2.7%; V/HCTZ 3.8%) and headache (overall 4.6%; V-low 5.5%; V-high 5.9%; V/HCTZ 2.3%) were higher compared with those observed at week 4 (dizziness: overall 2.3%; V-low 0.9%; V-high 3.1%; V/HCTZ 2.8% and headache: overall 1.5%; V-low 2.3%; V-high 1.4%; V/HCTZ 0.9%) and week 6 (dizziness: overall 0.9%; V-low 1.4%; V-high 1.8%; V/HCTZ 0.5% and headache: overall 0.5%; V-low 0.5%; V-high 0.5%; V/HCTZ 0.5%).

There were no significant changes in any of the laboratory measures from baseline, including serum creatinine, glucose or lipid levels, during the study, except potassium levels (Table 3). Potassium levels decreased in all the groups, with significantly greater reductions (P<0.05) for V/HCTZ (−0.19 mmol l⁻¹) as compared with V-low (−0.09 mmol l⁻¹).

Serious AEs were experienced by five patients (2.3%) in the V-low group, three patients (1.4%) in the V-high group and five patients (2.3%) in the V/HCTZ group. Seventeen (2.6%) patients experienced AEs or SAEs, causing discontinuation from the study: 6 (2.8%) in the V-low, 5 (2.3%) in the V-high and 6 (2.8%) in the V/HCTZ group. Suspected AEs leading to withdrawal from the study included dizziness, headache, anxiety, asthenia, fatigue and nausea, and were distributed among the three treatment groups. There were no drug discontinuations for hypotension in the study. There were no deaths reported in this study.

### Discussion

Although evidence from clinical trials suggests that BP reduction to goal is crucial in reducing CV outcomes, at least half of all hypertensives remain untreated, with most of those that are treated requiring combination therapy to achieve the target BP control rate.⁹ Results from this study suggest that for patients with stage-1 and stage-2 hypertension, initiating treatment with combination therapy using the ARB, valsartan and low-dose HCTZ (160/12.5 mg and increasing the dose to 160/25 mg if needed) provided greater benefit in reaching BP control rates compared with initiating treatment with low- or high-dose valsartan monotherapy. The study demonstrated that by initiating therapy with two antihypertensive medications and titrating the dose every 2 weeks, if required, will lead to more effective BP control rates in a shorter period of time as compared with initiating treatment by monotherapy. After only 4 weeks of therapy, 58% of patients on the initial combination agent achieved BP control as compared with only 26% initiated with valsartan (80 mg). Furthermore, AEs between V/HCTZ and the two valsartan monotherapy arms were similar, confirming the excellent tolerability achieved with
combination of an ARB and low-dose diuretic. Risks associated with excessive drops in BP in V/HCTZ were also not observed, as noted by similar incidences of AEs related to low BP and hypotensive episodes among the three groups during the study. The preliminary concern of ‘over-treatment’ in the V/HCTZ group was also not observed, since over 85% of patients initiated on valsartan monotherapy required add-on HCTZ therapy.

In theValsartan Antihypertensive Long-term Use Evaluation (VALUE)study, which compared the CV outcomes of 15,314 eligible patients randomized to a valsartan or an amlodipine-based treatment, higher odds ratios in favour of amlodipine were noted for all endpoints during the first 6 months, when BP differences between the treatment groups were greatest. The starting dose of valsartan in the VALUE trial was 80 mg. Patients remained on the valsartan 80-mg dose for at least 1 month (4 weeks) before being up-titrated to the next step in the protocol. In our current study, initiating treatment with higher dose valsartan monotherapy (160 mg) was associated with higher BP control rates and a shortened time to reach BP control as compared with low-dose valsartan (80 mg) monotherapy, but the BP differences were largely influenced by addition of low-dose HCTZ at week 4 (Figure 4). Perhaps the early outcomes of the VALUE trial were not favourable for valsartan as the trial not only underestimated the proportion of patients requiring combination therapy, but also underutilized the add-on of HCTZ (40% of patients in the trial stayed on valsartan monotherapy, with only 70% of those patients having their BP controlled).

Studies with initial combination therapy using an ARB and low-dose HCTZ have demonstrated superior BP control rates and BP-lowering efficacy as compared with initiating therapy with monotherapy in patients with stage-2 hypertension or diabetes. There is a consensus that initial combination therapy works for high-risk patients with stage-2 hypertension; however, this does not have current support as an option for stage-1 hypertension. Evidence supporting initial use of combination therapy for patients with stage-1 hypertension largely comes from recent findings from the ACCOMPLISH study. Over 9000 patients with stage-1 or stage-2 hypertension were initiated with ACE-inhibitor + HCTZ or ACE-inhibitor + amlodipine combination therapy. The study demonstrated that use of initial combination therapy was very effective and safe for both stage-1 and stage-2 hypertension, as it reported some of the highest BP control rates for any large outcomes study.

One of the clinical challenges with treating a multifactorial disease like hypertension is that it is very difficult to predict an individual’s response to any given treatment. An individual’s response to therapy is not only influenced by baseline factors, such as activity of the renin–angiotensin system and sodium intake, but is also affected by the patient’s compensatory response to the therapy in an attempt to prevent further lowering BP. Using two well-tolerated antihypertensive agents with complementary modes of action to reduce BP will act to limit the counter-regulatory response and thus ensure effective antihypertensive response in a majority of patients. Initiating antihypertensive therapy for patients with stage-1 and stage-2 hypertension, using a well-tolerated combination agent such as an ACE-inhibitor or ARB and low-dose diuretic, is perhaps a more effective approach to enable more patients in the primary care setting to reach the BP goal. A recent study adopted this treatment approach in primary care offices where patients were initiated with combination therapy using a renin–angiotensin system blocker (ACE inhibitor or ARB) and low-dose diuretic as compared with the conventional guideline treatment approach of starting with monotherapy. The study demonstrated excellent tolerability and superior BP control rates using initial combination therapy as compared with those patients who were started with monotherapy and titrated upwards following established treatment guidelines. Thus there is good evidence to recommend wide use of combination agents as frontline therapy for hypertensive patients, regardless of their baseline BP, in the clinical practice setting.

**Study limitations**

This study was not designed to demonstrate the complete treatment strategy approach for using a valsartan-based regimen, as it did not allow achievement of the maximum antihypertensive effect. The study did not include the maximum dose of valsartan (320 mg) in combination with HCTZ, was of 6 weeks duration and the dose titration period was only 2 weeks. The study, rather, was designed to test the efficacy and tolerability of using initial combination therapy for patients with primary stage-1 and stage-2 hypertension.

In conclusion, initial use of combination therapy using a renin–angiotensin system blocker and low-dose diuretic in the standard treatment of hypertension in the primary care setting is an idea whose time has not yet come but which finds support in this study. In this study, initiating therapy with valsartan and low-dose HCTZ (160/12.5 mg) resulted in higher BP control rates, greater antihypertensive effect and prompt BP control with no significant increase in AEs in patients with stage-1 or stage-2 hypertension. The study has provided a template one could follow for treating hypertension effectively and safely using initial combination therapy, including uncomplicated cases of stage-1 to stage-2 hypertension. This study has demonstrated that initial combination therapy with an ARB and low-dose diuretic should become routine for treatment of hypertension, thereby improving BP control rates for patients with primary, essential hypertension.
What is known about the topic

- Earlier and more frequent use of combination therapy in the management of hypertension would greatly improve BP control rates.
- The guidelines mention that patients with baseline BP measures more than 20 mm Hg above the goal (that is, stage-2 hypertension) are candidates for initial combination therapy as they would not have their BP controlled by monotherapy.
- In patients unresponsive to valsartan or low-dose HCTZ monotherapy, addition of another agent (addition of HCTZ to valsartan or vice versa) has resulted in further reductions of BP without increase in AEs.

What this study adds

- This study examined the relative benefits of initiating combination therapy with valsartan+low-dose HCTZ as compared with valsartan monotherapy for patients with mild-to-moderate (stage-1 or 2) uncomplicated hypertension.
- This study has provided strong support for wide use of combination agents as first-line therapy for hypertensive patients, regardless of their baseline BP, in the clinical practice setting.
- Safety concerns about initiating combination therapy for patients with primary hypertension have been alleviated through use of an ARB combined with a low-dose thiazide diuretic.

Abbreviations: AE, adverse event; ARB, angiotensin-receptor blocker; BP, blood pressure; HCTZ, hydrochlorothiazide.

Conflict of interest

KAJ: Consultant for Novartis Pharmaceuticals Corporation, Merck and Daiichi Sankyo; received lecture fees from Novartis Pharmaceuticals Corporation, Abbott, Bristol-Myers Squibb, GlaxoSmithKline and Merck; received research support from Novartis Pharmaceuticals Corporation and King Pharmaceuticals.

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