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Valsartan
More Than a Decade of Experience

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Contents

Abstract

Valsartan is a nonpeptide angiotensin receptor antagonist that selectively blocks the binding of angiotensin II to the angiotensin II type 1 receptor. The efficacy, tolerability and safety of valsartan have been demonstrated in large-scale studies in hypertension, heart failure (HF) and post-myocardial infarction (MI). This review focuses on what was learned from the valsartan clinical research programme and other comparative trials published from 1997 to the present.

Many studies have demonstrated the efficacy of valsartan in lowering blood pressure (BP) in a variety of patient populations (including elderly, women, children, obese patients, patients with diabetes mellitus, patients with chronic kidney disease [CKD], patients at high risk of cardiovascular [CV]

disease, African Americans, Hispanic Americans and Asians) and in improving outcomes in CV disease and CKD. In hypertension, valsartan exhibits dose-dependent efficacy in reducing both systolic and diastolic BP over the once-daily dose range of 80–320 mg; doses as high as 640 mg/day have been studied and found to be efficacious and safe. BP control can be enhanced with a more consistent 24-hour BP-lowering profile by using single-pill, fixed-dose combination therapy with valsartan plus hydrochlorothiazide (HCTZ).

The cardioprotective benefits of valsartan have been demonstrated in large-scale outcome trials and include significant reductions in CV morbidity and mortality in HF, following MI, and in patients with co-morbid hypertension and coronary artery disease and/or HF; reductions in HF hospitalizations; and reductions in the incidence of stroke. The magnitude of these effects is comparable with that demonstrated with angiotensin-converting enzyme (ACE) inhibitors; however, valsartan has a more favourable tolerability profile, with a significantly lower incidence of cough and only rare reports of angio-oedema, both class effects of ACE inhibitor use. Consistent with its angiotensin receptor-blocking effects, valsartan also reduces circulating levels of biochemical markers that are associated with angiotensin II-mediated endothelial dysfunction and CV risk (e.g. high-sensitivity C-reactive protein or oxidized low-density lipoprotein).

Improvements in CKD with valsartan include statistically and clinically meaningful reductions in urinary albumin and protein excretion in patients with type 2 diabetes and in nondiabetic patients with CKD. In short-term studies, valsartan has improved or stabilized various indices of metabolic function in at-risk patients, including those with co-morbid hypertension, obesity and/or metabolic syndrome. Because of this, valsartan is being prospectively investigated for its ability to reduce the incidence of new-onset diabetes and provide cardioprotection in patients with impaired glucose tolerance.

Valsartan and valsartan/HCTZ are well tolerated. In clinical trials, adverse events during valsartan treatment were similar to those occurring with placebo. The combination of valsartan/HCTZ was better tolerated than HCTZ alone. Valsartan is administered once daily for hypertension; doses are usually taken upon awakening. In patients with HF or MI, valsartan is administered twice daily.

Valsartan is a nonpeptide angiotensin receptor antagonist (angiotensin receptor blocker; ARB) that blocks the binding of angiotensin II (the main effector peptide of the renin-angiotensin-aldosterone system [RAAS]) to the angiotensin II type 1 (AT_1) receptor. Based on the physiological activity of angiotensin II in regulating blood pressure (BP), agents that inhibit the RAAS (i.e. angiotensin-converting enzyme [ACE] inhibitors) were first developed for hypertension more than 25 years ago. ARBs were developed later as a more selective means of RAAS inhibition to improve upon the safety and tolerability profile of ACE inhibitors, since the adverse effects of cough and angio-oedema, which commonly occur with ACE inhibitors, can be a significant problem for many patients. As the role of angiotensin II as a major cardiovascular (CV) risk factor – beyond its pressor activity and role in fluid/salt homeostasis – became better understood,[1] the benefits of RAAS inhibition on improving outcomes throughout the CV continuum also became

appreciated. This progress resulted in the following conditions being considered to be 'compelling indications' for the recommended use of RAAS inhibitors: heart failure (HF), post-myocardial infarction (MI), coronary artery disease, diabetes mellitus and chronic kidney disease (CKD).[2,3]

Hypertension and CV disease are major causes of morbidity and mortality worldwide. The relationship between BP and the risk of CV disease is consistent, continuous and independent of other risk factors.[2] Thus, the main goal of treating hypertension is to reduce adverse CV and CKD outcomes. Evidence indicates that systolic BP (SBP) has a greater bearing on CV risk after age 50 years,[2] and it has been suggested that, for most patients with hypertension, the clinical focus of treatment should be on reducing SBP.[4]

Valsartan was initially approved in Europe in 1996 for the treatment of hypertension in adults; approval in the US was granted shortly thereafter in 1997. Since that time, fixed-dose combinations (FDCs) of valsartan/hydrochlorothiazide (HCTZ), valsartan/amlodipine and valsartan/amlodipine/HCTZ have become available. In the more than 10 years since its initial approval, indications for valsartan have grown to include HF, post-MI to reduce CV mortality, and hypertension in children aged 6–16 years.[5] RAAS inhibitors have also been recommended for use in type 2 diabetes and CKD, given their ability to slow the progression of CKD.[2] To date, valsartan has been investigated in more than 60 studies involving over 100 000 patients. More than 50 000 patients have been enrolled in valsartan CV morbidity and mortality trials. This article reviews valsartan and valsartan/HCTZ randomized clinical trial data published between 1997 and 2009.

Table I. Pharmacokinetic properties of orally administered valsartan 80 mg (reproduced from Flesch et al.,[7] © Springer-Verlag 1997)

Parameter	Value
C_{max} (mg/L)	1.6
t_{max} (h)	2.0
AUC (mg • h/L)	8.5
$t_{½}$ (h)	7.1
Absolute bioavailability (%)	23

AUC = area under the concentration-time curve; $\mathbf{C_{max}}$ = maximum concentration; $\mathbf{t_{½}}$ = half-life; $\mathbf{t_{max}}$ = time to reach C_{max}.

1. Pharmacokinetic and Pharmacodynamic Profile

The pharmacokinetic and pharmacodynamic profile of valsartan has been described in detail elsewhere.[5,6] The main pharmacokinetic parameters of valsartan are summarized in table I. Valsartan is not a unique ARB; it has a higher affinity for the AT_1 receptor than losartan, but a lower affinity than candesartan, telmisartan and olmesartan. Valsartan has a shorter circulating half-life than telmisartan and olmesartan, but that does not appear to affect its ability to reduce BP over 24 hours and, thus, it can be given once a day. Valsartan undergoes minimal liver metabolism (~20%) and is excreted primarily as the unchanged drug. It has minimal potential for drug interactions. Valsartan does not block the ACE-mediated catabolism of, or response to, bradykinin, nor does it bind to or block other hormone receptors or ion channels known to be important in regulating the CV system.

2. Efficacy in Blood Pressure (BP) Control

2.1 Monotherapy

The antihypertensive efficacy of valsartan as a single antihypertensive agent is well defined. In general, valsartan exhibits dose-dependent efficacy in reducing both SBP and diastolic BP (DBP) over the once-daily dose range of 80–320 mg (table II). Efficacy has also been demonstrated in patients with isolated systolic hypertension (ISH). Results of monotherapy with valsartan are comparable to those achieved with other antihypertensive agents, including other ARBs, ACE inhibitors, diuretics, β-adrenoceptor antagonists (β-blockers) and calcium channel antagonists (table II).

2.2 Combination Therapy

Despite the awareness of hypertension as the leading contributor to cerebrovascular disease, CV disease, CKD and death worldwide, and the availability of numerous drugs to treat hypertension, only about one-third of patients reach goal BP,[22] and most individuals will need more

Table II. Antihypertensive efficacy of valsartan (VAL) monotherapy and in combination with hydrochlorothiazide (HCTZ) or amlodipine; randomized controlled trials

BP criteria at study entry (mmHg)	VAL dosage (mg/day)	No. of pts	Comparator dosage (mg/day)	No. of pts	Double-blind treatment period (wk)	Mean change in SBP/DBP (mmHg)		p-Value for comparison between treatments
						VAL	comparator	
VAL vs VAL/HCTZ								
SBP between 160 and 200[8]	80 titrated to 160 at 4 wk	255	VAL/HCTZ 160/12.5 *or*	252	8	–20.7/–6.6	–27.9/–10.2	$p < 0.05$ for both combinations vs VAL
			VAL/HCTZ 160/25 (after 4 wk of VAL 160)	247			–28.3/–10.1	
DBP between 95 and 115[9]	160	666	VAL/HCTZ 160/12.5 *or*	670	8	–15.7/–10.8	–19.4/–12.8	$p \leq 0.01$ for VAL vs VAL/HCTZ combinations and for comparisons between the VAL/HCTZ groups
			VAL/HCTZ 160/25	666			–21.8/–14.2	
SBP between 140 and 200; DBP between 110 and 120[10]	160 titrated to 320 after 2 wk	301	VAL/HCTZ 160/12.5 titrated to 160/25 after 2 wk and to 320/25 after 4 wk	307	6	–23.8/–17.8	–33.2/–24.2	$p < 0.001$
DBP between 95 and 110[11]	160	166	HCTZ 12.5	168	8	–14.5/–11.7	–11.1/–9.0	$p < 0.05$ for all active treatments vs PL; $p < 0.05$ for combinations vs same dose of either monotherapy; $p < 0.05$ for VAL/HCTZ 320 mg/25 mg vs 160 mg/12.5 mg
	320	166	HCTZ 25	164		–13.7/–11.3	–14.5/–10.8	
	VAL/HCTZ 160/25.5	165	PL	165		–20.3/–15.2	–5.9/–7.0	
	VAL/HCTZ 320/12.5	168				–21.7/–15.0		
	VAL/HCTZ 320/25	167				–24.7/–16.6		
VAL vs β-blockers								
DBP between 111 and 120[12]	160 (± HCTZ 25 as needed)	67	ATN 100 (± HCTZ 25 as needed)	36	6	–30.0/–20.0	–25.5/–20.4	NS
DBP between 95 and 105; postmenopausal women[13]	80; doubled at 4 wk in nonresponders (DBP ≥90 mmHg)	60	ATN 50; doubled at 4 wk in nonresponders	60	16	–19.6/–15.7	–19.1/–15.3	NS

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Table II. Contd

BP criteria at study entry (mmHg)	VAL dosage (mg/day)	No. of pts	Comparator dosage (mg/day)	No. of pts	Double-blind treatment period (wk)	Mean change in SBP/DBP (mmHg)		p-Value for comparison between treatments
						VAL	comparator	
VAL vs **ACE inhibitors**								
DBP between 95 and 120[14]	80	94	ENA 20	95	12	–19.7/–15.5	–20.4/–13.7	NS
DBP >100[15]	80–160	64	LIS 10–20	64	10	–22.9/–17.1	–19.3/–17.6	NS
SBP between 160 and 200; DBP between 95 and 110[16]	160 (+ HCTZ 12.5 if needed after 4 wk for SBP ≥150 mmHg or a decrease of ≤20 mmHg from baseline)	518	LIS 20 (+ HCTZ 12.5 as noted for VAL)	501	16	–31.2/–15.9	–31.4/–15.9	NS
VAL vs other ARBs								
DBP between 95 and 115[17]	80 titrated to 160 at 6 wk if DBP ≥90 mmHg	248	LOS 50 titrated to 100 at 6 wk if DBP ≥90 mmHg	247	12	–11.9/–10.1	–10.6/–9.9	NS
SBP between 140 and 179; DBP between 90 and 109[18]	160	36	TEL 80	34	12	–18.6/–12.1	–10.8/–8.4	$p < 0.001$
DBP between 95 and 115[19]	160	55	OLM 20	52	8	–15.7/–12.2[a]	–14.6/–11.2[a]	$p < 0.05$ for DBP
Studies involving calcium channel antagonists								
ISH in elderly (SBP between 160 and 220; DBP <90[20])	80 doubled to 160 after 8 wk as needed	204	AML 5 doubled to 10 at 8 wk as needed	206	24	–30.2/–5.3	–31.7/–6.1	NS
SBP ≥160 plus at least one other cardiovascular risk factor[21]	VAL/HCTZ 160/12.5	357	AML 10	359	24	–27.1/–9.5	–27.6/–10.8	$p < 0.05$ for SBP change, VAL/HCTZ 160 mg/25 mg vs amlodipine
	VAL/HCTZ 160/25	363				–29.7/–11.1		

a Mean 24-h ambulatory BP data are reported.

AML = amlodipine; **ARB** = angiotensin receptor antagonist (blocker); **ATN** = atenolol; **BP** = blood pressure; **DBP** = diastolic blood pressure; **ENA** = enalapril; **ISH** = isolated systolic hypertension; **LIS** = lisinopril; **LOS** = losartan; **OLM** = olmesartan; **NS** = not significant; **PL** = placebo; **pts** = patients; **SBP** = systolic blood pressure; **TEL** = telmisartan.

than one antihypertensive agent to achieve and maintain their goal BP.[2] Combinations of antihypertensive agents with different mechanisms of action often result in additive or synergistic effects by targeting multiple mechanisms that lead to hypertension, and a number of single-pill, FDC products have been introduced, especially recently, for patient convenience and presumed improved adherence to the regimen.

Valsartan is available in combination with the diuretic HCTZ in a single tablet containing valsartan 80–320 mg and HCTZ 12.5–25 mg. This FDC is approved for once-daily dosing and provides additional BP lowering beyond that of its individual components (see table II). Although single-pill FDCs traditionally were prescribed for stage 2 hypertension or as a second-line therapy (after failure of monotherapy) to achieve the BP goal, evidence is accumulating that single-pill FDCs also may be appropriate as initial therapy. The US FDA recently approved valsartan/HCTZ (160 mg/12.5 mg) for the initial treatment of hypertension. Furthermore, the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends that all patients with stage 2 hypertension (SBP ≥160 mmHg and/or DBP ≥100 mmHg) begin therapy with two antihypertensive drugs, although JNC 7 does not specifically recommend using an FDC.[2] Valsartan is also available as an FDC in combination with the calcium channel antagonist amlodipine, and with both amlodipine and HCTZ. Discussion of the efficacy of these combinations is beyond the scope of this review.

A recent study also demonstrated that, for patients whose BP is not controlled with a diuretic, combination therapy with an ARB/diuretic is a more effective strategy than initiating and increasing the dose of diuretic therapy. The Val-DICTATE trial (see table III for study acronym definitions) compared HCTZ 25 mg with the combination of valsartan/HCTZ 160 mg/12.5 mg daily for the treatment of hypertension in patients (n = 291) whose SBP was >140 and/or DBP >90 mmHg but <180/110 mmHg after 4 weeks of monotherapy with HCTZ 12.5 mg.[23] After 4 weeks of double-blind treatment, 20.7% more of the patients whose BP was <140/90 mmHg had received valsartan/HCTZ 160 mg/12.5 mg than the higher dose (25 mg) of HCTZ. Mean BP was reduced 12.4/7.5 mmHg with valsartan/HCTZ compared with 5.6/2.1 mmHg for HCTZ 25 mg ($p < 0.001$ for both SBP and DBP).[23]

Table III. Definitions of study names

Acronym	Definition
DROP	Diovan Reduction Of Proteinuria study
EVALUATE	Evaluation of Valsartan's Uniqueness and Twenty-Four Hour Blood Pressure Efficacy
GISSI-AF	Gruppo Italiano per lo Studio della Sopravvive nell'Infarto Miocardio – Atrial Fibrillation trial
JUPITER	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin
MADE-ITT	Metabolic Assessment of Diovan's Efficacy In Comparison to Thiazide Therapy
MARVAL	MicroAlbuminuria Reduction with VALsartan
NAVIGATOR	Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research
SMART	Shiga Microalbuminuria Reduction Trial
Val-DICTATE	Valsartan Hydrochlorothiazide Diuretic for Initial Control and Titration to Achieve Optimal Therapeutic Effect
Val-HeFT	Valsartan Heart Failure Trial
VALIANT	Valsartan in Acute Myocardial Infarction Trial
Val-MARC	Valsartan-Managing Blood Pressure Aggressively and Evaluating Reductions in hs-CRP
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation
VAST	Valsartan/HCTZ versus Amlodipine in Stage II Trial
VITAE	Valsartan and Hydrochlorothiazide In Hypertensive Abdominally Obese Patients
VIVALDI	Study to inVestIgate the efficacy of telmIsartan versus VALsartan in hypertensive type 2 DIabetic patients with overt nephropathy

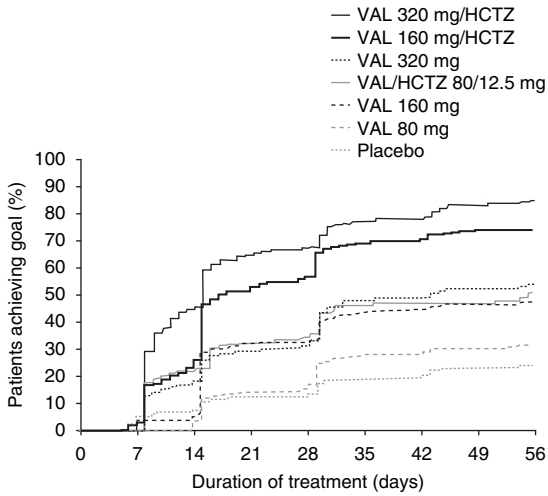

Fig. 1. Kaplan-Meier estimates for time to achieve blood pressure <140/90 mmHg in an intent-to-treat analysis of hypertensive patients receiving placebo, valsartan (VAL) or VAL/hydrochlorothiazide (HCTZ); pooled results from nine randomized, double-blind, placebo-controlled trials (n = 4278). Unless otherwise noted, VAL/HCTZ doses include patients receiving VAL with either HCTZ 12.5 or 25 mg/day (reprinted with permission from Macmillan Publishers Ltd: Weir et al.,[26] copyright 2007).

2.3 Rapidity of BP Control

Prompt reduction of BP may reduce the CV risk associated with hypertension.[24,25] Thus, time-to-onset data can be useful for clinical decision making and dose selection. A number of investigators have observed a dose-related onset of BP reductions with valsartan and valsartan/HCTZ (figure 1).[26-28] To prospectively assess onset of BP reduction, 648 patients with stage 1 or 2 hypertension were randomly assigned in a double-blind fashion to receive valsartan 80 mg, valsartan 160 mg or valsartan 160 mg plus HCTZ daily as initial therapy.[27] The mean time to achieve BP goal (<140/90 mmHg) occurred significantly sooner with valsartan/HCTZ (2.8 weeks) and with valsartan 160 mg (3.9 weeks) than with valsartan 80 mg (4.3 weeks, $p < 0.05$ vs both higher-dose groups). There were no differences in safety or tolerability between groups.

Another randomized double-blind study in 1285 patients with uncontrolled hypertension found a valsartan with stepped dose HCTZ strategy to be superior to an amlodipine with stepped dose HCTZ strategy for rapid achievement of BP goal.[28] Doses of all three drugs were increased at 4-week intervals in a 3- or 4-step sequence in patients whose BP was >140/90 mmHg. BP goal rates after 4 weeks of treatment at step 1 were similar for patients assigned to valsartan ± HCTZ (58.1%) and amlodipine ± HCTZ (53.9%), but thereafter significantly more patients receiving valsartan ± HCTZ achieved the goal BP: 70.3% versus 64.5% at 8 weeks, 75.6% versus 66.7% at 11 weeks and 78.8% versus 67.8% at 14 weeks (the study endpoint) [all $p < 0.05$].

2.4 Ambulatory BP Monitoring

The control of BP for the full dosing interval is an important component of the efficacy of any antihypertensive agent. Antihypertensive efficacy should extend throughout the 24-hour period in order to reduce the risk of CV events and should mimic the normal circadian pattern of BP, which tends to be higher during active and awake hours, lower during inactive and sleep hours, and surge during the first 4–6 hours after awakening.[29] CV events, specifically MI and cerebrovascular accident, more often occur during the morning BP surges.[30-32] Conversely, higher night-time (vs daytime) BP, or a less-pronounced dip in night-time BP, is associated with a higher risk for death and CV events.[33-35] These observations support the importance of ambulatory BP (ABP) monitoring (ABPM) for providing a more thorough assessment of the BP-lowering profile of antihypertensive agents (relative to isolated office BP measurements). The demonstration of a significant BP-lowering effect at the end of the dosing interval and throughout a 24-hour period is prerequisite for FDA approval of any new antihypertensive drug.[36]

The efficacy of valsartan and valsartan/HCTZ using 24-hour ABPM has been evaluated in a number of studies.[19,37-44] In general, results demonstrate consistent BP reduction throughout the 24-hour dosing interval for valsartan and valsartan/HCTZ, with daytime and night-time reductions being of comparable magnitude. Figure 2 illustrates the mean hourly ambulatory SBP and DBP reductions with valsartan

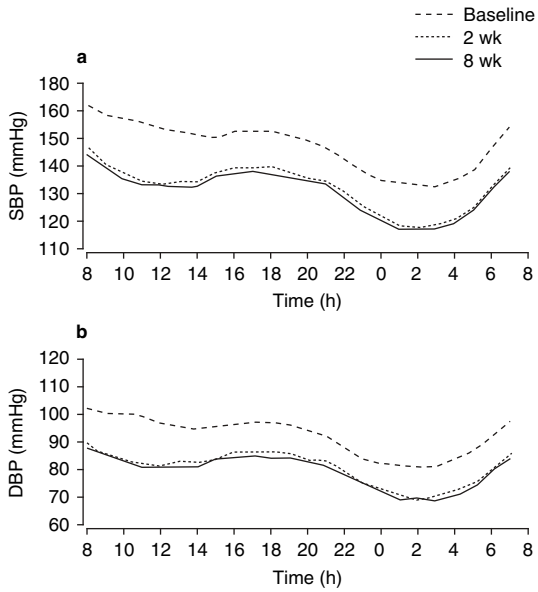

Fig. 2. 24-Hour (**a**) systolic blood pressure (SBP) and (**b**) diastolic blood pressure (DBP) in hypertensive patients before and after treatment with valsartan 160 mg/day for 2 and 8 weeks (completers, n = 55) [reproduced from Destro et al.,[19] copyright 2005, with kind permission from Springer Science and Business media].

160 mg/day after 2 and 8 weeks of treatment in 55 patients with stage 1 or 2 hypertension.[19] As shown, reductions in BP from baseline were maintained throughout the dosing interval, mimicking normal circadian variations in BP.

Using ABPM, valsartan has been compared with other antihypertensive agents.[18,19,45-47] Comparable 24-hour ABP reductions were observed for valsartan 80 mg/day and losartan 50 mg/day in a 6-week, randomized, double-blind trial that included 187 patients with stage 1 or 2 hypertension; mean 24-hour reductions were –9.3/–6.0 mmHg and –10.7/–7.2 mmHg, respectively (p = not significant [NS]).[45] In an 8-week, prospective, randomized, open-label, blinded endpoint (PROBE) study in 114 patients with stage 1 or 2 hypertension, both valsartan 160 mg/day and olmesartan 20 mg/day significantly reduced ABP from baseline; however, valsartan was superior in reducing 24-hour and daytime SBP and DBP values at 2 weeks ($p < 0.001$). By 8 weeks, the differences were less marked, but still favoured valsartan for 24-hour and night-time DBP ($p < 0.05$).[19] Antihypertensive efficacy was maintained throughout the dosing interval with both agents. In another study using PROBE design, 24-hour ABP reductions were significantly greater with valsartan 160 mg/day (–18.6/–12.1 mmHg) than telmisartan 80 mg/day (–10.8/–8.4 mmHg; $p < 0.001$) after 3 months of treatment.[18]

In a randomized, double-blind, placebo-controlled study in 354 patients with stage 1 or 2 hypertension, valsartan (160 mg titrated to 320 mg daily) produced reductions in 24-hour ABP comparable with those of the direct renin inhibitor aliskiren (150 mg titrated to 300 mg daily) after 8 weeks of treatment (–10.1/–7.1 mmHg and –9.8/–7.1 mmHg, respectively).[38] These reductions were significant compared with baseline and placebo values (–1.3/–1.1 mmHg; $p < 0.001$).

Studies assessing ABP values for valsartan and amlodipine have yielded varying results.[35,48] In one study, 164 elderly patients with ISH were randomized in double-blind fashion to receive valsartan 80 mg/day or amlodipine 5 mg/day for 24 weeks. Doses could be doubled, followed by the addition of HCTZ at designated times, if BP was considered uncontrolled.[48] At 24 weeks, the mean 24-hour daytime and night-time systolic ABPs were significantly lower than baseline (all $p < 0.001$), with no differences between groups. Among the 138 patients who were considered treatment responders (mean 24-hour and peak SBP lower on therapy than at baseline), valsartan-based treatment had a greater antihypertensive effect than amlodipine-based treatment during daytime hours ($p = 0.02$) and over the 24-hour period ($p = 0.02$). In another study of patients (n = 659) at high CV risk, after 1 year of treatment with valsartan (80–160 mg/day ± HCTZ as needed for BP control) or amlodipine (5–10 mg/day ± HCTZ as needed to achieve BP goal) the mean ABP was similar (valsartan 132.5/74.8 mmHg; amlodipine 131.5/75.2 mmHg).[35] However, ABP was lower with valsartan during the first 7 hours post-dose and lower with amlodipine during the last 4 hours of the dosing interval.

Additional ABPM studies have compared the 24-hour efficacy of valsartan/HCTZ and amlodipine in hypertensive patients with additional CV risk factors[41] and in African Americans.[42] Valsartan/HCTZ 160 mg/12.5 mg daily was as effective as

amlodipine 10 mg/day when measured by 24-hour ABPM in these studies; valsartan/HCTZ 160 mg/25 mg was superior to amlodipine 10 mg in 24-hour SBP, daytime SBP, night-time DBP and the proportion of patients achieving BP of ≤130/80 mmHg ($p < 0.05$ for between-group comparisons).[41]

In a trial that compared the effectiveness of valsartan plus HCTZ with that of amlodipine plus HCTZ (EVALUATE), 482 patients with stage 2 hypertension were randomized in a double-blind fashion to receive valsartan 160 mg/day or amlodipine 5 mg/day initially, force-titrated at 2-week intervals to eventually receive valsartan/HCTZ 320 mg/25 mg or amlodipine/HCTZ 10 mg/25 mg daily.[49] After 10 weeks of treatment, mean ABP reductions were −21.1/−12.5 mmHg for valsartan/HCTZ and −18.1/−9.7 mmHg for amlodipine/HCTZ ($p < 0.0001$ for ambulatory SBP and DBP).[49] At the same timepoint, the individual percentages of patients achieving the ABP goal of <130/80 mmHg were significantly greater with valsartan/HCTZ (23.3%) than with amlodipine/HCTZ (16.7%) [$p = 0.007$].[49] In addition to superior efficacy, valsartan/HCTZ exhibited a more favourable safety profile (see section 4).

ABPM also has been used to compare the efficacy of morning and evening dosing with valsartan. In one study, 90 patients with stage 1 or 2 hypertension were assigned randomly to receive valsartan 160 mg daily upon awakening or at bedtime.[37] After 3 months, mean 24-hour and daytime and night-time ABP were comparable between groups (figure 3). Valsartan was especially effective in reducing nocturnal BP when administered at bedtime, increasing the diurnal-nocturnal ratio by 6% ($p < 0.001$), which subsequently resulted in 73% of patients who had been 'non-dippers' (nocturnal BP <10% lower than daytime BP) becoming 'dippers'. ('Dippers' tend to have a better long-term prognosis than 'non-dippers'.[50])

2.5 Smoothness Index

ABPM data can be used to calculate the smoothness index (SI), defined as the ratio of the average change in BP from baseline over 24 consecutive hourly segments divided by the standard deviation of these changes, to estimate the homogeneity of the BP-lowering effect throughout the dosing interval.[51] Compared with the trough : peak ratio, the SI correlates more closely with the ability of antihypertensive agents to reverse or delay the progression of target-organ damage.[51]

In a 26-week, randomized, double-blind, placebo-controlled, crossover study (4-week treatment periods with 2-week washouts in-between) in 30 patients with stage 1 or 2 hypertension, 24-hour ABP was reduced significantly (vs placebo) with valsartan 80 mg, losartan 50 mg and telmisartan 40 mg daily, and BP reductions were significantly greater with valsartan than with losartan or telmisartan ($p < 0.05$ for valsartan vs losartan and telmisartan).[52] The mean diastolic trough : peak ratio was >50% (a standard of efficacy for antihypertensives) with all three treatments after 4 weeks, although calculated SIs were higher for

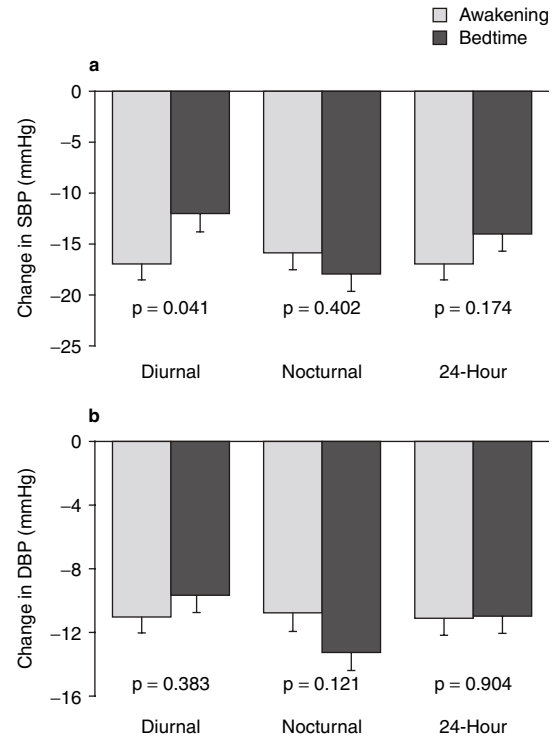

Fig. 3. Changes in mean diurnal, nocturnal and 24-hour (**a**) systolic blood pressure (SBP) and (**b**) diastolic blood pressure (DBP) on awakening (n = 46) and at bedtime (n = 44) in hypertensive patients after treatment with valsartan 160 mg/day for 3 months (reproduced from Hermida et al.,[37] with permission).

valsartan (1.29 SBP, 1.45 DBP) than for losartan (0.98 SBP, 1.18 DBP) and telmisartan (1.04 SBP, 1.29 DBP) [$p < 0.01$ for between-group comparisons for both SBP and DBP].[52]

In the study using ABPM to compare valsartan and amlodipine in 164 elderly patients with ISH, the mean SBP trough : peak ratio was 0.56 for valsartan and 0.77 for amlodipine (p = NS). Corresponding SIs were 1.70 and 1.58, respectively (p = NS).[48]

2.6 Efficacy Beyond the Dosing Interval

Forgetting to take medication at prescribed intervals is a common but challenging problem that can compromise drug efficacy. In the case of hypertension, missed doses can lead to a lack of BP control and increase vulnerability for target-organ damage. Thus, knowledge of whether the efficacy of a drug can extend beyond its dosing interval could have important clinical implications, particularly for patients whose adherence to medication is not ideal.

A recent study using ABPM found that valsartan 160 mg/day, but not enalapril 20 mg/day, exhibited BP-lowering efficacy that was maintained for at least 48 hours after dosing.[53] This study (PROBE design) included 148 patients with previously untreated stage 1 or 2 hypertension. After 16 weeks of treatment, ABPM was performed. After the first 24 hours, patients were instructed to skip their morning dose of study

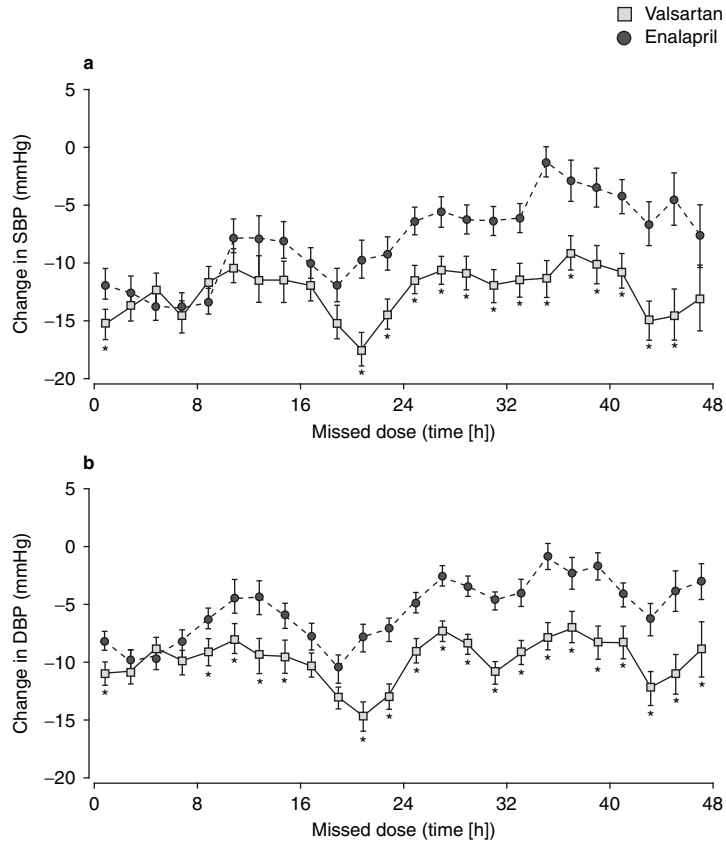

Fig. 4. The effect of a missed dose on blood pressure (BP) in hypertensive patients receiving valsartan 160 mg/day (n = 74) or enalapril 20 mg/day (n = 74) for 16 weeks captured using 48-hour ambulatory BP monitoring. Changes from baseline in (**a**) systolic BP (SBP) and (**b**) diastolic BP (DBP) are depicted (reprinted from Hermida et al.,[53] copyright 2008, with permission from Excerpta Medica, Inc.). * $p < 0.05$ vs enalapril.

medication, and ABPM was continued for an additional 24 hours. Results are shown in figure 4.[53] Prior to the skipped dose, BP reductions were comparable for valsartan and enalapril.

2.7 Efficacy in Special Populations

2.7.1 Elderly Patients

Several studies have evaluated the efficacy and safety of valsartan as monotherapy and in combination with HCTZ in elderly patients.[9,20,54] Reductions in SBP and DBP have been clinically and statistically significant, with SBP changes generally being higher in elderly patients than in younger subjects. In those with ISH, SBP reductions with either valsartan 160 mg/day or amlodipine 10 mg/day exceeded 30 mmHg (table II); however, valsartan was better tolerated (20.2% vs 31.9% experienced adverse events [AEs], respectively; $p < 0.003$) and associated with a lower incidence of peripheral oedema.[20] Mallion and colleagues[9] reported dose-dependent reductions in BP among patients ≥65 years of age (n = 425) and <65 years (n = 1559) with valsartan 160 mg, valsartan/HCTZ 160 mg/12.5 mg and valsartan/HCTZ 160 mg/25 mg daily, with similar BP reductions for both age groups. Response rates (i.e. reflecting patients who achieved DBP <90 mmHg or a decrease of >10 mmHg) among the elderly were 59.1%, 66.7% and 70.7% for valsartan 160 mg, valsartan/HCTZ 160 mg/12.5 mg and valsartan/HCTZ 160 mg/25 mg, respectively, which were higher than for the overall population (corresponding rates of 49.0%, 61.7% and 68.0%).[9] A pooled analysis of data from two randomized controlled trials showed that, among individuals with stage 2 hypertension, the response to antihypertensive treatment declined with advancing age.[55] The use of valsartan/HCTZ versus valsartan alone attenuated this age-related decline in BP response, which suggests that earlier use of combination therapy in the older patient may be necessary to achieve BP goals.[55]

2.7.2 Obese Patients

Valsartan 160 mg/day provided BP-lowering efficacy comparable with that of amlodipine 10 mg/day and felodipine 10 mg/day in obese hypertensive patients in studies of 12–16 weeks' duration.[56,57] However, valsartan may offer advantages because it also significantly lowered plasma leptin (10% from baseline), resistin (14–18% from baseline) and Homeostasis Model Assessment of Insulin Resistance (12–20% from baseline) in these studies, whereas amlodipine was metabolically neutral.

2.7.3 Patients with Diabetes Mellitus

Several studies have evaluated the effect of valsartan and valsartan/HCTZ in patients with diabetes, a population for whom strict BP control is advocated (<130/80 mmHg).[2,58] A further consideration in the treatment of hypertension in diabetes is to lower microalbuminuria. The presence of microalbuminuria and frank proteinuria is a common clinical finding in patients with hypertension and diabetes; it is predictive of worsening renal function and is a risk marker for CV disease.[59,60] For this reason, RAAS inhibitors are recommended for patients with diabetes. Valsartan doses of up to 640 mg/day have been efficacious and safe in this population.[61]

The MADE-ITT study was designed to determine whether treatment with valsartan negated the metabolic effects of HCTZ during combination treatment in prediabetic, obese, hypertensive patients with the cardiometabolic syndrome.[62] A total of 566 patients were randomized to receive valsartan 320 mg/day, HCTZ 25 mg/day or the combination in a double-blind, forced-titration design. After 16 weeks of treatment, the combination of valsartan/HCTZ showed greater reductions in BP from baseline (–20/–12 mmHg) than monotherapy with valsartan (–14/–9 mmHg) or HCTZ (–12/–7 mmHg). Significantly more patients receiving the combination (50%) achieved the more aggressive BP goal of <130/80 mmHg than those receiving HCTZ monotherapy (20%; $p < 0.001$ vs combination) or valsartan monotherapy (32%; $p < 0.0017$ vs HCTZ).[62] The reduced antihypertensive response to HCTZ observed in this study was most pronounced among patients with significant abdominal obesity (waist circumference >44 inches [>118.8 cm]) [see section 3.4].

A second randomized, double-blind, forced-titration study (VITAE) compared the efficacy

and metabolic effects of valsartan/HCTZ 320 mg/25 mg with amlodipine/HCTZ 10 mg/25 mg daily in prediabetic, obese, hypertensive patients.[63] After 16 weeks, reductions in BP were −31/−14 mmHg with valsartan/HCTZ and −28/−13 mmHg with amlodipine/HCTZ (p = NS between groups). Fasting and postprandial glucose levels increased with amlodipine/HCTZ but not with valsartan/HCTZ ($p < 0.01$ between groups).

2.7.4 Specific Ethnic Groups

In African Americans, a population with a reduced response to RAAS inhibition, the antihypertensive efficacy of valsartan can be optimized by using HCTZ in combination. In a 12-week, randomized, double-blind study comparing valsartan/HCTZ 160 mg/12.5 mg and amlodipine 10 mg daily in 482 African Americans with stage 1 or 2 hypertension, ABP reductions from baseline were comparable between treatments (−15.9/−10.2 mmHg with valsartan/HCTZ and −14.5/−9.1 mmHg with amlodipine; $p < 0.001$ for noninferiority); however, tolerability favoured valsartan/HCTZ (see section 4).[42]

Valsartan is as effective as ACE inhibitor therapy in hypertensive Indonesian[64] and Taiwanese[65] patients, and is more effective than bendroflumethiazide (bendrofluazide) in patients of South Asian descent.[66]

3. Efficacy Beyond BP Control

3.1 Cardiovascular Outcomes

A number of large outcome trials have established the value of valsartan in reducing CV morbidity and mortality in patients at high CV risk (table IV). Val-HeFT and VALIANT have demonstrated that valsartan is comparable with ACE inhibitor therapy in terms of cardioprotective benefits, but that valsartan is better tolerated. In VALIANT, a smaller proportion of the valsartan group than of the captopril group discontinued therapy because of AEs (5.8% vs 7.7%; $p < 0.05$).[72]

In VALUE, valsartan- and amlodipine-based therapy resulted in similar rates of the composite CV endpoint (10.6% and 10.4%, respectively), despite smaller reductions in BP in the valsartan-based therapy group (2.1/1.7 mmHg difference at

Table IV. Results of large-scale trials of valsartan (VAL) in patients with cardiovascular conditions

Study	Patient population	No. of patients	Comparison	Mean follow up	Primary endpoint results	Other results
Val-HeFT[67-71]	HF receiving recommended therapy	5010	VAL vs PL	23 mo	13% ↓ in combined all-cause morbidity and mortality ($p = 0.009$)	28% ↓ HF hospitalizations ($p < 0.001$) Significant improvement in LV structure and function and levels of HF-related biochemical markers Effects were most pronounced in patients not receiving/intolerant of ACE inhibitors Less AF with VAL
VALIANT[72]	Previous acute MI	14 703	VAL vs CAP	25 mo	Comparable in all-cause mortality	No difference in secondary CV endpoints, including atherosclerotic events Better tolerability with VAL
VALUE[24,73]	Treated or untreated hypertension	15 313	VAL vs AML	4.2 y	Similar reductions in cardiac mortality and morbidity (despite greater BP reductions with AML)	Less nonfatal MI and stroke with AML Among patients who remained on monotherapy, BP reductions were comparable and there was less HF with VAL Less new-onset diabetes mellitus and AF with VAL

AF = atrial fibrillation; **AML** = amlodipine; **BP** = blood pressure; **CAP** = captopril; **CV** = cardiovascular; **HF** = heart failure; **LV** = left ventricular; **MI** = myocardial infarction; **PL** = placebo; ↓ indicates decrease.

Table V. Studies evaluating the efficacy of valsartan (VAL) in atrial fibrillation (AF)

Study	Description	Findings
Val-HeFT subanalysis[67]	Patients with HF receiving VAL vs patients receiving PL plus standard HF therapy (see table IV)	37% ↓ AF incidence in patients receiving VAL vs PL ($p = 0.0002$)
VALUE subanalysis[76]	Patients with hypertension receiving VAL or AML (see table IV)	16% ↓ incidence of new-onset AF ($p = 0.045$) and 32% ↓ new persistent AF with VAL vs AML ($p = 0.005$)
Prospective study[77]	369 patients with hypertension and paroxysmal AF receiving VAL (up to 320 mg/d), RAM (up to 10 mg/d) or AML (up to 10 mg/d) for up to 1 y	Recurrent AF at 1 y developed in 47%, 28% and 16% of patients receiving AML, RAM and VAL, respectively ($p < 0.05$ VAL vs AML or RAM; $p < 0.05$ RAM vs AML)
Prospective study[78]	296 patients with hypertension, type 2 diabetes mellitus and a recent history of paroxysmal AF receiving AML (up to 10 mg) plus either VAL (160 mg) or ATN (100 mg) for 1 y	Recurrent AF developed in 20.3% and 34.1% of patients receiving AML/VAL vs AML/ATN, respectively ($p < 0.01$)
GISSI-AF[79]	1442 patients in normal sinus rhythm with underlying CV disease (HF and/or LVD; hypertension; history of diabetes, stroke, peripheral vascular disease or coronary artery disease; or lone AF with left atrial dilation) and ≥2 AF episodes in last 6 mo or successful cardioversion receiving VAL 320 mg/d or PL in addition to standard therapy	AF recurred in 51.4% of VAL and 52.1% of PL patients, respectively (HR 0.97; 96% CI 0.83, 1.14) 26.9% of VAL and 27.9% of PL patients had >1 AF episode Trend for ↓ AF recurrence favoured VAL in the 114 patients with HF and/or LVD (HR 0.81; 95% CI 0.48, 1.35)

AML = amlodipine; **ATN** = atenolol; **CI** = confidence interval; **CV** = cardiovascular; **HF** = heart failure; **HR** = hazard ratio; **LVD** = left ventricular dysfunction; **PL** = placebo; **RAM** = ramipril; ↓ indicates decrease.

study end; $p < 0.0001$).[24,74] However, the incidence of fatal plus nonfatal MI was surprisingly higher in the valsartan-based therapy group (4.8% vs 4.1%; $p < 0.05$), possibly as a result of the greater early BP reductions in the amlodipine-based arm (−4.0/−2.1 mmHg vs the valsartan-based therapy). The maximum dose chosen for valsartan was also probably too low (160 mg), since it is now thought that 320 mg is a more appropriate dose, and the titration schedule too slow. These design issues could have made a major contribution to these findings.

Given the secondary finding of a reduced incidence of atrial fibrillation (AF) in the Val-HeFT and VALUE trials, and the observation that the presence of AF is an independent risk factor for poor clinical outcome in patients with HF[67] and diabetes,[75] other studies have explored this relationship (table V).[67,76-79] Taken together, the data suggest a role for valsartan in the primary prevention of AF but, as shown in the recent large-scale GISSI-AF trial, no role in the secondary prevention of AF. In GISSI-AF, there was no significant reduction in AF recurrence with valsartan (vs placebo) in AF patients with underlying CV disease.[79]

Consistent with its angiotensin receptor-antagonising effects, valsartan may reduce circulating levels of biochemical markers that are associated with angiotensin II-mediated endothelial dysfunction and CV risk (table VI). HCTZ monotherapy raised plasma high-sensitivity C-reactive protein (hs-CRP) values, whereas valsartan monotherapy lowered these levels.[62] These results support previous findings in which valsartan lowered hs-CRP but the combination of valsartan/HCTZ had a neutral effect.[80] To the extent that hs-CRP levels reflect a direct inflammatory process, these data suggest that valsartan has an inhibitory effect and that HCTZ has a possible stimulatory or permissive effect on vascular inflammation. Aldosterone is known to have inflammatory effects and may have a modulating effect on the hs-CRP response to these therapies, which may be relevant considering the increase in plasma aldosterone observed during treatment with HCTZ and valsartan/HCTZ. The prognostic importance of elevated hs-CRP was illustrated in the recent JUPITER trial; low-dose statins significantly reduced the incidence of major CV events and all-cause mortality in healthy individuals without elevated levels of low-density lipoprotein cholesterol but with increased hs-CRP.[81] The relationship of hs-CRP and other drugs is still uncertain.

3.2 Cerebrovascular Outcomes

Large-scale studies have shown that valsartan reduces the risk of stroke to a degree similar to

Table VI. Effect of valsartan (VAL) on circulating biomarkers implicated in endothelial dysfunction and cardiovascular risk

Biomarker	Effect of VAL
hs-CRP	*VAST:* hs-CRP levels were 13% and 16% lower than baseline levels after 12 wk of daily treatment with VAL/HCTZ 160 mg/12.5 mg and VAL/HCTZ 160 mg/25 mg, respectively, in patients with hypertension and at least one other cardiovascular risk factor compared with a 1% reduction in patients who received AML 10 mg/d ($p < 0.05$ for both comparisons)[21] *Val-MARC:* The median hs-CRP level decreased from baseline to 8 wk by 0.12 mg/L in 1188 patients with stage 2 hypertension who received open-label VAL 320 mg/d, and increased slightly (0.05 mg/L) with VAL/HCTZ 320 mg/12.5 mg daily ($p < 0.001$). Further analyses showed that the reduction in hs-CRP was independent of BP reductions[80] *MADE-ITT:* Treatment with VAL 320 mg/d or VAL/HCTZ 320 mg/25 mg daily in prehypertensive patients with cardiometabolic syndrome reduced hs-CRP levels by 9% and 5%, respectively, from baseline; conversely, hs-CRP levels increased significantly in patients who received HCTZ 25 mg/d (16%; $p < 0.05$ vs baseline, VAL and VAL/HCTZ[62]
t-PA antigen	*VAST:* Treatment with VAL/HCTZ 160 mg/12.5 mg and VAL/HCTZ 160 mg/25 mg daily resulted in significant and sustained decreases in t-PA levels with both Co-Diovan regimens compared with levels in patients on AML 10 mg/d ($p < 0.05$ for both comparisons). After 24 wk of treatment, t-PA levels were significantly lower ($p < 0.05$) in patients treated with VAL/HCTZ 160 mg/12.5 mg daily than in those on AML 10 mg/d[21]
IL-6	*VAST:* IL-6 levels were significantly lower in patients treated with VAL/HCTZ 160 mg/25 mg daily at wk 12 (but not at wk 24) than in those who received AML 10 mg/d ($p < 0.05$)[21]
Oxidized LDL	*VAST:* Oxidized LDL levels at wk 12 and 24 were approximately 10% lower than baseline levels in patients treated with VAL/HCTZ or AML[21]

AML = amlodipine; **BP** = blood pressure; **HCTZ** = hydrochlorothiazide; **hs-CRP** = high-sensitivity C-reactive protein; **IL** = interleukin; **LDL** = low-density lipoprotein; **t-PA** = tissue plasminogen activator.

ACE inhibitors or amlodipine. Both valsartan and captopril reduced the incidence of CV (including atherosclerotic) events by 48% in patients with MI in VALIANT; stroke occurred in 3.6–4.3% of patients receiving valsartan, captopril or the combination.[82,83] In a VALUE *post hoc* analysis, stroke occurred in 2.9% of patients receiving valsartan and 2.9% of patients taking amlodipine (odds ratio 1.02; 95% CI 0.81, 1.28; $p = 0.899$).[74] Cognitive function testing after 18 weeks of valsartan 160 mg/day or enalapril 20 mg/day in 144 elderly hypertensive patients showed significantly higher scores (indicating better cognitive performance) with valsartan relative to enalapril on tests of word-list memory and recall.[84]

3.3 Renal Outcomes

Improvements in CKD outcomes with valsartan include statistically and clinically meaningful reductions in microalbuminuria in patients with type 2 diabetes; effects appear to be independent of its BP-lowering capability (table VII). Hyperkalaemia occurred rarely and was not dose dependent at once-daily doses up to 640 mg.[61] Valsartan also is effective in lowering urinary protein excretion in patients with nondiabetic renal insufficiency. In a single-blind crossover study in which patients received valsartan 40–80 mg/day or placebo for 1 year each, valsartan reduced urinary protein excretion by 33% ($p < 0.001$) but placebo subjects had an increase of 32% ($p = 0.002$).[88] Valsartan did not affect haemoglobin levels in stage III–IV CKD (glomerular filtration rate 15–59 mL/min/1.73 m^2).[89] It slowed the decline in residual renal function in patients new to peritoneal dialysis,[90] and maintained renal function in patients with chronic allograft nephropathy.[91] Galle and colleagues[87] reported that the renoprotective effects of 1 year of treatment with valsartan 160 mg/day were similar to those of telmisartan 80 mg/day in a population of patients with type 2 diabetes, hypertension and overt nephropathy (table VII).

3.4 Metabolic Outcomes

In short-term studies, valsartan has improved or stabilized a number of indices of metabolic function in certain groups of patients or was metabolically neutral compared with other antihypertensive agents (table VIII). Additionally, the VALUE study showed a reduction in the development of new-onset diabetes with valsartan or valsartan/HCTZ relative to amlodipine or amlodipine/HCTZ.[95] Further analyses from

VALUE showed that, while patients with diabetes at study entry had a significant, 2-fold greater rate of cardiac morbidity (MI or HF) and mortality than those without diabetes at baseline, patients who developed diabetes during the trial had intermediate rates of cardiac morbidity, i.e. between those with and without diabetes at baseline (hazard ratio 1.43; 95% CI 1.16, 1.77 compared with no diabetes at baseline), which were highest for HF.[98] Patients who developed diabetes during the study period also had significantly more new-onset AF and persistent AF than patients without diabetes (hazard ratios 1.49 and 1.87, respectively; both $p < 0.05$), which may explain the increased HF risk.[75] Undoubtedly, the development of AF in diabetes patients increased the risk of HF 3.5-fold and stroke 2-fold compared with patients who developed diabetes but not AF.[75]

In light of these observations, valsartan is being prospectively investigated for its ability to reduce the incidence of new-onset diabetes and provide cardioprotection in patients with impaired glucose tolerance, a group at high risk for the development of diabetes and CV disease.[99] The NAVIGATOR trial has a 2×2 factorial design with four treatment arms: valsartan 80–160 mg/day plus placebo, valsartan plus the antidiabetic nateglinide (30–60 mg/day), nateglinide plus placebo, and placebo plus placebo. Efficacy assessments include progression to diabetes and the composite of CV-related death or the first occurrence of nonfatal MI, nonfatal stroke, hospitalization for HF or unstable angina pectoris, or revascularization. To date, NAVIGATOR is the largest study of type 2 diabetes prevention, with more than 9500 patients from 40 countries enrolled. It is the only outcome study adequately powered to determine whether the risk for CV disease can be reduced in patients with impaired glucose tolerance. The study duration is estimated to be 6 years, with completion expected in the near future.

4. Safety and Tolerability

As a class, ARBs are noted for their improved tolerability profile relative to ACE inhibitors.

Table VII. Renal outcome studies with valsartan (VAL)

Study	Patient population	No. of patients	Treatment comparisons (mg/day)	Mean follow up	Main findings
MARVAL[85]	Type 2 diabetes mellitus, microalbuminuria ± hypertension	332	VAL 80–160 or AML 5–10	24 wk	Primary endpoint: UAER ↓ 44% with VAL, 8% with AML ($p < 0.001$) Normoalbuminuria achieved in 30% in VAL and 15% in AML patients ($p < 0.001$) BP reductions similar between groups
SMART[86]	Type 2 diabetes, persistent microalbuminuria and uncontrolled hypertension	153	VAL 80–160 or AML 10–20	24 wk	Primary endpoints Normoalbuminuria achieved in 23% VAL and 11% AML patients ($p = 0.011$) ≥50% improvement in ACR achieved by 34% VAL and 16% AML patients ($p = 0.008$) ACR improved (32% ↓) with VAL and worsened (18% ↑) with AML ($p < 0.001$) Reduction in ACR independent of BP control with VAL
DROP[61]	Hypertension, type 2 diabetes and albuminuria	391	VAL 160, 320 or 640	30 wk	Urinary albumin excretion rate ↓ 25% with VAL 160 mg, 51% with VAL 320 mg and 49% with VAL 640 mg ($p < 0.001$ for 320 and 640 mg doses vs 160 mg dose) High doses of VAL were well tolerated
VIVALDI[87]	Hypertension, type 2 diabetes and proteinuria	885	VAL 160 or TEL 80	1 y	Primary endpoint: 24-h urinary protein excretion ↓ 33% with VAL and TEL No differences in serum creatinine or eGFR

ACR = albumin : creatinine ratio; **AML** = amlodipine; **BP** = blood pressure; **eGFR** = estimated glomerular filtration rate; **TEL** = telmisartan; **UAER** = urinary albumin excretion rate; ↓ indicates decrease; ↑ indicates increase.

Table VIII. Effects of valsartan (VAL) on indices of metabolic function

Parameter	Patient characteristic	Results	References
Improvement in insulin sensitivity	Non-obese, hypertensive patients	After 3 mo of VAL 80 mg/d, plasma fasting insulin ↓ from 19.6 μIU/mL to 8.7 μIU/mL ($p < 0.001$) and HOMA-IR scores ↓ from 4.4 to 2.2 ($p < 0.001$)	92
	Obese, hypertensive patients	12–16 wk of VAL 160 mg/d significantly ↓ HOMA-IR, leptin and resistin levels, and ↑ adiponectin levels	56,57
	Obese, prediabetic patients with hypertension and cardiometabolic syndrome	*MADE-ITT:* No change in HOMA-IR, fasting or postprandial glucose, or free fatty acid levels between VAL 320 mg/d, HCTZ 25 mg/d and the combination after 16 wk of treatment HbA_{1c} also remained stable with VAL and VAL/HCTZ but worsened with HCTZ ($p < 0.05$ vs VAL)	62
Lipid parameters	Patients with hypertension or metabolic syndrome	Significant improvements in total and low- and high-density lipoprotein cholesterol, lipoprotein levels	93,94
	Obese, prediabetic patients with hypertension and cardiometabolic syndrome	*MADE-ITT:* After 16 wk of treatment, increases in triglyceride levels (10% increase) observed with HCTZ 25 mg were absent in patients treated with VAL 320 mg/d or VAL/HCTZ 320 mg/25 mg/d	62
New-onset diabetes mellitus	Patients with hypertension	Subanalyses from large-scale outcome studies and a retrospective health claims study observed 23% risk reductions in the development of new-onset diabetes compared with VAL patients receiving amlodipine	95,96
Arterial stiffness	Patients with type 2 diabetes, systolic hypertension and albuminuria	After 24 wk, VAL/HCTZ ↓ aortic pulse wave velocity 0.9 m/s more than AML ($p = 0.002$) at similar brachial and central aortic pulse pressures UAER ↓ 12.6 μg/min with VAL/HCTZ ($p = 0.01$ vs AML)	97

AML = amlodipine; **HbA_{1c}** = glycosylated haemoglobin; **HCTZ** = hydrochlorothiazide; **HOMA-IR** = Homeostasis Model Assessment of Insulin Resistance; **UAER** = urinary albumin excretion rate; ↓ indicates decrease; ↑ indicates increase.

The AE profile of ARBs is similar to that observed with placebo; common AEs are usually transient and mild in severity and include dizziness, headache, nasopharyngitis and malaise/fatigue.[5] The tolerability profile of valsartan is independent of dose and duration of treatment, and is consistent regardless of age, sex and ethnic group at dosages up to 320 mg/day; headache and possibly dizziness appear to be dose related at a very high dose.[61] In placebo-controlled clinical trials, the discontinuation rate due to AEs was low (2.3%), primarily for headache and dizziness.[5] In trials of patients with HF, the tolerability profile of valsartan is as expected pharmacologically and based on the overall health status of the patients. Dizziness was the primary AE, reported by 17% of valsartan and 9% of placebo recipients.[5] Rates of discontinuation due to AEs were similar for valsartan and placebo recipients.[5]

The main advantage of ARBs over ACE inhibitors relates to the reduced incidence of cough and angio-oedema. Cough is a common reason for therapy discontinuation among ACE inhibitor users, but it occurs much less frequently in patients taking ARBs (figure 5). Reports of angio-oedema have been rare with valsartan.[5] In post-MI patients, there were fewer AE-related discontinuations with valsartan (5.8%) than with ACE inhibitor therapy (7.7%).[5]

The safety and tolerability profile of valsartan/HCTZ is similar to, or better than, what would be expected from each component given as

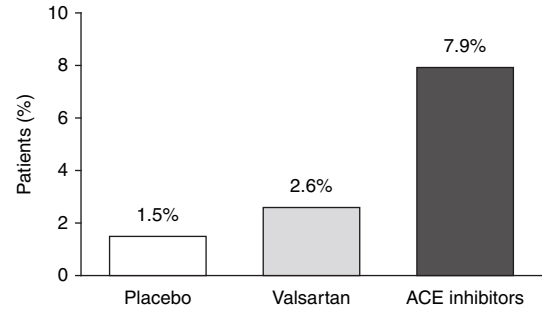

Fig. 5. The incidence of dry cough in hypertensive patients during treatment with valsartan vs placebo and ACE inhibitors. Results are from comparative trials.[5]

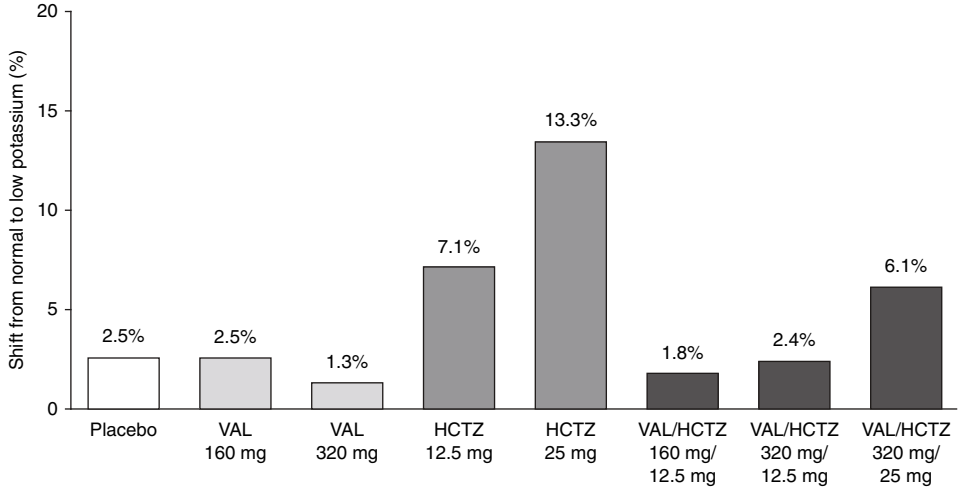

Fig. 6. Incidence of serum potassium reductions from normal levels at baseline in hypertensive patients during treatment with valsartan (VAL), hydrochlorothiazide (HCTZ) or the combination for 8 weeks. Results are from a randomized double-blind study (n = 1346) [reprinted from Pool et al.,[11] copyright 2007, with permission from Excerpta Medica, Inc.].

monotherapy. In general, the frequency and severity of AEs with valsartan/HCTZ are similar to those of patients on valsartan monotherapy or receiving placebo.[11,62,100] In a long-term study comparing valsartan, HCTZ and the combination in 1346 hypertensive patients, downward shifts in serum potassium levels were greater in patients receiving HCTZ versus valsartan/HCTZ and valsartan monotherapy, demonstrating that valsartan attenuates HCTZ-induced hypokalaemia (figure 6).[11] Similarly, in the Val-DICTATE trial, reductions in serum potassium occurred less frequently with valsartan/HCTZ 160 mg/12.5 mg daily (1.4% of patients) than with HCTZ 25 mg/day (6.4%).[23] Corresponding rates of serum uric acid elevations were 5.0% and 8.6%, respectively.

Compared with amlodipine, valsartan has been consistently associated with lower rates of peripheral oedema. In a 24-week study of elderly patients with ISH, the incidence of peripheral oedema was more than 5-fold higher with amlodipine 10 mg/day (26.8%) than with valsartan 160 mg/day (4.8%) [$p < 0.001$].[20] Compared with amlodipine monotherapy, valsartan/HCTZ is better tolerated at comparable efficacy, owing to the lower incidence of peripheral oedema with this combination. Among hypertensive patients at risk for CV events, seven times more patients receiving amlodipine 10 mg/day reported AEs than patients receiving valsartan/HCTZ 160 mg/12.5 mg daily (31.8% vs 4.4%), primarily because of the greater incidence of ankle oedema with amlodipine (15.9% vs 2.2% with valsartan/HCTZ).[101] In a 12-week trial in hypertensive African Americans, peripheral oedema and joint swelling occurred significantly more often with amlodipine 10 mg/day (5.8% and 2.9%, respectively) relative to valsartan/HCTZ 160 mg/12.5 mg daily (1.7% and 0%, respectively; $p < 0.05$ for both comparisons).[42] In EVALUATE, rates of peripheral oedema were significantly lower with valsartan/HCTZ (3.3%) than with amlodipine/HCTZ (12.4%) [$p < 0.001$].[49]

All direct RAAS inhibitors can potentially cause fetal and neonatal injury and death; therefore, these agents are contraindicated during pregnancy and should not be used during lactation. It is not clear whether all RAAS inhibitors should be avoided in women of child-bearing age who might be considering pregnancy.

5. Dosage and Administration

Although the package labelling recommends a starting dose of 80–160 mg once daily for

non-volume-depleted adults with hypertension,[5] results show that a starting dose of 160 mg/day is optimal for essential hypertension.[102,103] Valsartan can be taken in the morning or at bedtime (same time each day) and with or without food. Effects generally are evident within 2 weeks and are maximal by 4 weeks. No dose adjustments are needed in elderly patients, or in patients with mild or moderate renal or hepatic insufficiency; care should be exercised in patients with more severe hepatic impairment because valsartan exposure is increased in this group.[5,104] In hypertensive children aged 6–16 years, the recommended starting dose of valsartan is 1.3 mg/kg, titrated as needed to 2.7 mg/kg, to a maximum of 40–160 mg/day. For children who cannot swallow tablets, an oral suspension can be prepared.[5]

The recommended starting dose of valsartan in HF is 40 mg twice daily, which should be up-titrated as tolerated to 160 mg twice daily. Increasing the dose increases the exposure to valsartan in patients with HF, although the pharmacokinetics are predictable over this dose range.[105]

Valsartan may be administered 12 hours after the occurrence of acute MI, at a starting dose of 20 mg twice daily, which can be up-titrated to 40 mg twice daily within 7 days to a maximum of 160 mg twice daily as tolerated.[5] Dose reduction can be considered in patients with symptomatic hypotension or renal dysfunction.

In CKD and type 2 diabetes, results of clinical studies have demonstrated that daily doses of 80–640 mg are effective and well tolerated (table VII).

6. Summary and Conclusions

In the more than 10 years since its approval for hypertension, a wealth of experience with valsartan has been gained through an extensive clinical research programme. To date, valsartan has been studied in more than 100 000 patients. Hypertension trials have included short- and long-term BP evaluations, time-to-effect analyses and ABP assessments. In addition to providing effective BP lowering and demonstrating good tolerability across broad patient populations (e.g. elderly, women, paediatric, obese, diabetic, chronic renal disease, high-risk CV disease, African American, Hispanic American and Asian patients), ARBs provide protective effects beyond their ability to lower BP, changing the natural course of CV and renal disease in a positive manner. Valsartan is a valuable member of the cardiorenal treatment armamentarium, with robust clinical trial evidence demonstrating its ability to reduce the incidence of CV and cerebrovascular events in patients with HF, left ventricular dysfunction following MI, diabetes and CKD, and in other groups at risk for CV events. An ongoing, large-scale outcome study in patients with impaired glucose tolerance will further elucidate the role of valsartan in preventing or delaying progression to diabetes. The availability of a single-pill, FDC such as valsartan/HCTZ provides convenience for patients who often need multiple agents for long-term control of BP, and simplifies the treatment regimens for others who require multiple medications for co-morbid conditions.

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