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Valsartan plus hydrochlorothiazide: a review of its use since its introduction

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Introduction: This review focuses on the role of the fixed-dose combination (FDC) drug valsartan/hydrochlorothiazide (HCTZ) in the treatment of hypertension. Effective blood pressure control often is not achieved with monotherapy and, instead, requires combinations of drugs with different mechanisms of action to produce additive or synergistic effects.
Areas covered: FDC valsartan/HCTZ enhances not only efficacy for blood pressure control but also provides beneficial effects on target organs beyond that expected from arterial pressure reduction alone. Data describe key clinical trial experiences with the FDC, with particular attention to efficacy and tolerability. Literature searches of these various topics were conducted in January 2011. There is evidence of potential benefits with this combination associated with left ventricular hypertrophy, left ventricular dysfunction and renal disease. The FDC is an effective treatment for patients with hypertension and is superior to monotherapy than either drug alone.
Expert opinion: In addition to the benefits of each drug, valsartan/HCTZ's metabolic interactions reduce some of the negative effects of both compounds. With its increased simplicity, minimal side-effect profile and efficacy without a significant cost penalty, valsartan/HCTZ represents an excellent choice for antihypertensive therapy.

Keywords: fixed-dose combination, hydrochlorothiazide, hypertension, valsartan

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1. Introduction

This review focuses on the role of the fixed-dose combination (FDC) drug valsartan/hydrochlorothiazide (HCTZ) in the treatment of hypertension (**Box 1**). Hypertension has a continuous, linear relationship with the incidence of cardiac and cerebrovascular events. Patients maintained at < 140/90 mmHg have a considerably better cardiovascular prognosis than those whose blood pressure remains above this threshold. Progressive blood pressure reduction with treatment results in proportional reduction in the incidence of stroke, cardiovascular disease and mortality. An overview of randomized drug trials concluded that by lowering DBP by about 5 mmHg for 5 years, the risk of stroke is reduced 42% and the risk of coronary heart disease is reduced by 14% [1]. Guidelines presented by the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of high blood pressure (JNC-VII) and World Health Organization – International Society of Hypertension (WHO-ISH) recommend a blood pressure under 140/90 mmHg in low-risk adult patients with no signs of vascular abnormalities, early disease markers or target organ damage [2,3]. Based on the results of several clinical trials including HOPE (Heart Outcomes Prevention Evaluation), ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) and LIFE (Losartan Intervention For Endpoint Reduction in

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Box 1. Drug summary.

Drug name	Valsartan plus HCTZ
Phase	Launched
Launched indication	Hypertension/heart failure
Pharmacology description	Angiotensin II antagonist
Route of administration	Alimentary, p.o.
Chemical structure	Valsartan is chemically described as N-(1-oxopentyl)-N-[[2′-(1H-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-L-Valine. Its empirical formula is $C_{24}H_{29}N_5O_3$ Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$
Pivotal trial(s)	[46,47,49,51-54,57,58,60,64,66,71]

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Hypertension Study), recommendations suggest even lower targets of < 130/80 mmHg for patients with diabetes or chronic renal disease [4-6]. While the guidelines continue to suggest lower and more rigorous blood pressure goals, in one study only 31% of affected patients maintained controlled blood pressure below 140/90 mmHg [7]. Often this requires combinations of drugs with different mechanisms of action to produce additive or synergistic effects, as both the HOT (Hypertension Optimal Treatment) and ALLHAT trials demonstrated that the majority of study patients required at least two antihypertensive medications to achieve blood-pressure control [8-10]. FDC therapy is ideal in terms of convenience and compliance with one tablet providing more timely achievement of blood pressure targets and accelerating treatment effect by targeting multiple physiologic mechanisms that lead to hypertension control. The FDC valsartan/HCTZ combines an angiotensin II receptor antagonist and thiazide diuretic for use in hypertensive patients as initial therapy and for those not controlled on monotherapy.

2. Angiotensin receptor blocker (ARB)

Valsartan is an angiotensin II receptor blocker that selectively binds to the AT1 receptor subtype, which is responsible for the cardiovascular effects of angiotensin II. Angiotensin II is responsible for aldosterone secretion, vasoconstriction, sympathetic stimulation, renal sodium reabsorption and cardiac hypertrophy. The equilibrium achieved by these factors governs the effects of the renin-angiotensin system (RAS) system on blood pressure.

In response to decreased renal perfusion pressure, the enzyme renin is released from juxtaglomerular cells in the kidney. It catalyzes the conversion of angiotensinogen to the inactive peptide angiotensin I. The majority of angiotensin I is hydrolyzed by the angiotensin-converting enzyme (ACE) to the active peptide angiotensin II. The remainder can be converted through ACE-independent pathways mainly by chymase but also including tissue plasminogen activator, cathepsin G and chymostatin-sensitive angiotensin II-generating enzyme, allowing for the ACE escape phenomenon [11]. Ultimately, angiotensin II binds to either the AT_1 or AT_2 receptor subtypes to exert its physiologic effects. The AT_1 and AT_2 receptors exert very different effects. AT_1 receptor activation exerts the primary blood-pressure maintenance and osmoregulatory actions of angiotensin II [12-15]. Normally quiescent AT_2 receptors potentiate angiotensin II's beneficial effects, which include vasodilatation, inhibition of cell growth and proliferation, and cell differentiation. AT_2 receptors are generally downregulated in adults and are upregulated in response to tissue injury and ischemia under condition such as heart failure and postinfarct repair. ARBs, by selectively blocking the AT_1 receptors, allow angiotensin II to stimulate the unoccupied AT_2 receptors. Valsartan has been shown to reduce blood pressure, cardiac remodeling, coronary arterial thickness and perivascular fibrosis by way of AT_2 stimulation [16,17].

Left ventricular hypertrophy (LVH) is a strong, independent predictor of cardiac morbidity and mortality. Mechanical stretch induced by pressure overload is shown to release angiotensin II and stimulate cardiac fibroblast proliferation and cardiac hypertrophy by means of the AT_1 receptor [18]. LIFE was an early clinical trial that compared an ARB-based regimen with a beta-blocker-based regimen in patients who had essential hypertension and echocardiographic evidence of LVH. Patients in the ARB-based arm had a significant reduction in the primary end point of the study, a composite of cardiovascular mortality, myocardial infarction and stroke. In both arms of the study, there was a reduction of ECG-defined LVH, and the reduction was greater in the ARB-based arm. An echocardiographic substudy of LIFE in patients with ECG LVH noted that sustained blood pressure reduction with ARB-based therapy resulted in a greater reduction of echocardiographic left ventricular mass index than with beta-blocker-based therapy [6,19-20]. Valsartan has also been shown to decrease left ventricular mass in previously untreated patients with LVH [21].

ARBs reduce both all-cause mortality and heart failure hospitalizations in patients with chronic heart failure due to left ventricular systolic dysfunction [22]. In patients with New York Heart Association (NYHA) class II, III or IV, the Valsartan Heart Failure Trial (ValHeFT) demonstrated that ARB therapy significantly reduced the combined end point of morbidity and mortality along with improvement of heart failure symptoms [23]. In patients with LVH and left ventricular dysfunction additional confirmation was seen with the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) study, which also found that ARB

therapy significantly reduced all-cause mortality, death from cardiovascular causes and heart failure hospitalizations when added to existing therapies [24].

Apart from its role in the pathophysiology of hypertension and cardiovascular disease, angiotensin II is linked to progressive renal disease. Angiotensin II blockade preserves renal function by reducing intraglomerular pressure and proteinuria, which play a key role in renal scarring and disease progression in diabetes as well as other renal diseases [6]. ARB therapy in patients with established nephropathy associated with type 2 diabetes and hypertension was evaluated in the RENAAL (Reduction of Endpoints in Non-insulin-dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan) study, which noted a significant risk reduction in the development of end-stage renal disease [25].

As understanding of the effects of RAS on cardiovascular mortality has evolved beyond simply its role in regulating pressor activity and fluid/sodium homeostasis, indications for the use of RAS inhibitors now include not only hypertension but also other conditions such as heart failure, post-myocardial infarction for secondary prevention, diabetes mellitus and chronic kidney disease.

3. Valsartan

Valsartan was approved in Europe for the treatment of essential hypertension in adults in 1996 and in the USA in 1997. It is a highly selective, nonheterocyclic, noncompetitive (insurmountable) AT_1 receptor antagonist with ~ 30,000-fold lower affinity for the AT_2 receptor [26]. Valsartan is effective and well tolerated when used alone or in combination with other medications to treat high blood pressure.

After ingestion of 80 mg valsartan, the drug is rapidly absorbed with a peak plasma concentration (C_{max}) of 1.6 mg/liter reached postdose at a t_{max} of 2 h. The area under the plasma concentration-time curve from 0 to 24 h (AUC mg × h/liter) is 8.5 with a 7.1-h half-life ($t_{½}$) and 23% absolute bioavailability [27]. The bioavailability and peak plasma concentration of valsartan are altered when administered with food but clinical use does not require a dose adjustment. Valsartan provides 51% AT_1 receptor blockade over 24 h with a single 160 mg dose [28]. Although its circulating half-life is only 7.1 h, it effectively controls blood pressure over a 24-h period [29]. Orally administered valsartan is excreted mostly unchanged, with 71% excreted unchanged in feces and 10% excreted unchanged in urine. Metabolism by the CYP2C9 isoenzyme is responsible for the formation of valeryl-4-hydroxy-valsartan, an inactive metabolite that appears in plasma as the remainder of the excreted dose [30]. Valsartan is 85 – 99% bound to plasma proteins. In elderly patients, valsartan 80 mg has a higher mean $AUC_{24\ h}$ but dose adjustments are not necessary based on age [31]. Dose adjustments in patients with mild-to-moderate renal impairment are not required as there is no correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan. In patients with stable renal insufficiency, the drug has no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance or renal plasma flow in the absence of renal artery stenosis or congestive heart failure. Notably, it has minimal potential for drug interactions with no clinically significant pharmacokinetic interactions with HCTZ, warfarin, amlodipine, atenolol, cimetidine, digoxin, fursemide or glyburide [32].

4. Monotherapy clinical efficacy

Valsartan is a well-established antihypertensive medication and multiple studies confirm that it reduces both systolic (SBP) and diastolic (DBP) blood pressures in a dose dependent fashion over the 80 – 320-mg recommended dose range. It is comparable to other ARBs, ACE inhibitors, diuretics, B-adrenoceptor antagonists (beta-blockers), and calcium channel antagonists [29]. Its efficacy for blood pressure control has been established in controlled studies in patients with hypertension of mild to moderate severity in outpatient settings [33-35]. One randomized, placebo-controlled 8-week study measuring change in SBP from baseline showed valsartan produced statistically significant reductions at all doses from 80 to 320 mg [34]. Its long-term effectiveness has been established in noncontrolled, follow-up studies in which the drug was used for up to 2 years as well [32].

In mild to moderate hypertension, an ambulatory blood pressure study with valsartan 160 mg versus telmisartan 80 mg revealed better blood pressure reduction for valsartan (-18.6/-12.1 mmHg) in the 24-h mean blood pressure [36]. In severe hypertension, a 6-week study of patients randomized to either valsartan (160 mg) or atenolol (100 mg) once daily with add-on therapy as needed, demonstrated that valsartan was both as well tolerated and effective in lowering blood pressure as atenolol with a mean blood pressure reduction of -30.0/-20.0 mmHg [37]. Effective control was also demonstrated in the Val-Syst study in which a SBP reduction of 30 mmHg was demonstrated in elderly patients treated with valsartan and HCTZ if needed [38]. Increasing the dose of valsartan from 80 to 160 mg minimally impacts its peak antihypertensive effect but clearly augments receptor blockade at trough (24 h), prolonging its antihypertensive effect [39].

5. HCTZ

Thiazide diuretics have been used in the antihypertensive arsenal since 1957. Most outcome studies so far have involved thiazides, and these diuretics are relatively inexpensive, well tolerated and effective in preventing cardiovascular complications of hypertension. The ALLHAT trial demonstrated the benefits of chlorthalidone and provided the foundation for the continued recommendation of thiazide-type diuretics as first-line agents in hypertension therapy [5].

HCTZ acts in the earliest segments of the distal convoluted tubule of the nephron by blocking the sodium chloride

co-transport mechanism, which is responsible for reabsorbing ~ 25% of the filtered sodium. The blood-pressure-lowering effect of thiazides in hypertensive patients has been linked to the urinary loss of sodium ion and trace metals, decreased responsiveness to endogenous vasopressor substances, direct action on the vascular system, and chronic intracellular dehydration. In the acute phase, the blood pressure response is manifest in volume loss with a reduction in plasma volume and venous return, thereby reducing cardiac output and blood pressure. This initial reduction in blood pressure is moderated by stimulation of hypovolemia-induced activation of RAS, and the subsequent increase in systemic vascular resistance governs the magnitude of the acute blood pressure response. The initial effects evolve after a few weeks to a chronic maintenance phase with partial reversal of the initial hemodynamic responses. The blood pressure reduction continues while the plasma volume and cardiac output rise towards slightly less than pretreatment levels. Though inadequately understood, HCTZ reduces peripheral vascular resistance in responders, probably through decreasing the stimulatory effects of angiotensin II on vascular tissue. The blood pressure reduction is maintained despite near normalization of the plasma volume, perhaps as a result of chronic contraction of the extracellular fluid compartment and the vasodepressor effects on systemic vascular resistance [40,41]. The acute phase of thiazide response is preserved as a mild state of volume contraction returns with continued blood pressure reduction.

HCTZ exhibits linear pharmacokinetics. Onset of diuresis is ~ 2 h postingestion with a peak effect of 4 – 6 h and duration of diuretic effect of 6 – 12 h. After administration of 12.5 mg of HCTZ, a peak plasma concentration (C_{max}) of 0.075 mg/liter is reported 1.9 h postdose, with a t_{max} of ~ 2 h. The plasma half-life ($t_{1/2}$) of HCTZ ranges from 5.6 to 15 h. Its oral bioavailability is 66 – 75%. Approximately half of the drug is protein bound. The drug is not metabolized and 61% is excreted unchanged in the urine within 24 h post-dose [42]. Food decreases the rate and extent of absorption of HCTZ capsules, but no dose adjustment is necessary. The pharmacokinetics of the drug are affected by anionic exchange resins such as cholestyramine and colestipol, which reduce its absorption. Drug interactions include potentiation of orthostatic hypotension with alcohol, barbiturates and narcotics; hypokalemia with corticosteroids; reduced renal clearance of lithium and high risk of lithium toxicity; and reduced antihypertensive effects with nonsteroidal anti-inflammatory drugs [32].

6. Valsartan/HCTZ fixed-dose combination

Valsartan/HCTZ (valsartan 80, 160 or 320 mg and HCTZ 12.5 or 25 mg) is a once-daily FDC angiotensin II AT_1 receptor blocker/thiazide diuretic combination indicated as treatment of essential hypertension not adequately controlled by monotherapy and as initial therapy in patients with blood pressure > 160/100 mmHg likely to need multiple drugs to achieve their blood pressure target. Recommended initial or add-on therapy is 160/12.5 mg and can be titrated to a maximum dose of 320/25 mg with once-daily dosing. Maximum effects are expected within 2 – 4 weeks of dose change. The drug may be administered with or without food. It is not recommended for patients with severe renal impairment with a creatinine clearance < 30 ml/min and is contraindicated in patients with anuria or hypersensitivity to any sulfonamide-derived drug.

7. Phamacokinetics/pharmacodynamics

Pharmacokinetic data on the valsartan/HCTZ combination are scarce, but there seems to be no clinically significant pharmacokinetic interaction between valsartan and HCTZ [43]. HCTZ has no effect on the pharmacokinetics of valsartan. In one study evaluating valsartan/HCTZ 160/25 mg, valsartan did cause a clinically insignificant effect on HCTZ by reducing $AUC_{24\ h}$, C_{max} and half-life 22, 26 and 35% respectively [27,32,44]. In an animal study, potentiation of the antihypertensive effects was seen with coadministration of HCTZ and valsartan. This effect was more than simply additive, producing a synergistic response with increasing doses of HCTZ [45].

8. Fixed-dose combination clinical efficacy

The therapeutic efficacy of the FDC valsartan/HCTZ has been evaluated extensively. A 3-month, noncomparative postmarketing study of 28005 patients (mean blood pressure 172/99 mmHg) on background therapy demonstrated that 89% of patients responded to treatment with valsartan/HCTZ 80/12.5 mg with an overall blood pressure reduction of 27/14 mmHg. In the subset of patients not taking other antihypertensive drugs (n = 21558), similar results were noted with a reduction of 26/14 mmHg from baseline blood pressure [46]. In addition, the efficacy of the FDC is maintained in 1-, 2- and 3-year nonblinded extension studies [47-50]. Compared with the 2-year core trial, third-year extension results demonstrated further mean reductions in SBP for the valsartan 80 mg/HCTZ 12.5 mg and the valsartan 80 mg/HCTZ 25 mg combinations [51].

A number of trials initiating treatment for stage 1 or stage 2 hypertension with combination valsartan/HCTZ result in early, improved blood pressure control with similar tolerability compared with monotherapy. In a prospective, double-blind study of 648 patients, initial combination therapy with valsartan/HCTZ 160/12.5 mg was associated with higher blood pressure control rates and greater blood pressure reductions and required fewer titration steps compared with initial valsartan monotherapy [49]. In another trial, FDC valsartan (80 or 160 mg)/HCTZ (12.5 or 25 mg) results in greater blood pressure reduction than monotherapy with either drug alone with a mean reduction of -22.5/-15.3 mm/Hg with valsartan

160 mg/HCTZ 25 mg [52]. Also, in patients inadequately controlled with valsartan 80 mg alone, the FDC valsartan 80 mg/HCTZ 25 mg produces a significantly greater reduction in DBP (-10.8 mmHg) than in patients receiving valsartan 160 mg (-6.2 mmHg). Though not as large, this statistically significant reduction is seen even with 12.5 mg of HCTZ in the FDC [53]. In an 8-week study, doses of the FDC up to 320/25 mg resulted in significantly greater blood pressure reductions compared with FDC 160/12.5 mg, and this effect was maintained through the 54-week extension [54]. An 8-week study evaluating the effect of valsartan/HCTZ through its 24-h dosing interval noted day- and night-time reductions sustained throughout the dosing interval which mirrored normal circadian variations [29].

In a pooled analysis of 1313 patients in two similar randomized, double-blind, 8-week trials, the FDC valsartan/HCTZ 160/12.5 mg was more effective than either monotherapy with HCTZ 12.5 – 25 mg or valsartan 160 mg in reducing blood pressure in the overall population (mean blood pressure reduction 19.5/14.5 mmHg) as well as all patient subgroups including age < 65 years, age > 65 years, stage 1 hypertension, stage 2 hypertension, obese and non-obese [55]. And in a pooled analysis of nine randomized, double-blind, fixed-dose, placebo-controlled trials (n = 4278), median time-to-goal was fastest with FDC valsartan/HCTZ, achieving a better percentage of blood pressure at goal by week 4 with FDC therapy than at week 8 with monotherapy [56].

For patients whose blood pressure is inadequately controlled with HCTZ 12.5 mg, the VAL-DICTATE (Valsartan HCTZ Diuretic for Initial Control and Titration to Achieve Optimal Therapeutic Effect) trial established that FDC therapy with valsartan 160 mg/HCTZ 12.5 mg was more effective than increasing the dose of diuretic to 25 mg, with mean blood pressure reductions -12.4/-7.5 mmHg and -5.6/-2.1 mmHg respectively and similar tolerability [57]. Multiple other studies have demonstrated a statistically significant improvement in response rates with FDC therapy than with valsartan or HCTZ monotherapy alone [52,53,58-59].

VALVET (Valsartan in the Very Elderly Trial), evaluating individuals over age 70 years with SBP 150 – 200 mmHg, demonstrates that antihypertensive regimens initiated with valsartan/HCTZ result in a greater blood pressure reduction from baseline than the reduction achieved with either HCTZ or valsartan monotherapy. Initiation of therapy with the FDC reduced the time to achieve blood pressure goal without additional adverse events [60,61]. This improved blood pressure control was confirmed in an ambulatory blood pressure (ABP) measurement substudy analysis [62].

Comparisons with amlodipine have been mixed. Importantly, a randomized, double-blinded, prospective study of 482 black hypertensive patients with mean seated blood pressure 140 – 180/90 – 110 mmHg noted comparable reductions in mean 24-h SBP for valsartan/HCTZ and amlodipine [63]. The 24-week VAST (Valsartan/HCTZ versus Amlodipine in Stage II Trial) study resulted in superior reductions of office and ambulatory blood pressures with valsartan [64,65]. The VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial did not show this same difference with the valsartan-based regimen, having a smaller reduction in blood pressure than amlodipine and requiring *post hoc* analysis excluding the extreme ranges in blood pressure to show comparable cardiac benefits [66-68]. A small Brazilian trial revealed comparable efficacy but a better adverse event profile for FDC valsartan/HCTZ [69].

Comparison trials of valsartan/HCTZ and amlodipine/HCTZ in a multicenter, double-blind, parallel-group study on ABP with forced-titration to a maximum dose of valsartan/HCTZ 320/25 mg or amlodipine/HCTZ 10/25 mg over 6 weeks and continued through week 10 showed that by study end, both FDC regimens reached statistical significance in mean office blood pressure and mean 24-h ABP reductions. In addition, patients receiving the FDC valsartan/HCTZ achieved additional SBP (-3.8 mmHg; p = 0.0042) and DBP (-2.7 mmHg; p = 0.0002) reduction compared with amlodipine/HCTZ on the basis of ABP monitoring [70].

More studies have demonstrated the efficacy of valsartan/HCTZ in select patient groups. In a subgroup analysis of Val-MARC (Valsartan-Managing Blood Pressure Aggressively and Evaluating Reductions) with 1668 patients looking at female, black, Hispanic, elderly and obese patients, the difference between the blood pressure reductions for the combination drug and valsartan monotherapy treatment were significant (p < 0.01) in all patient groups, with the exception of the 109 Hispanic patients (FDC therapy compared withvalsartan monotherapy resulted in mean change in SBP of -21.7 and -16.3 respectively), with no statistically significant difference in overall adverse event rate [71]. In prediabetic, obese hypertensive patients over a 16-week period, the MADE-ITT study (Metabolic Assessment of Diovan's Efficacy in Comparison to Thiazide Therapy) demonstrated that valsartan/HCTZ 320/25 mg reduced blood pressure from baseline more than valsartan 320 mg monotherapy or HCTZ 25 mg monotherapy [72].

9. Tolerability

Overall, the combination valsartan/HCTZ is well tolerated in patients and the overall incidence of adverse events is similar to placebo. In controlled trials the most common adverse events were dizziness, headache and fatigue, all of which occurred with similar frequency in the placebo arm [52]. The most common causes for discontinuation of therapy with valsartan/HCTZ are headache and dizziness. In general, the tolerability profile of valsartan monotherapy remains consistent across age, sex and ethnic groups in doses up to 320 mg/daily [46]. Incidence of hyponatremia and adverse experiences such as serum uric acid increase and bilirubin increase was less than 1% [32]. A postmarketing surveillance study of valsartan/HCTZ in 28 440 patients noted no adverse events for 99.3% of patients and low incidence for dizziness

Table 1. Comparative Drug Costs.

Drug	Drugstore.com (US$/tablet)
Valsartan	
40 mg	2.34
80 mg	2.90
160 mg	2.99
320 mg	4.13
HCTZ	
12.5 mg	0.19
25 mg	0.08
Valsartan/HCTZ	
80/12.5 mg	3.06
160/12.5 mg	3.32
160/25 mg	3.68
320/12.5 mg	4.13
320/25 mg	4.64
Losartan	
50 mg	1.95
Losartan/HCTZ	
50/12.5 mg	2.15

(0.2%), headache (0.1%), nausea (0.1%) and cough (0.1%) with only one episode of angioneutotic edema reported [46]. As is the case with all drugs in the ARB class, valsartan/HCTZ is rated pregnancy category D and must be discontinued once pregnancy is detected, as medications that act on the RAS system have a number of fetal effects including hypotension, neonatal skull hypoplasia, anuria, renal failure and the potential to cause fetal death.

Combination therapy can act to offset the counter-regulatory mechanisms and even adverse events evoked by one of the drug components. The addition of an ARB allows the sodium balance to be maintained at lower arterial pressures and blunts the thiazide-induced volume loss that may activate renin release as a compensatory mechanism and limit overall antihypertensive effects [73]. The opposing effects of valsartan and HCTZ on serum potassium approximately balanced each other in controlled trials demonstrating that valsartan attenuates HCTZ-induced hypokalemia, with the average change is serum potassium nearly zero with valsartan/HCTZ [32]. HCTZ monotherapy is known to cause hyperuricemia, hypercholesterolemia and hyperglycemia, but the FDC does not result in these metabolic abnormalities [66,74]. The manufacturer notes that in controlled trials of patients with uncomplicated hypertension treated with the FDC, excessive reduction of blood pressure is rarely seen (0.7%.) Although incidence is comparable to monotherapy, caution is still advised in situations in which patients may become hypovolemic such as inadequate fluid intake, excessive perspiration, diarrhea or vomiting [32].

Achieving goal blood pressure is dependent on both drug efficacy and patient compliance. The FDC has consistently been shown to increase compliance, and this compliance can translate into higher rates of blood pressure goal achievement [75-79]. A retrospective physician-assisted chart review found that patients treated with the FDC valsartan/HCTZ and FDC valsartan/amlodipine have a higher likelihood of achieving goal blood pressure than patients receiving ARB-based free combinations [80]. Although outside the scope of this study, we assume that improved compliance led to the improved efficacy.

Sexual dysfunction and impaired sexual activity are common in hypertensive patients and often exacerbated by antihypertensive medications, resulting in noncompliance with treatment. A study of 2202 patients evaluated the effect of valsartan or its combination with hydrochlorothiazide versus non-ARB conventional therapy (control) on sexual activity in hypertensive patients. SBP decreased to a similar degree in all the three groups. Sexual activity assessed by questionnaire decreased slightly in the control group from 1.3 to 0.9 times/week (NS), whereas it increased in the valsartan group from 1.0 to 1.6 times during follow-up ($p < 0.0001$) and in the FDC valsartan/HCTZ (80 – 160/12.5 mg) group from 0.9 to 1.3 times/week during follow-up ($p < 0.0001$) [81]. Fewer intolerable side effects and less sexual dysfunction may improve compliance [82].

The costs of valsartan, HCTZ and the FDC valsartan/HCTZ are listed in **Table 1**. HCTZ is less expensive than valsartan monotherapy and the FDC. The FDC is comparable in cost to valsartan monotherapy and offers superior blood pressure control than either drug alone. The difference in cost versus generic losartan/HCTZ is < 30%.

10. Conclusion

Hypertension is a continuous and independent risk factor for cardiovascular disease and the most common primary diagnosis of American patients. Combination therapy is frequently required for adequate control of blood pressure. Valsartan/HCTZ FDC provides superior blood-pressure control with an adverse-event profile similar or comparable to the individual monotherapies. It maintains the potential benefits of each drug in patients with LVH, left ventricular dysfunction and renal disease. It is an appropriate choice for patients with suboptimal control with monotherapy or as initial treatment for patients with SBP > 160 mmHg or DBP > 100 mmHg.

11. Expert opinion

Although current therapies are much more effective and better tolerated than ever before, hypertension continues to represent a significant healthcare issue both in treatment cost and contribution to cardiovascular mortality and morbidity. The use of fixed-dose combination products has become more widespread, simplifying treatment regimens with one-pill-a-day convenience and minimal impact on cost.

The beneficial effects of ARB therapy on cardiac mass, congestive heart failure, left ventricular dysfunction and renal disease with and without diabetes mellitus (DM) are well

documented. HCTZ's effect on stroke and myocardial infarction rates are indisputable. In addition to the benefits of each drug, valsartan/HCTZ's metabolic interactions reduce some of the negative effects of both compounds. Serum potassium is generally maintained in the normal range with the hypokalemic effects of HCTZ being offset by the hyperkalemic actions of valsartan. The lower doses required of both drugs also reduce other associated metabolic abnormalities.

With its increased simplicity, minimal side-effect profile and efficacy without a significant cost penalty, valsartan/HCTZ represents an excellent choice for antihypertensive therapy.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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