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Valsartan/Hydrochlorothiazide

A Review of its Pharmacology, Therapeutic Efficacy and Place in the Management of Hypertension

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Data Selection

Sources: Medical literature published in any language since 1980 on valsartan/hydrochlorothiazide, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'valsartan hydrochlorothiazide'. EMBASE search terms were 'valsartan hydrochlorothiazide'. AdisBase search terms were 'valsartan hydrochlorothiazide'. Searches were last updated 14 August 2002.

Selection: Studies in patients with hypertension who received valsartan plus hydrochlorothiazide. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Hypertension, valsartan, hydrochlorothiazide, blood pressure, angiotensin II receptor antagonist, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

The combination of valsartan [an angiotensin II type 1 (AT_1) receptor blocker] and hydrochlorothiazide (a thiazide diuretic), administered once daily, has been evaluated in the treatment of patients with hypertension in clinical trials ranging in duration from 8 weeks to 3 years. These studies showed that combination treatment with valsartan 80 or 160mg and hydrochlorothiazide 12.5 or 25mg induced significant reductions from baseline in systolic blood pressure (SBP) and diastolic BP (DBP) in patients with mild to severe hypertension.

Clinical trials have demonstrated that the combination of valsartan 80 or 160mg with hydrochlorothiazide 12.5 or 25mg is significantly more effective than either drug alone. Furthermore, valsartan plus hydrochlorothiazide was effective at reducing BP in patients unresponsive to monotherapy with either agent alone. Effective BP control with valsartan plus hydrochlorothiazide was maintained in long-term studies, with reductions observed after 3 months of treatment being similar to those seen after 1, 2 or 3 years.

Fixed-dose valsartan/hydrochlorothiazide showed similar BP reductions to amlodipine and to valsartan plus benazepril. Valsartan/hydrochlorothiazide also provided effective 24-hour ambulatory SBP/DBP control.

Headache, dizziness and fatigue were the most common adverse events occurring in clinical trials; the incidence of these events in valsartan plus hydrochlorothiazide recipients was not significantly different to that in placebo recipients. Hypokalaemia occurred in 4.5% of valsartan plus hydrochlorothiazide recipients; valsartan attenuated the hydrochlorothiazide-associated decrease in serum potassium concentrations.

Conclusions: the combination of valsartan and hydrochlorothiazide is an effective treatment for patients with hypertension. Clinical trials have demonstrated that the combination is more effective than either drug alone, and is effective in patients not responding to monotherapy with either agent. Furthermore, the adverse event profile of valsartan/hydrochlorothiazide is similar to that of placebo. Unless there are compelling or specific indications for other drugs, current data support the use of valsartan/hydrochlorothiazide when patients are unresponsive to monotherapy with either agent. Results from clinical trials evaluating the effects of valsartan/hydrochlorothiazide on cardiovascular morbidity and mortality will help to further define the role of the combination in the management of hypertension.

Pharmacodynamic Properties

Valsartan is an angiotensin II receptor blocker with affinity for the type I (AT_1) receptor subtype, which is responsible for most of the known effects of angioten-

sin II. *In vitro* studies have shown that valsartan is a partially insurmountable antagonist with a relatively long dissociation half-life (17 minutes) from the AT_1 receptor. This may contribute to its prolonged hypotensive effect in the clinical setting. Indeed, recent results showed 51% AT_1 receptor blockade 24 hours after a single dose of valsartan 160mg in healthy volunteers.

Hydrochlorothiazide therapy in patients with hypertension produces changes in plasma volume, cardiac output, mean arterial pressure, stroke volume, heart rate and total peripheral resistance. Although the mechanism by which thiazide diuretics exert their hypotensive effects is not fully understood, it has been recently suggested that thiazides reduce peripheral resistance during long-term therapy via a direct vascular effect.

In spontaneously hypertensive rats, the hypotensive effects of valsartan were potentiated by the addition of hydrochlorothiazide. Indeed, when rats were administered subcutaneous valsartan 3 mg/kg/day with hydrochlorothiazide 10 mg/kg/day, the hypotensive effect was synergistic.

Pharmacokinetic Properties

A peak plasma concentration (C_{max}) of 1.64 mg/L was achieved 2 hours (t_{max}) after oral administration of a single dose of valsartan 80mg to healthy volunteers; the area under the plasma concentration-time curve from 0 to 24 hours (AUC_{24h}) was 8.54 mg • h/L. A higher valsartan dose (200mg) produced a proportionately higher C_{max} (3.46 mg/L) with a similar t_{max}. The bioavailability of valsartan was 23%.

Valsartan is extensively bound to plasma proteins (85 to 99%); the estimated volume of distribution and plasma clearance are 17L and 2.2 L/h. The mean elimination half-life ($t_{1/2}$) after a single dose of valsartan 80mg was 7.05 hours. Faecal excretion accounts for ≈86% of an orally administered dose of valsartan, whereas ≈13% is excreted renally. Renal excretion is largely complete 2 days postdose but substantial faecal elimination continues until day 4. The drug is predominantly excreted unchanged.

After 15 days of treatment with oral valsartan 80mg, the AUC_{24h} of valsartan was 52% higher in patients with hypertension on haemodialysis than in those with hypertension and normal renal function. Mild or moderate hepatic impairment approximately doubled the AUC of valsartan compared with that seen in healthy volunteers. Compared with younger volunteers (mean age 23 years), elderly volunteers (mean age 76 years) experienced higher systemic exposure to a given dose of valsartan; however, dosage adjustment based solely on age is not considered necessary.

After administration of a single dose of hydrochlorothiazide 12.5mg to healthy adults, a C_{max} of 0.075 mg/L was achieved 1.9 hours postdose; C_{max} after administration of hydrochlorothiazide 12.5mg once daily for 5 days was 0.091 mg/L, and t_{max} was 2 hours. The bioavailability of orally administered hydrochlorothiazide is 66 to 75%, and 40 to 58% is protein-bound. Hydrochlorothiazide does not undergo metabolism, and ≥61% of an oral dose is excreted unchanged in the urine within 24 hours of the dose; reports of the $t_{1/2}$ range from 2.5 to 18.9 hours.

Hydrochlorothiazide has no effect on the pharmacokinetics of valsartan, but valsartan does modify hydrochlorothiazide pharmacokinetics. The mean AUC_{24h}, C_{max} and $t_{1/2}$ after a single dose of hydrochlorothiazide 25mg were reduced by 22, 26 and 35% when administered with valsartan 160mg; the amount of hydrochlorothiazide excreted in the urine was reduced by 15%.

C_{max} and AUC_{48h} values for valsartan and hydrochlorothiazide after the ad-

ministration of fixed-combination tablets or each drug alone to 37 volunteers were within the limits of bioequivalence.

Therapeutic Efficacy

Results from a dose-response study demonstrated that the combination of valsartan 80 or 160mg with hydrochlorothiazide 12.5 or 25mg, administered once daily, was significantly more effective than either drug alone in the treatment of patients with mild to moderate essential hypertension. The greatest reductions in blood pressure (BP) were seen in the valsartan plus hydrochlorothiazide 80 plus 25mg and 160 plus 25mg group [reductions in systolic/diastolic BP (SBP/DBP) of 21.2/15.7 and 22.5/15.3mm Hg]. Reductions in SBP/DBP in patients who received valsartan plus hydrochlorothiazide 80 plus 12.5mg or 160 plus 12.5mg were 16.5/11.8 and 17.8/13.5mm Hg.

Valsartan plus hydrochlorothiazide was also effective at reducing BP in patients who did not respond to monotherapy with either valsartan or hydrochlorothiazide. Among nonresponders to monotherapy with valsartan 80mg, SBP/DBP reductions in patients who recieved valsartan 80mg in combination with hydrochlorothiazide 12.5 (9.8/8.2mm Hg) or 25mg (16.0/10.8mm Hg) were significantly higher than those seen in patients who received monotherapy with valsartan 80 (3.9/5.1mm Hg) or 160mg (6.5/6.2mm Hg). Similarly, nonresponders to hydrochlorothiazide 12.5mg achieved significantly better BP control with fixed-dose valsartan/hydrochlorothiazide 80/12.5mg (14.9/11.2mm Hg) than with hydrochlorothiazide 12.5 (5.2/2.9mm Hg) or 25mg (6.8/5.7mm Hg).

Effective BP control with valsartan plus hydrochlorothiazide was maintained in long-term studies, with reductions observed after 3 months of treatment being similar to those seen after 1, 2 or 3 years. Reductions from baseline in SBP/DBP after 3 years of treatment with valsartan 80mg plus hydrochlorothiazide 12.5mg or 25mg were 11.7/12.5 and 16.4/12.6mm Hg.

Fixed-dose valsartan/hydrochlorothiazide 80/12.5mg showed similar BP reductions to amlodipine 10mg (in patients who did not respond to valsartan 80mg or amlodipine 5mg, respectively), and to valsartan 80mg plus benazepril 10mg in patients not responding to valsartan 80mg. Both valsartan/hydrochlorothiazide and amlodipine provided effective 24-hour ambulatory SBP/DBP control, with trough-to-peak ratios of 0.61/0.57 and 0.56/0.56. However, when only responders to treatment were considered, night-time BP was controlled more effectively with valsartan/hydrochlorothiazide than with amlodipine 5 or 10mg.

Tolerability

Valsartan plus hydrochlorothiazide is well tolerated. Headache, dizziness and fatigue were the most common adverse events occurring in clinical trials; however, the incidence of these events in valsartan plus hydrochlorothiazide recipients was not significantly different to that in placebo recipients. Moreover, the overall incidence of adverse events in patients who received valsartan plus hydrochlorothiazide was similar to that in placebo recipients, and 3.6 *vs* 4.3% of patients discontinued treatment because of adverse events. There was no increase in the incidence of adverse events in long-term (1 to 3 years' duration) studies.

The incidence of hypokalaemia in patients who received valsartan plus hydrochlorothiazide in clinical trials was 4.5%. Data from one study showed valsartan attenuated the hydrochlorothiazide-associated decrease in serum potassium concentrations. Orthostatic hypotension has been reported in two patients receiving valsartan plus hydrochlorothiazide. There have been no cases of treatment-related angioneurotic oedema.

Valsartan was similarly well tolerated in combination with either hydrochlorothiazide or benazepril. Valsartan/hydrochlorothiazide was, however, associated with significantly fewer adverse events than amlodipine, predominantly because of a higher rate of lower-limb oedema in amlodipine recipients.

Dosage and Administration

The fixed combination of valsartan/hydrochlorothiazide is indicated for the treatment of patients with hypertension who have not achieved adequate BP control after receiving monotherapy with either drug. The recommended initial starting dosage is valsartan/hydrochlorothiazide 80/12.5mg administered once daily. If BP remains uncontrolled after 3 to 4 weeks, the dosage of valsartan or both components can be titrated to valsartan/hydrochlorothiazide 160/25mg.

Valsartan/hydrochlorothiazide can be administered to patients with renal impairment, as long as creatinine clearance is >1.8 L/h (30 ml/min). Patients with hepatic insufficiency receiving valsartan/hydrochlorothiazide should be monitored for alterations in fluid volume and electrolyte imbalance.

Because of the hydrochlorothiazide component, valsartan/hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

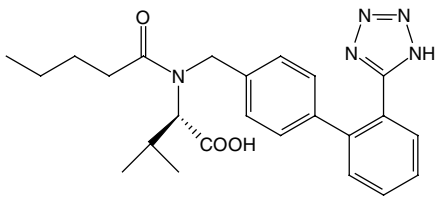
1. Introduction

Essential hypertension, defined as resting diastolic blood pressure (DBP) ≥90mm Hg and/or systolic BP (SBP) ≥140mm Hg with no clear identifiable cause,[1] is a common disease which increases in incidence with age.[2] Chronically elevated BP is associated with an increased risk of cardiovascular morbidity and mortality, and with end-stage renal failure;[3] the minimisation of cardiovascular risk through the achievement of BP control is one of the primary goals of the treatment of hypertension.[4] Although the lowering of DBP has been traditionally regarded as the most important goal in the management of hypertension, lowering SBP is now regarded as being at least as important as decreasing DBP.[5] Recent guidelines presented by the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC-VI)[6] and the World Health Organization-International Society of Hypertension (WHO-ISH),[3] recommend a target SBP <140mm Hg and DBP <90mm Hg, whereas British guidelines suggest a target of <140/85mm Hg.[7] A lower target is advised for patients with comorbidities; in patients with hypertension and diabetes mellitus, the BP target suggested by the American Diabetes Association is <130/80mm Hg.[8] Effective BP control is often not achieved with monotherapy. Indeed, 70% of 18 790 patients with hypertension enrolled in the HOT trial required combination therapy to achieve a DBP ≤90mm Hg.[9] Effective combinations comprise antihypertensive agents with different primary actions, thus eliciting an additive hypotensive effect.

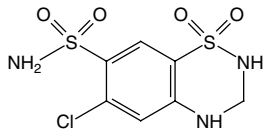
Valsartan (figure 1), an orally active angiotensin II receptor blocker (ARB) with selectivity for the type I (AT_1) receptor subtype, is an established drug for the treatment of hypertension and has been reviewed previously in *Drugs*.[10]

Thiazide diuretics such as hydrochlorothiazide (figure 1) have been used in antihypertensive therapy since the advent of chlorothiazide in 1957, often in combination with other antihypertensive drugs such as β-blockers, ACE inhibitors or, more recently, ARBs.[11]

This review focuses on the use of the combination valsartan/hydrochlorothiazide in the treatment of patients with predominantly mild to moderate essential hypertension. Although fixed-dose combination tablets are available, data from studies in which patients received the two drugs as separate tablets are included. The combination has been briefly reviewed previously in *Drugs*.[12]



Valsartan



Hydrochlorothiazide

Fig. 1. Chemical structure of valsartan and hydrochlorothiazide.[13]

2. Pharmacodynamic Properties

Available data concerning the pharmacodynamic effects of the two drugs when coadministered are limited. Consequently, this section mainly provides a brief overview of each agent.

2.1 Valsartan

Renin is an enzyme secreted by the juxtaglomerular cells in response to decreases in renal perfusion pressure or sodium chloride transport in the distal nephron, or increases in sympathetic tone. It converts angiotensinogen into angiotensin I, an inactive moiety which is rapidly converted to angiotensin II by angiotensin-converting enzyme (ACE).[1] Angiotensin II is the principal effector hormone of the renin-angiotensin system (RAS), and has a key role in maintaining arterial BP, and fluid and electrolyte homeostasis, by binding to angiotensin II receptors. These receptors are located mainly in cardiac and vascular tissue, but also in other tissues such as lung, liver, kidney, adrenal gland, prostate gland, placenta and brain.[14,15] However, angiotensin II is also thought to be involved in the pathophysiology of hypertension, arterial disease, cardiac hypertrophy, heart failure and renal disease.[15] Although angiotensin II interacts with both the AT_1 and type II (AT_2) receptor subtypes, the AT_1 receptor appears to be responsible for most, if not all, of the cardiovascular effects of angiotensin II (i.e. vasoconstriction, aldosterone secretion, renal sodium resorption, sympathetic stimulation, vasopressin release and cardiac and vascular cell hypertrophy and proliferation).[16] Therefore, blockade of the AT_1 receptor would subsequently block the major cardiovascular effects effects of AII. Table I provides an overview of the pharmacodynamic properties of valsartan.

Results from early *in vitro* studies showed that valsartan competitively inhibits the binding of radiolabelled angiotensin II to AT_1 receptors [dissociation constant (K_i) 2.38 nmol/L] in rat aortic smooth muscle cells, but has ≈30 000 times less affinity for human myometrial AT_2 receptors.[17] Valsartan had a similar affinity for AT_1 receptors in human and rat adrenal tissue [concentration required for 50% inhibition (IC_{50}) 2.43 *vs* 8.18 nmol/L)].[18] At a concentration of 10 nmol/L, valsartan had no affinity for α_1-, α_2- or β_1-adrenoceptors, substance P receptors, γ-aminobutyric acid-A and -B receptors, muscarinic, serotonin 5-HT_1 or 5-HT_2 receptors or calcium channels.[19]

When valsartan and angiotensin II were added simultaneously to human AT_1 receptor-transfected Chinese hamster ovary cells (CHO-hAT_1), valsartan produced a parallel rightward shift of the dose-response curve indicating competitive inhibition at the AT_1 receptor; similar results were observed for candesartan, irbesartan and EXP3174 (the active metabolite of losartan).[20] However, in pre-incubation experiments (where valsartan was added to CHO-hAT_1 cells before angiotensin II), valsartan inhibited the maximal response to angiotensin II (as measured by inositol phosphate accumulation) by up to 55%, i.e. partially insurmountable AT_1 receptor antagonism; irbesartan and EXP3174 display a similar characteristic.[20] The insurmountable aspect of antagonism by valsartan may be related to its relatively slow dissociation from the AT_1 receptor (half-life of 17 minutes), and may contribute to its prolonged hypotensive effect in the clinical setting.[20] In a randomised, crossover

Table I. Overview of the pharmacodynamic properties of valsartan (VAL)

Reference	Model/patient group	Drug	Effect
***In vitro* studies**			
Mueck et al.[22]	Isolated human coronary artery endothelial cells incubated with AII 10 μmol/L	VAL 10 μmol/L	Prevented AII-induced decrease in endothelial-derived nitric oxide synthase ($p < 0.01$ *vs* AII). Prevented AII-induced increases in endothelin, PAI-1 and pro-MMP-1 ($p < 0.01$ *vs* AII for all comparisons)
Mueck et al.[23]	Isolated human coronary artery smooth muscle cells incubated with AII 1 μmol/L	VAL 1μmol/L	Inhibited AII-induced proliferation of vascular smooth muscle cells ($p < 0.01$)
Animal studies			
Hayashi et al.[24]	Normotensive, anaesthetised dogs	Intravenous VAL 10 mg/kg	Increased renal blood flow, urinary sodium and chloride excretion and urine volume, and decreased renal vascular resistance and filtration fraction without affecting BP
Yamamoto et al.[25]	Renal hypertensive and spontaneously hypertensive rats	Single dose oral VAL 3-30 mg/kg	Dose-dependent decreases in BP
Studies in patients			
Hanefeld et al.[26]	112 patients with mild to moderate hypertension	VAL 80mg once daily for 12wk	As well as reducing BP, VAL reduced concentrations of LDL cholesterol (by 4.8%, $p < 0.03$) and total cholesterol (by 3.4%, $p < 0.01$) compared with placebo (increases of 3.2 and 2.8%); glucose metabolism was not affected
Plum et al.[27]	9 patients with chronic renal failure and hypertension	VAL 80mg once daily for 6mo	Lowered arterial BP (by 13mm Hg, $p < 0.05$), proteinuria (by 26%, $p < 0.05$) and albuminuria (by 41%, $p < 0.05$); the glomerular filtration rate and effective renal plasma flow remained unchanged during therapy
Thürmann et al.[28]	58 patients with essential hypertension and left ventricular hypertrophy	VAL 80 or 160 mg/day or ATE 50 or 100 mg/day for 8mo (31% and 28% of patients also received an unspecified dosage of hydrochlorothiazide)	VAL and ATE reduced LV mass by 16.5 and 7.9%. LV mass index was reduced from 127 to 106 g/m^2 during treatment with valsartan ($p < 0.0001$ *vs* baseline) and from 127 to 117 g/m^2 with ATE ($p = 0.008$ *vs* baseline)
Viberti and Wheeldon[29]	332 patients with type 2 diabetes mellitus and microalbuminuria with or without hypertension	VAL 80 mg/day or AML 5 mg/day for 24wk	VAL and AML reduced BP to a similar extent, but reduced elevated urine albumin excretion by 44 and 8% ($p < 0.001$), respectively, from baseline

AII = angiotensin II; **AML** = amlodipine; **ATE** = atenolol; **BP** = blood pressure; **LDL** = low-density lipoprotein cholesterol; **LV** = left ventricular; **MMP-1** = matrix metalloproteinase 1; **PAI-1** = plasminogen activator inhibitor 1.

study in seven healthy volunteers,[21] a single dose of valsartan 160mg provided effective 24-hour AT_1 blockade, as measured by radial artery systolic pressure response to exogenous angiotensin II (51% AT_1 receptor blockade 24 hours postdose; $p < 0.05$ *vs* placebo). Although AT_1 receptor blockade with a single dose of valsartan 80mg (35% at 24 hours) was lower than with valsartan 160mg ($p < 0.05$), it was still significantly higher than with placebo (7%, $p < 0.05$).[21]

2.2 Hydrochlorothiazide

Thiazide diuretics, including hydrochlorothiazide, are thought to act mainly within the distal

nephron by inhibiting the luminal transmembrane-coupled Na-Cl transport system, possibly via competitive inhibition of the chloride binding site.[30,31] Table II summarises the pharmacodynamic properties of thiazide diuretics. The mechanism by which thiazide diuretics exert their hypotensive effects is not fully understood; however, it has been proposed that thiazides reduce peripheral resistance during long-term therapy, probably via a direct vascular effect and a decrease in vascular responsiveness to noradrenaline (norepinephrine) and angiotensin II.[31,32] A small vasodilator effect was observed in the forearm of normotensive and hypertensive individuals after acute intravenous administration of high doses of hydrochlorothiazide (80, 250 and 750 μg/min/L).[11] This effect has been suggested to arise from the inhibition of vascular smooth muscle cell carbonic anhydrase which results in an increase in intracellular pH, activation of potassium channels and vasorelaxation.[31] However, *in vivo* vasodilation was only achieved at plasma concentrations of hydrochlorothiazide higher than those reached during long-term oral administration.[11]

Table II. Overview of the pharmacodynamic properties of thiazide and thiazide-like diuretics[30]

Reduce blood pressure
Moderately increase Na^+ and Cl^- excretion
Some thiazide diuretics (e.g. hydrochlorothiazide) are weak inhibitors of carbonic anhydrase
Increase excretion of K^+
Short-term administration effects on Ca^{2+} excretion are variable while long-term administration decreases Ca^{2+} excretion
Short-term administration increases excretion of uric acid
Stimulate renin secretion
May cause mild magnesuria, while long-term use may cause magnesium deficiency
Attenuate the ability of the kidney to excrete dilute urine during water diuresis
May cause extracellular volume depletion, hypotension, hypokalaemia, hyponatraemia, hypochloraemia, metabolic alkalosis, hypomagnesaemia, hypercalcaemia and hyperuricaemia
May decrease glucose tolerance and unmask latent diabetes mellitus
May increase plasma concentrations of low density lipoprotein cholesterol, total cholesterol and total triglycerides

Hydrochlorothiazide therapy in patients with hypertension produces changes in plasma volume, cardiac output, mean arterial pressure, stroke volume, heart rate and total peripheral resistance.[32] However, the effects of hydrochlorothiazide on some of these parameters differed in responders and nonresponders to treatment.

Hydrochlorothiazide 50mg twice daily for 12 or 36 weeks after a 4-week placebo run-in lowered mean arterial pressure for the duration of the study in patients with essential hypertension (baseline DBP >100mm Hg).[32] Thirteen patients completed the 12-week study, and nine patients completed the 36-week study. Compared with the mean baseline value (117.2mm Hg), mean arterial pressure was significantly lower at week 1 (110.5mm Hg, $p < 0.01$) and continued to fall until week 36 (101.4mm Hg, $p < 0.01$). Cardiac output was significantly reduced from baseline at weeks 4 (a reduction of 0.5 L/min, $p < 0.05$) and 12 (0.6 L/min, $p < 0.01$), but the reduction was not statistically significant at weeks 24 and 36; a similar pattern was observed for stroke volume reductions. Plasma renin concentrations were significantly ($p < 0.001$) elevated during treatment. Significant changes in heart rate or total peripheral resistance were not observed. However, when patients were classified as responders (>10% reduction in mean arterial pressure, n = 7) and nonresponders (<10% reduction, n = 6), substantial differences between the two groups in cardiac output, total peripheral resistance and heart rate, in addition to differences in mean arterial pressure, were evident. Although cardiac output was reduced in both groups during the first 12 weeks, it thereafter returned to pretreatment levels in responders, but remained lowered (by ≈13%) in nonresponders; a 10% reduction in heart rate was also observed in nonresponders. Furthermore, total peripheral resistance was reduced by ≈20% ($p < 0.01$) by week 36 in responders, whereas it was increased by ≈10% in nonresponders ($p < 0.05$). Plasma renin concentrations were also higher in nonresponders than in responders, although the difference did not reach statistical significance.[32]

2.3 Valsartan/Hydrochlorothiazide Combination

The hypotensive effects of valsartan were potentiated by the addition of hydrochlorothiazide in spontaneously hypertensive rats (SHR). The animals were given subcutaneous injections of valsartan 1 or 3 mg/kg/day or hydrochlorothiazide 3 or 10 mg/kg/day or combinations thereof for 2 weeks; control animals received subcutaneous injections of the vehicle.[33]

Valsartan 1 and 3 mg/kg/day produced dose-dependent and significant ($p < 0.05$ *vs* vehicle) reductions in mean arterial pressure (mean reductions of ≈12 and 21mm Hg); mean reductions with hydrochlorothiazide 3 or 10 mg/kg/day were dose independent (≈8 and 6mm Hg, $p < 0.05$ for both).[33] When valsartan 1 mg/kg/day was administered with hydrochlorothiazide 3 or 10 mg/kg/day, an additive hypotensive effect was observed (mean reductions of ≈19mm Hg with both regimens). An additive hypotensive effect was also obtained when valsartan 3 mg/kg/day and hydrochlorothiazide 3 mg/kg/day were coadministered (mean reduction of ≈37mm Hg); the result almost achieved statistical significance for synergy. However, when the two higher dosages of valsartan and hydrochlorothiazide were coadministered, a synergistic hypotensive effect was observed, with a mean reduction in arterial pressure of ≈38mm Hg. Although heart rate was ≈30 beats per minute faster in animals treated with the higher dosage combination than that recorded in vehicle-treated animals, it gradually diminished over the 2-week treatment period, and was the same in both groups on day 14.[33]

3. Pharmacokinetic Properties

There are few data available pertaining to the pharmacokinetics of valsartan and hydrochlorothiazide when administered together. Therefore, the majority of the information presented in this section relates to studies performed in healthy volunteers or patients with hypertension who received valsartan or hydrochlorothiazide alone. Results from these studies are summarised in (table III).

Table III. Pharmacokinetic parameters of valsartan and hydrochlorothiazide after oral administration of a single dose of each drug alone to healthy volunteers[30,34,38]

Parameter	Valsartan 80mg	Hydrochlorothiazide 12.5mg
C_{max} (mg/L)	1.64	0.075
AUC_{24h} (mg • h/L)	8.54	NR
t_{max} (h)	2	1.9
$t_{½}$ (h)	7.05	2.5-18.9
F (%)	23	66-75

AUC_{24h} = area under the plasma concentration-time curve from 0 to 24 hours; **C_{max}** = peak plasma concentration; **F** = bioavailability; **NR** = not reported; **$t_{½}$** = elimination half-life; **t_{max}** = time to Cmax.

3.1 Valsartan

3.1.1 Absorption and Distribution

After oral administration of a single 80mg capsule to 12 healthy volunteers, valsartan was rapidly absorbed, with a peak plasma concentration (C_{max}) of 1.64 mg/L reached 2 hours (t_{max}) postdose; the area under the plasma concentration-time curve from 0 to 24 hours (AUC_{24h}) and absolute bioavailability of valsartan were 8.54 mg • h/L and 23%.[34] C_{max} (3.46 mg/L) and AUC_{24h} (21.33 mg • h/L) values were correspondingly higher after oral administration of single-dose valsartan 200mg to 16 healthy volunteers, but t_{max} was similar (2 hours).[35] Valsartan is extensively bound to plasma proteins (85 to 99%);[19,36] the volume of distribution after bolus intravenous administration of valsartan 20mg to 12 volunteers was approximately 17L.[34]

In a randomised, double-blind, placebo-controlled study in patients with hypertension (presented as an abstract), minimal accumulation was observed after repeated administration (once daily for 4 weeks) of valsartan 10 to 160mg. On day 28, mean C_{max} of valsartan 80mg was ≈1.5 mg/L (estimated from a graph) and was reached 2 hours postdose.[37]

3.1.2 Metabolism and Elimination

Valsartan is eliminated mainly by hepatic clearance; faecal excretion accounts for ≈86% of an

orally administered dose of valsartan, whereas ≈13% is excreted renally. The drug is predominantly excreted unchanged; 71% of an orally administered dose of valsartan is excreted unchanged in the faeces and 10% is excreted unchanged in the urine. Approximately 9% of the excreted dose (1 and 8% in the urine and faeces) is accounted for by valeryl-4-hydroxy-valsartan, the predominant metabolite (inactive) of valsartan which appears in the plasma about 8 hours postdose. Renal excretion is largely complete 2 days postdose but substantial faecal elimination continues until day 4.[39] Although it is not known which enzymes are involved in the metabolism of valsartan, the structurally related drug losartan is metabolised by cytochrome P450 (CYP) 2C9 and 3A4. Because valsartan is dianionic, CYP2C9 (which has shown preference for anionic substrates) is thought to be involved.[39]

The mean terminal half-life ($t_{½}$) after administration of an 80mg dose of valsartan to 12 healthy volunteers was 7.05 hours. The $t_{½}$ and plasma clearance after bolus intravenous administration of valsartan 20mg to 12 volunteers was 9.45 hours and 2.19 L/h; 29% of the dose was excreted unchanged in the urine.[34]

3.1.3 Special Patient Populations

Mean systemic exposure to valsartan was greater in 12 elderly (mean age 76 years) than in 12 young (mean age 23 years) volunteers in a study evaluating the effects of age on the pharmacokinetics of valsartan.[40] After administration of single-dose valsartan 80mg, the mean AUC_{24h} was 52% higher in the elderly than in the young volunteers (23.7 *vs* 15.6 mg • h/L). Although t_{max} was similar in both groups, the median $t_{½}$ of valsartan was 46% higher in the elderly patients. These differences were not attributable to any measured covariates, including creatinine clearance, bilirubin or ALT concentrations, body surface area or weight, or concomitant medication. Moreover, age did not entirely account for these differences. Therefore, initial dosage adjustments based solely on age were not considered necessary.[40]

Results from a study in patients with mild to moderate renal dysfunction showed no relationship between renal function and the pharmacokinetics of valsartan.[41] However, in contrast to these results, a more recent study showed that the AUC_{24h} of valsartan at steady state was significantly ($p \leq 0.05$) higher in patients with hypertension undergoing long-term haemodialysis than in patients with hypertension and normal renal function.[42] Once-daily valsartan 80mg was administered for 15 days to 40 patients with hypertension (DBP ≥90 and <115mm Hg) with either normal renal function [creatinine clearance >70 ml/min (4.2 L/h)] or renal impairment requiring long-term (≥3 months) haemodialysis. On day 15, the AUC_{24h} of valsartan was 52% higher in patients on haemodialysis than in those with normal renal function (16.9 *vs* 11.1 mg • h/L; $p \leq 0.05$). Although mean C_{max} and t_{max} values were higher (by 22 and 67%) in patients on haemodialysis, the mean differences did not reach statistical significance. The increase in plasma concentrations of valsartan in patients with renal insufficiency may be explained by the 12.5% lower concentration of plasma albumin, and, presumably, a lower concentration of protein-bound valsartan, observed in the group on haemodialysis.[42] The incidence of adverse events, however, was similar in both groups of patients.

After oral administration of single-dose valsartan 160mg to patients with mild (n = 6) or moderate (n = 6) hepatic impairment, the AUC_{36h} was approximately 2-fold higher than that in healthy volunteers (≈46 *vs* 21 mg • h/L). C_{max} values of 5.9 and 3.9 mg/L were reached 3.5 and 4.0 hours postdose in patients with mild and moderate hepatic insufficiency, respectively.[43]

3.2 Hydrochlorothiazide

After administration of a single dose of hydrochlorothiazide 12.5mg to healthy adults, a C_{max} of 0.075 mg/L was achieved 1.9 hours postdose; C_{max} after administration of hydrochlorothiazide 12.5mg once daily for 5 days was 0.091 mg/L, and t_{max} was 2 hours.[30] The bioavailability of orally administered hydrochlorothiazide is 66 to 75%, and 40 to 58% is protein-bound.[30,38,44] Hydrochlorothiazide does not undergo metabolism, and ≥61% of

an oral dose is excreted unchanged in the urine within 24 hours of the dose; reports of the $t_{1/2}$ range from 2.5 to 18.9 hours.[30,38,44]

3.3 Valsartan/Hydrochlorothiazide

Results from a crossover study in which 12 healthy volunteers received single doses of valsartan 160mg, hydrochlorothiazide 25mg or valsartan/hydrochlorothiazide 160/25mg demonstrated that hydrochlorothiazide has no effect on the pharmacokinetics of valsartan, but valsartan does modify hydrochlorothiazide pharmacokinetics, albeit to a clinically insignificant extent.[45] The mean AUC_{24h}, C_{max} and the apparent $t_{1/2}$ for hydrochlorothiazide were reduced by 22, 26 and 35% when administered with valsartan. The amount of hydrochlorothiazide excreted in the urine was reduced by 15% (not significant), although it was not reported over what time period this reduction was recorded.

C_{max} and AUC_{48h} values for valsartan and hydrochlorothiazide after the administration of fixed-combination tablets or each drug alone to 37 volunteers were within the limits of bioequivalence.[45]

3.4 Drug Interactions

Coadministration of valsartan with amlodipine, atenolol, cimetidine, digoxin, furosemide, glibenclamide (glyburide), hydrochlorothiazide, indomethacin or warfarin produced no clinically significant pharmacokinetic interactions.[44] Because metabolic clearance of valsartan is low (section 3.1.2), coadministration of a drug that inhibits or induces CYP enzymes should not significantly affect the pharmacokinetics of valsartan.[39]

Coadministration of hydrochlorothiazide with anionic exchange resins reduces the absorption of hydrochlorothiazide from the gastrointestinal tract; single doses of cholestyramine or colestipol resins reduced hydrochlorothiazide absorption by up to 85 and 43%.[44]

Hydrochlorothiazide may interact with alcohol, barbiturates, narcotics, antidiabetic drugs, corticosteroids and NSAIDs. Because diuretics reduce the renal clearance of lithium, hydrochlorothiazide should not generally be coadministered with lithium (section 6).[44]

4. Therapeutic Efficacy

The therapeutic efficacy of valsartan/hydrochlorothiazide in patients with essential hypertension has been evaluated in several randomised, double-blind, multicentre studies (n = 217 to 871),[46-49] and in nonblind,[50] (n = 148), noncomparative[51] (n = 28 005; duration 3 months) or extension studies.[52,53] The valsartan/hydrochlorothiazide combination was administered once daily as either a fixed combination tablet[47,49-51] or as separate tablets of each drug.[46,48,52,53]

In general, comparative trials included patients ≥18 years of age with mild to moderate essential hypertension [sitting DBP (sDBP) 95 to 115mm Hg], although two studies enrolled patients with more severe disease (sDBP 95 to 120mm Hg[48] or 95 to 130mm Hg[49]). Studies generally included patients who were without significant comorbidities. Most studies were preceded by a 1- to 3-week washout period during which previous antihypertensive medication was discontinued. Only the large noncomparative study allowed patients to take other antihypertensive drugs concurrently.[51] Some of the studies evaluated the efficacy of valsartan/hydrochlorothiazide combination therapy in patients unresponsive to either valsartan[48-50] or hydrochlorothiazide[47] monotherapy.

In all studies, the primary endpoint was the mean reduction from baseline in trough sDBP, although sitting SBP (sSBP) was also reported. In some of the studies,[46-48,51] patients were classified as responders if, at treatment endpoint, sDBP was <90mm Hg or they had a ≥10mm Hg reduction from baseline in sDBP. In studies evaluating the use of combination therapy in patients unresponsive to monotherapy with valsartan or hydrochlorothiazide,[47,48] patients were deemed nonresponders if sDBP was ≥95mm Hg and ≤115mm Hg after the 4-week monotherapy treatment phase. In a comparative trial with amlodipine, patients were deemed unresponsive to 4 weeks' monother-

apy with valsartan or amlodipine if sSBP was ≥150mm Hg, sDBP was ≥90mm Hg or if they had a decrease in sSBP of ≤20 or ≤30mm Hg if baseline sSBP was <180 or >180mm Hg, respectively.[49]

4.1 Comparisons with Valsartan or Hydrochlorothiazide Monotherapy

4.1.1 Dose-Response Study

Combinations of valsartan (80 or 160mg) and hydrochlorothiazide (12.5 or 25mg) were effective in the treatment of patients with mild to moderate essential hypertension and produced greater reductions in BP than the corresponding dosage of either drug alone (table IV and figure 2).[46] After a 2-week washout period and a further 2- to 4-week single-blind placebo run-in during which placebo responders were identified and excluded, 871 patients were randomised to receive double-blind valsartan 80 or 160mg, hydrochlorothiazide 12.5 or 25mg, or a combination of valsartan 80 or 160mg with hydrochlorothiazide 12.5 or 25mg or placebo, administered once daily for 8 weeks.

At week 8, although monotherapy with valsartan 80 or 160mg ($p < 0.001$ for both dosages) or hydrochlorothiazide 12.5 ($p < 0.05$) or 25mg ($p < 0.001$) produced significant reductions in sSBP and sDBP compared with placebo, the greatest reductions were recorded in the valsartan plus hydrochlorothiazide 80 plus 25mg and 160 plus 25mg groups (table IV). Moreover, doubling the dosage of the hydrochlorothiazide component of the combination appeared to have a greater hypotensive effect than doubling the dosage of valsartan.

The percentage of patients who had responded to treatment at week 8 was significantly ($p < 0.05$) higher with valsartan plus hydrochlorothiazide 80 plus 25mg, 160 plus 12.5mg and 160 plus 25mg groups than with valsartan or hydrochlorothiazide monotherapy at either dosage; response to valsartan plus hydrochlorothiazide 80 plus 12.5mg was significantly higher than that to hydrochlorothiazide ($p < 0.05$) but not valsartan monotherapy (table IV).[46]

4.1.2 In Patients Not Achieving a Response with Valsartan or Hydrochlorothiazide Monotherapy

Valsartan in combination with hydrochlorothiazide was effective at reducing BP in patients with hypertension not responding to either valsartan[48] or hydrochlorothiazide[47] monotherapy in two double-blind studies. In one study,[48] patients with essential hypertension (sDBP ≥95 and ≤120mm Hg) received 4 weeks of single-blind treatment

Table IV. Results from an 8-week randomised, double-blind, parallel-group, multicentre, dose-response study in patients with mild to moderate hypertension[46]

Treatment (mg/day)	No. of evaluable patients	Mean baseline sitting SBP/DBP (mm Hg)[a]	Reduction in mean sitting SBP/DBP at endpoint (mm Hg)	Response rate (%)[b]
VAL 80	99	153.7/101.5	8.8***/8.6***	54***
VAL 160	97	153.5/101.5	12.1***/9.4***	59***
HCTZ 12.5	99	153.6/101.2	7.3**/7.2*	41***
HCTZ 25	100	152.0/100.8	12.7***/9.3***	54***
VAL 80 + HCTZ 12.5	96	153.0/101.0	16.5***††‡/11.8***†‡	64***φ
VAL 80 + HCTZ 25	91	152.0/100.4	21.2***††‡/15.7***††‡	81***§φ
VAL 160 + HCTZ 12.5	96	154.5/101.0	17.8***†‡/13.5***††‡	76***§φ
VAL 160 + HCTZ 25	94	155.9/101.4	22.5***††‡/15.3***††‡	81***§φ
PL	93	152.7/101.4	1.9/4.1	29

a Baseline data include 6 patients who discontinued therapy prior to any postrandomisation measurements and were not evaluated for response.

b Response was defined as a sitting DBP of <90mm Hg or a ≥10mm Hg reduction in sitting DBP from baseline.

DBP = diastolic blood pressure; **HCTZ** = hydrochlorothiazide; **PL** = placebo; **SBP** = systolic blood pressure; **VAL** = valsartan; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* placebo; † $p < 0.01$, †† $p < 0.001$ *vs* VAL monotherapy at the corresponding dosage; ‡ $p < 0.001$ *vs* HCTZ monotherapy at the corresponding dosage; § $p < 0.05$ *vs* VAL monotherapy at either dosage; φ $p < 0.05$ *vs* HCTZ monotherapy at either dosage.

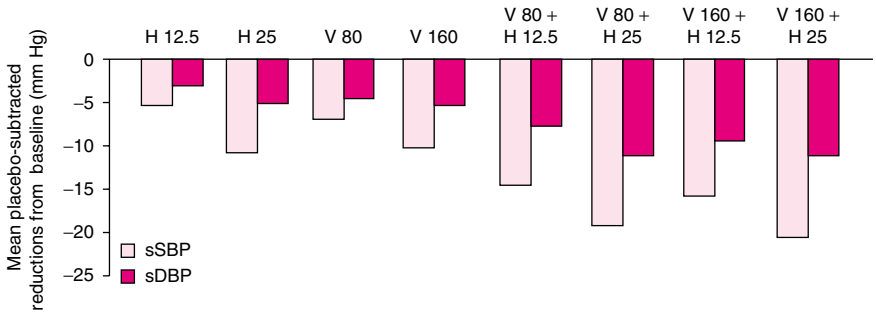


Fig. 2. Efficacy of valsartan (V) plus hydrochlorothiazide (H) compared with monotherapy with either agent; placebo-subtracted reductions from baseline in sSBP and sDBP. 871 patients with mild to moderate hypertension were randomised to receive double-blind valsartan 80 or 160mg, hydrochlorothiazide 12.5 or 25mg, or a combination of valsartan 80 or 160mg with hydrochlorothiazide 12.5 or 25mg or placebo, administered once daily for 8 weeks.[46] **sDBP** = sitting diastolic blood pressure; **sSBP** = sitting systolic blood pressure.

with valsartan 80mg after a 2-week placebo run-in. Following this lead-in period, 708 patients with sDBP ≥95 and ≤115mm Hg (i.e. inadequately controlled after monotherapy) were randomised (stratified by age) to receive valsartan 80 or 160mg or valsartan plus hydrochlorothiazide 80 plus 12.5mg or 80 plus 25mg for 8 weeks. A similar protocol was followed in the other study; 217 patients with an sDBP of ≥95 and ≤114mm Hg after a single-blind 2-week placebo run-in and 4 weeks of single-blind treatment with hydrochlorothiazide 12.5mg were randomised to receive hydrochlorothiazide 12.5 or 25mg or fixed-dose valsartan/hydrochlorothiazide 80/12.5mg for 8 weeks.[47]

Patients in both studies who received combination therapy had significantly greater reductions in sSBP and sDBP than patients who received valsartan ($p < 0.025$) or hydrochlorothiazide ($p < 0.001$) monotherapy (table V).[47,48] Among the valsartan monotherapy nonresponders, mean reductions from baseline in sSBP and sDBP were significant for all treatment groups ($p < 0.0001$);[48] a statistical analysis on corresponding data for the hydrochlorothiazide nonresponders was not reported.[47]

The greatest reduction in sDBP among nonresponders to valsartan monotherapy was seen in the valsartan plus hydrochlorothiazide 80 plus 25mg group (10.8mm Hg); this reduction was significantly greater than that in patients who received valsartan 80 (5.1mm Hg, $p < 0.0001$) or 160mg (6.2mm Hg, $p < 0.0001$) [table V]. Moreover, although the reduction in sDBP in valsartan plus hydrochlorothiazide 80 plus 12.5mg recipients (8.2mm Hg) was not as large as that in the valsartan plus hydrochlorothiazide 80 plus 25mg group, it was still significantly greater than the reduction observed in patients treated with valsartan 80 ($p = 0.0002$) or 160mg ($p < 0.025$) [table V].[48]

At week 8, response rates were significantly higher with valsartan plus hydrochlorothiazide 80 plus 12.5mg ($p \leq 0.01$) or 80 plus 25mg ($p < 0.0001$) than with valsartan monotherapy (table V),[48] and more than double the number of patients who responded to hydrochlorothiazide 12.5 or 25mg (≈26% in each group) responded to treatment with valsartan/hydrochlorothiazide 80/12.5mg (table V).[47]

4.2 Long-Term Efficacy

The efficacy of valsartan plus hydrochlorothiazide was maintained over the long-term in 1-, 2- and 3-year nonblind extension studies in patients with mild to moderate essential hypertension.[52,53] The 1-year extension study followed an 8-week randomised, double-blind, monotherapy study in which 736 patients received valsartan 20, 80, 160

Table V. Results from two 8-week randomised, double-blind, parallel studies in patients with hypertension inadequately controlled by valsartan (VAL) or hydrochlorothiazide (HCTZ) monotherapy.

Reference	Treatment (mg/day) [no. of evaluable pts]	Mean baseline sitting SBP/DBP (mm Hg)[a]	Reduction in mean sitting SBP/DBP at endpoint (mm Hg)	Response rate (%)[b]
Patients unresponsive to VAL monotherapy				
Hall et al.[48]	VAL 80 [179]	150.1/100.2	3.9/5.1	36
	VAL 160 [171]	149.2/99.8	6.5/6.2	37
	VAL 80 + HCTZ 12.5 [176]	149.6/99.9	9.8***†/8.2**†	51*††
	VAL 80 + HCTZ 25 [176]	152.4/100.6	16.0***†††/10.8***†††	59***†††
Patients unresponsive to HCTZ monotherapy				
Schmidt et al.[47]	HCTZ 12.5 [73]	153.8/102.9	5.2/2.9	25.4
	HCTZ 25 [72]	156.3/102.6	6.8/5.7	26.8
	VAL/HCTZ 80/12.5 [70][c]	155.8/103.5	14.9‡/11.2‡	60.3

a Baseline data in the study by Hall et al.[48] include 6 patients who discontinued therapy prior to any postrandomisation measurements and were not evaluated for response.

b Response was defined as a DBP of <90mm Hg or a ≥10mm Hg reduction in DBP from baseline.

c Patients received fixed-dose combination tablets.

DBP = diastolic blood pressure; **SBP** = systolic blood pressure; * $p \leq 0.01$, ** $p = 0.0002$, *** $p < 0.0001$ *vs* VAL 80mg; † $p < 0.025$, †† $p \leq 0.01$, ††† $p < 0.0001$ *vs* VAL 160mg; ‡ $p < 0.001$ *vs* HCTZ 12.5 or 25mg.

or 320mg or placebo.[54] Upon completion, 376 patients were then enrolled in the year-long study and received valsartan 160mg once daily for 52 weeks; hydrochlorothiazide 12.5 or 25mg could be prescribed after week 4 if sDBP was ≥90mm Hg.[52] The 2-year study was preceded by an unpublished 6-week randomised, double-blind, monotherapy study in which patients received valsartan 20, 40 or 80mg or placebo. 399 patients were subsequently enrolled in the 2-year extension study and initially received valsartan 20mg, with titration to 40 or 80mg over 6 weeks dependent on BP control; hydrochlorothiazide 12.5 or 25mg could be added to the treatment regimen at any time during the study.[52] At the completion of this 2-year study, 73 patients who had been receiving valsartan 80mg plus hydrochlorothiazide 12.5 or 25mg for ≥1 year entered an additional year-long extension.[53]

At the end of the year-long study, 52% of patients had received at least one dose of hydrochlorothiazide 12.5 or 25mg. At week 52, mean sSBP-/sDBP was reduced from baseline (pre-double-blind study) by 13.2/14.1mm Hg in the valsartan 160mg group and by 20.6/14.2mm Hg in the valsartan 160mg plus hydrochlorothiazide 12.5 or 25mg groups;[52] mean reductions from baseline at the end of the 8-week double-blind study ranged from 6.3/5.4 to 10.6/8.5mm Hg in the valsartan 20 to 320mg groups.[54]

Mean reductions in sSBP/sDBP observed during the first few months of treatment with valsartan plus hydrochlorothiazide were comparable to those seen after 1 and 2 years of therapy in the 2-year extension study.[52] At the end of the second year, sSBP/sDBP was 14.3/11.8mm Hg lower than pre-treatment values in the valsartan plus hydrochlorothiazide group, compared with 9.7/12.4mm Hg in the valsartan monotherapy group. These values were similar to the 3-year reductions in BP seen in patients who received valsartan plus hydrochlorothiazide 80 plus 12.5mg (n = 18) or 80 plus 25mg (n = 55) for ≥2 years; reductions in sSBP/-sDBP compared with pre-treatment values were 11.7/12.5 and 16.4/12.6mm Hg.[53]

4.3 Comparison with Amlodipine

Results from a randomised, double-blind, multicentre study suggest that fixed-dose valsartan/hydrochlorothiazide 80/12.5mg is as effective as amlodipine 10mg in the treatment of patients with mild to moderate essential hypertension,[49] and

that valsartan/hydrochlorothiazide provides effective 24-hour ambulatory BP control.[55]

After a 2-week, single-blind, placebo washout period, 690 patients with an sDBP of ≥95mm Hg and an sSBP of ≥160mm Hg were randomised to receive valsartan 80mg (n = 342) or amlodipine 5mg (n = 348) for 4 weeks. After this 4-week period, patients who did not meet any of the response criteria (sSBP <150mm Hg, sDBP <90mm Hg or a decrease in sSBP of >20 or >30mm Hg if baseline sSBP was <180 or >180mm Hg, respectively) received valsartan/hydrochlorothiazide 80/12.5mg or amlodipine 10mg for 8 weeks (patients initially randomised to valsartan 80mg or amlodipine 5mg received valsartan/hydrochlorothiazide 80/12.5mg or amlodipine 10mg, respectively).[49] 24-hour ambulatory BP was recorded in 259 patients after 12 weeks of treatment with valsartan/hydrochlorothiazide 80/12.5mg (n = 133) or amlodipine 5 or 10mg (n = 126) and was reported separately.[55]

After 4 weeks of monotherapy, 57.4 and 61.9% of valsartan and amlodipine recipients, respectively, had responded to treatment (not significantly different);[49] mean reductions from baseline in sSBP/sDBP were similar in the valsartan (19.5/10.1mm Hg) and amlodipine (20.2/10.3mm Hg) groups (figure 3). At week 12, 74.9% of patients receiving valsartan 80mg or valsartan/hydrochlorothiazide 80/12.5mg had responded, compared with 72.1% of those receiving amlodipine 5 or 10mg (not significant). During weeks 5 to 12, sSBP/sDBP fell a further 6.9/4.2mm Hg in patients receiving valsartan or valsartan/hydrochlorothiazide, compared with reductions of 6.2/3.5mm Hg in amlodipine (5 or 10mg) recipients (not significant; figure 3). An analysis including only the patients receiving valsartan/hydrochlorothiazide 80/12.5mg or amlodipine 10mg (i.e. the nonresponders after 4 weeks of monotherapy) was not reported.[49]

At week 12, both valsartan/hydrochlorothiazide 80/12.5mg and amlodipine 5 or 10mg provided effective 24-hour ambulatory BP control. The trough-to-peak ratio was 0.61/0.57 for valsartan/-hydrochlorothiazide and 0.56/0.56 for amlodipine.

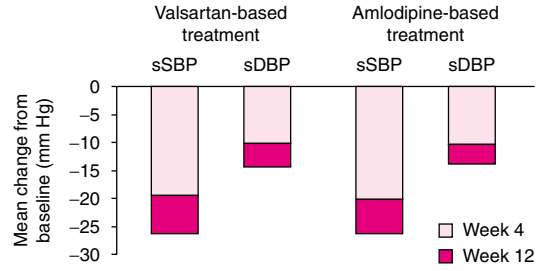


Fig. 3. Antihypertensive efficacy of valsartan/hydrochlorothiazide compared with that of amlodipine. 690 patients with mild to moderate hypertension were randomised to receive valsartan 80mg (n = 342) or amlodipine 5mg (n = 348) for 4 weeks. After this 4-week period, patients unresponsive to treatment with valsartan 80mg or amlodipine 5mg received valsartan/hydrochlorothiazide 80/12.5mg or amlodipine 10mg, respectively, for 8 weeks.[49] **sDBP** = sitting diastolic blood pressure; **sSBP** = sitting systolic blood pressure;

When only responders to treatment were considered, night-time BP was controlled more effectively with valsartan/hydrochlorothiazide than with amlodipine 5 or 10mg (p = 0.03).[55]

4.4 Comparison with Valsartan Plus Benazepril

Valsartan/hydrochlorothiazide 80/12.5mg and valsartan 80mg plus benazepril 10mg produced similar reductions in sSBP/sDBP after 4 weeks of combination therapy in patients unresponsive to 4 weeks of valsartan 80mg monotherapy in a randomised, nonblind, multicentre study in 327 patients with mild to moderate essential hypertension.[50]

After a 2-week wash-out period, 327 patients with sDBP >95 and <115mm Hg received valsartan 80mg for 4 weeks. At week 4, patients with sDBP ≤90mm Hg continued to receive valsartan 80mg (n = 153), whereas patients with sDBP >90 but ≤110mm Hg were randomised to either valsartan/hydrochlorothiazide 80/12.5 (n = 74) or valsartan 80mg plus benazepril 10mg (n = 74) for a further 4 weeks.[50]

Although mean BP in the monotherapy group was significantly lower than in the combination therapy groups at week 8 (p < 0.001 for both), both

valsartan/hydrochlorothiazide ($p < 0.001$) and valsartan plus benazepril ($p < 0.05$) induced significant reductions in sSBP/sDBP from week 4 in patients unresponsive to valsartan monotherapy (figure 4). There were no statistically significant differences in sSBP or sDBP reductions between the two combination therapy groups.[50]

4.5 Post-Marketing Study

Valsartan/hydrochlorothiazide 80/12.5mg effectively reduced sSBP/sDBP in patients with mild to severe essential hypertension enrolled in a large 3-month noncomparative study.[51] Of the 28 005 evaluable patients with mild (59.2%), moderate (27.3%) or severe (5.0%) hypertension who received valsartan/hydrochlorothiazide for 3 months, 6447 were taking concomitant antihypertensive medication. Of all patients, 76.8% had been previously treated for hypertension, and mean baseline sSBP/sDBP was 172.4/99.6mm Hg. Concomitant hypercholesterolaemia, cardiovascular disease and/or type 2 diabetes mellitus were present in 39.9, 36.5 and 19.8% of patients.

The overall mean sSBP/sDBP was reduced to 145.0/84.9mm Hg (a reduction of 27.4/14.7mm Hg). 89.0% of patients responded to treatment, and 62.5% were classified as having normalised BP. Similar results were obtained in those patients who received valsartan/hydrochlorothiazide without concomitant antihypertensive medication (n = 21 558). In this patient group, mean sSBP/sDBP fell from baseline values of 171.2/99.4mm Hg to 144.1/84.6mm Hg (mean reduction of 27.1/14.9mm Hg) after three months of treatment. Valsartan/hydrochlorothiazide was effective irrespective of age, gender, concomitant illness or severity of hypertension.[51]

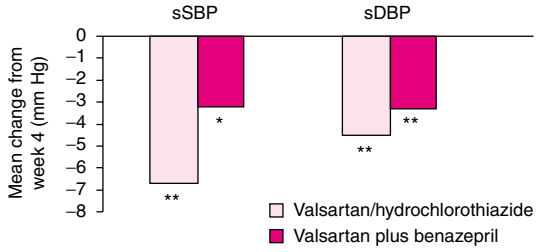


Fig. 4. Antihypertensive efficacy of valsartan/hydrochlorothiazide and valsartan plus benazepril in patients unresponsive to valsartan monotherapy. 327 patients with sDBP >95 and <115mm Hg received valsartan 80mg for 4 weeks. At week 4, patients with sDBP >90 but ≤110mm Hg (i.e. nonresponders to monotherapy) were randomised to either valsartan/hydrochlorothiazide 80/12.5mg (n = 74) or valsartan 80mg plus benazepril 10mg (n = 74) for a further 4 weeks.[50] * $p < 0.05$, ** $p < 0.001$ *vs* week 4 values. **sDBP** = seated diastolic blood pressure; **sSBP** = seated systolic blood pressure.

5. Tolerability

The combination of valsartan with hydrochlorothiazide is generally well tolerated in patients with mild to moderate essential hypertension. The most common adverse events in controlled trials were dizziness, headache and fatigue, and occurred at a similar frequency in the valsartan plus hydrochlorothiazide and placebo groups.[44,46,48] Adverse event data from the dose-response study discussed in section 4.1.1 are presented in figure 5.[46] In this study, dizziness, headache and fatigue were the most common adverse events occurring in >3% of patients who received combination therapy with valsartan plus hydrochlorothiazide; there were no statistically significant differences in the incidence of these adverse events between valsartan or combination groups and the placebo group.

In the manufacturer's prescribing information,[44] data from >1300 patients who received treatment with valsartan/hydrochlorothiazide in controlled clinical trials (duration of 8 weeks to >1 year) also indicate good tolerability, with the overall incidence of adverse events with valsartan/hydrochlorothiazide being similar to that with placebo. Of valsartan/hydrochlorothiazide recipients, 3.6% discontinued treatment because of adverse events, compared with 4.3% of placebo recipients; headache, dizziness and fatigue were the most common reasons for discontinuation.[44]

According to the manufacturer,[44] hypokalaemia (serum potassium concentration <3.5 mEq/L) was observed in 4.5% of patients who received various dosages of valsartan/hydrochlorothiazide in controlled clinical trials. In the dose-response study,[46] valsartan attenuated the hypokalaemic

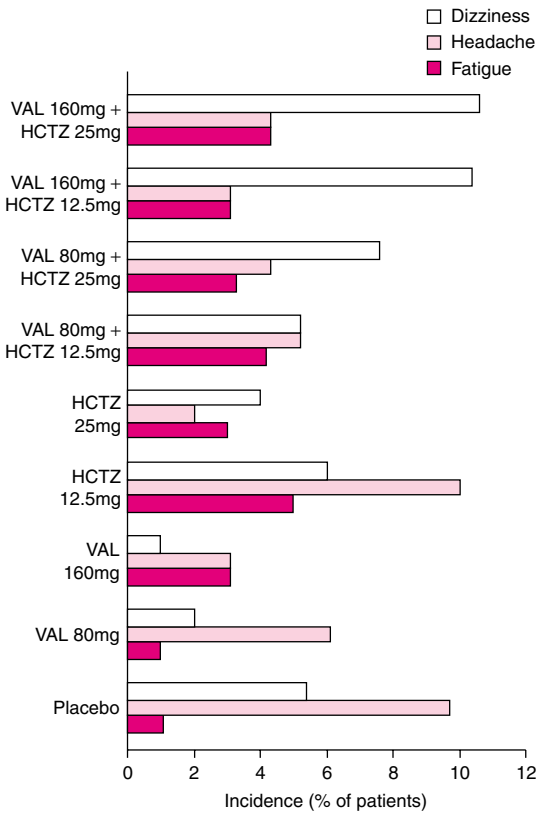


Fig. 5. Tolerability of valsartan plus hydrochlorothiazide (VAL + HCTZ); results from a randomised, double-blind, placebo-controlled, multicentre study in patients with essential hypertension. 871 patients were randomised to receive a once-daily dose of placebo, VAL 80 or 160mg, HCTZ 12.5 or 25mg, or a combination of VAL 80 or 160mg with HCTZ 12.5 or 25mg for 8 weeks.[46]

effect of hydrochlorothiazide; indeed, as stated by the authors, the differing effects of valsartan and hydrochlorothiazide on serum potassium may balance each other in many patients. Among patients who received placebo or valsartan 80 or 160mg monotherapy, 3.3, 1.1 and 0% of patients had a >20% decrease in serum potassium concentrations, compared with 6.2 and 11.1% of patients who received monotherapy with hydrochlorothiazide 12.5 or 25mg. However, in the combination therapy groups, 1.0, 2.1, 8.9 and 4.4% of patients who received valsartan plus hydrochlorothiazide 80 plus 12.5mg, 160 plus 12.5mg, 80 plus 25mg or 160 plus 25mg had more than a 20% reduction in serum potassium concentrations.

In randomised double-blind trials,[46-49] there was one reported case of orthostatic hypotension in a patient who was receiving valsartan plus hydrochlorothiazide 160 plus 25mg; there were no reported cases of treatment-related angioneurotic oedema.

Long-term (1 to 3 years' duration) nonblind extensions of controlled trials reported similar drug-related adverse events to those seen in shorter term studies, and no increase in incidence over time.[52,53] In a 2-year extension study,[52] one patient receiving valsartan plus hydrochlorothiazide experienced symptomatic orthostatic hypotension.

Valsartan/hydrochlorothiazide and valsartan plus benazepril were both well tolerated in 148 patients receiving these combinations in a nonblind study, with 15% of patients in each group reporting ≥1 adverse event.[50] However, valsartan/hydrochlorothiazide was shown to be better tolerated than amlodipine in a randomised, double-blind trial in 690 patients with hypertension.[49] The combined incidence of adverse events among patients who received valsartan 80mg monotherapy or valsartan/hydrochlorothiazide 80/12.5mg was 1.5%, compared with 5.5% in patients who received amlodipine 5 or 10mg ($p = 0.006$). The predominant difference in adverse events was the higher rate of lower-limb oedema in amlodipine recipients (3.2 *vs* 0.6%).

In a double-blind study designed to compare the incidence of cough in 129 patients with essential hypertension and a history of ACE inhibitor-induced cough treated with valsartan, hydrochlorothiazide or lisinopril, significantly fewer patients treated with valsartan (19.5%) or hydrochlorothiazide (19.0%) experienced a persistent dry cough compared with lisinopril recipients (68.9%, $p < 0.001$ for both).[56]

6. Dosage and Administration

Valsartan/hydrochlorothiazide is indicated for the treatment of patients with hypertension who have not achieved adequate BP control after re-

ceiving monotherapy with either drug. The following information has been taken from the US prescribing information.[44] When used as monotherapy, recommended daily doses of valsartan and hydrochlorothiazide range from 80 to 320mg and 12.5 to 50mg, respectively. In patients unresponsive to monotherapy, combination treatment should be initiated at a dosage of valsartan/hydrochlorothiazide 80/12.5mg once daily. If BP remains uncontrolled after 3 to 4 weeks, the dosage of valsartan or both components may be titrated to valsartan/-hydrochlorothiazide 160/25mg once daily depending on clinical response. Studies evaluating doses of valsartan >160mg in combination with hydrochlorothiazide 25mg have not been conducted.

In patients who have inadequate BP control or are experiencing hypokalaemia with hydrochlorothiazide 25mg once daily, the recommended initial dosage of valsartan/hydrochlorothiazide is 80/12.5mg once daily. The dosage of valsartan/hydrochlorothiazide may then be titrated to 160/25mg if BP remains uncontrolled after 3 to 4 weeks of treatment with the lower dosage.[44]

Valsartan/hydrochlorothiazide can be administered to patients with renal impairment as long as creatinine clearance is >1.8 L/h (30 ml/min). In patients with more severe renal insufficiency, loop diuretics should be used instead of thiazide diuretics; therefore, valsartan/hydrochlorothiazide is not recommended in patients with a creatinine clearance ≤1.8 L/h. Patients with hepatic insufficiency should be monitored carefully during administration of valsartan/hydrochlorothiazide because minor alterations in fluid volume or electrolyte balance by thiazide diuretics may precipitate hepatic coma. Furthermore, patients should be advised not to use potassium supplements without consulting the prescribing physician. Because of the hydrochlorothiazide component, valsartan/hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.[44]

Valsartan/hydrochlorothiazide should not be administered to pregnant women (pregnancy category D). Drugs acting directly on the RAS (i.e. valsartan) can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Therefore, when pregnancy is detected, valsartan/hydrochlorothiazide should be discontinued. Although it is not known if valsartan is excreted in human breast milk, it does appear in the milk of lactating rats; thiazides are excreted in human breast milk. Therefore, nursing mothers should be advised to discontinue nursing or discontinue the medication.[44]

Valsartan/hydrochlorothiazide may be administered with other antihypertensive agents and can be administered with or without food; no dosage adjustments are required for elderly patients.[44]

Thiazide diuretics may interact with other drugs when administered concurrently (section 3), causing orthostatic hypotension (with alcohol, barbiturates or narcotics), hypokalaemia (with corticosteroids and adrenocorticotropic hormone), decreased response to pressor amines (e.g. noradrenaline) and increased response to skeletal muscle relaxants. Concurrently administered antidiabetic drugs may require dosage adjustments. Hydrochlorothiazide should generally not be administered with lithium because it may cause lithium toxicity. Coadministration with NSAIDs can reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients.[44]

7. Place of Valsartan/ Hydrochlorothiazide in the Management of Hypertension

Hypertension is associated with an increased risk of coronary heart disease, heart failure, stroke, renal disease and recurrent cardiovascular events; lowering BP results in significant decreases in the risk of cardiovascular morbidity and mortality.[3,6] Indeed, a retrospective analysis of randomised trials involving patients with hypertension concluded that lowering DBP by 5 to 6mm Hg for about 5 years with antihypertensive drugs is associated with a 42% reduction in risk of stroke and a 14% reduction in risk of coronary heart disease.[57] Furthermore, these relative risk reductions may underestimate the benefits gained from lowering BP, as

patients are often treated for more than 5 years in clinical practice, and high-risk patients are often excluded from clinical trials.[3,6] However, despite the benefits associated with reducing BP, the majority of people with hypertension have either inadequately controlled BP or are not receiving treatment at all.[3,6]

The approach to treatment of hypertension is dependent on patient characteristics and severity of disease. Nonpharmacological approaches to BP control, including smoking cessation, bodyweight reduction, increased physical exercise and moderation of alcohol and salt intake, are advised in all patients with hypertension, particularly those with additional risk factors for cardiovascular disease such as hyperlipidaemia or diabetes mellitus.[6] If adequate nonpharmacological measures are taken this may preclude or reduce the need for drug treatment; however, for the majority of patients with hypertension, pharmacological treatment is required to achieve and maintain adequate BP control. As mentioned earlier, the primary goal of antihypertensive therapy is to achieve the maximum reduction in total risk of cardiovascular morbidity and mortality. Recent guidelines presented by the JNC-VI[6] and the WHO-ISH,[3] recommend a target SBP <140mm Hg and DBP <90mm Hg, whereas British guidelines suggest a target of <140/85mm Hg.[7] Lower targets are advised for patients with comorbidities. In patients with hypertension and diabetes mellitus, the JNC-VI suggests a BP target of <130/85mm Hg;[6] an even lower target of <130/80mm Hg is advised by the American Diabetes Association.[8]

There are currently six main classes of antihypertensive agents available (diuretics, β-blockers, ACE inhibitors, calcium channel antagonists, ARBs and α-blockers), with each class of drug offering generally similar antihypertensive efficacy.[3] Which class of drug to choose for the initiation of therapy is dependent on a number of factors, such as the cardiovascular risk profile of the patient, the presence of end-organ damage, patient response to drugs from different classes, potential drug interactions and cost of the drug.[3] However, in the absence of contraindications or indications for other agents, the JNC-VI and British guidelines recommend diuretics or β-blockers for the initial treatment of uncomplicated hypertension.[6,7] These recommendations are based on results from randomised, controlled trials which demonstrated a reduction in cardiovascular morbidity and mortality with these drugs. The WHO-ISH guidelines, however, state that the choice of drug for the initiation of treatment should be tailored to the individual patient, as there is no compelling evidence that one class of drug is more beneficial than another.[3]

In addition to valsartan, six other ARBs (losartan, irbesartan, eprosartan, candesartan cilexetil, telmisartan and olmesartan medoxomil) are approved for treatment of hypertension in the US. ARBs were developed with the aim of improving upon the tolerability of ACE inhibitors. Although both classes of drug inhibit the RAS, ACE inhibitors act by inhibiting the nonspecific dipeptidase ACE, which is involved in the conversion of angiotensin I to angiotensin II. However, ACE is also involved in the inactivation of other peptides such as bradykinin and substance P. Accumulation of these peptides is associated with an increase in the incidence of cough (and, albeit rarely, angioneurotic oedema) in patients receiving ACE inhibitor treatment.[56,58] Furthermore, prolonged ACE inhibitor therapy leads to angiotensin I accumulation, some of which may 'escape' ACE inhibition and subsequently generate angiotensin II.[59] ARBs, however, bind specifically to AT_1 receptors and thus block the binding of angiotensin II, without interfering with other metabolic pathways. Indeed, in a double-blind study designed to compare the incidence of cough in patients with a history of ACE inhibitor-induced cough, treatment with valsartan or hydrochlorothiazide was associated with a significantly lower incidence of cough than treatment with lisinopril (section 5). ACE inhibitor-induced cough is therefore a compelling indication for the use of ARBs.[3,6,7]

Randomised, double-blind trials have demonstrated that valsartan as monotherapy is an effec-

tive antihypertensive agent and reduces BP to a similar extent as losartan, lisinopril, enalapril, amlodipine or hydrochlorothiazide in patients with mild to moderate hypertension.[10] Effective BP control, however, is often not achieved with monotherapy. In the Hypertension Optimal Treatment (HOT) trial, 90% of 18 790 patients with hypertension achieved a DBP ≤90mm Hg; however, 70% of patients required combination therapy.[9] Effective combinations comprise antihypertensive agents with different primary actions, thus eliciting an additive hypotensive effect. Common effective combinations include a diuretic with a β-blocker, a diuretic with an ACE inhibitor or an ARB, a calcium channel antagonist with a β-blocker or an ACE inhibitor and an α-blocker with a β-blocker.[3] Furthermore, low compliance levels in patients with hypertension remain problematic; 50 to 70% of patients change or discontinue their medication in the first 6 months of therapy, probably because of drug-related adverse events, cost of treatment and/or poor efficacy, among other reasons.[60] Therefore, fixed-dose combination products such as valsartan/hydrochlorothiazide should also increase compliance levels, and thus be particularly useful in achieving target BP levels.[5]

Data from clinical trials indicate that valsartan/hydrochlorothiazide administered once daily substantially reduces BP in patients with mild to moderate hypertension (section 4) and is well tolerated (section 5). The extent to which valsartan/hydrochlorothiazide reduced SBP and DBP was shown to be greater than reductions induced by either drug alone; i.e. the hypotensive effects of valsartan and hydrochlorothiazide are additive (section 4.1.1). The combination also effectively reduced BP in patients unresponsive to monotherapy with either valsartan or hydrochlorothiazide (section 4.1.2), and demonstrated similar efficacy to a combination of valsartan plus benazepril in patients unresponsive to valsartan monotherapy (section 4.4). In patients unresponsive to valsartan 80mg or amlodipine 5mg, valsartan/hydrochlorothiazide 80/12.5mg elicited similar reductions in BP as amlodipine 10mg, the maximum recommended dose. Although both regimens provided effective 24-hour ambulatory BP control (section 4.3), when only responders to treatment were considered, night-time BP was controlled more effectively with valsartan/hydrochlorothiazide than with amlodipine.

Although the majority of studies evaluated the combination of valsartan 80mg with hydrochlorothiazide 12.5 or 25mg, results from a dose-response study demonstrated that reductions in BP were greatest (and of a similar extent) in patients who received valsartan/hydrochlorothiazide 80/25 or 160/25mg (section 4.1.1). Patient response to treatment among recipients of valsartan/hydrochlorothiazide 80/12.5, however, was greater than that to monotherapy with hydrochlorothiazide 25mg (64 *vs* 54%). This, coupled with the observation that valsartan ameliorated the hypokalaemic effect of hydrochlorothiazide (section 5), implies that patients who have adequately controlled BP while receiving hydrochlorothiazide 25 mg/day but are experiencing hypokalaemia may be switched to therapy with valsartan/hydrochlorothiazide 80/12.5 or 160/12.5 mg/day to achieve similar BP control without the same degree of electrolyte disturbance.[46]

The overall incidence of adverse events associated with valsartan/hydrochlorothiazide in clinical trials was similar to that with placebo (section 5) and lower than that with amlodipine (1.5 *vs* 5.5%). This difference was mainly attributable to the higher rate of lower-limb oedema among amlodipine-treated patients (3.2 *vs* 0.6%), a common adverse event associated with calcium channel antagonist therapy.[61]

Although the cardiovascular protective effects of hydrochlorothiazide are well established, the clinical relevance of the significant BP reductions achieved with valsartan/hydrochlorothiazide in terms of cardiovascular morbidity and mortality remains to be established. However, the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial in 15 314 patients with mild to moderate essential hypertension is currently underway and is designed to compare the effects of

valsartan with amlodipine on cardiac mortality and morbidity; two months into the trial, patients will be administered hydrochlorothiazide 12.5 or 25mg as add-on therapy.[62,63] Furthermore, results from the recently completed Valsartan Heart Failure Trial [Val-HeFT, n = 5010] demonstrated that valsartan, when used in combination with conventional therapy for heart failure (e.g. diuretics, ACE inhibitors or β-blockers), reduces combined mortality and morbidity, and improves clinical signs and symptoms in patients with chronic heart failure.[64] The use of valsartan in patients with heart failure has recently been reviewed elsewhere.[65]

Left ventricular hypertrophy is an independent risk factor for cardiovascular morbidity and mortality[66] and is estimated to be present in 50 to 60% of patients with hypertension.[67] Because angiotensin II concentrations have been shown to correlate with left ventricular posterior wall thickness,[68,69] ARBs have the potential to prevent cardiac hypertrophy. Treatment with valsartan (plus add-on hydrochlorothiazide in 31% of patients) for 8 months significantly reduced left ventricular mass index (by 16.5%) in a small randomised comparative trial (table I).

In conclusion, the combination of valsartan (an ARB) and hydrochlorothiazide (a thiazide diuretic) is an effective treatment for patients with hypertension. Clinical trials have demonstrated that the combination is more effective than either drug alone, and is effective in patients not responding to monotherapy with either agent. Furthermore, the adverse event profile of valsartan/hydrochlorothiazide is similar to that of placebo. Unless there are compelling or specific indications for other drugs, current data support the use of valsartan/hydrochlorothiazide when patients are unresponsive to monotherapy with either agent. Results from clinical trials evaluating the effects of valsartan/hydrochlorothiazide on cardiovascular morbidity and mortality will help to further define the role of the combination in the management of hypertension.

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